APPLICATION OF CONTRAST SENSITIVITY IN CLINICAL NEUROLOGY

TOEPASSING VAN CONTRAST GEVOELIGHEID IN DE KLINISCHE NEUROLOGIE

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"The shop seemed to be full of all manner of curious things – but the oddest part of it all was that, whenever she looked hard at any shelf, to make out exactly what it had on it, that particular shelf was always quite empty, though the others around it were crowded all full as they could hold".

(From Alice's Adventures Through the Looking Glass, by Lewis Caroll.)

Some parts of this thesis were adapted for articles that have been or will be published.

- Bulens C, Meerwaldt JD, Van der Wildt GJ, Keemink CJ.
  Contrast sensitivity in Parkinson's disease.
  Neurology (NY) 1986; 36: 1121-1125.

- Bulens C, Meerwaldt JD, Van der Wildt GJ, Van Deursen JBP.
  Effect of levodopa treatment on contrast sensitivity in Parkinson's disease.
  Ann Neurol 1987; 22: 365-369.

- Bulens C, Meerwaldt JD, Van der Wildt GJ.
  Effect of stimulus orientation on contrast sensitivity in Parkinson's disease.
  Neurology (NY) 1988; 38: 76-81.

- Bulens C, Meerwaldt JD, Van der Wildt GJ, Keemink CJ.
  Spatial contrast sensitivity in clinical neurology.
  Clin Neurol Neurosurg 1988; 80: 29-34.

- Bulens C, Meerwaldt JD, Van der Wildt GJ, Keemink CJ.
  Spatial contrast sensitivity in unilateral cerebral ischaemic lesions involving the posterior visual pathway.
  Brain 1988, in press.

- Bulens C, Meerwaldt JD, Koudstaal PJ, Van der Wildt GJ.
  Spatial contrast sensitivity in Benign intracranial hypertension.
  J Neurol Neurosurg Psychiatry 1988, in press.

- Bulens C, Meerwaldt JD, Van der Wildt GJ, Keemink CJ.
  Visual contrast sensitivity in drug-induced Parkinsonism.
  J Neurol Neurosurg Psychiatry 1988, in press.

- Bulens C, Meerwaldt JD, Van der Wildt GJ, Keemink CJ.
  Spatial contrast sensitivity in patients with cerebral tumours.
  Submitted, 1988.

CONTENTS

SPATIAL CONTRAST SENSITIVITY IN CLINICAL NEUROLOGY

GENERAL INTRODUCTION

The visual system is the most complex sensory system known to man. This is not surprising if one considers its enormous capacities, ranging from finding one's way to the appreciation of art. Fortunately, the system can be studied by many approaches and the results, in addition to elucidating the process of vision, advance the understanding of brain function in general.

This thesis is devoted to one new diagnostic technique called spatial contrast sensitivity (CS) measurement, to study visual function. This technique provides a much more comprehensive measure of visual efficiency than a standard acuity score. The visibility of objects depends not only on their size, but also on their relative brightness with respect to the background. Spatial contrast sensitivity measurement takes into account the contrast necessary for an object of any size to be detected. For its proper application in clinical neuro-ophthalmology, knowledge about the principles underlying human spatial contrast sensitivity is required.

Chapter I reviews the neurophysiological concepts underlying human contrast sensitivity (part 1). Based on results of both electrophysiological studies of single cells in animals and psychophysical investigations of the human visual system, many investigators have proposed that there might be parallel pathways in the visual system, selectively responding to different spatial frequencies. It will be shown why spatial contrast sensitivity is not predictable from visual acuity. The equipment and procedures necessary for performing clinical contrast sensitivity measurement are described in part 2. The results of contrast sensitivity measurement in 54 control subjects with normal visual acuity, the influence of age and intrasubject variability are discussed in part 3.

Following the description of the normal contrast sensitivity curve, the effects of various neurological disorders involving the visual pathway are discussed: Parkinson's disease, drug-induced Parkinsonism, cerebral infarctions, cerebral tumours and Benign intracranial hypertension.

Parkinson's disease is a generalized dopaminergic deficiency syndrome. The visual system functions in part by dopaminergic mechanisms. In view of this contrast sensitivity function was investigated in patients with Parkinson's disease. In Chapter II, part 1, the results of contrast sensitivity measurement in 39 patients with Parkinson's disease are described.

It was hypothesized that if dopamine is a functional transmitter in the visual system, levodopa treatment will change contrast sensitivity function in patients with Parkinson's disease. The effect of this therapy on contrast sensitivity is described in part 2.

An intriguing question concerns the site of involvement in the visual system to explain contrast sensitivity abnormalities in Parkinson's disease. It has been demonstrated in animal studies that orientation-selective neurons are almost exclusively located at a cortical level. Since dysfunction of the visual cortex may play a role in shaping contrast sensitivity loss, we were curious whether orientation-specific losses could be demonstrated in Parkinson's disease. Therefore, the effect of stimulus orientation on contrast sensitivity in 21 patients with Parkinson's disease was investigated. The results of this part of the study are described in part 3.

Drug-induced Parkinsonism is a generalized condition that resembles Parkinson's disease clinically and biochemically. If it can be assumed that there is a dependence of contrast sensitivity function on the dopaminergic system, systemic administration of dopamine antagonists will affect contrast sensitivity in a similar way as in idiopathic Parkinson's disease. This hypothesis was tested by comparing contrast sensitivity function in both conditions (part 4).

The assumed existence of parallel spatial frequency channels in the human visual system brings up the possibility that anatomical lesions of the visual pathway might selectively damage some frequency-selective channels, while the others continue to function normally. Such lesions might implicate central visual funtion, without affecting visual acuity. Contrast sensitivity examination might designate which part of the spatial frequency range is affected by different lesions comprising the posterior visual pathway. In Chapter III contrast sensitivity function in 16 patients with unilateral ischaemic lesions involving the posterior visual pathway are documented.

Patients with cerebral tumours may exhibit a variety of visual symptoms and signs each of which relates to an important aspect of the underlying pathophysiology. Tumours involving the visual pathway itself usually account for visual acuity impairment or field defects. Tumours without direct effect on the visual pathway, but interfering with CSF flow (papilloedema, hydrocephalus), can also exhibit visual damage. In Chapter IV the results of a study of contrast sensitivity function in 23 patients with cerebral tumours causing visual disturbances by diverse mechanisms are discussed.

Finally, the clinical application of contrast sensitivity measurement in Benign Intracranial Hypertension (BIH) was investigated in 20 patients. BIH is a syndrome with raised CSF pressure not due to a space-occupying lesion, and with a normal CSF and ventricular system. Loss of visual acuity is the only serious complication, and may occur either early or late in its course. Progression or regression of the disease can be monitored as is illustrated by serial measurements in 11 patients (Chapter V).

Chapter I

CONTRAST SENSITIVITY IN CLINICAL NEUROLOGY

Part 1: Neurophysiological concepts underlying human contrast sensitivity

Many neurological disorders are accompanied by visual disturbances, which can be studied by various approaches. In clinical practice, visual acuity estimations and charting of the visual fields are the two most generally accepted measures of visual function. A test for visual acuity by means of the Snellen chart describes the ability to resolve fine spatial detail. The letters used are highly contrasted with their background. In this method of assessing visual function, assumptions are made about the visual competence and the stimulus used. One is that the capacity to resolve the smallest detectable letters will describe the capacity of the visual system to resolve objects of all size. Another implicit assumption is that contrast is not of primary importance in assessing visual competence. However, the capacity of the visual system to resolve larger objects of different levels of contrast is also of great importance. Patients with visual acuities of 10/10 or more may complain of visual disturbances in seeing large objects blurred or 'misty'. Such visual loss is not shown by Snellen's test. The visibility of objects does not only depend on their size, but also on their relative brightness with respect to the background.

Spatial contrast sensitivity (CS) measurements take into account the contrast necessary for an object of any size to be detected. Over the last 15 years it has become clear that CS measurements can give information about visual function not obtainable by other methods. Campbell and Green (1965) first measured visual CS using sinusoidal grating patterns. The term "grating" indicates that the pattern is composed of regularly alternating light and dark bars. The grating usually employed in visual studies is sinusoidal, where the luminance of the dark and light bars are varied in sinusoidal fashion. The mean luminance of the grating is kept constant while the contrast is varied. The contrast threshold of a person is defined as the minimum of contrast required to distinguish a grating pattern rather than a uniform screen. The contrast of the grating pattern was defined as $C = (L_{max} - L_{min})/(L_{max} + L_{min})$, where L_{max} and L_{min} are the maximum and minimum luminance, respectively. The CS has been defined as the reciprocal value of the threshold contrast. The spatial frequency of a grating represents the number of cycles (dark-light pairs) of the sinusoid per unit distance, measured in degrees of visual angle. A plot of the CS over a range of spatial frequencies is called the CS curve. Such a curve shows a person's ability to detect fine and coarse targets, the capacity for visual discrimination of everyday objects. The physiological im-

portance of CS measured with sinusoidal gratings is related to concepts concerning system analysis. Any visual image can be considered as a combination of many spatial frequencies at multiple orientations in two or three dimensions. Any such stimulus can be constructed by superimposing sinusoidal gratings of different spatial frequencies, contrasts, and phases (positions). The amount and phase of each spatial frequency contained in a stimulus are given by the Fourier transform of the stimulus obtained through the process of Fourier analysis.

Electrophysiological studies in animals have demonstrated that single neurons in the visual pathway are 'tuned' to respond to a restricted range of spatial frequencies. The band of frequencies narrows from retina to the striate cortex where 'simple cells' have the narrowest band or 'sharpest' tuning (Maffei et al., 1973). Psychophysical investigations of the human visual system have similarly shown that the sensitivity of the visual system to the detection of contrast varies according to the spatial frequency, over a range of approximately 0.1 to 60 cycles per degree of visual arc (Campbell, 1977; Campbell & Maffei, 1974; Watson et al., 1983). The highest contrast sensitivity is in the range of two to three cycles per degree.

Considering these single-unit and psychophysical findings, many investigators have proposed that visual information is transmitted via multiple channels, each channel carrying a limited range of spatial frequencies, or other aspects, of a visual image (Campbell & Robson, 1968; Regan, 1982). The channel hypothesis holds that aspects of the visual image are 'filtered' as they enter the retina (e.g. by a center-surround receptive field, by colour-selective cone receptors or by a cell 'tuned' to specific spatial frequencies), and are transmitted via parallel channels, more or less independent of one another (Regan, 1982).

Visual disturbances can result from damage to some or all spatial frequency channels. Such abnormal visual function does not necessarily result in abnormal Snellen acuity. This can be applied in clinical neurology.

Part 2. Methods of measurement of contrast sensitivity

Apparatus

CS functions were obtained by means of sine wave gratings displayed on a video monitor (Bosch, type M 38 BA 487 TA). The gratings were generated conventionally (Campbell & Robson, 1968; Keemink et al., 1979) and controlled by a micro-processor.

Contrast was measured to be linear up to 100 per cent for all spatial frequencies used. The mean luminance for all stimuli presented was 5 cd/m^2. To avoid afterimages, the phase of the grating was alternated with a frequency of 0.8 Hz. The light and dark bars changed places periodically, so that each part of the retina was light adapted to the same extent. It is known that, in measurements

using gratings consisting of less than four or five cycles, the CS is strongly dependent on the number of cycles presented (Savoy & McCann, 1975; Van der Wildt et al., 1976). To realize that all gratings presented, consisted of four or more cycles, it was not possible to measure CS for all spatial frequencies at one viewing distance. Therefore the monitor was placed at a distance of 50 cm from the eye of the subject for spatial frequencies of 0.1 to 0.8 cycles/degree. For higher spatial frequencies (0.8 to 25.6 cycles/degree) the distance from the eye was automatically changed into 200 cm to compensate for limitations in the monitor system at high frequencies.

The stimulus field for vertical gratings subtended a visual angle of 32.5° horizontally and 23.5° vertically at 50 cm and 8.5° and 6.0° respectively, at 200 cm. For horizontal gratings the monitor was simply rotated. The visual angle of the stimulus field was 23.5° horizontally and 32.5° vertically at 50 cm and 6° and 8.5°, respectively, at 200 cm. The stimulus field was viewed in a dark surrounding. Each eye was tested separately.

Test procedure

The measuring technique was based on a modified version of the Von Békésy tracking method (Von Békésy, 1947). This procedure was conducted under computer control. The subject reduced the contrast of the grating by depressing a push button. As soon as the contrast was subthreshold, the button had to be released, which caused the contrast to increase. When the grating became just visible the subject depressed the button again. Repeating this procedure, the contrast of the grating varied around the subject's threshold. The higher and lower contrast-reversal values were averaged, and this value was taken as the subject's threshold for that spatial frequency. To avoid adaptation effects, the first four reversal values were not used. The computer ignored the two highest and the two lowest values and stored the remaining eight consecutive reversal points. Contrast sensitivity was taken to be the reciprocal of the mean of the eight stored contrast values. Contrast sensitivity was plotted as a function of spatial frequency by a microprocessor on a X-Y plotter. The CS was recorded over a spatial frequency range from 0.1 to 25.6 cycles/degree. Fig. 1 shows examples of sinusoidal gratings at one spatial frequency but of different contrasts. The measuring procedure started at the lowest frequency. When the CS at this frequency was plotted, the next frequency, twice the first, was automatically presented on the screen, and so on, until CS at all the preselected spatial frequencies had been measured. Optional was the possibility to measure a number of specified spatial frequencies with a minimum mutual difference to a factor $\sqrt{2}$. This could be used when a particular part of the spatial frequency range was of interest. The method made it possible to determine a complete CS function for both eyes in about 20 minutes.

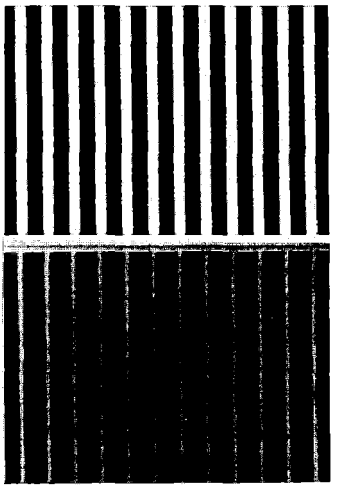


Figure 1. Two examples of sinusoidal grating patterns of one spatial frequency and equal mean luminance. The pattern at the top is higher in contrast than the one at the bottom.

Part 3. Contrast sensitivity in normal subjcets

Introduction

It is generally accepted that the efficiency of the visual system declines with aging. For many of the visual and ocular motor subsystems, data are available to define normal according to the patient's age. For others it is not (Weale, 1975). Visual acuity is probably the most studied visual parameter in aging (Anderson & Palmore, 1974; Richards, 1977). A modest decline in visual acuity prior to age 60 has been documented, followed by a rapid decline, in many patients, from 60 to 80 years of age. One of the problems with acuity testing is that most chart systems do not have sufficient gradations to test vision better than 10/10, a Snellen acuity that is actually at the lower limit of 'normal'. Feisen and Frisén (1979) found that 10/10 vision requires no more than 44% functional acuity channels.

Contrast Sensitivity measurement is an additional means of analyzing central vision. Ginsburg (1981) demonstrated that threshold detection and identification of letters of various sizes are directly related to a subject's CS, not his visual acuity. CS measurement is a subjective test, and may be affected by several factors, such as the compliance of the subject to guess or wait until certain before responding, the rate of exposure of the grating pattern to the subject, and so on. These factors will cause a substantial intersubject variability without affecting the shape of the curve. For the investigation of CS function in pathological conditions, it is necessary to establish 'normal values' and analyze

the effect of age to differentiate the effects of the normal ageing process from visual pathology. A fundamental assumption implicit in valid diagnosis and monitoring the CS in the individual patient is a subject's test and retest consistency. In this study CS was measured in a normal population, comparing several age-groups. In addition the intrasubject variability was examined in five subjects.

Subjects

The group of 54 normal subjects consisted of hospital personnel and patients without CNS disease. All had ophthalmological examination and were free of ocular disease. Subjects with known astigmatism were excluded. Snellen acuities, measured with refractive correction where necessary, were 10/10 or better.

Results

The group of 54 normal subjects (108 eyes) was divided in five decades of age: 11 subjects were in their third decade, 15 in their fourth, nine in their fifth, ten in their sixth, and nine in their seventh decade. The mean age was 47 years (range, 21-70). There was no influence of age on the mean score (Fig. 2). The mean CS curve, based on all data (108 eyes) is shown in

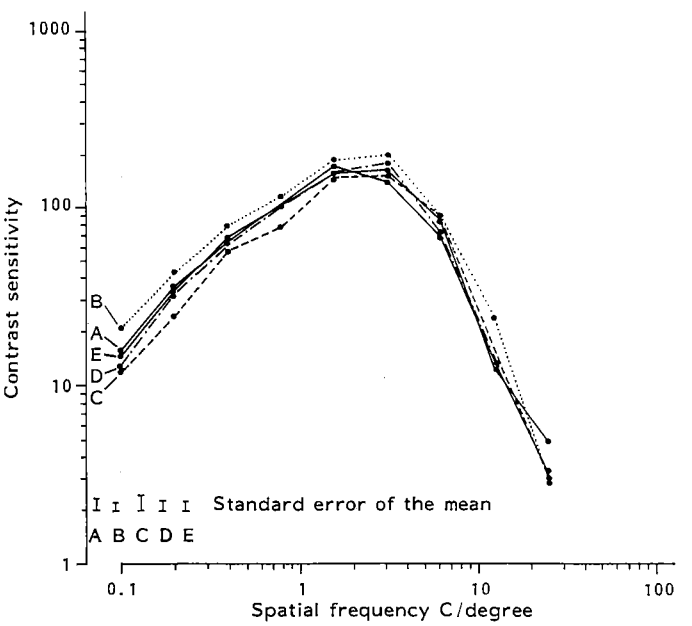


Figure 2. The average score of contrast sensitivity in normal subjects in five decades of age. (A = 21-30; B = 31-40; C = 41-50; D = 51-60; E = 61-70).

Fig. 3. Five subjects, one of each decade, were retested one to six months later. The mean magnitude of variability was only 1.4 (2 SD 0.3), which means a great test-retest consistency.

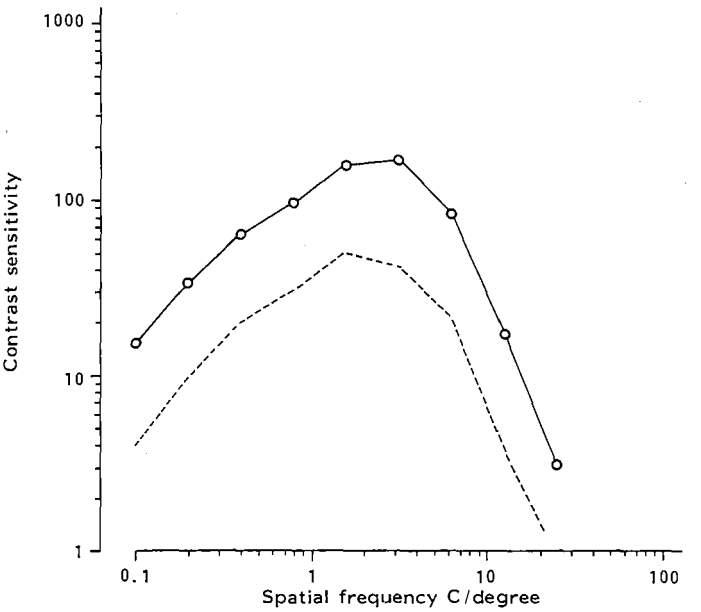


Figure 3. Mean contrast sensitivity curve of 108 normal eyes. 2 SD (— — —).

Discussion

The normal CS curve increased linearly in the low spatial frequency range, packed at the middle frequency area of 1.6 to 3.2 cycles/degree and fell off exponentially at higher frequencies. CS varied within each age-decade subgroup (intersubject variability), but was not affected by age in this group of normal subjects. These results are in disagreement with previous reports. Skalka (1980) found advancing age to be associated with reduction of CS, irrespective of spatial frequency. This could not be confirmed by Sekuler and Hutman (1980) who found a reduction only at low spatial frequencies. In subsequent papers Sekuler and colleagues (Owsley 1982; Sekuler & Owsley, 1982) reported CS to be reduced at high spatial frequencies. Singh et al. (1981) found only very slight reduction of CS, only after the sixth decade. A major problem in the study of the results reported in the literature is that many different stimulation methods and conditions of investigation were used. The conflicting results mentioned above may be explained because some of these workers used grating booklets of Arden (Arden, 1978) to measure CS, which is a less accurate method. High spatial frequencies (above 6.4 cycles/degree) cannot be tested with this

method. Moreover, Skalka (1980) biased his results by repeating the test only if abnormal results were obtained. Schlotterer et al. (1983), who used methods similar to those described here, found that 'old people' had high spatial frequency loss. In their study CS was determined at six different spatial frequencies, up to 12 cycles/degree. Visual acuities in their older group, however, were significantly poorer than in the younger group. It is not surprising to find high frequency loss in subjects with 'significant poorer visual acuities'.

Age-related changes of the visual system are well known. Optical transmission is reduced, lenticular changes and senile miosis cause increased light scatter (Ruddock, 1965; Corso, 1971). Little is known, however, about changes in central visual processes with increasing age. Important aspects of brain functional activity are not reduced in the elderly (Creasey & Rapoport, 1985). CS function in this study of subjects with normal Snellen acuities was not affected by age.

The intrasubject variability was measured in five subjects by retesting CS one to six months later. The mean magnitude of variability was only 1.4 (2 SD 0.3). This great repeatability of a subject's CS function by the adjusted Von Békéksy tracking method is in disagreement with the observations of Ginsburg and Cannon (1983) on CS measurements by this psychophysical method. A possible explanation of the variance might be that they did not control for the effects of afterimages by changing the spatial phase of the gratings periodically. Unusual CS values in the order of 1,000, as they found, were not measured in the subjects of this study.

In obtaining CS function in neurological patients, it is important to be prepared to deal with a number of pitfalls. Neurological patients do not only distinct from normal subjects in having a specific disease, some additional features can also contribute to his or her test condition. Some patients are easily tired, which makes the measurements rather time consuming.

In conclusion, CS function using stimulation methods and conditions of investigation as described above is not affected by aged. There is a great test-retest consistency.

Chapter II

CONTRAST SENSITIVITY IN PARKINSON'S DISEASE

Part 1. Loss of contrast sensitivity in Parkinson's disease

INTRODUCTION

Although motor manifestations are the main sequelae of Parkinson's disease (Parkinson, 1817), the disorder is probably more generalized (Barbeau et al., 1975), and due to a generalized dopaminergic deficiency. The retina and lateral geniculate body function in part by dopaminergic mechanisms (Häggendal & Malmfors, 1965; Deffenu et al., 1967; Phillis et al., 1967; Lindvall et al., 1973; Dyer et al., 1981). In view of the assumed dopaminergic transmission visual evoked potential (VEP) studies have been undertaken in Parkinson's disease (PD). Abnormal responses were seen by some investigators (Bodis-Wollner & Yahr, 1978; Mintz et al., 1981; Kupersmith et al., 1982; Bodis-Wollner et al., 1982), but not by others (Delwaide et al., 1980; Ehle et al., 1982). Both abnormal and normal responses were found in the same PD patient depending on the stimulus used (Tartaglione et al., 1984). In this study contrast sensitivity (CS) measurements were used to analyse visual function in PD.

SUBJECTS

The control group of 25 subjects consisted of hospital personnel and patients without CNS disease. All had ophthalmological examination and were free of ocular disease. Subjects with known astigmatism were excluded. Snellen acuities were 10/10 or better.

Thirty-nine patients with the diagnosis of PD, who had not been treated with levodopa, were examined. The severity of their disease was rated according to Hoehn and Yahr (1967). All but eight patients were treated with anticholinergics and/or amantadine. The eight patients who had no therapy were all in stage I. The patients were also classified in three subgroups according to the main initial sign of disease (hypokinesia, tremor, or rigidity). All had ophthalmological examination, including corrected visual acuity measurement. Patients with known astigmatism were excluded.

RESULTS

Control group

The mean age of the control group was 67 years (range, 53-80). The CS

functions of the 50 control eyes were obtained and the mean CS curve is shown in Fig. 4. Twenty-eight eyes (20 subjects) showed a slight decrease in CS at different spatial frequencies between 0.2 and 12.8 cycles/degree. The decrease factor (DF) of these minor deflections was defined as the ratio of the measured CS and the expected value of the non diverged individual curve for a given spatial frequency. The mean decrease factor (DF) of these 28 eyes was 1.3 (2 SD 0.6), which is completely within intraindividual variability.

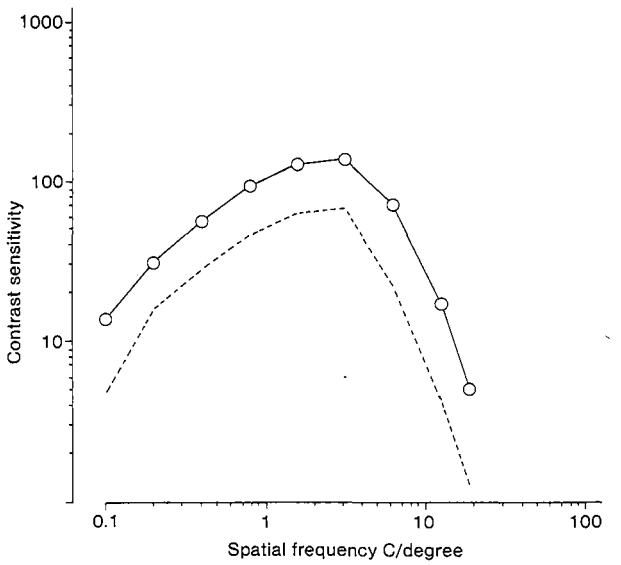


Figure 4. Mean contrast sensitivity curve of 50 normal eyes. 2 SD (———).

Patients

The mean age of the PD patients was 65 years (range, 52-79). Of the 39 patients, 16 were in stage I, 20 in stage II, and 3 in stage III (Hoehn & Yahr, 1967). Eight of the 16 patients in stage I of the disease were given no therapy. The remaining eight patients in stage I, and all patients in stages II and III, were treated with anticholinergics, amantadine or both. The main initial sign was hypokinesia in 20, tremor in 14, and rigidity in five. CS function was obtained in 73 eyes of the 39 patients. The remaining five eyes were excluded because of concomitant ophthalmological disease (amblyopia, four eyes, and unilateral cataract, one eye). The visual acuities of all patients were 7/10 or more, and are summarized in Fig. 5.

The mean normal CS curve was taken as reference for the curves of the PD patients. A curve was considered abnormal when the reduction of CS resulted in a displacement of (a part of) the curve below the control curve for more than two SDs. Intermediate frequency loss was judged abnormal (notch loss) when the decrease factor (DF) was more than 1.9, being the mean DF in 28 of the 50 normal eyes, plus two SDs.

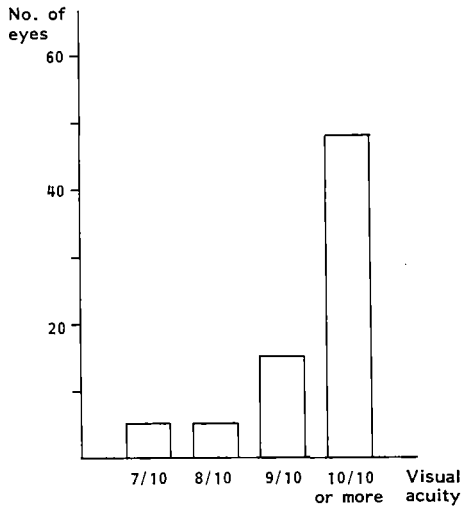


Figure 5. Distribution of visual acuity in 39 PD patients (73 eyes).

Of the 39 PD patients, 14 (25 eyes) had normal CS curves. Twenty-five patients had abnormal curves, 11 of them unilaterally. High frequency loss (above 3.2 cycles/degree) was found in 22 eyes, low spatial frequency loss (below 3.2 cycles/degree) was found in 9 eyes. Sixteen eyes showed notch losses, in eight combined with high frequency loss, and in the remaining eight eyes the rest of the curve was unaffected. Sixty-nine per cent of the notches were centered at the spatial frequency of 0.8 cycles/degree. All notches are summarized in Table 1. Examples of abnormal CS function in PD patients are shown in Fig. 6.

Table 1. Notch losses in 39 patients with Parkinson's disease

Spatial frequency	Number of eyes	Decrease factor
0.6	3	3.03
0.8	11	2.94
1.2	2	4.66

Abnormal CS was not related to severity of disease, rated according to Hoehn and Yahr (1967). CS loss was found in 11 of the 16 patients (70%) in stage I, and in 15 of the 20 patients (75%) in stage II. Two of the three patients in stage III had abnormal CS functions. No differences were found in the PD subgroups with respect to the main initial sign. High frequency loss, low frequency loss and notch losses occurred in all stages and subgroups. Unilateral abnormality was not related to severity of disease. There was no difference in CS function between patients with visual acuities of 7/10 and patients with acuities of 10/10 or more.

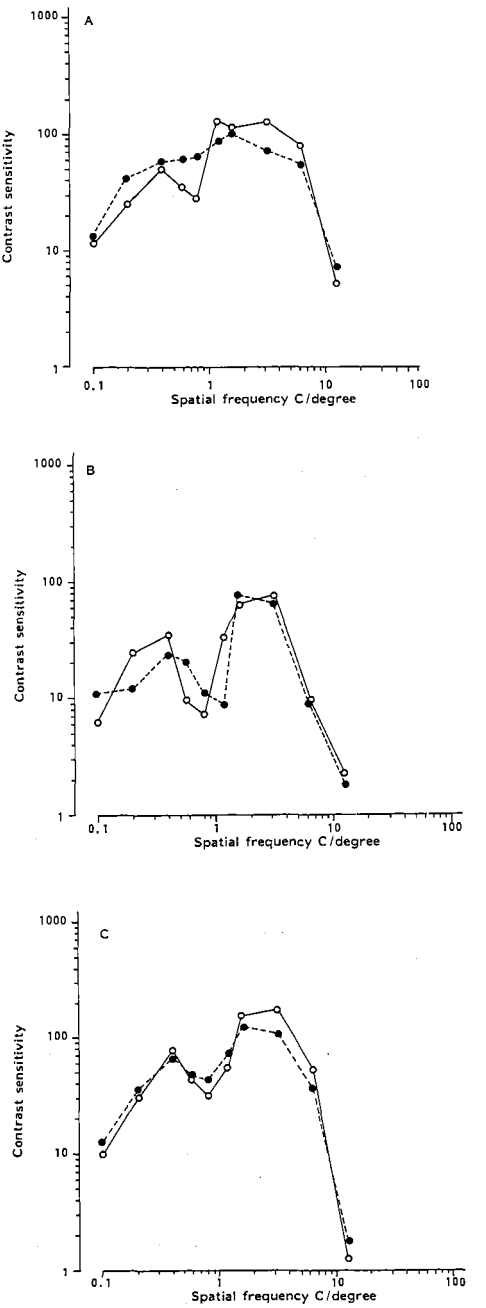


Figure 6. Examples of contrast sensitivity curves of three PD patients, notch loss centered at 0.8 cycles/degree spatial frequency, unilateral (A) and bilateral (B and C).

DISCUSSION

Sixty-four per cent of the PD patients had CS loss in one or both eyes. Most had high frequency loss, intermediate frequency loss (notch loss), or both (62%). Eleven of the 16 notch defects were centered at the 0.8 cycles/degree spatial frequency. The other five notches occurred in the low spatial frequencies as well.

The PD patients had normal subjective visual function, and the visual acuities were 7/10 or more. The relationship between visual acuity and CS is complex. High frequency loss was seen even in patients with visual acuities of 10/10 or more and normal curves were found in patients with acuities of 7/10.

Abnormality of CS was not related to severity of the disease. There were no differences in the three subgroups based on the main initial sign. If dopaminergic transmission is important in the visual system, it is strange that there is no correlation between the severity of PD and abnormality of CS. Perhaps the decrease of dopamine levels in the basal ganglia and the visual system are not parallel. In addition, the scale according to Hoehn and Yahr (1967) is rather crude.

These data confirm other reports that CS is abnormal in PD. Bodis-Wollner et al. (1984) described spatial CS losses in 10 of 12 PD patients over a range of spatial frequencies, centered at the region between four and nine cycles/degree. Kupersmith et al. (1982) and Herishanu et al. (1986) also found reduced CS in their PD patients. These authors, however, mentioned only mean CS scores. It is obvious that notch defects of individual patients cannot be established by summation of contrast sensitivities at all spatial frequencies.

Loss of sensitivity at some spatial frequencies has been reported in other neurological disorders. Bodis-Wollner and Diamond (1976) found selective frequency loss at intermediate frequency ranges in five patients with occipital tumours and in one patient with a posterior cerebral artery occlusion. Notch losses have also been seen in MS and optic neuritis (Zimmern et al., 1979; Regan et al., 1981; Medjbeur & Tulunay-Keesey, 1985), but marked notch losses like those in the patients described here, have never been documented before. One could argue whether the notch losses found in this study could not be explained by technical factors, such as the alteration of the phase of the grating and the measuring of low and high spatial frequencies at different viewing distances. These technical factors could not have been responsible for the notch defects at the 0.8 cycles/degree spatial frequency because the place, width and the depth of the loss were unchanged when we reexamined some patients with a fixed pattern and there was no change of CS at 0.8 cycles/degree when measured at both viewing distances.

Although simple visual disturbances are not a clinical symptom in PD, peculiar visuospatial anomalies have been noted (Bowen, 1976; Boller, 1980; Boller et al., 1984). The patients of the present study had no visual symptoms. The site of altered visual function in PD is unknown. In animals, there are dopamine projections in parts of the peripheral visual system (Häggendal & Malmfors,

1965; Deffenu et al., 1967; Phillis et al., 1967; Lindvall et al., 1973; Dyer et al., 1981). Dopamine-sensitive cells are also known to exist in the human retina (Frederick et al., 1982). Dopamine deficiency or synaptic dysfunction may explain abnormalities in VEP studies in PD (Bodis-Wollner et al. 1982). Unilateral CS loss, which occurred in 44% of the PD patients, could also imply prechiasmal, possibly retinal, involvement. Interocular differences have been found in VEP studies as well (Bodis-Wollner & Yahr, 1978; Gawel et al., 1981). The occurrence of sensitivity loss at intermediate frequencies in 16 of the 48 "affected" eyes in the PD patients, however, may implicate cortical involvement, as spatial frequency selectivity is mainly attributed to cortical neurons and not, or only in a less degree, to neurons of the retina and geniculate body (Campbell & Robson, 1968; Regan, 1982). Grating patterns are optimal stimuli for neurons in the visual cortex, in the interpretation of which the association areas play an important role. Although the basal ganglia are concerned primarily with motor organization, there has been a lot of speculation concerning the mechanisms whereby the basal ganglia modulate higher cortical functions (Nauta, 1979; Krauthamer, 1979; Koller, 1984).

In conclusion, abnormal CS function occurs in a high frequency in PD patients. Notch losses, which occurred in 30% of the affected eyes, may implicate cortical involvement. Regardless of the explanation, the present results are consistent with the concept that in PD there is a generalized dopaminergic deficiency (Barbeau et al., 1975).

Part 2. Effect of Levodopa treatment on contrast sensitivity in Parkinson's disease

INTRODUCTION

In part 1 of this Chapter abnormal CS in PD was described, which occurred in a considerable proportion (25/39) of patients. Since marked alterations in dopamine content occur in brains of parkinsonian patients, CS measurements were next conducted on patients in whom we could pharmacologically alter the content of monoamines in the central nervous system. Only if dopamine is a functional transmitter in the visual pathway, this therapy will change CS function.

SUBJECTS

The control population of 20 subjects consisted of hospital personnel and patients without CNS disease. All had an ophthalmological examination and were free of ocular disease. Snellen acuities were 10/10 or better. Ten patients with PD who were to start on levodopa substitution were chosen for the investigation. They had an ophthalmological examination, including corrected visual measurement (Table 2), and were free of ocular disease. Subjects with known astigmatism were excluded in both groups.

RESULTS

Control group

The mean age of the control group was 61 years (range, 53-70). The CS functions of the 40 eyes of the control subjects were obtained and the mean CS curve is shown in fig. 7. Fourteen eyes (11 subjects) showed a slight decrease in CS at intermediate spatial frequencies (between 0.2 and 6.4 cycles/degree). The mean decrease factor (DF) of these 14 eyes was 1.3 (2 SD 0.4), which is completely within intraindividual variability.

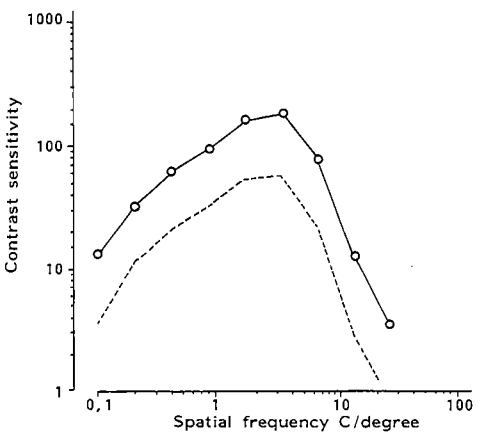


Figure 7. Mean contrast sensitivity curve of 40 normal eyes. 2 SD (— — —).

Patient group

The mean age of the 10 patients with PD was 66 years (range, 56-77). The visual acuities of all patients were 7/10 or more. The CS function of the patient's eyes was individually compared with the mean CS curve of the control subjects. A curve was judged abnormal when a CS deficit resulted in a displacement of (a part of) the curve below the control curve for more than 2 SDs. Intermediate frequency loss was considered abnormal (notch defect) when the DF was more than 1.7, which was the mean DF in 14 of the 40 normal eyes plus 2 SDs. The width of the notch was defined as the spatial frequency band width over which CS loss was observed (octaves). Because in the test procedure mostly preselected spatial frequencies were used, only an upper limit for the band width could be estimated. It is clear that, the more intermediate CS values are measured, the more acurately the width of a notch can be estimated. The mean width of the notch defects was 1.85 octaves (range, 1.5-2.0). Before levodopa treatment, 16 of the 20 eyes (9 patients) had abnormal CS function. Losses that could be classified as selective were seen in 11 eyes. The loss affected

selectively the high frequency range in five eyes and the low frequency range in two eyes. A notch loss was present in four eyes. In two other eyes, notch loss was combined with high frequency loss and in another with generalized loss.

The intrasubject variability was measured in four patients (before therapy) by retesting CS four to eight weeks following the first test. The mean magnitude of variability was only 1.3 (2 SD 0.3), which means a high intrasubject consistency.

Three to 15 months after the institution of levodopa treatment six of the 20 eyes (5 patients) still showed abnormal CS curves. After therapy, however, only high frequency loss was observed. All other types of deficit had disappeared under treatment. The results of the follow-up neuro-ophthalmological examination of all patients are listed in Table 2. Three examples of CS change (Patients 5, 8 and 10) are shown in Fig. 8.

Table 2. Clinical data and results of neuro-ophthalmological investigations in 10 patients with Parkinson's disease

No.	Sex	Age	Visual Acuity	CS before L-dopa	Treatment L-dopa (mg)	Follow-up (months)	CS after L-dopa
1	M	74	R 9/10	h loss	600	4	R h loss
			L 9/10	h loss			L no loss
2	F	56	R 10/10	n loss (0.8)	600	12	R no loss
			L 10/10	n loss (0.8)			L no loss
3	F	64	R 10/10	no loss	375	10	R no loss
			L 10/10	l loss			L no loss
4	F	67	R 8/10	h loss	1000	3	R h loss
			L 9/10	h loss			L h loss
5	F	67	R 10/10	generalized loss & n loss (0.6)	500	15	R no loss
			L 7/10	generalized loss			L h loss
6	M	64	R 10/10	no loss	300	8	R no loss
			L 10/10	no loss			L no loss
7	F	64	R 10/10	generalized loss	600	11	R no loss
			L 10/10	l loss			L no loss
8	F	68	R 10/10	h loss & n loss (0.8)	250	10	R no loss
			L 10/10	h loss & n loss (0.8)			L h loss
9	M	77	R 9/10	h loss	800	12	R h loss
			L 9/10	n loss (0.4)			L no loss
10	M	59	R 10/10	n loss (0.8)	1500	4	R no loss
			L 10/10	no loss			L no loss

CS Contrast sensitivity
R Right eye
L Left eye
l loss Low-frequency loss
h loss High-frequency loss
n loss Notch CS loss (spatial frequency, cycles per degree)

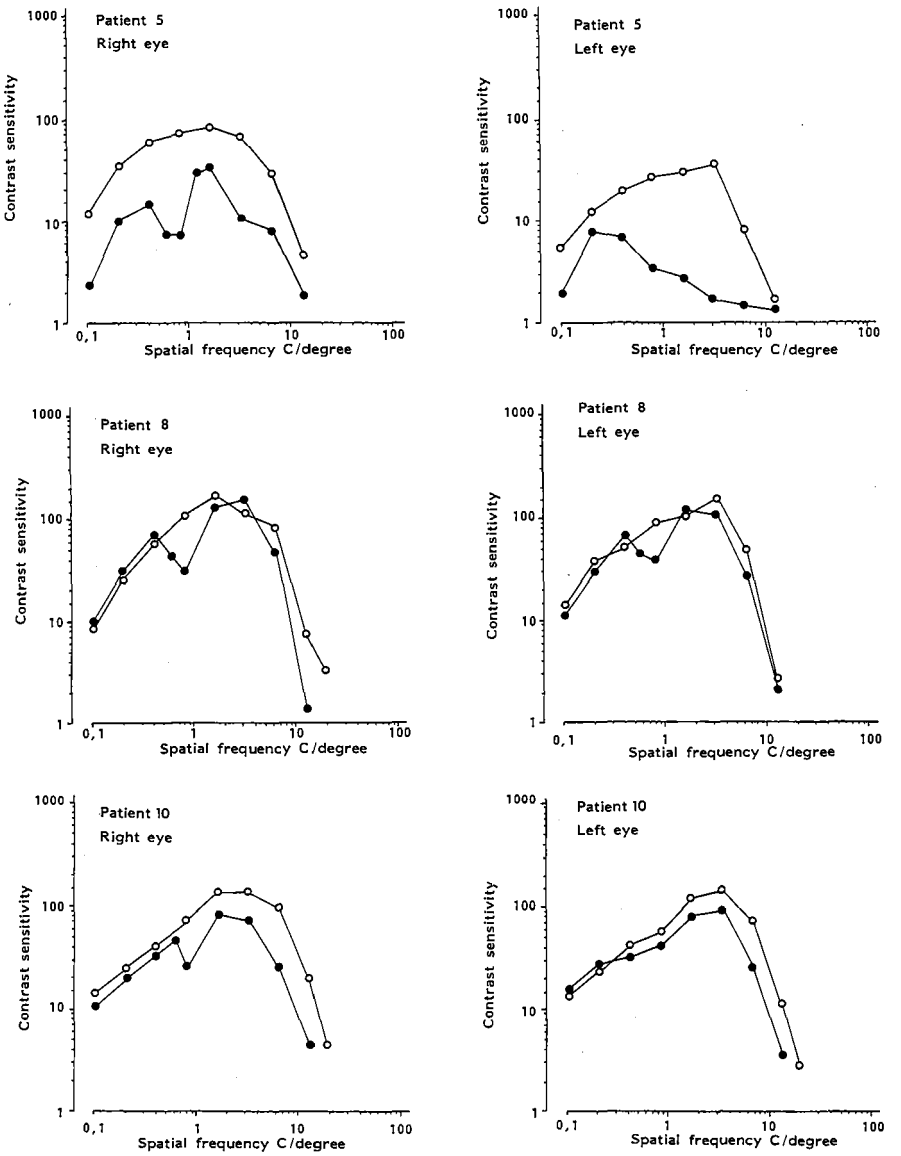


Figure 8. Three examples of contrast sensitivity change under levodopa treatment (filled circles = before levodopa; open circles = after levodopa).
(A) Patient 5 showed generalized loss in both eyes, in one (right eye) combined with notch loss centered at 0.6 cycles/degree. During treatment, complete normalization occurred except for persisting high-frequency loss in left eye.
(B) Patient 8 had similar contrast losses (high-frequency loss and notch loss centered at 0.8 cycles/degree) in both eyes. During treatment only high-frequency loss in left eye was observed.
(C) Patient 10 showed unilateral (right eye) notch loss centered at 0.8 cycles/degree, which resolved on treatment.

DISCUSSION

Before levodopa treatment, 16 of the 20 eyes showed abnormal CS function. After treatment, only six of the 20 eyes still showed abnormalities. The only patient who had normal pretreatment CS function showed no CS loss after levodopa treatment. The change of CS function in this group of patients with PD following treatment suggests that dopamine is a functional transmitter in the visual pathways.

Because the motor expression of PD is primarily a reflection of dopamine deficiency (Bernheimer et al., 1973), the improvement of motor function after levodopa treatment could in theory bias the posttreatment results. This is unlikely, as the method of CS measurement used in this study requires very simple motor responses. Further, changes in CS function were mostly restricted to a part of the frequency range. If improvement of motor function was responsible for the posttreatment improvements, a generalized improvement in most cases should have been exhibited.

The present findings are supported by related neurophysiological work. Visual evoked potential (VEP) studies have shown that abnormal delay could be normalized in patients with PD under the influence of levodopa therapy. Bodis-Wollner and Yahr (1978) showed an abnormal delay with normalization after levodopa therapy, in five of 24 patients with PD. Yaar (1980), however, was not able to detect significant overall changes in the VEPs in response to levodopa treatment. In subsequent studies (Mintz et al., 1981; Bodis-Wollner et al., 1982) normalization of abnormal VEPs after levodopa treatment has again been demonstrated.

A substantial proportion of CS loss was restricted to a particular band of spatial frequencies. In addition, all intermediate spatial frequency losses appeared reversible under levodopa treatment. The existence of selective deficits in the pretreatment group might be explained in terms of involvement of cortical neurons. In animal studies, spatial frequency selectivity for visual stimuli has been demonstrated in visual cortical neurons as well as in neurons of the retina and lateral geniculate body. Visual cortical neurons, however, are much more selective for spatial frequencies than are neurons of the peripheral visual system (Campbell et al., 1969; Cooper & Robson, 1968; De Valois et al., 1977; 1978; 1982). The severity of spatial frequency-selective CS losses in patients with PD would be most easily explained in terms of involvement of cortical neurons. A dopamine deficiency in the mesocortical pathway, as recently demonstrated by positron emission tomography (Garnett et al., 1984), could cause dysfunction of cortical neurons. Javoy-Agid and Agid (1980) have suggested that this deficiency could account for some of the cognitive deficits commonly seen in PD. These deficits, however, are not consistently reversible by replacement of dopamine. Regardless of the explanation, the present results indicate a dependence of CS function on the dopaminergic system in PD. CS loss is reversible under levodopa treatment in a considerable proportion of patients with PD.

Part 3. Effect of stimulus orientation on contrast sensitivity in Parkinson's disease

INTRODUCTION

In the previous parts of this chapter it has been demonstrated that a considerable proportion of patients with PD had CS loss. A substantial proportion of these losses were restricted to a particular band of spatial frequencies, which may imply cortical dysfunction. Spatial frequency selectivity is attributed to cortical neurons and not, or only to a less degree to neurons of the retina and lateral geniculate body (Campbell & Robson, 1969; Regan, 1982). How the visual system transforms the retinal neural code into perception is not known. From animal studies it has been demonstrated that the visual cortex is organized in columns with orientation-selective neurons (Hubel et al., 1977; 1978). Such neurons are almost exclusively at a cortical level (Hubel & Wiesel, 1968; Bauer et al., 1980). Since dysfunction of the visual cortex may play a role in shaping CS loss, we were interested in whether orientation-specific losses could be demonstrated in patients with PD. Therefore, the effect of stimulus orientation on CS in normal subjects and in patients with PD was studied. This was done by measuring CS function over a range of spatial frequencies for vertical and horizontal orientations.

CONTROL SUBJECTS AND PATIETNS

Control subjects

The control group of 10 subjects consisted of hospital personnel and patients without CNS disease. All had ophthalmological examinations and were free of ocular disease. Subjects with known astigmatism were eliminated from the control group. Snellen visual acuities, measured with refractive correction where necessary, were 10/10 or better.

Patients with Parkinson's disease

Twenty-one patients with PD were examined. All had ophthalmological examinations, including corrected visual acuity measurements. Patients with ocular disease or known astigmatism were excluded. The severity of their disease was rated according to Hoehn and Yahr stages categories (Hoehn & Yahr, 1967). All but one patient were taking anticholinergics, amantadine, or levodopa substitution. The only patient who had no therapy was in stage II.

RESULTS

Control group

The mean age of the control group was 68 years (range, 56-84). The CS functions of the 20 control eyes were obtained and the mean CS curves for

vertical and horizontal stimuli are shown in Fig. 9. It shows that the results obtained when the grating was orientated vertically or horizontally were very similar. Although intersubject variability was substantial, no orientation-specific loss was found. Slight decreases in CS at intermediate spatial frequencies were observed using vertical as well as horizontal stimuli. Twelve of the 20 measurements using vertical stimuli showed slight decrements; in a comparable proportion (14/20) of the measurements using horizontal stimuli such decrements were observed. These decrements were expressed by their depths (decrease factor) and their widths (frequency ranges). The mean decrease factor (DF) of 26 measurements was 1.2 (2 SD 0.5).

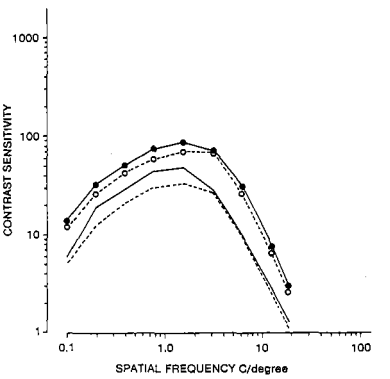


Figure 9. Mean contrast sensitivity curve of 20 normal eyes for vertical (closed circles) and horizontal (open circles) gratings. Lines show 2 SD.

PD patients

The mean age of the PD patients was 66 years (range, 53-78). Of the 21 patients, two were in stage I, 14 in stage II, and five in stage III (Hoehn & Yahr, 1967). All but one were treated with anticholinergics, amantadine, levodopa, or a combination of these drugs. The visual acuities of all patients were 7/10 or more.

The CS function for vertical and horizontal gratings of each of the patients' eyes was individually compared with the mean CS curves of the controls. A curve was judged abnormal when a CS deficit resulted in a displacement of (a part of) the curve below the control curve for more than 2 SDs. Selective frequency loss was taken for abnormal (notch defect) when the DF was more than 1.7, being the mean DF in the normal group plus 2 SDs. The width of the notch was defined as the spatial frequency bandwidth over which contrast loss was observed (octaves). Five PD patients were retested one to three months later. The magnitude of variability was 1.6 (2 SD 0.3). This test and retest consistency included the site, width and depth of the notch defects in these patients.

CS function was obtained in 42 eyes. Six patients had normal CS functions in both eyes for vertical and horizontal gratings. Fifteen patients had at least one eye with CS deficit for either stimulus orientation (Table 3). CS for vertical orientations was abnormal in 21 eyes. Generalized loss was seen in two eyes.

Table 3. Type of contrast sensitivity loss in 15 PD patients for vertical and horizontal stimuli

Type of CS loss	Number of eyes	
	Vertical stimuli	Horizontal stimuli
Generalized loss	2	4
Selective loss		
Notch loss	7	2
Notch loss & low-frequency loss		1
Notch loss & high-frequency loss	2	1
Low-frequency loss	6	7
High frequency loss	4	5

Losses that could be classified as selective were found in 19 eyes (90%). Of these 19 eyes, notch losses were present in seven. In two other eyes, notch loss was combined with high-frequency loss. The loss affected selectively the low-frequency range in six eyes and the high-frequency range in four. The mean bandwidth of these 10 notches in nine eyes was 2.4 octaves (range 1.5-3).

CS for horizontal orientations was abnormal in 20 eyes. Generalized loss was observed in four eyes and selective loss in 16 (80%). Low-frequency range was selectively affected in seven eyes and the high-frequency range in five. A notch loss was present in two eyes and in two other eyes combined with other deficits. The mean bandwidth of these four notches was 1.8 octaves (range, 1.5-2).

The results of the measurements of CS functions for all patients are shown in Table 4. In 17 of the 25 affected eyes, CS loss was confined to only one orientation, and in eight eyes CS loss was orientation independent. Of these eyes with orientation-independent losses, three showed losses restricted to lower spatial frequencies, in two other eyes only high frequency range was affected, while in two generalized loss was observed. Twelve of the 13 notch defects could only be observed with either stimulus orientation. One patient (case 4) had an orientation-selective CS deficit in the right eye while a notch defect of two octaves in the left eye narrowed to 1.5 octaves when CS was measured with horizontal gratings. Although some patients had similar CS deficits in both eyes, orientation-specific losses that were the same in both eyes were not seen. Some examples of orientation-specific losses of CS are shown in Fig. 10.

Abnormal CS was not related to the severity of disease, rated according to Hoehn and Yahr (1967). CS loss was found in one of the two patients in stage I and in two of the five patients in stage III. Three of the 14 patients in stage II had abnormal CS functions with horizontal or vertical stimulus orientation in at least one eye. There was no difference in CS function in patients with visual acuities of 7/10 and patients with acuities of 10/10 or more.

Table 4. Clinical data and results of neuro-ophthalmological investigations in 21 PD patients

No.	Sex	Age	Disease stage	Therapy	Snellen acuity	Contrast sensitivity function vertical stimuli	horizontal stimuli
1	F	53	III	Amantadine	R 10/10	no loss	no loss
					L 10/10	no loss	no loss
2	F	54	III	Amantadine	R 10/10	no loss	no loss
					L 7/10	no loss	no loss
3	M	55	II	A-chol. &	R 10/10	n loss (0.2-1.6)	no loss
				amantadine	L 10/10	n loss (0.4-1.6) & h loss	h loss
4	M	55	II	A-chol.	R 7/10	n loss (6.4-19.2)	no loss
					L 7/10	n loss (1.6-6.4)	n loss (1.6-4.8)
5	F	56	I	Levodopa	R 10/10	no loss	no loss
					L 10/10	no loss	no loss
6	F	59	II	A-chol.	R 10/10	h loss	generalized loss
					L 10/10	generalized loss	generalized loss
7	F	61	III	A-chol.	R 15/10	n loss (0.4-1.6)	no loss
					L 15/10	l loss	no loss
8	M	66	III	Levodopa	R 15/10	no loss	n loss (0.4-1.2) & l loss
					L 15/10	no loss	no loss
9	F	66	II	Levodopa	R 10/10	l loss	l loss
					L 7/10	l loss	l loss
10	M	67	II	Amantadine	R 10/10	no loss	no loss
					L 10/10	no loss	no loss (0.4-1.6)
11	F	67	II	A-chol. &	R 10/10	no loss	no loss
				amantadine	L 10/10	no loss	no loss
12	M	69	II	A-chol.	R 10/10	no loss	no loss
					L 10/10	no loss	no loss
13	F	69	II	Levodopa	R 10/10	n loss (3.2-12.8)	h loss
					L 7/10	no loss	l loss
14	F	69	II	A-chol.	R 10/10	no loss	no loss
					L 10/10	no loss	no loss
15	M	70	II	A-chol. &	R 10/10	l loss	generalized loss
				amantadine	L 10/10	generalized loss	generalized loss
16	F	70	II	None	R 10/10	no loss	l loss
					L 10/10	no loss	no loss
17	M	71	III	Amantadine	R 7/10	n loss (0.8-6.4) & h loss	l loss
					L 10/10	l loss	l loss
18	F	72	II	Levodopa	R 9/10	h loss	n loss (0.8-3.2) & h loss
					L 9/10	h loss	h loss
19	M	73	I	Amantadine	R 15/10	no loss	no loss
					L 10/10	l loss	h loss
20	M	77	II	A-chol.	R 10/10	n loss (0.1-0.8) & n loss (3.2-12.8)	no loss
					L 9/10	n loss (0.8/6.4)	l loss
21	M	78	II	Levodopa &	R 9/10	h loss	h loss
				amantadine	L 9/10	no loss	no loss

R Right eye
L Left eye
l loss Low-frequency loss
h loss High-frequency loss
n loss Notch CS loss
(spatial frequency, cycles per degree)

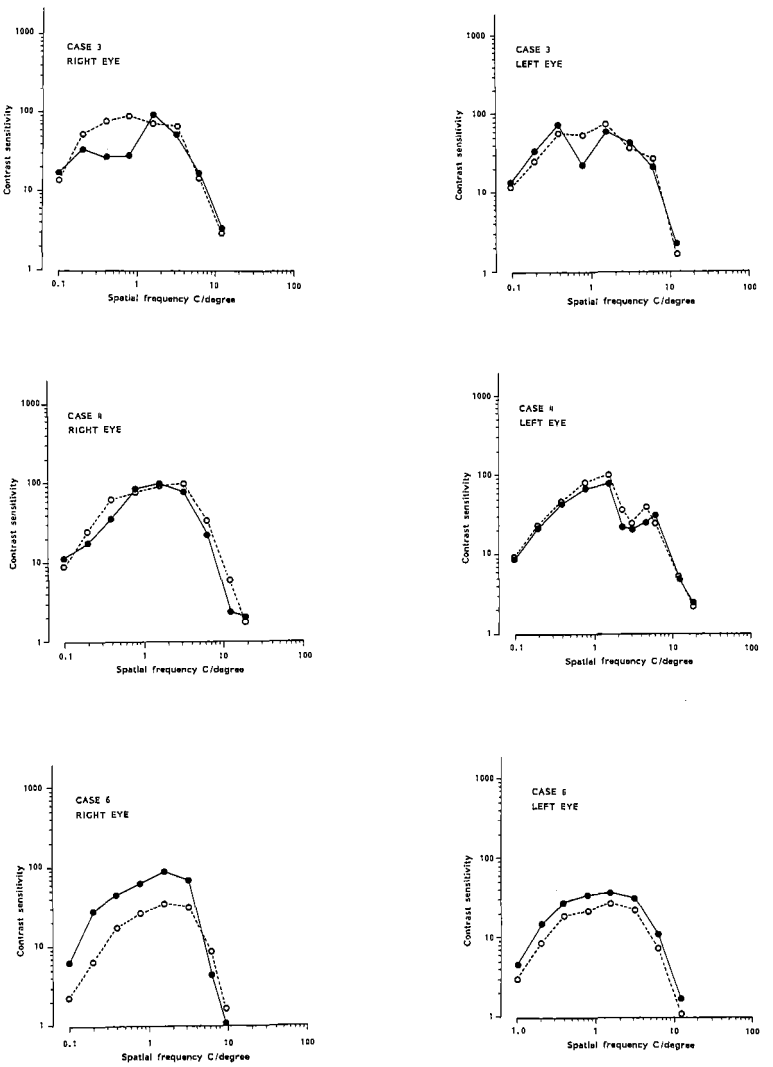
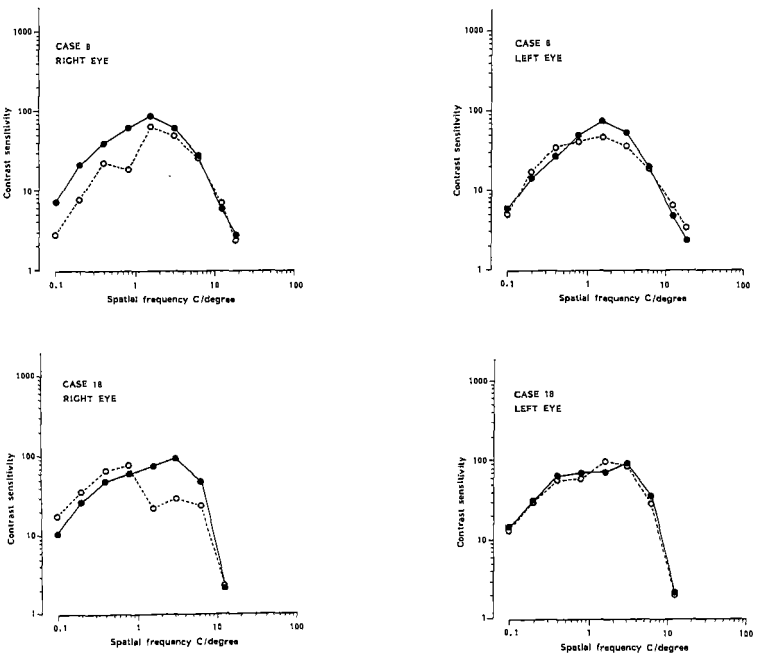


Figure 10. Examples of contrast sensitivity curves in five PD patients. Key to symbols as in figure 9. Case 3 shows n loss (0.2-1.6) in right eye and n loss (0.4-1.6) in left eye for vertical gratings only and persisting h loss in left eye, stimulus independent.
Case 4 shows orientation-specific loss (6.4-19.2) in right eye, while n loss (1.6-6.4) in left eye narrows to 1.6-4.8 when CS is measured with horizontal gratings.
Case 6 shows orientation-independent generalized loss in left eye and orientation-specific loss for all spatial frequencies except high-frequency range in right eye.

Figure 10 continued



Case 8 shows n loss (0.4-1.2) and l loss in right eye for horizontal gratings only and normal CS curves in left eye for both orientations.
Case 18 shows orientation-specific n loss (0.8-3.2) in right eye and orientation-independent h loss in both eyes.
l loss = low-frequency loss; h loss = high-frequency loss; n loss = notch loss (spatial frequency range in cycles/degree).

DISCUSSION

Study of CS function with grating stimuli of different orientations showed CS deficit in 15 of the 21 PD patients in at least one eye. All patients had visual acuities of 7/10 or more. This means that CS measurments can demonstrate disturbances of visual function despite a good visual acuity. More importantly, CS measuring for different orientations revealed that 17 of the 25 affected eyes showed orientation-selective deficits. The most frequent type of orientation-selective loss, observed in 12 cases, was a notch defect, which preferentially affected the middle spatial frequencies. These defects were mostly asymmetrical and in some only one eye was affected.

In a previous part of this chapter the results of CS measurements in 39 PD patients were described. A considerable proportion (25/39) of these patients, tested with vertical gratings only, had abnormal CS function. The present study verifies and extends these findings by testing CS by variable stimulus orientations.

These data confirm earlier reports that CS is abnormal in PD patients. Bodis-Wollner et al. (1984) described spatial CS losses in 10 PD patients. Specific losses in sensitivity were observed near the peak of the spatial CS curve, often with no noticeable low frequency attenuation. These authors used only vertical orientations to test CS function. Regan and Maxner (1987) reported also orientation-dependent CS loss in six of 10 PD patients. Because they measured CS using temporally modulated stimuli, their findings cannot be compared with the data of this study. Nevertheless, they also concluded that orientation selectivity implicates visual cortical cells. Kupersmith et al. (1982) and Herishanu et al. (1986) also found reduced CS in their PD patients. These authors, however, mentioned only mean CS scores. It is obvious that intermediate and orientation-specific CS losses of individual patients cannot be established from the averages of CS curves showing diverse, multifocal types of disturbances. Moreover, it should be noted that intersubject variability of CS is substantial in control subjects as well as in patients. A fundamental assumption implicit in diagnosing CS deficits is a subject's test and retest consistency. The intrasubject variability was measured in five PD patients by retesting CS one to six months later. The mean magnitude of variability was only 1.6 (2 SD 0.3), which means a great intrasubject test-retest consistency. The site, width and depth of the notch defects were highly reproducible.

An intriguing question concerns the site of orientation-specific pathology. Although recent work suggests that some grating orientation tuning exists in retinal ganglion cells (Hammond, 1974; Levick & Thibos, 1980) and in the lateral geniculate bodies (Vidyasagar & Urbas, 1982; Albus et al., 1983), orientation-selective CS loss in PD must be attributed to functional disruption of cortical neurons because orientation-selective neurons are not found peripheral to the visual cortex. Hubel et al. (1977; 1978) have demonstrated that the visual cortex is organized in columns with orientation-selective neurons. Although there is no direct evidence that orientation-selective neurons have anything to do with visual perception, it is attractive to assume that this functional architecture represents some stage in the analysis of visual forms. Whether or not peripheral effects contribute to CS loss in PD remains to be established.

Bodis-Wollner et al. (1984) suggested an abnormality in monocular excitatory-inhibitory interactions of the visual system to explain CS loss in PD. Indeed, CS defects are often asymmetrical and in some monocular. In visual evoked potential (VEP) studies, asymmetrical results have also been reported in PD (Bodis-Wollner & Yahr, 1978; Bodis Wollner et al., 1980); Gawel et al., 1981; Mintz et al., 1981; Bodis-Wollner et al., 1982). Neurophysiologic studies have demonstrated, however, that identical stimuli do not usually give quantitatively identical reponses if first one eye and then the other one is tested (Hubel & Wiesel, 1979). Asymmetrical CS deficits and VEP asymmetry therefore are not necessarily explained by monocular disturbances.

PD is due to a generalized dopaminergic deficiency (Barbeau et al., 1975). The main source for dopaminergic influences on a cortical level arises from

the basal ganglia via the mesocortical dopaminergic pathway (Moore & Bloom, 1978). Degeneration of these dopamine fibers in PD gives rise to cortical dopamine deficiency. Positron emission tomographic studies in PD patients (Garnett et al., 1984) have demonstrated that dopamine concentrations are also decreased in the visual cortex. The role of dopamine in cortical neurons might be important in normal visual function. A functional disruption of these dopamine-containing neurons in PD may play an important role in generating frequency-selective and orientation-specific CS loss.

In summary, the following conclusions can be drawn: (1) CS loss in PD is orientation-selective in a considerable proportion of patients, and (2) the responsible disturbance for spatial frequency-selective and orientation-specific loss is, at least in part, situated at, or central to the primary visual cortex.

Part 4. Contrast sensitivity loss in drug-induced Parkinsonism

INTRODUCTION

In the previous parts of this Chapter it was found that a considerable proportion (25/39) of patients with Parkinson's Disease (PD) had visual Contrast Sensitivity (CS) loss. The reversibility of CS losses under levodopa treatment suggested a dependence of visual function on dopaminergic transmission. Drug-induced Parkinsonism (DIP) is a generalized condition that resembles PD clinically and biochemically. If dopamine is a functional transmitter in the visual pathway, systemic administration of dopamine blockers will, in theory, affect CS function in a similar way as in PD. In this study, we evaluated CS function in 10 patients with DIP.

SUBJECTS

Control subjects

The control group comprised 10 subjects, none of whom had any history of neurological or ophthalmological disorder. Subjects with known astigmatism were excluded. All had ophthalmological examination and were free of ocular disease. Snellen acuities, measured with refractive correction where necessary were 10/10 or better.

Patients

Ten previously untreated patients, who were alert, were selected. They were all receiving dopamine blockers (haloperidol and/or fluspirilene) for at least three weeks at the time of testing. All patients had drug-induced parkinsonism, the severity of which was rated according to Hoehn and Yahr's stages categories.

Clinical summaries and medication are listed in Table 5. To exclude possible effects of sedation on CS testing in the patient group, we also examined three age-matched epileptic patients receiving phenytoin (dose 300 mg/day). All patients had ophthalmological examination, including corrected visual acuity testing. Patients with known astigmatism were excluded.

Table 5. Clinical summaries of 10 patients with drug-induced Parkinsonism

No.	Sex	Age (yrs)	Medication* H	B	F	Psychiatric diagnosis
1	f	17	15	5		Schizophrenia
2	m	21	5	5		Schizophrenia
3	f	22	2.5			Puerperal Psychosis
4	f	25	2.5			Puerperal Psychosis
5	m	35		5	4	Schizophrenia
6	m	38	5			Manic-depressive Psychosis
7	m	39			5	Schizophrenia
8	f	40	5	5	10	Schizophrenia
9	m	42	10			Melancholia
10	f	51	10	5		Schizophrenia

*haloperidol (H) and benzhexol (B) in daily dose (mg); fluspirilene (F) in weekly dose (mg).

RESULTS

Control group

The mean age of the control group was 35 years, (range, 23-51). The CS functions of the 20 control eyes were obtained for vertical and horizontal gratings and the mean CS curves for both orientations are shown in Fig. 11. Close

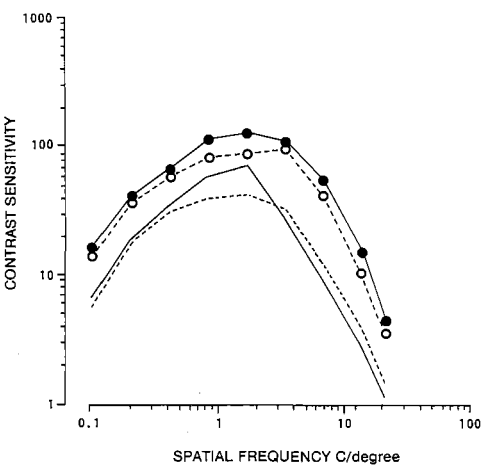


Figure 11. Mean contrast sensitivity curve of 20 normal eyes for vertical (filled circles) and horizontal gratings (open circles). Lines show 2 SD.

inspection of individual CS curves in normal subjects can reveal that at intermediate spatial frequencies a CS curve can diverge slightly from the pure inverted U shape. Minor deflections at intermediate spatial frequencies were observed for vertical as well as horizontal stimuli. In 12 of the 20 measurements using vertical stimuli slight decrements were found, while in 10 of the 20 measurements using horizontal stimuli such decrements were observed. These decrements were expressed by their depths (decrease factor) and their widths (frequency ranges). The mean decrease factor (DF) of the 22 measurements was 1.2 (2 SD 0.2). These slight decrements in the individual CS function of the controls are completely within intrasubject variability.

Patient group

The mean age of the patient group was 33 years, (range, 17-51). All patients had Snellen acuities of 10/10 or better. Rated according to Hoehn and Yahr they were all in stage II. The CS function for vertical and horizontal gratings of each of the patient's eyes was individually compared with the mean CS curves of the controls. A curve was judged abnormal when a CS deficit resulted in a displacement of (a part of) the curve below the control curve for more than two standard deviations. Intermediate frequency loss was taken for abnormal (notch defect) when the decrease factor (DF) was more than 1.4, being the mean D.F. in the normal group plus two standard deviations. The width of the notch was defined as the spatial frequency bandwidth over which contrast loss was observed (octaves). Two of the ten DIP patients were retested four weeks later. The magnitude of variability was 1.5 (2 SD 0.3). This test and retest consistency included the site, width and depth of the notch defects in these patients. CS function was obtained in 20 eyes. Only one patient had normal CS functions in both eyes for vertical and horizontal gratings. All other nine patients had at least one eye with CS deficit for vertical and/or horizontal stimuli. Six of these nine patients had some CS losses in both eyes. The different types of CS loss for all patients are shown in Table 6. CS losses affecting all the spatial frequencies tested were observed in both eyes of patient no. 9. These deficits are referred to as generalized losses. All other CS losses were spatial frequency-selective. The most frequent type of deficit, observed in 14 eyes, was a notch loss. In two eyes multifocal notch losses were found and in four other eyes they occurred in combination with other types of loss. Seventeen of the total number of 19 notches for either stimulus orientation occurred in the middle and low spatial frequency range (below 32. cycles/degree). Other types of spatial frequency selective CS loss were seen in three eyes. The loss affected selectively the high spatial frequency range in one eye, and the low spatial frequency range in two eyes. Although there was some overlap concerning orientation specificity in two eyes (no. 4, 5), all spatial frequency-selective CS deficits were orientation dependent. The generalized losses in both eyes of patient no. 9 were orientation independent. Some examples of orientation-specific CS losses are shown in Fig. 12. The three epileptic patients all receiving

Table 6. Contrast sensitivity function for vertical and horizontal stimuli in 10 patients treated with dopaminergic blockers

	CONTRAST SENSITIVITY	
No.	Vertical Stimuli	Horizontal Stimuli
1	R n loss (0.4-1.6) & h loss	no loss
	L n loss (0.8-3.2)	no loss
2	R no loss	no loss
	L no loss	no loss
3	R n loss (3.2-12.8)	no loss
	L n loss (0.1-0.4)	no loss
4	R no loss	n loss (0.1-0.4) & (0.4-1.6)
	L n loss (0.2-1.6)	n loss (0.1-0.8)
5	R n loss (0.2-1.6)	no loss
	L n loss (0.8-3.2)	n loss (0.4-3.2)
6	R no loss	no loss
	L no loss	n loss (0.8-3.2)
7	R n loss (0.8-3.2)	no loss
	L no loss	no loss
8	R n loss (0.4-1.6)	n loss (1.6-6.4)
	L no loss	no loss
9	R generalized loss & n loss (0.2-0.8) & (0.8-3.2)	generalized loss
	L generalized loss	generalized loss & n loss (0.8-3.2)
10	R l loss	no loss
	L l loss & n loss (0.4-3.2)	no loss

Key to symbols as in table 4.

phenytoin (300 mg/day) had normal curves for vertical as well as horizontal stimuli.

DISCUSSION

Sine-wave grating CS determinations for vertical and horizontal orientations revealed CS loss in 9 of the 10 patients with DIP. The most frequent type of deficit, observed in 14 eyes was a notch loss, which preferentially affected the middle and low spatial frequencies. All spatial frequency-selective CS loss was orientation dependent. Generalized loss, found in two eyes was orientation independent.

In the first part of this Chapter it was demonstrated that abnormal CS function occurred in a high frequency in PD. In part 3, it was shown that these losses were greatly stimulus orientation-dependent. The most frequent type of CS loss was also a notch defect, which especially affected the middle spatial frequencies. In a recent study by Regan and Maxner (1987), who used temporally modulated stimuli at one spatial frequency (2 cycles/degree), orientation-selective loss was also demonstrated in 6 of 10 PD patients. CS loss was most marked at a temporal frequency of 4 to 8 Hz. The maximum of CS loss was found for horizontally

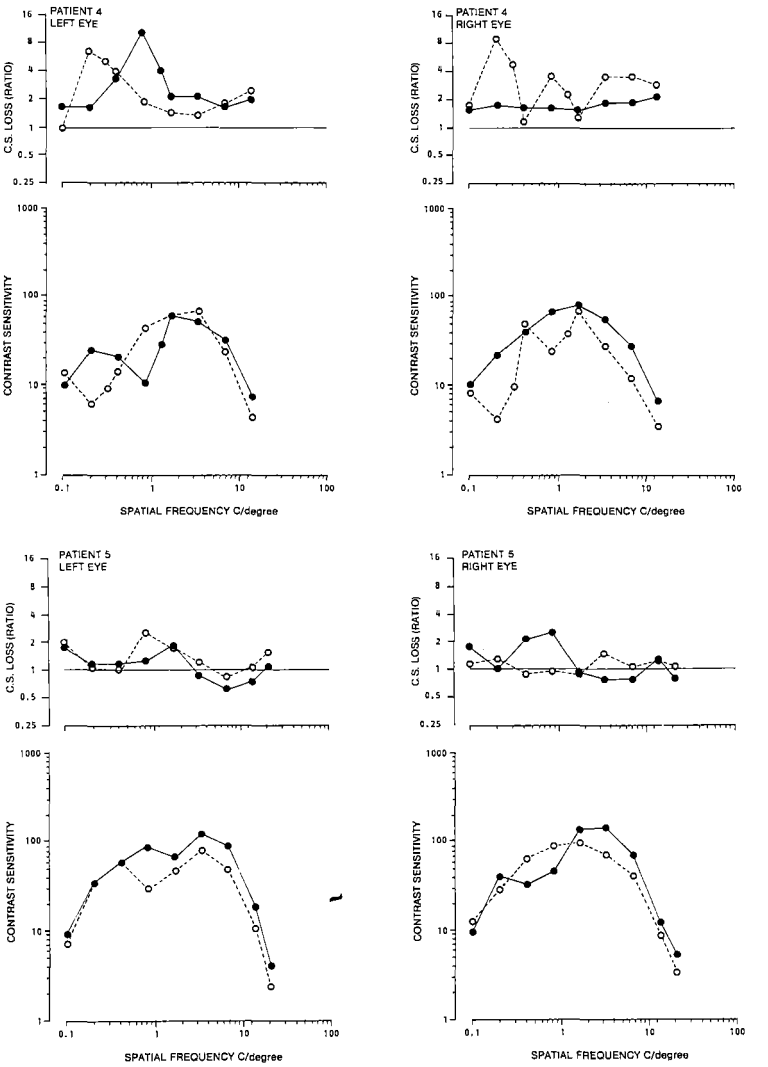
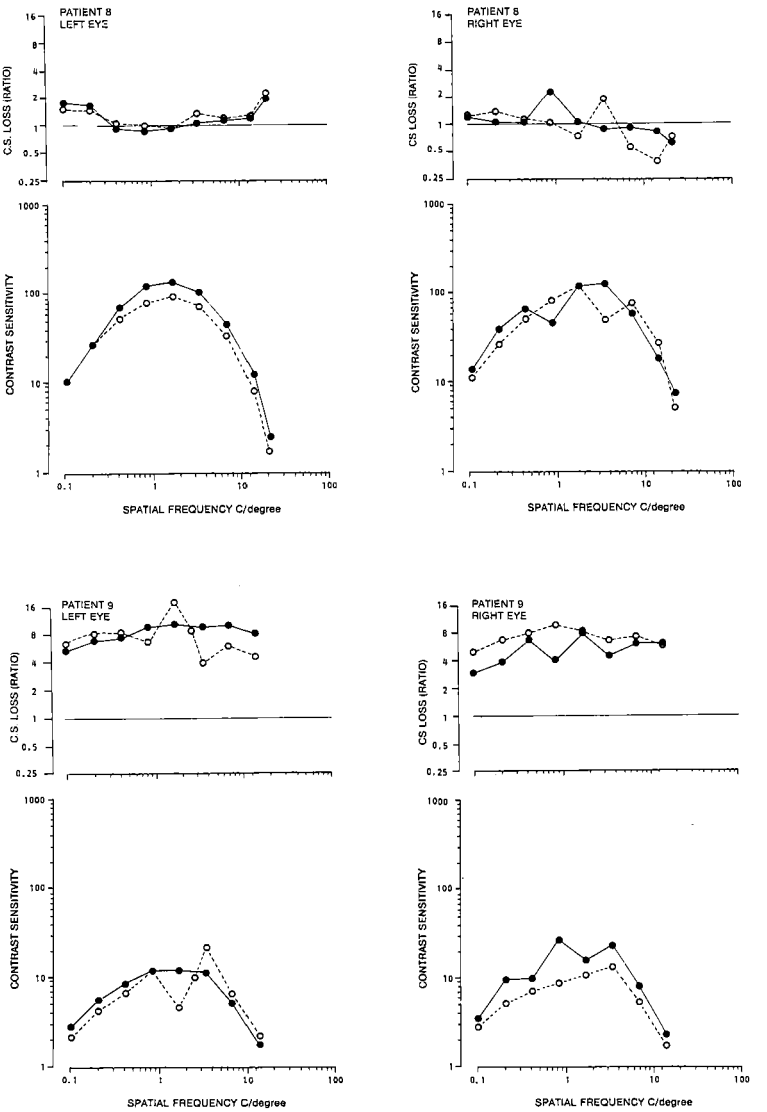


Figure 12. Examples of contrast sensitivity curves in 4 patients with drug-induced Parkinsonism. Key to symbols as figure 11. The upper part of each figure shows the ratio of the altered contrast sensitivity to normal contrast sensitivity function for corresponding spatial frequencies.
(A) Patient 4. Left eye shows orientation-specific notch losses: a 3 octaves wide notch loss for horizontal gratings centered at 0.2 cycles/degree and a 3 octaves wide notch loss for vertical gratings at 0.8 cycles/degree. Right eye shows a notch loss centered at 0.2 cycles/degree and another notch loss centered at 0.8 cycles/degree for horizontal gratings only. Both notches are 2 octaves wide.
(B) Patient 5. Left eye shows a notch loss (0.4-3.2), which narrows to 0.8-3.2 when CS is measured with vertical gratings. Right eye shows orientation-specific, 3 octaves wide notch loss centered at 0.6 cycles/degree for vertical gratings.

Figure 12 continued



(C) Patient 8. Left eye shows normal curves for both orientations. Right eye shows a 2 octaves wide notch loss centered at 0.8 and another of the same width at 3.2 cycles/degree, both orientation-specific, for vertical and horizontal gratings respectively.
(D) Patient 9. Both eyes show orientation-independent generalized loss. Left eye shows also a 2 octaves wide orientation-selective notch loss centered at 1.6 cycles/degree. Right eye shows beside generalized loss a notch loss centered at 0.4 and another notch loss centered at 3.2 cycles/degree, both 2 octaves wide and orientation-selective.

orientated stimuli. They proposed a possible explanation of their findings based on animal studies. In the visual cortical area V2 in the baboon there is a marked bias for neurons to prefer vertically orientated stimuli, while in area VI there is a roughly similar preference for horizontal and vertical orientations (Kennedy et al., 1985). Patients with a selective loss of CS for horizontal stimuli might have selective damage to the human equivalent of VI striate cortex. Although comparison of the data of the present study with their findings is rendered difficult because of different techniques of CS measurement, the selective loss of CS for horizontal stimuli was not encountered in our results of PD and DIP patients. The roughly equal CS losses for vertically and horizontally orientated stimuli, on the contrary, might indicate involvement of other visual cortical areas than the human equivalent of VI striate cortex. Spatial and temporal 'channels of vision' can apparently be affected differentially in a variety of ways in PD.

A major assumption implicit in diagnosing CS deficits is the intrasubject test-retest consistency. We measured this by retesting CS in three DIP patients, four weeks later. The mean magnitude of variability was only 1.5 (2 SD 0.3), which means a great test-retest consistency. The site, width and depth of the notch defects were highly reproducible. To minimize any possible effect of sedation on CS testing in our DIP patient group we also examined three epileptic patients receiving 300 mg phenytoin per day. All three patients showed normal CS curves for vertical and horizintal grating stimuli.

Patients treated with neuroleptics like butyrophenones (haloperidol) and diphenylbutylpiperidines (fluspirilene) may develop a clinical picture which mimics PD very closely. DIP and PD are two conditions that share pharmacologic (Ambani et al., 1973), and biochemical (Chase et al., 1970) characteristics. The fact that DIP is mainly produced by drugs that interfere with storage of dopamine pre-synapticly, or block post-synaptic dopamine receptors, indicates that "dopamine deficiency" is the biochemical basis of this clinical condition. PD and DIP are classically associated with motor manifestations, but the disorders are probably more generalized (Barbeau et al., 1975). Abnormalities of visual evoked potentials (Bodis-Wollner & Yahr, 1978; Gawel et al., 1981; Bodis-Wollner et al., 1982) and CS function in PD indicate that the visual system is also involved.

There is a striking resemblance of the pattern of CS loss in drug-induced Parkinsonism to that in PD. This curious parallel suggests that generalized dopaminergic hypofunction, from whatever cause, has similar effects on visual function. The present results, once again support the view that dopamine is a functional transmitter in the visual pathway.

Chapter III

CONTRAST SENSITIVITY IN UNILATERAL CEREBRAL ISCHAEMIC LESIONS INVOLVING THE POSTERIOR VISUAL PATHWAY

INTRODUCTION

The organization of the posterior visual pathway is known in general outline, but little is known about details of topography, and what perceptual deficits may occur under pathological circumstances. Acuity tests, as measured with the Snellen letters, are good means for the detection of optic nerve and chiasmal disorders. However, they have no value in the detection of unilateral lesions of the posterior visual pathway (Frisén, 1980). Acuity remains normal as long as either the crossing or the non crossing neural outflow from the retinal fovea remains intact.

Nevertheless, in spite of clinically normal visual acuity patients with cerebral lesions may complain of blurred vision (Bodis-Wollner & Diamond, 1976). Such patients might have a peculiar sort of visual disturbance, reducing central visual function, without affecting visual acuity. Such neurally caused visual disturbances could be revealed by a more extensive test of central vision, determinations of spatial contrast sensitivity (CS).

Electrophysiological studies of single cells in the animal brain and psychophysical investigations of the human visual system have demonstrated that there might be parallel channels in the visual system, selectively responding to different spatial frequencies (Enroth-Cugell & Robson, 1966; Campbell & Robson, 1968; Campbell et al., 1969; Blakemore & Campbell, 1969; Albrecht et al., 1980). The overall bandwidth of frequencies narrows from the retina to the striate cortex where 'simple' cells have the narrowest bandwidth (Maffei et al., 1973). This approach to vision assumes the existence of subsystems operating in parallel channels, each channel carrying a limited range of spatial frequencies. Functional disruption or anatomical lesions of the posterior visual pathway could selectively damage some frequency-selective channels, while the others continue to function normally (Regan et al., 1977; 1980; 1981). Such lesions can implicate central visual function, without affecting visual acuity. CS examination as a function of spatial frequency might designate which part of the spatial frequency range is affected by different lesions comprising the posterior visual pathway.

Another issue, concerning properties of neurons subserving central visual function, is orientation selectivity. Striate cortex neurons are not only sensitive to restricted ranges of spatial frequencies, they also appear sensitive to the orientation of the stimulus. Hubel et al. (1977; 1978) have demonstrated that

orientation selective neurons are organized in columns in the primary visual cortex. These orientation-sensitive neurons are not found peripheral to the primary visual cortex in primates. Orientation-selective CS loss, which has been described in multiple sclerosis (Regan et al., 1980; Kupersmith et al., 1984) and Parkinson's disease (Regan & Maxner, 1987; Bulens et al., 1988a) have been explained therefore, in terms of involvement of cortical neurons. It is not surprising that true anatomical lesions of the posterior visual pathway can also generate abnormal CS function (Bodis-Wollner & Diamond, 1976; Kobayashi et al., 1985). Measurements of spatial CS function for different orientations in this group of patients could yield information about visual perceptual deficits, not obtainable by conventional visual tests.

In this Chapter, CS function in patients with unilateral ischaemic lesions involving the posterior visual pathway is described. An important question was whether CS function was affected in a qualitative different way according to the site of the lesion, and whether orientation-selectivity was restricted to lesions of the primary visual cortex.

SUBJECTS

The control group consisted of 10 subjects without CNS disease. All were free of ocular disease. Subjects with known astigmatism were excluded. Snellen acuities, measured with refractive correction where necessary, were 10/10 or better. This group had a mean age of 68 years (range, 56-84).

Sixteen patients, all having visual field defects consistent with unilateral cerebral ischaemic lesion and confirmed by CT scanning were selected. The duration after onset varied from three days to 10 years. All patients had ophthalmological examination, including corrected visual acuity measurement and Goldmann perimetry. Patients with retinal abnormalities, lens opacity, or known astigmatism were excluded. The mean age of the patients was 65 years (range, 53-77). The patients were classified according to the site of the lesion: occipital and occipitotemporal lesions (group I); temporal and parietal lesions (group II). Location and extent of lesions were determined from CT scans, referring to standard atlases (Gado et al., 1979). Clinical summaries are given in the Tables 7 and 8.

RESULTS

Control group

The CS functions of the 20 control eyes were obtained and the mean CS curves of the control group for vertical and horizontal stimuli are shown in Fig. 13. Close inspection of individual CS curves in normal subjects can reveal that at intermediate spatial frequencies a CS curve can diverge slightly from the pure inverted U shape. Such minor deflections of the CS curve at intermediate

spatial frequencies were observed for vertical as well as horizontal stimuli. In twelve of the 20 measurements using vertical stimuli slight decrements were found, while in 14 of the 20 measurements using horizontal stimuli such decrements were observed. The decrease factor (DF) of these decrements was defined as the ratio of the measured CS and the expected value of the non diverged individual curve for a given spatial frequency. The mean decrease factor (DF) of 26 measurements was 1.2 (2 SD 0.5). These slight decrements in the individual CS function of the controls are completely within intrasubject variability. There was no orientation specific CS loss within the spatial frequency range.

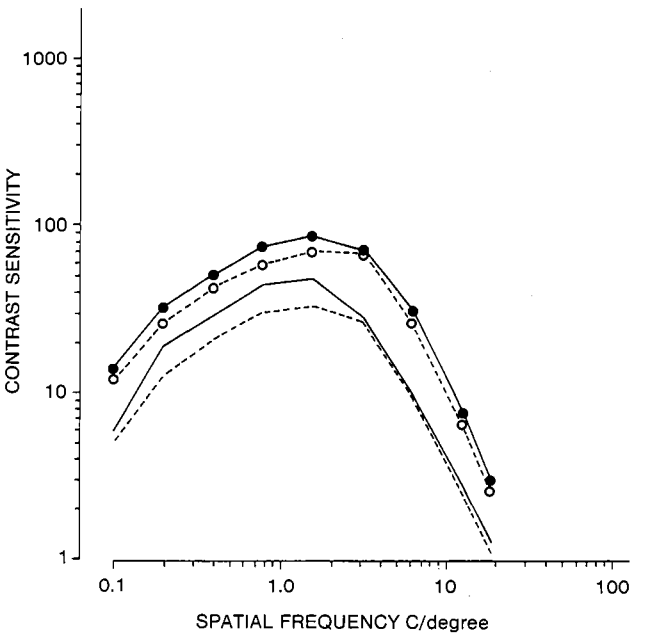


Figure 13. Mean contrast sensitivity curve of 20 normal eyes for vertical (filled circles) and horizontal gratings (open circles). Lones show 2 SD.

Patients

The CS function for vertical and horizontal gratings of each of the patient's eyes was individually compared with the mean CS curves of the controls. A curve was judged abnormal when a CS deficit resulted in a displacement of (a part of) the curve below the control curve for more than two standard deviations. Intermediate frequency loss was taken for abnormal (notch defect) when the decrease factor (DF) was more than 1.7, being the mean DF in the normal group plus two standard deviations. The width of the notch was defined as the spatial frequency bandwidth over which contrast loss was observed

(octaves). CS function was obtained in 32 eyes. Six patients had normal CS functions in both eyes for vertical and horizontal gratings. Of these six patients five were in group I, and one patient in group II. Ten patients had at least one eye with CS deficit for either stimulus orientation. Three of these 10 patients had a unilateral CS deficit for both stimulus orientations. The different types of CS loss for all patients are shown in Table 7. Contrast loss was confined

Table 7. Investigations in 16 patients with unilateral ischaemic lesions of the posterior visual pathway. Group I: Occipital and Occipitotemporal lesions, Group II: Temporal and Parietal lesions

Case No.	Sex	Age	Duration after Onset	Visual Field	Visual Acuity	Contrast Sensitivity Function Vertical Stimuli	Horizontal Stimuli
GROUP I							
1	m	68	1 month		R: 10/10	no loss	no loss
					L: 7/10	h loss	no loss
2	m	60	10 years		R: 10/10	no loss	no loss
					L: 10/10	no loss	no loss
3	m	77	3 days		R: 10/10	no loss	no loss
					L: 7/10	no loss	no loss
4	m	58	2 months		R: 10/10	no loss	n loss(6.4-19.2)
					L: 10/10	n loss(9.4-19.2)	no loss
5	m	53	3 weeks		R: 10/10	no loss	no loss
					L: 10/10	no loss	no loss
6	m	53	2 weeks		R: 10/10	no loss	no loss
					L: 10/10	no loss	n loss(3.2-12.8)
7	f	61	9 months		R: 15/10	no loss	no loss
					L: 15/10	no loss	no loss
8	f	75	1 month		R: 10/10	no loss	no loss
					L: 8/10	no loss	no loss
9	f	72	18 months		R: 10/10	n loss(6.4-19.2)	no loss
					L: 10/10	no loss	n loss(6.4-19.2)
GROUP II							
10	m	72	2 months		R: 8/10	n loss(0.2-0.8)	l loss
					L: 7/10	l loss	l loss
11	m	56	6 weeks		R: 10/10	no loss	no loss
					L: 10/10	no loss	n loss(0.2-3.2)
12	m	67	1 month		R: 10/10	n loss(0.2-0.8)	no loss
					L: 10/10	n loss(0.2-1.6)	n loss(0.8-3.2)
13	m	53	3 months		R: 10/10	no loss	no loss
					L: 10/10	no loss	no loss
14	f	66	2 weeks		R: 10/10	no loss	n loss(0.6-3.2)
					L: 8/10	n loss(0.4-1.6)	no loss
15	m	73	2 years		R: 10/10	l loss	no loss
					L: 10/10	l loss	n loss(0.2-0.8)
16	f	76	4 years		R: 7/10	l loss	l loss
					L: 7/10	no loss	no loss

Key to symbols as in table 4.

to one eye for either stimulus orientation in two patients. CS loss was spatial frequency-selective in all 'affected' eyes. Two patients (case 10 and 16) showed a stimulus independent low frequency loss in one eye, all other CS deficits were orientation dependent. We measured the intrasubject variability in three patients, by retesting CS two to three weeks later. The mean magnitude of variability was only 1.3 (2 SD 0.4), which means a great intrasubject test-retest consistency. The locations of the isachemic lesions are summarized in Table 8, with particular emphasis on the visual cortical areas involved.

Table 8. Location and extent of ischaemic lesions in 16 patients

Case no.	Location (Brodmann Areas)
Group 1	
1	17, 18
2	17, 18, 19, 23, 31
3	17, 18
4	17, 18, 19, 20, 37
5	17, 18, 19
6	17, 18, 19
7	17, 18
8	18, 19
9	17
Group 2	
10	22, 28
11	21, 22, 37
12	20, 28, 34, 35, 37
13	20, 21, 38, 39, 40
14	Temporal genu of right optic radiation
15	39, 40
16	39, 40

Group I: occipital and occipitotemporal lesions

Four of the nine patients in this group had abnormal CS function in at least one eye for either stimulus orientation. All six 'affected' eyes showed preferential loss at high spatial frequencies (above 3.2 c/d). Five of these six eyes showed a notch loss in the frequency range 3.2 to 19.2 c/d. The mean bandwidth of these notches was 1.5 octaves (range, 1-2 octaves). All CS deficits were stimulus orientation dependent. Involvement of Brodmann's cortical area 17 was observed in seven of the nine patients (Table 8). All four patients with abnormal CS curves had involvement of Brodmann's cortical area 17 (striate cortex). Three patients with normal CS function, however, had also lesions of the striate cortex. Both patients with lesions of the peri-striate areas (case 7 and 8) and sparing of the primary visual cortex, had normal CS functions for both orientations in right and left eye. Fig. 14 shows examples of orientation dependent CS loss in two patients. Case 4 illustrates orientation dependent CS

loss in both eyes. A notch defect with a bandwidth of 1.5 octaves in the right eye for horizontal gratings and a notch defect of 1 octave in the left eye for vertical gratings. Both notches were centered at 12.8 c/d. Case 6 shows a notch loss centered at 6.4 c/d with a bandwidth of two octaves in the left eye for horizontal gratings only, and normal CS curves for both orientations in the right eye.

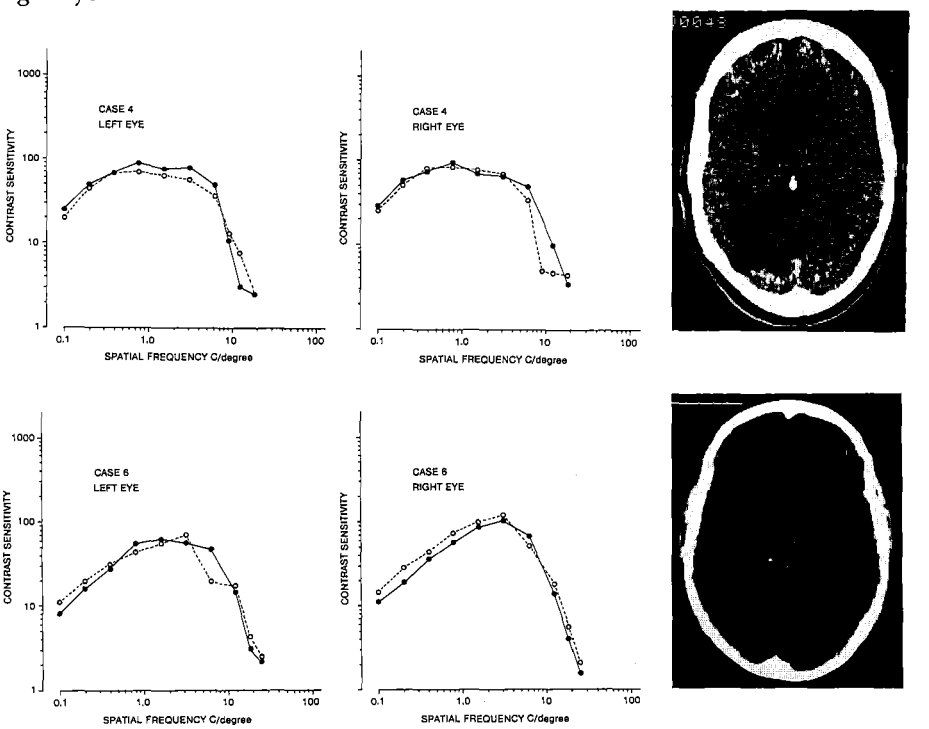


Figure 14. Contrast sensitivity curves and CT scans of a patient with a left sited occipitotemporal infarction (Case 4) and of a patient with a left sited occipital lesion (Case 6). Key to symbols as in figure 13. Orientation dependent CS loss in the high spatial frequency range, bilateral (Case 4) and unilateral (Case 6).

Group II: temporal and parietal lesions

Six of the seven patients in this group had abnormal CS function in at least one eye for either stimulus orientation. Ten of the 14 eyes showed CS loss at low spatial frequencies (below 3.2 c/d), all but two, orientation-dependent. Notch defects (frequency range 0.2-3.2 c/d) were seen in seven eyes, all stimulus orientation-dependent. The mean bandwidth was 2.5 octaves (range, 2-4). All seven patients had no direct involvement of the striate cortex (Table 7). Eight of the 10 CS deficits, however, were nevertheless stimulus orientation-dependent. Detailed findings in three cases are shown in Fig. 15. Case 10 shows a notch

defect of two octaves centered at 0.4 c/d for vertical stimuli and low frequency loss for horizontal stimuli in the right eye. Stimulus orientation independent low frequency loss was seen in the left eye. Case 14 shows a notch defect

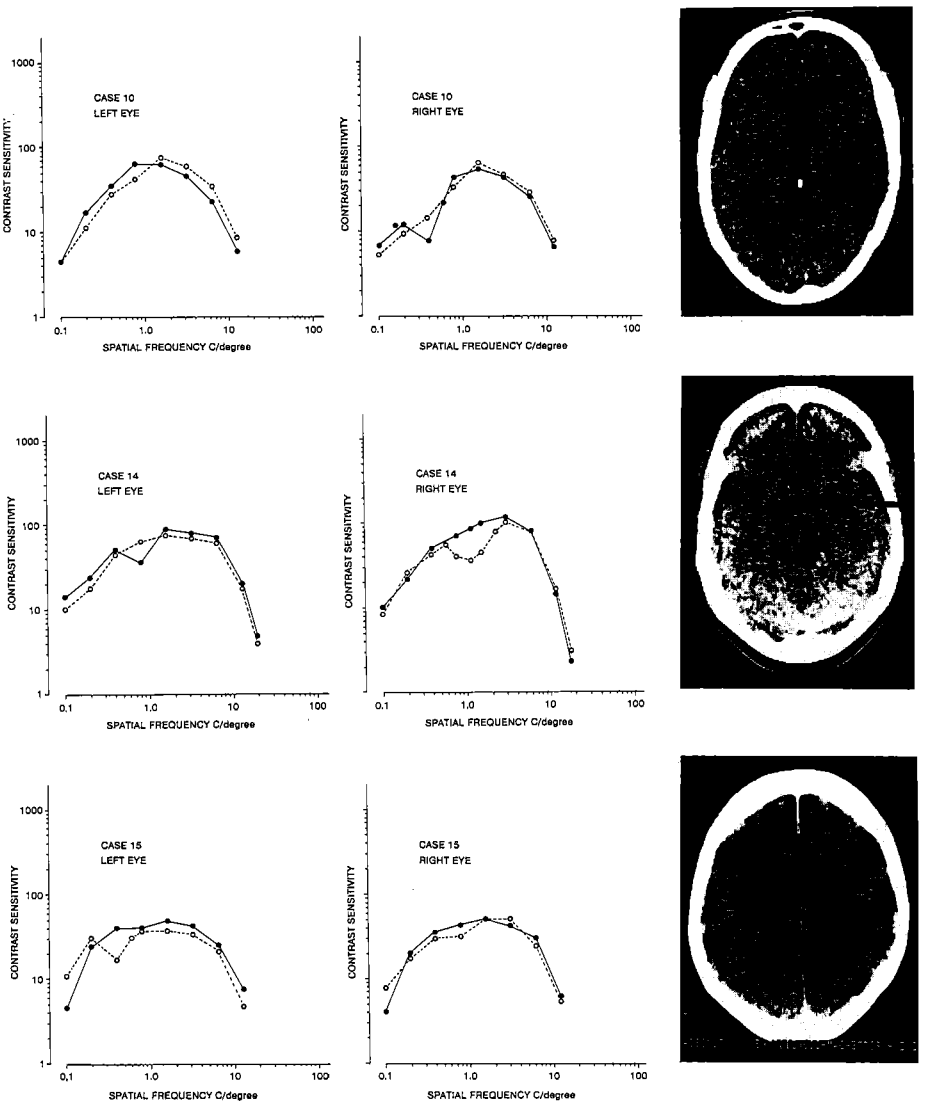


Figure 15. Contrast sensitivity curves and CT scans for Cases 10, 14 and 15. Arrow indicates right subinsular infarction, affecting the genu of the right optic radiation (Case 14). Case 10 shows stimulus independent low frequency loss in the left eye, and stimulus dependent notch loss centered at 0.4 cycles/degree in the right eye. Both stimulus dependent notch losses in Case 14 are also in the low spatial frequency range. Case 15 shows orientation dependent low frequency loss in both eyes and a stimulus dependent notch loss at 0.4 cycles/degree in the left eye.

of 2 octaves wide, centered at 0.8 c/d, in the left eye for vertical gratings and a 2.5 octaves wide notch defect centered at 1.2 c/d in the right eye for horizontal gratings. Case 15 is an example of a patient with a parietal infarction. Orientation-dependent low frequency CS loss was demonstrated in both eyes for vertical gratings, and a notch defect with a bandwidth of 2 octaves centered at 0.4 c/d was observed in the left eye for horizontal gratings. Clinical data of all patients are listed in the Table 7.

DISCUSSION

Spatial CS function, elicited by sinewave gratings in 16 patients with unilateral ischaemic lesions involving the posterior visual pathway was abnormal in 10 patients. All patients had visual acuities of 7/10 or more. Visual perception was distorted in a qualitatively different way according to the site of the lesion. Visual losses restricted to medium and high spatial frequencies were confined to occipital and occipitotemporal lesions. Low spatial frequency losses were only seen in patients with temporal and parietal lesions. The mean width of the notch defects narrowed from 2.5 octaves (range, 2-4) in patients with temporal and parietal lesions to 1.5 octaves (range, 1-2) in patients with lesions affecting the visual cortex. Anatomical lesions of the posterior visual pathway can damage neurons with a restricted spatial frequency range, while others continue to function normally.

The CS measured for different orientations revealed that 14 of the 17 'affected' eyes showed orientation dependent visual loss. This stimulus orientation selectivity was observed in patients with lesions of the striate cortex as well as in patients with lesions anterior to the primary visual cortex. In three patients the CS loss was confined to only one eye for either stimulus orientation. It is possible that CS measurements with more than vertical and horizontal stimuli may reveal more binocular CS deficits than those encountered in this study.

These data confirm earlier reports of abnormal visuospatial CS due to cerebral lesions. Bodis-Wollner and Diamond (1976) found impairment of CS in 35 patients with cerebral lesions of heterogeneous aetiology. Four of these had unilateral posterior ischaemic lesions. Uniform loss was established in two patients, high frequency loss in one patient and notch losses at six and 14 c/d were present in another patient. They concluded that cerebral lesions involving the human visual system have non-uniform effects on central vision. Kobayashi et al. (1985) studied CS function in 23 patients with cerebral infarctions involving the posterior visual pathway. They found abnormal CS function especially in patients with lesions of the nondominant parieto-occipital cortex. Their results are unfortunately based on the Arden grating test (Arden, 1978). This method generates substantial intrasubject variability. Moreover, their curves of CS function are almost flat, indicating a lack of difference in CS for low, intermediate and high spatial frequencies. Their data are in disagreement with the results obtained by all previous reports concerning CS measurements.

From psychophysical investigations of the human visual system and electrophysiological studies of single cells in the animal brain, many authors have proposed that visual input is processed via spatial frequency channels of unequal sensitivity (Enroth-Cugell & Robson, 1966; Campbell & Robson, 1968; Campbell et al., 1969; Blakemore & Campbell, 1969; Albrecht et al., 1980). According to this view, it has been suggested that the channels carrying low spatial frequencies have dissimilar characteristics from those dealing with high spatial frequencies (Lennie, 1980; Graham, 1981). The present results seem relevant to the channel hypothesis. When it is assumed that the selective spatial CS losses in our patient groups indicate a dysfunction of one or more channels of a restricted range of spatial frequencies, lesions at different sites of the posterior visual pathway apparently affect different spatial frequency channels. In this study the affected spatial frequency range was systematically related to the anteroposterior site of the lesion. Contrast losses for spatial frequencies above 3.2 c/d were only observed in patients with occipital and occipito-temporal lesions and losses for spatial frequencies less than 3.2 c/d in patients with temporal and parietal lesions. Neural mechanisms in the anterior part of the postchiasmal visual pathway seem selectively sensitive (tuned) to low spatial frequencies, while high frequency tuning might exist in the posterior part, at the level of the primary visual cortex.

Visual neurons may be viewed as neural filters of visual signals, and spatial filtering properties can be measured by determining CS for a range of spatial frequencies. In animal studies spatial frequency selectivity for visual stimuli has been demonstrated in visual cortical neurons as well as in neurons of the retina and lateral geniculate body. Cortical neurons, however, are much more selective for spatial frequencies (highly tuned) than neurons of retina or lateral geniculate body (Cooper & Robson, 1968; Campbell et al., 1969; Maffei et al., 1973; De Valois et al., 1977; 1978; 1982). The degree of spatial tuning can be quantified in terms of the width of the spatial frequency selective CS loss (notch defect). These bandwidths are usually expressed in octaves. From electrophysiological studies of single cells in the animal brain it has been demonstrated that the band of spatial frequencies narrows from the retina to the primary visual cortex. The average bandwidth of visual cortical cells in cats is around 1.5 octaves (De Valois et al., 1977, 1978; Tolhurst & Thompson, 1981) and by comparison, the average bandwidth in the lateral geniculate nucleus 4 to 5 octaves (So & Shapley, 1981; Thibos & Levick, 1983). The average bandwidth of the notch defect in our two patient groups also varied according to the anteroposterior site of the lesion. Although the distribution of bandwidths for a population of neurons is rather broad, and the ischaemic lesions of the patients in the present study are relatively large in some cases, the narrower average bandwidth of the notch defects in the patient group with (temporo)-occipital lesions (1.5 octaves) compared with the wider average bandwidth in patients with temporal and parietal lesions (2.5 octaves) is conspicious.

Another issue, concerning properties of neurons subserving central visual function, is orientation selectivity. Orientation selectivity is a prominent attribute

of primary visual cortex neurons (Hubel & Wiesel, 1962), so analysis has usually emphasized the distribution of orientation selectivity at that level (Hubel & Wiesel, 1962; Mansfield, 1974; Rose & Blakemore, 1974; Mansfield & Ronner, 1978). A particular point of interest in the present results is that they indicate that orientation dependent loss is not restricted to lesions of the primary visual cortex. Orientation bias apparently also exists in the aanterior parts of the postchiasmal pathway. Orientation-selective CS loss is not confined to cerebral infarctions. Such losses have also been reported in multiple sclerosis (Regan et al. 1980; Kupersmith et al., 1984) and Parkinson's disease (Regan & Maxner, 1987; Bulens et al., 1988a) and have been explained in terms of involvement of cortical neurons.

Clinicopathologic and radiographic studies have repeatedly accentuated the importance of the occipital striate cortex to human vision (Atensaas et al., 1974). Electrophysiological studies in animals have demonstrated that the cortical visual areas are much more comprehensive than the striate cortex (van Essen, 1979). In addition to the striate cortex at least 12 extrastriate areas have been demonstrated in the cat, and similar results have been found in primates (van Essen, 1979; Tusa et al., 1981). These studies also have shown the existence of nonoccipital areas that are involved in complex visual function. It has been demonstrated that there is an occipito-parieto-frontal pathway involved in spatial vision and an occipito-temporo-frontal pathway involved in object recognition (Denny Brown & Chambers 1976; Macko et al., 1982; Mishkin et al., 1983). Homologies between cortical areas of humans and other primates are not always clear, and the pattern of intercortical connections in the human brain is only partly understood. It is therefore difficult to compare the details of cerebral organization in different primates with that of man. Nevertheless, there is a lot of evidence that the primary visual cortex in the human has ample connections with surrounding association areas, the peristriate and inferotemporal cortex. Receptive-field properties have been extensively analysed only for VI in monkeys (corresponding with the striate cortex or area 17 of Brodmann in human). Neurons in secondary visual areas may also prove to respond selectively to spatial frequency and stimulus orientation. The functional columnar arrangement that clearly exists in VI is not yet well demonstrated beyond VI. Experiments showing the effects of removing a visual area on receptive-field properties of cells, in areas prior to VI are unknown. As monkeys in which VI has been totally removed can still discriminate a wide variety of patterned stimuli (Butter et al., 1980), the contribution to sensory analysis of pathways other than those from VI is presumably far from unimportant.

Postchiasmal interference in the visual pathway produces homonymous hemianopia, in spite of clinically normal visual acuity. When visual field defects encroach upon the region of the field tested, orientation-selective CS loss may occur as a result of these field defects. In a simulation study Hess and Plant (1986) demonstrated that various types of CS loss can be modelled by different types of visual field loss. A deficit maximal in the centre of the visual field

affected high spatial frequencies, parafoveal deficit caused medium spatial frequency loss, and peripheral deficit gave rise to low frequency loss. Studies of CS across the visual field have shown that CS is maximum at the fovea for all spatial frequencies and falls off, monotonically at increasing eccentricities (Robson & Graham, 1981; Regan & Beverly, 1983; Wright & Johnston, 1983; Plant & Hess, 1987). Visual field defects encountered in our patient groups are given in Table 7. Ten of the 16 patients had homonymous hemianopia, nine of the 20 eyes showed normal CS function for both stimulus orientations, while the remaining 11 eyes showed various CS deficits ranging from low frequency CS loss to high frequency CS loss. Multifocal types of CS loss were also observed in six patients showing homonymous quadrantanopia. So, very different CS functions were found in patients showing similar visual field defects. It is therefore unlikely that uniform hemianopic involvement of the visual field encountered in our patient group, could be related with the observed CS losses.

In conclusion, the results of this study attest to the hypothesis that visual processes are mediated by frequency selective channels (1). Orientation selectivity is not confined to primary visual cortex neurons, but also exists in the posterior visual pathway prior to the striate cortex (2).

Chapter IV

SPATIAL CONTRAST SENSITIVITY IN PATIENTS WITH CEREBRAL TUMOURS

INTRODUCTION

Cerebral tumours can cause visual disturbances by various mechanisms. Tumours involving the visual pathway itself usually produce visual acuity losses or visual field defects, according to the site of the lesion. Tumours outside the visual pathway can also generate visual disturbances. Tumours interfering with CSF flow can lead to hydrocephalus or papilloedema. Ventricular distention may stretch fibres of the optic pathways and may alter their function (Ehle & Sklar, 1979). Cerebral tumours leading to severe obstruction of CSf flow to the superior sagittal sinus cause papilloedema as a result of elevated CSF pressure (Van Crevel, 1979). All these conditions may implicate visual damage.

Visual acuity, as measured with the Snellen letters, is often diminished in optic nerve disorders and may be spared or diminished in chiasmal syndromes (Frisén, 1980). It is a well-established clinical fact, however, that blurred vision without acuity impairment can occur in optic nerve dysfunction caused by papilloedema (Cogan, 1966; Walsh & Hoyt, 1969. The major clinical concept that separates papilloedema of intracranial origin from other forms of acquired disc swelling is that visual acuity and visual field are typically normal. Tumours with postchiasmal interference of the unilateral visual pathway produce hemianopic field defects, whereas visual acuity generally remains normal (Frisén, 1980). Nevertheless, in spite of clinically normal acuity there may also be complaints of blurred vision (Bodis-Wollner & Diamond, 1976).

Such peculiar sort of visual losses could be revealed by a more extensive test of central vision: determination of spatial contrast sensitivity (CS). Patients with cerebral tumours may exhibit a variety of visual symptoms and signs each of which relates to an important aspect of the underlying pathophysiology. In this Chapter a study is reported of spatial visual function in patients with cerebral tumours. The results were compared with those of conventional tests for visual function.

SUBJECTS

Control subjects

The control population of 25 subjects consisted of patients without CNS disease. Subjects with known astigmatism were excluded. All had ophthalmological examination and were free of ocular disease. Snellen acuities were 10/10 or better.

Patients

Twenty-three patients with cerebral tumours were examined. The diagnosis cerebral tumour was made by CT study and in most cases (16/23) confirmed by neurosurgical procedures. Patients with known astigmatism were excluded. All had a complete neuro-ophthalmological examination including measurements of corrected Snellen acuity, Goldmann perimetry, and Contrast Sensitivity.

RESULTS

Control group

The mean age of the control group was 45 years (range, 26-76). The CS functions of the 50 control eyes were obtained and the mean CS curve is shown in Fig. 16. At intermediate spatial frequencies an individual curve can diverge slightly from the pure inverted U shape. These minor deflections occurred in 33 of the 50 normal eyes at different spatial frequencies (between 0.2 and 12.8 c/d). The mean decrease factor (DF) of these minor deflections was 1.2 (2 SD 0.2), range: 1.1 at 6.4 c/d-1.3 at 12.8 c/d, which is completely within intraindividual variability.

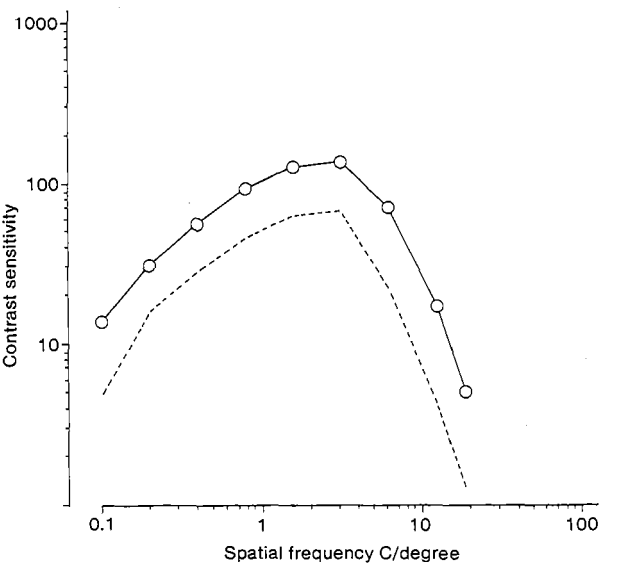


Figure 16. Mean contrast sensitivity curve of 50 normal eyes. Broken line shows 2 SD.

Patient group (see Tables 9 & 10)

The mean age of the 23 patients was 48 years (range, 26-78). Seven patients had bilateral papilloedema in association with a cerebral tumour. Sixteen patients had a cerebral tumour but normal fundus appearance.

The CS function of each of the patient's eyes was individually compared with the mean CS curve of the controls. A curve was judged abnormal when a CS deficit resulted in a displacement of (a part of) the curve below the control curve for more than 2 SDs. Selective frequency loss was taken for abnormal (notch defect) when the DF was more than 1.4, being the mean DF in the normal group plus 2 SDs. The width of the notch was defined as the spatial frequency bandwidth over which contrast loss was observed (octaves).

Table 9. 23 patients with cerebral tumours

16 patients without papilloedema	5 patients: no direct or indirect involvement visual pathway	CS normal (10/10)
	7 patients: direct involvement visual pathway	Notch loss (9/14)
	4 patients: hydrocephalus	2 no Occipital distention: CS normal (4/4)
		2 Occipital distention: CS abnormal (4/4)
7 patients with papilloedema	3 patients: cerebello-pontile tumour	Notch loss (6/6)
	4 patients: direct involvement visual pathway	Various types of CS loss (8/8)

(I) Patients with cerebral tumours and no papilloedema

Five of the 16 patients in this group (no. 1-5) had cerebral tumours without direct or indirect involvement of the visual pathway. They had normal visual acuities and visual fields. All 10 CS functions were normal.

Seven patients (no. 6-12) had cerebral tumours with direct interference of the unilateral visual pathway. Visual acuities were 10/10 or better. All showed visual field defects according to the site of the lesion. Nine of the 14 eyes showed CS losses, all notch defects (range, 0.2-3.2 c/d). Four notch losses resulted from an occipital lesion (3 patients). The mean bandwidth was 2.8 octaves (range, 2-3), with a mean depth of 1.5 (2 SD 0.1). The three notch defects which occurred in two patients with (occipito-) parietal lesions had a mean bandwidth of 1.8 octaves (range, 1.5-2) and a mean depth of 1.5 (2 SD 0.2). Two patients with a lesion of the temporal genu of the optic radiation had notch defects of two and four octaves wide and 1.6 and 2.1 deep (DF). All notches occurred in the low spatial frequency range (below 3.2 c/d) (Table 10).

Table 10. Clinical data and results of neuro-ophthalmological examination in 23 patients with cerebral tumours.

No.	Age	Sex	Diagnosis	Visual field	Snellen acuity	CS function
			(I) PATIENTS WITH CEREBRAL TUMOURS AND NO PAPILLOEDEMA			
1	21	m	Suprasellar tumour	Intact	R 15/10 L 15/10	normal normal
2	25	m	R Cerebello-pontile tumour	Intact	R 15/10 L 15/10	normal normal
3	32	m	R Parieto-temporal glioma	Intact	R 13/10 L 12/10	normal normal
4	55	f	R Parietal Meningioma	Intact	R 12/10 L 12/10	normal normal
5	78	m	R Frontal Metastasis	Intact	R 10/10 L 10/10	normal normal
6	30	m	L Occipital Metastasis	R homonymous hemianopia	R 10/10 L 12/10	notch loss (0.4-3.2) notch loss (0.4-3.2)
7	55	f	R Temporal Glioma	L homonymous quadrantoanopia	R 15/10 L 15/10	notch loss (0.8-3.2) notch loss (0.8-3.2)
8	57	m	R Occipital Metastasis	L homonymous hemianopia	R 10/10 L 13/10	normal notch loss (0.2-1.6)
9	57	f	L Parietal Metastasis	R homonymous hemianopia	R 10/10 L 10/10	normal notch loss (0.8-2.4)
10	62	m	L Optic radiation Metastasis	R homonymous quandrantoanopia	R 10/10 L 12/10	notch loss (0.2-3.2) normal
11	66	f	R Optic radiation Metastasis	L homonymous quadrantoanopia	R 12/10 L 12/10	normal notch loss (0.4-1.6)
12	70	f	R Occipital Meningioma	L homonymous hemianopia	R 10/10 L 10/10	normal notch loss (0.4-1.6)
13	36	f	Colloid cyst third ventricle	Intact	R 15/10 L 15/10	normal normal
14	40	m	Colloid cyst third ventricle	Intact	R 10/10 L 10/10	normal normal
15	55	f	R Cerebellair Metastasis	Intact	R 12/10 L 12/10	notch loss (0.4-1.6) notch loss (0.2-0.8)
16	58	f	R Cerebellair Metastasis	Intact	R 10/10 L 10/10	h loss notch loss (0.4-1.6)

Four patients (no. 13-16) had obstructive hydrocephalus. Two patients had a cerebellar tumour and two others a colloid cyst of the third ventricle. Visual acuity scores and visual fields were normal. Both patients with obstruction of the fourth ventricle and distention of the occipital horns of the ventricle system had abnormal CS functions. One patient had high frequency loss in one eye and a notch loss of two octaves wide centered at 0.8 c/d in the other eye. The other patient had a notch loss of two octaves wide in both eyes in the low frequency range (0.2-1.6 c/d). The two patients with a colloid cyst of the third ventricle and no involvement of the occipital horns, had normal CS functions in all four eyes.

Table 10 continued

No.	Age	Sex	Diagnosis	Visual field	Snellen acuity	CS function
			(II) PATIENTS WITH CEREBRAL TUMOURS AND PAPILLOEDEMA			
17	26	m	L Parieto-temporal glioma	Enlarged blind spots	R 6/10 L 8/10	h loss h loss & notch loss (0.2-0.8)
18	33	m	L Cerebello-pontile tumour	Enlarged blind spots	R 15/10 L 15/10	notch loss (0.4-1.6) notch loss (0.8-3.2)
19	33	f	Suprasellar tumor	Bitemporal hemi-anopia & enlarged blind spots	R 9/10 L 7/10	h loss generalized loss
20	43	m	R parietotemporal metastasis	Enlarged blind spots	R 7/10 L 6/10	h loss h loss
21	54	f	R Cerebello-pontile tumour	Enlarged blind spots	R 15/10 L 10/10	notch loss (0.8-3.2) notch loss (0.8-3.2)
22	55	m	R Parietal Meningioma	L homonymous hemianopia	R 3/10 L 3/10	generalized & notch loss (0.4-1.2) generalized & notch loss (0.2-0.8)
23	56	f	L Cerebello-pontile tumour	Enlarged blind spots	R 15/10 L 15/10	notch loss (0.8-3.2) notch loss (0.8-3.2)

Key to symbols as in table 4.

(II) Patients with cerebral tumours and papilloedema

All seven patients in this group (no. 17-23) had abnormal CS function in both eyes.

Three patients with a cerebellopontile angle tumour without direct effect on the visual pathway had normal visual acuities and only enlarged blind spots on visual field examination. The only type of CS deficit observed in all six eyes was a notch defect. The width of these six notches was two octaves and the mean depth (DF) 1.9 (2 SD 0.6). Five of the six notches were centered at 1.6 c/d, the other at 0.8 c/d.

The other four patients with papilloedema had tumours that directly interfered with the visual pathway. These four patients had visual acuity impairments and visual field defects in both eyes. They showed diverse types of CS loss: four eyes had high frequency CS loss, one eye high frequency CS and notch CS loss, one eye generalized CS loss and two other eyes a combination of generalized and notch CS loss. One notch with a depth of 3.5 (DF) and two octaves wide was centered at 0.8 c/d and the two other notches with a depth of 1.9 (DF) and also two octaves wide were centered at 0.4 c/d.

Clinical data and the results of neuro-ophthalmological examination in all patients are shown in Table 10. Examples of abnormal CS function in six patients are given in Fig. 17.

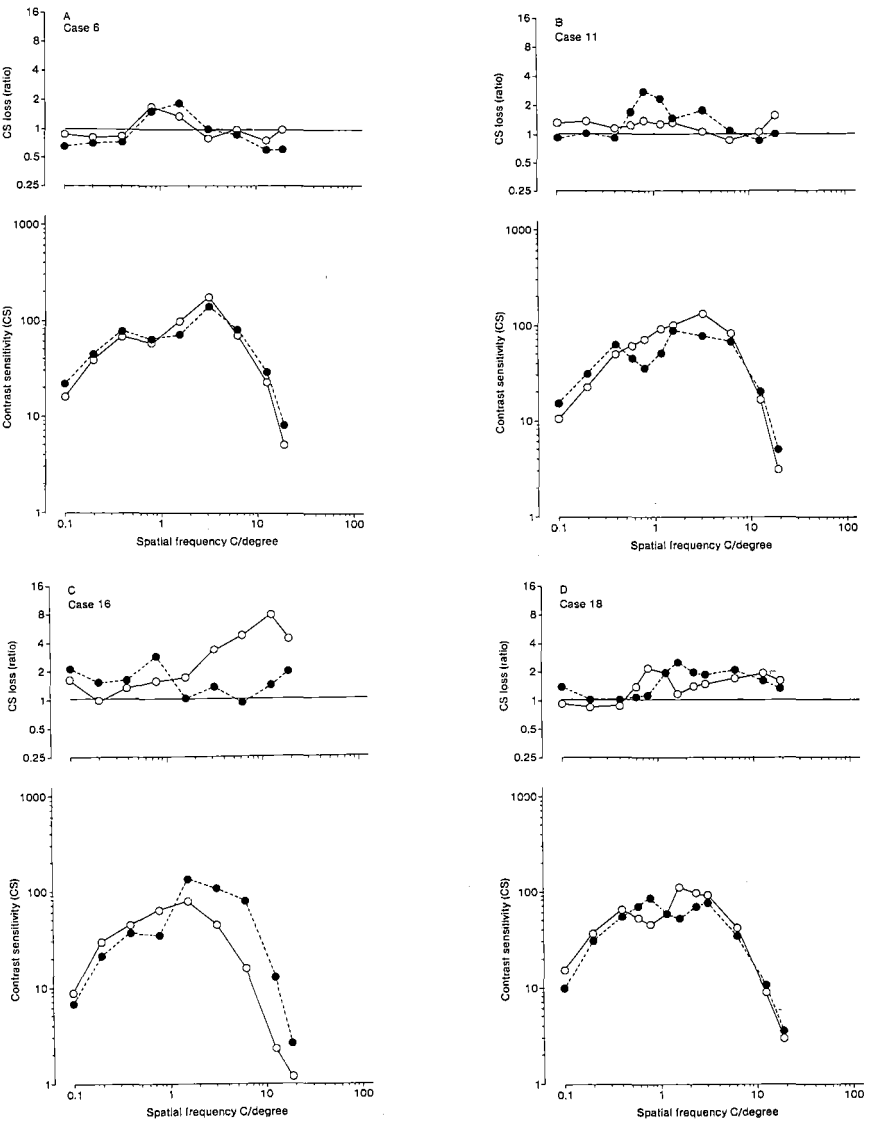
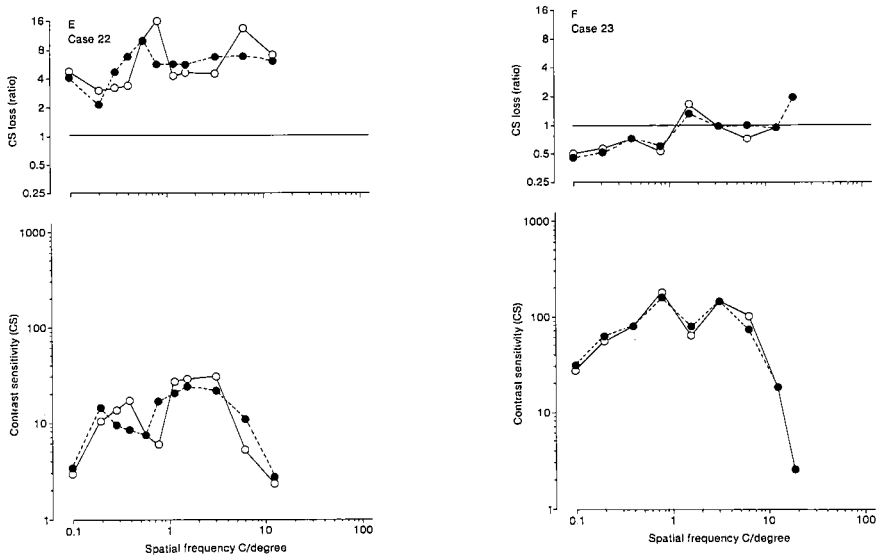


Figure 17. Examples of contrast sensitivity curves in six patients with a cerebral tumour. The upper part of each figure shows the ratio of the altered contrast sensitivity to normal contrast sensitivity function for corresponding spatial frequencies (visuogram).
Right eye = open circles and Left eye = closed circles.
(A) Case 6 (L Occipital metastasis) shows n loss (0.4-3.2) in both eyes.
(B) Case 11 (R Optic radiation metastasis shows n loss (0.4-3.2) in right eye and normal CS curve in left eye.
(C) Case 16 (Obstructive hydrocephalus) shows h loss in right eye and n loss (0.4-1.6) in left eye.
(D) Case 18 (L Cerebello-pontile tumour, bilateral papilloedema) shows n loss (0.4-1.6) in right eye, and n loss (0.8-3.2) in left eye.

Figure 17 continued



(E) Case 22 (R Parietal Meningioma, bilateral papilloedema and impaired visual acuities) shows generalized & n loss (0.4-1.2) in right eye and generalized & n loss (0.2-0.8) in left eye.
(F) Case 23 (L Cerebello-pontile tumour, bilateral papilloedema) shows n loss (0.8-3.2) in both eyes.
(L = left, R = right, n loss = notch contrast sensitivity loss, h loss = high frequency contrast sensitivity loss; spatial frequency range in cycles/degree.

DISCUSSION

Cerebral tumours may produce various visual symptoms and signs. Tumours involving the visual pathway itself usually account for visual acuity impairment or field defects. Tumours without direct effect on the visual pathway, but interfering with CSF flow (papilloedema, hydrocephalus), can also exhibit visual damage. A diagram to show the possible mechanisms leading to visual damage is shown in Fig. 18. The present findings showed that there is no distinctive correspondence of visual acuity and field charting to CS.

Eighteen of our group of 23 patients with cerebral tumours had direct or indirect involvement (including papilloedema) of the visual pathway. Spatial CS function was abnormal in 27 of the 36 eyes (75%). The remaining group of five patients without direct or indirect interference of the visual pathway had, not surprisingly, normal CS function for both eyes. Of the 27 eyes with abnormal CS function only eight had also visual acuity loss. All eyes with impairment of visual acuity showed high frequency or generalized CS loss. CS measurement was therefore, superior in comparison to Snellen acuity testing by revealing visual disturbances in patients with cerebral tumours.

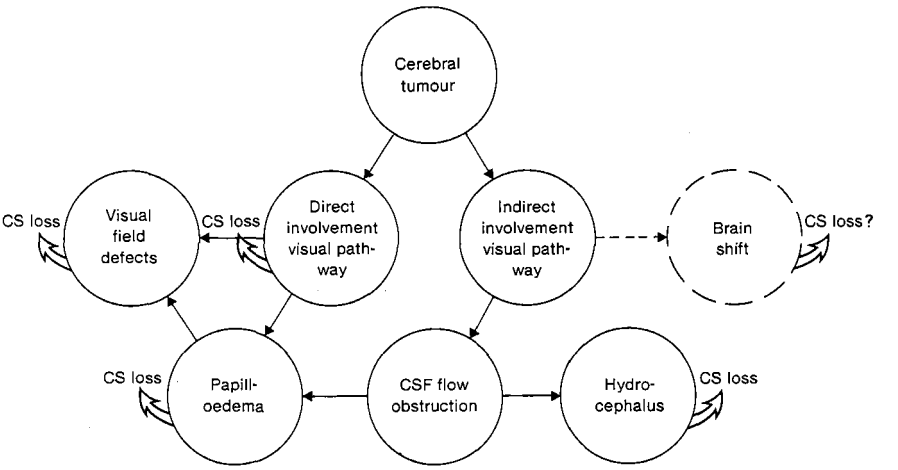


Figure 18. Diagram showing the possible mechanisms leading to visual damage.

(A) Seven patients with tumours that directly interfered with the visual pathway and no papilloedema had hemianopic field defects but normal Snellen acuity scores. The only type of CS deficit, observed in nine of the 14 eyes, was a notch defect, selectively affecting the low spatial frequency range. The mean bandwidth of the notches in patients with occipital lesions was 2.8 octaves wide and in patients with (parieto-)temporal lesions 1.8 octaves. Two of the four patients with obstructive hydrocephalus showed abnormal CS functions. These patients both had distention of the occipital horns of the ventricular system.

(B) Of the seven patients with papilloedema three had a tumour outside the visual pathway and papilloedema as a result of elevated CSF pressure was the only neuro-ophthalmological sign. All six eyes showed notch defects of two octaves wide affecting the low spatial frequency range. Five of the six notches were centered at 1.6 c/d. These patients had preservation of Snellen acuity and only enlarged blind spots on visual field examination. The four patients with papilloedema and impaired visual acuity had tumours compromising the visual pathway and showed generalized- and high spatial frequency CS loss.

The present data confirm earlier reports of abnormal CS function in patients with cerebral tumours. Bodis-Wollner and Diamond (1976) using methods similar to those described in this study, found impairment of CS in 35 patients with cerebral lesions of heterogeneous aetiology. Seventeen of these had a cerebral tumour. High frequency loss was established in six patients, generalized loss in another six patients and a notch loss in five patients. Six of the 12 patients with high frequency or generalized CS loss, however, had normal Snellen acuities, and only one of the five patients with a notch defect had unimpaired

visual acuity. Kupersmith et al. (1981) found a reduction in CS in 80 of the 85 eyes with proved chiasmal compression. These workers used Arden's grating plates (1978) to measure CS. With this method high spatial frequencies (above 6.4 c/d) cannot be tested; CS loss was observed at all spatial frequencies (generalized loss), even in patients with normal Snellen acuities.

According to the theory of pattern recognition, it has been proposed that visual input is processed via spatial frequency channels of unequal sensitivity (Enroth-Cugell & Robson, 1966; Campbell & Robson, 1968; Campbell et al., 1969; Blakemore & Campbell, 1969; Albrecht et al., 1980; Regan, 1982). Spatial frequency selectivity is mainly attributed to cortical neurons and not, or only to a less degree to neurons of the retina or geniculate body (Campbell & Robson, 1968; Regan, 1982). Neurophysiological work on the spatial frequency tuning of cortical neurons is of particular significance because of its relevance to the idea that the human visual system contains highly tuned channels or spatial frequency filters (Campbell & Robson, 1968; Blakemore & Campbell, 1969; Graham, 1977). The degree of spatial tuning may be quantified by calculating the spatial frequency bandwidth over which contrast loss is observed. Several investigators have established that individual striate cortex neurons have narrow bandwidths, but also a broad distribution of optimal spatial frequencies. Depending on the type of experiment different workers found that the visual pathway contains spatial frequency channels of one to four octaves wide (Blakemore & Campbell, 1969; Spitzberg & Richards, 1975).

In this study seven patients had a cerebral tumour with direct involvement of the visual pathway and no papilloedema. The only type of CS deficit observed, was a notch loss in the low spatial frequency range, which occurred in nine of the 14 eyes. If we assume that the notch defects represent a partial or complete loss of one or more channels sensitive to a restricted range of spatial frequencies, our finding that cerebral tumours confined to the visual pathway can selectively reduce CS in the low spatial frequency range, can be taken as further evidence for the existence of such channels. The frequency-selective CS losses, generated by patients with normal Snellen acuities, establishes that cerebral lesions may produce a disruption of a limited number of frequency channels subserving central vision. Though the present results are unsuitable for statistical analysis, the notch losses with a wider bandwidth in patients with occipital lesions compared to the narrower bandwidth in patients with (occipito-)parietal lesions are of interest. They might indicate that the degree of spatial tuning at different sites of the visual system can be studied under pathological conditions.

Two of the four patients with obstructive hydrocephalus had abnormal CS functions, both had obstruction of the fourth ventricle and distention of the occipital horns. The localization of the disruption of the visual pathways that causes these CS losses is less certain. Because of the long pathway, and its close relationship to the ventricular system, compromise of the optic radiations could be responsible in part for the CS abnormalities. Direct effects on the occipital cortex could also account for the CS losses. Both patients with CS

deficits demonstrated a prominent distention of the occipital horns of the ventricular system.

In three of the seven patients with papilloedema there was no direct involvement of the visual pathway and bilateral papilloedema was the only neuro-ophthalmological sign. The six notch defects in these patients were all two octaves wide, while five of the six deficits were centered at the 6,4 c/d spatial frequency. The notch defects in these patients did not differ from the patterns of CS loss in patients with direct involvement of the visual pathway and normal Snellen acuities. It is difficult to specify how similar frequency-selective deficits arise in patients with papilloedema, because such losses are mainly attributed to involvement of the cortical visual neurons. Apparently peripheral damage can also in some degree degrade spatial processing. In animal studies, spatial frequency selectivity has also been demonstrated in neurons of the retina and lateral geniculate body. It has been suggested that the retinal image is encoded by the ratio of activity in neuronal populations responsive to different spatial frequencies (Pollen et al., 1971; Maffei & Fiorentini, 1973). In papilloedema, neural deficit may decrease spatial processing and result in frequency-selective CS losses, closely resembling CS losses of post-chiasmal lesions.

When field defects encroach upon the region of the field tested, CS loss may occur as a result of these field defects. In a simulation study Hess and Plant (1986) demonstrated that various types of CS loss can be modelled by different types visual field loss. Visual field defects encountered in our patient group are given in Table 10. Patients with similar field defects had markedly different CS deficits. Moreover, patients with unilateral CS deficits had homonymous hemianopia and quadrantanopia on visual field charting. It is therefore unlikely that involvement of the visual field encountered in our patient group, could be related with the observed CS losses.

Although the results of our study are by no means conclusive, they attest to the hypothesis that visual processes are mediated by frequency-selective channels. Functional disruption or anatomical lesions of the visual pathway can selectively damage some frequency-selective channels, while the others continue to function normally. Spatial frequency-selective CS losses can result from lesions involving the visual pathway from optic radiation to primary visual cortex. Even tumours without direct involvement of the posterior visual pathway (papilloedema, hydrocephalus) can cause frequency-selective CS loss.

Chapter V

CONTRAST SENSITIVITY IN PATIENTS WITH BENIGN INTRACRANIAL HYPERTENSION

INTRODUCTION

In Benign Intracranial Hypertension (BIH), loss of visual acuity is the only serious complication, and may occur either early or late in its course (Corbett et al., 1982). Regular ophthalmological examination, including assessment of the visual fields, is mandatory. A major problem, however, is that there is no reliable warning sign of impending visual failure, which obstructs rational decision in treatment (Bulens et al., 1979). Patients with papilloedema from whatever cause – tumour or benign intracranial hypertension – may present with obscurations or blurred vision (Cogan, 1966; Walsh & Hoyt, 1969; Boddie et al., 1974; Johnston & Paterson, 1974; Weisberg, 1975; Bulens et al., 1979; Rush, 1980; Corbett et al., 1982; Orcutt et al., 1984). Optic nerve dysfunction caused by papilloedema can decrease central visual function, in spite of clinically normal visual acuity.

Subtle visual deficits may not be detected using routine tests, such as Snellen acuity scores, visual field estimation, or colour vision testing. Such patients might have a peculiar sort of visual disturbance, reducing central visual function, without affecting visual acuity. For evaluating spatial vision, sensitivity measurements to visual contrast using stimuli ranging from low spatial frequencies (coarse patterns) to high spatial frequencies (fine patterns) can be determined. In the present study we investigated the effect of BIH on CS function.

SUBJECTS

The control population of 20 subjects consisted of hospital personnel and patients without CNS disease. All had neuro-ophthalmological examination and were free of ocular disease. Snellen acuities were 10/10 or better.

Twenty patients were studied who complied with the definition of BIH: syptoms and signs of raised CSF pressure including papilloedema, without a space-occupying lesion, normal CSF under raised pressure, and normal ventricular size on CT-scan. All had a complete neuro-ophthalmological examination which included measurements of corrected Snellen acuity, Goldmann perimetry, and Contrast Sensitivity.

RESULTS

Control group

The mean age of the control group was 40 years (range, 26-59). The CS functions of the 40 control eyes were obtained and the mean CS curve is shown in Fig. 19. Close inspection of individual CS curves in normal subjects can reveal that at intermediate spatial frequencies a CS curve can diverge slightly from the pure inverted U shape (Fig. 19). These minor deflections occurred in 27 of the 40 normal eyes at different spatial frequencies (between 0.2 and 12.8 c/d). The mean decrease factor (DF) of these minor deflections was 1.2 (2 SD 0.2), range: 1.1 at 6.4 c/d - 1.3 at 12.8 c/d, which is completely within intraindividual variability.

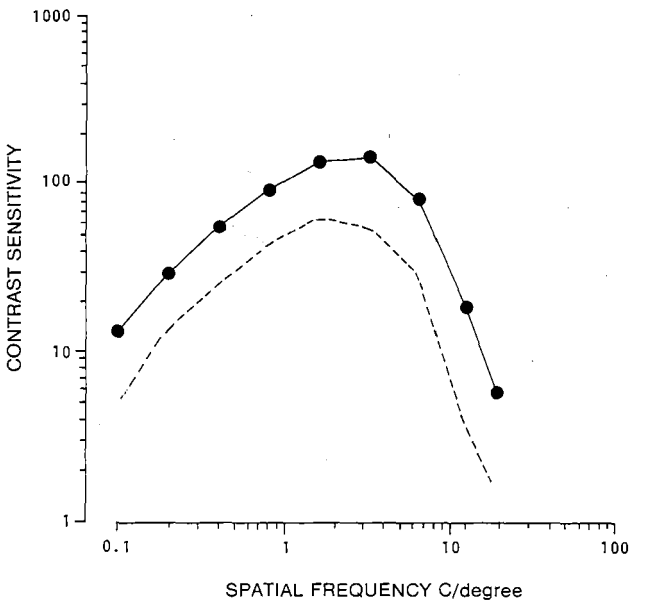


Figure 19. Mean contrast sensitivity curve in 20 normal subjects. Broken line shows 2 SD.

Patients

The mean age of the 20 BIH patients was 39 years (range, 16-59). There were 16 females and four males. Eleven patients were obese and systemic hypertension (BP of 170/95 or higher) was present in four. Papilloedema, the cardinal feature, was present in all patients and was confirmed by fluorescein angiography in eight cases. Neuroradiological investigations (skull radiographs and CT scans) revealed that two patients had an empty sella. Carotid angiography, carried out in four males and two females, was normal in all. The increased CSF pressure ranged from 30 to 60 cm water (lumbar puncture).

Impairment of visual acuity was defined as Snellen acuity of less than 10/10. Nine patients had impairment of visual acuity (9 eyes). In three of these (patient 3, 7, 19) the poor visual acuity was unrelated to BIH (unilateral amblyopia since childhood). Five patients had mild impairment (7/10 or more), one patient had a marked degree of impairment of vision (3/10).

Visual fields were assessed by Goldmann perimetry in all patients. Only four showed abnormalities other than enlarged blind spots. One patient had severe concentric constrictions in both eyes. Another patient had a cecocentral scotoma with impaired visual acuity in one eye and a normal visual field with unimpaired visual acuity in the other. One patient had inferior binasal field defects with unilateral acuity loss. The fourth patient had an unilateral inferior nasal field defect and normal acuity in both eyes.

The contrast sensitivity function of each of the patient's eyes was individually compared with the mean CS curve of the controls. A curve was judged abnormal when a CS deficit resulted in a displacement of (a part of) the curve below the control curve minus two standard deviations. Intermediate frequency loss was considered abnormal (notch defect) when the decrease factor (DF) was more than 1.4, being the mean DF in 27 of the 40 normal eyes plus two standard deviations. The width of the notch was defined as the spatial frequency bandwidth over which contrast loss was observed (octaves). CS function was obtained in 40 eyes. Of the 37 non-amblyopic eyes 16 had abnormal CS function. Generalized loss was seen in three eyes. Losses that could be classified as frequency selective were found in 13 eyes. Of these 13 eyes a notch loss was present in eight eyes. The loss affected selectively the high frequency range (above 3.2 c/d) in three eyes and the low frequency range (below 3.2 c/d) in two eyes.

Abnormalities of CS function were not related to visual acuity loss. Of the 37 non-amblyopic eyes 16 had CS loss (43%). Twelve of these 16 eyes had normal visual acuities. Six of the eight eyes with notch defects had a normal vision. Of the three eyes with high frequency loss two had normal visual acuities, and of the two eyes with low frequency loss none had acuity loss attributed to BIH. Two of the three eyes with generalized loss had normal visual acuities.

Two of the three patients with impaired acuity not related to BIH (amblyopia) showed CS loss. One patient had low frequency loss with a vision of 7/10, and the other showed high frequency loss with a visual acuity of 1/10. The third patient with unilateral amblyopia (acuity 9/10) had a normal CS curve of the affected eye.

Six eyes (16%) had acuity impairment at presentation, attributed to BIH. Only two eyes with slight acuity impairment (9/10) had normal CS functions. The remaining four eyes with acuity impairment had diverse types of CS loss (generalized-, notch- and high-frequency loss).

Transient visual obscurations were an initial symptom in four patients. Three of these had unilateral visual acuity impairment at presentation. Blurred vision with normal visual acuity was an initial complaint in five patients. All these

nine patients had abnormal CS functions (12 eyes). The results of neuro-ophthalmological investigations of all 20 patients are listed in Table 11.

Table 11. Results at presentation of neuro-ophthalmological investigations in 20 BIH patients.

No.	Sex	Age	Vision	Snellen acuity	Papill-oedema	Visual field	CS function
1	F	16	Blurred	R 11/10	2	Enl. blind spot	no loss
				L 10/10	2	Enl. blind spot	n loss (0.4-3.2)
2	F	17	Blurred	R 15/10	2	Enl. blind spot	n loss (0.8-2.4)
				L 10/10	2	Enl. blind spot	no loss
3	F	24	Normal	R 9/10 (amblyopic)	2	Enl. blind spot	no loss
				L 10/10	1	Enl. blind spot	no loss
4	F	33	Obscurations	R 12/10	2	Enl. blind spot	n loss (3.2-12.8)
				L 15/10	1	Enl. blind spot	n loss (0.4-1.6)
5	F	34	Blurred	R 10/10	1	Severe concentric constriction	1 loss
				L 10/10	1	Severe concentric constriction	1 loss
6	M	34	Normal	R 15/10	1	Enl. blind spot	no loss
				L 15/10	1	Enl. blind spot	no loss
7	F	37	Blurred	R 13/10	1	Enl. blind spot	generalized loss
				L 7/10 (amblyopic)	1	Normal	1 loss
8	F	40	Blurred	R 10/10	1	Enl. blind spot	generalized loss
				L 3/10	1	Enl. blind spot	generalized loss
9	F	40	Blurred	R 10/10	1	Enl. blind spot	no loss
				L 10/10	2	Enl. blind spot	n loss (0.2-0.8)
10	F	41	Normal	R 10/10	1	Enl. blind spot	no loss
				L 10/10	1	Enl. blind spot	no loss
11	F	41	Normal	R 10/10	2	Enl. blind spot	no loss
				L 10/10	1	Enl. blind spot	no loss
12	F	42	Blurred	R 10/10	2	Enl. blind spot	n loss (0.8-6.4)
				L 10/10	2	Enl. blind spot	no loss
13	M	43	Obscurations	R 10/10	1	Normal	no loss
				L 7/10	2	Cecocentral scotoma	n loss (1.6-6.4)
14	F	46	Normal	R 11/10	1	Enl. blind spot	no loss
				L 9/10	1	Enl. blind spot	no loss
15	F	47	Normal	R 12/10	1	Normal	no loss
				L 12/10	1	Nasal defect	no loss
16	F	49	Obscurations	R 10/10	1	Enl. blind spot & nasal defect	no loss
				L 8/10	1	Enl. blind spot & nasal defect	n loss (0.8-3.2)
17	F	51	Obscurations	R 11/10	1	Enl. blind spot	h loss
				L 8/10	2	Enl. blind spot	h loss
18	F	55	Normal	R 9/10	2	Enl. blind spot	no loss
				L 10/10	1	Enl. blind spot	no loss
19	M	57	Normal	R 10/10	1	Enl. blind spot	no loss
				L 1/10 (amblyopic)	1	Enl. blind spot	h loss
20	M	59	Normal	R 12/10	2	Enl. blind spot	no loss
				L 10/10	2	Enl. blind spot	h loss

Key to symbols as in table 4

Eleven patients had repeated CS measurements after one to 60 months. The results of the follow-up investigations of these 11 patients are listed in Table 12.

Table 12. Follow-up results of neuro-ophthalmological investigations in 11 BIH patients

Results at presentation					Results at follow-up		
No.	Snellen acuity	CS function	Treatment	Follow-up (months)	Snellen acuity	CS function	Comment
2	R 15/10	n loss (0.8-2.4)	none	1	R 15/10	no loss	normal fundi
	L 10/10	no loss			L 10/10	no loss	& fields
3	R 9/10	no loss	diuretics	60	R 9/10	h loss	amblyopia R;
	L 10/10	no loss			L 10/10	h loss	chronic oedema normal fields
6	R 15/10	no loss	none	8	R 15/10	no loss	normal fundi
	L 15/10	no loss			L 15/10	no loss	& fields
7	R 13/10	generalized loss	weight reduction	29	R 13/10	h loss	normal fundi & fields
	L 7/10	l loss			L 7/10	no loss	amblyopia L;
8	R 10/10	generalized loss	weight reduction	20	R 10/10	l loss	normal fundi & fields
	L 3/10	generalized loss			L 3/10	generalized loss	
11	R 10/10	no loss	weight	3	R 10/10	no loss	normal fundi
	L 10/10	no loss	reduction		L 10/10	no loss	& fields
12	R 10/10	n loss (0.8-6.4)	none	3	R 10/10	no loss	subsiding oedema, enl.
	L 10/10	no loss			L 10/10	no loss	blind spots
13	R 10/10	no loss	lumbar	3	R 10/10	no loss	normal fundi
	L 7/10	n loss (1.6-6.4)	peritoneal shunt		L 11/10	no loss	& fields
15	R 12/10	no loss	none	18	R 12/10	generalized & n loss (0.4-1.6)	chronic oedema optic atrophy R & L
	L 12/10	no loss			L 12/10	generalized loss	
16	R 10/10	no loss	none	6	R 12/10	no loss	normal fundi
	L 8/10	n loss (0.8-3.2)			L 10/10	no loss	& fields
18	R 9/10	no loss	none	8	R 9/10	n loss (0.8-3.2)	chronic oedema enl. blind
	L 10/10	no loss			L 10/10	no loss	spots

Key to symbols as in table 4

Six patients had a normal CS function for both eyes at follow-up, they all had restored visual acuities. Fig. 20A shows the changes of serially CS measurements in patient no. 2. Initially there was un unilateral notch loss centered at 1.6 c/d (right eye). Two weeks later notch losses centered at the same spatial frequency were observed in both eyes. Another two weeks later, after papilloedema had disappeared, CS losses had completely resolved. Of this group of patients with normal CS function at follow-up, one had developed optic disc pallor and another still had subsiding papilloedema in spite of normal

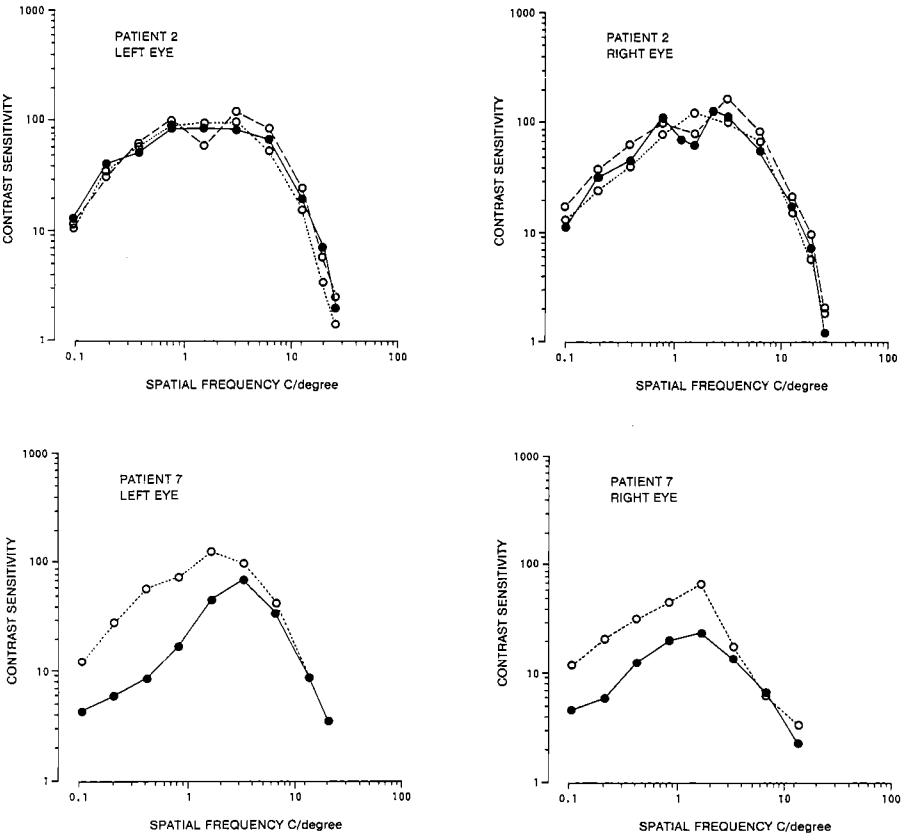
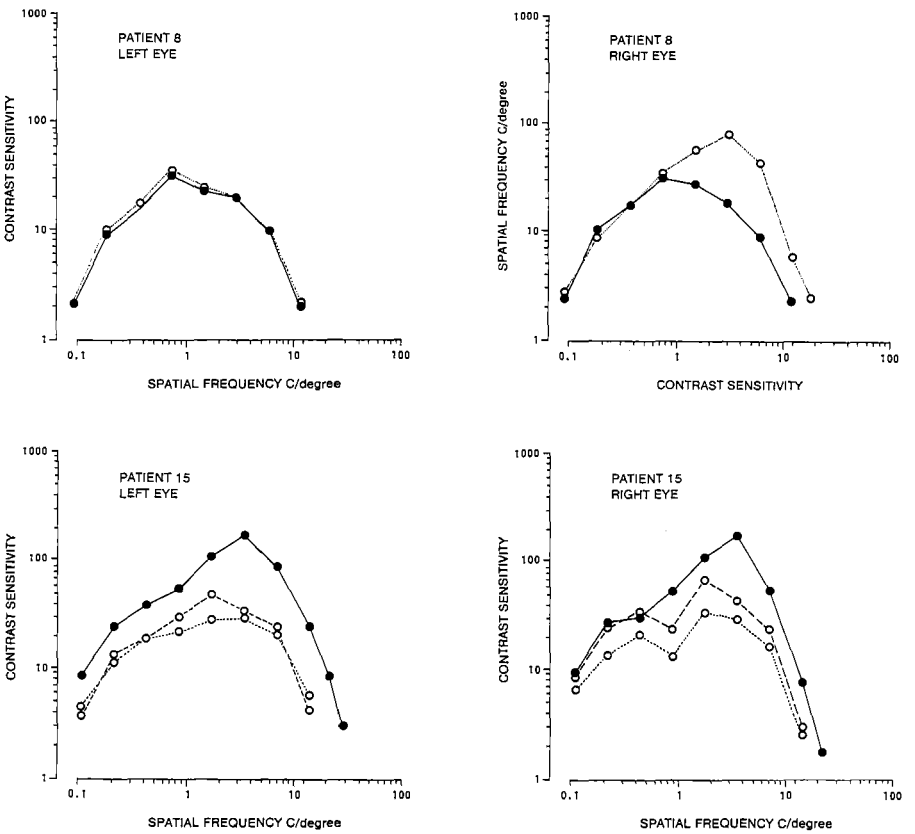


Figure 20. Examples of serial contrast sensitivity (CS) measurements in 4 patients.
(A) Patient 2 had a unilateral notch loss centered at 1.6 c/d (right eye) at presentation (filled circles), 2 weeks later notch losses centered at 1.6 c/d in both eyes (open circles-broken lines) and complete resolution of the CS losses after 4 weeks (open circles-dotted lines).
(B) Patient 7 showed initially generalized CS loss (right eye) and 1 loss (left eye) (filled circles) with good improvement after 29 months except for h loss in the right eye (open circles).

acuities. Five patients had abnormal CS functions. One patient (no. 3) had developed high frequency loss in both eyes without visual acuity deterioration. She had bilateral papilloedema of one dioptre for 60 months. Patient no. 7 (Fig. 20B) had good improvement of CS function for both eyes except for high frequency loss in the right eye. During her illness of three years, visual acuity scores had not changed and her visual fields had become normal. Patient no. 8 (Fig. 20C) had persisting general CS loss in the left eye with marked degree of acuity loss (3/10), which was unchanged after 20 months. CS function of the right eye had ameliorated and only low frequency loss was present at follow-up. Patient no. 15 (Fig. 20D) illustrates progressive CS loss for both eyes

Figure 20 continued



(C) Patient 8 had generalized CS loss in both eyes at presentation (filled circles) with recovery in the high spatial frequency range (right eye) and unchanged CS curve in the left eye (open circles) after 20 months.
(D) Patient 15 had initially normal CS curves (filled circles) and progressive CS loss at follow-up without any change of acuity scores, after 12 months notch loss centered at 0.8 c/d and h loss (right eye), generalized loss (left eye) (open circles-broken lines); after 18 months generalized CS loss and n loss at 0.8 c/d (right eye), generalized loss in left eye (open circles-dotted lines).

during 18 months follow-up without any change of visual acuities or visual fields. Patient no. 18 with normal CS functions and unilateral acuity impairment developed a notch defect without any acuity deterioration.

DISCUSSION

Spatial CS function, in 20 BIH patients, elicited by sinewave gratings, was abnormal in 16 of the 37 non-amblyopic eyes. Six eyes had Snellen acuity

impairment attributed to BIH. Only four of the 16 eyes with abnormal CS function had also acuity loss. Only two eyes with slight visual acuity impairment attributed to BIH had normal CS function. In one of these two, a notch defect later developed during follow-up, without deterioration of visual acuity. CS measurement was, therefore, superior in detecting visual loss in comparison with the Snellen acuity tests.

Our data confirm one earlier report of abnormal visuospatial CS function in BIH. Wall (1986) found CS loss in 13 of 24 eyes of BIH patients. His results were based on the Arden grating test (Arden, 1978).

Visual obscurations and blurred vision are the most frequent visual symptoms in BIH (Boddie et al., 1974; Johnston & Paterson, 1974; Weisberg, 1975; Bulens et al., 1979; Rush, 1980; Corbett et al., 1982; Orcutt et al., 1984). In this study there was a close relationship between the presence of these visual symptoms and CS abnormality. All 11 patients with blurred vision or visual obscurations had abnormal CS functions. Six of these 11 patients had normal visual acuities at presentation. Seven of the nine patients with normal subjective vision had also normal CS curves for both eyes. One patient had unilateral high frequency CS loss with normal visual acuity and another patient had also high frequency CS loss in one eye with impaired visual acuity due to amblyopia since childhood. The CS loss of this patient probably was not related to BIH.

Although there was no unitary type of CS loss in our patient group, the most frequent type of deficit, observed in eight eyes, was a notch defect. These intermediate spatial frequency losses affected the middle-frequency region preferentially. These CS losses are not unique to papilloedema. Results similar to those described here, have also been reported in conditions ranging from optic neuritis (Zimmern et al., 1979; Medjbeur & Tulunay-Keesy, 1985) and cortical lesions (Bodis-Wollner & Diamond, 1976; Bulens et al., 1988b) to Parkinson's disease (Regan & Maxner, 1987; Bulens et al., 1988a). Spatial frequency selectivity is attributed to cortical neurons and not, or only in a less degree to neurons of the retina or geniculate body (Campbell & Robson, 1968; Regan, 1982). Peripheral damage, however, can also in some degree selectively degrade CS. It has been suggested that the retinal image is encoded by the ratio of activity in neuronal populations responsive to different spatial frequencies (Pollen et al., 1971; Maffei & Fiorentini, 1973). A neural deficit that distorts the sensitivity of these harmonic analysers may impair spatial processing. Sinewave gratings effectively stimulate populations of neurons responsive to only limited bands of spatial frequency. In papilloedema, neural deficit may result in depression of CS restricted to intermediate spatial frequencies.

When field defects and enlarged blind spots encroach upon the region of the field tested, CS loss may occur as a result of these field defects. In a simulation study Hess and Plant (1986) demonstrated that various types of CS loss can be modelled by different types of visual field loss. A deficit maximal in the centre of the visual field affected high spatial frequencies, parafoveal dificit

caused medium spatial frequency loss, and peripheral deficit gave rise to low frequency loss. Visual field defects encountered in our patient group are given in Table 11. An enlarged blind spot is the classic defect in BIH and was detected in 31 non-amblyopic eyes of 17 patients either as the only visual defect or associated with other disc-related defects. The stimulus field subtended the enlarged blind spots only when CS was measured for low spatial frequencies. For higher spatial frequencies (0.8 to 25.6 c/d) the enlarged blind spot did not encroach upon the field tested, bound with the relative small stimulus field at 200 cm (8.5 degrees by 6.0 degrees). The generalized losses (3 eyes), high frequency losses (3 eyes) and notch defects in the frequency range above 0.8 c/d (4 eyes) could therefore not have been accounted for by the enlarged blind spot. Some effect of the enlarged blind spot in generating the intermediate spatial frequency losses below 0.8 c/d (3 eyes) cannot be excluded. Two of the three eyes showing nasal field defects, had normal CS function; the remaining eye had a two octaves wide CS loss centered at 1.6 c/d. Only one patient (no. 5) had marked field defects. It is well known that the thresholds for gratings are significantly raised if less than four cycles of the gratings are visible (Campbell & Robson, 1968; Savoy & McCann, 1975; Van der Wildt et al., 1976). In this patient the low frequency CS loss in both eyes, could be considered therefore, as a result of the severe concentric field constriction. It seemed unlikely that the cecocentral scotoma in the left eye of patient no. 13 could account for the two octaves wide notch loss centered at 3.2 c/d, because CS for higher spatial frequencies were unaffected. The vast majority of CS deficits encountered in our patient group could not be explained by the visual field abnormalities.

The clinical application of CS measurement in monitoring the progression or regression of BIH is well illustrated by the serial measurements in 11 patients with BIH. Progressive visual loss in longstanding papilloedema and important improvement of visual function in subsiding papilloedema can occur without any change in Snellen acuity or visual field charting. In our limited follow-up study important visual acuity deterioration was not observed, even progressive CS loss did not predict subsequent visual acuity loss.

Although some factors as systemic hypertension, raised intraocular pressure, choroidal folds with subretinal neovascularisation may predispose to severe loss of acuity (Corbett et al., 1982; Orcutt et al., 1984), general outcome in BIH cannot be predicted reliably. Visual acuity loss can occur at presentation or late during the course of the disease. Blurred vision and visual obscurations do not necessarily predict subsequent visual acuity loss. Visual field abnormalities, including nasal field defects and concentric constrictions have not proved to determine long-term prognosis for visual acuity. Even optic atrophy is not always accompanied by acuity loss or field defects. A more extensive, prospective study of BIH with sequential measurements of CS, visual fields and Visual Evoked Potentials is warranted to reliably demonstrate warning signs of impending visual failure.

Chapter VI

GENERAL DISCUSSION

In the previous chapters the application of contrast sensitivity (CS) measurements in clinical neurology has been described. The investigations in normal subjects and patients with various neurological disorders have demonstrated the importance of this psychophysical method for studying visual function.

Based on psychophysical experiments, Campbell and Robson (1968) proposed that there might be functionally separate mechanisms (channels) in the visual nervous system, selectively responding to different spatial frequencies. Although this channel hypothesis is not universally held, spatial frequency analysis has provided great insight into visual information processing.

The current approach to investigate the neural basis of human vision is to relate psychophysical studies of humans to neurophysiological studies of animals. Psychophysics involves the 'objective' testing of visual performance and supplies information about the sensitivity and limitations of vision. Neurophysiology involves outlining the processing capacity of single neurons at different levels of the visual pathway and tells us about the neural organization and structure of the visual system.

CS measurements conducted on patients with various neurological disorders have suggested that the spatial channels of vision can be affected differentially in a large variety of ways.

The investigations in Parkinsonian patients have demonstrated that a selective loss of visual function can be associated with a certain pathology. A substantial proportion of patients with dopaminergic deficiency, from whatever cause, showed frequency-selective and orientation-specific CS losses (Chapter II). On the other hand, from the standpoint of normal vision, these findings may indicate that dopamine is a functional transmitter in the visual pathway.

Another example of how our knowledge about the neural basis of human vision can benefit from results under pathological conditions has been demonstrated by CS measurements in patients with cerebral infarctions. The observation that visual perception was distorted in a qualitatively different way according to the antero-posterior site of the lesion may indicate that neural mechanisms in different parts of the visual pathway are tuned to different spatial frequencies (Chapter III).

The selective damage of some frequency-selective channels has also been demonstrated in patients with cerebral tumours. Even tumours without direct involvement of the visual pathway (papilloedema and hydrocephalus) showed frequency-selective CS losses (Chapter IV).

Psychophysics can also have a role in translating the dysfunction which

characterizes the condition into a neurophysiologically meaningful code. Since in most cases neurophysiological investigation cannot be carried out on the diseased structure, psychophysics may represent the only quantitative link between the human condition and its neurophysiological investigation and simulation in animals. The results of CS measurements in patients with Benign Intracranial Hypertension (BIH) showed a close relationship between the presence of its characteristic visual symptoms (obscurations and blurred vision) and abnormal CS function (Chapter V).

The relationship between psychophysics and neurophysiology of disease can also have a number of useful secondary functions. It can contribute to early detection of disease and to more sensitive methods of monitoring the progress of a disease. This has been illustrated by the serial measurements in 11 patients with BIH. Progressive visual loss in longstanding papilloedema and improvement of visual function in subsiding papilloedema was demonstrated without any change in Snellen acuity or visual field charting.

Clearly, we are at an interesting stage in the study of the psychophysical defects in neuro-ophthalmological disorders. We need to refine our stimulus on the basis of what has already been learned and proceed.

GENERAL SUMMARY

In this thesis studies are described investigating contrast sensitivity (CS) function in normal subjects and in patients with various neurological disorders.

Chapter I gives a review of neurophysiological concepts underlying human contrast sensitivity function. These developed from basic research conducted on the electrophysiology and psychophysics of animals and humans. It has been proposed that visual information is transmitted via parallel channels, each channel carrying a limited range of spatial frequencies. Visual disturbances can result from damage to some or all spatial frequency channels. Such abnormal visual function does not necessarily result in abnormal Snellen acuity.

Part 2 of this Chapter deals with the methods of measurement of contrast sensitivity.

In part 3 the results of contrast sensitivity (CS) measurements in 54 normal subjects are described. Although CS varies within age-decade subgroups, it is not affected by age. It is demonstrated that there is a great test-retest consistency.

Chapter II is devoted to studies of CS on Parkinsonian patients. Although motor manifestations are the main sequelae of Parkinson's disease (PD), the disorder is probably more generalized, perhaps a generalized dopaminergic deficiency syndrome. In animals there are dopamine projections in parts of the peripheral visual system and dopamine-sensitive cells are also known to exist in the human retina. In the mesocortical pathway dopamine deficiency has been demonstrated in PD by positron emission tomography. In view of the assumed dopaminergic transmission in the visual system, CS measurements were used to analyse visual function in idiopathic and drug-induced Parkinsonism.

Part 1 describes CS measurements in 39 patients with PD, without levodopa therapy. Sixty-four per cent of the patients had CS loss in one or both eyes. Most had high frequency loss, intermediate frequency loss (notch loss), or both. The patients had normal subjective visual function, and the visual acuities were 7/10 or more. Abnormality of CS was not related to severity of the disease or the first symptom. The occurrence of sensitivity loss at intermediate frequencies in 16 of the 48 "affected" eyes may implicate cortical involvement, as spatial frequency selectivity is mainly attributed to cortical neurons and not or only to a less degree, to neurons of the retina and geniculate body. The results of this study are consistent with the concept that PD is a widespread transmitter deficiency syndrome.

In part 2 changes in CS function after institution of levodopa substitution therapy are described in 10 PD patients. Before levodopa treatment, 16 of 20 eyes showed abnormal CS function. After treatment only six of the 20 eyes still showed abnormalities, all high frequency loss. In the pretreatment group

a substantial proportion of the CS loss was restricted to a particular band of spatial frequencies. All these intermediate spatial frequency losses appeared reversible under levodopa treatment. The change of CS function after treatment suggests that dopamine is a functional transmitter in the visual pathway.

Part 3 shows the results of a study investigating the effect of stimulus orientation on CS in 21 PD patients. Fifteen of these showed CS deficit in at least one eye. CS measuring for different orientations revealed that 17 of the 25 'affected' eyes showed orientation-selective deficits. The most frequent type of orientation-selective loss, observed in 12 cases, was a notch defect, which preferentially affected the middle spatial frequencies. Because orientation-selective neurons are not found peripheral to the primary visual cortex in primates, the finding that 68 per cent of the 'affected' eyes showed orientation-selective deficits, indicates that the visual disturbances in PD are, at least in part, situated at the primary visual cortex.

The effects of systemic administration of dopamine blockers on CS function in previously untreated patients were investigated in the study presented in part 4. CS determinations for vertical and horizontal orientations revealed CS loss in nine of the 10 patients with drug-induced Parkinsonism. There was a striking resemblance of the pattern of CS loss in drug-induced Parkinsonism to that in idiopathic PD. The most frequent type of deficit observed in 14 eyes was also a notch loss, which preferentially affected the middle and low spatial frequencies. All spatial frequency-selective CS losses were stimulus orientation dependent. This curious parallel suggests that dopaminergic deficiency, from whatever cause, has similar effects on visual function.

Chapter III presents the results of CS measurements in patients with unilateral ischaemic lesions involving the posterior visual pathway. Ten of the 16 patients had at least one eye with CS deficit for vertical and/or horizontal stimuli. Visual perception was distorted in a qualitatively different way according to the antero-posterior site of the lesion. Patients with occipital or occipito-temporal lesions showed high spatial frequency-selective losses and patients with temporal and parietal lesions low frequency-selective losses. Neural mechanisms in the anterior part of the postchiasmal visual pathway seem selectively sensitive (tuned) to low spatial frequencies, while high frequency tuning might exist in the posterior part, at the level of, or central to the primary visual cortex. Stimulus orientation selectivity was observed in patients with lesions of the primary visual cortex as well as in patients with lesions anterior to the striate cortex. Orientation selectivity is not confined to primary visual cortex neurons, but also exists in the posterior visual pathway prior to the striate cortex.

Chapter IV describes the results of CS measurements in patients with cerebral tumours. Cerebral tumours may produce various visual symptoms and signs depending on the site of the tumour. In 18 of the 23 patients the tumour had directly or indirectly involved the visual pathway. CS function was abnormal in 27 of the 36 eyes (75%). There was no apparent correspondence of visual acuity or visual field loss to CS function. Intermediate spatial frequency loss

was observed in 18 of the 27 'affected' eyes, in three other eyes combined with other types of CS loss. Three patients with a tumour outside the visual pathway, and bilateral papilloedema as the only neuro-ophthalmological sign, showed notch losses in both eyes. Functional disruption or anatomical lesions of the visual pathway, from optic nerve to primary visual cortex, can selectively damage some frequency-selective channels, while others continue to function normally.

Chapter V deals with CS function in patients with Benign Intracranial Hypertension (BIH). Spatial CS function, in 20 BIH patients, was abnormal in 16 of the 37 non-amblyopic eyes. Only four of these 16 eyes had also acuity loss, indicating that CS measurement is superior in detecting visual loss than Snellen acuity tests. Visual obscurations and blurred vision are the most frequent visual symptoms in BIH. In this study all 11 patients with these symptoms had abnormal CS functions. The clinical application of CS measurement in BIH for monitoring the progression or regression of the disease is illustrated by serial measurements in 11 patients. Progressive visual loss in longstanding papilloedema and improvement of visual function in subsiding papilloedema can occur without any change in Snellen acuity or visual field charting.

SAMENVATTING

Dit proefschrift behelst een klinisch onderzoek over de visuele contrast gevoeligheid bij proefpersonen en patiënten met verschillende neurologische aandoeningen.

Hoofdstuk I geeft een kort overzicht van neurofysiologische begrippen die aan de contrast gevoeligheid functie ten grondslag liggen. Deze zijn gebaseerd op resultaten van elementair electrofysiologisch en psychofysisch onderzoek bij dier en mens. Er zijn aanwijzingen dat de visuele informatie wordt overgebracht via parallel lopende 'kanalen', waarbij elk kanaal een beperkt aantal spatiële frequenties bevat. Visuele stoornissen kunnen veroorzaakt worden door een beschadiging van enkele of alle spatiële frequentie kanalen. Een dergelijke visuele stoornis behoeft niet noodzakelijkerwijs te leiden tot verminderde gezichtsscherpte, zoals die wordt onderzocht met de Snellen kaart.

In het tweede deel van hoofdstuk I wordt de methode om de contrast gevoeligheid te meten beschreven.

In het derde deel worden de resultaten vermeld van de contrast gevoeligheid (CG) metingen bij 54 proefpersonen. Ofschoon de individuele CG binnen de subgroepen, verdeeld in leeftijd-decaden varieert, heeft de leeftijd geen invloed op de CG. De individuele test resultaten bleken in hoge mate reproduceerbaar.

In hoofdstuk II worden de resultaten besproken van de CG bepalingen bij patiënten met de ziekte van Parkinson en patiënten met medicamenteus geïnduceerd Parkinsonisme. De belangrijkste gevolgen van de ziekte van Parkinson worden waargenomen aan het motorische systeem. Er zijn echter aanwijzingen dat de "stoornis" meer gegeneraliseerd is, mogelijk is er sprake van een gegeneraliseerd dopaminerg deficiëntie syndroom. In onderdelen van het visuele systeem zijn bij verschillende diersoorten dopamine projecties aangetoond, terwijl ook bij de mens 'dopamine-gevoelige' cellen voorkomen in de retina. Met behulp van positron emissie tomografie is bij Parkinson patiënten bovendien een dopamine deficiëntie waargenomen in de meso-corticale banen. De veronderstelde dopaminerge transmissie was de beweegreden om m.b.v. CG metingen het visuele systeem bij patiënten met de ziekte van Parkinson en patiënten met Parkinsonisme te analyseren.

In het eerste gedeelte van hoofdstuk II worden de resultaten weergegeven van de CG metingen bij 39 patiënten met de ziekte van Parkinson. Deze patiënten werden niet behandeld met levodopa. Vierenzestig procent van de patiënten hadden een CG verlies van één of beide ogen. Verminderde CG in het hoog frequente gebied en intermediair CG verlies ('notch loss'), of een combinatie van deze kwam het meest frequent voor. Het subjectieve gezichtsvermogen van de patiënten was normaal en de gemeten Snellen visus was 7/10 of beter. Er bleek geen relatie te bestaan tussen de CG test resultaten en de ernst of het eerste symptoom van de ziekte. Omdat spatiële frequentie selectiviteit een eigenschap is die wordt toegeschreven aan corticale neuronen en niet, of in veel mindere mate, aan retina- of corpus geniculatum neuronen, zou het intermediaire gevoeligheidsverlies dat werd gevonden bij 16 van de 48 'aan-

gedane' ogen er op kunnen wijzen dat de visuele cortex bij de ziekte betrokken is. De resultaten van deze studie zijn in overeenstemming met de opvatting dat de ziekte van Parkinson een wijd verspreid transmitter deficiëntie syndroom is.

In het tweede gedeelte worden de veranderingen beschreven in de CG curve bij 10 Parkinson patiënten, na het instellen van levodopa substitutie therapie. Voor de behandeling hadden 16 van de 20 ogen een afwijkende CG curve. Na het instellen van de behandeling vertoonden zes van de 20 ogen nog een abnormale curve, terwijl bij deze behandelde patiënten alleen afwijkingen in het hoog frequente gebied gevonden werden. Voor de levodopa therapie bleek bij een groot gedeelte van de patiënten het gevoeligheidsverlies beperkt te zijn tot een band van spatiële frequenties. Al deze intermediaire CG dalingen bleken reversibel te zijn onder levodopa therapie. De verandering van de CG functie onder invloed van deze medicatie suggereert dat dopamine een functionele transmitter is in het visuele systeem.

Het onderzoek in deel drie van dit hoofdstuk gaat na wat de invloed is van de oriëntatie van de stimulus op de CG bij 21 Parkinson patiënten. Vijftien van de 21 patiënten hadden een gevoeligheidsverlies aan tenminste één oog. Door de CG met verschillende stimulus oriëntaties te meten kon worden aangetoond dat 17 van de 25 'aangedane' ogen een oriëntatie-selectief CG verlies hadden. Het meest voorkomende type van oriëntatie-selectief verlies, dat werd waargenomen bij 12 ogen, was een 'notch defect', vooral optredend in het mid-frequente gebied. Het wordt verondersteld dat oriëntatie-selectieve neuronen bij de primaten niet perifeer van de primaire visuele cortex voorkomen. Deze studie toont aan dat 68 procent van de 'aangedane' ogen een oriëntatie-selectieve gevoeligheidsdaling heeft. Hieruit zou kunnen worden afgeleid dat de visuele stoornissen bij Parkinson patiënten, tenminste gedeeltelijk, hun oorsprong hebben in de primaire visuele cortex.

De effecten op de CG curve van medicamenten die een 'dopamine blokkerende' werking hebben, worden beschreven in deel 4 van dit hoofdstuk. CG metingen met verticale en horizontale stimuli, lieten een gevoeligheidsdaling zien bij negen van de 10 patiënten met medicamenteus geïnduceerd Parkinsonisme. Het patroon van CG verlies bij deze groep patiënten geleek sterk op het patroon dat gevonden werd bij patiënten met de idiopathische ziekte van Parkinson. Het meest frequent voorkomende type van CG verlies, bij 14 van de 20 ogen, was ook hier een 'notch defect'. Deze frequentie-intermediaire gevoeligheidsdalingen werden gevonden in de mid- en lage spatiële frequentie gebieden. Alle spatiële frequentie-selectieve CG dalingen waren stimulus-oriëntatie afhankelijk. Deze opmerkelijke parallel suggereert dat dopamine deficiëntie, waar ook door veroorzaakt, een gelijkvormig effect heeft op de visuele functie. Al deze bevindingen duiden erop dat dopamine een functionele transmitter is in het visuele systeem.

Hoofdstuk III geeft de resultaten weer van CG metingen bij patiënten met een eenzijdige ischaemische laesie van het visuele systeem, posterior van het corpus geniculatum laterale. Tien van de 16 patiënten hadden tenminste één oog met een CG daling voor verticale en/of horizontale stimuli. De voor-achterwaartse lokalisatie van de laesie bleek bepalend voor het spatiële frequentie gebied waar het CG verlies optrad. Patiënten met een occipitale of

occipito-temporale laesie hadden frequentie-selectieve gevoeligheidsdalingen in het hoog frequente gebied en patiënten met temporale en parietale laesies frequentie-selectieve CG dalingen in het laag frequente gebied. Neuronale mechanismen in het voorste gedeelte van het post-chiasmale visuele systeem lijken selectief gevoelig te zijn voor lage spatiële frequenties, terwijl het posterior gelegen gedeelte van het visuele systeem, t.h.v. de primaire visuele cortex en gebieden centraal daarvan, een selectiviteit voor hogere spatiële frequenties hebben. Selectiviteit van de stimulus oriëntatie werd zowel waargenomen bij laesies van de primaire visuele cortex als bij laesies vóór de area striata gelegen. Oriëntatie-selectiviteit is niet alleen een eigenschap van neuronen van de primaire visuele cortex, maar deze bestaat klaarblijkelijk ook in meer centraal gelegen gebieden van het post-chiasmale visuele systeem.

Hoofdstuk IV beschrijft de resultaten van CG metingen bij patiënten met hersentumoren. Afhankelijk van de lokalisatie van de tumor, kunnen verschillende visuele verschijnselen optreden. Bij 18 van de 23 patiënten was er sprake van een direct of indirect effect van de tumor op het visuele systeem. De CG functie was abnormaal bij 27 van de 36 ogen (75%). Er bleek geen duidelijke overeenkomst te bestaan tussen verminderde Snellen visus en gezichtsveld-defecten en CG verlies. CG dalingen beperkt tot intermediaire spatiële frequenties, werden bij 18 van de 27 'aangedane' ogen gevonden, bij drie andere gecombineerd met andere typen CG verlies. Drie patiënten hadden een tumor buiten het visuele systeem gelegen, bij wie bilateraal papiloedeem het enige neuro-ophthalmologisch verschijnsel was. Alle zes ogen vertoonden een 'notch defect' bij CG onderzoek. Functionele en anatomische laesies van het visuele systeem, van nervus opticus tot en met area striata, kunnen een beschadiging veroorzaken van sommige frequentie-selectieve kanalen, terwijl andere normaal blijven functioneren.

Hoofdstuk V is gewijd aan de CG functie bij patiënten met Benigne Intracraniële Hypertensie (BIH). Bij de 20 BIH patiënten werd een abnormale CG functie gevonden bij 16 van de 37 niet-amblyope ogen. Slechts vier van deze 16 ogen hadden ook een verminderde Snellen visus, waaruit zou kunnen worden afgeleid dat een CG meting gevoeliger is voor het ontdekken van visueel functie verlies i.v.t. een Snellen visus bepaling. Visuele obscuraties en wazig zien zij de twee meest voorkomende visuele symptomen bij BIH. Alle 11 patiënten, die deze symptomen hadden, vertoonden abnormale CG curven. De klinische toepassing van CG meting bij BIH om progressie of regressie van de ziekte te constateren wordt geïllustreerd aan de hand van opeenvolgende metingen bij 11 BIH patiënten. Progressieve visuele stoornissen bij langdurig bestaand papiloedeem en verbetering van de visuele functie bij verdwijnend papiloedeem kunnen vóórkomen zonder enige verandering van de Snellen visus of gezichtsvelden.

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CURRICULUM VITAE

De schrijver van dit proefschrift werd op 20 november 1946 te Rotterdam geboren. Hij bezocht de Willem de Zwijger HBS te Rotterdam, waar hij in 1966 het eindexamen aflegde. Hij studeerde geneeskunde aan de Medische Faculteit te Rotterdam en werd in 1972 tot arts bevorderd. Gedurende zijn militaire dienst was hij werkzaam op de Militaire Specialisten Polikliniek (Lt. Kolonel Hartman). Van januari 1974 tot januari 1975 was hij werkzaam als assistent in het psychiatrisch ziekenhuis Bloemendaal te Loosduinen (Dr. J. Schipper). Na een half jaar assistentschap op de afdeling Inwendige Ziekten van het Diaconessenhuis te Voorburg (Dr. P.C. Brinkerink), vervolgde hij zijn opleiding op de afdeling Neurologie van het Academisch Ziekenhuis Dijkzigt te Rotterdam (Prof. Dr. A. Staal). In augustus 1979 werd hij in het specialisten register voor neurologie ingeschreven. Zijn opleiding tot klinisch neurofysioloog genoot hij in l'Hôpital de La Salpétrière te Parijs (Dr. A. Rémond). Sedert april 1981 is hij als staflid verbonden aan het Sint Franciscus Gasthuis te Rotterdam.