CLINICAL STUDIES OF SPATIAL AND TEMPORAL ASPECTS OF VISION

An investigation using psychophysical and electrophysiological techniques

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SUMMARY

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Separate physiological mechanisms which respond to spatial and temporal stimulation have been identified in the visual system. Some pathological conditions may selectively affect these mechanisms, offering a unique opportunity to investigate how psychophysical and electrophysiological tests reflect these visual processes, and thus enhance the use of the tests in clinical diagnosis.

Amblyopia and optical blur were studied, representing spatial visual defects of neural and optical origin, respectively. Selective defects of the visual pathways were also studied - optic neuritis which affects the optic nerve, and dementia of the Alzheimer type in which the higher association areas are believed to be affected, but the primary projections spared.

Seventy control subjects from 10 to 79 years of age were investigated. This provided material for an additional study of the effect of age on the psychophysical and electrophysiological responses.

Spatial processing was measured by visual acuity, the contrast sensitivity function, or spatial modulation transfer function (MTF), and the pattern reversal and pattern onset-offset visual evoked potential (VEP). Temporal, or luminance, processing was measured by the de Lange curve, or temporal MTF, and the flash VEP.

The pattern VEP was shown to reflect the integrity of the optic nerve, geniculo striate pathway and primary projections, and was related to high temporal frequency processing. The individual components of the flash VEP differed in their characteristics. The results suggested that the P2 component reflects the function of the higher association areas and is related to low temporal frequency processing, while the P1 component reflects the primary projection areas.

The combination of a delayed flash P2 component and a normal latency pattern VEP appears to be specific to dementia of the Alzheimer type and represents an important diagnostic test for this condition.

KEYWORDS: visual evoked potential - psychophysics - Alzheimer's disease - optic neuritis - reduced vision

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LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1 THE VISUAL SYSTEM

1A ANATOMY OF THE VISUAL PATHWAY

1B PROCESSING OF THE VISUAL IMAGE

1C PARALLEL NEURAL CHANNELS

1 THE VISUAL SYSTEM

A complete description of the visual system would be very complex and beyond the scope of this review. The aim of this summary is to provide a foundation for the topics covered in later sections of the thesis and will therefore be limited to the photopic system, and monocular, monochromatic processing.

1A Anatomy of the visual pathway

The anatomical arrangement of the visual pathways is represented in Figure 1.1 and is explained in the following summary (1, 2, 3, 4). The visual image falling on the retina initiates a photochemical reaction in the receptors, the rods and cones. As the name suggests, the retina is a network of cells, the electrical signals from the cones passing by means of synapses through the bipolar cells to the ganglion cells. The horizontal and amacrine cells modify the signals. The axons of the ganglion cells leave the eye as the optic nerve, a bundle of about a million fibres. At the chiasm the nasal fibres from each eye cross while the temporal fibres remain uncrossed, with the result that the entire representation of one half of the visual field is contained in each optic tract. Although the corresponding fibres from the two eyes are travelling together, there is little or no binocular interaction at this stage and the fibres from each eye enter separate layers of the lateral geniculate body (LGB). The fibres from the ipsilateral eye innervate layers, 1, 4 and 6 and those from the contralateral eye innervate layers 2, 3 and 5 to synapse with the fibres of the optic radiations along which the visual signals are transmitted to the visual cortex.

Figure 1.1 Schematic representation of the visual pathways in the brain, seen from above. From Hubel and Wiesel (1)

Figure 1.2 An elementary unit of primary visual cortex
Containing one set of orientation columns subserving all orientations and one set of ocular-dominance slabs subserving both eyes. From Hubel and Wiesel (1)

The primary visual cortex is approximately 30cm^2 in area on each hemisphere and 1.5 to 2.0mm thick. It can be differentiated histologically into six horizontal layers, with vertical intercellular connections. Of these the pyramidal cells are found in the 5th and 6th layers and stellate cells predominate in the 4th layer. The 4th layer of the primary visual cortex has particular significance as it is in this layer that the myelinated fibres from the LGB terminate, giving rise to the white 'line of Gennari' which is visible to the naked eye. As a result of this the primary visual cortex is also known as the striate cortex. A third name is area 17, after Brodman's classification. Areas 18 and 19 can be also identified histologically in the visual cortex. These areas are often known jointly as the secondary visual cortex or the extrastriate cortex. These areas have traditionally been believed to process the image in a serial manner, with the primary visual stimulus entering area 17, being synthesised into visual impressions in area 18 and being linked with ~~into~~ other parts of the brain and memory through area 19. These visual areas are duplicated, the left visual cortex representing the right visual field and the right visual cortex representing the left visual field. Connections between the two cortices are found in abundance in area 18 and in the parts of area 17 near the vertical meridian.

1B Processing of the visual image

As the visual signals pass through the visual system a very large amount of information is compressed into a form the cortex can analyse, and important information is enhanced at the expense of less relevant information. The sites for these stages in the visual processing are the synapses at which the strength of signal transmitted is determined by the number of nerve fibres converging on a single

cell and the distribution of excitatory and inhibitory endings (5).

The retina is designed to enhance images falling on the central 2^{o} - the fovea - by the means of a high concentration of cones in this area. In addition, the high number of ganglion cells means that almost every ganglion cell receives the output of one cone, in comparison to the peripheral retina where many cones converge onto each ganglion cell. The area of receptor mosaic feeding into each ganglion cell is known as the receptive field, the size of which increases with increasing distance from the fovea, with a consequent reduction in visual acuity (Section 3A). It has been found by Kuffler (5) that the retinal receptive fields give a maximum response when stimulated by neighbouring areas of contrasting luminance but hardly respond at all to overall changes in luminance. This is due to the differentiation of the receptive field into a circular centre and concentric surround. In some types of receptive field the centre gives a maximum response when stimulated by light (excitatory or 'ON' centre), while the response of the surround is decreased by light stimulation and responds maximally when the light is switched off (inhibitory or 'OFF' surround). The reverse arrangement (OFF centre and ON surround) is also found. It can be seen that both types of receptive field will give a maximum response when the stimulus is confined to the excitatory area alone. A diffuse light will stimulate both excitatory and inhibitory areas, leading to complete cancellation if there is a linear relationship between the two areas. As a result of this, changes in the overall luminance of the visual world go relatively unnoticed - for example, as clouds move across the sun, or the eyelid blinks.

The signals transmitted along the optic nerve fibres are now each

representing units of the visual field in topographical arrangement with the central field having the major representation. The impulses are equal in amplitude - changes in stimulus intensity resulting in changes in impulse frequency (5). About a quarter of the fibres project to the superior colliculi which seem to be concerned with aspects of visual attention and centering of the visual image on the retina (6, 3). The remaining fibres synapse in the LGB where the retinotopic arrangement of the fibres is maintained. The receptive fields are still found to be of concentric centre surround arrangement and it appears that they have enhanced inhibitory properties (5). Thus, the optimum stimulus for the retina and LGB is a small patch of light, the optimum diameter depending on its position in the visual field. A bar of light of width approximately equal to the diameter of the ON centres will also be effective in stimulating the receptive fields, whatever its orientation. These receptive field properties have also been found for the very first cells in layer 4 of area 17 of the visual cortex which receive the geniculate fibres. However the research of Hubel and Wiesel has shown that these characteristics change markedly as the visual processing progresses through the cortex.

Using microelectrode recordings in area 17 of the cat and monkey, Hubel and Wiesel (1, 7) found a progressive refinement in the processing of visual images which enhances contours. They found cells with ON and OFF receptive fields, as before, but this time the receptive fields were found to be elongated so that they were maximally stimulated by line stimuli. These 'simple cells' were each found to be sensitive to one specific stimulus orientation, the response being markedly reduced when the stimulus orientation differs by 10^{o} or 20^{o} from the optimum and completely absent when it differs by 90^{o}. These

simple cells were mostly found around layer 4 and it was suggested that the circular ON centres of the LGB input are in an overlapping arrangement so that a line stimulus will give maximum stimulation.

A further type of cortical cell, named a complex cell with a larger receptive field, is maximally stimulated by a line or slit of a specific orientation but in this case the actual position of the line in the receptive field is not as important. It is suggested that the complex cell receives an input from a number of simple cells with slightly different receptive field positions, suggesting a serial organisation of image processing. This is also suggested by the positions of the cells - the simple cells in layer 4 of the cortex and complex in layers 2, 3, 5 and 6. Complex cells require a moving stimulus and about half are sensitive to the direction of the movement. It is also thought that this is the first level at which the signals from the two eyes converge. It has been noticed that about 10 to 20% of simple and complex cells respond best to a line of specific length - the response being diminished by a shorter or longer line. These were initially thought to be a form of hypercomplex cell but they are now thought to be a specialised 'end-stopped' type of simple and complex cell (7). The complex cells in layers 2 and 3 of the cortex have been found to project to other cortical regions, in layer 5 to the super colliculus and layer 6 back to the LGB. Kelly and Van Essen (8) produced evidence to suggest that cells with 'simple' characteristics correspond to stellate cells in layer 4 and that complex cells correspond to the pyramidal cells which are found in layers 2, 3 and 5.

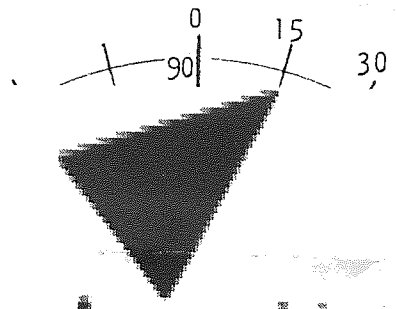
Hubel and Wiesel have shown that these orientation specific cells in area 17 are arranged to form an elementary unit of about $1mm^2$ and

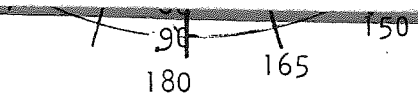
2mm deep for each point of the visual field, within which cells responding to every orientation are represented in an orderly fashion. They found that all the cells encountered by a penetration perpendicular to the surface of the cortex had the same orientation specificity, as if they were arranged in a column (the exception being the granular cells with circular receptive fields in layer 4). Tangential penetration revealed that neighbouring columns changed in orientation specificity by only about 10^{o} at a time, leading to a systematic representation of the entire 180^{o} within a short distance. The orientation columns are duplicated so that right and left eyes are represented in neighbouring columns. The whole unit is represented schematically in Figure 1.2. In reality a cross section parallel to the cortical surface shows swirling and branching formations, rather than a rectangular block. However, the width of each unit seems remarkably uniform at about 1mm, regardless of the area of field under investigation. However, as the receptive fields of the central retina are much smaller than those of the periphery a correspondingly larger area of cortex is required to represent an equivalent retinal area.

The uniform mapping of the receptive fields on the cortex means that the entire visual field is represented on the visual cortex in a systematic manner (3, 9, 10,11); Figure 1.3.

Most of area 17 is hidden on the inner medial surface of the hemisphere. However, some of the large foveal representation at the occipital pole extends to the outer surface, the actual exposed area varying between species and individuals. The representation of the vertical meridian of the lower field extends above and that of the upper field extends below the foveal projection, while the representation of the horizontal meridian extends anteriorly through the medial surface of the cortex.

a) The temporal half visual field of the right eye





b) Medial view of the occipital pole of the left cerebral hemisphere. Calcarine fissure opened out for clarity

Figure 1.3 Holmes' mapping of the systematic projection of the visual field on the occipital cortex. From Brindley (3)

Within these limits the entire visual field is represented, with a systematic relationship between successively deeper cortical regions and increasingly eccentric areas of the visual field. The cortical area representing each part of the field decreases with distance from fixation - one estimate for the 5cm length of area 17 is that the first centimetre represents the central 8-10°, 2.5cm up to 30°, 3.5cm up to 50° and 4.5cm up to 70° (12). The entire outer circumferance of the half field is represented at the anterior point of area 17 (11).

Area 17 is unique in that the horizontal representation is folded into the calcarine fissure so that the representation of the upper and lower octants adjoining the horizontal meridian are facing each other. The upper and lower octants adjoining the vertical meridian are represented on the lower and upper medial surfaces of the cortex respectively - the lips of the calcarine fissure corresponding approximately to the 45° and 135° meridians of the visual field (13). This arrangement has been described as an approximation to a cruciform configuration (9).

The representation of the visual field is repeated in a mirror image on area 18, then again on area 19. The boundary between areas 17 and 18 is therefore marked by the representation of the vertical meridian, and between 18 and 19 by the horizontal meridian (10).

1C Parallel neural channels

In the 20 years since Hubel and Wiesel first proposed their model of serial processing in the visual cortex, evidence has accumulated to suggest that parallel processing also plays an important part in the transmission of information through the visual pathways. Three

channels have been proposed, named the X, Y and W systems. Although there are still some differences in the reported characteristics of these systems mainly due to the different criteria employed by different researchers for identification of the cells, (8, 14) general properties have been recognised and are summarised below (8, 15, 16, 17, 18, 19) Table 1.1.

X and Y ganglion cells were first identified in the retina on the basis of their receptive field characteristics. The X cells have a clearly defined centre and surround which show a linear interaction. They comprise about 40-50% of cat ganglion cells and predominate in the central retina. The diameters of the receptive field centres are smaller than those of the Y cells, ranging from 20 min at the fovea to 70 min at 4.5mm eccentricity, compared with a range of 50 to 140 min for Y cells at the same retinal positions. The Y cells comprise 5-10% of cat ganglion cells and are relatively more numerous in the retinal periphery with large less well defined receptive fields which are non linear. Y cells respond to a stimulus with a transient burst of activity while the X cells show a sustained response and the conduction velocity of the Y cells is much faster. Since the discovery of X and Y cells in the retina, ganglion cells with other characteristics have been described, and grouped by some researchers into a third system, the W cells (8, 15). W cells have large receptive fields and slow conducting fibres and can constitute as many as 50-55% of the ganglion cells of the cat. 90% of the retinal input to the superior colliculus consists of W fibres. Some Y fibres also project to the superior colliculus (15).

Separate X, Y and W fibres are found at the LGB (20), and at the

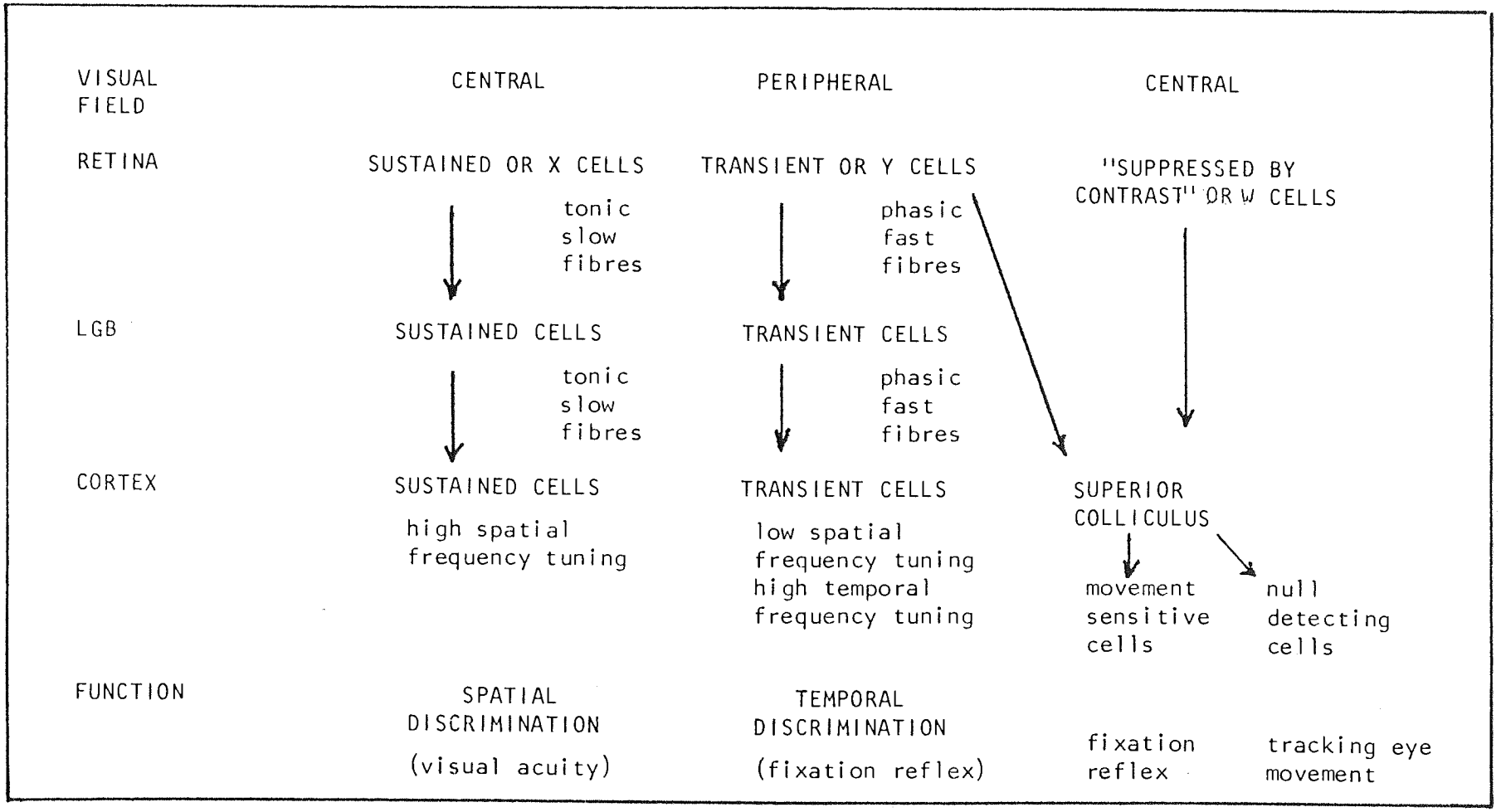


TABLE 1.1 Showing proposed "sustained" or X and "transient" or Y pathways in the visual nervous system. The likelihood of the receptive field position in the visual space and possible functional roles for each pathway are also indicated

After Ikeda and Wright (15)

input to the visual cortex (8, 19). It is believed (8, 19) that the major input to area 17 of the cat is from the X cells, area 18 from Y cells and area 19 from W cells. Area 17 also receives a lesser input from Y and W cells and area 18 a lesser input from W cells. It has also been suggested (21) that X cell fibres project to the simple cortical cells and Y cell fibres project to complex cells, although other reports (15) suggest that both types of cortical cell receive inputs from X and Y cells.

Psychophysical evidence suggests that the X system forms the basis for spatial vision as suggested by the small dimensions and sharp differentiation between centre and surrounds of the X cell receptive fields (15), and the predominance in the central retina (18). The large, less well defined receptive fields of the Y cells make them poor spatial discriminators and it is thought that they signal temporal changes (15, 21, 22). Psychophysical evidence indicates that directional (movement) and non directional (flicker) temporal information is transmitted by the same system, which is believed to be the correlate of the Y cells (22).

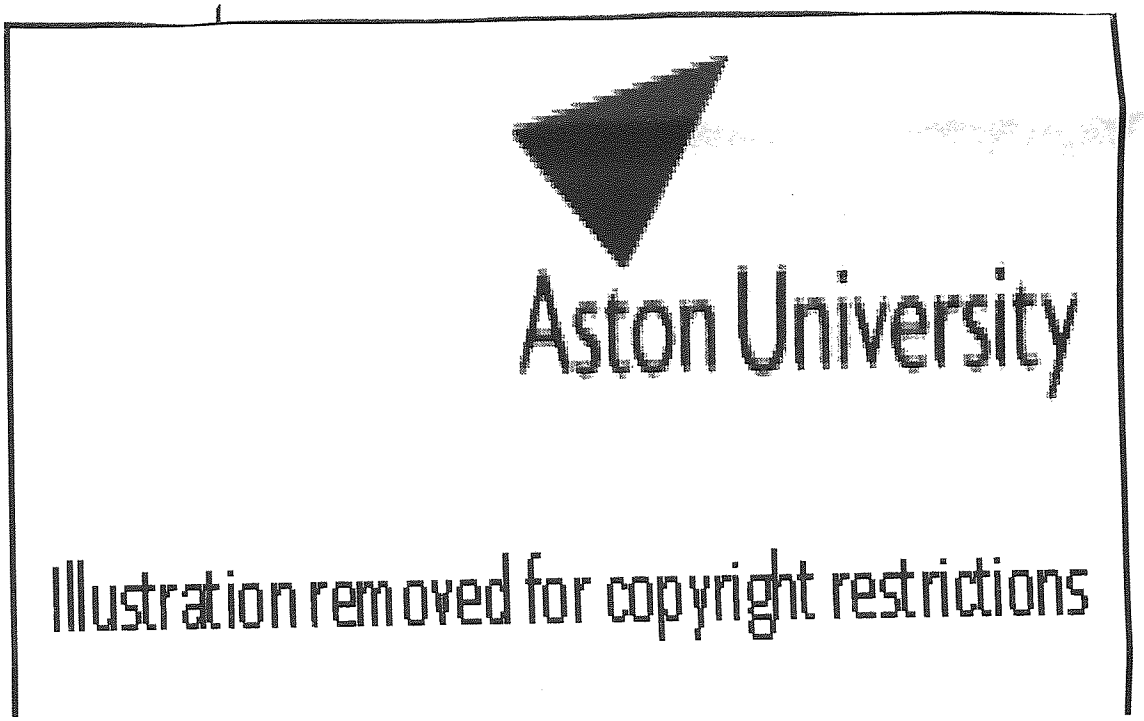
These characteristics would be consistent with psychophysical evidence for two independent systems - a 'pattern detecting mechanism' which is most sensitive to stimuli of high spatial frequency which are stationary or presented at a low temporal frequency, and a 'movement detecting mechanism' which is most sensitive to low spatial and high temporal frequencies (8, 22, 23, 24, 18). Evidence for these two systems includes the observation that the contrast sensitivity of the visual system to low spatial frequency stimuli is enhanced by temporal modulation (25). Comparison of flicker and

pattern detection thresholds for a modulated grating show that the two systems are equally sensitive at high spatial frequencies, but at low spatial frequencies flicker sensitivity is better than pattern by a factor of two (23).

It has been estimated that gratings of 0.25c/deg are detected by the Y system alone while gratings of 10c/deg are detected by the X system alone (24). However, estimates of the relative contributions of the two systems in the intermediate regions vary, with estimates of a Y cell contribution up to 30c/deg (23), or alternatively a Y cell contribution up to 3-4c/deg with temporal information at higher spatial frequencies transmitted by the X system (22) Figure 1.4. The low spatial frequency cut off of the X system is estimated at about 3c/deg (22).

The W cells may be involved in control of slow tracking eye movements or maintenance of fixation (15).

If the suggested cortical termination of X and Y cells in areas 17 and 18 respectively prove correct, it would seem that area 17 is predominantly associated with spatial processing while area 18 is associated with temporal processing. Such a hypothesis would require some modification of Hubel and Wiesel's original model in which the signals entered the cortex in the striate area of area 17 and then went through a serially organised elaboration of visual information. However, the parallel and serial processing models could well prove to be compatable, with the separate aspects of visual information undergoing serial processing in parallel channels (6).



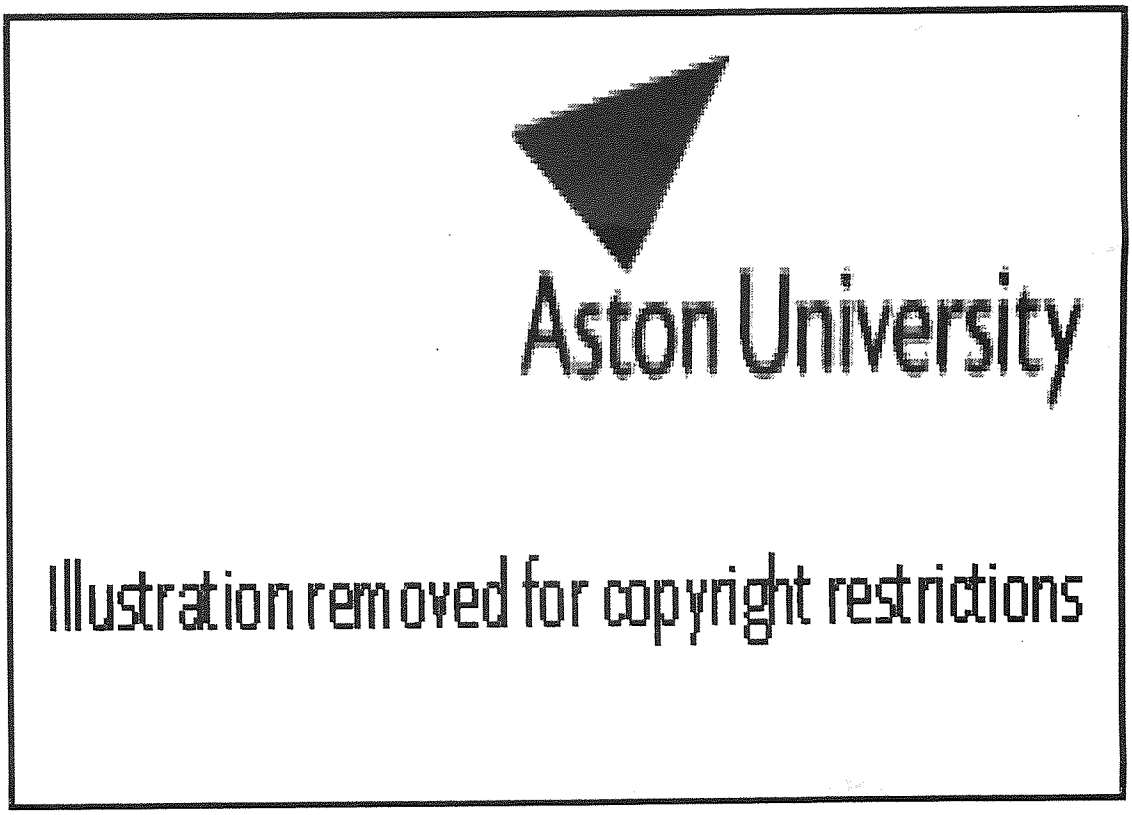


Figure 1.4 Schematic representation of the spatial frequency tuning of the sustained and transient systems as proposed by a) Kulikowski and Tolhurst and b) Legge From Green (22)

The higher mechanisms by which the brain combines these different aspects of visual information and the signals from the different parts of the visual field into the final visual image are yet to be understood (1).

CHAPTER 2 THE VISUAL EVOKED POTENTIAL (VEP)

2A TECHNIQUES

2B THE FLASH VEP

2B1 Properties of the flash VEP

2C THE PATTERN VEP

2C1 Physiological mechanisms

2C2 Spatial stimulus parameters

2C3 Temporal stimulus parameters

2D CORTICAL ORIGINS OF THE VEP

2D1 Cellular theories and dipole models

2D2 Topographical VEP studies

2 THE VISUAL EVOKED POTENTIAL (VEP)

2A Techniques

The response of the visual system to a flashing light can be seen as a series of spikes in the electroencephalogram (EEG) recorded from electrodes over the occipital area of the brain (26, 27). However, in most people, the response is too small to be studied and is frequently obscured by the background activity of the EEG. The technique of averaging (26, 28) enhances the visual response and reduces the spontaneous background activity by the computer addition of a number of sections of the EEG immediately following each flash. The assumption behind this technique is that the visual response is time-locked to the visual stimulus and the summated samples will therefore increase in amplitude in proportion to the number of samples, N, while the background activity is not related to the visual stimulus, but random and will therefore increase in amplitude as a function of $\sqrt{N}$ (29). Averaging 50 responses will lead to a signal/noise ratio of 7:1 while the ratio can be improved to 10:1 by increasing the number of samples to 100. Further increases in the number of samples lead to smaller incremental benefits (29) while requiring concentration by the subject for longer periods of time, so a compromise must be reached, taking into account whether the aim of the study is for clinical information or fundamental VEP research. Some information about the individual VEPs is lost in the averaging process (26, 28, 29).

The changes in potential recorded from the brain in response to a visual stimulus are known as the Visual Evoked Potential or VEP. The averaging process records the transient response of the visual system

to each stimulus, allowing the system to return to its normal resting state before the next stimulus. The resulting transient averaged VEP is displayed as a plot of change in potential against time and shows a series of positive and negative waves occurring within the 500 msec following the stimulus (26).

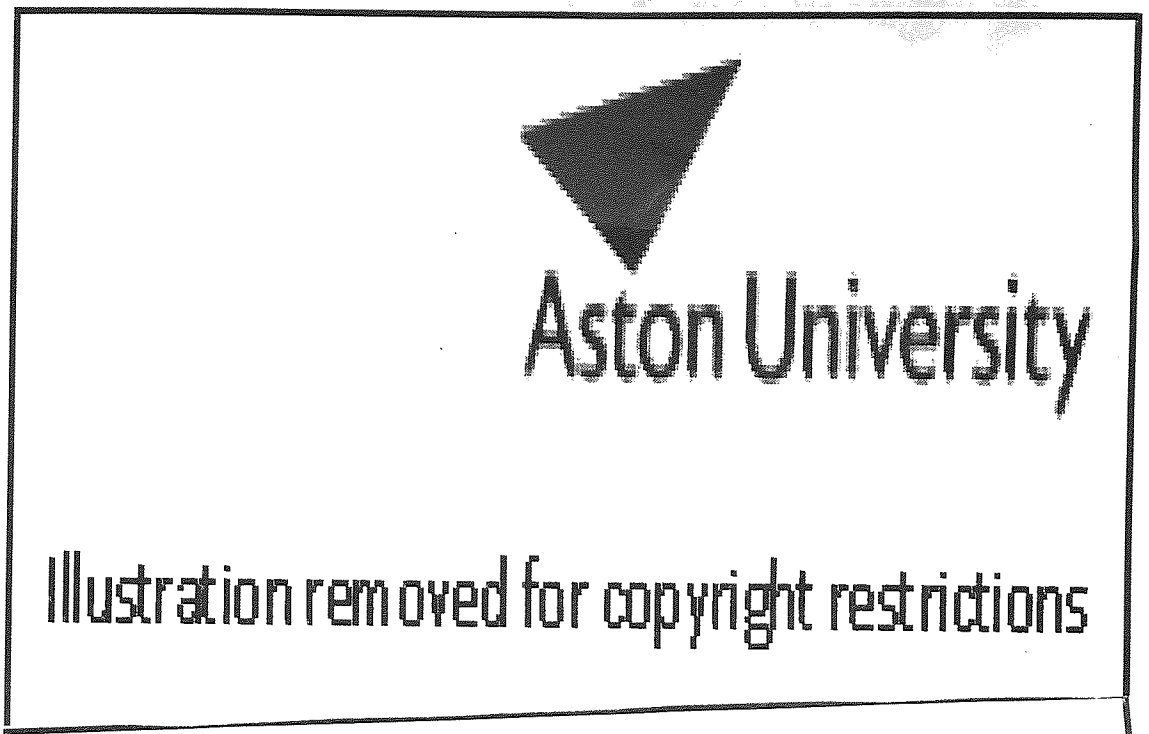
An alternative method of evoking a VEP is to present the visual system with a long train of repetitive stimuli varying sinusoidally in time. The resultant VEP obtained by Fourier analysis is a sine wave of the same frequency (if operating within the linear range of the visual system) and is assumed to reflect the dynamic steady state of the brain. This signal is therefore known as the steady state VEP and is characterised by plots of phase or amplitude against stimulation frequency (30).

The repetition frequency of the steady state stimulation is such that the individual components of the VEP overlap and merge to form a simple sinusoidal waveform (30, 31). This makes a single amplitude measurement easier, but potentially rewarding information about the behaviour of individual components is lost (27). The steady state signal may not require averaging which means that the effect of a change in stimulus parameters on the VEP can be seen immediately. This makes steady state recording the method of choice for the development of rapid VEP assessment techniques (30). Caution must be exercised when using steady state techniques for theoretical studies, as the non linearity of the visual system at suprathreshold levels limits the extent to which steady state results can be extrapolated (27, 30). Transient and steady state VEPs are therefore complementary in their applications (27, 30). This thesis is concerned

with the study of the transient VEP, and so only passing reference will be made to the results of steady state VEP studies where applicable.

The placement of the electrodes is of crucial importance in the recording and subsequent interpretation of the VEP. The International convention for EEG electrodes introduced by Jasper (26) recommends that, in order for consistency between subjects, measurements should be related to easily detectable landmarks on the skull such as the inion (the protruberence above the base of the skull), the nasion (the dip at the top of the nose) and the pre-auricular depressions, and that the distances between electrodes should be expressed as a percentage of the distance between these points (Figure 2.1.). The electrode positions are named with an initial letter corresponding to the area of the brain over which they lie and numbered with even numbers representing the right side of the head and odd numbers representing the left side. Midline electrodes are indicated by a letter Z. Therefore, the electrode positions relevant to VEP recording are those lying over the occipital area of the brain - O_z which is 10% of the longitudinal inion-nasion distance above the inion on the midline and O_2 and O_1 which are 10% of the circumferential distance from the inion to the nasion either side of O_z. However, these electrode positions were developed for EEG recording over the whole scalp and only sample the occipital area. Detailed VEP studies, therefore, often involve the use of more electrodes over the occipital areas and these are usually specified in terms of the distance above or lateral to the inion in cm.

The technique of monopolar recording is based on the principle of recording the difference between an electrode over an active area of



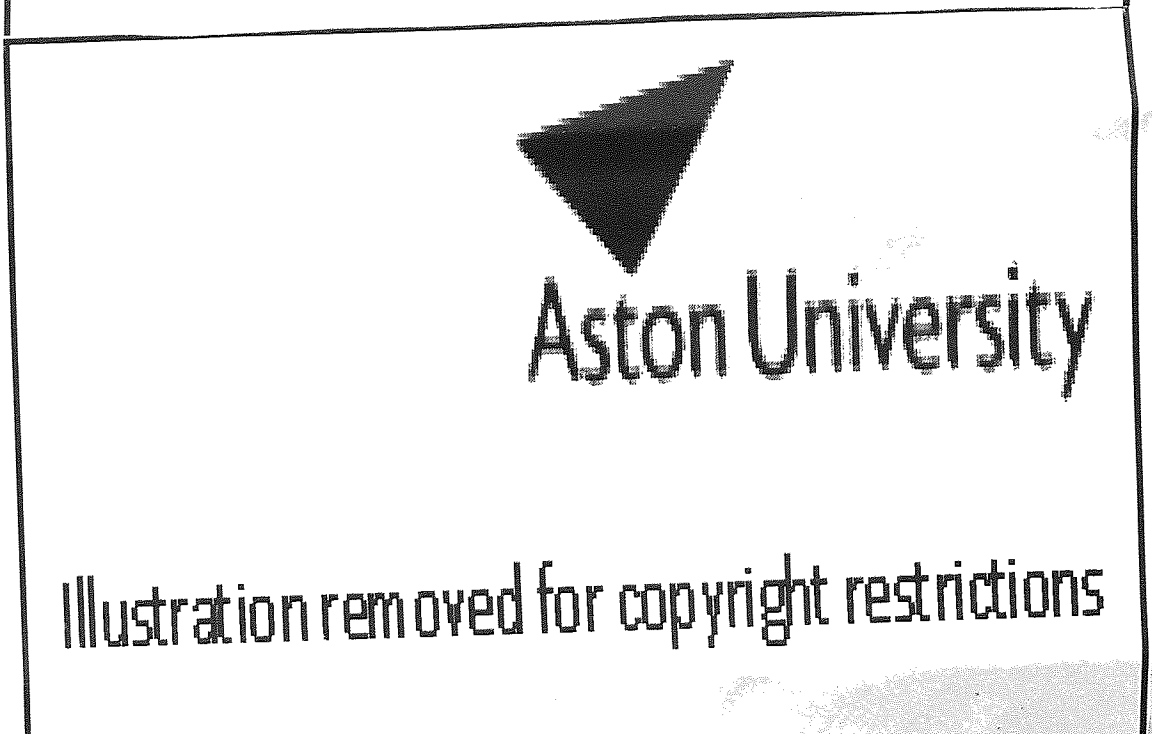


Figure 2.1 Jasper's 10-20 electrode system

F, frontal; C, central; P, parietal; O, occipital
Odd numbers = left side Even numbers = right side
Z = midline From Kinney (51)

cortex and a reference electrode over an inactive area. The selection of an inactive reference site is difficult as very few areas of the scalp are truly inactive so a compromise must be reached. Many VEP studies have used ear, or linked ear references (eg. 32,9) although this site has been shown to be active for upper field pattern reversal responses (33) and early subcortical visual responses (34) when high intensity flashes are used. A frontal reference (F_z) (eg 35, 10) is symmetrically placed with respect to electrodes on the right and left of the occiput (36) and is almost diametrically opposite the occipital area on the scalp. However, central references such as C_3 and C_4 are recommended in recordings from babies and unco-operative subjects as a frontal reference will pick up potentials from excessive blinking and eye movements (37).

Bipolar recording techniques involve the recording of the relative potential difference between two electrodes over active areas of cortex. Chains of bipolar electrodes used in EEG recording can be used to locate an area of activity as shown in Figure 2.2. Activity arising midway between two electrodes will affect them both equally, so no potential difference will be recorded. However, a potential difference will result between these and the next electrodes in the chain resulting in a phase reversal if the electrodes are linked in sequence (26). The use of two bipolar electrodes for VEP recording is however rather limited, particularly for topographical studies, as it is impossible to tell whether a particular deflection is due to a positive potential under one electrode or a negative potential under the other. A potential arising midway between the two will be missed altogether as no potential difference will result.

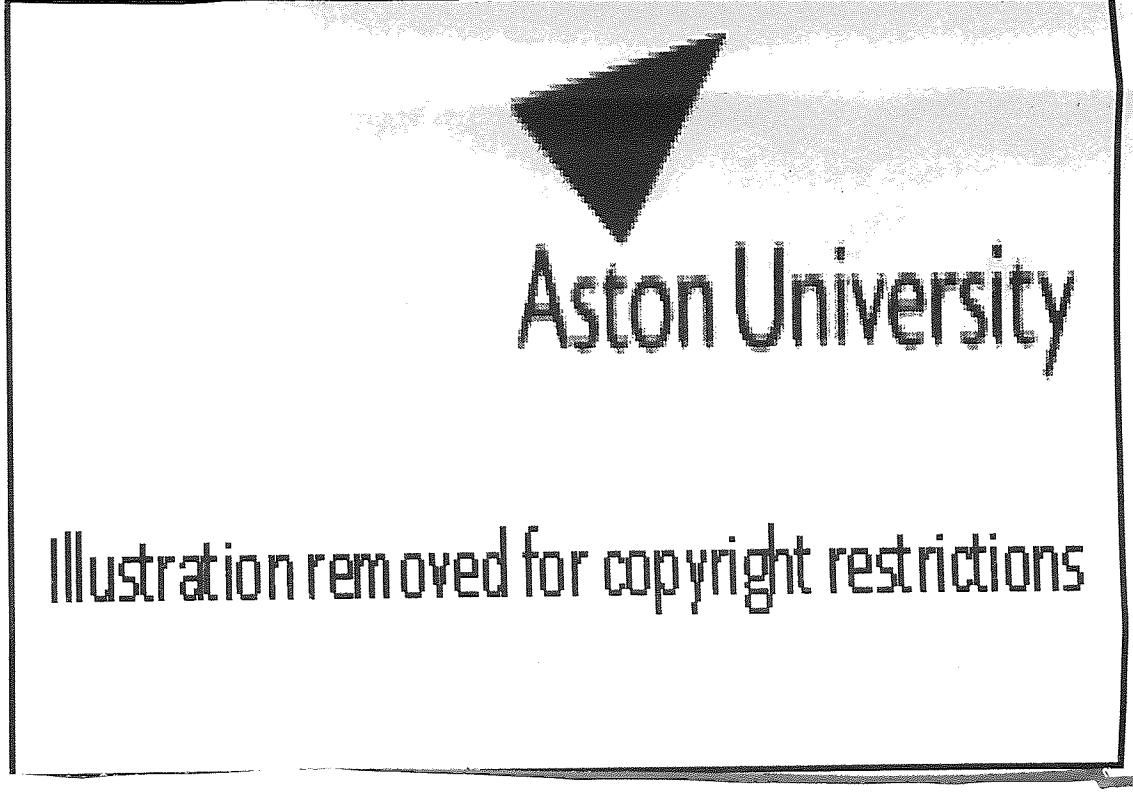
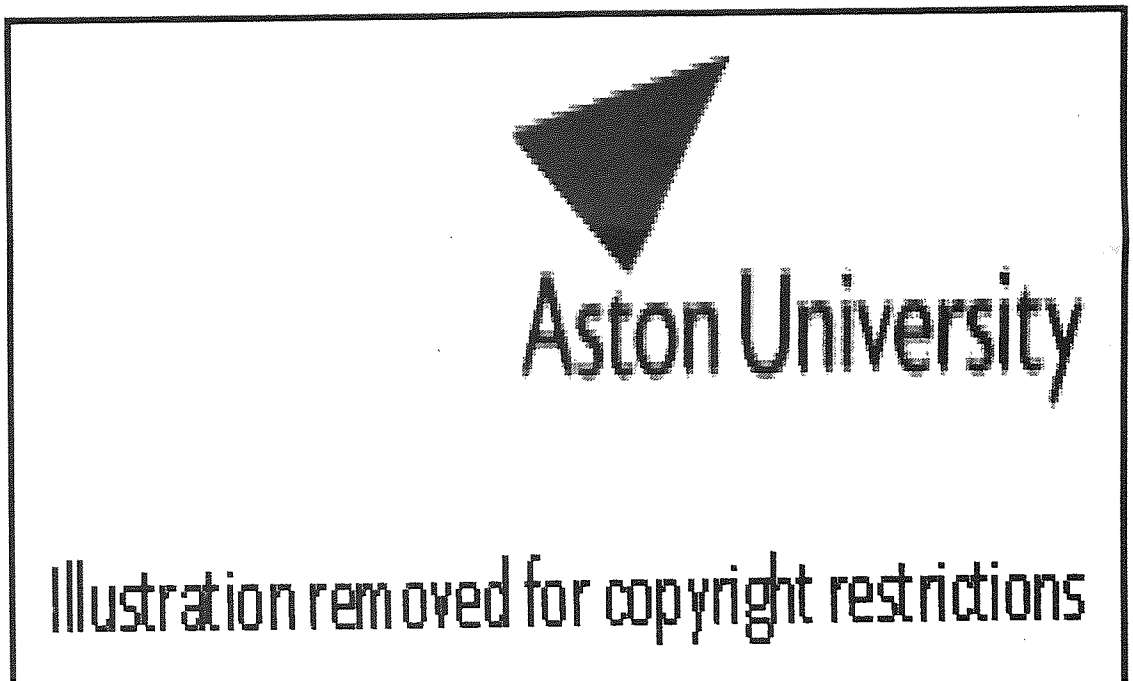


Figure 2.2 Bipolar recording. A negative potential midway between electrodes b and c produces an equipotential recording of channel 2 and phase reversal of the adjacent channels 1 and 3. From Harding (26)

Figure 2.3 The flash VEP. Generalised waveform showing all known components and the nomenclature used in this study. Postitive is indicated by a downward deflection

From Harding (26)



Conventions on the display of the VEP on the oscilloscope or pen write-out varies between laboratories. In general, researchers with a background in EEG work adopt the system of displaying a positive potential by a downward deflection (26) while those with a background in visual science or physics use the opposite convention, where an upward wave denotes a positive potential (eg. 38, 39). It is, therefore, important to determine which convention is being used before interpreting a VEP waveform.

This review will concentrate on the potential changes evoked by a visual stimulus and insights that this VEP gives us into the visual system and pathology. The effect of psychological variables and non visual contributions to the VEP will not be considered in detail, except to say that the recording of the VEP depends on the maintenance of attention by the subject to minimise alpha activity, and the elimination of muscle artifacts by ensuring that the subject is relaxed (27). Isoelectric potentials, such as those arising from the heart, should not be recorded as a potential difference and other artifacts can be minimised by secure attachment of the electrodes to the scalp, reduction of the skin resistance and appropriate filter settings (26).

2B The flash VEP

The transient averaged VEP evoked by an unstructured flash of light consists of a series of positive and negative waves as illustrated in Figure 2.3. Studies on the flash VEP show close agreement on the morphology of the waveform, although the system of nomenclature has varied, with some authors naming the components sequentially with numbers or alphabetical letters and others denoting the polarity of

the component by a letter P or N, followed either by the peak latency (eg. P100) or a sequential numbering system. The latter system will be used in this study, as recommended by Harding (26). The most prominent component in the flash VEP is a positive wave occurring between about 95 and 120 msec, known as P_2 in our terminology (eg. 26, 40, 41).

Ciganek (42) studied the variability of the single VEP traces making up the averaged flash VEP recorded between O_z and P_z. Within each subject the variability of the evoked potential itself was found to be small. Background activity caused some variability of the response, although about half of the subjects showed a reduction in variability about 80 msec after the flash, due to blocking of the background activity as confirmed by the EEG. Variability between subjects was most marked in the amplitude measurements, while the latencies of the components were fairly consistent, with waves P_1 and N_2 showing the smallest standard deviation. The slightly higher variability of the earlier waves seemed to be due to the influence of background activity, while the variability of the later components appeared to be an inherent property of the VEP. The low latency variance of component P_1 was also observed by Nakamura and Biersdorf (32).

A study on one subject by Aunon and Cantor (43) noted that the amplitude of the flash VEP recorded between O_z and the vertex was more variable than the latency. This variability was greater between separate recording sessions than within one session and was also increased when recordings were made in different laboratories, presumably due to differences in equipment.

Comparison of the flash VEPs recorded over the two hemispheres of the brain led to a report of a higher amplitude of the order of 1-5uV recorded over the left hemisphere from central electrodes (44). However, a study of hemispheric differences in 139 subjects (45) shows symmetry in most cases, with 85% of all subjects having a latency difference of less than or equal to 5 msec between hemispheres and 90% having an amplitude asymmetry of less than 40%.

The amplitude and latency of the flash VEP changes throughout life. Within puberty and adulthood (as studied in this project) the amplitude has decreased from the high values found in childhood and, after an abrupt increase between 13-14 and 16 years, stabilises. In the 60 and 70 year age groups, the amplitude of the earlier components (up to 100 msec) increases (41, 46, 47, 48) while that of the components after 100 msec has been reported to decrease (41, 46, 48) or remain stable (47). The latency of the flash VEP increases with age, with the P_2 component increasing by about 20 msec between the teenage years and old age (44, 47, 48).

The amplitude of the flash VEP is found to be higher in adult females than males (44, 48). A study by Buchsbaum, Henkin and Christiansen (48) excluded differences in skull thickness or hormone or endocrine balance as the cause, and suggested that the absence of the Y chromasome was a relevant factor. A genetic contribution to the waveform and amplitude of the flash VEP was suggested by Dustman Schenkenberg, Lewis and Beck (44) after studies which showed a much closer similarity between the VEPs of monozygotic twins than between those of dizygotic twins.

2B1 Properties of the flash VEP

Ciganek (40) observed that the 'primary' flash response - the early components N_1 P_1 and N_2 - showed a specific visual response, while the characteristics of the 'secondary' part of the VEP were non-specific, being affected by factors such as sleep. He suggested a striate origin for the primary response, with a more diffuse origin for the secondary response. This would be consistent with the expected pattern of neural activity outlined by Young (29) in that a short time after the stimulus, neural activity has not branched far beyond the immediate system being stimulated. After this, the activity will spread into other parts of the brain, often with complex feedback loops. Subsequent studies have shown the 'primary' components to be relatively invariable, whilst the 'secondary' components are affected by stimulus and subjective variables, thus challenging Ciganek's definition of the secondary response as 'non-specific' (26).

The early components of the flash VEP show localisation over the scalp consistent with the area of retina being stimulated, while the later components show a less specific, more posterior localisation (32). This would be consistent with reports that the major component, P_2, is foveal in origin (26) and is markedly attenuated when the central part of the stimulus is occluded (49). The fovea makes a major contribution to the flash VEP due to the large cortical foveal representation and its proximity to the scalp electrodes. It has been calculated that the central 2^{o} of a 5^{o} field contributes about 65% of the VEP amplitude (50).

The luminance of the stimulus has a marked effect on the latency of

the flash VEP, a luminance decrease of a log unit causing a latency increase of the order of 8-12 msec (51, 52). It appears that the latency of each component is affected equally so that the waveform is unaffected (52). The latency of the VEP has also been shown to obey Bloch's law in that luminance and stimulus duration are interchangeable up to stimulus durations of 50 msec (53).

The VEP amplitude has been reported to be directly proportional to the stimulus intensity (52,) , although very variable (52). Other reports only found this relationship at low levels of illumination close to threshold with saturation occurring at moderate intensities (51, 27). One study showed that both amplitude and latency relationships with luminance could be described by power functions with exponents of 0.1 to 0.3 or the classical Weber-Fechner logarithmic relationship, as these two functions are similar within a wide range and both fall within the scatter of the results (52).

2C The Pattern VEP

Spehlmann (54) first attempted to relate the stimulus to normal visual conditions by superimposing a checkerboard over the flash stimulus. He found that the VEP evoked by this flashed-on pattern was larger, despite the fact that the luminance had been reduced by 50% due to the black checks. The waveform of the flashed pattern VEP was also different to that of the flash VEP with the replacement of the positive component around 100 msec. by a negative component and the appearance of a large positive component at 180-375 msec (54, 55). The pattern origin of this waveform was established by showing that the VEP reverted to the flash waveform when the pattern was blurred with a +10D lens (54).

Early workers attempted to isolate the pure pattern specific contribution to the flashed-on pattern VEP by subtracting the VEP to either a blank field or the defocussed pattern (55, 56, 50) which assumes a linear relationship between the luminance and pattern components of the response. This has been shown to be a reasonable approximation (39) although other other reports have suggested that the luminance component can be enhanced by the presence of contours (38, 27).

More recent techniques isolate the pattern specific response by the maintenance of constant luminance throughout the stimulus cycle. A full account of these techniques and the equipment used can be found in the report of the Brussels Symposium ad-hoc Committee (58) and their recommended terminology will be used in this thesis. The two main constant luminance techniques for pattern stimulation are pattern reversal and pattern onset-offset. In pattern reversal stimulation the bright and dark pattern elements interchange rhythmically, the number of reversals per second being twice the temporal modulation frequency expressed in cycles per second or Hz. (Figure 2.4). In pattern onset-offset stimulation the pattern appears once per cycle and then disappears after a set time to be replaced by a blank field of equal mean luminance for the remainder of the cycle (Figure 2.5). The contrast change of the pattern elements is therefore half of the change in pattern reversal stimulation (59).

Modifications of these techniques have been made for special investigations. One set of pattern elements only can be modulated so the pattern onset coincides with a decrease in luminance (modulation of dark elements) or an increase in luminance (modulation of bright elements) while the luminance of the blank field is equal to the

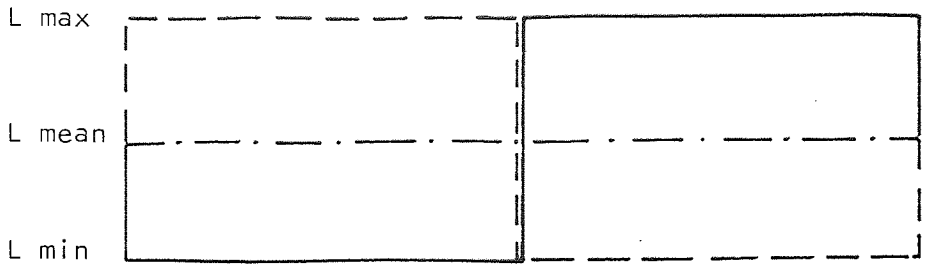
luminance of the unmodulated pattern elements (60) (Figure 2.7). Contrast modulation is another mode of stimulation in which a steady pattern is presented at higher and lower contrast levels without altering the mean spatial or temporal luminance of the pattern (61, 62). Modulation depth and mean contrast can be varied independently.

The above mentioned report also gives a full account of the advantages and disadvantages of different types of equipment which are used to produce patterned stimuli. These include oscilloscopes (eg. 31, 62), television displays (eg. 65), slide projectors (eg. 35, 63, 64), tachistoscopes (eg.39) rotating polaroid systems (eg.66) and patterned mirrors consisting of reflecting and transparent elements (38).

The VEP evoked by pattern reversal stimulation consists of a major positive component with peak latency of about 100 msec (39, 67, 68, 69, 35). (Figure 2.4). The consistency of this component is shown by Halliday's review of normative studies (70) in which the major positive peak occurred between 90 and 120 msec in all 25 studies and between 90 and 110 msec in 20, despite widely varying experimental conditions. He also showed that the pattern reversal VEP was much less variable than the flash VEP. The pattern onset VEP is more variable (67) and consists of three major components, a positive peaking between 55 and 80 msec, a prominent negative component between 90 and 120 msec and another positive at about 150 to 160 msec (39,71) (Figure 2.5). These have been labelled C1, C11 and C111 respectively (9) and this nomenclature has, in general, been adopted in studies using checkerboard stimuli (eg. 71), researchers using sine wave grating stimuli preferring to use the labels P or N followed by the peak latency (eg. 72, 73, 74). An apparent early negative component, Co, has been observed at high spatial frequencies (10, 72, 73, 75). The offset response merges with C111 of the onset response when short stimulus durations are used (76) but can be identifie

Figure 2.4 Pattern Reversal

a) Luminance profile of stimulus



b) The pattern reversal VEP

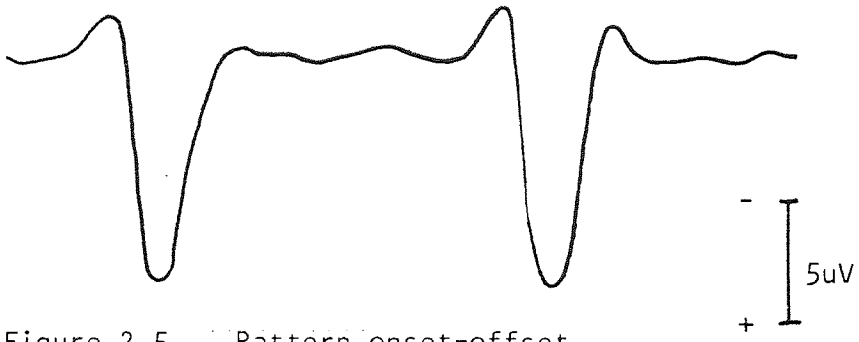
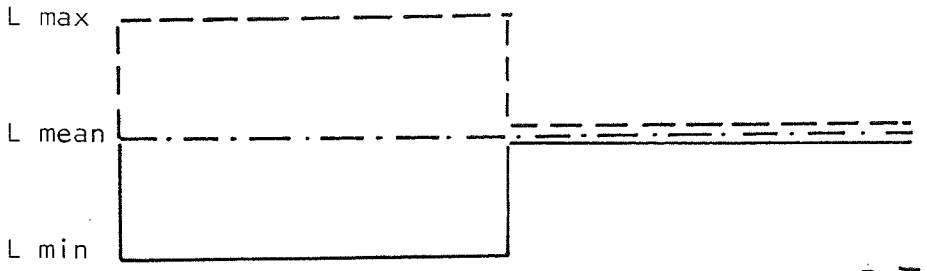
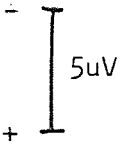


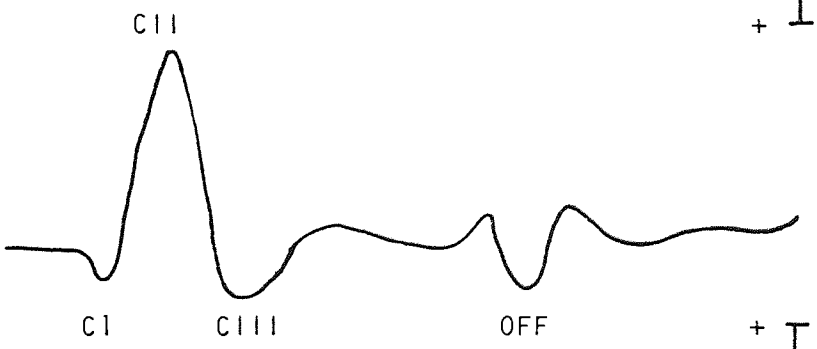
Figure 2.5 Pattern onset-offset

a) Luminance profile of stimulus

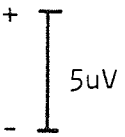


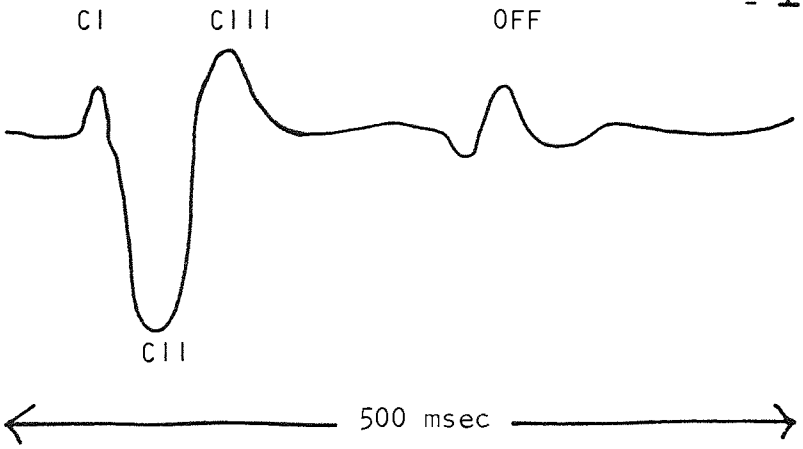
b) The pattern onset-offset VEP





C) As above, but reversed polarity





as a separate positive component with stimulus durations of greater than 100 msec (71). The exact latency values of these two types of pattern VEP depend on the stimulus parameters (77) as shown by studies using lower luminance levels in which CII occurred at about 150 msec (75, 78, 79). Between individuals, latency has been found to be much less variable than amplitude measurements (80, 81).

Investigations into the relationship between the reversal and onset-offset VEP have involved the transition from one form of stimulation to the other (82, 39). As patterns of increasing contrast below saturation are introduced into the blank field of the onset-offset stimulus until reversal is reached, the CII and CIII components show a gradual attenuation and the remaining CI and offset responses interact until the familiar positive peak of the pattern reversal VEP is produced (Figure 2.6). The introduction of a continuously present pattern configuration is the reason for the attenuation of the highly adaptive CII component and its virtual absence from the pattern reversal response (39, 68, 83) (Section 2C3). Observations on the topographic distribution of the different components (84, 39) and variation of waveform with check size (68) confirm similarities between the reversal and offset responses, whilst indicating a different origin for the onset response. The subjective impression of the offset of a high contrast pattern, followed by a negative afterimage has been compared with pattern reversal stimulation (68).

The preservation of separate components in the onset-offset response makes it the method of choice in fundamental research into the nature of the VEP (38, 39). However, the smaller variability of the pattern reversal response particularly at high contrasts has many advantages giving the two techniques complementary uses (83).

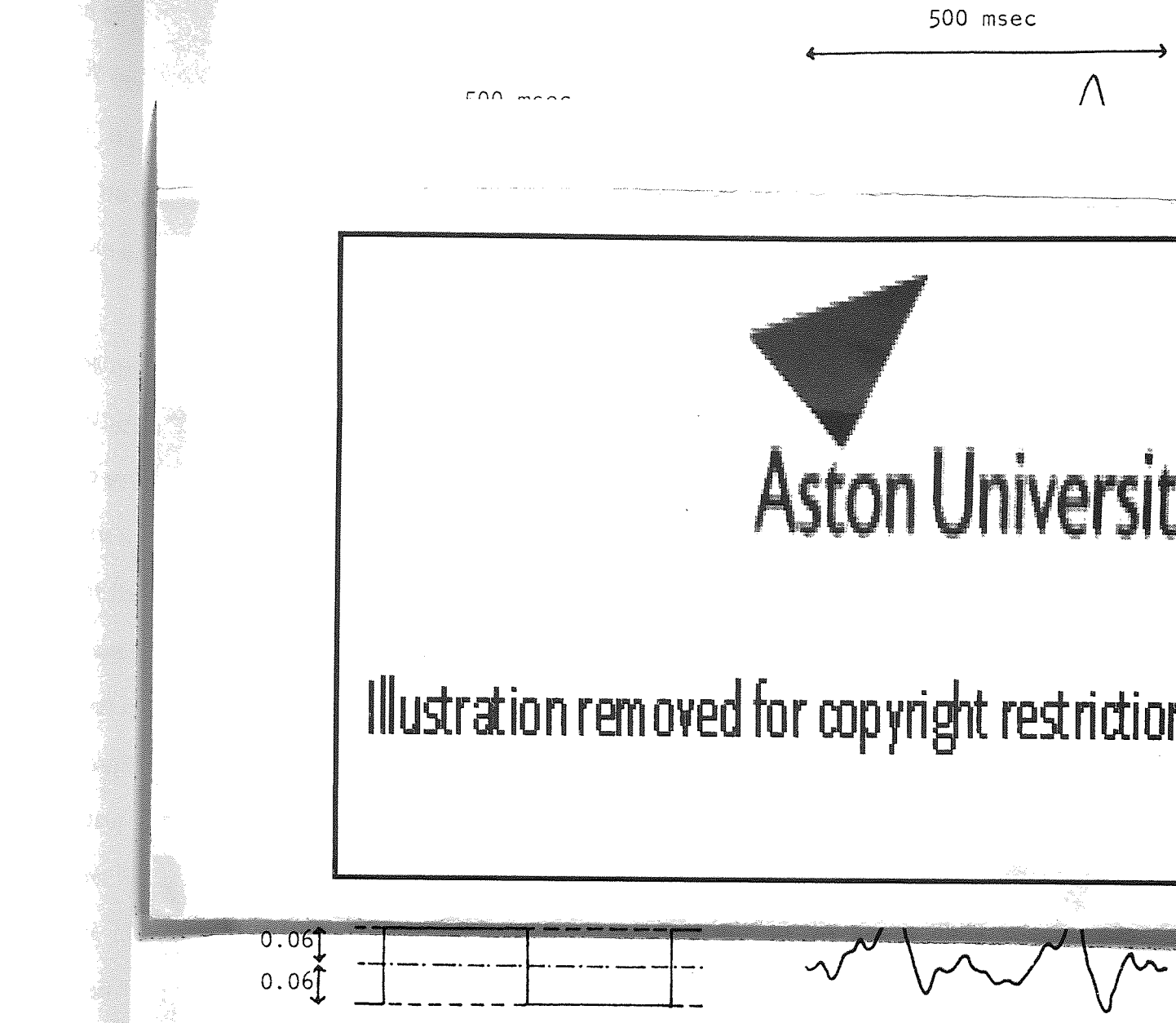
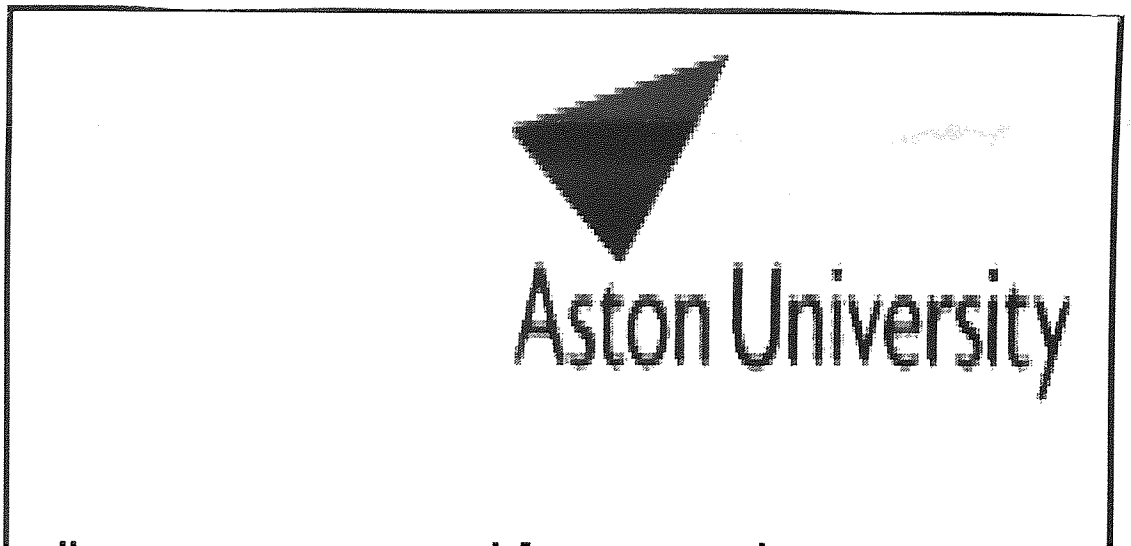


Figure 2.6 Transition from pattern onset-offset to pattern reversal stimulation showing gradual attenuation of CII component. From Estevez and Spekreijse (82)

Figure 2.7 Showing that the onset VEP is evoked by the onset of a pattern, regardless of whether this is accompanied by an increase (a) or decrease (b) in mean luminance. From Spekreijse, Estevez and Reits (92)



Normative studies have shown a small difference in pattern reversal latency and amplitude between males and females. Halliday, Barrett, Carroll and Kriss (85) report that the mean female pattern reversal VEP is between 3.5 and 4 msec. shorter and between 4 and 5uV larger in amplitude than the mean of an equivalent group of males. The authors attribute this to a smaller average head size and skull thickness in women. In addition, the VEP latency of the female group showed a more pronounced and earlier increase with age, which could be related to structural, metabolic or temperature changes associated with the menopause.

The major positive component of the pattern reversal VEP elicited by small checks increases in latency by about 10-15 msec between the ages of 20 and 70 years (86, 87). The VEP evoked by larger checks is less sensitive, only showing a latency increase of the order of 5-7 msec in the older age groups (88, 85). The amplitude of the pattern reversal VEP decreases rapidly from childhood to adolescence (89, 90). Opinions on the amplitude after the age of 20 years vary - with one study reporting that the amplitude was too variable to draw any conclusions (88) three reporting no significant change with age (90, 87, 85) and one reporting a decline until the 30's followed by a small increase in amplitude, and then another decline after the 50's (89).

De Vries Khoe and Spekreijse (91) studied the pattern onset-offset VEP from birth to adolescence. The waveform develops continuously up to puberty, the normal latencies of the characteristic VEP waveform only being attained at the age of about 16 years. The onset VEP during infancy consists of a single positive peak at about 150 msec which is probably a combination of CI and CIII. CII was not found in the VEP

of any infants between 5 and 10 months, in about 40% of infants of 20 months and in 100% of children of 100 months of age ($8^{1}/_{3}$ years). It is suggested that the development of CII reflects the development of the foveal contrast mechanism.

2C1 Physiological mechanisms

There is much evidence to indicate that the pattern and flash VEPs reflect different visual processes. The VEP evoked by the modulation of checks in counterphase (pattern reversal) is much larger in amplitude than that evoked by 'in phase' (homogenous field) modulation of the checks by the same amount, indicating a different origin for the two types of response (92, 93).

If the pattern VEP was only elicited by local changes in luminance on the retina, the responses to the onset and offset of a checkerboard would be identical, as in both cases half the checks increase and half decrease in luminance (63, 59, 83). It has already been shown that this is not the case. A pure luminance origin would also predict that, once the check size exceeds the receptive field size, the amplitude of the VEP would be the same whatever the size of check (63). In fact, the plot of VEP amplitude against check size shows a peak at intermediate check sizes (Section 2C2). This could be explained by a centre-surround receptive field response to local luminance changes - the peak corresponding to the check size which elicits a maximum exitatory and minimum inhibitory response (94).

However, clear evidence that the pattern VEP is a pure pattern response of the visual system is given by experiments in which the appearance

of a checkerboard could be produced by either decreasing or increasing the luminance of one set of checks, while that of the other set was constant throughout. Spekreijse, Estevez and Van der Tweel (60) showed that the VEP was evoked by the appearance of the pattern in both cases, regardless of whether this caused an increase or decrease in the mean luminance (Figure 2.7).

Investigations into the properties of the pattern VEP have shown that the components respond differently to different aspects of the pattern. It is believed that the CII component of the onset response reflects the pattern detail (or contours) and clarity while the CI, offset and pattern reversal components reflect mechanisms responding to transient changes in contrast, and movement (39, 38, 59). As the contours of a checkerboard become more important in relation to the areas of contrast as the checks are made smaller, the contour response predominates for checks smaller than 15 min (57, 91) while the contrast response predominates for larger checks. Jeffreys (39) suggests that contrast responses might reflect simple cortical cells and contour responses reflect hyper complex cortical cells.

Several investigators have attempted to relate these properties to those of the X and Y cell systems. It is suggested that the pattern specific VEP mechanism corresponds to the X cell, or sustained system and would therefore respond to the onset of a stimulus and predominate at high spatial and low temporal frequencies. The Y cell or transient system would correspond to the movement or local luminance response and would be evident at the onset and offset of the stimulus. It would predominate at low spatial and high temporal frequencies (59, 61).

Evidence for two separate pattern and movement systems was presented by Kulikowski (59) who showed that the pattern onset, offset and reversal components were almost identical when a low spatial frequency sinusoidal grating was used. The temporal frequency was 1.67Hz which is believed to stimulate the pattern and movement detectors equally well. As higher spatial frequencies were introduced, differences between the onset and reversal VEPs became more prominent, indicating the increasing contribution of the pattern response to the onset VEP.

Further evidence for two separate systems was provided by adaptation experiments. Pre-adaptation to a high contrast grating hardly affected the reversal VEP to the same grating, for frequencies of 2-6 c/deg. However, the onset VEP was attenuated - the degree of attenuation increasing with increasing spatial frequency. The adaptation is orientation specific with the effect becoming almost negligible when the VEP and adaptation gratings differed in orientation by more than 20^{o}.

Experiments in which 3.5 and 7 c/deg gratings are presented simultaneously, provide further evidence for two separate channels. When the 7 c/deg grating is presented in an onset-offset form to favour pattern mechanisms and the 3.5 c/deg grating is reversed to favour transient mechanisms, the resulting VEP is very similar to the addition of the two VEPs to each grating presented separately. A similar result was found when both gratings were reversed in order to stimulate movement mechanisms. However, when both gratings were presented in onset-offset form for maximum pattern stimulation, the resulting VEP was lower in amplitude than the addition of the separate VEPs, indicating the operation of some form of inhibition.

Bodis-Wollner and Hendley (61) sought to isolate the local luminance VEP responses by contrast modulation of a steady 6 c/deg grating. From the slope of the VEP threshold - contrast modulation plot, they concluded that the VEP is produced by a balance of local luminance detectors (responding to absolute contrast) and spatial contrast detectors (responding to relative contrast).

Parker and Salzen (72) suggest that the increase in latency of pattern onset components with increasing spatial frequency is due to a gradual transition from the faster transient responses to slower sustained responses. However, as there is no evidence of a bimodal change, they consider the alternative explanation that the increase in latency takes place within the transient system alone. Vassilev and Strashimirov (95) supported the former explanation after showing that the increase in latency was not caused by the decrease in contrast sensitivity of the visual system with increasing spatial frequency as it was still present when the contrast of each grating was a constant multiple of the contrast threshold.

Drasdo (10) suggests that this increase in latency at high spatial frequencies is due to the movement of the CI peak across the CII trough (see Section 2C2). He suggests that the CI component represents transient detector activity in the deeper layers, and CII represents sustained detector activity in the superficial layers of the cortex. At high spatial frequencies, sustained activity begins before the transient, causing the CI component to occur in the middle of the CII component.

2C2 Spatial stimulus parameters

Early studies of the pattern VEP used checkerboards as stimuli (54, 55, 96). This stimulus was adopted by the Amsterdam group as the closest approximation to the radial arrangement of the retinal receptive fields whilst maintaining a simple enough shape for pattern reversal stimulation (92). Other workers use sine or square wave gratings as they consider these to be the optimum stimuli for the receptive fields of the visual cortex and consist of one spatial frequency only (61, 73, 97). Both types of stimuli contain equal proportions of black and white so the pattern size can be changed without altering the mean luminance (54), and the pattern can be easily reversed (94).

It has been found that the VEP evoked by a checkerboard is sharply defined while that evoked by a grating is smaller in amplitude and more sluggish (38, 27, 94, 83). One reason that the checkerboard elicits a larger response from the visual system could be that it contains a larger number of constituent frequencies, according to Fourier theory (Section 3B). A sine wave grating is composed of one fundamental frequency, while the checkerboard is composed of two oblique fundamentals at 45^{o} and 135^{o} with the higher harmonics forming the edges of the checks (98, 99). Campbell and Maffei (31) provide evidence that the amplitude of the steady state VEP is proportional to the number of spatial frequency channels activated. Checkerboards have been observed to evoke a larger CI than gratings (10).

Another factor which enhances the VEP to checkerboards is the presence of corners in the pattern. Rietveld, Tordoir, Hagenouw, Lubbers and Spoor (55) showed that the amplitude of the flashed-on pattern

VEP was maximum when the pattern was composed of right angles or acute angles, and was not affected by the orientation of the pattern. A pattern of isosceles right angled triangles gave the largest response, followed by a checkerboard. The VEP elicited by a diamond pattern decreased in amplitude as the acute angles became smaller, presumably due to the corresponding increase in the obtuse angle. Spekreijse and Estevez (71) observed that the pattern onset response become more complex as the acute angle of the diamonds decreased, but the disappearance response increased in amplitude and maintained its waveform.

Van der Tweel (83) showed that the VEP evoked by the presentation of a vertical grating to one eye and a horizontal grating to the other was more similar to the grating VEP, even though the subjective appearance was that of a checkerboard. This implies that the pattern contribution to the VEP is determined at a relatively early stage in the visual process.

It seems that the crucial factor for the generation of CII (and probably CIII) is the pattern detail itself, as the VEP is equivalent when evoked by a checkerboard or by a grid pattern consisting of the square outlines only, even though the integrated contrast of the latter is lower (39, 68, 99). However, the CI component is diminished with a grid stimulus as it is more dependent on the integrated contrast (99). Discontinuous contours also produce a larger CII component than equivalent continuous contours (39). All these properties of the pattern VEP apply whether the pattern details are black on a white background or the reverse (39, 71).

Drasdo (99) attempted to find the ideal stimulus for the generation

of CII using a theoretical, rather than an empirical approach. A hypothetical plot of spatial frequency and orientation characteristics of cortical neurones showed that, in order to stimulate the maximum number of neurones a stimulus should contain spatial frequencies with predominent orientations at 90^{o} and 180^{o}, the high spatial frequencies at higher contrasts than the low spatial frequencies. The patterns showing Fourier characteristics closest to this model are a rectangular grid or isolated square outlines. The CII component evoked by this pattern is not larger in amplitude but broader, suggesting that a large number of neurones are responding at a range of latencies.

The spatial frequency of the pattern stimulus is found to affect the amplitude of the pattern VEP. For small field central stimulation the amplitude is maximum when checks of between 10 and 20 minutes of arc are used. This has been shown for the negative component at about 100 msec of the flashed on pattern VEP (55, 100, 101, 96), the CII component of the constant luminance onset VEP (71) and the steady state pattern reversal VEP (93, 102). Studies using transient pattern reversal stimulation with larger fields found the major positive component was largest with checks of 28 min. (94) and 60-70 min (103). The peak of the amplitude - check size function is found to be unaffected by the contrast of the stimulus for values of 4-100% (102).

A sine wave grating stimulus of 4 c/deg has been found to produce the maximum amplitude of an initial occipitally negative component of the onset VEP under bipolar recording conditions (74). The latency of this component was also minimum with this grating. Another study has reported that the latency of the positive component between 100 and 180 msec increases with increasing spatial frequency above 1 c/deg (72).

This relationship was shown with stimulus contrasts of 50% (72) and 21% (104) and also when the contrast at each spatial frequency was a constant multiple of the contrast threshold, (95) implying that this phenomenon is not due to the decrease in contrast sensitivity with increasing spatial frequency (Section 3C).

The spatial frequency of the stimulus also affects the waveform of the VEP. Spekreijse and Estevez (71) report that for large checks of the order of 40 to 80 min. the onset response becomes sluggish and the offset response is markedly reduced. The offset response becomes relatively larger as the check size is reduced down to about 5 min. The waveform of the onset response remains constant as check size is reduced from 20 min. to 7 min. but CII is replaced by an apparent double negative wave when checks smaller than this are used. This double negative formation can also be seen when sine wave gratings of high spatial frequency are used (72, 104, 73, 10). Drasdo (10) suggests this waveform is due to the occurence of the CI peak in the middle of the CII trough, splitting it into two. Figure 2.8 shows that the CI component evoked by 17.5 and 7.5 min. checks appears to move across CII as the check size is decreased, causing the double negative waveform at the highest spatial frequencies.

It has been suggested that the peak of the check size function relates to the size of the antagonistic centre-surround receptive fields in the retina - the maximum response corresponding to the check size which produces a maximum excitatory and minimum inhibitory response (Figure 2.9). Larger or smaller checks stimulate both areas, leading to a smaller response (94, 103, 105). Harter (105) observed that the check sizes producing maximum VEP amplitude of 7.5-30 min in the central 3^{o}

Aston University

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Figure 2.8 The changing morphology of the VEP is partially dependent on check size and electrode position. Starting at the lower right corner CI occurs before CII. Proceeding leftwards its position changes progressively, apparently disappearing where it coincides with the steep gradient of CII. CI appears to move across CII as one proceeds sideways or vertically.

From Drasdo (10)

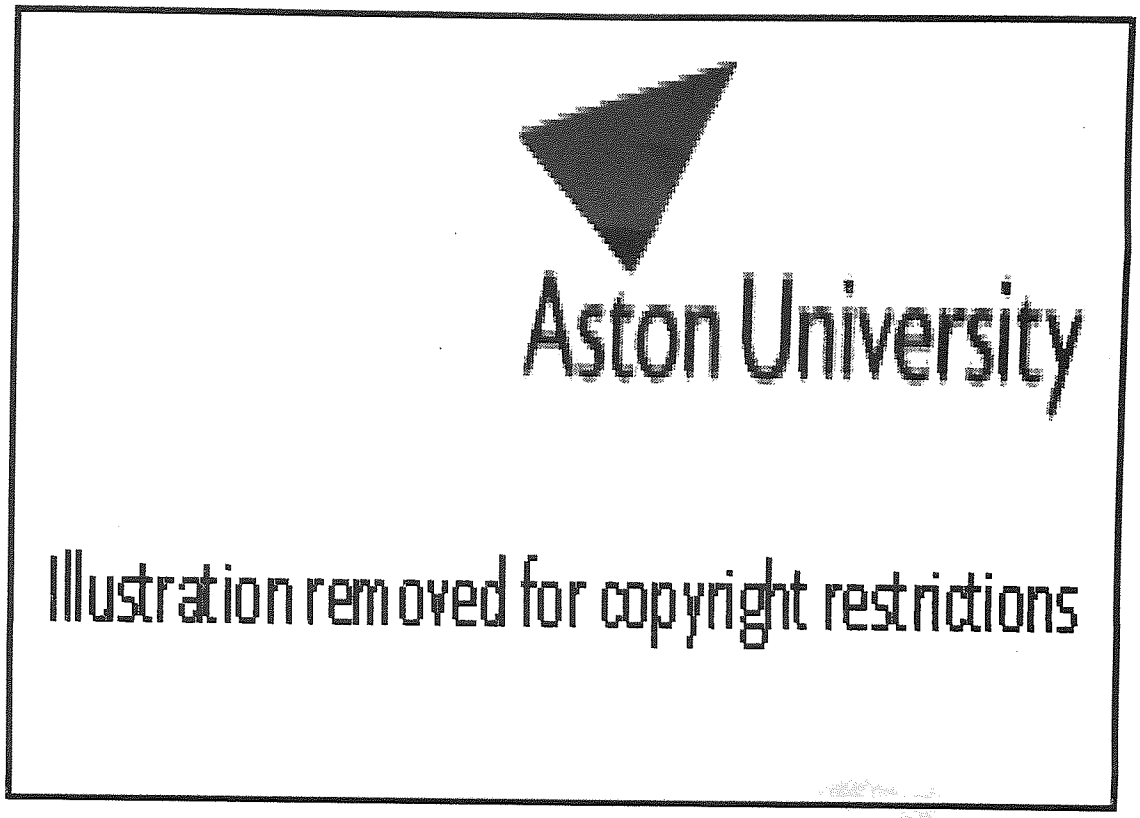


Figure 2.9 Relationship of a hypothetical circular 'ON' centre 'OFF' surround receptive field to the retinal images of grating and checkerboard stimuli

This model predicts that the maximum excitatory and mininum inhibitory stimulation is produced by the medium spatial frequency

From Armington, Corwin and Marsetta (94)

and 30-60 min. in the peripheral retina corresponded with estimates of the receptive field sizes in these areas of the retina. Armington and Brignell (106) also observed this qualitativity. Clearly, the check size - receptive field ratio will influence the strength of signal transmitted along the optic nerve (92). In addition, there will be signals from any antagonistic cells with smaller receptive fields which have coincided with the edges of the checks and any luminance detectors which have been stimulated by a bright check. These signals provide the input to the visual cortex, composed of spatial frequency and orientation selective cells, which respond to the fundamental and harmonic frequencies of the stimulus. The peak of the VEP amplitude - spatial frequency function therefore corresponds to the spatial frequency at which all these factors combine to produce a maximum response.

The pattern VEP to checks of between 10 and 30 min. comes from the central $3\text{-}5^{o}$ of the retina. This has been shown for all types of pattern stimulation and VEP recording, by experiments in which the stimulus diameter was increased until the VEP amplitude no longer increased (55, 93, 66) in which the diameter of an occluded portion in the centre of the patterned stimulus is increased until the VEP is abolished (55, 66) and experiments in which a reduction in the amplitude of the VEP is recorded as a stimulus of constant size is moved further away from fixation (107, 106). The predominance of the central response is partly due to the proximity of the central field representation to the scalp electrode, and also to the higher receptive field density and consequent cortical magnification of this area (106, 57). The contribution of the extrafoveal retina increases as the check size increases, (66, 57, 83) predominating when checks of greater than 1^{o} in fields

of greater than 8^{o} are used (107). Application of the invariance principle of Rovamo and Virsu (Sections 3A and 3C) has shown that a VEP of approximately equal amplitude can be obtained from each retinal location if the stimulus is scaled to stimulate an equal number of cortical neurones (107, 108, 109).

Reduction in the mean luminance of the pattern stimulus has a marked effect on the latency of the VEP (110, 111). Halliday (111) showed that the pattern reversal VEP latency increased by about 15-20 msec for a ten fold reduction in luminance, while the amplitude was only reduced by about 15% (70). Van der Tweel, Estevez and Cavonius (110) showed that an equivalent luminance change increased CII latency by about 30 msec. This could indicate a difference in the two types of VEP, although the former study does not state if artificial pupils were used. If the pupil was free to react normally, it would have dilated as the luminance was reduced, partially overcoming the change and accounting for the difference in results. Decreasing luminance also causes a delay in the steady state pattern reversal VEP, but does not affect the amplitude (66, 93).

A decrease in pupil diameter from 8mm to 2mm can cause a ten fold reduction in retinal illumination (112). An increase in the latency of the pattern reversal VEP has therefore been observed in experiments in which the pupil diameter has been reduced by miotic drugs (112, 113) or artificial pupils (112, 114). Dilation of the pupil with mydriatic drugs produced an equivalent decrease in latency (112, 113, 114). The change in latency is of the order of 20 msec for a 8mm change in pupil diameter (112, 113, 114) and must therefore not be overlooked when comparing sizes due to pathology, drug therapy or age.

Van der Tweel et al. showed that, despite the increase in latency, the shape of the VEP remained constant if the contrast of the stimulus at each luminance level was a constant multiple of the threshold.

From this they inferred that decreasing luminance only affects the speed of signal transmission along the optic nerve but not the generation of the signal itself. The same study shows that, at these levels, contrast has an even more marked effect on latency than luminance, a two fold contrast change having the equivalent effect of a ten fold change in retinal illuminance.

Studies on the effect of stimulus contrast on VEP latency have mainly used pattern onset-offset sinewave gratings. A linear decrease in latency with log contrast has been reported in the early N70-120 (73) and the P100-150 components (73, 104). A decrease in latency followed by saturation has been reported for a P200-250 component (73) and a prominent occipitally negative component obtained under bipolar recording conditions (74). These findings applied to gratings of between 1.5 and 15 c/deg. Musselwhite and Jeffreys (115) found that the latency of CI and CII of the onset VEP to 10.5 min. checks also decreased linearly with the log of stimulus contrast. The latency decrease was of the order of 30-35 msec. for a contrast increase of 1.4 log units.

Campbell and Maffei (31) first showed that the subsaturation amplitude of the steady state pattern reversal VEP is linearly proportional to the log of stimulus contrast for gratings of frequency 3 c/deg or higher. Campbell and Kulikowski (97) examined this and further data and showed that a linear log function described the data more accurately

than a log-log function, or a power or modified power function. This relationship has also been demonstrated for pattern onset-offset steady state (97) and transient (38, 73) recording, and contrast modulation (61, 62). These studies included both sine wave grating (97, 73, 61, 31) and checkerboard (38) stimuli.

The point at which this plot intersects the contrast axis (equivalent to a VEP of zero amplitude) corresponds closely to the psychophysical contrast threshold (31, 73). A more difficult method of threshold determination is to actually measure the VEP at very low contrast to determine the contrast level corresponding to the 50% probability of seeing (the definition of threshold). It has been shown that a VEP is evoked when the stimulus is seen and not when it is not seen (116) and that the contrast value at which a VEP is evoked 50% of the time corresponds closely with the psychophysical threshold obtained by this definition (97). At such low contrast levels about 14,000 sweeps are required to obtain a recognisable VEP signal. When the calculated VEP amplitude is plotted against contrast, the regression line extrapolates to close to zero voltage at zero contrast, showing that it is indeed valid to assume equivalence of these two factors (97). At these near-threshold contrasts, VEP amplitude appears to be proportional to contrast not log contrast as at suprathreshold levels (97, 73). Using the extrapolation technique, Kulikowski (73) found that the amplitude of the N160-P200 configuration (probably corresponding to CII-CIII) extrapolated to subjective threshold, while the amplitude of the N90-P130 configuration (probably corresponding to Co-CI) did not, showing that the individual components of the onset-offset VEP have different properties.

The amplitude of the VEP saturates at higher contrasts, - the exact

saturation contrast varying between 10 and 50% depending on the stimulus parameters (38, 117, 71, 63, 74). For example, the saturation point decreases with increasing luminance and check size (38). Jeffreys (39) found that the saturation amplitudes of CII and CIII are more dependent on the structural details of the pattern than the contrast and luminance levels. He also shows that CIII builds up more rapidly and saturates at lower contrast values than CI.

Spekreijse, Van der Tweel and Zuidema (38) have shown that the amplitude of the CI-CII configuration of the onset VEP is dependent on the initial and final values of contrast, as predicted by the VEP amplitude - contrast plot (Figure 2.10). The shape and amplitude of the onset VEP is dependent on the relative change in contrast, rather than the absolute change. The offset response is found to be unaffected by the initial or final contrast levels, but is only dependent on the contrast change.

2C3 Temporal Stimulus Parameters

Pre-exposure to a high contrast 12 c/deg grating pattern produces an attenuation in the amplitude of the steady-state VEP evoked by a reversing grating of the same spatial frequency. This effect decreases with increasing difference in spatial frequency or orientation of the test and adapting gratings, becoming negligible with a difference in spatial frequency of greater than an octave, or orientation of greater than 15-20^{o} (31).

The components of the pattern onset-offset VEP show different adaptation characteristics. Jeffreys (39) reported that short pattern

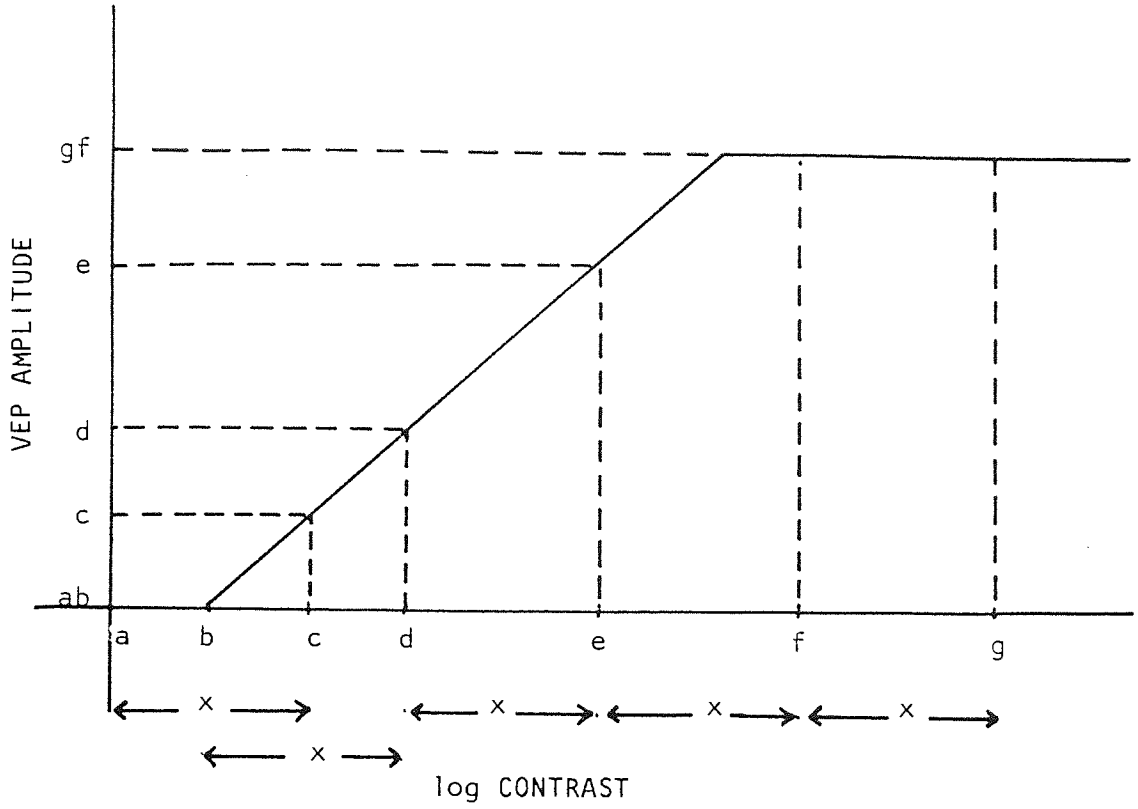


Figure 2.10 To show that the effect of a contrast change, x, on VEP amplitude depends on the initial and final contrast values

- contrast increases b to d and d to e fall within the linear section below saturation and therefore cause the same increase in VEP amplitude

- a to c and e to f cause a small VEP amplitude increase, as shown, as they include the threshold and saturation contrast values respectively

- above saturation, the same contrast change f to g has no effect on VEP amplitude

After Spekreijse, Van der Tweel and Zuidema (38)

pre-exposure attenuates and raises the threshold of CII and CIII markedly but does not affect CI. Similarly, the presence of the steady outlines of the isolated squares throughout the stimulus cycle attenuates the contour specific components CII and CIII markedly but has relatively little effect on CI. This is still shown when the steady outlines are not aligned with the test pattern, but only applies to discontinuous contours.

With a checkerboard stimulus, Smith and Jeffreys (118) showed that CI and CII both showed adaptation characteristics which were spatial frequency specific. The effect declined with differences in spatial frequency of the adapting and test checkerboards to become negligible at differences of greater than 1.5 octaves. CII shows a peak attenuation of about 10% greater than CI which is consistent with the theory that CII has a greater pattern specific contribution. CI also shows adaptation to a grating stimulus which is orientation and spatial frequency specific (the CII component was not studied under these conditions).

Kulikowski (59) also produced evidence that the pattern detectors show greater adaptation characteristics. The reversal VEP to gratings of between 2 and 6 c/deg was not attenuated by pre-exposure to the grating, while the onset VEP was attenuated when gratings of 2 c/deg and higher were used.

The highly adaptive properties of CII have to be taken into account during a conventional averaging run. Barber and Galloway (65) studied the individual VEPs within an average to show that the CII

amplitude rapidly decreases, reaching an equilibrium level after the first few stimulus presentations. The CII amplitude in the final averaged VEP is more influenced by the equilibrium value than the initial CII amplitude, as equilibrium is reached so quickly. The averaged CII amplitude is reduced when the stimulus duration is long enough to produce adaptation. It is shown that CII shows an exponential amplitude decline with increasing stimulus duration of a flashed on pattern. However, Barber and Galloway show in a later paper (119) that increasing stimulus duration while maintaining a constant interstimulus interval (ISI) causes a rapid CII attenuation at the beginning of an averaging run, but does not have a large effect on the equilibrium value. It seems that the ISI has a more marked effect on the equilibrium CII amplitude. Jackson and Barber (78) reported that CII amplitude increases rapidly as the ISI is increased from 0.1 to 9 seconds while CI and CIII show little or no adaptive effects. The increase in CII amplitude with increasing ISI shows a duplex linear function with a steep slope up to between 1 and 2 seconds ISI, above which the slope is more gradual. Psychological factors such as expectation appear to only affect the second part of the curve, so they would not be significant under most conventional recording conditions. Barber and Galloway (119) also found that the actual ISI value is of more importance in the determination of CII amplitude than the ratio of stimulus duration to ISI.

For presentation times of up to 50 msec, presentation time is interchangeable with contrast, showing that the CI-CII amplitude behaves according to a contrast equivalent of Bloch's Law (38, 73, 39, 115). Spekreijse, Van der Tweel and Zuidema (38) showed that CI-CII amplitude increases linearly with increasing presentation time, saturating at

higher levels. The slope of this function increases with increasing contrast, and the presentation time at which saturation occurs decreases. The interchangeability of contrast and presentation time is shown by plotting the log of the product of these two factors against VEP amplitude (115, 38). A single straight line plot is obtained, the intercept with the abcissa corresponding to the psychophysical threshold. This is therefore equivalent to the relationship already shown between VEP amplitude and log contrast. Due to the interchangeability of presentation time and contrast the VEP contrast threshold was found to be inversely proportional to presentation time (73). The relationship has been used to decrease stimulus contrast in VEP studies by decreasing the presentation time (120). However, this will cause overlap of the on and off responses, as the presentation must be at least 100 msec for these responses to be separated (71). The contrast equivalent of Bloch's Law does not apply to the amplitude of the off response, nor to the effect of disappearance time on the on response (38, 83). In addition, it has been found that the latencies of CI and CII are independent of stimulus duration and determined by contrast alone, and therefore do not obey Bloch's Law (115).

The waveform of the VEP is also dependent on the rate of contrast change at the onset and offset of the stimulus. Use of a gradual, rather than an abrupt rate of change attenuates the transient CI and off responses (57, 38, 117, 64). The CII component is relatively unaffected, so this technique has been used to isolate the CII component (117, 64, 92). The pattern reversal VEP latency increases as the contrast change becomes more gradual, the peak latency corresponding to the point at which maximum contrast is reached (82).

These results, and the interchangability of contrast and presentation time at short presentation times have led Spekreijse, Van der Tweel and Zuidema (38) to suggest that CII reflects an integrative mechanism with a time constant of about 50 msec.

2D Cortical Origins of the VEP

2D1 Cellular theories and dipole models

A simplified explanation of the sequence of events when a visual signal enters the visual cortex is put forward by Babel, Stangos, Korol and Spiritus (4). The signal enters the primary visual cortex in the fourth cortical layer, and is amplified at the synaptic relays with type II Golgi cells which then activate the pyramidal and large stellate cells. The stellate cells then depolarise the pyramidal cells in the fifth and sixth layers. Activation of the large pyramidal cells results in a post-synaptic depolarisation current which is recorded on the cortical surface as a positive wave. When this depolarisation reaches the apical dendrites in the superficial layers, the electrical potential is reversed to become a negative wave on the cortical surface as polarisation occurs.

Creutzfeldt and Kuhnt (52) also present an explanation of the generation of the VEP based on the pyramidal cortical cells. Slow surface potentials (more than 15-20 msec rise time) are assumed to reflect the post-synaptic potentials of the average cortical neurone. They propose that the seven waves of the flash VEP are due to a sequence of interactions between excitatory and inhibitory post-synaptic potentials. It is suggested that waves N1, N2, N3 and N4 (I III, V and VII in

their terminology) represent an excitation or depolarisation of most cortical cells and that P_2 and P_3 represent an inhibitory response or polarisation.

Intracranial recordings by Vaughan (121) show that the fields within the active cortex change with time as the distribution of inward and outward transmembrane current flows, due to synaptic activity. As the microelectrode passes through the striate cortex from the surface to the deeper layers, the early negative VEP components undergo an inversion in polarity. He suggests that this relates to an initial superficial excitatory post synaptic activation with a subsequent return of the current in the deeper layers.

These various theories show that the VEP waveform could reflect changes in potential arising from a single cortical generator area, although other work described later, suggests separate origins for the different components of the pattern VEP (e.g. 9, 122). Vaughan considers that the origin of the varying positive and negative charges can be thought of as an intracortical dipole generator which varies in strength over time as the internal currents change in strength and location.

The theoretical dipole model has gained wide acceptance in localisation studies of the VEP. In a review of the subject, Wood (123) shows that well accepted mathematical analysis of the potential distribution over the surface of a homogeneous spherical volume conductor arising from a dipole generator inside can be applied to the distribution of the VEP over the scalp. As the cells believed to generate the VEP are arranged in parallel with each other, perpendicular to the surface of the cortex, they can be considered as a dipole sheet of generators. This sheet can be considered in terms of a single equivalent dipole located

near the centre of the sheet.

In general, VEP studies have attempted to draw conclusions from qualitative comparisons between topographic VEP potential distributions and calculated potential distributions for theoretical models (9, 122, 124, 125). The most simple representation of the visual cortex is to consider the representations of the fovea on areas 17, 18, 19 as represented by a single equivalent dipole radial to the scalp, and the medial surface of the cortex (corresponding to the projections of the vertical octants of the field) as represented by an equivalent dipole tangential to the scalp. The potential distributions predicted by this arrangement for monopolar recording are shown in Figure 2.11 (125). The representation of the upper visual field on the under surface of the cortex and the lower field on the upper surface also lead to differences in predicted potential distribution for half field stimulation as shown in Figure 2.12 (124).

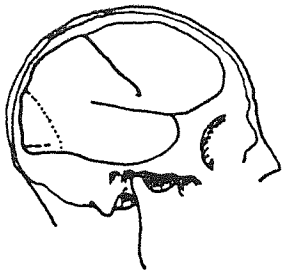
The position of the relevant generator sites must be taken into consideration when designing electrode placements. The foveal projections at the occipital lobe are ideally situated for VEP recording. The amount of the striate foveal projection exposed to the posterior surface in the human has been estimated at about 2^{o} (9). However, Drasdo's investigations (10) have shown that, on average, the right and left occipital poles are separated by about 3 cm, meaning that a significant portion of the medial surface will contribute to the signal recorded from a midline electrode appropriately placed. Drasdo calculated that electrodes 4% above the inion on the midline and 10% and 20% lateral to this are optimally placed to sample the foveal projections of areas 17, 18 and 19 respectively. Large field stimulation will stimulate larger areas of cortex, including the medial surface, leading to a more complex VEP distribution.

a) Dipole tangential to the back of the head

Figure 2.11 Theoretical potentials from equivalent dipoles in the brain (Horizontal plane) showing the predicted potentials arising from stimulation of a) the medial surface of one occiput, and b) the cortex parallel to the scalp. From Biersdorf (125)

Figure 2.12 Theoretical potentials from equivalent dipoles in the brain (vertical plane)

i) shows approximate position of occipital lobe (bounded by dotted line) and calcarine fissure (dashed line)



ii)

ii) shows the theoretical potential field distributions at the surface of a homogeneously conducting sphere from dipoles perpendicular (a) and parallel (b) to the surface

From Jeffreys (124)

Figure 2.13 Diagrammatic representation of the relative positions and orientations of the hypothetical dipoles representing the central and peripheral parts of the upper and lower visual field

From Michael and Halliday (33)

Schematic dipole models of the visual cortex present a simplified picture. The amplitude of the VEP is attenuated and the distribution made more diffuse by the layers of membrane, skull and scalp (123, 29, 9). The scalp response is 1000 times less than that on the cortex (4). The distribution and amplitude of the VEP recorded from the scalp are also dependent on the proximity of the generator site - the distribution over the scalp increasing and the amplitude decreasing with increasing distance (29, 123). The cortex is very convoluted (121) and different signals from different areas add and partially cancel in a linear relationship (121, 123). Individual variations in cortical architecture also cause variations in the scalp distribution of VEPs (121, 64).

Topographic VEP studies have attempted to reduce signal overlap and interaction by various methods. Many studies have used half field stimulation to confine the signal to one hemisphere and minimise cancellation of signals from the medial surfaces. Quadrant and octant stimulation has been used to minimise cancellation within the calcarine fissure (9, 13) and foveal stimulation has been used to confine the signal to the posterior, relatively flat, cortical surface (10). An alternative approach is to isolate components of the VEP by using stimuli with properties which are known to enhance one component but inhibit others (e.g. 64, 99). Another method of artificial component enhancement which has been used involves bipolar recording from electrode positions corresponding to the maximum and minimum amplitude of the component under investigation, or at positions where the component appears to reverse in polarity (e.g. 126).

Changes in the scalp distribution of apparent dipole sources during the course of the VEP can be interpreted as changes in the location

or orientation of a single source, or the combined effect of many sources with asynchronous activation.

2D2 Topographic VEP studies

Flash VEP - The topography of the VEP can best be studied by recording from a multiple array of electrodes. In this way, individual variations in the localisation of the VEP can be seen, and the relationship of ~~one of the VEP can be seen, and the relationship of~~ one component to another can be studied. Using such an array, Allison, Matsumiya, Goff and Goff (127) showed that the maximum amplitude of the positive components between 80 and 95 msec (P_1) and around 130 msec (P_2) evoked by a 10^{o} flash was localised over the occipital pole, while the distribution of the N70 (N_1) N110 (N_2) and N145 (N_3) components was more widespread over the posterior half of the head. Examination of these changes in potentials over time led Bourne, Childers and Perry (128) to interpret them as a rotating positive potential spread from the occipital area at up to 120 msec followed by a second between 190 and 310 msec. Nakamura and Biersdorf (32) also reported that the flash VEP spread in a clockwise rotation.

Nakamura and Biersdorf also showed that the early components N_1 P_1 and N_2 (up to 100 msec) were more prominent over the parietal areas and showed more consistent localisation than the later components. A study of these early components evoked by half field red stimulation under light adapted conditions showed a maximum amplitude over the hemisphere contralateral to the half field stimulated with a zero or opposite potential over the ipsilateral. The amplitude was zero around the occipital region, explaining the absence of the early components in

the flash VEP when recorded from the O_z electrode. They also showed a polarity reversal below the inion but this was not studied further due to contamination by potentials arising from the neck muscles. The authors suggest two possible dipole models to account for these results - either a single dipole below the occipital pole, tangential to the brain surface, or two radially orientated dipoles in the parietal areas, surface positive in the contralateral hemisphere and surface negative in the ipsilateral hemisphere on half field stimulation. The former dipole model would predict an origin in the primary visual cortex and the latter would predict an origin in secondary visual cortex. A later paper favoured the former model.

Components P_2 and N_3 showed a maximum amplitude near the midline but did not show localising properties with half field stimulation. Harding, Smith and Smith (129) also found conflicting localisation of the P_2 component, occurring ipsilteral to the stimulated half field in normal subjects but contralateral in patients with homonymous hemianopia.

Creutzfeldt and Kuhnt (52) report that the scalp distribution of the flash VEP is confined to the occipital area in neonates, spreading across the scalp in later years. They suggest that this reflects a gradual maturation of non-specific projection and association fibres which are known to be myelinated later than specific sensory afferent fibres.

Comparison of the distribution of flash and pattern VEPs shows that the flash is widely distributed, suggesting diffuse neural connections, while the pattern VEP is less variable and highly localised (51, 64). Research into the topographic distribution of the pattern VEP has shown

that it is consistent with the retinotopic organisation of the visual cortex (124, 13).

Pattern Reversal VEP - Halliday and Michael (13, 33) observed that the polarity of the major pattern reversal component was positive with maximum amplitude 2.5-5cm above the inion when a lower field stimulus was used, and negative with a maximum amplitude 7.5cm above the inion with an upper field stimulus. They concluded that this component originated in a surface positive dipole sheet in the extrastriate region of the visual cortex. These results and conclusions have been reached by other researchers (130). A striate origin for this component was considered unlikely, as octant stimulation did not show a distribution consistent with an origin in the cruciform arrangement of the striate cortex, nor was the amplitude maximum at the electrode over the occipital pole (within 2.5cm above the inion). They concluded that the polarity reversal was due to the folding of the surface of the visual cortex (Figure 2.13) so that an electrode above the inion would be facing opposite sides of the cortex representing the upper and lower fields. This theory was confirmed by recordings with a mid frontal reference which show that the upper field becomes positive when recorded from electrodes below the inion. When an ear reference is used, the traces from these lower electrodes are relatively flat, indicating that the ear reference is also picking up the signal from the upper field generator on the under surface of the cortex.

It would be expected that the upper field VEP would be of substantially smaller amplitude than the lower field VEP due to the larger distance of the generators from the electrodes. However, this was not the case, indicating that the orientation of the generator sheet with respect to the electrode is more important than the actual distance. However,

the lower field response predominates in the full field VEP recorded from electrodes above the inion as the prominent pattern reversal component is positive.

Left and right half field stimulation of radius 7.9^{o} elicited a clear positive component over the hemisphere contralateral to the half field stimulated, as would be expected from anatomical considerations. However, later work using a larger field of 16^{o} radius and checks of 50 minutes showed a surprising lateralisation of the response over the hemisphere ipsilateral to the half field stimulated (131). Two alternative explanations of this result are either that the signal is actually generated in the ipsilateral cortex or that the electrodes over the ipsilateral hemisphere are in fact ideally placed to record potentials arising from the medial surface of the contralateral hemisphere. The latter explanation was proved to be the more plausible by recordings from patients who had had a hemispherectomy (132). The VEP was still recorded over the ipsilateral side, despite the absence of an occiput under these electrodes.

When a foveal half field stimulus of 2^{o} radius was used, the VEP was lateralised over the contralateral hemisphere, consistent with the cortical generators. Barrett, Blumhardt, Halliday, Halliday and Kriss (131) attributed this to the different orientation of the central field representation on the posterio-medial surface of the scalp.

Harding, Smith and Smith (129) confirmed that field size is the crucial factor in the lateralisation of the half field response in normal subjects. Using a transverse row of electrodes 10% above the inion referred to a mid frontal electrode they showed that the ipsilateral

response shown with half fields of 14^{o} radius became slightly contralateral when the radius of the field is reduced to 2.5^{o}. However, reduction of the check size in a 14^{o} radius half field does not affect the ipsilateral lateralisation of the VEP. This was confirmed by studies using multiple electrode arrays (130, 133).

The exact distribution of the half field pattern reversal VEP in a transverse row of electrodes consists of a maximum over the midline electrode with a gradual reduction in amplitude over the ipsilateral electrodes. Bipolar linkage of these electrodes will therefore give the appearance of a contralateral localisation of the response since this is the point of steepest potential gradient (134, 131, 79). Comparatively little response will be recorded over the bipolar ipsilateral electrodes as they are each picking up an evoked response of approximately equal amplitude. It has also been shown (132) that the transverse distribution of the full field VEP is equivalent to the addition of the distribution of the two half fields, that is, a maximum at the midline with a gradual amplitude reduction either side.

Pattern onset-offset VEP - Investigations into the effect of upper and lower half field stimulation on the pattern onset VEP show similar results to that observed with pattern reversal stimulation (124). Lower field stimulation elicits a positive CI and a negative CII component, maximum 2-5cm above the inion, and upper field stimulation produces a VEP of opposite polarity, maximum at 5-10cm above the inion. However, CI and CII show different distributions to right and left half field stimulation, indicating that they are of different origin (124, 9, 122).

The CI component has clear lateralising features, consistently appearing over the hemisphere contralateral to the visual half field stimulated, as would be predicted by anatomical considerations (9, 10, 75, 135). A transverse row of electrodes show a polarity reversal across the midline and this, in addition to the polarity reversal in a longitudinal direction observed above, led Jeffreys and Axford (9) to suggest that CI is produced by surface negative activity within the cruciform configuration of the striate cortex. This hypothesis has been accepted by other researchers (136, 137, 92). However, this theory supposes that the CI component is recorded from the back of the hypothetical negative dipole sheet as CI is positive in polarity.

Jeffreys and Axford could not obtain a CI component when a small central field of 2^{o} radius was used and therefore concluded that it does not arise in the central representation of the striate cortex on the occipital pole. However, Drasdo (64) obtained a clear CI component with a foveal stimulus of 2.5^{o} diameter, recorded from a transverse row of electrodes optimally placed to sample the foveal projections of areas 17, 18 and 19. This row was about 3.5cm lower than the electrodes used by Jeffreys and Axford. The advantage of Drasdo's foveal field is that only the foveal projections on the outer convexity of the scalp are stimulated. These signals can easily be picked up by appropriately placed electrodes and are easier to interpret than signals arising from the medial folded areas of visual cortex. With this electrode array, Drasdo found that CI predominated over areas 18 and 19 when large stimulus details were used and was fairly equally distributed over areas 17, 18 and 19 when small details were used. The apparent interaction of CI and CII at high spatial frequencies (mentioned earlier) makes the exact magnitude of CI over area 17 difficult to evaluate.

Lesevre and Joseph (75) consider the polarity reversal of CI with upper and lower field stimulation and the bipolar characteristics across the midline to be more consistent with an origin in surface positive generators in area 19. This would also be more consistent with the 4cm difference in the location of maximum amplitude upper and lower field VEPs. The VEPs recorded by Parker, Salzen and Lishman (137) using sine wave gratings reproduced the polarity inversion of CI to quadrant stimuli reported by Jeffreys and Axford, and they therefore accept the theory of a surface negative striate origin of CI. However, they suggest that the appearance of an early negative component at high spatial frequencies (equivalent of Drasdo's Co) could be a CI component of reversed polarity arising from the portion of exposed surface negative striate cortex exposed at the occipital pole. This would contradict their earlier observations and those of Drasdo which indicate a latency increase in CI at high spatial frequencies and would therefore indicate that the CI component is in fact the succeeding positive component.

The prominent CII component was shown by Jeffreys and Axford (122) to reverse in polarity between lower and upper field stimulation, but not between left and right half fields. From this they deduce an extrastriate origin of CII. CII was also shown to contain a large contribution from the central 1^{o} of the visual field (122) and is maximum over the midline (39).

Drasdo (10) found that the CII component to a foveal stimulus was of maximum amplitude over the foveal projection of the striate cortex. The apparent negative component Co observed at high spatial frequencies and believed to be the leading edge of CII is also maximum in amplitude

over the midline, indicating a striate origin. This latter observation was confirmed by Lesevre and Joseph (75) and supported by showing that this negative component disappeared when the central 5^{o} was occluded (135). Lesevre and Joseph considered area 17 to be an unlikely source for CII as it does not show the amplitude differences between macular and paramacular stimulation they would expect from the striate area. They consider area 18 to be the most probable site.

There have been few reports on the topography of the CIII and offset components. Jeffreys (39) suggested that CIII arose in the extra-striate cortex. A study by Kriss and Halliday (84) indicated that the distribution of the offset response over the scalp showed a greater similarity to that of the reversal rather than the onset VEP.

Clearly, there is still some way to go before agreement is reached on the generator sites of the VEP. A fuller understanding of this question will greatly advance the uses of the VEP in both visual research and clinical diagnosis.

CHAPTER 3 PSYCHOPHYSICAL MEASURES OF SPATIAL AND TEMPORAL VISION

3A VISUAL ACUITY

3A1 Neural factors determining visual acuity

3A2 VEP measurement of visual acuity

3A3 Visual acuity in pathology

3B VISUAL MODULATION TRANSFER FUNCTIONS (MTF)

3B1 Theory

3B2 Spatial and temporal modulation transfer functions

3C THE SPATIAL MTF OR CONTRAST SENSITIVITY FUNCTION (CSF)

3C1 The psychophysical CSF curve

3C2 VEP measurement of the CSF curve

3C3 Channel theory of spatial processing

3C4 The CSF in pathology

3D THE TEMPORAL MTF OR DE LANGE CURVE

3D1 The psychophysical de Lange curve

3D2 VEP measurement of the temporal MTF

3D3 Neural factors in the processing of flicker

3D4 The de Lange curve in pathology

3A VISUAL ACUITY

Visual acuity (VA) is a measure of the high spatial frequency resolution limit of the visual system, with full refractive correction. Traditionally, this threshold has been measured in four different ways: (138, 139).

i) The minimum detectable threshold is the smallest perceptable object. The thinnest dark line that can be perceived is 0.5 seconds of arc, which has been found to correspond to a 'dip' in retinal illumination of just 1% of the surrounding luminance level. The limit of resolution of a bright object, however, is determined by the brightness, rather than the angular size, of the object, due to the enlargement of the retinal image by light scattering within the eye.

It is, therefore, more appropriate to measure the resolution limit of the eye with dark objects on a light background.

ii) The minimum perceivable misalignment, or vernier acuity, is measured by displacement of one target segment relative to another in close proximity. The eye can perceive a displacement of as small as 2 seconds of arc.

iii) The minimum angle of resolution is the minimum angular distance between two objects while still appearing as separate. This is about 1 minute of arc when measured with pairs of dots or bars, or parallel light and dark bars (gratings).

Gratings are favoured for research, as the parameters are easily varied and measured, and calculations of the light distribution in the

retinal image are possible. They are used extensively in the determination of contrast sensitivity functions (Section 3C).

VA is determined as the highest spatial frequency (or finest grating) resolved, measured directly or by extrapolation of the contrast sensitivity function. This value is close to the threshold and is claimed to be higher than VA measured with a Snellen chart (140, 141). However, gratings are not the most suitable targets for screening for refractive error, as VA might be considerably over or under estimated in astigmats, depending on the relationship between the axis of astigmatism and the orientation of grating.

iv) The minimum recognisable threshold is the smallest object that can be named, or orientation identified, by the subject. This is the most common test in clinical use, as it is most easily understood by subjects of all ages and levels of intelligence.

The most frequently used target is the Snellen chart, consisting of black alphabetical letters in high contrast with a white background, decreasing in size from line to line. The limbs of the letters are one fifth of the width of the whole letter, and the distance at which these subtend 1 minute and 5 minutes of arc respectively at the eye is specified. In conventional VA notation, this value is the denominator, while the numerator of the 'Snellen fraction' represents the actual distance of the observer from the chart. This is usually 6 metres, at which a negligible amount of accommodation (0.17D) is required.

VA values measured at different distances can be equated by expressing the results in decimal form or as the reciprocal, which is the minimum

angle of resolution (MAR). $^{6}/_{18}$ can therefore be expressed as 0.33 or as a minimum angle of resolution of 3 minutes of arc. 'Normal' VA is defined as $^{6}/_{6}$ or 1 minute of arc.

"Landolt C" or "Illiterate E" charts have been designed to overcome the possibility of guessing letters on their overall shape and for use with illiterate patients by using one letter only at different orientations and sizes. However, this provides fewer possible variations and is not as easily understood by some patients.

3A1 Neural factors determining visual acuity

The attenuation of high spatial frequencies by the optical components of the eye is considered in Section 4B. The major neural limiting factor is the ganglion cell receptive field density. Sampling theory expresses in mathematical form the theory of Helmholtz that, in order for a grating to be resolved, two stimulated receptors must be separated by at least one relatively unstimulated receptor (142, 143). Figure 3.A.1 shows that the highest resolvable spatial frequency corresponds to the stimulation of neighbouring receptors by alternative bright and dark bars - the separation between the receptors (s) being equivalent to half the wavelength. VA is therefore equal to $^{1}/_{S}$, or MAR equals S. Green (142) showed this to be valid in the central 2^{o} of the retina as the MAR measured with interference fringes corresponded to estimates of intercone separation. Rovamo and Virsu (144) estimate a linear cone density in the fovea of 121 cones/deg which would predict a high frequency limit of about 62 c/deg, according to sampling theory. This fits well with the neural limit of the eye measured with interference fringes (145).

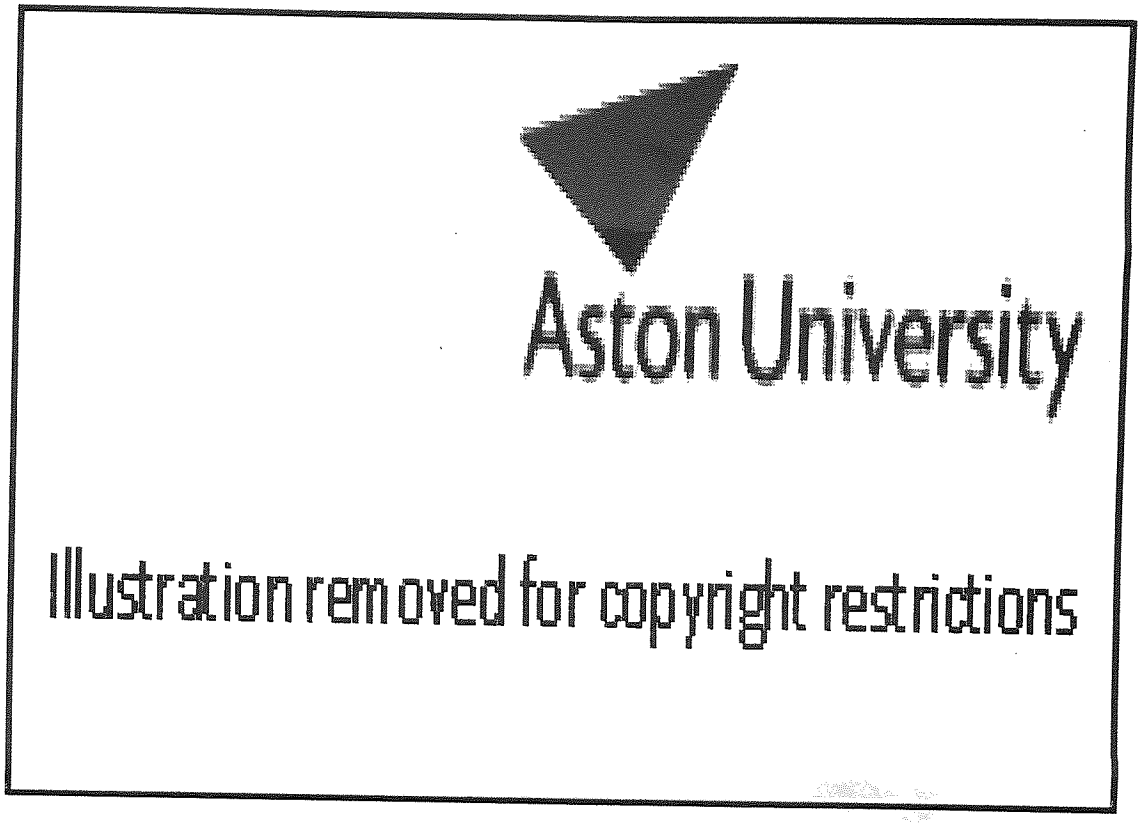


Figure 3A1 Sampling theory. A sampling array of frequency 2fc optimally samples a grating of frequency fc, with no information loss, as shown by the reconstruction. Frequencies lower than the critical value, such as fc/2 are oversampled but reconstructable. Frequencies which are high than the critical value, such as 3fc, are undersampled and 'alias' as lower frequencies. From Hughes (143)

However, the failure of this relationship beyond the central 2^{o} reported by Green is due to the fact that the resolution of the retina is limited by the receptive field, or ganglion cell separation, which is only equivalent to cone separation at the fovea (by a factor of 0.9 : 1) (144, 146). The evidence for this relationship is presented by Drasdo (146). Results from different studies are re-plotted to show firstly a linear relationship between the peripheral retinal angle up to 35^{o} and the reciprocal of the square root of ganglion cell receptive field density (or ganglion cell receptive field separation). Secondly, a linear relationship was shown when peripheral angle was plotted against MAR, receptive field separation and cortical magnification^{-1}.

Cortical magnification (M) is the linear extent of visual cortex corresponding to a degree of arc in visual space and the square of this value gives the area of cortex corresponding to a solid degree. M is proportional to $\sqrt{}$ganglion cell receptive field density (D_r) or, alternatively M^2 is proportional to D_r. (144, 146). Rovamo and Virsu cite evidence for four basic assumptions underlying this relationship : (1) the density of afferent fibres entering the striate cortex is constant everywhere (2) each retinal ganglion cell innervates a constant size area of the striate cortex (3) there is little excitatory convergence onto the cells of the lateral geniculate nucleus and visual cortex (4) the whole striate cortex consists of a set of anatomically identical building blocks.

Resolution, or VA, is therefore directly proportional to M (146, 147). This relationship was shown by Rovamo and Virsu to apply to resolution

at various retinal eccentricities, leading to the statement that "we can assume that the sampling performed by visual cells has the same constant relation to $D^{0.5}$ and M at all retinal locations and spatial frequencies" (the invariance principle).

The size of receptive fields, or sampling units, in use is partly determined by the illumination level. Foveal VA increases linearly with increasing log luminance of the test object (148) due to the decrease in receptive field size. At values approximating to room illumination photopic VA reaches a plateau (138). Over a wide range of luminance levels, the natural pupil adopts a size very close to the optimum for visual resolution (149).

These physiological mechanisms are most effective when the eye is fully adapted to the prevailing light level, so it is important that the room illumination is approximately equal to that of the test field (138, 150).

3A2 VEP measurement of visual acuity

The VEP is an ideal objective technique for assessment of the resolving power of the visual system, as it reflects visual processing up to the level of the cortex, in contrast with other objective methods such as retinoscopy or automated refraction which can only determine the refractive error of the eye (151). Important applications of this technique are the study of development of VA in babies (152, 153, 154, 91) and the study of amblyopia (Section 4A).

The VEP pattern size function has been used to determine VA by the following methods:

i) Pattern size* producing peak VEP amplitude - Estimation of VA by comparison of the 'peak pattern size' with that of an adult with $^{6}/_{6}$ vision has been used in studies of amblyopes (155, 156) and infants (152). The assumption behind this method is that the 'peak pattern size' reflects relative receptive field size (105, 157, 91).

However, the peak VEP amplitude is a suprathreshold measurement, and cannot strictly be considered as a measurement of VA which is the high frequency threshold (153). In addition, as the peak pattern size is larger than the threshold pattern size, the response is less likely to be purely contour-specific (91). Despite this, a study of the development of VA in the first 8 months of life show a similar decrease in both peak and threshold check sizes indicating that this is a valid method in the estimation of VA in such cases, where the level of noise makes determination of threshold unreliable (91).

ii) Estimate of the limit of high spatial frequency resolution:

(a) Determination of the smallest pattern* which will elicit a VEP (151, 154, 158, 159) - This is the most direct method to use in the clinical situation, but the speed and precision of the VA estimate depends on the background noise level of the VEP, and the number of recordings necessary to determine the presence or absence of a VEP with any confidence.

(b) Determination of the pattern size* corresponding to a VEP of zero amplitude (158, 153, 160, 156, 161, 162, 163) - This should give a VA value very close to threshold, as the zero microvolt

criterion has been shown to correlate well with the limit of perception (31).

The validity of this method has been claimed by Tyler, Apkarian, Levi and Nakayama (161, 162) to rest on the linear relationships between VEP amplitude and log contrast at near threshold levels (31) and between log contrast sensitivity and spatial frequency above 5 c/deg (145). However, the latter relationship applies to contrast threshold measurements, so care must be taken in applying it directly to supra-threshold VEP amplitude measurements. Spekreijse (164) therefore considers that the most accurate VEP determination of VA is found by extrapolation of the plot of check size against VEP contrast threshold, rather than VEP amplitude.

iii) Absolute amplitude measurements - Within individuals, VEP amplitude has been shown to parallel changes in VA caused by optical blur (Section 4B) and recovery after optic neuritis (111). However, the large variation in amplitude between individuals means that it is very difficult to predict the VA of a patient on the basis of VEP amplitude alone, and this approach has not proved successful in the assessment of amblyopia (Section 4A). Chiba, Adachi-Usami and Asanagi (165) attempted to reduce this variability by using 12Hz. pattern reversal stimulation to record the VEP amplitude corresponding to various levels of VA produced by optical blur under cycloplegia.

* A fuller description of the relationship between VA measurement in minutes of arc and spatial frequency of grating and checker-board stimuli can be found in Appendix 1.

Although the 55 controls gave consistent results, the amplitude values obtained were still higher than those of 23 patients with reduced VA due to central serous retinopathy, indicating that additional factors contributed to the amplitude reduction in the pathological condition.

The type of patient who is unable to give a subjective VA result is likely to have a limited span of attention, and so VEP techniques should be as short as possible. Regan (156) has developed a technique which reduces the time taken to obtain a VEP amplitude v check size plot from about 30 to 2 minutes by measuring the steady state VEP amplitude while all the spatial frequencies are presented in zoom cycles. Tyler, Apkarian, Levi and Nakayama (161) have developed this technique still further and claim that a complete amplitude v spatial frequency plot can be obtained in 10 seconds.

3A3 Visual acuity in pathology

VA abnormality can be detected by comparison with age matched control values. Frisen and Frisen (166) show that the 90% VA threshold shows a rapid increase from 1.0 at 10 years up to a maximum of 1.57 at about 25 years. This is followed by a gradual decline, becoming more marked after the age of 60 and eventually reaching a level of 1.1 at 75 years. However, they emphasise that substantial neural loss can occur before VA drops below normal age limits, for example, a drop in VA of 1.5 to 1.0 corresponds to a loss of 56% of the foveal cones, or foveo-cortical neural channels, while still remaining within the definition of normal VA. It is recommended that factors such as previous VA (where available) and asymmetry between the eyes are taken into account and VA of below 1.0 should always be considered as abnormal (167).

VA can be reduced by a lesion in any of the structures involved in the

transmission of the image onto the retina and through the visual system.

The effect of a lesion is much more marked if it affects the formation or processing of the foveal image.

Any lesion which stops or scatters the light passing through the optical media of the eye will prevent the formation of a sharp image on the retina, reducing the VA. Such factors can include growths, opacities, distortions, deposits and haemorrhages. Vision may be reduced by refractive error though, according to clinical usage, this should not strictly be defined as a reduction in visual acuity (168).

Retinal lesions which affect the macula can markedly affect the VA, while peripheral lesions might pass unnoticed by the patient. The resolving power of the fovea can also be reduced by any pathology which causes an increase in the separation of the receptors, such as oedema.

The following effects of visual pathway lesions on VA have been reported by Frisen (167) :

Retrobulbar optic nerve lesions markedly affect central VA. The papillomacular fibre bundles seem to be particularly vulnerable, possibly due to their high metabolic demand or to an easily disturbed capillary circulation. Another possibility is that the receptive fields at the fovea do not overlap like those in the periphery so the effect of damage to any of these fibres will be more marked. In these cases, the VA loss will nearly always be unilateral.

Chiasmal lesions can cause very characteristic field defects. VA reduction relates fairly well with the site and severity of field

defects, but not to the position of tumours. Cogan (2) considers loss of VA as an important sign which often differentiates a chiasmic from a post-chiasmic lesion.

After the chiasma, the fibres from the two halves of each retina run in completely separate optic tracts. Frisen and Cogan both agree that the resolving power of half the fovea is as good as that of the whole fovea, so VA is preserved in the presence of a unilateral lesion. The anatomical arrangement of the visual pathway s (Figure 1.1) means that a single lesion could only affect the fibres from both halves of each fovea at the occipital lobes. This preservation of VA in the presence of a unilateral lesion such as a complete hemianopia is related to a concept known as 'macular sparing'. This refers to the relative absence of hemianopic defects in the central and paracentral areas often associated with parietal or parieto-occipital lesions. Cogan considers that this could be an artifact of testing, or possibly reflects higher thresholds of visbility in the central region. The latter explanation would be consistent with the progressive decrease, and then disappearance of the macular sparing with the advance of the lesion. A homonymous hemianopia with normal VA is characteristic of a post chiasmal lesion.

3B VISUAL MODULATION TRANSFER FUNCTIONS (MTF)

3B1 Theory

The measurement of the spatial and temporal properties of the visual system has developed considerably over the past 25 years with the application of electronics principles (169).

The performance of an electronic system can be assessed by comparison of the phase and amplitude of the output signal with that of the known input signal. Once the response of a sine wave to a linear system has been determined, Fourier analysis enables the response of any complex waveform to be predicted by considering each one as the sum of a number of sine waves of different phase and amplitude. The sine wave equal in frequency to the repetition rate of the original waveform is the fundamental and all other components, the harmonics, are integral multiples of this frequency. A square wave consists of a fundamental plus odd harmonics with amplitudes of $^{1}/_{3}$, $^{1}/_{5}$ etc. of the fundamental amplitude (170, 171).

The form of a sine wave passing through a linear system remains unchanged, even though the phase and amplitude might be altered. However, a non-linear system will distort the wave. The output form of a sine wave will therefore show whether an unknown system was linear or non-linear (172).

In the measurement of the spatial visual system, the input signal consists of a grating with a sinusoidal luminance profile. The number of bars per degree of visual angle is determined by the spatial frequency and the contrast of the bars is determined by the modulation of the sine wave (Figure 3B1). In the measurement of temporal vision the luminance of the input signal flickers sinusoidally in time. The rate of flicker is determined by the temporal frequency and the luminance variation is determined by the modulation of the signal.

It is not possible to have negative luminance values (unlike electrical current) so the sinusoidal variation is superimposed on a steady luminance value. This determines the mean luminance of the input

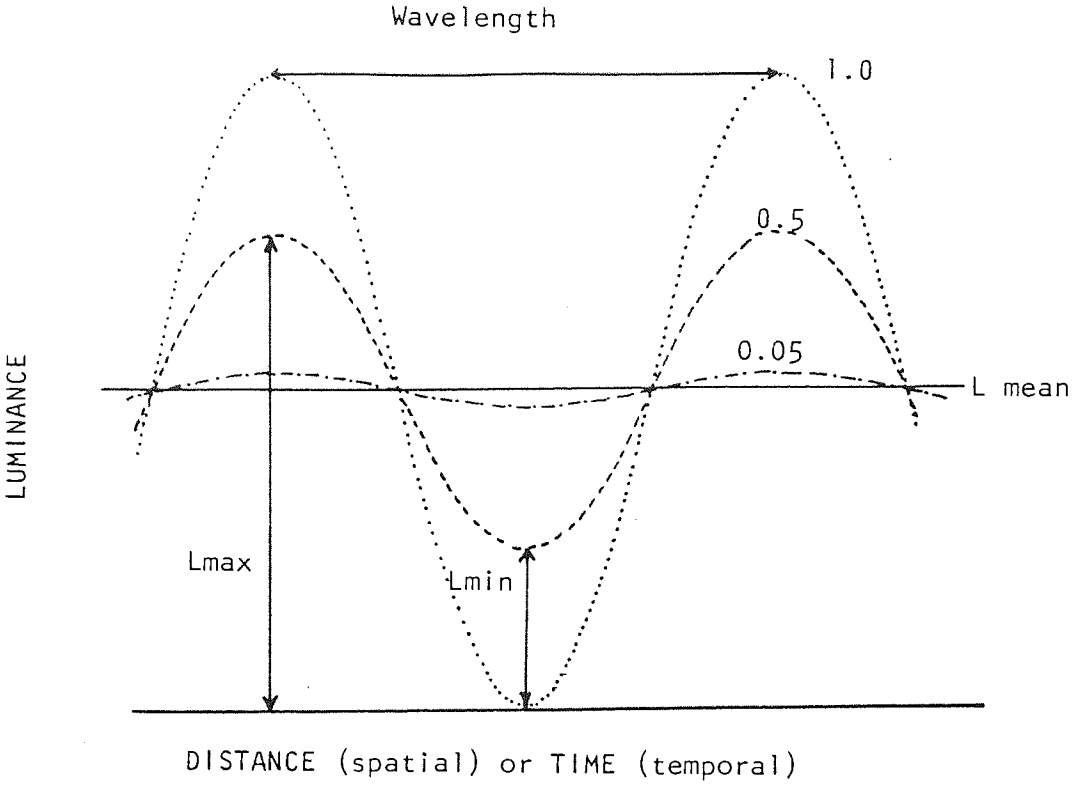


Figure 3B1 Characteristics of a sine wave stimulus showing modulation (or contrast) ratios of 1.0, 0.5, and 0.05, defined as Lmax-Lmin/Lmax + Lmin. Note that mean luminance does not change as contrast changes. Frequency of the sinusoidal luminance modulation is the reciprocal of the wavelength in cycles per degree (c/deg) in the spatial domain and cycles per second (c/sec or Hz) in the temporal domain

After Campbell and Green (145)

Figure 3B2 A simple schematic model for threshold judgments From Sperling (172)

signal and remains constant whatever the sinusoidal modulation. Constant mean luminance ensures constant adaptation of the retina, enabling linear assumptions to be made (173).

Modulation is defined by the following equation (139) which is independent of the mean luminance:

$$\text{Modulation} = \frac{(L_{max} - L_{min})}{(L_{max} + L_{min})} \qquad \text{(Figure 3B1)}$$

The minimum point of the modulation is only completely black (zero luminance) when modulation is 1.0 .

The amplitude of the output of the human visual system is more difficult to measure than that of an electrical system. Two approaches are used, subjective and objective.

The amplitude of the output signal is often determined subjectively by measurement of the threshold, which is assumed to be of constant amplitude. This represents the value at which the spatial or temporal modulation is just perceived and is therefore inversely proportional to the sensitivity of the visual system. The threshold is precise and easy to determine and corresponds to an input signal of low amplitude so that linearity can be assumed (170, 93).

Electrophysiological methods can be used to assess the amplitude of the output signal objectively in two ways. Firstly, the amplitude of the VEP can be measured directly. VEP amplitude is linearly related to log modulation in both spatial (31) and temporal (174) vision. However, above a certain level of modulation, saturation

occurs and the relationship is no longer linear.

The second approach is to determine the modulation required to elicit a response of constant amplitude. This constant amplitude might be an arbitrary value, or zero mivrovolts as determined by extrapolation of the linear amplitude versus modulation plot. The zero amplitude measurement has been shown to correspond to the psychophysical threshold (31, 174).

3B2 Spatial and temporal modulation transfer functions

The modulation transfer function (MTF) describes the relationship of the output of the visual system to the input modulation signal. Both spatial and temporal MTFs are usually plotted on log/log co-ordinates with frequency on the abcissa and sensitivity (reciprocal of threshold modulation) on the ordinate.

The sensitivity of the visual system is not the same at all frequencies. Both spatial and temporal MTFs show a peak sensitivity at intermediate frequencies, with progressive reduction at both higher and lower frequencies (Figures 3C2 and 3D1). The curve of the MTF plot defines the junction between visible and invisible modulation.

This curve can be considered to represent the attenuation characteristics of a hypothetical filter in the visual system (172). As these are threshold measurements, they are assumed to be within the linear range of the visual system (93, 170). This hypothetical linear filter is also clearly frequency dependent. However, threshold determination also involves a non-linear response, as the modulation is either 'seen'

or 'not seen'. Assuming that an input of constant amplitude is necessary to elicit a threshold response, regardless of frequency, then the frequency dependent functions must have occurred at a previous stage in the visual system (172). The study of the filter characteristics of the visual system is a very complex area which is beyond the scope of this thesis, but the most simple schematic representation is shown in Figure 3B2.

Details of the spatial and temporal MTFs of the visual system will be found in the following sections. To avoid confusion, and in view of possible problems of non-linearity, the spatial MTF will be referred to by the more common term 'Contrast Sensitivity Function' and the temporal MTF will be referred to as the 'de Lange Curve'.

3C THE SPATIAL MTF OR CONTRAST SENSITIVITY FUNCTION

3C1 The psychophysical CSF curve

Visual acuity measures the ability of the visual system to discriminate small objects at high contrast, but does not give any indication of the ability to resolve larger areas of lower contrast which are encountered in the visual world. The contrast sensitivity function (CSF) gives a much more complete description of the visual system by measuring the relationship between different values of size and contrast.

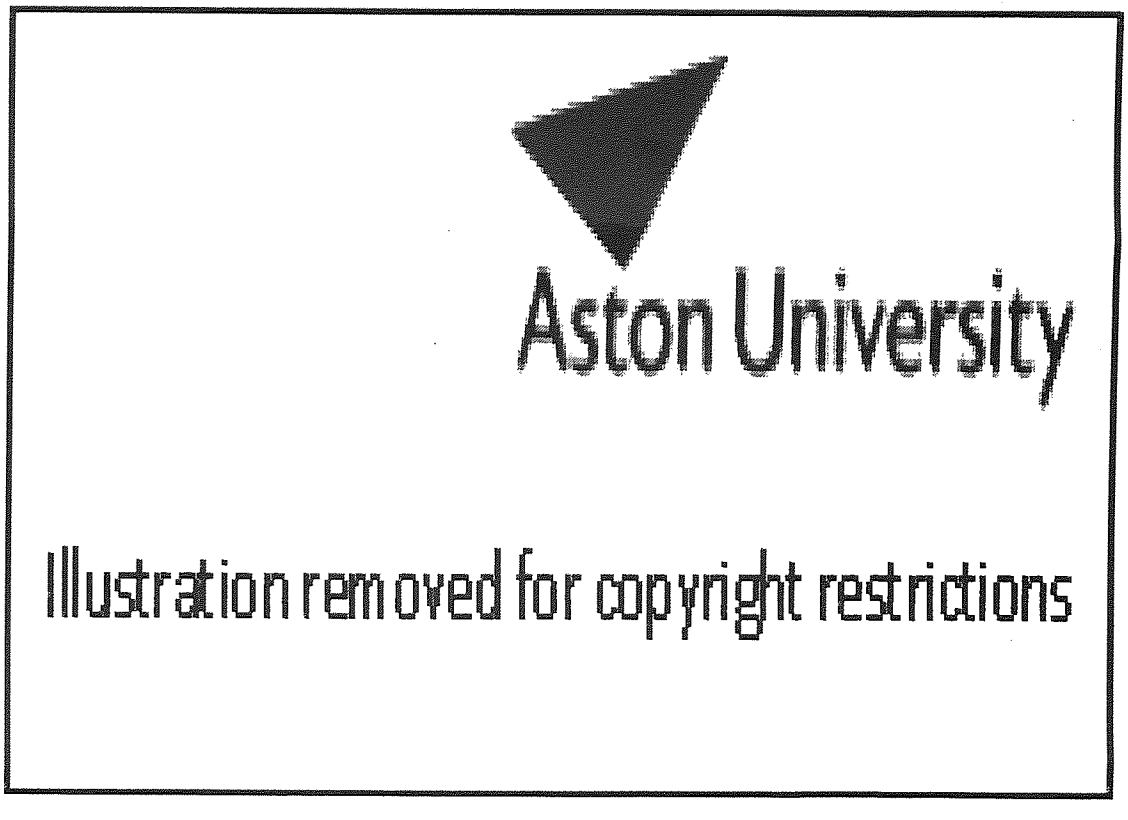
The CSF is an inverted U shape with a peak at intermediate spatial frequencies (Figure 3C1). The high frequency limit of the visual system at 100% contrast can be determined by extrapolation of the

Figure 3C1 The contrast sensitivity function plotted on a log/linear scale. Luminance 5 cd/m^2

From Abadi (16)

Figure 3C2 The contrast sensitivity function plotted on a log/log scale. Luminance 500 cd/m^2

From Campbell and Robson (182)



CSF plot to a linear spatial frequency axis, and is usually between 30 and 40 c/deg (175). This value theoretically corresponds to visual acuity - each bar of a 30 c/deg grating subtending 1 minute of arc at the eye. A log/log plot (Figure 3C2) will have the effect of contracting the high frequency portion and extending the low frequency section of the CSF curve and is used when both extremes of the curve are being studied.

Sine wave gratings for CSF measurement can be produced on oscilloscopes. Appropriate technical modifications can vary the spatial and temporal frequency, luminance, contrast and orientation of the gratings, and can also produce square wave gratings. Television systems are less expensive and can give larger, brighter displays, although it is more difficult to produce drifting or oblique gratings (175).

Arden (175) has produced a booklet of printed gratings for CSF screening. The six gratings cover the low spatial frequency range 0.2 to 6.4 c/deg. which is considered sufficient to reveal neural defects while remaining unaffected by refractive error. The contrast increases from the bottom to the top of each page, and the point at which the grating is first seen is measured on a scale at the side. The results are usually presented as the sum of the scores from the individual gratings. This 'Arden score' is raised by a defect in contrast sensitivity. It has been suggested that the accuracy of this method can be improved by the presentation of the gratings in a four alternative 'forced choice' format (176).

Printed gratings would not be the method of choice for detailed research, due to the difficulties in standardisation of luminance and

field size and the limited information provided by the method of scoring. However, they can be useful in a clinical setting for the identification of patients who would benefit from further investigation.

The Peak of the CSF Curve - Contrast sensitivity is maximum for gratings of about 4 c/deg when a field of between 3^{o} and 6^{o} is used (177, 178, 179, 180, 181, 182, 183, 184, 185, 145). However, a peak at frequencies as high as 10 c/deg has been found when a 1^{o} foveal stimulus is used (186, 187) and as low as 1 c/deg with a target 30^{o} from fixation (188) showing that the peak depends on the area of retina stimulated.

This apparent change in peak sensitivity has been studied in depth by Rovamo and Virsu (144, 147). Using a constant target size, they demonstrated a progressive decrease in contrast sensitivity and shift of the peak to lower spatial frequencies with increasing retinal eccentricity (Figure 3C3). They next increased the target size at each eccentricity to stimulate an equal number of ganglion cells and showed that the contrast sensitivity no longer decreased with retinal eccentricity, although the peak of the curve still shifted towards lower frequencies (Figure 3C4).

However, the CSF curve is found to be exactly the same for all areas of the retina if these results are replotted with spatial frequency defined in terms of the extent of visual cortex stimulated (cycles per mm) instead of the area of retina stimulated (cycles per degree) (Figure 3C5). The authors state that "the simplest interpretation of these results is that contrast sensitivity depends on the number of visual cells stimulated by a grating".

The peak of the CSF curve is also shifted towards lower spatial

SPATIAL FREQUENCY (c/deg)

Figure 3C3 Contrast sensitivity as a function of retinal spatial frequency and eccentricity showing progressive decrease in sensitivity and shift of peak to lower spatial frequencies. Method required discrimination between horizontal and vertical gratin

100 F

SPATIAL FREQUENCY (c/deg)

Figure 3C4 Retinal image size and spatial frequency scaled by M^{-1} to produce similar calculated cortical projection images at different eccentricities. Contrast sensitivity is now equal at each sensitivity, but the peak still shifts to lower spatial frequencies. Method and subject as above.

From Virsu and Rovamo (147)

Figure 3C5 Retinal image size and spatial frequency scaled by M^{-1} and plotted in terms of estimated cycles per mm on the primary visual cortex. When plotted in these terms, contrast sensitivity is shown to be equal for all eccentricities. From Rovamo, Virsu and Nasanen (188)

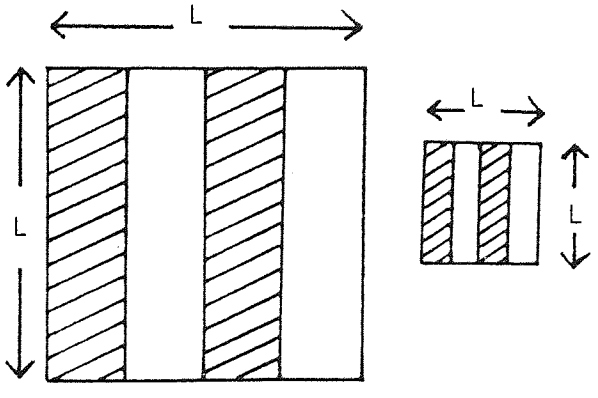


Figure 3C6 Stimuli equated in terms of area and spatial frequency, or 'square cycles'. In both cases, side length, L, is equal to twice the spatial wavelength of the grating, giving an area of 4 square cycles

frequencies with decreasing luminance due to the use of larger receptive fields at lower adaptation levels (190, 191, 189).

High Spatial Frequency Attenuation - Contrast sensitivity decreases exponentially with increasing spatial frequency (145). This section of the CSF curve is particularly sensitive to optical blur, and the effect of refractive error and optical degradation within the eye are described more fully in Section 4B.

However, when optical effects are bypassed by the use of laser interferometry to generate gratings on the retina, the CSF curve still shows high frequency attenuation. Comparison of these results with the CSF curve obtained by viewing a grating under normal conditions show that the optics of the eye only account for one third of the attenuation in the 30-40 c/deg range, with a 2mm pupil (145).

The remainder of the attenuation must, therefore, be due to neural factors, such as the limitations of the retinal mosaic. An additional neural factor affecting high frequency sensitivity is the level of light adaptation (189). High frequency sensitivity has been shown to be proportional to the square root of the average luminance within the mesopic range (up to 24 cd/M^2) but becomes less dependent at higher luminance levels (190).

Changes in pupil diameter affect contrast sensitivity at high spatial frequencies, as they influence both factors mentioned above - retinal luminance and optical blur. The effect of pupil size on optical image quality is considered more fully in Section 4B.

Low Spatial Frequency Attenuation - Attenuation of the CSF curve at low spatial frequencies has often been attributed to neural properties of the visual system, such as lateral inhibition (192, 193, 191). This attenuation decreases with increasing stimulus area, while the high frequency response is nearly independent of target area for targets above 0.5^{o} diameter (192). This can be partly attributed to the increase in receptive field size with eccentricity.

Another factor is the increase in the number of cycles as the area of the stimulus is increased, which experiments have shown to be the dominant influence at low spatial frequencies. In this region, contrast sensitivity is proportional to the number of cycles in the stimulus and independent of spatial frequency (187, 194). The number of cycles corresponding to the upper limit of this effect has been estimated by different investigators as eight (187) six (195) five (194) and four (182). This critical number has been found to be proportional to luminance (187).

Virsu and Rovamo (147) took these observations further by considering them in neural terms. It has already been shown that the response of the visual system is constant, regardless of retinal location, as long as a constant number of cortical neurones are activated. This is achieved by equating stimuli in terms of area and spatial frequency, or 'square cycles'. A square cycle is a unit in which each side is equal to the spatial wavelength of the grating (Figure 3C6), for example, a low spatial frequency grating with a large area and a high spatial frequency grating with a small area could be considered as equivalent stimuli in terms of square cycles and number of cortical neurons stimulated. When considered in these terms, the response of

the visual system to increasing number of square cycles saturated at approximately the same number for all spatial frequencies. This saturation value was about 144 square cycles, which corresponds to 12 cycles across a square field. Inspection of these results suggests that the saturation number is slightly lower at low frequencies, bringing the critical number close to that estimated by other investigators.

Low spatial frequency sensitivity is also progressively improved with increasing temporal modulation of the stimulus (191, 25) (Section 1C). When the bars of the grating are modulated in counterphase at temporal frequencies of 6Hz and above there is no low frequency attenuation (25) (Figure 3C7). The maximum overall CSF curve is obtained at stimulus frequencies of about 8Hz (191). The interaction between spatial and temporal frequency is diagramatically represented in Figure 3C8.

3C2 VEP measurement of the CSF curve

It has been shown in Section 2C3 that a plot of VEP amplitude against log contrast is linear, with a close correspondence between the point at which the extrapolated plot crosses the contrast axis and the psychophysical threshold. It has been found that the electrophysiological CSF curve obtained by plotting these extrapolated thresholds against spatial frequency corresponds very closely with the psychophysical CSF curve (31, 196).

Saturation of the VEP amplitude at higher levels of contrast means that suprathreshold VEP amplitude - spatial frequency plots must be interpreted with caution and cannot be strictly equated with the psychophysical CSF as this is a threshold function (164). However,

Figure 3C7 The CSF curve for different temporal frequencies. From Robson (25)

Figure 3C8 Spatio-temporal threshold surface showing the effects of combined spatial and temporal sine wave modulation on the contrast sensitivity. From Kelly (191)

qualitative similarities between these two functions have been found in strabismic, anisometropic (140) and meridional (197) amblyopia, and the recovery of cerebral blindness after hypoxia (198).

It has been suggested that correspondence between psychophysical and evoked potential defects in pathology indicate lesions up to and including the visual cortex, while psychophysical defects in the presence of normal evoked potentials indicate damage to higher levels of visual processing (198, 197, 199). However, the VEP latency and CSF results in a study of multiple sclerosis were so different that the authors concluded that the two measures must be determined by completely different pathways (200).

3C3 Channel theory of spatial processing

Much evidence has been published over recent years to suggest that the CSF curve represents the combined response of a wide range of independent spatial frequency channels. This work is comprehensively reviewed by Campbell (201). This forms the basis of the theory that the visual system acts according to Fourier principles, with information about the constituent sinusoidal components of the image transmitted separately through the neural channels. Such a theory is, in turn, based on evidence that the visual system is capable of linear behaviour, which is provided by the study of the X cell system (202).

Campbell and Robson (182) have provided evidence that the behaviour of the CSF curve can be predicted by Fourier principles. They showed that the thresholds of different waveforms can best be described by considering the fundamental and harmonics as separate channels. Therefore, a sine wave and square wave grating will appear identical at high

spatial frequencies, as the frequencies of the square wave harmonics exceed the upper frequency limit of the eye and the threshold is determined by the fundamental amplitude alone. However, contrast sensitivity with the square wave is higher by a factor of $4/\pi$ (1.273), corresponding to the ratio between the amplitudes of the fundamentals of the two waveforms. At low spatial frequencies contrast sensitivity with the square wave grating is up to 5 times higher, due to the contribution of the 3rd harmonic. The point at which the curves join denotes the threshold of the 3rd harmonic (Figure 3C9).

Similarly, at spatial frequencies too low for the fundamental to be perceived, the visbility of a square wave is determined by the harmonics alone. In this region it is impossible to distinguish between a square wave grating and a 'missing fundamental' grating (a square wave grating consisting of the harmonics only) (Figure 3C10). Strangely enough, the visual system 'fills in' the missing fundamental to give the appearance of a square wave grating in both conditions - although the gratings become invisible as soon as the higher harmonics are removed (Figure 3C11) (204, 205, 203).

Pathological processes producing spatial frequency selective CSF defects have provided further evidence of neural channels. If the CSF curve were the response of a single channel mechanism, pathology would affect the curve uniformly across the spatial frequency spectrum. Specific low or medium 'notch' CSF defects have been reported in multiple sclerosis (180) and cerebral lesions (206).

Both these studies reported that the magnitude of these defects were consistent with the bandwidths of the spatial frequency channels

SPATIAL FREQUENCY (log scale)

Figure 3C9 Raised low frequency sensitivity to a square wave stimulus due to the contribution of the 3rd harmonic. After Campbell and Robson (182)

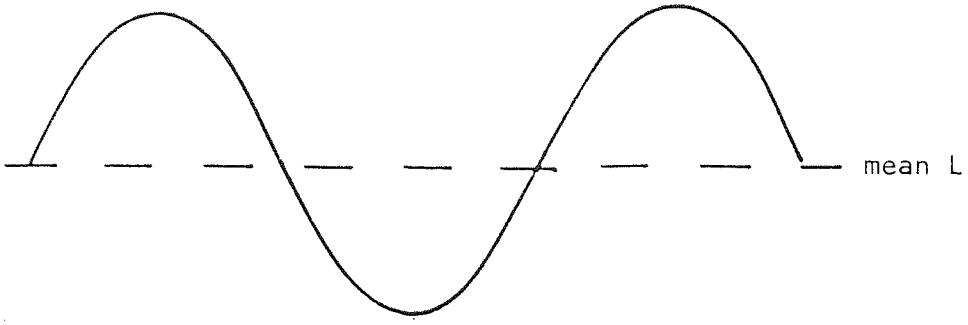
sine wave

square wave

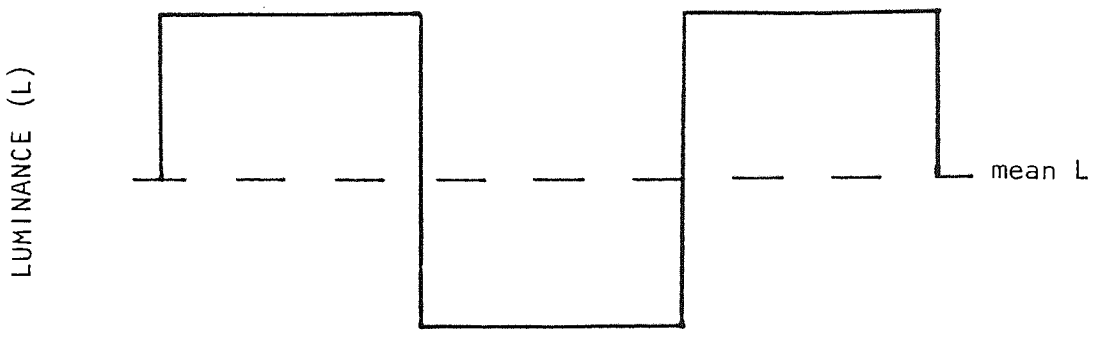
SPATIAL FREQUENCY (log scale)

Figure 3C11 The missing fundamental illusion. To schematically show spatial and contrast constraints on the illusion. From Sullivan and Georgeson (204)

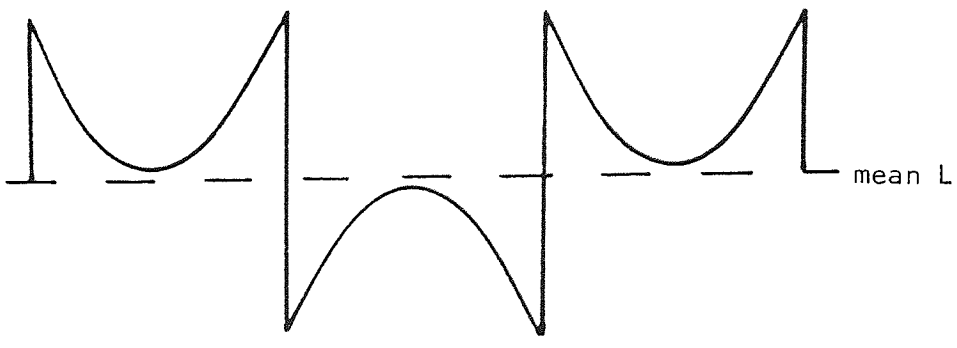
Figure 3C10 Luminance profiles of three types of grating stimuli of equivalent contrast and spatial frequency



a) Sine wave



b) Square wave



c) Missing fundamental wave

DISTANCE

measured by Blakemore and Campbell (207). The latter investigators showed that the elevation in threshold produced by adaptation was specific to the spatial frequency of the adapting grating. Comparison of the CSF before and after adaptation shows a 'notch' depression in the curve corresponding to this spatial frequency. This phenomenon is also orientation specific and shows partial interocular transfer, indicating a cortical origin. These experiments indicate the presence of channels with a bandwidth of about 1 octave tuned to spatial frequencies ranging from 3 c/deg to about 48 c/deg.

If the visual system does use Fourier principles to analyse images then it must be capable of transmitting information about the spatial frequency, amplitude and phase of the sine wave components of the image. Maffei and Fiorentini (208) have reported direct electrophysiological evidence for this theory from the retina, radiations from the lateral geniculate body (LGB) and simple and complex cortical cells of the cat. They found cells with spatial frequency tuning showing a wide range of peak response frequencies in all these areas. The interesting feature was a progressive narrowing of the response curves (and thus the spatial frequency selectivity) from the retina to the LGB and then to the simple cells of the cortex under the same recording conditions. The simple cortical cells were found to be practically insensitive to frequencies at half or twice ($\pm$ 1 octave) the peak response frequency, approximating to Blakemore and Campbell's psychophysical measurements of the bandwidth of the postulated spatial frequency channels (207). The simple cells also showed a resolution limit corresponding to the estimated visual acuity of the cat, while the complex cells had a lower resolution limit and broader spatial frequency response.

Increasing contrast (amplitude) of the sine wave grating produced an increase in impulse frequency for cells of the retina and LGB. The simple cortical cells showed a linear increase in response with log contrast, corresponding to the relationship of contrast and the VEP (31). The phase of the grating with respect to the receptive field was found to affect the temporal phase of the response of the simple cortical cells.

Hence, the simple cortical cells of the cat have the capacity to encode information about the spatial frequency, amplitude and phase of the stimulus, providing the basis for the visual system to act as a Fourier analyser.

3C4 The CSF in pathology

As CSF measurement gives a more complete description of the visual system than VA alone, it will also give more information about defects of the visual system.

Patients with an equal reduction in VA can have completely different perceptions of the visual world depending on how many other spatial frequencies are affected (Figure 3C12). CSF measurement would differentiate between patients with high frequency loss only and loss at all spatial frequencies - the latter representing a far more serious disability. Alternatively, the same degree of VA reduction could represent a shifting of the peak of the CSF curve to lower frequencies.

Patients with high frequency defects alone can partly overcome their disability by moving closer to objects to increase magnification (180). Such defects can be caused by selective damage to the central retina - as in macular pathology (209) and eclipse burns (210) - or by selective

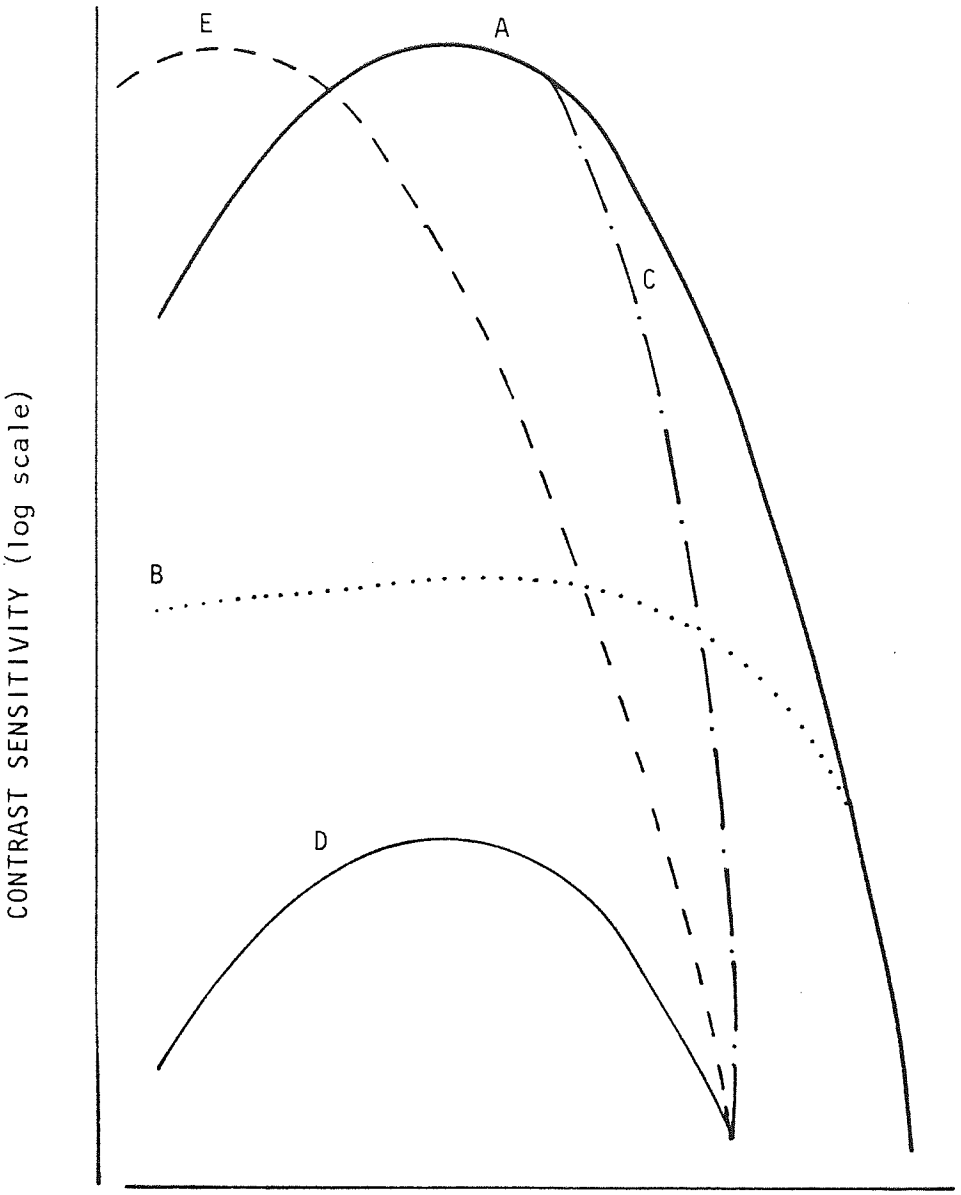


Figure 3C12 The effect of pathology on the CSF

CURVE A	Normal curve
CURVE B	Low and medium frequency affected
CURVE C	High frequency affected
CURVE D	All frequencies affected
CURVE E	Curve shifted to lower frequencies

The visual Acuity is the same in C, D and E

After Arden (175)

damage to the papillo macular fibres in the optic nerve, as in optic neuritis (Section 4C). High spatial frequency selective defects are also produced by optical blur (Section 4B) and some types of amblyopia (Section 4A).

Normal VA coexisting with low, or low and medium frequency CSF defects could not be explained by refractive error, so must be attributed to pathology (180, 175). These are the defects which would be missed by routine VA testing, although the patient might complain that vision appeared 'washed out' (180). Such defects could be caused by large peripheral retinal lesions. Spatial frequency or orientation selective defects can be indicative of cortical lesions, as the neurones of the cortex are arranged systematically according to spatial frequency and orientation (211, 210, 18, 180).

CSF defects have also been reported to precede other evidence of visual disturbance in diabetes, glaucoma (195) and cortical lesions (189).

A summary of reports of the CSF in pathology is found in Table 3C1.

It is very important to use age related controls in any study of the CSF in pathology. The exact effect of age on the CSF is not clear as the methods and selection of subjects differ in almost every study making comparisons difficult.

The Arden score on all the plates has been found to increase with age in two adult studies (213, 212).

Studies on children must ensure that any apparent CSF reduction is not due to lack of understanding or ability to do the test. Two

TABLE 3.C.1. THE CSF IN PATHOLOGY

Key: X = Defect; Blank = No Defect; - = Not Applicable.

Location of Lesion	Pathological Condition	Field Size	No. of Cases	Affected Spatial Frequencies				Comments.
				Low	Med	High	Arden Score	
CORNEA	Distortion (18)				X	X	-	
	Oedema (216)			X	X	X	-	
LENS	Cataract (211)	35^{o} & 4.3^{o}	4			X	-	Low frequency defects can also indicate neural defects.
			6	X	X	X	-	- important for prognosis (175)
	Aphakia (217)			X			-	Seems to be an artifact caused by magnification of high power spectacles, therefore use contact lenses.
RETINA	"Macular Diseases" (Mixed) (218)	1.40^{o}	11		X	X	-	Medium and high defects in early stages, all frequencies in advanced cases. Large field, low frequency stimuli give normal results in some cases.
	(186)	2^{o} 6^{o} and	22	X	X	X	-	
	(199)	-	41	-	-	-	X	
	Senile Macular Degeneration (195)	-	14	-	-	-	X	
	Diabetic Retinopathy (195)	-	37/37	-	-	-	X	VA = 0.5 to 0.1) CSF
		-	47/79	-	-	-	X	VA = 1.0 to 0.67) defects found when retinopathy is present, therefore could be an early diagnostic test. (195)
	(184)	16.5^{o} or 5.5^{o}	4		X	X	-	

continued/...

TABLE 3.C.1. continued

RETINA Cont.	Retinitis Pigmentosa	(18)				X	-	High frequency defect could indicate macular involvement (18), or retinal oedema (195)
		(195)	-		-	-	-	
	Glaucoma	(219)	4^{o}	10/11	X	-	-	8Hz modulation.
		(220)	-	50 Eyes	-	-	-	X	VA = 1.0 visual loss greater with severity of disease. NB this effect can also be due to miosis with lens opacities (213).
	Contusional Eye Injuries	(221)	-	15/95	-	-	-	X	VA = 1.0 in all cases.
OPTIC DISC.	Papilloedema	(210)	-		-	-	-	X	
OPTIC NERVE	"Optic Nerve Diseases"	(199)	-	25	-	-	-	X	
	Optic Neuritis (Recovered)	(181)	11^{o}	4	X	X	X	-	)
				2		X		-	) VA = 1.0
			or	1		X	X	-	)
			43^{o}	1				-	)
		(222)	-	29	-	-	-	X	
			-	7	-	-	-		
	Multiple Sclerosis	(222)	-	21	-	-	-	X	Previous optic neuritis.
		(180)		15				-	
			4^{o}	6	X	X	X	-	
			or	13		X	X	-	
			2^{o}	11		X		-	
				3	X			-	

continued/...

TABLE 3.C.1. continued

VISUAL CORTEX	Cerebral Lesions (206)	3.8°	11	X	X	X	-	
		or 1.9°	18			X	-	
			6		X		-	
	Minamata Disease (223)	-	30				X	Methyl mercury poisoning.
	Amblyopia (177)	3°	4	X	X	X	-	VA 0.4 to 0.1
	(186)	1.4°	6	X	X	X	-	VA 0.4 to 0.05
	Anisometropic (224) Strabismic	11.5°	10			X	-	
		or	5			X	-	
		6.2°	5	X	X	X	-	
	Strabismic (225)	3.7°	5			X	-	
		or 1.3°	5	X	X	X	-	
	Meridional (197)	2.3°	6	X	X	X	-	Defect when grating at axis of higher astigmatism (even when optically corrected).

reports show a slight reduction at low frequencies (3 - 5 years) (214) or low and middle frequencies (6 - 10 years) (185) although neither reduction is statistically significant. One other report shows increasing contrast sensitivity from 3 years of age to adolescence, when adult levels are reached (183).

All the other end of the age scale, Derefeldt, Lennerstrand and Lundh (185) report a decline in high frequency sensitivity in a 40 - 60 year age group, leading to medium and high frequency defects in a 60 - 70 year age group. However, Sekuler, Hutman and Owsley (215) reported a low frequency reduction with normal high frequency sensitivity in an elderly group (mean age 73.2 ± 3.8 years). The latter study used temporally modulated gratings at 0.3Hz and 6Hz, so possibly the elderly observers did not show the normal low frequency increase with temporal modulation. This would be consistent with Sekuler et al's. other finding of reduced sensitivity to moving gratings in the elderly. If this were the case, the stationary presentation used by Derefeldt et al. would not have revealed this type of defect.

3D THE TEMPORAL MTF OR DE LANGE CURVE

3D1 The psychophysical de Lange curve

The study of the processing of flicker in the visual system was advanced greatly by the work of de Lange in the 1950's, and it was in recognition of his work that the 1963 flicker symposium (172) proposed that the temporal MTF he first described should be known as the 'de Lange Curve'. De Lange was a telecommunications engineer, so many very technical papers have resulted from his original work. The purpose of this

review is to outline the points which are most relevant to clinical studies.

The de Lange curve (Figure 3D1) shows a maximum sensitivity at frequencies between 10 and 20Hz (93) with attenuation either side of this peak. At high temporal frequencies (greater than 20Hz) and low temporal frequencies (less than 10Hz) the responses seem to be mediated by completely different systems (226). There is a gradual transition from one system to the other in the intermediate region (226, 93).

The Critical Flicker Frequency (CFF) - The maximum temporal frequency discernable by the visual system is known as the critical flicker frequency and corresponds to the point at which the de Lange curve cuts the frequency axis.

At one point, the CFF was the only known method of defining temporal vision and a large volume of literature was produced on this subject. However, this work has largely been superceded by the work of de Lange which extended the study of temporal vision and only the major points concerning the CFF will be outlined in this and following sections (170).

(i) The CFF is proportional to the log of flash luminance (Ferry-Porter Law). This applies in the photopic region for flicker rates greater than 10 c/sec.

(ii) The Talbot law states that subjectively fused intermittent ~~mediate~~ lights have exactly the same average luminous energy per unit time as objectively steady light of equal brightness

(iii) The highest CFF is obtained when the surround luminance

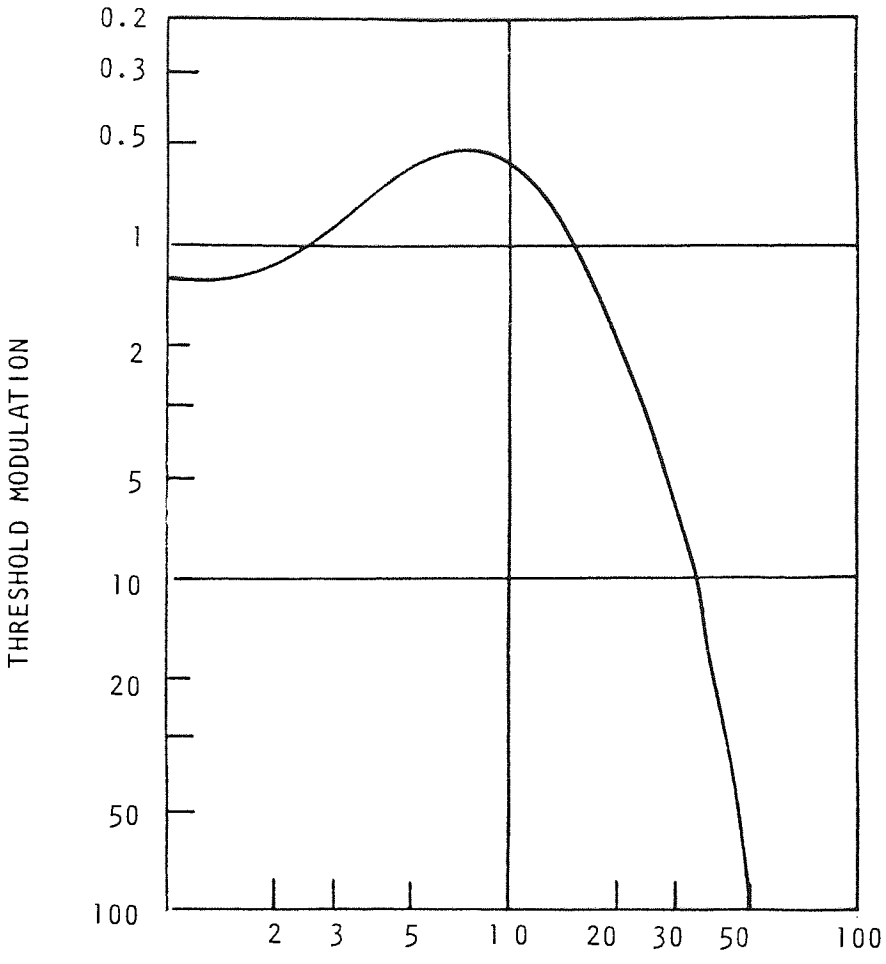


Figure 3D1 The de Lange curve

Sinusoidal modulation of white light in a 2^{o} field. Mean retinal illuminance 100 trolands. From Sperling (172)

is equal to the mean luminance of the flickering stimulus.

(iv) The CFF is proportional to log stimulus area (Granit-Harper Law) for luminances in the range of 1 to 1000. However, the border of the field appears to be the critical factor, as the same results are found when an annulus of the same diameter is used

(v) The CFF is proportional to log surround area for small foveal test fields and surround diameters of up to 4^{o}

(vi) The higher the level of light adaptation of the eye, the higher the CFF for a given test stimulus

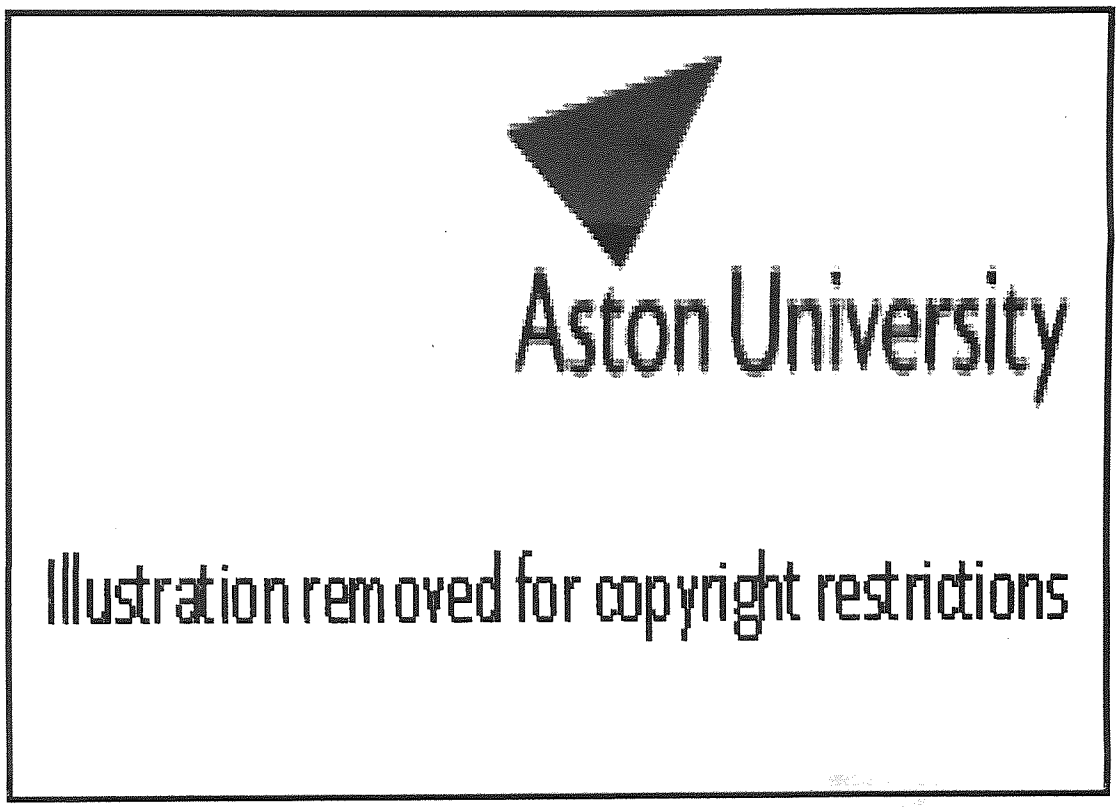
(vii) The CFF decreases with increasing age

Low and High Frequency Attenuation - Major factors determining the performance of the visual system at low and high frequencies are summarised in Table 3D1. Those points requiring fuller explanation are discussed below.

Increasing field size has a completely different effect on low and high temporal frequencies as shown in Figure 3D2. High frequency sensitivity, or CFF, increases as would be expected from the Granit-Harper Law, but low frequency sensitivity is markedly decreased (170). Kelly (226) suggests that large test areas enhance inhibitory mechanisms which are operative in the low frequency region. He suggests that wide field

TABLE 3.D.1. FLICKER SENSITIVITY AT LOW AND HIGH FREQUENCIES

	LOW FREQUENCIES	HIGH FREQUENCIES
a) AREA (170)(226)	Sensitivity decreases with increasing area.	Sensitivity increases with increasing area to a lesser extent.
b) LUMINANCE (226)	Sensitivity independent of average luminance.	Sensitivity increases with increasing luminance.
c) MODULATION (226)	Sensitivity dependent on relative amplitude of modulation.	Sensitivity dependent on absolute amplitude of modulation.
d) SURROUND (227)(228)	Sensitivity increases markedly with surround of equal luminance.	Unaffected by surround
e) WAVEFORM (226)	Sensitivity dependent upon waveform.	Sensitivity determined by fundamental only.



TEMPORAL FREQUENCY (c/deg)

Figure 3D2 The effect of field size on the de Lange curve showing the decrease in low frequency sensitivity with increasing field size. Results taken from four laboratories who used approximately equal stimulus luminance

From Kelly (226)

stimulation is nearest to natural visual conditions as his results obtained with a 65^{o} field approximate closely to those obtained by modulation of room illumination while the subject read a book.

Early research on the effect of increasing retinal luminance (or adaptation level) on the de Lange curve, showed that sensitivity was increased at high temporal frequencies as would be expected from the Ferry-Porter law, but unaffected at low temporal frequencies (226) (Figure 3D3).

However, further analysis of these results (226) showed that modulation, not luminance, was the critical factor. The low frequency response is dependent on the relative modulation of the stimulus while the high frequency response is dependent on the absolute modulation. The early workers had made adjustments to keep the relative modulation constant as the luminance was increased. In effect, they were showing the effect of increasing absolute modulation on the de Lange curve. It is now realised that the same effect could be produced at high frequencies by keeping the mean luminance constant throughout and increasing the absolute modulation alone.

The same results can be replotted to show the effect of temporal frequency when the threshold is considered in terms of absolute modulation (Figure 3D4). It can now be seen that the high frequency response is no longer dependent on luminance, but forms a single curve for all luminances (the maximum possible value for each section of the curve being equivalent to 100% modulation). It is the low frequency response which now appears to be dependent on luminance - reflecting the fact that a constant point when the graph was plotted in terms of relative modulation becomes a series of different points when the same graph is replotted in terms of

Figure 3D4 The effect of retinal illuminance on absolute sensitivity. Data from 3D3 replotted to show that low frequency sensitivity increases with increasing absolute modulation. From Kelly (226)

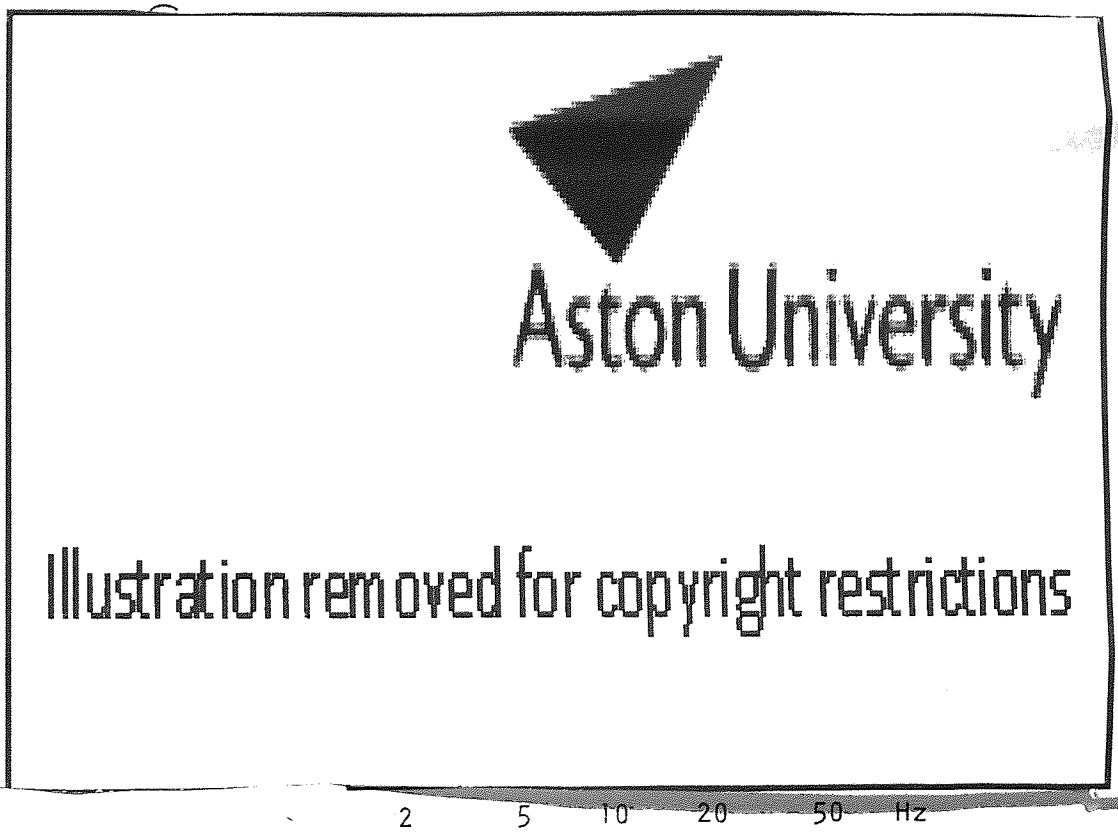


Figure 3D3 The effect of increasing retinal luminance on the de Lange curve. Sensitivity is increased at high frequencies but is unaffected at low frequencies. From Kelly (226)

absolute modulation.

This discussion has concerned retinal illumination, thus assuming that the pupil size has remained constant or has been taken into account in the calculation of retinal illumination. As changes in pupil size influence the amount of light reaching the retina, the error caused by inadvertent comparison of two subjects with different pupil sizes, under identical stimulus conditions, for example, would be significant at high temporal frequencies but negligible at low temporal frequencies.

3D2 VEP measurement of the temporal MTF

Investigations into the relationship between the VEP and temporal frequency have, by definition, required stimulus frequencies too high for transient VEP recording techniques. It is beyond the scope of this project to examine the details of the steady state techniques involved, but a qualitative comparison between psychophysical and electrophysiological temporal MTFs will be attempted.

Early papers by Van der Tweel and Verduyn Lunel (171) showed that the VEP produced by sinusoidally modulated diffuse large fields was approximately sinusoidal at frequencies of between 9 and 18Hz, peaking in amplitude at around 10Hz. At temporal frequencies lower and higher than this range the responses became distorted, with a predominance of the second harmonic. However, they found that VEPs could be elicited at frequencies above 35Hz when strong illumination and small fields were used. Unlike contrast VEPs, these luminance VEP seemed to bear no relationship to psychophysical thresholds, ~~and~~ as they could be elicited at frequencies far higher than the CFF.

With large field square wave modulation, Sokol and Riggs (229) found a similar CFF value for both VEP and psychophysical measurements. The temporal MTF curve, plotted using a criterion of constant VEP amplitude, showed a more shallow high frequency attenuation than the psychophysical de Lange curve.

The pattern reversal steady state VEP does not show the very high frequency responses reported for luminance VEPs (57). In addition, the VEP takes the form of the second harmonic, which avoids the ambiguities outlined above (174). It has been found that studies using a temporally modulated spatially structured field obtained VEP results closer to the psychophysical threshold.

Both Cavonius and Sternheim (174) and Adachi-Usami and Morita (230) demonstrated a linear relationship between VEP amplitude and log modulation, providing a temporal correlate of the relationship between VEP amplitude and log contrast. The latter study showed that the slope of the function varied with temporal frequency, VEPs at frequencies of less than 10Hz showing saturation at about 7-10% modulation, while frequencies higher than 15Hz showed no saturation up to 70%. Therefore, studies using suprathreshold measurements of VEP amplitude should be interpreted with caution, unless saturation is taken into account.

Cavonius and Sternheim plotted the extrapolated VEP threshold data against temporal frequency and found a very close similarity to the de Lange curve.

3D3 Neural factors in the processing of flicker

The site of flicker processing in the brain is still not fully understood.

Schwartz and Chaney (170) suggest that a high frequency system is located in the visual cortex, lateral geniculate body and nearby thalamic nucleus, and a low frequency system is located in the tectal region (or superior colliculus).

Spekreijse, Estevez and Reits (92), using steady state VEPs, suggest that the visual system incorporates separate high, medium and low frequency subsystems. Topographical studies suggest that the high frequency VEP response (40-60Hz) originates in the primary visual cortex (area 17) while the medium frequency response (14-20Hz) originates in the secondary visual cortex (areas 18 and 19). The low frequency response (9-12Hz) does not seem to originate from a specific cortical region, but is distributed more widely over the scalp.

The authors suggest that the high and medium frequency channels are probably in parallel rather than in sequence, possibly separating as early as the retinal ganglion cell layer. Spekreijse (68) later compares these three subsystems to the three components of the flash VEP identified by Ciganek (40) - a primary component originating in area 17, a secondary component originating in area 18 and possibly 19, and a rhythmic after-discharge that cannot be attributed to a specific cortical region.

In the same paper, Spekreijse suggests that these three subsystems reflect the proposed X, Y and W systems (Chapter 1). These two theories would be consistent with the reported termination of the X system in area 17 and Y system in area 18 of the cat by Movshon Thompson and Tolhurst (19). They found that area 17 and some area 18 cells showed 'low pass' temporal tuning curves which would be consistent with X cell characteristics while the majority of cells in area 18 showed 'band pass' curves tuned to higher

temporal frequencies, which would be more consistent with Y cell characteristics. The Y system is believed to be responsible for processing temporal changes within the visual system and evidence suggests that it responds maximally to stimuli of high temporal and low spatial frequency (Chapter 1).

Green (22) has reviewed other studies and carried out experiments to determine whether the visual system contains independent channels tuned to different temporal frequencies as proposed for the spatial visual system. It appears that the temporal system contains some degree of temporal tuning, but that the channels are broader and less well defined than the spatially tuned channels.

3D4 The de Lange curve in pathology

There have been few studies of the effect of pathology on the de Lange curve. Table 3D2 summarises the published reports.

Breukink and Ten Doesschate (169) who investigated a large range of conditions, point out that low temporal frequencies are particularly affected in many macular diseases. Selective high temporal frequency loss was only observed in some cases of optic nerve atrophy, leading the authors to suggest that this could possibly have significance for the differential diagnosis of retinal and neural lesions.

Measurement of the full de Lange curve clearly gives more information than conventional CFF measurement alone, as the latter would not detect specific low, or low and medium temporal defects. De Lange (170) suggested that testing the flicker sensitivity of patients with sinusoidally modulated light at about 10Hz might give greater sensitivity than measurement of CFF.

TABLE 3.D.2. THE de LANGE CURVE IN PATHOLOGY

X represents a temporal frequency defect.
All results from Breukink and Ten Doesschate (169) and measured with a 2^{o} field unless otherwise stated.

Location of Lesion	Pathological Condition	No. of Cases	Affected Temporal Frequencies Low	Medium	High	Comments
RETINA	Central chorioretinitis	1	X	X	X	VA = 0.25
	Juxtapapillary chorio-retinitis	1	X			Normal VA. Fibre bundle scotoma.
	Juvenile macular degeneration.	4				More pronounced at higher luminance.
	Senile macular degeneration.	1	X			
		1				
	Central serous retinopathy	2	X	X	X	
	Diabetic retinopathy	4				Normal VA
	Tapetoretinal degeneration	8				Normal field
			X			10^{o} field normal VA no defect at low luminance.
			X	X	X	5^{o} field VA 0.25
	Reattachment of the macular after retinal detachment.	5	X			
	Albinism	4	X			More pronounced at higher luminance.
	Vascular Disturbances: Hypertension	7				Normal VA
	Toxicosis	2				Mild cases
	Temporal arteritis (retinal involvement)	1	X	X	X	partly improved after treatment.

Continued/...

TABLE 3.D.2. continued

RETINA (Cont)	Rod monochromasy	7	X	X	X	More pronounced at low frequencies and high luminance.
	Rod achromatism (Van der Tweel & Spekreijse) (231)	1	X	X	X	More pronounced as field size is reduced (field size 8^{o}) and when checkerboards are used.
OPTIC NERVE	Optic Nerve Atrophy	5	X		X	Low frequency defects in some patients, high in others.
	Chronic simple glaucoma	5	X		(X)	Only affected in very severe cases with large field losses.
	Papillitis	3			X	
	Retrobulbar neuritis	(3				
	a) Breukink & Ten Doesschate (169)	(2	X			
	b) Van der Tweel and Estevez (228)	1			X	Acute phase - recovery of high frequencies parallels recovery of neuritis.
	Multiple Sclerosis					
	Spekreijse et al. (232)	(1 (1	X	X	X	Definite diagnosis of MS Probable diagnosis of MS
HIGHER VISUAL PATHWAYS	Heteronymous hemianopia	3				Normal VA. Bitemporal quadrant defects.
	Homonymous hemianopia with macular sparing	2				
	Homonymous hemianopia with macular involvement.	2	X			

continued/...

TABLE 3.D.2. continued

AMBLYOPIA	Bilateral amblyopia	1	X			VA = 0.5
	Strabismic amblyopia					
	Eccentric fixation	(3				
		(3	X			
	Central fixation	3				VA = 0.5, 0.1, 0.25.
	Anisometropic amblyopia (Spekreijse et al. 227)	1	X			VA = 0.16 Does not show normal increase at low frequencies with equal luminance surround. Defect more pronounced with 20 min field than 2^{o} field.
	Strabismic and Anisometropic (Wessen & Loop 233)	(2	X	X	X	VA = 6/47 and 6/120
		(3				VA = 6/12 or better
		(4	X	X		
	(Manny & Levi 251)	(4				Two had increased low frequency sensitivity.

CHAPTER 4 CONDITIONS PRODUCING SELECTIVE DEFECTS OF VISION OR THE VISUAL PATHWAYS

4A AMBLYOPIA

4A1 Aetiology

4A2 Psychophysics of amblyopia

- 4A21 Visual acuity
- 4A22 Spatial MTF (constant temporal frequency)
- 4A23 Spatio-temporal interactions
- 4A24 Temporal MTF (constant spatial frequency)

4A3 The effect of amblyopia on the VEP

4B OPTICAL BLUR

4B1 Psychophysics of optical blur

- 4B11 Visual acuity
- 4B12 The contrast sensitivity function
- 4B13 Temporal resolution

4B2 Factors involved in the perception of blur

4B3 Image quality in the eye and visual system

4B4 The effect of optical blur on the VEP

4C OPTIC NEURITIS

4C1 Aetiology

4C2 Symptoms and signs of optic neuritis

- 4C21 Visual acuity
- 4C22 The contrast sensitivity function
- 4C23 Temporal resolution

4C3 The effect of demyelination on the VEP

- 4C31 Mechanisms of the VEP abnormalities

4D DEMENTIA OF THE ALZHEIMER TYPE

4D1 Aetiology

4D2 Diagnosis of Alzheimer's Disease

4A AMBLYOPIA

4A1 Aetiology

Amblyopia is defined as "low or reduced central vision not correctable by refractive means and not attributable to obvious structural or pathological anomalies of the eye". The literature on this subject is extensive and for a comprehensive text Schapero's book 'Amblyopia' (138) is recommended. Information in this section refers to this text unless otherwise indicated.

Organic amblyopia arises from abnormal development of the visual pathway, or functional impairment of a normal pathway by metabolic or toxic disturbances. In functional amblyopia a normal visual pathway fails to develop or operate normally due to abnormal stimulation or use (234, 138). Two forms of functional amblyopia are studied in this project - strabismic amblyopia, in which the two eyes receive images from different directions in visual space, and anisometropic amblyopia, in which the image in one eye is blurred due to unequal refractive errors.

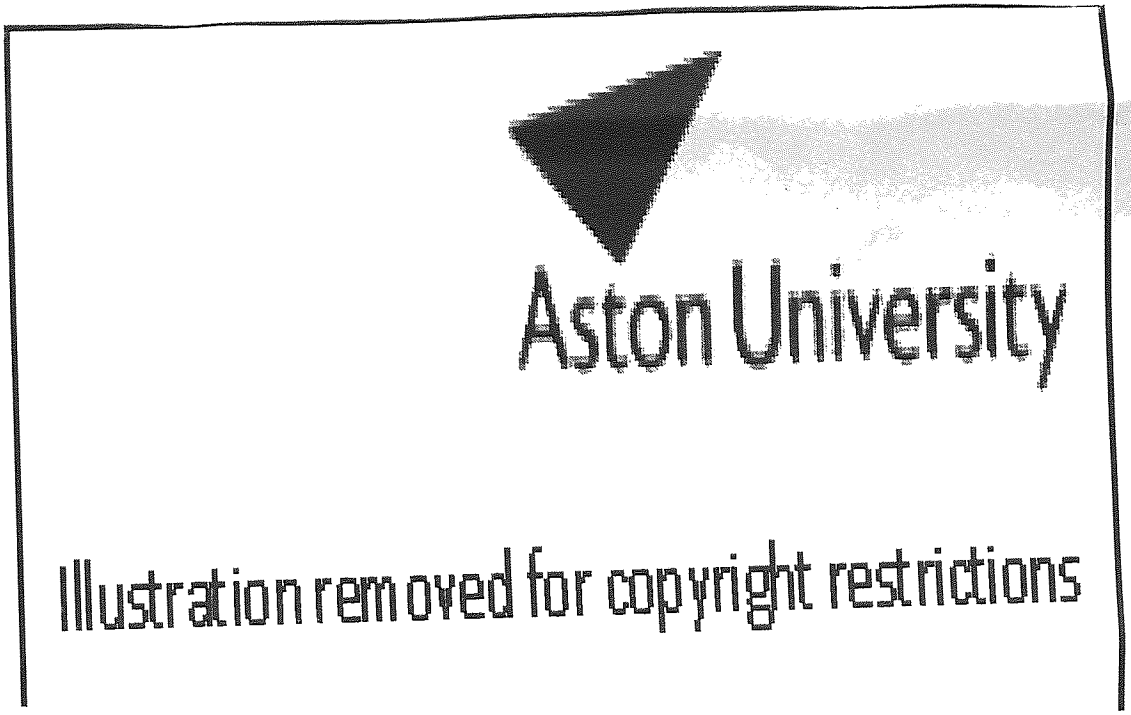
Estimates of the percentage of amblyopes in the population vary with differences in sample selection, method of testing and level of VA considered as abnormal. Schapero lists 14 studies in which the estimates range from 1% to 5.64% of the population. Six other studies show that the proportion of amblyopes with strabismus (mean 38%) is smaller than the proportion without strabismus (mean 62%). Of the 38% with strabismus, 30% were convergent (esotropic) and 8% were divergent (exotropic) (mean values). This is related to the greater incidence of esotropia and to the fact that esotropia occurs more frequently than exotropia in the first 10 years of life, with a consequently greater effect on the

development of VA.

The presence of strabismus or anisometropia in the early years of visual development will markedly reduce the vision of the affected eye. When the cortical image is in conflict with, or inferior to the image from the other eye, the inferior image is suppressed, preventing the further development of normal VA. The younger the obstacle to development occurs, the worse will be the VA and the harder its recovery. Incomplete development of the visual pathway can only be remedied if treatment is undertaken during the developmental years. However, subsequent loss of VA relative to that previously attained can be recovered with appropriate treatment.

In strabismic amblyopia two factors contribute to the visual confusion (235, 138) (Figure 4A1). Firstly, any object fixated by the dominant eye will be imaged on an extrafoveal point in the retina of the deviating eye, resulting in diplopia and poorer VA due to the lower resolution of the peripheral retina ('motor' factors). Secondly, the image on the fovea of the deviating eye represents another part of the visual field. This image will be blurred if the object is at a different distance from that fixated by the dominant eye, or if the deviating eye has a refractive error, and will therefore be suppressed to reduce the confusion. This will prevent the VA from developing to its full capacity (sensory factors). Amblyopia is less likely to occur in alternating strabismus as both eyes receive normal visual stimulation in turn.

In anisometropia, there is no confusion in locating images in visual space, as both eyes are directed towards the object of regard (235, 138) (Figure 4A1). However, sensory inhibition of the blurred image in the anisometropic eye occurs. Unequal refractive errors can also affect



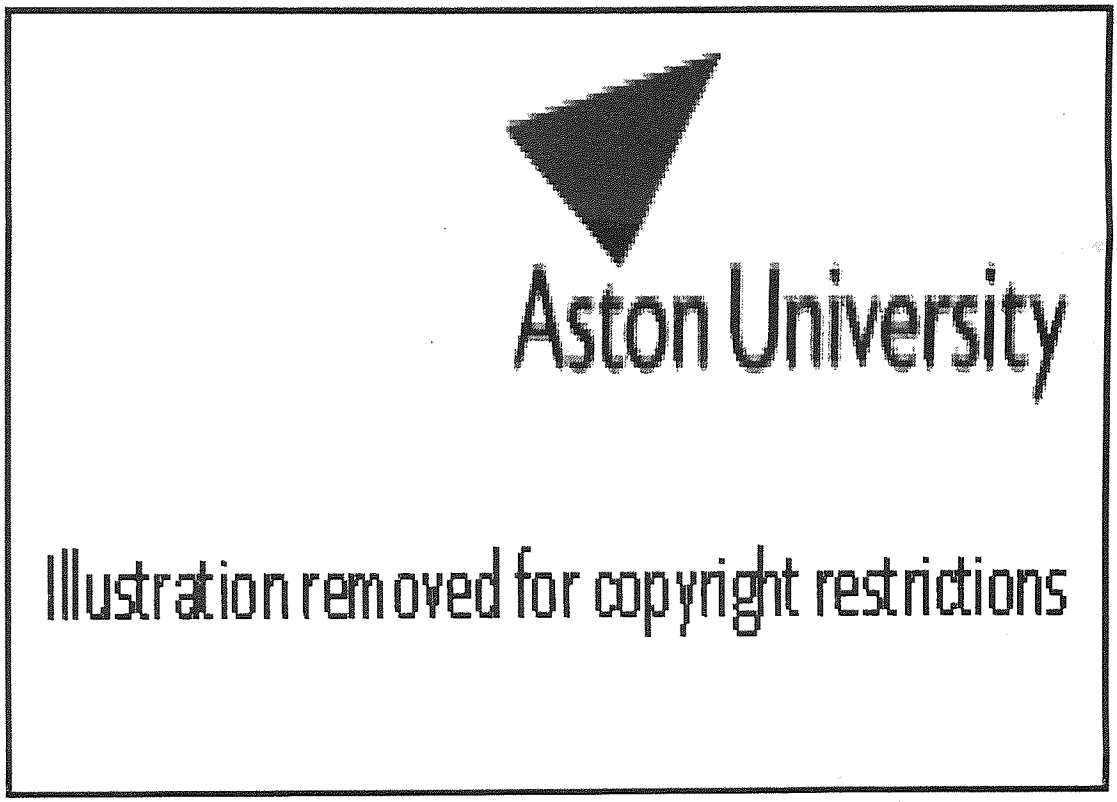


Figure 4A1 Strabismic and anisometropic amblyopia

In a) the image of an object fixed by the left eye falls on a nasal element (e) of the right esotropic eye, causing diplopia The image of a second object falling on the fovea of the right eye causes confusion. In b) the fovea of the right myopic eye receives a blurred image of the object fixated by the left eye. From Von Noorden (235)

depth perception. Anisometropic amblyopia occurs most frequently in unilateral hypermetropia. Normal VA can often develop in both eyes of a unilateral myope as the myopic eye is used for near fixation and the emmetropic eye for distance.

Strabismic amblyopia is usually more severe than anisometropic amblyopia. In practice, the two conditions often occur together, resulting in a deeper amblyopia.

Current concepts on the manner in which abnormal visual stimulation affects the visual pathways are mainly based on animal experiments. It is believed that the highly specific innate neuronal connections require visual stimulation early in life for their maintenance and full development (236). Inadequate stimulation during a critical period leads to degeneration of the affected pathways functionally (15) and anatomically (236, 237, 238). The critical period is estimated as up to $1\frac{1}{2}$ to 2 years in the monkey and 3-4 months in the cat. Clinical observations on humans suggest that the plasticity of the visual system is greatest in the first year and declines with age up to between 5 and 10 years (236). Refractive error or strabismus should therefore be detected and corrected at the earliest possible opportunity.

It has been found that selective visual deprivation can produce selective defects of the visual system. Kittens reared in a visual environment of contours of only one orientation during the critical period show, on examination, cortical neurones only sensitive to stimuli of that orientation with apparent behavioural blindness to orthogonal contours (238). Humans with high astigmatism uncorrected during early childhood show similar meridional defects. Psychophysical (197, 238) and electrophysiological (239) studies on fully corrected high astigmats show that

VA and contrast sensitivity are maximally reduced when the stimulus orientation corresponds to the meridian which was most blurred during development. Bypass techniques, using interference fringes on the retina show that this is a neural, not a residual optical defect (238).

It is believed that the X cell, or 'pattern detecting' system is selectively affected in amblyopia, due to deprivation of sharply focussed images during the critical period (15). This theory is supported by psychophysical (177, 240, 241) and electrophysiological (140) results which show that high spatial and low temporal frequency mechanisms (corresponding to the 'X system') are defective in amblyopia, while low spatial and high temporal frequency mechanisms (corresponding to the 'Y system') are normal. These results confirm the observations of Wald and Burian forty years ago (242) that amblyopia represents a defect of form vision with normal light perception.

4A2 Psychophysics of amblyopia

4A21 Visual Acuity (VA)

Amblyopia is, by definition, a reduction in VA which cannot be corrected by refractive means. The VA reduction is attributable to sensory inhibition in anisometropic amblyopia, but both sensory and motor factors contribute to strabismic amblyopia.

To evaluate the motor contribution to the VA reduction, Kirschen and Flom (243) measured the VA at various retinal locations from both eyes of 4 amblyopes with eccentric fixation. Both eyes showed a maximum VA at the fovea, decreasing with increasing retinal eccentricity. The

peak VA was lower in the amblyopic eye, as expected, and the VA reduction with eccentricity was greater, indicating an additional sensory VA inhibition. The proportion of sensory VA reduction decreases as the reduction in VA due to motor factors increases, and is negligible for eccentric fixation of greater than 10 degrees (Figure 4A2). The authors consider that these findings combine the sensory theory of Worth at zero or small degrees of eccentric fixation with the motor (retinal locus) theory of Flom and Weymouth at larger degrees of fixation. In practice, most amblyopic eyes have VA of 6/18 or better, and eccentric fixation of 3^{Δ} or less which results in a combination of motor and sensory factors, as in the theory of Alpern.

Unlike a normal eye, or an eye with organic amblyopia, an eye with strabismic or refractive amblyopia does not show reduced VA in low illumination. This can be used to differentiate between organic and functional amblyopia (244, 138). Hess (245) found this effect to be more pronounced in strabismic amblyopia and can be reproduced in a normal eye with an artificial central scotoma. It has been suggested that the amblyopic eye uses an extrafoveal part of the retina which performs equally well in reduced illumination (245, 138).

When VA is being measured, the design of the acuity chart must be taken into consideration. Normal and amblyopic eyes both showed reduced acuity when the spaces between Landolt C symbols were only equivalent to twice the width of the gap, but unimpaired VA when the spaces were 5 gap widths or greater. This ratio held for large and small letters (138).

Amblyopes, particularly strabismic amblyopes, experience particular difficulty distinguishing letters within a line, due to 'contour interaction' or the 'crowding phenomenon' (138, 244). Proposed reasons for

Aston University

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Figure 4A2 Showing that the relative proportions of amblyopic VA loss due to sensory and retinal locus (motor) components vary with the amount of eccentric fixation. Upper curve shows normal decline in VA with retinal eccentricity from 5 non amblyopic eyes. Lower curve shows acuity contour of an amblyopic eye with 2^{o} eccentric fixation and VA of 6/15 at the fovea and 6/20 at the eccentric fixation point.

From Kirschen and Flom (243)

this difficulty include unstable fixation, monocular diplopia, defects in lateral inhibition, enlarged receptive fields and localisation difficulties. The site of the abnormality is believed to be cortical as the effect can be produced by viewing a single letter with one eye and surrounding bars with the other (138).

As a result of the crowding phenomenon, the VA of an amblyope will probably appear higher when tested with single letters than with a chart, and this must be bourne in mind when testing young children. Due to the differences in the number of letters on each line of the Snellen chart, the VA of an amblyope could be underestimated when the smaller letters are used, or overestimated if the VA is so poor that only the single large letters can be seen. Another disadvantage of the Snellen chart is that there are large jumps in the sizes of large letters from one line to the next, meaning that poor VA can only be roughly estimated. Various charts have been designed in which each size of symbol is equally represented and the spacing bears a constant relationship to the symbol size (138, 246).

Davidson and Eskridge (246) show that the amblyopic eye does not show a clear VA 'cut off' on the lines of a chart, but instead makes an increasing number of mistakes as the letters get smaller. This might be due to variations in letter difficulty or spacing on the Snellen chart, or to fixational errors. The authors suggest that VA testing is made more accurate by making the amblyope read every letter on each line, or by plotting the number of correct responses against letter size and determining the 50% threshold.

4A22 Spatial M T F (constant temporal frequency)

Two types of contrast sensitivity reduction have been observed in

amblyopia - reduction at high spatial frequencies only (225, 224) and reduction at all spatial frequencies (225, 224, 186, 177). Selby and Woodhouse (224) observed that anisometropic anisometropes showed the former type only, and pointed the similarity to the effect of optical blur on the CSF. Both types of defect have been found in strabismic amblyopia (225, 224). In addition, the peak of the CSF curve and the high frequency cut off are shifted to lower spatial frequencies in amblyopia (186, 224, 177, 178). Hess (247) reviews his publications which show that these defects are not due to optical factors, eccentric fixation or abnormal eye movements and must therefore be neural in origin. The CSF defect is reduced or absent for luminance levels of less than 0.21 trolands in strabismic amblyopes which is consistent with VA observations.

Selby and Woodhouse (224) found that amblyopic eyes showed interocular transfer at spatial frequencies for which contrast sensitivity was normal, but not at the affected spatial frequencies. In the same paper they suggest that low frequency CSF defects are related to strabismus of early onset, while medium and high frequency defects indicate a later onset. However, Hess and Howell (225) did not observe such a relationship. Lennerstrand and Lundh (248) demonstrated a CSF and VA improvement in 16 young amblyopes after therapy. Of the 8 children showing no VA improvement, 4 showed improvement as measured by the more detailed CSF.

Hagemans and Van de Wildt (249) showed that the CSF of 4 amblyopic eyes (2 anisometropic, 2 strabismic) was reduced in comparison to the fellow eyes for fields of 0.25^{o} - 1^{o} diameter, but equal for fields of about 2^{o} and greater at low spatial frequencies for fields of 4^{o} and 8^{o}. This low frequency enhancement was only observed in eyes with VA of better

than 6/60. Plots of contrast sensitivity against field size showed that the sensitivity of the amblyopic eyes increased more rapidly with increasing field size than the fellow eye, reaching a maximum at a greater field diameter. These results indicate that the amblyopic eye uses the extrafoveal retina more than the fellow eye.

4A23 Spatio-temporal interactions

Several studies have investigated the effect of amblyopia on pattern detection and flicker or movement detection separately, in order to isolate the X and Y cell systems. The studies measured these thresholds with changes in either spatial or temporal frequency.

(i) CSF curve (Spatial MTF) - A normal eye shows higher sensitivity to flicker than pattern at low spatial frequencies (178, 250, 177). Pattern sensitivity has been reported to be higher than flicker at spatial frequencies higher than 2-4 c/deg (178, 250) although they were found to be equal when 10Hz stimulation was used (177).

CSF studies using slow rates of stimulus presentation reported an overall CSF reduction in amblyopia (178, 250). However, other amblyopes, particularly at faster stimulation rates, showed defects at medium to high spatial frequencies only, with normal low frequency sensitivity (177, 178, 241). This would be consistent with a selective defect of the X cell system (177) with the Y system responding normally when optimal stimuli are used.

Thomas (178) found that the differences in pattern and movement thresholds between the two eyes of three amblyopes decreased with increasing retinal eccentricity. The central response from the amblyopic eye resembled

the parafoveal response from the normal eye in its overall reduction in sensitivity and shift of the peak and cut off frequency to lower spatial frequencies.

(ii) De Lange curve (temporal MTF) - Manny and Levi (240) reported that the flicker threshold de Lange curve showed a low temporal frequency reduction in amblyopia which was most marked with medium or high spatial frequency stimuli. Flicker detection can therefore appear normal with a low spatial frequency stimulus even in the presence of a pattern threshold defect (240, 247). The pattern threshold de Lange curve showed a similar low temporal frequency defect which was most marked with high spatial frequency stimuli. These results provide further evidence of a selective X system defect in amblyopia.

The authors found that these spatio-temporal defects were more marked in these 7 amblyopes than the homogenous field temporal defects reported in the following section. Unlike the uniform field defects, the spatio-temporal defects were still present at low luminance levels.

4A24 Temporal MTF (constant spatial frequency)

The most common amblyopic de Lange curve defect, when present, occurs at low temporal frequencies (227, 233, 251, 169). However, some amblyopes do not show any defect (233, 251, 169) while a few have reduced sensitivity at all temporal frequencies (233). Wessen and Loop (233) found the severity of the temporal defect corresponded to the VA reduction in 5 subjects, but this was not confirmed by the study of Manny and Levi (251).

Manny and Levi reported that the temporal defects disappeared when the

luminance of the stimulus was reduced ten fold to 0.32 cd/M^2. The luminance of the surround has also been shown by Spekreijse, Khoe and Van der Tweel (227) to be an important factor. Unlike a normal eye, the amblyopic eye does not show an increase in flicker sensitivity at low temporal frequencies when a black surround is replaced by one of equal luminance to the stimulus. Use of an equal luminance surround in diagnosis therefore exaggerates the differences between the two eyes. The authors suggest that the amblyopic eye does not utilise the extra clues given by the increased border contrast.

4A3 The effect of amblyopia on the VEP

The earliest VEP investigations of amblyopia used flash stimuli. They show a wide variation in stimulus and recording parameters. In general, no significant difference was found between the two eyes of amblyopic subjects with respect to VEP amplitude (252, 253, 254, 255, 227) or latency (255, 256, 227). The only researchers who reported a significant latency increase (of up to 10 msec) was Nawratzki, Auerbach and Rowe (257) using early superimposition techniques and measuring components occurring between 37 and 80 msec.

Potts and Nagaya (254) reported that a component of between 100 and 200 msec was absent from the amblyopic VEP when a 0.06^{o} red stimulus was used for maximum foveal stimulation. The two eyes showed a greater similarity when the red stimulus was increased to 0.6^{o} and were identical when a 0.6^{o} white flash was used.

Three of these papers showed that, despite a normal flash VEP, the amblyopia affected the pattern VEP (227, 252, 255). This would be consistent with the proposed selective defect of pattern detector

mechanisms in amblyopia already discussed. Many reports show reduced pattern VEP mean amplitude when group data of amblyopia and fellow eyes are compared. Stimulation techniques used include flashed-on pattern (252, 255), constant luminance pattern onset-offset (227, 140) and pattern reversal (258, 259, 260, 261) and both transient and steady state recording methods were included.

Of those recording steady state VEPs, two reported that the response from the amblyopic eye was out of phase with the other eye (261, 140) one observing that this effect was more pronounced at high spatial frequencies (140). Two studies using transient recording techniques found the VEP latencies of the amblyopic group were significantly increased when compared with those from the fellow eyes (259, 262) while one other reported no significant latency difference between the two groups (255).

However, within these groups there are still large individual variations. Many amblyopes show VEPs which are normal in latency and amplitude, so a normal VEP could not clinically totally exclude the possibility of amblyopia (252, 259, 261). The diagnostic accuracy of the VEP might be improved by more precise stimulus design.

Many studies have found that the amplitude of the amblyopic VEP is reduced for high spatial frequency stimuli (260, 156, 155, 227, 258, 140, 259). Some studies have reported reduced amplitude at all spatial frequencies (140, 227) while others report that the defect is only found at high spatial frequencies (140, 156, 258, 259). Levi and Harwerth (140) observed both types of defect in their studies, using identical techniques, suggesting that these findings are analogous to the two types of spatial frequency defect observed psychophysically. In

addition, the normal amblyopic responses at low spatial frequencies might have been favoured by the high temporal frequencies used in most of the studies. One amblyope showed enhanced low frequency sensitivity with 12Hz, 12^{o} field stimulation (155) similar to that observed psychophysically with larger fields (249).

As a result of the VEP amplitude reduction at high spatial frequencies, the peak of the VEP amplitude/spatial frequency plot is shifted to lower spatial frequency values. This can be used diagnostically to detect differences in resolution between the two eyes of a suspected amblyope (155, 156), although this is not strictly a measure of VA. However, this could be a tedious procedure unless rapid sweep techniques are used (156).

Lawwill (263) suggests that these abnormalities in the spatial tuning function could be either due to abnormally large receptive fields, or to a selective defect in the pattern processing system.

Levi and Harwerth (140) have shown that, when the spatial frequency of the stimulus is kept constant, the relationship between contrast and VEP amplitude in an amblyopic eye is abnormal. The normal linear relationship between VEP amplitude and log contrast is demonstrated, but the slope of the plot is lower. Since optical blur in a normal eye does not affect the slope of the plot, but just shifts it to the right, these results indicate that amblyopia is of a neural, rather than an optical origin.

One of the most important applications of the pattern VEP in amblyopia is in the measurement of VA. The development of reliable VA assessment techniques in infants will have important implications for early

diagnosis and treatment. However, adult studies have shown that a clear relationship between VA and the degree of VEP amplitude reduction is hard to demonstrate (255, 260). Two other studies found a significant relationship in their group data (258, 259) although individual results showed a large variation (259), limiting the diagnostic significance of VEP amplitude reduction in individual cases.

Extrapolation of the spatial frequency - VEP amplitude function appears to give more reliable results. The VA estimated using this technique with sine grating stimuli was consistently higher than the Snellen VA, showing similarities to the psychophysical superiority of grating VA (140, 141). Mayles and Mulholland (259) used an unusual adaptation of this method. They plotted the product of pattern size and VEP amplitude against log pattern size for 8 amblyopes with known VA and recorded the cut off point. This value was then plotted against the known Snellen acuity, and this graph was used to estimate the VA of the remaining amblyopes. They claimed that the VA predicted in this way was within one line of the Snellen VA in 70 out of the 95 eyes.

The success of the VEP in detecting amblyopia also depends on the field size used. One anisometropic (227) and a group of anisometropic and strabismic amblyopes (258) showed a greater VEP defect with a small 3^{o} stimulus. This would seem to be consistent with the view of amblyopia as a defect of high spatial frequency discrimination, to which the central retina is specially adapted. However, the amblyopic VEP defects of one strabismic amblyope (155) disappeared when the field was reduced from 12^{o} to 3^{o}. It was suggested that was analogous to the higher VA obtained by single letter testing in this subject, a phenomenon which is more marked in strabismic amblyopia. An anisometropic amblyope (261) also showed normal VEPs when the central 1^{o} or the parafoveal retina were

stimulated separately. However, when the central 5^{o} was stimulated the VEP was absent, suggesting that the parafovea is suppressing the response of the fovea.

The amblyopic VEP is believed to contain a larger response from the parafovea - between about 3^{o} and 6^{o} from fixation - than the normal VEP. This has been inferred firstly from the observation that a change from a 3^{o} central field to an annulus of inner diameter 3^{o} and outer diameter 5^{o} gives a decrease in the amplitude of the VEP from the normal eye but little change in the amplitude of the VEP from the amblyopic eye (227). Secondly, the VEP from the normal eye is only suppressed by a steady 10^{o} pattern continuously presented to the amblyopic eye when parafoveal stimulation of the normal eye is used (227). Thirdly, the amblyopic eye has been found to produce a VEP of larger amplitude than the normal eye when large checks are used. The amplitude decreased as field size was reduced (155).

Amblyopia does not appear to affect the peripheral retina. VEP studies revealed no differences between normal and amblyopic eyes when the stimulus was outside the central 6^{o} (155) or was an annulus of inner diameter 6^{o} and outer diameter 14^{o} (258).

There have been few comments on the waveform of the VEP in amblyopia as most studies used steady state recording. However, Levi and Harwerth (140) observed that at low temporal frequencies (2Hz) the VEP was no longer 'steady state' and differences in harmonic composition between the VEPs from the two eyes can be observed.

Three studies of the flashed-on pattern VEP in amblyopia reported differences in waveform between the two eyes (255, 252, 262), one of

these consisting of the absence of a negative component at 220 msec in amblyopia (255). Mayles and Mulholland (259) observed that the transient pattern reversal VEP waveform was abnormal in 21/24 amblyopes with VA worse than 6/18, 10/19 of those with VA between 6/12 and 6/18 and 11/61 of those with VA between 6/4 and 6/9. This abnormality consisted of a broadening of the positive peak, apparently due to the merging of two positive components caused by the loss of a negative component at 150 msec.

Spekreijse, Khoe and Van der Tweel (227) studied the pattern onset-offset VEP of one amblyope. The pattern-specific components were markedly reduced, while the contrast specific C1 component was relatively unaffected. These findings would again be consistent with a selective defect of the pattern detecting mechanisms in amblyopia.

4B OPTICAL BLUR

4B1 Psychophysics of optical blur

4B11 Visual Acuity

Visual acuity measurement is by far the most common method for the clinical determination of refractive error. Its high sensitivity to optical blur lies in the fact that visual acuity represents the high spatial frequency limit of the eye, and it is the high spatial frequencies which are most sensitive to the reduction in contrast caused by blur.

The most popular clinical VA target is the Snellen chart. The theoretical effect of blur on Snellen letters is difficult to calculate, due to the complex spatial frequency composition of alphabetical letters and to the clues given by the residual low frequency components when the high frequencies have been lost through blur (264, 265). However, clinical measurement of the reduction in VA with refractive error have been published, and some typical values are given in Table 4B1. (Experimental details not published).

TABLE 4B1 (266)

SPHERICAL REFRACTIVE ERROR (DIOPTRES)	VISION
0.50	6/9
1.00	6/15
1.50	6/30
2.00	6/45
2.50	6/60
3.00	6/75
3.50	6/90

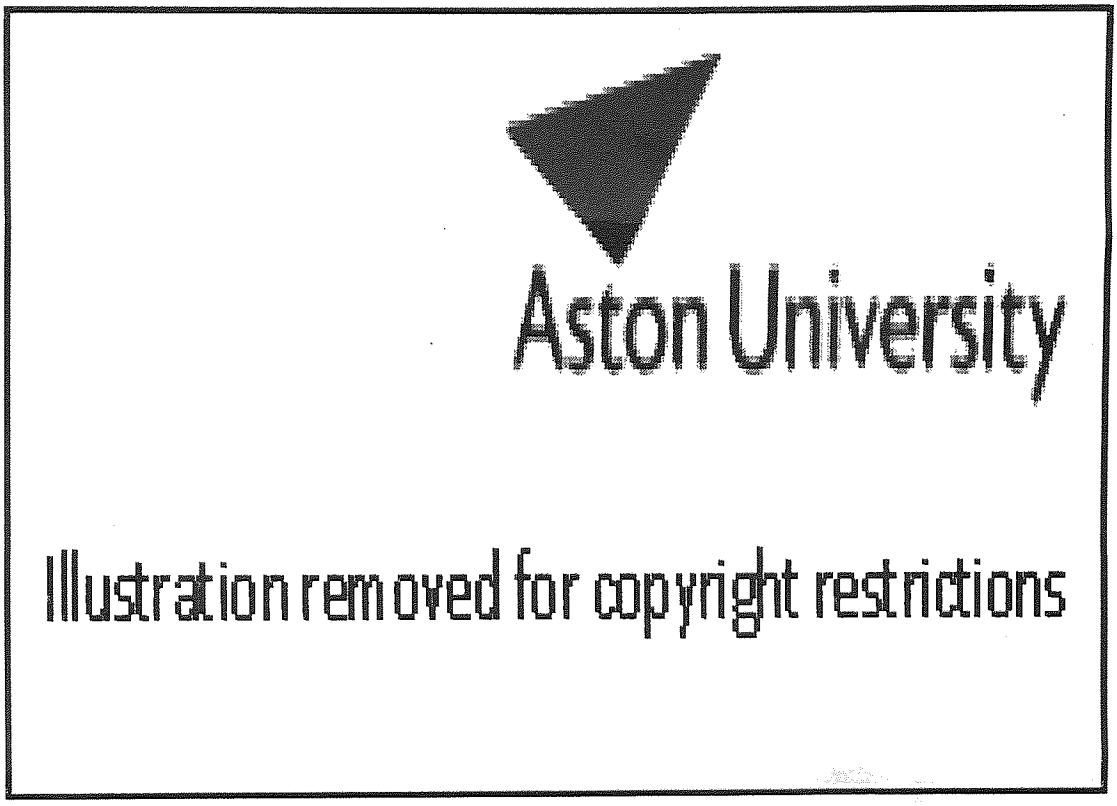
A graphical demonstration of the effect of optical blur on Snellen VA is given in Figure 4B1.

4B12 The contrast sensitivity function (CSF)

Contrast sensitivity is usually determined with sine wave gratings which show no change in harmonic composition when defocussed (267, 145). The effect of optical blur is to decrease the contrast through light scattering, so the contrast of the grating has to be increased to reach the threshold of the subject. The contrast sensitivity of a sharply focussed 20 c/deg sine wave grating has been found to fall by a factor of 0.6 when 0.50 DS of blur is introduced (3mm pupil) (267). Plots of contrast sensitivity show that the effect of defocus is more marked at high spatial frequencies. Low spatial frequencies are only affected by high levels of blur (145, 268, 148) (Figure 4B2). It is, therefore, very important that refractive error is fully corrected when CSF measurement is used for the investigation of ocular conditions. A low frequency abnormality is unlikely to be due to optical blur so is most likely to be of neural origin (175, 267).

The isoametropic amblyopic defects of patients with uncorrected high refractive errors during early childhood can indicate the effect of such high degrees of blur on the visual system. The CSF of high myopes of between -5.50D and -14D is reduced at all spatial frequencies (269, 250). The movement threshold of a -9D myope was found to be normal (despite the reduced pattern thresholds) indicating that refractive error affects the X or sustained, but not the Y or transient system.

Enoch, Ohzu and Itoi (217) point out a possible pitfall in CSF measurement with patients wearing high refractive corrections. Magnification



OPTICAL BLUR (dioptres)

Figure 4B1 Snellen visual acuity as a function of optical blur open symbols 6m, closed symbols 12m testing distance.

From Tucker and Charman (264)

Figure 4B2 Contrast sensitivity as a function of optical blur showing that the reduction in contrast sensitivity increases with increasing spatial frequency and increasing degree of blur

From Campbell and Green (145)

by convex lenses of high power causes a decrease in the spatial frequency of the grating on the retina, while minification by concave lenses of high power causes an increase. If this is not taken into account, an artifactual low frequency defect in aphakia and high frequency defect in myopia might be measured. Correction in the form of contact lenses, rather than spectacles, would reduce these effects.

In axial myopia the effects of the highly concave lenses are counteracted to a certain degree by the increase in image size caused by the increased axial length of the eye. However, the retinal receptors could be separated more than in a normal eye, due to the stretching of the retina, causing a reduction in high frequency resolution. The situation is clearly very complex, and a precise study on the effect of high refractive error on the CSF would have to take all these factors into account.

4B13 Temporal resolution

As optical blur is usually considered in terms of its effects on spatial vision, there have been few reports on its effect on luminance modulation. Those which have been published studied only the CFF, not the full de Lange curve.

It might be expected that if the light scatter caused by the blur was sufficient to reduce the luminance modulation, the CFF would be reduced. Jennings and Charman (270) found this to be the case for a flickering square wave source of 8 minutes of arc but not for a source of 50 minutes of arc (Figure 4B3). They estimated the blur circle on the retina to be about 18 minutes per dioptre which would affect the edges

Figure 4B3 Critical fusion frequency as a function of optical blur (± 1 S.D.). Showing that defocus reduces the CFF for the 8 min but not the 50 min source. Under cycloplegia. Fixed pupil diameter of 7.5mn. From Jennings and Charman (270)

Figure 4B4 Effect of blur on border contrast. The rate of change of border contrast, characterised by the slope angle (θ) of blur distribution, is dependent on the amount of blur ($\Delta\alpha$) and contrast level (ΔB)

From Newman (272)

not the centre of the 50 minute source, but would scatter the light - reducing retinal illumination and modulation - across the 8 minute source. Jennings and Charman used a surround of approximately equal luminance. However, if the surround luminance is low or completely dark, the CFF might be found to increase as the blur would cause an increase in the size of the source on the retina.

The effect of light scatter on the modulation of the source would be expected to be related to the degree of blur, as well as the size of the source. Ong and Wong (271) measured the CFF for a group of 12 ametropes with and without refractive correction and only found a significant reduction in the highest myopes (-6D to -8.25D). Unfortunately, they do not state the size of field used.

When combinations of a small source (8 min.) and high blur (greater than $\pm$ 4D) are used, the modulation on the retina is too low for the flicker to be perceived at all (270).

4B2 Factors involved in the perception of blur

A blurred image consists of overlapping blur circles instead of sharp points of light. The effect of this can be understood by the example of a square wave grating. Small amounts of blur cause scattering only at the borders of the light and dark bars, producing the effect of blurred edges. This will have little effect on wide bars (low spatial frequency) but a marked effect on narrow bars (high spatial frequency). Increase in the degree of blur will scatter the light over a larger area, having an increasing effect on targets of low spatial frequency. The luminance profile of the square wave (Figure 4B4)

shows this schematically as a decreasing rate of change of contrast with increasing blur (272).

The effect of this physical decrease in target contrast on the psychophysics of the visual system can be understood by consideration of the CSF curve. Reduction in the contrast of the image will have a more marked effect on the perception of high spatial frequencies, which have a high contrast threshold.

This decrease in the perception of high frequencies will mean that the harmonics of sharp edged stimuli will be affected more than the fundamental frequency. This will be significant for objects of intermediate to low spatial frequencies since their harmonics are within the visible spectrum. The effect of this will be to change the apparent form of the stimulus - for example a square wave with blurred edges will be indistinguishable from a sine wave. Sine wave gratings consist only of a fundamental frequency, so optical blur only affects the modulation, not the form, of the stimulus (267, 145).

Depth of focus - The precision with which the eye can detect the effects of defocus as described in the previous sections is dependent on various characteristics of the eye and stimulus. This is usually considered in terms of the minimum perceptable change in focus - depth of focus, measured in dioptres - or in terms of the distance through which an object must be moved to produce the equivalent change in focus - depth of field measured in metres (Figure 4B5). This can also be considered as tolerance to defocus.

So many factors influence the depth of focus of the eye that it is

a) Large pupil

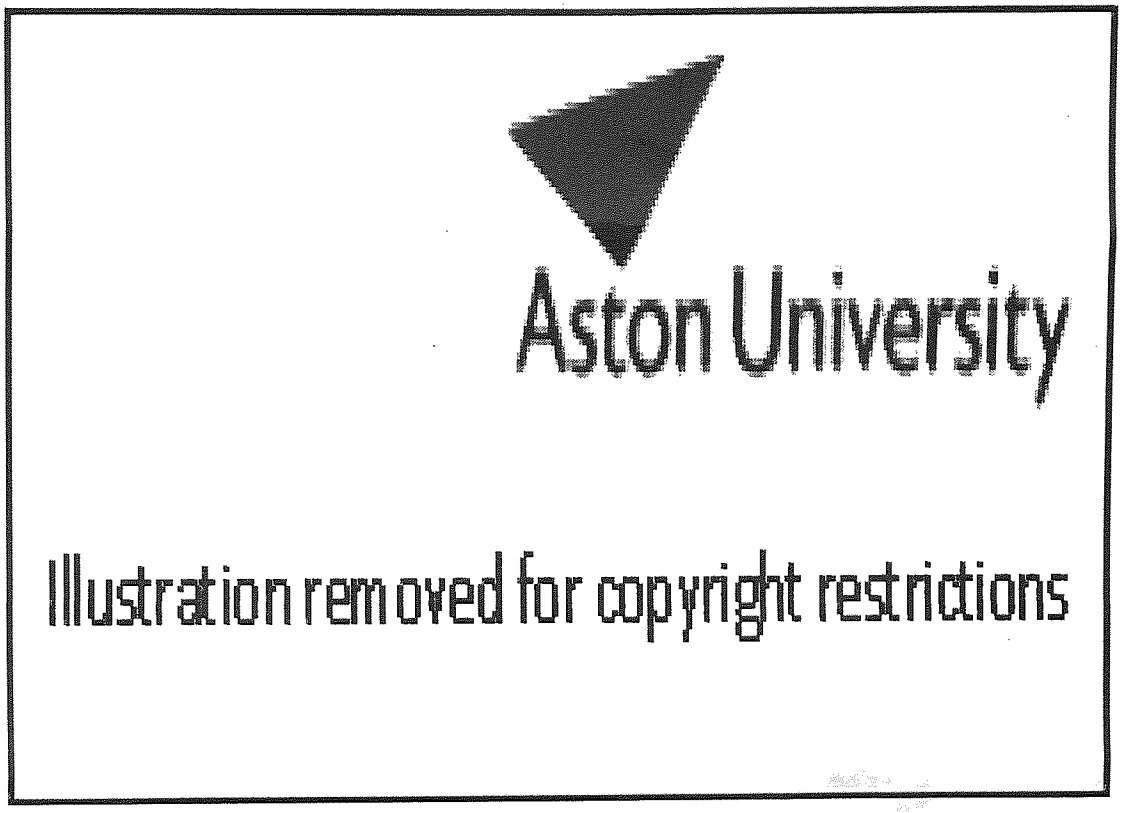


Figure 4B5 Depth of focus

Geometric depth of field is the range through which object point may be moved so that blur circle does not exceed receptor diameter. Size of blur circle produced on retina is proportional to size of pupil. Depth of field is inversely proportional to pupil size. From Adler (318)

impossible to give an absolute value. Geometric calculations often underestimate the actual depth of focus (148, 267), For example, Green, Powers and Banks (273) calculated the theoretical depth of focus of an eye with a 3mm pupil to be $\pm$ 0.10D while Campbell (148) obtained a value of $\pm$ 0.30D by practical measurement.

Different methods for assessing the depth of focus have included measurements of the deterioration of VA with refractive error (264), the discrimination of the least perceptible blurring of the image (148), the loss of visibiity or detectability of the target through loss of contrast (267) or the degree of blur which results in an accommodation response (265).

Figure 4B5 shows schematically that blur is not perceived until it extends beyond a single receptive field centre. In theory, therefore, a blur circle of up to 1 minute of arc will be undetected by an eye with 6/6 vision. An eye with a larger minimum angle of resolution (poorer VA) can therefore be presumed to have a larger depth of focus (273). This represents a neural limit on the perception of blur.

The depth of focus is also increased when low frequency targets are viewed (267) due to the fact that blur has less effect on low spatial frequencies, as already described. This will be more significant for an eye with poor VA. Whether an object will appear blurred or not will depend on the frequency composition of the object and the resolution of the eye, as high spatial frequencies must be able to be perceived first if their absence is to be appreciated (273, 274).

The depth of focus is also related to the clarity of the image, as it

is much more difficult to detect a small change in blur of a blurred, than a sharp, image (148). This is also related to the reduction of contrast caused by blur. As the edges of a sharp object become more blurred, it becomes more difficult to compare the contrast of the light and dark areas (272). The contrast reduction criterion for the detection of defocus has been estimated as 0.2 (275). Green, Powers and Banks (273) show that depth of defocus is related to the square root of this criterion, so it is not such an influentual factor on the depth of focus as pupil diameter or visual acuity.

Pupil diameter is a major factor in determining the depth of focus of the eye. Figure 4B5 shows that the depth of focus decreases as the pupil diameter increases due to the enlargement of the blur circles at the fovea by peripheral rays of light (318, 139, 148). This has been confirmed by studies of the effect of pupil diameter on depth of focus using Visual Acuity (264) and Contrast Sensitivity (267) methods.

The effect of peripheral aberrations with increasing pupil diameter is not as marked as would be expected due to the Stiles-Crawford effect (148, 264). This means that rays passing through the centre of the pupil are more effective in stimulating the cones than rays from the periphery, and so the effective pupil diameter is smaller than the actual pupil diameter. Taking this into account, Campbell (148) shows that the depth of field is inversely proportional to the effective pupil diameter, in a linear relationship when constant luminance is maintained. The Stiles-Crawford effect is negligible at pupil diameters of less than 2.5mm.

Examples of the depth of focus for three pupil diameters are shown in Table 4B2. Values determined experimentally are higher than those

calculated geometrically as previously observed.

TABLE 4B2

PUPIL DIAMETER	DEPTH OF FOCUS (DIOPTRES)	
	Geometrical calculations (318)	Experimental values (148)
2mm	± 0.06	± 0.44
4mm	± 0.03	± 0.24
8mm	-	± 0.15

The large depth of focus at small pupil diameters means that the effect of refractive error is less significant. This is applied clinically by the use of the pinhole disc to cut down refractive error. Any residual VA defect is therefore most likely to be due to neural factors. It is important that the luminance of the target is high enough to maintain an adequate level of retinal illumination in the presence of the pinhole disc.

Under normal conditions, changes in pupil diameter have a marked effect on retinal illumination. Over the large range of pupil diameters that Campbell investigated - 0.75 to 7mm - the pupil area changed by a factor of 87 times which causes a change in retinal illumination of 1.94 $\log_{10}$ units. Campbell found a linear relationship between the log luminance and the reciprocal of depth of focus, and suggested that this could be explained on the basis of change in retinal resolution as log luminance is also linearly related to the reciprocal of minimum angle of resolution (VA).

It can be seen that the interaction between all these ~~forms~~ factors makes depth

of focus difficult to quantify in natural settings. In general, some important practical points emerge. The absence of accommodation in older people is partly overcome by the increased depth of focus caused by their small pupils. At the other end of the age scale, the developing eye of a baby is not as sensitive to small refractive errors or aberrations of the eye as might be expected due to the lower resolving power of the retina.

4B3 Image quality in the eye and visual system

Optical media of the eye - Campbell and Gubisch (276) studied the quality of the optical media of the eye by measuring the reflection of the fundal image of a thin line source. The image is not a thin line, but is spread on the retina in proportion to the degree of light scattering and aberrations in the eye. It was found that the line spread function was minimum for a pupil diameter of 2.4mm. At larger pupil diameters the image is degraded by peripheral aberrations of the lens (272). Spherical aberration is due to the fact that a spherical lens is not a perfect focussing device, with rays from the periphery being brought to a focus closer to the lens than rays from the centre of the lens. Chromatic aberration occurs when the light consists of more than one wavelength - with light from the blue end of the spectrum being brought to a focus closer to the lens than light from the red end. At pupil diameters smaller than 2.4mm diffraction begins to degrade the image. This is caused by interaction between the rays of light bent at opposite pupil margins, causing augmentation and cancellation of the peaks and troughs of the waves. As a result, the image of each point of light on the retina will be surrounded by concentric light and dark rings.

The effect of the peripheral aberrations of the eye on the normalised

MTF has been measured physically (276) and psychophysically (145). Figure 4B6 shows that the MTF of the eye approximates more closely to that of an ideal optical system (limited only by diffraction) as the pupil diameter decreases.

Refractive components of the eye - Campbell and Green (145) measured the CSF with sine wave gratings viewed under normal conditions and gratings formed on the retina by laser interferometry. Since the latter method is unaffected by the refractive components of the eye, the effect of these components under normal conditions can be determined by the difference between these two CSF curves. The optical attenuation by the refractive components of the eye is found to increase with increasing spatial frequency (Figure 4B7) and is responsible for about one third of the attenuation of the CSF curve at frequencies of 30 - 40 c/deg and a pupil diameter of 2mm. Thus optical attenuation will increase for larger and smaller pupil diameters as described in the previous section.

The optical attenuation measured in this way is due to the refractive components alone and is independent of factors such as light scatter in the refractive components, and optical aberrations, as they are the same under both conditions. This is the major difference between the results obtained by this method and the double-pass techniques described in the previous section.

Neural factors - Ikeda and Wright (277) suggest that sustained (or X) cells are more sensitive to the effects of optical blur than transient (or Y) cells. This would be consistent with the idea that sustained cells are pattern detectors and transient cells are luminance detectors.

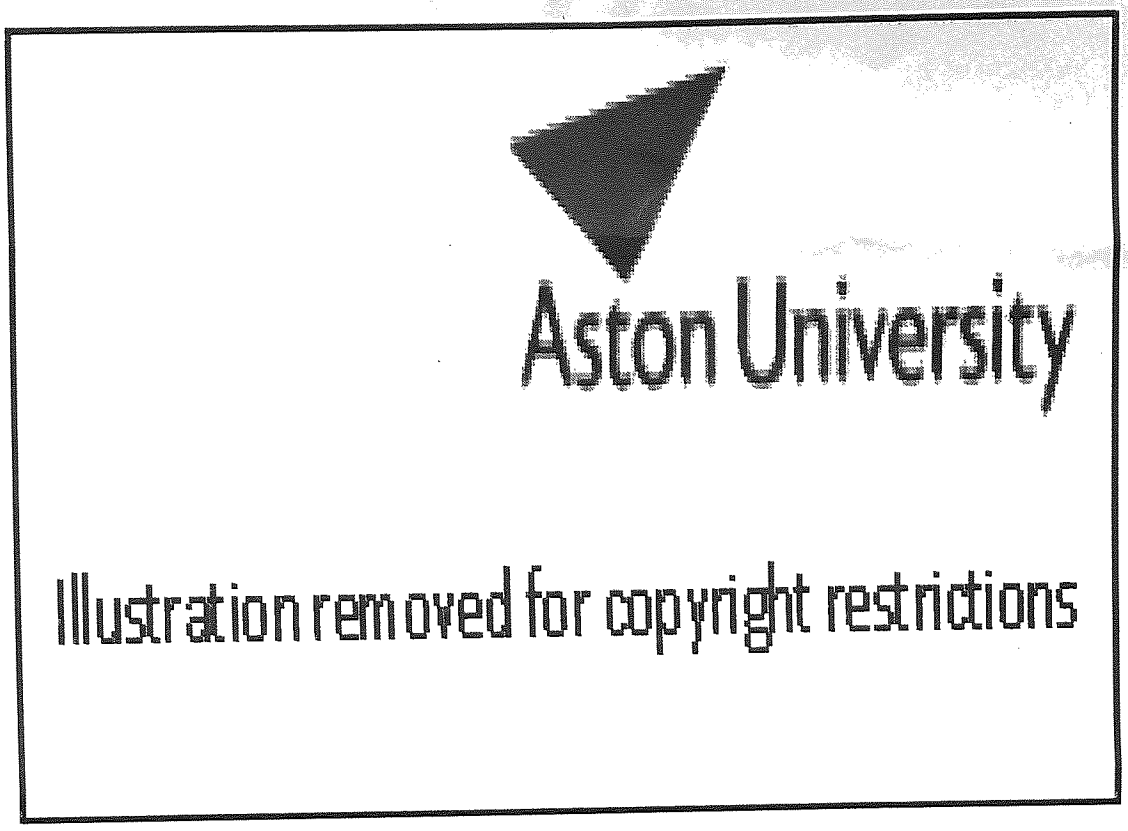


Figure 4B6 The transmission properties of the eye compared with those of a system free from geometric aberrations and limited only by diffraction. Increasing deviation of the results with increase in pupil size probably due to the addition of the effects of spherical aberration

From Campbell and Green (145)

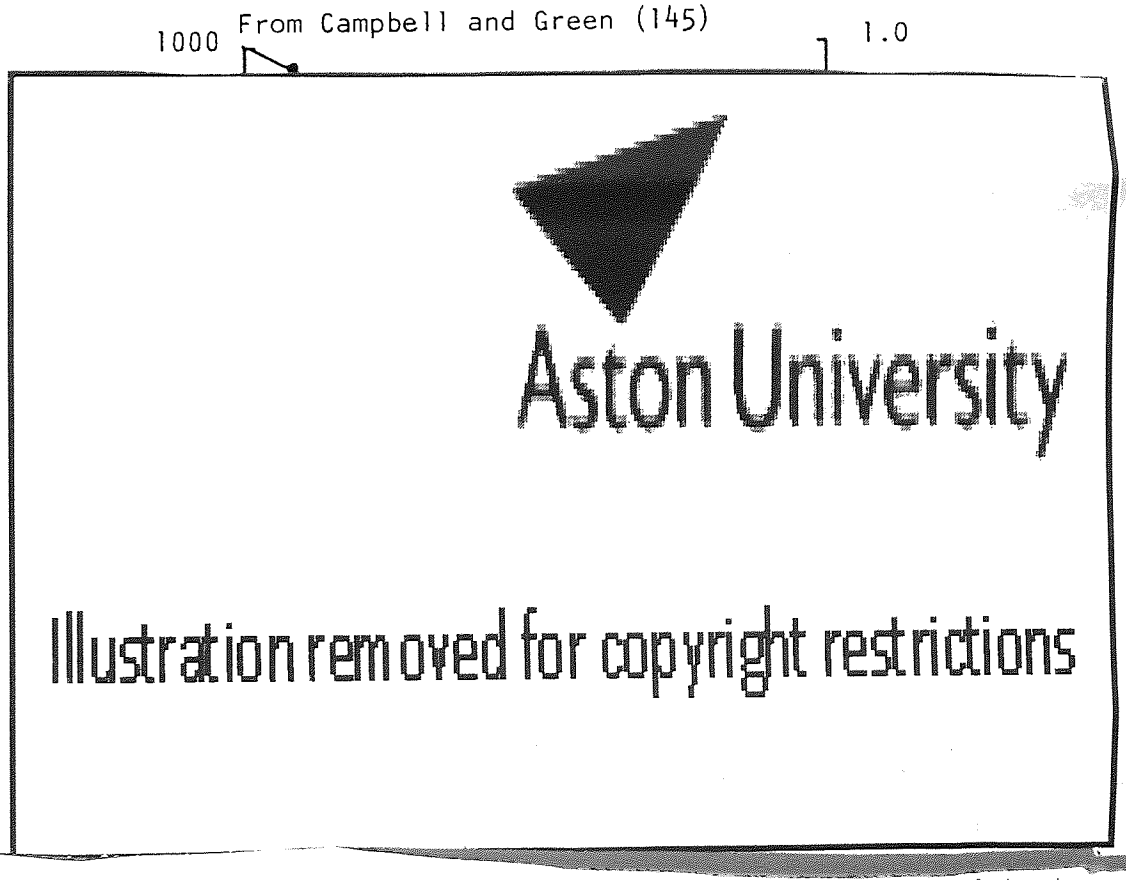


Figure 4B7 Comparison of normal CSF curve with the curve measured with interference fringes. Inset shows that the difference between the curves, due to the refractive components of the eye, increases with increasing frequency

They showed that the response of cells with sustained characteristics from the central 5^{o} of the retina is maximum to a small spot in sharp focus, reducing markedly with increasing optical blur and disappearing completely with optical blur of greater than 8D. However, peripheral cells with transient characteristics show a flattening and spreading of the response - decreasing at the centre of the receptive field but increasing at the outside of the field. This has the effect of increasing sensitivity at the expense of sharp vision.

4B4 The effect of optical blur on the VEP

There have been many reports which show that the amplitude of the VEP is maximum when a sharp image is viewed, and attenuates progressively with degradation of the image by optical blur (Figure 4B8) (102, 278, 279, 280, 281, 282, 283, 284, 285, 157, 163, 286). The refractive error of a subject can therefore be determined by recording the VEP as lenses are introduced in front of the eye. The best optical correction is represented by the lens which corresponds to the VEP of highest amplitude.

As most of these studies used steady state recording techniques - which merge the individual components of the VEP - there have been relatively few reports on the relationship between optical blur and VEP latency. However, an increase in latency (286, 287) and phase (288) with optical blur have been demonstrated, the best optical correction corresponding to the minimum latency. Sokol and Moskowitz (287) found that this effect was accentuated by cycloplegia, presumably due to the smaller depth of focus of the dilated pupil.

In addition to the determination of refractive error, these techniques

Figure 4B8 Reduction of the amplitude of the steady state VEP with optical blur. Check size 14min, contrast 0.4. From Millodot (151)

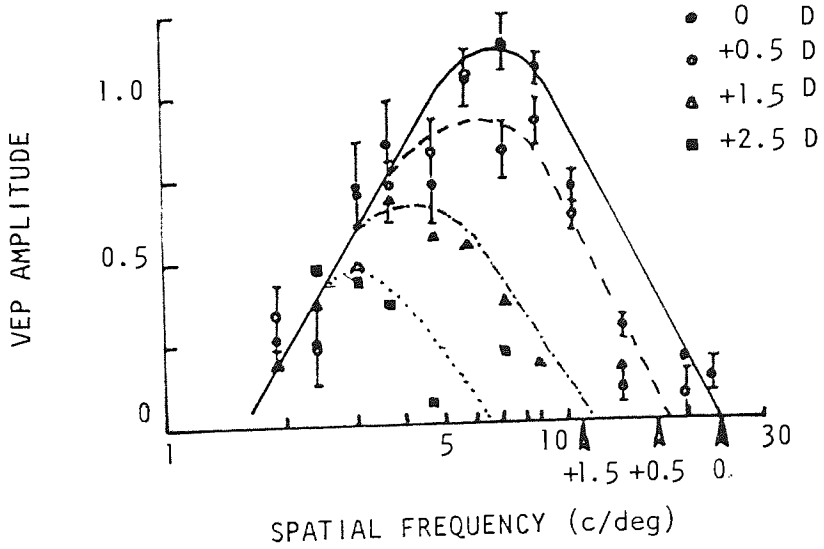


Figure 4B9 VEP amplitude reduction with optical blur as a function of spatial frequency. Square wave grating, contrast 0.40. Homatropinized eye viewing through 4mm diameter artificial pupil. Arrows show subjective visual acuity.

have been used to measure the amplitude of accommodation. As negative lenses are introduced, the subject exerts accommodation to keep the image in focus and the VEP amplitude (289) and latency (287) remain constant. When the limit of accommodation is reached, the image becomes blurred and the VEP amplitude decreases and latency increases.

Millodot and Newton (289) showed a very high correlation (0.91) between the amplitude of accommodation measured subjectively and that measured objectively by the VEP. They noted that about one third of their subjects did not show a great incentive for accommodation, with the amplitude of the VEP slowly decreasing until the limit of accommodation is reached.

The effect of optical blur varies with spatial frequency. As would be expected, the attenuation of the VEP with blur is greatest for small checks (284, 157, 283, 102) and gratings of high spatial frequency (284, 163) (Figure 4B9). The effect of blur on latency is also most pronounced for small checks (287). For the best results, gratings of higher than 5 c/deg (163) and checks of less than 15 minutes are recommended as these are purely contour specific (57).

The effect of optical blur on the VEP to large checks of the order of 40 minutes to 80 minutes is less marked but can still be demonstrated with higher degrees of blur in some subjects (283, 284, 287). Other subjects show no effect of blur when large checks are used (285, 102).

However, Regan and Richards (102) reported that optical blur had the effect of increasing the amplitude of the pattern reversal VEP to checks of greater than 22 minutes on one subject. Although this has not been reported by any other workers, examination of graphs of results show that one of Adachi-Usami's subjects (284) showed this phenomenon,

(steady state VEP to onset-offset gratings of 80 min.) and two of Harter and White's subjects (for a positive component of the flashed-on pattern VEP to 60 minute checks) (157). There is no obvious factor which connects these reports - in fact, they represent three completely different types of VEP stimulus. Both Regan and Richards and Adachi-Usami used small fields and all three studies used an active electrode in a scalp position which would correspond to the foveal projection on the visual cortex which is the most appropriate position for a study of the effect of blur.

It would appear then, that this is an individual phenomenon. Regan and Richards suggest that this is due to the combination of luminance and contour responses to large checks. It might be that these two types of response do not show a linear interaction, or that they arise in different parts of the visual cortex which cause partial cancellation and augmentation effects in certain individuals due to the arrangement of the visual cortex.

Astigmatism can also be determined and corrected using VEP techniques. The amplitude of the VEP of an astigmat will be maximum when the orientation of a grating stimulus corresponds to the clear meridian and minimum when the orientation corresponds to the blurred meridian (290,163, 281). Sokol and Moskowitz (287) have also shown that astigmatism can be determined using checkerboard stimuli and latency measurements, the latency of the VEP being minimum when the image is clearest.

One of the disadvantages of using a checkerboard stimulus is that the components vary in two dimensions, so the blurred meridian will be stimulated at the same time as the clear meridian. Sokol and Moskowitz describe the Fourier components of the checkerboard in terms of harmonics parallel to the edges of the checks and fundamental components at 45^{o}

and 135° to the harmonics. They show that the latency of the VEP is increased when both fundamentals are blurred but unchanged when one is blurred and the other is in focus. The former occurs when the axis of astigmatism corresponds to the axis of the edges of the checks (so one set of harmonics will also be blurred) and the latter occurs when the axis of astigmatism corresponds to the orientation of one of the fundamentals (blurring both sets of harmonics). This implies that the relative effect of the fundamentals is greater than the effect of the harmonics. The final result will be expressed in terms of two orthogonal meridians, but cannot distinguish between the two to give the exact axis of astigmatism.

Regan (290) preferred the use of a checkerboard stimulus as it elicits a larger VEP, so suggested that a slit was rotated in front of the eye to determine the axis, instead of rotating the stimulus. However, even in a perfectly spherical eye, there would be variations in the VEP amplitude as the slit was rotated due to retinal orientation effects and alignment with different components of the checkerboard. Presumably, only moderate to high degrees of astigmatism would be sufficient to overcome these effects.

The procedure for determining a full refractive correction with the VEP has been described as follows (290, 163).

1 Determine the axis of astigmatism

2 With the slit, or grating, at this axis, determine the best spherical correction

3 With the slit or grating at 90° to this axis, determine the best spherical (290) or cylindrical (163) correction

The former gives the final result in cross-cyl form and the latter in sphero-cyl form.

With this correction in front of the eye, the amplitude and latency of the VEP should be the same for all orientations of the slit.

4C OPTIC NEURITIS

4C1 Aetiology

Optic neuritis refers to inflammatory, demyelinative or vascular disorders of the optic nerve, leading to sudden, marked visual failure. Inflammation affecting the nerve head at the optic disc can be seen on ophthalmoscopy and is known as papillitis. The majority of cases involve the optic nerve behind the eye and are therefore known as retrobulbar neuritis. These present a more difficult diagnostic problem as the optic disc and fundus are normal in appearance (2, 291, 292).

The majority of patients with optic neuritis are aged between 20 and 50 (292). The age of onset can be an important guide to the cause of neuritis : a vascular origin is more likely in patients over 44 years, demyelination in the 20-40 age group and systemic diseases or poisons, frequently associated with encephalitis, in patients under 20 years (2).

Demyelination is the most common cause of optic neuritis (291) Parts of the myelin sheath which covers the nerve fibres from just behind the lamina cribrosa degenerate, impairing the conduction of impulses through the nerve. The myelin shows little tendency for regeneration and eventually the demyelinated areas are replaced by scar tissue. However, the actual nerve fibres are usually unaffected, accounting for the recovery of vision after the acute attack of neuritis (2, 292).

The recognition of demyelinative lesions of the optic nerve is of particular diagnostic significance, as they can be an early sign of the progressive disease multiple sclerosis (MS). MS is caused by multiple areas of demyelination all over the body, but it seems that the visual

pathway is particularly sensitive to this process (293).

Cogan (2) considers that MS is probably the most frequent cause of optic neuritis, and that about half of all patients already have, or will have other manifestations of MS. He states that optic neuritis is the first symptom in about 15% of MS patients, and about 40% have optic neuritis at sometime during the course of the disease. Perkin and Clifford Rose (292) review 10 studies of the percentage of cases of optic neuritis progressing to MS, but the estimates vary between 3.8 and 59% depending on differences in patient selection, definitions of optic neuritis and MS and duration of follow up period. Recurrent attacks of optic neuritis in either eye are often indicative of MS although it might be many years before more widespread symptoms become evident (291).

4C2. Symptoms and Signs of Optic Neuritis

Optic neuritis is characterised by a sudden dramatic loss of vision, usually in one eye (291). As the retrobulbar form is not evident on ophthalmoscopy, the initial diagnosis has to be made on the basis of other symptoms and signs.

There is often pain on movement of the eye, probably as a result of the close proximity of the affected optic nerve and the attachments of extraocular muscles at the apex of the orbit. The globe can also be tender when pressure is applied to the eye in the region of the insertion of the superior rectus tendon (2). Pupil reactions can appear to be normal, but contraction in the affected eye is poorly sustained in some cases (291). In other cases, the reactions in the affected eye are depressed, or the pupil is dilated in the acute phase (292).

Psychophysical testing frequently reveals central field defects which may be absolute, or relative for colours (292, 291). Red-green colour deficiencies are often found (292).

The three psychophysical methods relevant to this project will be considered in more detail in the following sections:

4C21 Visual acuity

Optic neuritis causes a marked loss of visual acuity during the acute phase which can progress to complete blindness of the affected eye within a week of the onset of symptoms (291). Figure 4C1 shows the range of visual acuities on presentation in one study of 165 cases of optic neuritis.

The papillo-macular bundle of fibres in the optic nerve seems to be particularly vulnerable to demyelinative inflammatory or compressive lesions, although the reasons for this are unclear. Anatomically, demyelination is no more frequent in the central fibres than in the other fibres of the optic nerve on autopsy. The particular vulnerability of the papillomacular fibres must therefore be functional, possibly as a result of pressure from the swollen nerve (2).

The effect of this particular vulnerability of the papillomacular fibres is to produce a central scotoma and therefore a marked reduction in visual acuity. Fortunately, this process is reversible, and visual acuity can return to normal levels over weeks or months as the oedema subsides and some repair of the fibres takes place (294). Perkin and Clifford Rose (292) reported that visual acuity returned to 6/6 in 69.7% of the patients in their study within 6 months of the onset of visual symptoms.

Figure 4C1 VA at presentation in 165 cases of optic neuritis From Perkin and Clifford Rose (292)

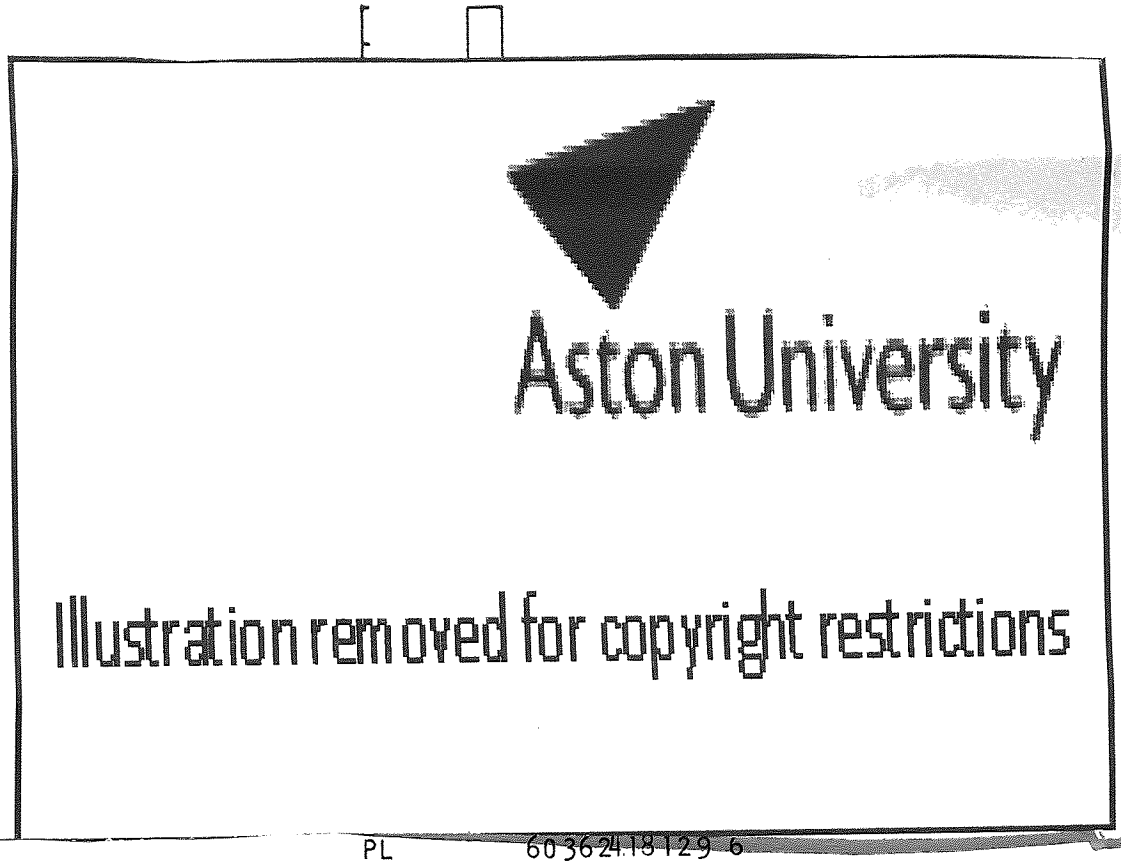
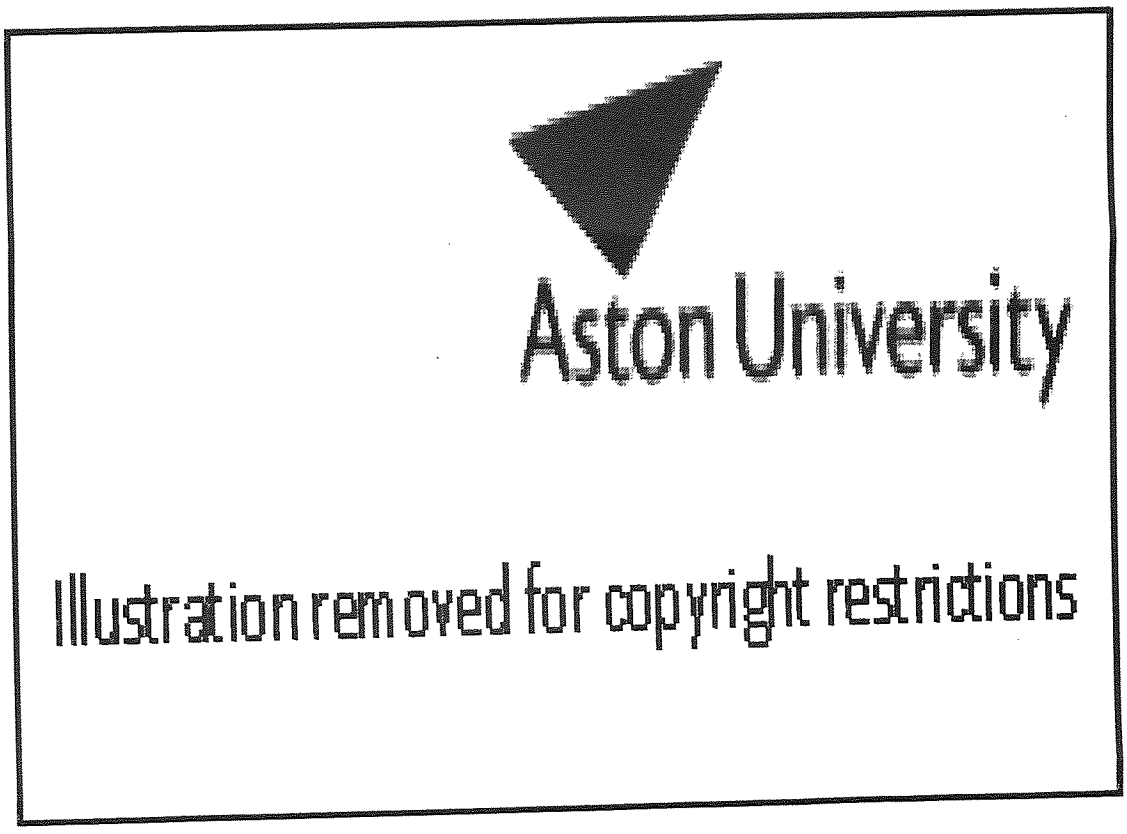


Figure 4C2 The flash and pattern VEP in 19 cases of acute unilateral optic neuritis. Mean latency and S.D shows smaller variability and overlap of pattern VEP.

From Halliday (70)



The mean length of time for recovery of 6/6 vision was 8.1 weeks. They found that the severity of the initial acuity loss did not affect the prospects for recovery in either of these respects.

However, even after full recovery of visual acuity some patients still report visual symptoms (180) and this had led to the investigation of vision at other spatial frequencies and contrast levels as shown in the following section.

4C22 The contrast sensitivity function

Contrast sensitivity defects in the presence of normal visual acuity have been found after optic neuritis (222, 181, 199) and in patients with multiple sclerosis (180, 200).

Regan, Silver and Murray (180) have described five categories of CSF findings in multiple sclerosis:

1) no loss of contrast sensitivity
2) similar loss at all spatial frequencies
3) preferential loss at high, or medium and high spatial frequencies
4) " " " medium spatial frequencies
5) " " " low spatial frequencies

Categories 1) - 4) have also been found in the presence of normal VA in multiple sclerosis (200) and optic neuritis (181). However, neither study reported any patient with a low spatial frequency defect alone.

The total Arden score is also raised in optic neuritis (199) but this score provides no information about the spatial frequencies affected.

However, Arden and Gucukoglu (222) reported that the types of defect measured with Arden gratings were varied, with more defects evident at the highest spatial frequency (6.4 c/deg) than at the lower frequencies (0.2 and 0.4 c/deg).

It is clear that visual acuity measurement alone would not have revealed the full extent of the visual disability in groups 2) 4) and 5) making CSF a more sensitive indicator of demyelination.

Selective spatial frequency abnormalities have been interpreted as indicative of post geniculate defects since spatial frequency selective neurones are not found outside the visual cortex (180, 18). The mean bandwidth of the selective spatial frequency defects in the 5 cases reported by Regan, Silver and Murray (180) is 2.6 octaves. The authors interpret this as representing defects in neighbouring narrow one octave channels.

However, 8 out of the 11 medium frequency defects in this study were unilateral, which would be more consistent with pre-geniculate pathology. The authors cite the observation of Kelly (295) that, although single spatial frequency selective neurons are only found in the cortex, damage to certain areas of the retina could be confined to medium-spaced or closely spaced ganglion cells, resulting in a selective spatial frequency defect.

4C23 Temporal resolution

Early studies showed that the CFF was reduced in multiple sclerosis (296, 297). Patients with a central scotoma due to optic neuritis did

not show a linear increase in CFF with log area of stimulus as predicted by the Granit-Harper law. Instead, the CFF was reduced for small stimulus fields within the scotoma, increasing only when the field extended beyond the central 1.25 degrees (298).

McDonald (294) suggested that three factors contributed to this decrease in the CFF with demyelination (see also Section 4C31).

i) Conduction block in some fibres prevent some retinal signals reaching the higher visual centres, effectively reducing the retinal area

ii) Increased refractory periods in some demyelinated fibres mean that the bursts of firing cannot synchronise with the frequency of the stimulus, causing a slowing and irregularity of the transmitted impulses. Failures in the transmission of trains of impulses at frequencies as low as 1Hz. have been found in critically demyelinated peripheral fibres (299)

iii) Unequal degrees of slowing in different fibres of the nerve result in complete desynchrony of the impulses arriving at the higher visual centres, so the original signal is lost

The few reports on the effect of demyelination on the de Lange curve show a variation in results. One definite MS patient had a marked unilateral defect at all temporal frequencies and one other probable case showed no defect (232). Optic neuritis has been reported to cause a marked high frequency defect in the acute phase, improving during recovery (228) but one other paper reports a slight low frequency defect

in two cases and no abnormality in a third (169). Clearly, there is room for further research on the effect of demyelination on the De Lange curve.

4C3 The effect of demyelination on the VEP

In this section optic neuritis and multiple sclerosis will both be considered under the term 'demyelination'.

The amplitude of the flash VEP is reduced during an acute attack of optic neuritis and the response can be abolished altogether if the vision is reduced to the perception of light only. The amplitude returns to normal as the visual acuity recovers (300, 301).

The latency of the flash VEP is increased in demyelinative lesions (300, 301, 302, 303, 77). However, the differentiation between a normal flash VEP and one delayed by demyelination is often blurred by the normal variability of waveforms (301) and the large variation in normal latency values, causing an overlap between the two groups (70) (Figure 4C2). The waveform of the flash VEP can also break up in demyelination, making the components hard to identify (303). It has been claimed that the diagnostic accuracy can be improved with the use of a macular flash stimulus (304, 69).

The accuracy of the VEP in the diagnosis of demyelination has been markedly improved by the introduction of the pattern VEP. Comparative reports have shown that the increase in latency is much greater for the pattern VEP than for the flash VEP (305, 77, 302, 304). As an example, the mean flash delay in Halliday, McDonald and Mushin's original study was 10.2 $\pm$ 14.5 msec while the mean pattern reversal delay was 33.6 $\pm$ 18.5 msec (301). In addition, the diagnostic accuracy is improved by the small variation in normal pattern reversal latencies, giving almost no overlap

between the two groups (Figure 4C2) (70). It has been suggested (305, 77) that the two types of VEP offer complimentary information - the pattern VEP reflecting macular integrity and the flash VEP reflecting the integrity of fibres from a wider area of retina. The high sensitivity of pattern VEP would therefore be reflecting the particular sensitivity of the papillo macular fibres to demyelination.

The marked delay of the pattern reversal VEP in demyelinative lesions has been confirmed by many studies (77, 69, 88, 200, 67, 222, 302, 304, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 111). The pattern onset-offset response also shows this marked delay giving a higher detection rate in Riemslag, Spekreijse and Van Walbeck's study (67) of MS patients. This was due to a small number of patients in which a reversal response could not be elicited, the authors pointing out that an absent response in itself is not diagnostic of MS.

This marked pattern VEP delay usually persists indefinitely after the eye has recovered from an acute attack of optic neuritis and visual acuity has returned to 6/6 (35, 304, 312, 315) although a few exceptions to this rule have been found (88). In this respect VEP latency shows very different characteristics from pattern VEP amplitude, which is reduced in the acute phase but usually returns to normal values as the visual acuity recovers (35, 304, 315). As before, exceptions to this rule have been observed (312). Amplitude has also been shown to parallel the reduction and subsequent recovery of visual acuity in two MS patients during and after exercise (313).

Changes in the waveform of the pattern VEP have also been observed in some cases. These have been described as an inability to identify the

components (308) a splitting of the major positive component into a W shaped wave (222, 307) and a broadening of the response (77, 307, 69). The latter effect has been ascribed to the differences in fibre conduction times caused by different degrees of demyelination (77, 307).

The steady state VEP is also affected by demyelination. Phase lag has been reported in the pattern reversal (304, 305, 232, 77) and the luminance (77) steady state VEP. The apparent delay of the VEP cannot be inferred directly from a phase lag but can be determined from the slope of the phase v frequency plot (77, 316). Milner, Regan and Heron (316) claim that the middle frequency flicker system is particularly affected in optic neuritis, but Duwaer and Spekreijse (77) challenge their conclusion. They found the normal range of steady state luminance VEPs too variable to be of diagnostic value, and recommend the use of the pattern VEP. They state that a low stimulus rate improves the specificity of latency determination. As latency is the important factor in the diagnosis of demyelination, transient stimulation would seem the more appropriate technique in this case.

These VEP findings have provided a major advance in the diagnosis of demyelinative lesions. Firstly, VEP latency delay and amplitude reduction provide powerful evidence that marked visual loss with no ophthalmological abnormality is due to retrobulbar neuritis rather than a hysterical cause.

Secondly, the persistence of the latency delay after the recovery of visual acuity can provide evidence of a previous attack of optic neuritis months or years after the event. Thirdly, it can also give evidence of clinically silent demyelinative lesions of the optic nerve in MS (306).

Halliday (70) has tabulated the results of different investigators and

shows that the percentage of delayed VEPs increases with the probability of demyelination of the optic nerve - being highest in patients with a history of optic neuritis, definite MS or a combination of the two (above 90%). It has also been suggested that the accuracy of the technique can be improved by decreasing the luminance of the stimulus (70, 317).

The pattern VEP has been found to be a more sensitive indicator of MS than the cervical somatosensory evoked response, saccadic velocity measurements or the CT scan (310). The luminance VEP was reported to be superior to perimetry in one report (300) although another investigation showed careful field examination to be as useful as the pattern VEP (314). One comparative report suggested the Arden grating test showed a greater probability of making a positive diagnosis than the VEP in optic neuritis (222) although another found them to be equally sensitive (199).

4C31 Mechanism of the VEP abnormalities

As the diagnosis of demyelination ~~of~~ by the VEP ~~results~~ rests on the detection of increases in latency, it is important that the effect of stimulus parameters is fully understood. Spekreijse, Duwaer, and Posthumus Meyjes (232) have shown that latency increases can be produced in normal subjects by refractive error and by changes in check size, field size, contrast and luminance. It is, therefore, important to standardise these parameters for patients and control measurements, so that pathological latency increases might be correctly identified.

McDonald (299) shows that the effect of extensive demyelination on a nerve fibre is to prolong the refractory period of transmission between impulses. This effect accumulates when stimulation is prolonged, causing periods of complete conduction block. With less severe demyelination

conduction is possible, but the velocity is decreased.

Applying animal data to man, McDonald estimated that such slowing of conduction in focal demyelinative lesions could account for VEP delays of up to about 24 msec. He therefore concludes that there is not enough evidence to show that this is the major explanation for large VEP delays. Larger delays could be explained by the additive effect of multiple lesions in the optic nerve and visual pathway although alternatively, multiple lesions might cause complete conduction failure.

Other factors contributing to the VEP delay could include delays in the generation of the cortical response due either to conduction block in many fibres, or as a result of unequal slowing in the responses received from different fibres.

Selective impairment of the faster optic nerve fibres is an unlikely cause of the delay as optic neuritis predominately affects central vision which is mediated by the slower fibres.

McDonald, and also Halliday and Mushin (35, 301) have suggested that the pattern of visual acuity loss in optic neuritis reflects an initial complete conduction block and its subsequent recovery, leaving the nerve fibres with decreased conduction velocity. The VEP amplitude reflects the degree of conduction block and is sensitive to the local changes associated with the swelling and oedema of the acute attack, such as electrolyte balance and temperature. The return of VEP amplitude to normal levels reflects the recovery process. The persistence of the VEP delay however, probably reflects a more stable anatomical feature, such as the areas of demyelination which cause the reduction in conduction velocity.

These theories have been cited by other authors to explain the changes in VEP amplitude (313) and latency (88). However, the magnitude of the VEP delay has still not been completely accounted for. Bodis-Wollner, Hendley, Mylin and Thornton (200) and Cook and Arden (302) both consider the theory that demyelination might selectively affect the X or Y cell system, but do not find evidence to support this. Both papers consider cortical processing delays to be a possibility which would be consistent with the spatial frequency defects observed in psychophysical CSF studies. Unilateral delays would seem to be inconsistent with this theory, but Bodis-Wollner, et al. put forward two theories which might reconcile these different pieces of evidence. They cite the finding that the first neurones in the striate cortex of the Rhesus monkey receive geniculate fibres from one eye only, and the suggestion that viral damage to the nerve fibres from one eye could extend as far as the cortex, but emphasise that this is all conjecture.

4D DEMENTIA OF THE ALZHEIMER TYPE

4D1 Aetiology

Dementia has been defined as "the global impairment of higher cortical function including memory, the capacity to solve the problems of day to day living, the performance of learned perceptuomotor skills, the correct use of social skills and control of emotional reactions in the absence of gross clouding of consciousness. The condition is often irreversible and progressive" (319).

The incidence of dementia in the population is hard to estimate, due to the misconception that dementia, or 'senility' is normal in old age. The known incidence has been reported as between 5 and 7% of the population, rising from 2.1% of the population under 60 years to 17.7% of those over 80 years of age (319).

Present day medical care and improved living conditions means that the proportion of elderly people in the population, and therefore the actual number suffering from dementia, is increasing (319, 320, 321). The urgent need for research into the diagnosis and treatment of dementia and for improved services and education has been emphasised by reports of the Medical Research Council (320) and the Royal College of Physicians (319).

Dementia can be of primary or secondary origin. The primary classification includes senile dementia and various forms of presenile dementia bearing the names of early researchers who attempted to group clinical signs and symptoms in order to define the disease. It is still unclear

whether these groupings represent separate diseases, or different aspects of the same process. They include Alzheimer's disease, the most common form, which is a diffuse cortical atrophy; Pick's disease, a lobar atrophy; Creutzfeldt-Jakob disease, a cortico-striato-spinal atrophy and Huntington's disease, a chronic progressive hereditory chorea which usually starts in the 3rd or 4th decade (322). It is now generally believed that senile dementia is a disease, not an inevitable result of old age (323) and pathologically bears many similarities to Alzheimer's disease (322). This project will be limited to the study of senile dementia and Alzheimer's disease, regarding them as the same process, differing only in the age of onset (323, 324, 325, 326, 327).

It is very important that an accurate diagnosis is made, to differentiate between primary dementia, for which no cure is known, and a secondary dementia which is caused by a treatable condition. Among the conditions which can lead to secondary dementia are cerebrovascular diseases, encephalitis, neoplasms, trauma, diffuse demyelinating diseases, metabolic or endocrine disorders, deficiency diseases, intoxications, epilepsy and hydrocephalus (322).

Clinical Features (319, 328) - Alzheimer's disease is characterised by marked memory loss. However, in the early stages this is often masked by the patient's retained intellectual capability and social competence, and, in the case of an older person, might be considered to be part of the normal forgetfulness of old age. As the disease progresses, it becomes more obvious to the patient and family that something is wrong. The patient might experience confusion and difficulty in tasks such as feeding, dressing, reading and writing. This inability to perform what were previously simple tasks may lead to depression, which could cause some diagnostic confusion. Other physical manifestations of the disease

can be loss of speech and swallowing difficulties, lack of concentration and insomnia, incontinence, loss of balance, and in some cases abnormal groping and jerking movements with possible fits or convulsions.

In the final stages of the disease the patient becomes bed-ridden and emaciated and is very susceptible to diseases such as pneumonia. Fortunately, the patient is usually unaware of his or her condition at this stage. The length of time taken for the disease to progress from early to final stages can vary from a few months to several years. Some clinical features for the differential diagnosis of Alzheimer's disease are given in Table 4D1.

Histological signs - Histological examination of a brain affected by Alzheimer's disease shows a widespread breakdown of tissues, which inevitably must affect the neural pathways (329). Two characteristic features were first documented by Alzheimer early this century, and are therefore often referred to as 'Alzheimer changes'. The first is the presence of abnormal tangles of fibres accumulating within the neurones. These have been shown to be made up of paired helical filaments which could indicate a defect in RNA metabolism (319). The second feature is revealed as collections of degenerating nerve endings known as neuritic, or senile plaques. These contain amyloid and are often found near blood vessels, which might indicate a metablic defect in the body (320) or an alteration in immunity (326).

Alzheimer's changes are scattered widely throughout the cerebral cortex but are particularly marked in the neurones of the hippocampus where memory process are consolidated. The changes are less evident

TABLE 4D1

DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE (338)

CLINICAL FEATURES	ALZHEIMER'S DISEASE	NON-ALZHEIMER'S DISEASE
Memory loss	Early	Late
EEG changes	Early	Late or never
Apraxia	Early	Late
Catastrophic reaction	Early	Late or never
Fits	Late	Early
Incontinence	Late	Early
Confabulation	Late or never	Early
Personality changes	Late	Early
Social incompetence	Late	Early
Psychotic features	Late	Early
Reaction to deficit	Appropriate	Inappropriate
Social class	Grade III and above	All grades
Age of onset	After 55 years	Frequently before 55 years
Resembles senile dementia	Always	Never
Family history	Rare	Common
Cerebral biopsy	Always positive	May be positive

in the deep grey matter and brainstem (319).

It has been suggested that these abnormalities could be caused by a virus or, alternatively, by a toxic substance such as Aluminium (as dementia has been found in patients with "dialysis encephalopathy" where there is a raised concentration of Aluminium in the brain).

Cortical atrophy - Studies of the biochemical composition of the temporal lobe indicate loss or shrinkage of cells of about 30% in the late stages of Alzheimer's disease, compared with controls. This results in cortical atrophy, in which the brain shrinks and the ventricles become enlarged (319). Some reports state that the frontal and temporal region of the brain are affected most and the occiput least (319) although other accounts show that there is no consensus of opinion on this matter (330). The brain of a patient with Alzheimer's disease can weigh as little as 1000g as compared with 1200 - 1350g in a normal person (319).

It has been suggested that the loss of nerve cells is due to an immunological response either to autoantigens or to an infective agent (319). There is a degree of loss of nerve cells in the normal ageing brain, but this process is believed to be much more marked in Alzheimer's disease.

Biochemical factors - Acetylcholine is the transmitter substance believed to be responsible for higher mental function in the brain. It is now widely accepted that there is a reduction in the enzyme

responsible for synthesing acetylcholine in Alzheimer's disease (331, 319). This reduction seems to be specific to Alzheimer's disease and not due to such factors as drug treatment or hospitalisation, and is not found to be significantly reduced in Huntingdon's disease, Parkinson's disease, depression, multi-infarct dementia or renal encephalography (331). The enzyme reduction is greatest in the temporal and parietal cortex and hippocampus (331) and, it is suggested, could be due to the large degree of cell destruction found in the nucleus basalis of Meynert which is one of the regions responsible for the production of acetylcholine. This nucleus lies deep in the centre of the brain and sends axons to both the cortex and the hippocampus (332). Research is in progress to find an agent which will replace the deficient enzyme and restore normal levels of acetylcholine (333).

Genetic factors - There is evidence that first degree relatives of a patient with Alzheimer's disease have an increased risk of developing the disease. There is also growing evidence of a similarity between the processes involved in Alzheimer's disease and Down's syndrome.

(i) Families of subjects with an autopsy diagnosis of Alzheimer's disease are claimed to have a higher proportion of Alzheimer's disease, Down's syndrome, and immunoproliferative disorders (334).

(ii) It appears that patients with Down's syndrome are very likely to develop Alzheimer's disease. A review of many reports shows that senile plaques and neurofibrillary tangles are almost universal in

Down's syndrome patients over 35 years of age at autopsy (334).

(iii) A study of 80 patients with Alzheimer's disease shows that, at birth, the median age of their mothers was 35.5 years and of the fathers was 38 years, both of which are about 10 years older than the average age of parents in the general population. All of the patients were the first born. The report points out that Down's syndrome is also linked to later childbirth (335).

This relationship has led to the suggestion that the neuropathological changes in Alzheimer's disease might be related to an acquired chromosomal defect which could be related to the assembly of microtubules or susceptibility to infection by a common virus (334).

This brief review shows that current research has raised the possibility of Alzheimer's disease being connected with metabolic, immunological, toxic, viral, biochemical or genetic factors. Clearly, research must be continued in order to clarify this situation. Once the factors involved in Alzheimer's disease are more clearly understood, a logical approach to treatment might become possible.

402 Diagnosis of Alzheimer's disease

The importance of early detection of Alzheimer's disease is widely recognised (319, 336). Although the extent of the condition might not be realised in the early stages, a person in a responsible job might be making serious errors of judgement. Early diagnosis will become even more important when treatment is developed as it will be important to halt the degenerative process before too much irreversible damage is

done (329). Screening techniques might assist in identifying patients with early dementia. However, the yield would be very small - about 6% of the population - and it would probably be difficult to persuade apparently healthy people to participate in such a scheme (337). To undertake a task of this magnitude, the screening test would have to be accurate, non-invasive and painless, and simple cheap and rapid to administer. Although techniques are being developed which give clear results in moderate and severe dementia, there are still very few studies on their success in early diagnosis. This is, therefore, one of the most important areas for future research (319, 320).

By the time a patient consults a doctor, the disease might be fairly well advanced. It is important that the diagnosis differentiates between dementia and other confusional states, and excludes treatable conditions. Once primary dementia is established, differential diagnosis of the various subgroups is of more academic importance and often difficult to establish due to the overlap of symptoms in the more advanced stages.

Histological confirmation of the diagnosis of Alzheimer's disease can only be made by cerebral biopsy, in which a small piece of the cerebral tissue of the patient is removed and examined for evidence of Alzheimer's changes.

This method of diagnosis is considered to be as accurate as clinical diagnosis, although false positives have been reported (338). Although the information obtained from cerebral biopsy can be very useful for both diagnosis and research, it is a potentially dangerous invasive technique (339). With the development of alternative non-invasive

techniques for diagnosis, there are very few circumstances in which cerebral biopsy would now be considered ethically acceptable (339).

The diagnostic value of the measurement of cerebral blood flow (CBF) in dementia has been studied by a Swedish group since the 1960s, and the following information is from Gustafson's summary of their work (340). This technique (see Appendix 2) measures the CBF which is dependent on the functional metabolic level of the brain. In normal individuals the CBF increases with mental activation. The results mainly reflect the blood flow in the superficial parts of the hemisphere (the cortex) as the radiation from deeper levels is attenuated by tissue.

It has been shown that reduction in cerebral blood flow is related to the severity of dementia in moderate or severe cases. In addition, the area of reduced CBF was found to correspond to the type of pathology. For example, patients with Alzheimer's disease and pronounced mental deterioration show CBF reduction in the postcentral temporo-parieto-occipital and posterior cingulate gyrus areas, but less involvement of the frontal lobes (Figure 4D1). The anterior cingulate gyrus and primary projection areas were comparatively spared, while a subnormal response to mental activation is found in the association cortex. CBF values from five patients with Pick's disease show reductions in the fronto-temporal areas, which corresponds to the accepted pattern of cortical atrophy in this condition. The CBF findings are less consistent in multi-infarct dementia, showing generalised hemispherical or regional asymmetries.

These differences show that differential diagnosis is potentially possible with this technique. The inhalation version of the technique

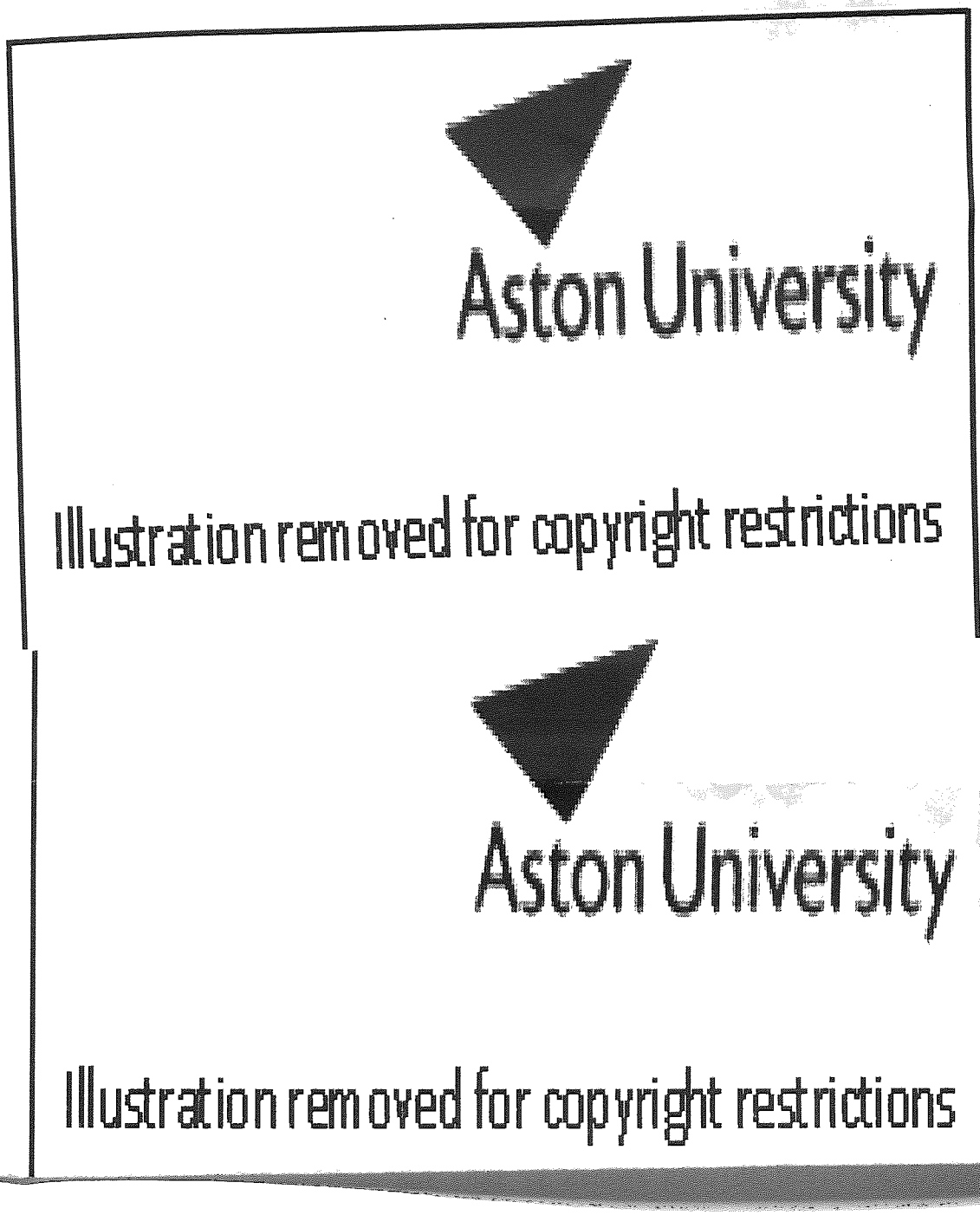


Figure 4D1 Distribution and degree of cortical degeneration in Alzheimer's disease as revealed by measurement of cerebral blood flow showing particular involvement of temporo-parieto-occipital areas. The patient died at 60 years with 10 years history of progressive dementia. From Gustafson (340)

is non-invasive and could therefore be used for monitoring of treatment. Research has yet to show whether CBF measurement is successful in the diagnosis of dementia in the early stages.

Techniques for the assessment of cortical atrophy, of which the computerised axial tomograph, or CT scan is now the most common (see Appendix 2) are often used in cases of suspected dementia. Atrophy of the cortex of the brain causes an increase in the size of the ventricles and sulci. At present, atrophy is usually assessed subjectively as slight, moderate or severe, but various indexes and computer programmes have been developed for this purpose. Standardisation of measurement would greatly facilitate comparison of research data from different hospitals (341).

The exact relationship between the presence of atrophy shown on a CT scan and the severity of dementia is unclear (341). There are cases of demented patients with no evidence of cortical atrophy, and normal patients who show cortical atrophy on the CT scan. It seems that an accurate description of the anatomy of the brain does not necessarily predict its function.

The view expressed in the 1979 colloquium on Alzheimer's disease (339) is that "the CT scan is valuable in providing exclusion criteria, e.g. of neoplasm or haematoma but that it cannot provide positive diagnostic evidence in the early case".

It appears that a more promising method of assessing the physiological functioning of the brain is offered by electrophysiological techniques. These include the electroencephalogram, or EEG (Appendix 2) and the visual evoked potential, or VEP (Chapter 2).

The EEG is a non-invasive and painless diagnostic aid. Localised EEG abnormalities can point to structural abnormalities such as brain tumours, while non-specific abnormalities can be indicative of generalised neurological or metabolic disorders. The technique is of established importance in the differentiation between dementia and other confusional states and in the exclusion of other cerebral lesions (337, 319).

Many researchers have claimed that the EEG can be used for differential diagnosis of dementia (339, 342, 343, 344). In Alzheimer's disease, EEG changes are very common and consist of a diminution of alpha activity with replacement by theta and eventually delta activity (338, 342, 343, 344, 345, 346, 347). However, the EEG is frequently normal in Pick's disease (342, 343, 344, 347). Creutzfeldt-Jakob disease is characterised by bilateral synchronous sharp waves which may be associated with myoclonus in the later stages of the disease (344, 348), while abnormalities of the cerebral circulation can be identified by intermittent lateralised slow waves (349). The general health of the patient must be taken into account when interpreting the EEG as systemic illness can cause EEG slowing (349).

The EEG abnormalities in Alzheimer's disease have been shown to be significantly related to the severity of the clinical picture (343, 350), and reduced cerebral circulation (346) and, on autopsy, the number of senile plaques (351) and degree of ventricular dilation, cortical atrophy and plaque and tangle formation (349). The EEG slowing was not related to brain weight, or sclerosis of the aorta, coronary or brain arteries on autopsy (349).

Muller and Schwartz (349) have suggested that the relationship between

EEG abnormality and dilatation of the ventricles is connected with damage to the thalamus. This structure is very important in the generation of normal EEG rhythms and atrophy of the thalamus is a major contributing factor in dilatation of the ventricles. In Pick's disease, thalamic atrophy and degeneration of the limbic system are less marked, and plaque and tangle formations are not found, which may be connected with the fact that EEG abnormalities are less frequent.

The reduction of alpha rhythm in Alzheimer's disease could be explained by consideration of the reported site of the lesions. Alpha rhythm is recorded from the electrodes over the posterior part of the skull, which could be related to previously mentioned CBF reports that the parieto-temporal-occipital areas are most affected in Alzheimer's disease.

Christie (342) reports Feinberg's finding that the sleep EEG shows a reduction in the Rapid Eye Movement (REM) stages of sleep in 'chronic brain syndrome' and points out that REM sleep is related to cholinergic mechanisms. This is of particular interest in view of the acetylcholine deficiency in Alzheimer's disease.

There have been very few investigations into the effect of Alzheimer's disease on the VEP. Visser, Stam, Van Tilburg, Op den Velde, Blom and de Rijke (352) reported that the latencies of the components of the flash VEP occurring after 100 msec were increased in a group of 19 patients with senile or presenile dementia of the Alzheimer type (mean P_2 latency = 155 msec) when compared with 6 young controls (mean P_2 latency = 114 msec). The amplitude was increased in the waves corresponding to P_2 and N_4. The presence of a delayed flash VEP in one patient with Alzheimer's disease investigated by Harding was also reported by

Sim (338). He points out that this finding is not inconsistent with the widespread distribution of the histological Alzheimer's changes in the occipital lobes.

Further evidence for the delay in the flash VEP in dementia comes from a study by Cosi, Vitelli, Gozzoli, Corona, Ceroni and Callieco (47) in which flash VEP and CT scan findings were compared. A group of patients with cerebral atrophy were found to have a delayed mean flash VEP (P_2 = 157.9 msec) when compared with a group of elderly control subjects with no cerebral atrophy (P_2 = 139.4 msec). However, when the group with atrophy was subdivided on the basis of clinical evidence of dementia, the demented subgroup showed a significantly higher flash latency (P_2 = 171.7 msec) than the non demented group (P_2 = 150.0 msec). This difference was not related to the degree of atrophy, as the cases with diffuse atrophy were evenly distributed between the two groups. The findings that the VEP shows changes with age (Section 2B) even in the presence of a normal CT scan, and can also differentiate between demented and non demented patients where the CT scan could not, led the authors to suggest that the VEP is capable of reflecting either degrees of atrophy too mild to be detected by the CT scan, or additional factors such as alterations in metabolism, biochemistry or circulation.

Laurian, Gaillard, Gruber, Heimann, Lobrinus, Reigner and Wertheimer (353) reported in an abstract that the flash VEP recorded from the O_z electrode in 12 patients with severe senile dementia was no different from that recorded from 12 young controls. It is unusual that they did not even observe any age-related differences in the responses. However, they reported that the vertex VEP was hardly discernable in

Alzheimer's disease. No experimental details were given. It is interesting to note that Lee and Blair (348) also reported an increase in latency of the components of the flash VEP occurring after 100 msec and a marked increase in amplitude in a study of one patient with Creutzfeldt-Jakob disease.

CHAPTER 5 THE PROJECT

5 AIMS OF THE PROJECT

The object of the clinical studies was to investigate the relationship between flash and pattern VEPs and psychophysical measures of spatial and temporal vision in order to establish which aspects of visual processing are reflected by each measure. Patients with selective disorders of vision and the visual pathways were studied so that the defects revealed by the various electrophysiological and psychophysical measures might be compared. It is important to establish that the aim was not to study the pathological conditions in themselves, but to use them as models in which to study spatial and temporal visual processing.

The hypothesis was that the flash VEP and de Lange curve results would both reflect temporal, or luminance processing, while the pattern VEP, contrast sensitivity function and VA measures would reflect spatial processing. Furthermore, it was hoped to demonstrate a relationship between the 'contour specific' CII pattern onset component and VA, and the 'contrast specific' CI and pattern reversal components and contrast sensitivity measures.

The selective nature of the spatial visual defects in amblyopia (Section 4A) and the pattern VEP delay in optic neuritis (Section 4C) is well established in the literature. The selective pattern VEP defects in optical blur and flash VEP defects in dementia (a global deterioration of higher cortical function) were first established by pilot studies. Having established the groups for study, all patients underwent the same spatial and temporal tests (described in Section 5.1). The equivalent results from the 70 control subjects provided material for an additional study of the effect of age on these measures of vision. With the exception of the pilot studies, all the patients were investigated between December 1980 and September 1981.

5.1 METHODS OF INVESTIGATION

All subjects underwent the following tests:

Psychophysical tests	Electrophysiological tests
1 Visual acuity	1 Flash VEP
2 Spatial MTF:	2 Pattern onset-offset VEP
1.3 c/deg	56 min check
4.0 c/deg	19 min check
12.0 c/deg	13 min check
3 Temporal MTF:	3 Pattern reversal VEP
3Hz	56 min check
10Hz	19 min check
30Hz	13 min check

Visual acuity was measured first in all cases in order to detect and correct any refractive error (for distance and near) and to exclude any control volunteers with ocular pathology. The other psychophysical tests were performed first in approximately half the subjects and the electrophysiological tests in the other half, in order to minimise any effects of fatigue. A break with a cup of tea or coffee was provided between the two groups of tests in order to minimise any tiredness and to maintain the alertness and co-operation of the patient.

Each eye was tested separately in those patients with amblyopia or unilateral optic neuritis in order that the unaffected eye might be used as a control. This provides the ideal control in that, not only are the two eyes perfectly age and sex matched, but they are actually linked to the same brain, greatly facilitating VEP comparisons.

Accordingly, all normal controls were also tested with both eyes separately.

Such a control was not relevant in the group with dementia, as this is a cortical condition which can be assumed to affect the responses from each eye equally. Time was also an important factor, as the span of attention was limited in these patients and the diagnostic investigations requested by the hospital also included an EEG.

The amblyopic subjects were also tested under a third condition - with the good eye blurred with ophthalmic lenses to the same level of visual acuity as the amblyopic eye. It was therefore possible to obtain a normal response and responses affected by both amblyopia and optical blur in the same subject. The normal volunteers in the optical blur study were tested with one eye only - firstly with optimal refractive correction (no blur) and then with vision blurred with +1D, +2D and +3D ophthalmic lenses.

The minimum length of the investigation was 1½ hours in the control and optic neuritis studies. In the amblyopia, optical blur and dementia studies the length could be up to 3 hours, and was usually split into two sessions.

5.2 Psychophysical Methods

Visual acuity was measured using a standard Snellen chart viewed at 6 metres by reflection in a wall-mounted mirror. The chart was on a roll and viewed through a square aperture in the unit of a size that the 6/9, 6/6 and 6/5 lines were visible at one time, while the 6/60

letter filled the aperture alone.

The chart was back illuminated, the luminance of the white background being 2850 cd/m^2 and of the black 6/60 letter being 80 cd/m^2. This represents a contrast of 0.94. The room ~~illumination~~ luminance was 42 cd/m^2.

The smallest line resolved by each eye was recorded, and the results converted to decimal notation for ease of statistical analysis. The sensitivity of the method was increased by recording the proportion of letters correctly identified and thus providing a series of intermediate values. These values were converted into decimal notation by dividing the interval between the lines by the number of letters as described by Drasdo and Haggerty (354). Their values are reproduced in Table 5.1 and extended to include 6/5 values.

The Snellen chart provided a simple test for visual acuity measurement and refraction which could be understood even by patients with pronounced psychiatric disturbances. The results could easily be compared with previous results obtained at the Eye Hospital using a Snellen chart.

Spatial and temporal MTF measurement

The spatial and temporal MTF was determined for each eye separately by the following method:

The modulation threshold was determined by the ascending and descending method of limits (355). After giving the subject clear instructions and a demonstration of the task, the modulation was set to zero. The experimenter slowly increased the modulation, noting the value at which

V.A.	-7	-6	-5	-4	-3	-2	-1	Full Score	+1	+2	+3	+4	+5	+6	+7
6/60								0.1	0.14						
6/36							0.14	0.17	0.20	0.22					
6/24						0.20	0.22	0.25	0.26	0.29	0.31				
6/18					0.26	0.29	0.31	0.33	0.36	0.40	0.43	0.47			
6/12				0.36	0.40	0.43	0.47	0.50	0.53	0.56	0.59	0.61	0.64		
6/9			0.53	0.56	0.59	0.61	0.64	0.67	0.71	0.75	0.80	0.84	0.88	0.92	0.96
6/6	0.71	0.75	0.80	0.88	0.88	0.92	0.96	1.0	1.025	1.05	1.075	1.1	1.125	1.15	1.175
6/5	1.025	1.05	1.075	1.1	1.125	1.15	1.175	1.2	1.238	1.275	1.313	1.351	1.388	1.426	1.463
6/4								1.5							

TABLE 5.1

Showing standard clinical notation and equivalent intermediate Snellen decimal values

it was first perceived by the subject. The modulation was then increased so that it was clearly visible, and slowly decreased until the subject reported that it was no longer seen. This procedure was repeated three times and the mean of the six recordings was determined. This ascending and descending method was simple for all patients to understand and ensured that differences in the speed of response of different patients due to nervousness or overconfidence was averaged out (particularly relevant in the psychiatric groups). The experimenter turned the modulation dial as quietly as possible and varied the speed of rotation and starting value to eliminate as many clues as possible.

The frequency corresponding to peak sensitivity (10Hz or 4 c/deg) was tested first so that the subject could begin with the easiest condition. The low frequency was tested next and the high frequency (the most difficult) last. The subject could not, therefore, predict a progressive effect, and was not given any clues as to what to expect. After a short rest, the other eye was tested in an identical manner. The order in which the two eyes and the spatial and temporal MTFs were measured was varied approximately equally between all subjects.

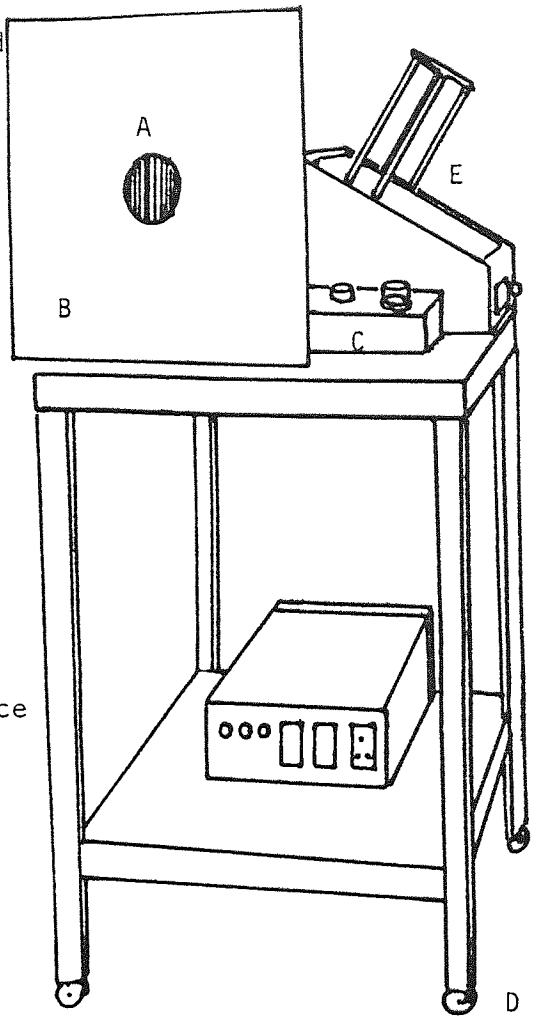
The apparatus for both spatial and temporal MTF measurement was mounted on one trolley as shown in Figure 5.1.

The CSF curve - Contrast sensitivity was measured with stationary gratings of sinusoidal luminance profile, generated by modulation of z axis of an oscilloscope (Telequipment).

Twelve cycles were displayed, which corresponds to the saturation value found by Virsu and Rovamo (147). Hoekstra, Van der Goot, Van der Brink

Figure 5.1 Showing the arrangement of apparatus for the measurement of spatial and temporal MTFs

i) to show the sinusoidal grating and surround as viewed by the subject



A Circular aperture revealing sinusoidal grating on the oscilloscope screen

B Green cardboard surround

C Control box with dials for adjustment of spatial frequency and modulation

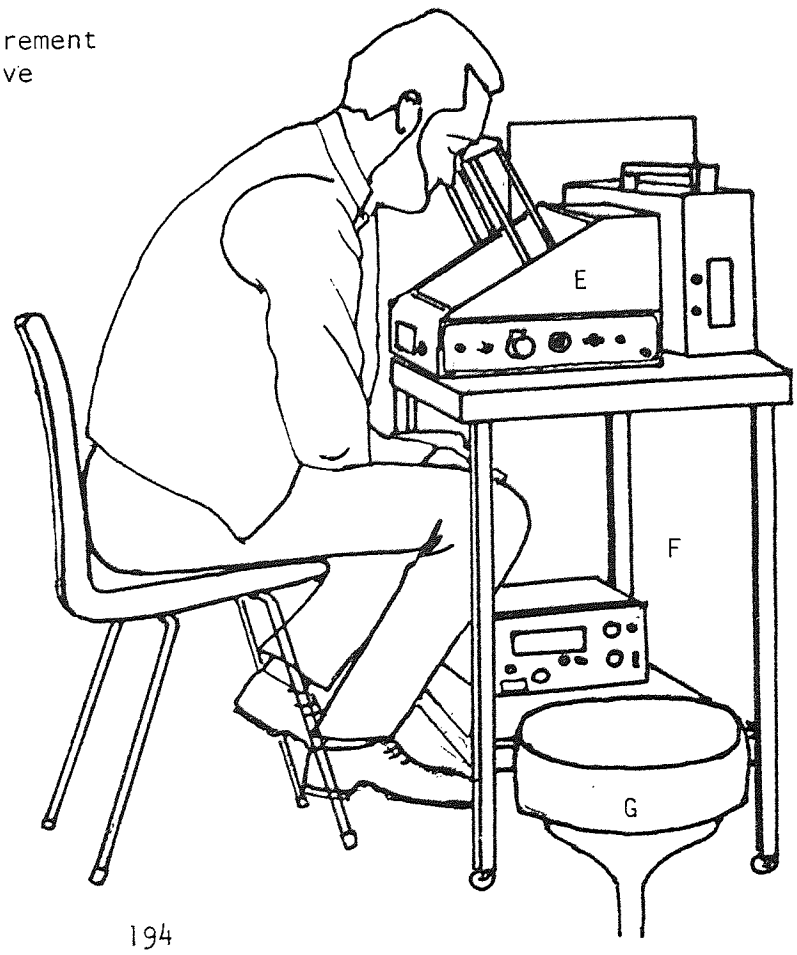
D Trolley mounted on castors for changes in viewing distance

ii) showing the flicker apparatus in use

E Apparatus for measurement of the de Lange curve

F Temporal frequency meter

G Stool for experimenter

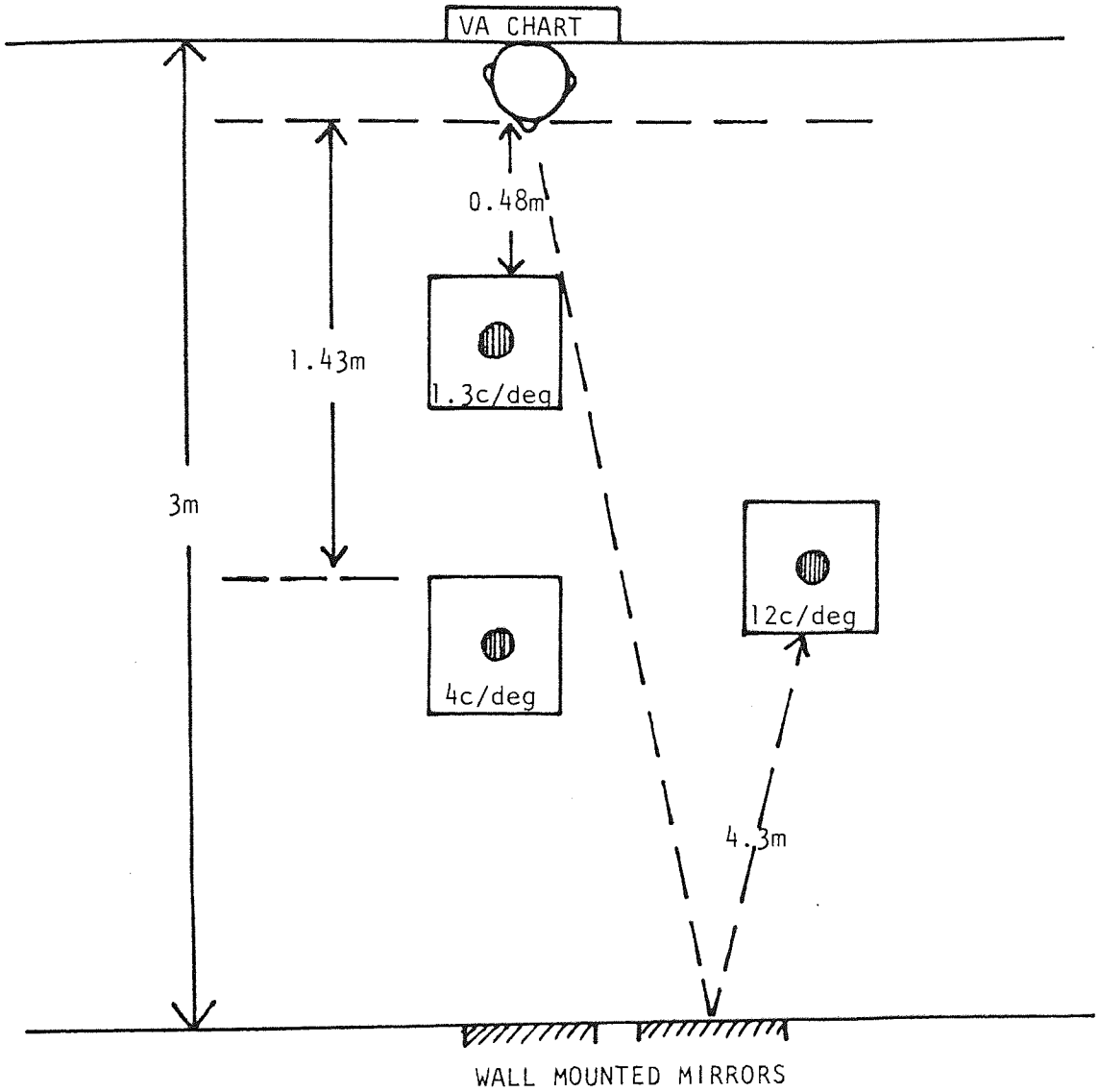


and Bilsen (187) estimate the critical number of cycles at an equivalent luminance level to be between 3 and 5. The number of cycles was the same for all spatial frequencies, ensuring that a constant number of cortical neurones were stimulated (147). This was achieved by mounting the apparatus on a trolley, enabling the spatial frequency of the grating subtended at the eye to be varied by changing the distance between the grating and observer. This method for changing spatial frequency has been used by other workers (147, 207) and has the advantage that, once set, the oscilloscope settings did not need to be touched throughout the entire study, ensuring accuracy. Observers were optically corrected for distance, and the appropriate convex addition for each testing distance was worn by presbyopic subjects and those participating in the optical blur study. Each eye was tested separately, the occluder being mounted in a trial frame, over the spectacles, or in the form of a black patch, where appropriate.

The spatial frequencies investigated were 4 c/deg, 1.3 c/deg and 12 c/deg, representing the peak, low and high frequency sections of the CSF curve respectively (209). An overall estimate of the spatial visual system could therefore be obtained, the inclusion of the low spatial frequency value ensuring that some estimate of contrast sensitivity was possible in patients with poor visual acuity. The testing distances were 143.2cm for a 4 c/deg grating, 47.6cm for 1.3 c/deg and 429.7cm for 12 c/deg. The latter was achieved by reflection of the grating in a wall mounted mirror of high optical quality (Figure 5.2).

The total field subtended 3^{o} when the 12 cycles subtended 4 c/deg at the eye, 9^{o} when the grating was 1.3 c/ deg and 1^{o} when the grating was 12 c/deg. The fovea alone was therefore used for the processing of

Figure 5.2 Showing arrangement of the apparatus for the measurement of visual acuity and contrast sensitivity



high spatial frequencies and a larger area of retina for low spatial frequencies.

The contrast of the sinusoidal grating could be varied between 0 and 0.35 (for calibration of the modulation settings, see Appendix 3). The mean luminance of the oscilloscope screen was 13.5 cd/m^2. The surround was illuminated to approximately the same level by an angle poise lamp. However, in order that the oscilloscope screen did not receive direct illumination from the lamp, the surround was illuminated from below, producing an unequal light distribution ranging from 11 cd/m^2 below the aperture to 6.5 cd/m^2 above. A surround of equal luminance ensures constant retinal adaptation and has been reported to produce higher contrast sensitivity values (356). The surround was colour matched, by eye, to the green of the oscilloscope phosphor. The grating was viewed through a 7.5cm diameter circular aperture. One advantage of a circular aperture is that it eliminates any border effects produced by the phase of the grating (i.e. whether the grating has a dark or light bar at the edge).

A complete CSF curve was measured using this method on ten subjects aged between 18 and 27 (Appendix 3).

The de Lange curve - The de Lange curve was determined using a yellow (588nm) light emitting diode source which produced a sinusoidal temporal luminance variation. The frequency and modulation of this sinusoidal flicker could be varied independently.

The frequency range of the apparatus was 0 to 50Hz. 10Hz, 3Hz and 30Hz were selected for investigation to represent the peak, low and high

frequency sections of the de Lange curve respectively and obtain an estimate of the overall functioning of the temporal visual system. The modulation of the source could be varied independently between 0 and 0.30 (for calibration of modulation values see Appendix 3).

The viewing distance of the observer was fixed at 17cm by means of a forehead rest. This had a section cut out in the middle so that one eye could view the flickering source while the other was behind the black opaque bar. A +5.75D plastics lens was mounted in the centre of the gap and this, and the edges of the cut-out section, were shaped so that the nose fitted comfortably in the two gaps either side of the lens. This focusing lens ensured that subjects of all ages could use the apparatus since no accommodation was necessary.

At this distance the circular flickering source subtended 2^{o} at the eye, corresponding to the field size used by de Lange (226), and the square surround subtended 68^{o}. The surround and source were approximately matched for both colour and luminance which ensures a constant level of retinal adaptation, and also has been reported to enhance sensitivity for low temporal frequencies (227) and the CFF (170). The mean luminance of the flickering source was 40 cd/m^2 and the luminance of the surround varied between 60 cd/m^2 in the centre to 130 cd/m^2 at the corners directly above the light bulbs. The room illumination was 6 cd/m^2.

A complete de Lange curve was determined using this apparatus on ten subjects aged between 21 and 30 years (Appendix 3).

5.3 Electrophysiological Methods

The patient sat in an upholstered reclining chair throughout the recording to ensure maximum comfort and relaxation. Standard silver-silver chloride electrodes were fixed to the scalp with collodion, filled with electrolyte and the resistance of the skin-electrode interface reduced to below 5Kohms. The positions of the three active electrodes were O_2 and O_1 (10-20 system) to sample both hemispheres and 4% above the inion to optimally sample the foveal projection of area 17 (10). These three electrodes were referred to a mid-frontal electrode F_z.

The signals were amplified by a Mingograf EEG machine (Siemens Elema) with a high frequency filter setting of 15Hz and time constant of 0.3 sec. The three channel EEG was monitored throughout the VEP recording in order to detect such factors as excessive alpha activity or muscle tension on the part of the subject, or technical artefacts such as mains interference or a faulty electrode connection. The output was fed into a PDP8 computer which averaged 50 sweeps consisting of 250 points at 2 msec intervals to give a 500 msec averaged VEP waveform. This was displayed on an oscilloscope (Tetronix type 611) and the size of the waveform expanded or contracted if necessary. An X-Y plotter then transferred the waveform and the 5uV calibration signal onto paper for a permanent record. In accordance with the polarity convention routinely used in this clinic, a positive potential was represented by a downward deflection of the pen. The latencies and amplitudes were calculated from hand measurement of the waveform components with a millimetre scale.

The flash VEP was evoked by an unstructured flashing white light of

1363 cd/m^2 intensity produced by a Grass PS22 stroboscope 33cm from the eye of the subject in a darkened room. The stroboscope was triggered from the averager twice per second. This introduced a 22 msec delay, for which allowance had to be made when measuring flash VEP latencies.

Patterned stimuli were produced by the back projection of transparencies onto a translucent screen. Checkerboard stimuli were selected as these give large, clear VEPs and have been used extensively for clinical work in our Unit and other centres. The check sizes selected were 56, 19 and 13 minutes of arc, which represented the low frequency, peak and high frequency sections of the VEP amplitude - check size functions. The diameter of the circular field subtended 28^{o} for the 56 and 19 min checkerboards, which ensured that a large area of retina was stimulated and that a response could be obtained even in cases with poor VA. However, since small checks are processed by the fovea, a 3^{o} field was used for 13 min checkerboard stimulation. Thus, the VEPs evoked by the 56 min and 13 min checkerboards should reflect different aspects of pattern processing - the 56 min check being processed by 'contrast specific' processes from a large retinal area while the 13 min checks are processed by 'contour specific' mechanisms in the foveal area. A red spot was provided in the centre of the field for fixation. The external illumination was 42 cd/m^2 and the mean luminance of the pattern was 1050 cd/m^2. The contrast between the black and white squares was 0.759 which is above saturation.

Pattern reversal was produced by the oscillation of a surface silvered mirror mounted on a pen motor which moved the checkerboard abruptly through one check width and back again every second (i.e. 2 reversals per second). The averager was simultaneously triggered twice per

second from the same signal. Pattern onset-offset stimulation was produced by the rotation of a perspex wheel in the beam of the projector (350). The checkerboard appeared on the screen for 150 msec while the clear section of the wheel crossed the beam and was replaced by a homogenous field of equal mean luminance for the remaining 500 msec of that cycle, while the lenticular perspex portion of the wheel which blurred pattern details crossed the beam. This presentation time was sufficient to ensure separation of the onset and offset components of the VEP (71) while the interval between presentations was sufficient to ensure negligible adaptation of the VEP components.

5.4 Patient Selection

Seventy control subjects undertook the full range of tests involved in this project. Each decade between 10 and 79 years of age was represented by 10 subjects, with care being taken to obtain a spread of ages within each age group and to approximately balance the number of males and females within each group.

The subjects were paid volunteers with no history of neurological or ophthalmological abnormalities and visual acuity of $^{6}/_{6}$ or better in each eye. Twenty-seven were found through personal contacts, 15 through advertisements posted within the University and 13 through a pensioners' group which attends the department weekly to provide subjects for undergraduate ophthalmic opticians. The remaining 15 were friends, colleagues or relations of the other subjects who volunteered after hearing about the project.

The unilateral amblyopia study involved 10 volunteers with visual acuity of $^{6}/_{12}$ or worse in the amblyopic eye and $^{6}/_{6}$ or better in the other eye. Two of these subjects responded as a result of letters sent to 3 amblyopes who had attended the department's orthoptic clinic. A friend of one of these subjects also wrote to volunteer for the project. The remaining 7 amblyopes were found through personal contacts. As the entire investigation took about 3 hours (due to the 3 conditions), 6 amblyopes chose to do the psychophysical and electrophysiological tests on separate days. The other 4 undertook them all in the same session, with appropriate breaks.

The 10 volunteers in the optical blur study were all University students or staff with visual acuity of $^{6}/_{6}$ or better. All subjects did the

psychophysical and electrophysiological tests on separate days.

The 10 patients in the optic neuritis study had all shown a unilateral pattern reversal VEP delay when investigated at the Birmingham and Midland Eye Hospital. The results reported in this study represent the follow-up appointment which took place at the Aston Clinical Neurophysiology Unit. A report was sent to the Consultant Ophthalmologist in every case.

The dementia study represents 59 patients who were referred from the Midland Nerve and Queen Elizabeth Hospitals by two psychiatrists who have shown considerable interest in the project. With the exception of a few established cases of dementia, the diagnosis had not been established in the majority of cases when investigated at the Unit in 1981. The patients were finally grouped according to the clinical diagnosis of three Consultant Psychiatrists in September 1982. The three clinical groupings were given the heading 'Dementia', 'Affective Disorders' and 'Other Cerebral Conditions'. A report was sent back to the Consultants in every case.

CHAPTER 6 RESULTS AND DISCUSSION

6 RESULTS AND DISCUSSION

All VEP latency and amplitude measures in these results represent the mean of the values from the O_2 - F_z and O_1 - F_z derivations, unless indicated otherwise. This was considered valid as the study of hemispheric differences in normals or pathology is not relevant to this research. The only exception will be where the results from the midline electrode 4% above the inion referred to Fz are used. As this electrode is designed to optimally sample the foveal projection on area 17 (10) the VEP results recorded from this derivation will only be used for comparison when the foveal 13 minute check 3^o field stimulus is used. These results will be indicated by a letter 0.

Analysis of variance tests (358, 359) are used in order to assess the statistical significance of the results. The means, standard deviations and standard errors of the mean for each group of results are tabulated, together with the variance ratio between groups, degrees of freedom for the numerator and denominator (df n/d) and significance level. The variance ratio between treatments and interaction of variance ratios are only included where significant or relevant.

All statistically significant results are plotted in graphical form for ease of inspection. In each case the mean values plus and minus one standard error of the mean are plotted for comparisons between group data. Where a single value for the number of subjects (N) in each group is indicated, this applies to every mean value on the graph, as the analysis of variance test required identical numbers in each group. Throughout the results an identical scale is used for every plot of

VEP latency (1cm = 5 msec) amplitude (3cm = 5uV) and contrast and flicker sensitivity (1cm = 0.1 log unit). Both the CSF curve and de Lange curve are plotted on log/log coordinates in common with many other published studies (e.g. 180, 206, 226) thereby facilitating study of both low and high frequency sections of the curve.

For inspection of the individual spatial and temporal frequency defects in amblyopia and optic neuritis, the ratio of the sensitivities of the two eyes was calculated in the manner of Regan, Silver and Murray (180). The ratios are plotted so that a defect in the affected eye, represented by a ratio of less than one, is shown as a downward displacement of the plot.

6.1 Study of normal subjects aged between 13 and 78 years

The characteristics of the 7 normal control groups can be seen in Table 6.1.1. There were 10 subjects in each group, and the proportion of males and females and distribution of ages within each group were balanced as evenly as possible. It can be seen that there is a systematic decrease in pupil diameter with age (significant at the 0.001 level). All results presented in this section are monocular (right eye).

Psychophysical results - The refractive correction of every subject was carefully checked, and no volunteer with VA of less than $^{6}/_{6}$ was accepted for the study. No significant change in VA with age was therefore expected. Table 6.1.2 shows, however, that contrast sensitivity was significantly different between the age groups ($p < 0.01$). The high variance ratio between treatments reflects the expected variation in contrast sensitivity with spatial frequency that is defined by the CSF curve. These variations are all shown in Figure 6.1.1. The significant interaction ratio ($p < 0.01$) is more clearly understood when the contrast sensitivity is plotted against age for each spatial frequency separately (Figure 6.1.2). It can be seen that contrast sensitivity for the low and medium spatial frequencies only shows a slight rise and fall with age, peaking in the 30-59 age groups. At the high frequency, however, contrast sensitivity decreases systematically between the 20-29 and 70-79 age groups, a total reduction of 0.35 log units.

A similar, but more marked, trend was observed for the de Lange curve. The overall difference between groups is highly significant ($p < 0.001$) with the expected difference between temporal frequencies, as defined by the de Lange curve ($p < 0.001$) as illustrated in Figure 6.1.3. The highly significant interaction of variance ratios ($p < 0.001$) is

GROUPS		10-19 yr	20-29 yr	30-39 yr	40-49 yr	50-59 yr	60-69 yr	70-79 yr
AGE (yrs)	Mean	16.1	23.3	35.6	43.9	55.0	63.2	73.8
	Range	13-19	20-28	32-39	40-46	50-59	61-67	70-78
	Males	5	6	5	3	6	5	6
	Females	5	4	5	7	4	5	4

								Variance Ratio	df n/d	Significant Level	
PUPIL DIAMETER (mm)	4.9 ± 1.15 SE 0.36	4.3 ± 0.63 SE 0.20	3.85 ± 0.75 SE 0.24	3.75 ± 0.68 SE 0.21	3.575 ± 0.44 SE 0.14	3.4 ± 0.84 SE 0.27	3.15 ± 0.58 SE 0.18	6.104	6/63	p<0.001	* *
VISUAL ACUITY	1.235 ± 0.11 SE 0.035	1.225 ± 0.10 SE 0.03	1.2 ± 0 SE 0	1.204 ± 0.11 SE 0.03	1.17 ± 0.15 SE 0.047	1.168 ± 0.07 SE 0.02	1.108 ± 0.136 SE 0.043	1.629	6/63	Not Sig	

TABLE 6.1.1 Characteristics of normal control groups.

TABLE 6.1.2 Effect of age on spatial and temporal modulation transfer functions

LOG CONTRAST SENSITIVITY	1.3 c/deg	4 c/deg	12 c/deg	Variance Ratio	df n/d	Significance Level	
10-19 years	1.892 ± 0.093 SE 0.030	1.870 ± 0.087 SE 0.028	1.638 ± 0.081 SE 0.026	Age Groups:			
20-29 years	1.939 ± 0.128 SE 0.040	1.923 ± 0.127 SE 0.040	1.669 ± 0.148 SE 0.047	3.746	6/63	p<0.01	* *
30-39 years	1.967 ± 0.035 SE 0.011	1.885 ± 0.148 SE 0.047	1.559 ± 0.199 SE 0.063	Spatial Frequencies:			
40-49 years	1.957 ± 0.094 SE 0.030	1.938 ± 0.104 SE 0.033	1.567 ± 0.192 SE 0.061	317.374	2/126	p<0.001	* *
50-59 years	1.947 ± 0.088 SE 0.028	1.897 ± 0.097 SE 0.031	1.520 ± 0.172 SE 0.054	Interaction:			
60-69 years	1.899 ± 0.113 SE 0.036	1.869 ± 0.111 SE 0.035	1.466 ± 0.182 SE 0.058	2.778	12/126	p<0.01	* *
70-79 years	1.849 ± 0.147 SE 0.046	1.765 ± 0.126 SE 0.040	1.315 ± 0.199 SE 0.063				
LOG FLICKER SENSITIVITY	3Hz	10Hz	30Hz				
10-19 years	1.683 ± 0.091 SE 0.029	1.812 ± 0.145 SE 0.573	1.406 ± 0.144 SE 0.045	Age Groups:			
20-29 years	1.715 ± 0.172 SE 0.054	1.851 ± 0.159 SE 0.050	1.278 ± 0.185 SE 0.059	11.368	6/63	p<0.001	* *
30-39 years	1.756 ± 0.129 SE 0.041	1.877 ± 0.131 SE 0.042	1.123 ± 0.166 SE 0.052	Temporal Frequency:			
40-49 years	1.684 ± 0.085 SE 0.027	1.797 ± 0.099 SE 0.031	1.003 ± 0.180 SE 0.057	774.754	2/126	p<0.001	* *
50-59 years	1.708 ± 0.067 SE 0.021	1.804 ± 0.054 SE 0.017	1.026 ± 0.279 SE 0.088	Interaction:			
60-69 years	1.604 ± 0.178 SE 0.056	1.709 ± 0.254 SE 0.080	0.753 ± 0.173 SE 0.055	9.244	2/126	p<0.001	* *
70-79 years	1.547 ± 0.118 SE 0.037	1.647 ± 0.115 SE 0.036	0.726 ± 0.101 SE 0.032				

Figure 6.1.1 Variation of the contrast sensitivity function with age

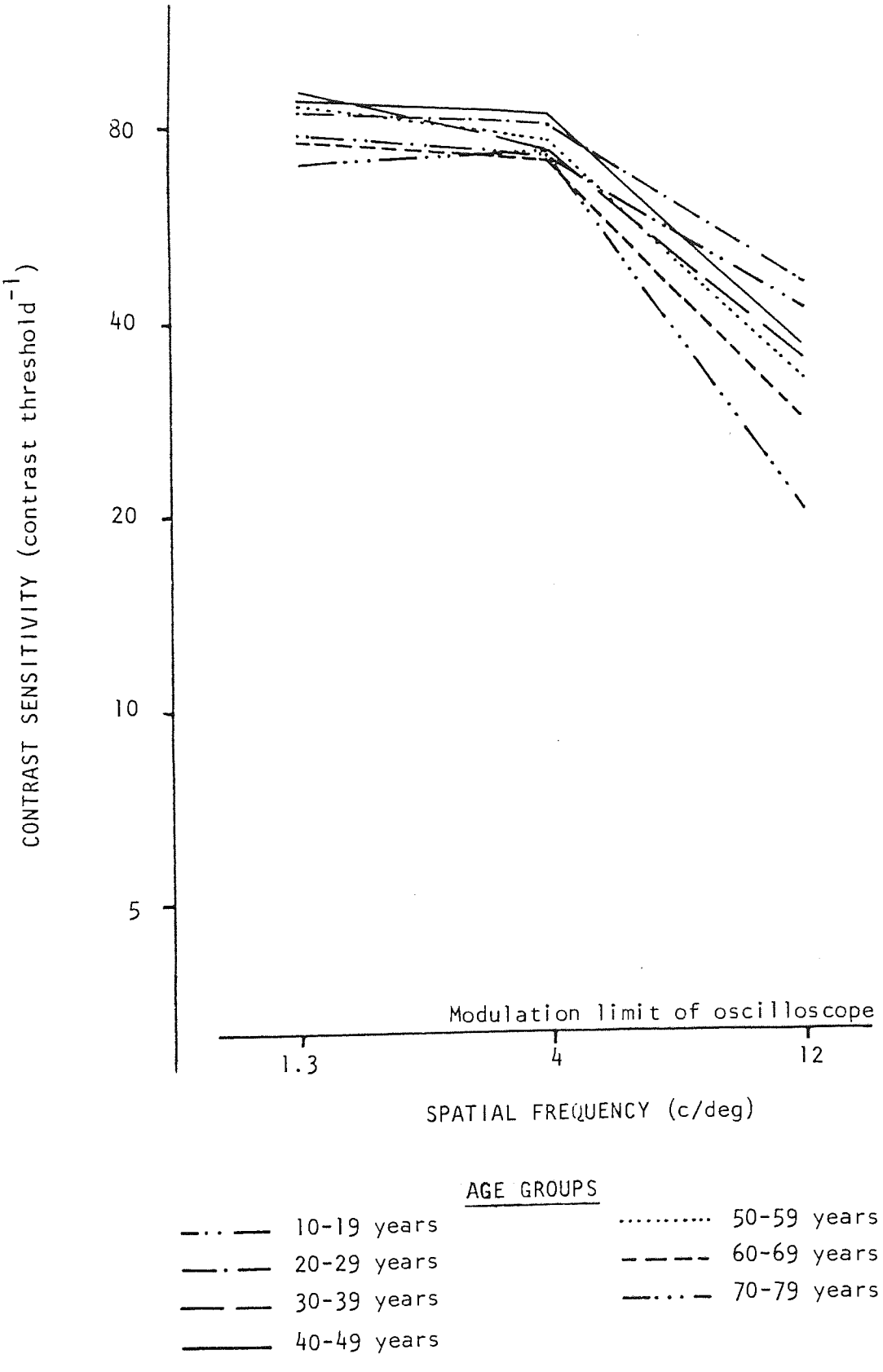


Figure 6.1.2 Effect of age on contrast sensitivity at low, medium and high spatial frequencies showing the mean ± 1 standard error of the mean N = 10 for each age group

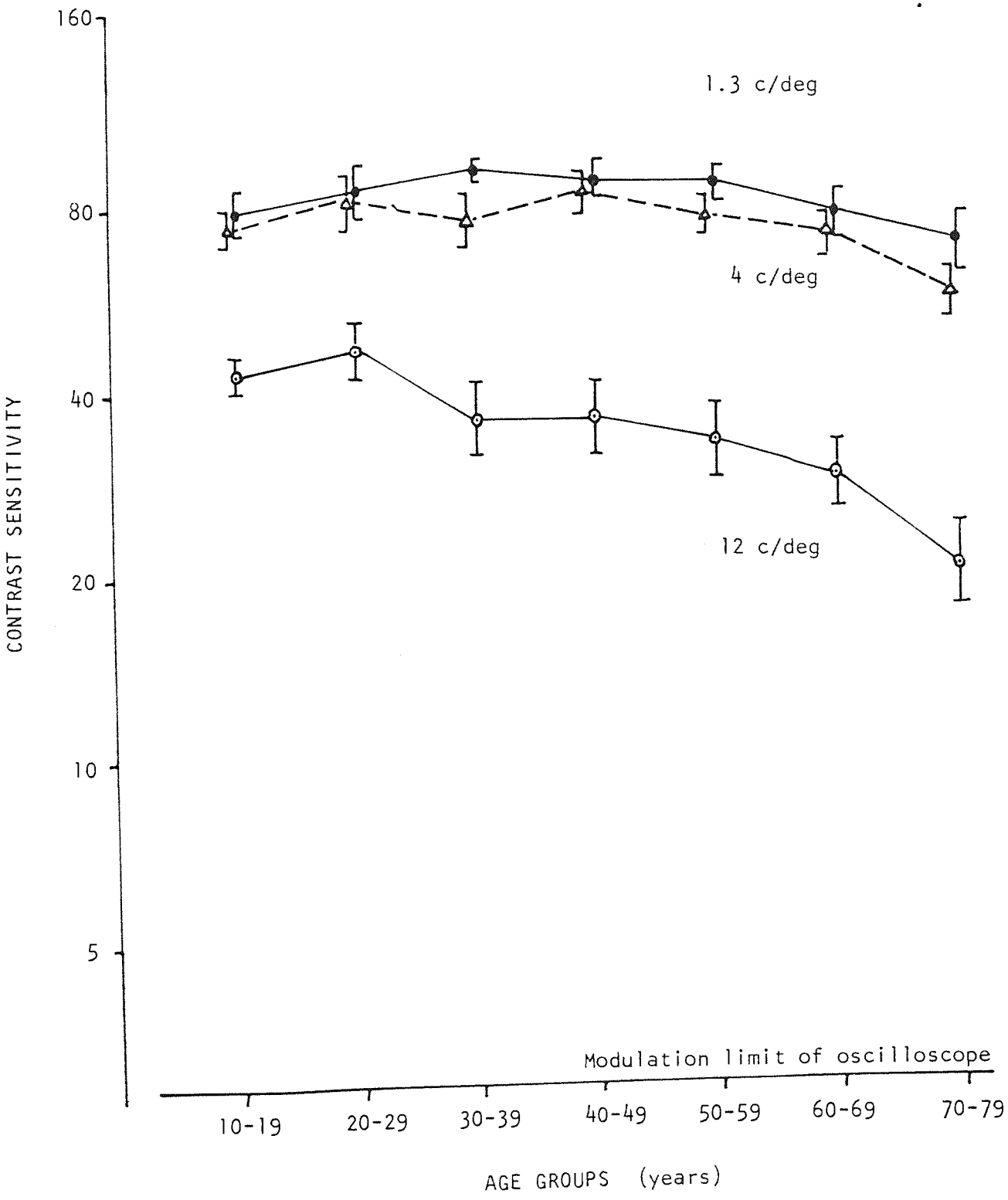


Figure 6.1.3 Variation of the de Lange curve with age

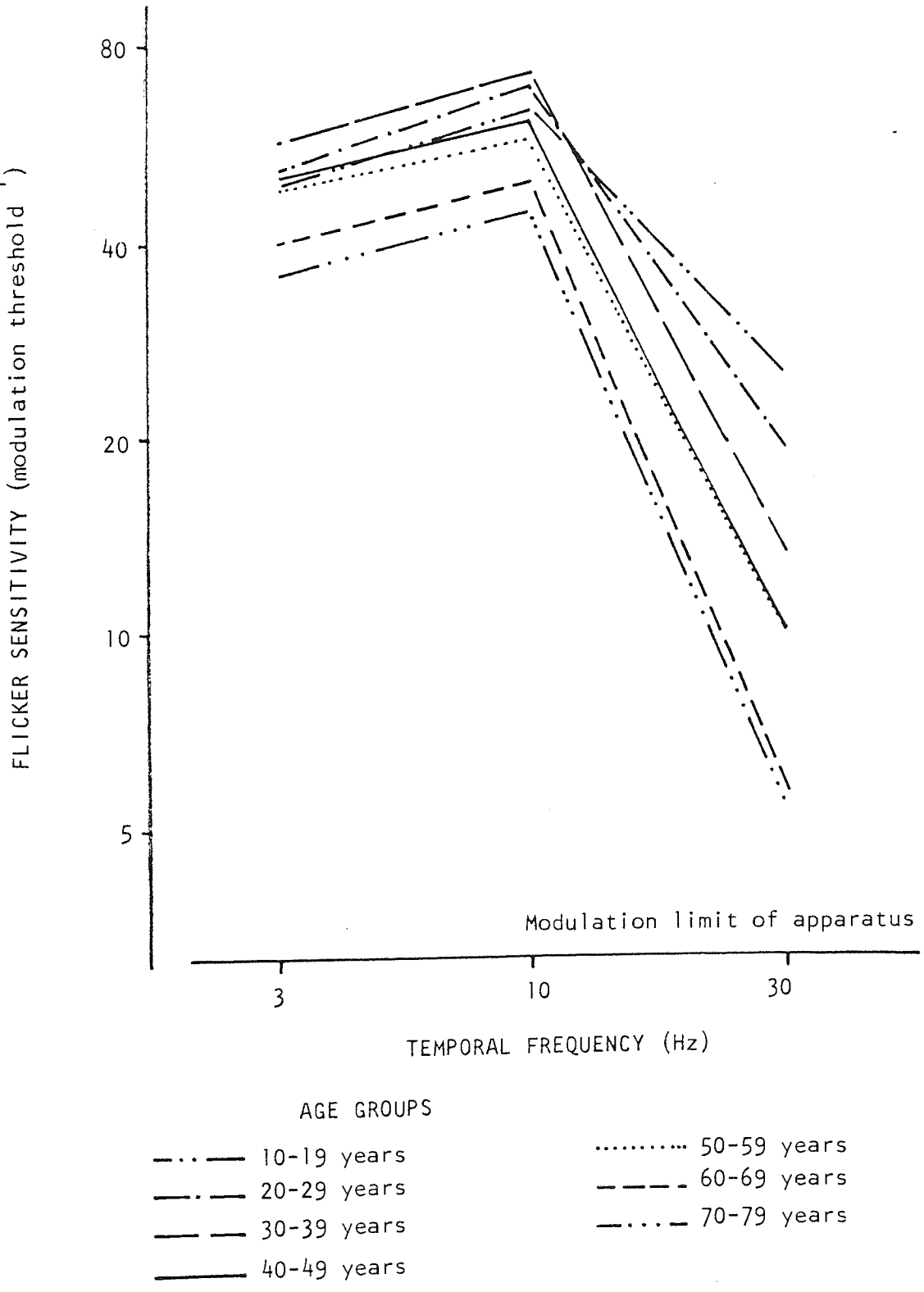
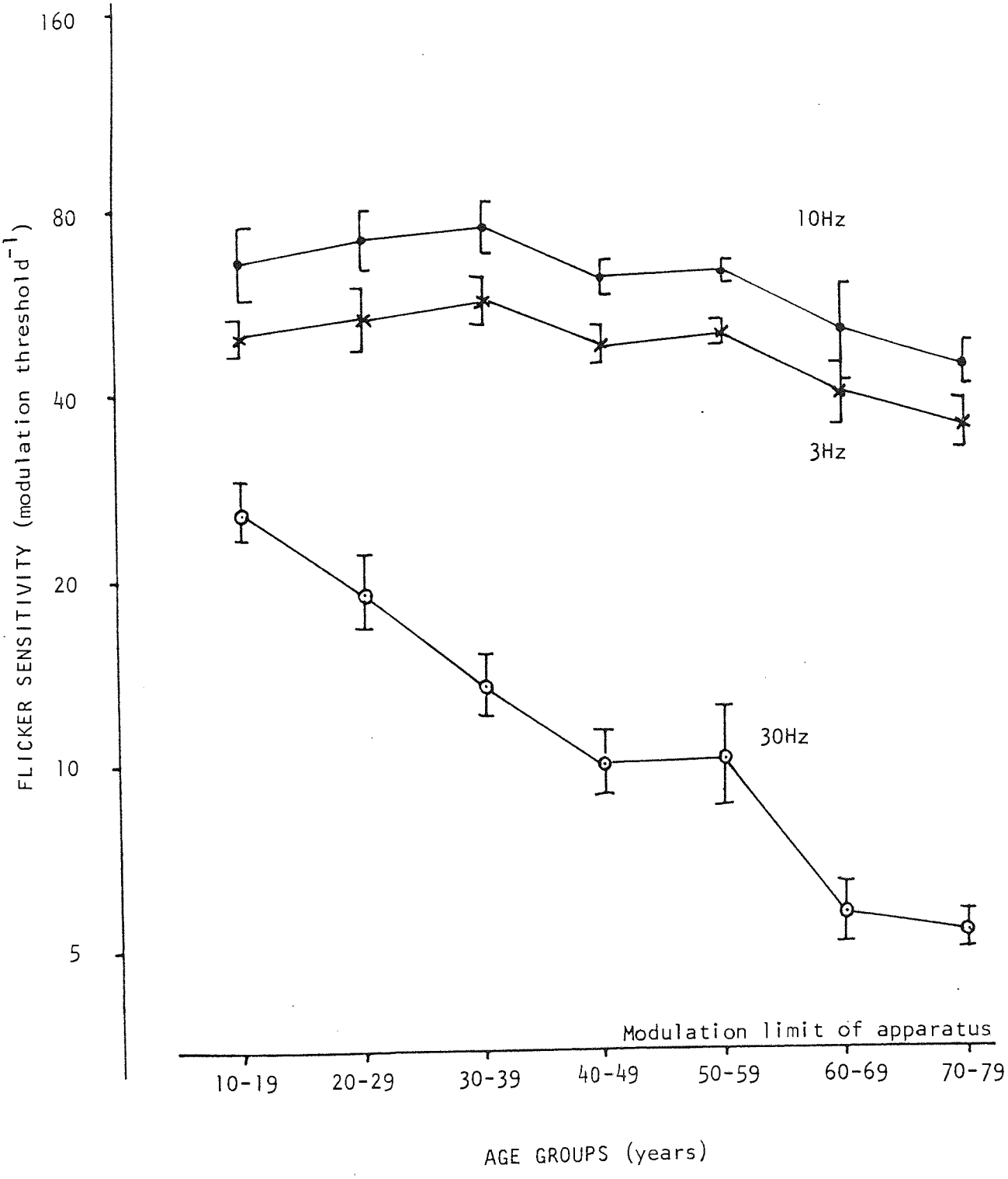


Figure 6.1.4 Effect of age on flicker sensitivity at low, medium and high temporal frequencies showing the mean ± 1 standard error of the mean
N = 10 for each age group



understood more clearly by reference to the plot of flicker sensitivity against age for each temporal frequency separately (Figure 6.1.4). Flicker sensitivity shows a slight increase up to the 30-39 year group followed by overall decrease of 0.21 and 0.23 log units for the 3 and 10Hz frequencies respectively. However, the highest temporal frequency shows a marked systematic reduction in sensitivity from the 10-19 to the 70-79 year age groups - a total reduction of 0.68 log units.

Electrophysiology - Examples of VEP waveforms obtained in this study are given in Figure 6.1.5. An idea of the consistency of each component of the flash VEP is given in Figure 6.1.6 which shows the number of subjects in each control group in which each component could be identified. It can be seen that the P2 component could be identified in both eyes of 69 out of the 70 control subjects and was therefore the most consistent component, followed by N3. Of particular interest is the observation that a N1 and P1 component could only be identified in one subject in the 10-19 year group. The remainder showed a flash VEP with a single large negative component occurring before P2. This has been shown in the row marked N2 although, in fact, the latency of the component (marked with a dotted line on Figure 6.1.7) suggests it could be a combination of N1 and N2 in the absence of P1. It can be seen that the incidence of P1 increases with age, from one eye of one subject in the 10-19 age group to 9 (right eye) and 8 (left eye) of the subjects in the 60-69 and 70-79 year groups. Analysis of variance tests on the latency and amplitude of each component across the age groups required an equal number of subjects in each group, so the low incidence of the early components in the younger age groups limited the number of comparisons which could be made. The only reliable comparisons which could be made were P2 and N3 latency and

Figure 6.1.5 Flash and pattern VEPs recorded in a control subject showing typical waveforms

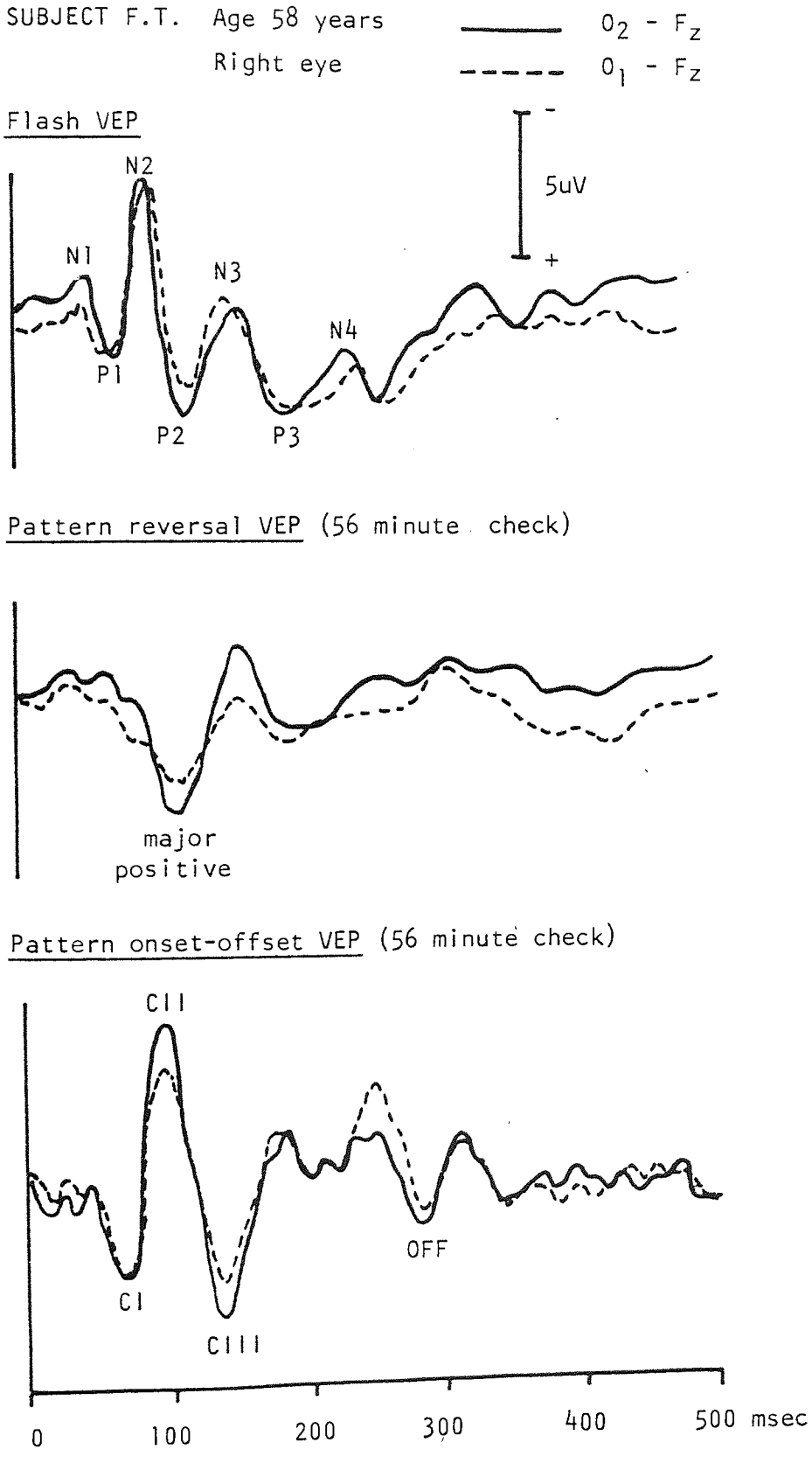


Figure 6.1.6 Showing number of control subjects in which each component of the flash VEP could be identified

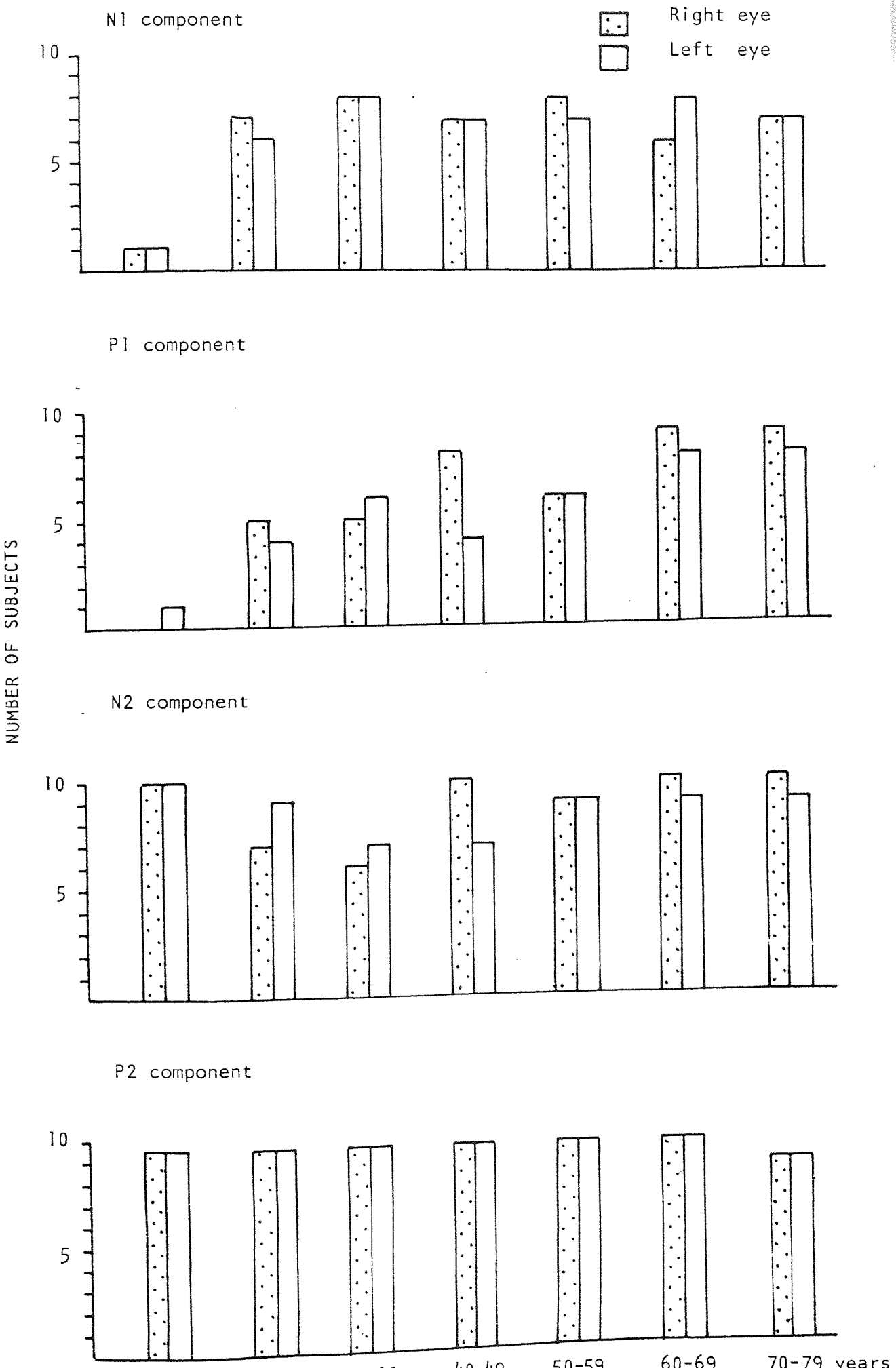
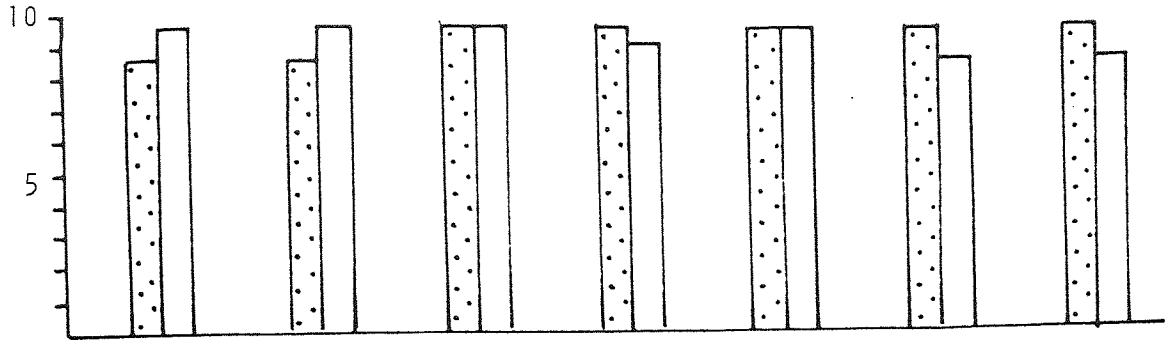
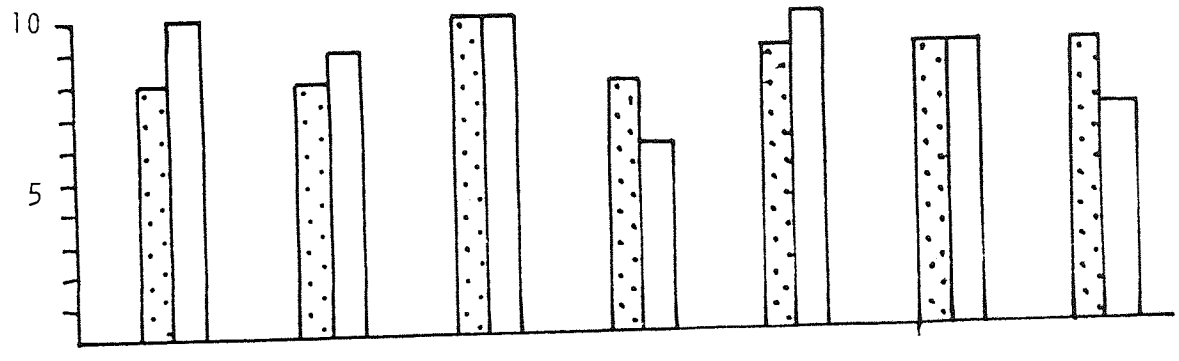


Figure 6.1.6 continued

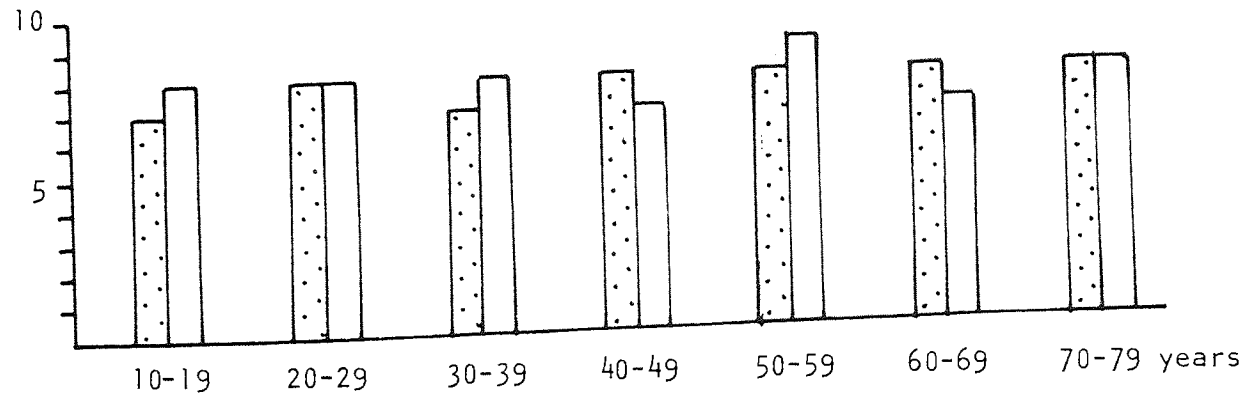
N3 component



P3 component



N4 component



		10-19 yr	20-29 yr	30-39 yr	40-49 yr	50-59 yr	60-69 yr	70-79 yr	Variance Ratio	d/f n/d	Signif-icance	
LATENCY (M.sec)	P_1	—	70.7 ± 14.12 SE 6.31	74.7 ± 11.15 SE 4.99	76.1 ± 5.28 SE 2.36	66.1 ± 9.77 SE 4.37	74.1 ± 9.97 SE 4.46	64.6 ± 7.96 SE 3.56	1.125	5/24	Not Sig	
	N_2	—	80.83 ± 11.96 SE 4.88	95.58 ± 6.35 SE 2.59	93.83 ± 9.60 SE 3.92	91.58 ± 9.83 SE 4.01	99.08 ± 8.21 SE 3.35	92.42 ± 7.15 SE 2.92	4.97	5/30	p<0.01	**
	P_2	114.5 ± 9.84 SE 3.11	120.75 ± 10.99 SE 3.48	121.7 ± 7.8 SE 2.47	126.8 ± 11.26 SE 3.56	122.5 ± 5.45 SE 1.73	127.28 ± 11.28 SE 3.57	134.25 ± 12.72 SE 4.03	6.403	6/63	p<0.001	**
	N_3	175.94 ± 28.88 SE 9.63	174.0 ± 19.09 SE 6.36	169.39 ± 13.01 SE 4.34	172.89 ± 18.95 SE 6.32	165.06 ± 19.47 SE 6.49	163.17 ± 8.17 SE 2.72	180.56 ± 16.94 SE 5.65	1.054	6/56	Not Sig	
AMPLITUDE (uV)	N_2-P_2	19.57 ± 10.73 SE 3.40	8.27 ± 4.61 SE 1.46	5.39 ± 2.48 SE 0.79	7.98 ± 6.48 SE 2.05	7.83 ± 5.56 SE 1.76	9.43 ± 8.91 SE 2.82	8.37 ± 5.61 SE 1.78	5.29	6/63	p<0.001	**
	P_2-N_3	17.02 ± 10.26 SE 3.42	9.66 ± 4.33 SE 1.44	6.03 ± 1.93 SE 0.64	6.95 ± 5.77 SE 1.92	8.93 ± 7.58 SE 2.53	9.49 ± 9.16 SE 3.03	6.18 ± 4.36 SE 1.45	2.52	6/56	p<0.05	*

Table 6.1.3 Effect of age on the latency and amplitude of the flash VEP

Figure 6.1.7 Effect of age on the latency of the flash VEP showing mean ± 1 standard error of the mean

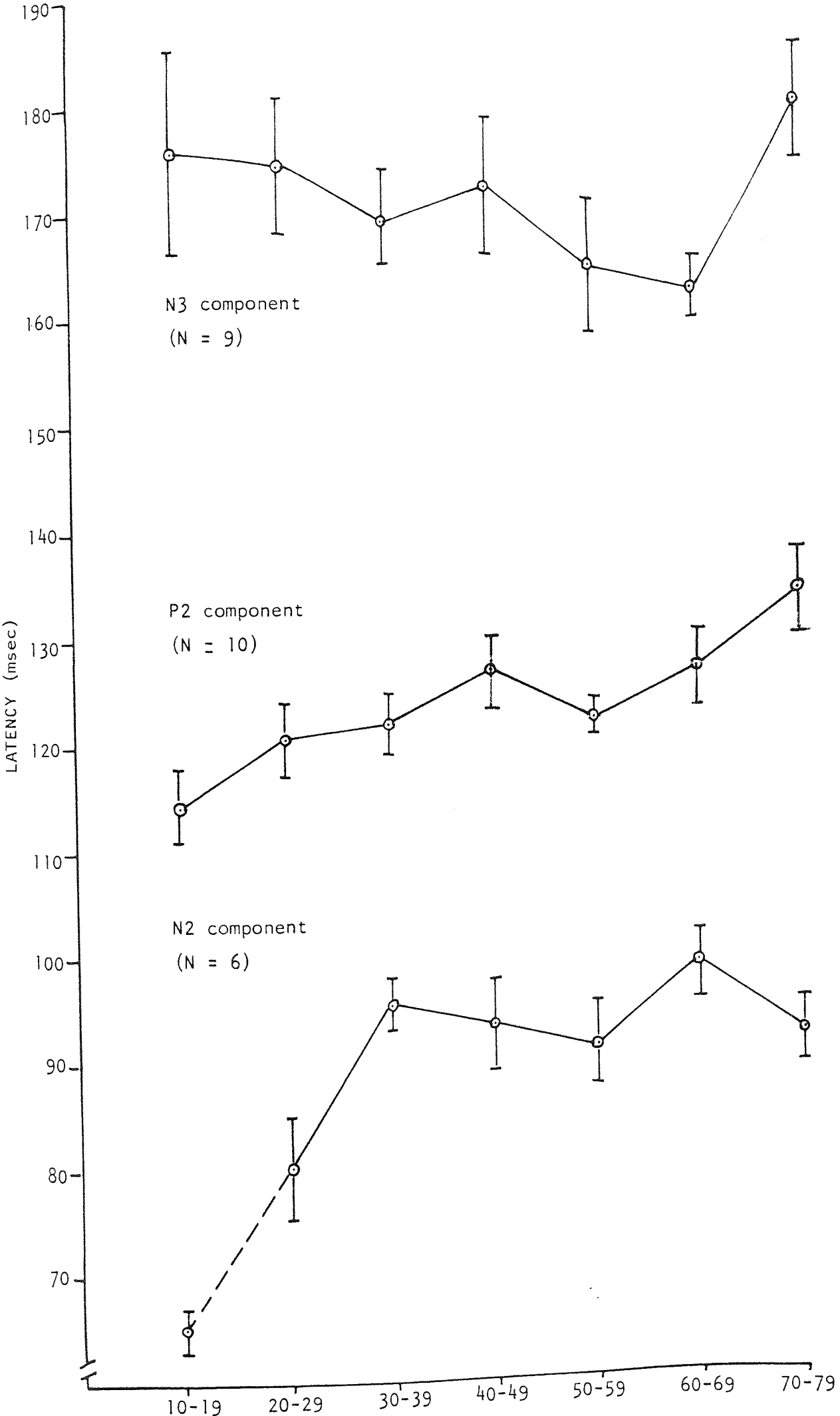
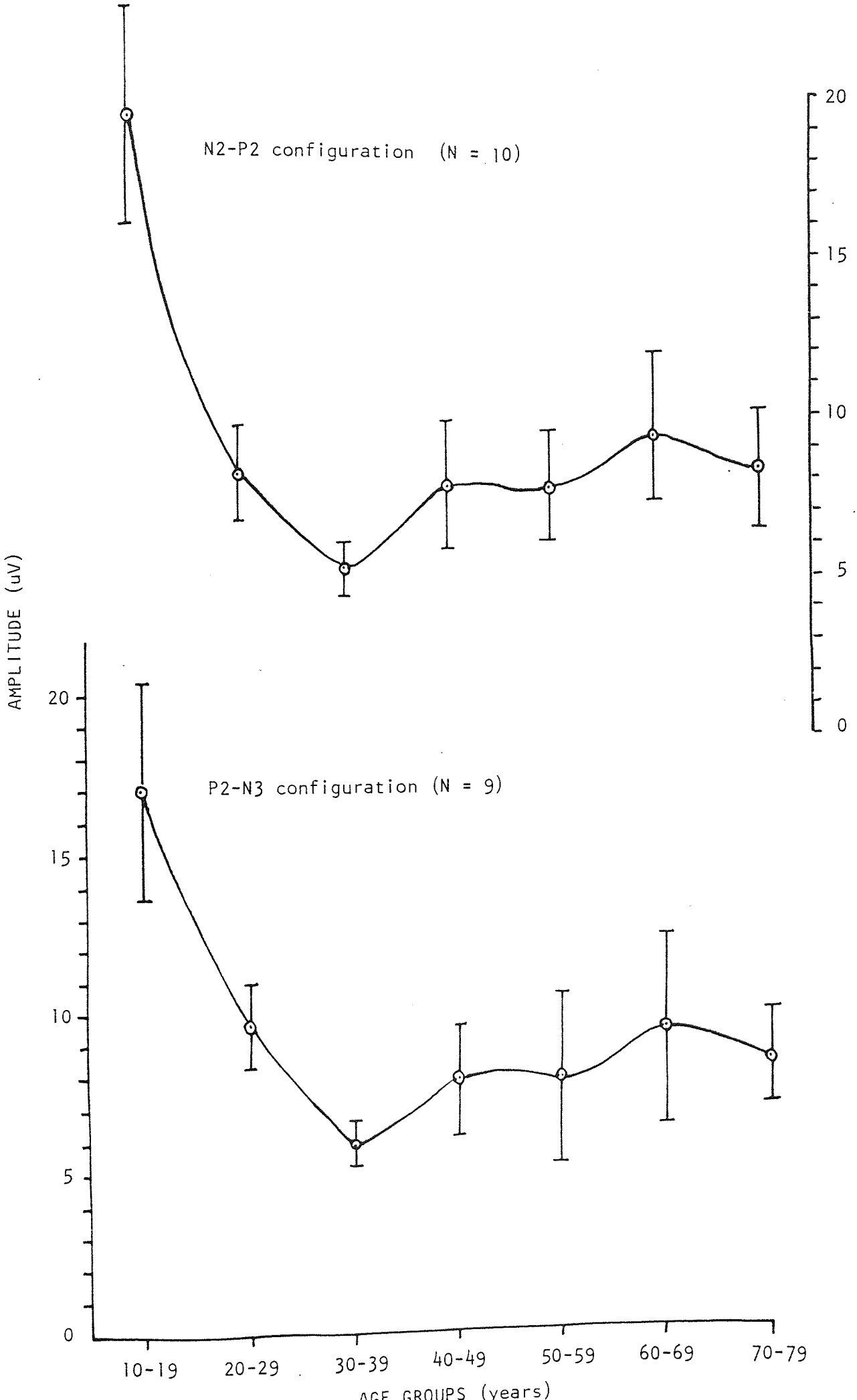


Figure 6.1.8 Effect of age on the amplitude of the flash VEP showing mean ± 1 standard error



amplitude (Table 6.1.3). N2 latency was included by omitting the 10-19 age group from the comparisons. Only 5 subjects in each group could be compared for the P1 component, but the results are included for reference, as this component is studied in Section 6.5. The only two components which show a significant change in latency with age are N2 and P2. Figure 6.1.7 shows that this change in the case of N2 consists of an earlier latency value in the 20-29 year age group, which is believed to be due mainly to one subject who showed a similar waveform to that observed in the 10-19 year group. Apart from this one value, no consistent latency trend with age is shown. The P2 latency, however, shows a consistent increase with age, a difference of 20 msec between the 10-19 and 70-79 age groups being found.

Both the N2-P2 and P2-N3 amplitudes show changes with age that are statistically significant (Table 6.1.3). As these both involved the P2 component these are not completely independent measures and the graphical plots follow each other closely (Figure 6.1.8). The major age related change is a marked reduction in amplitude of the order of 65% between the 10-19 and 30-39 year age groups. After this marked change, the amplitude shows no further changes with age.

The pattern reversal VEP was found to be very consistent indeed, as shown by Figure 6.1.9. Of the 70 subjects and 3 check sizes, the major positive component was reliably identified in 209/210 cases. Latency measurements (Table 6.1.4 and Figure 6.1.10) showed some variations between the means for the different age groups, but the only consistent trend was an increase in latency in the older age groups. This was more marked for the 13 minute check, where the increase was of the order of 11 msec, than for the 19 and 56 minute

checks where the overall increase was of the order of 2.5 and 6 msec respectively. Amplitude measurements (Table 6.1.4 and Figure 6.1.11) showed that the mean amplitude of the 10-19 year group was markedly higher than that of the other age groups for the 56 and 19 minute check sizes, being almost double that of the 20-29 year group. This trend was less marked for the 13 minute check VEP, although the mean amplitude of the 10-19 year group is still slightly higher than that of the other younger groups. Due to the variability of the standard errors of the other age groups for all check sizes, no consistent trend was observed.

Figure 6.1.9 shows that the components of the pattern onset-offset VEP could not be identified as consistently as the reversal VEP. Interaction of components caused ambiguities of measurement, as shown in Figure 6.1.12. This one subject shows the three types of waveform encountered in many subjects. The analysis of the onset-offset waveforms were based initially on published latency values of the components e.g. (38,39), with individual variations being determined, as far as possible, by comparison of the waveforms for each check size and each eye. Only those components which could be identified with confidence were included in the analysis. It can be seen that these interpretations were inevitably subjective.

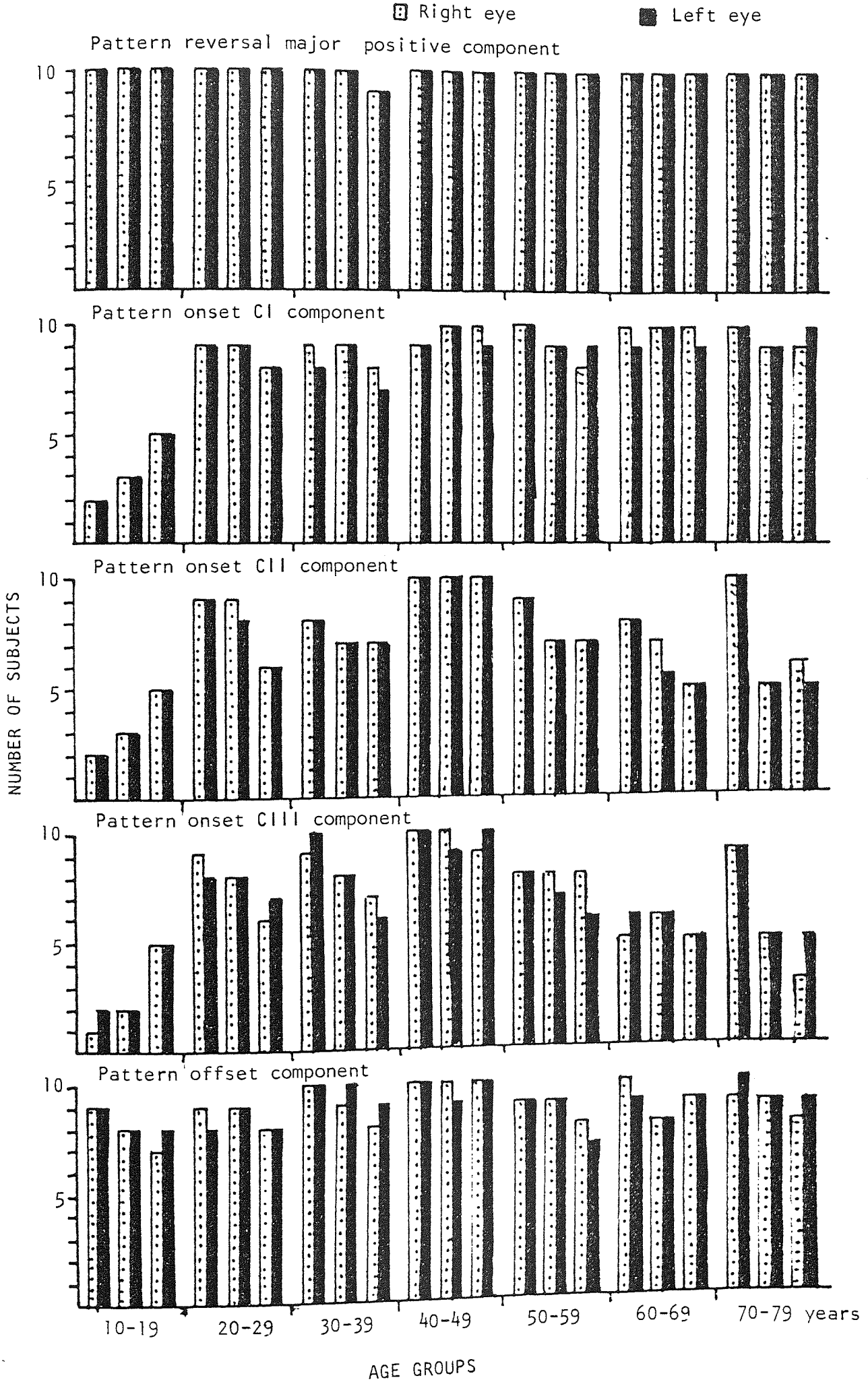
It can be seen from Figure 6.1.9 that the onset components were very difficult to identify in the 10-19 year age group. Eight out of the 10 subjects showed a very large positive wave in place of the onset VEP followed by a later positive offset response (Figure 6.1.12c). This positive appeared to be a combination of CI and CIII, as it was of an intermediate latency. The number of subjects showing a standard onset waveform increased to 5 when the foveal stimulus was used

(Figure 6.1.12a).

In view of these factors, the 10-19 age group was not included in the statistical analysis of the onset components. Figure 6.1.9 shows that, apart from this group, the CI component was the most consistent. The occurence of CII and CIII varied between age groups and between check sizes so the number of subjects used in the statistical tests was smaller.

CI showed a significant latency variation with age ($p < 0.01$) for the 13 minute check but not for the 56 and 19 minute checks (Table 6.1.5). Figure 6.1.13 shows that this is, in part, due to the variability of the results from the midline electrode for the 30-39 and 40-49 year age groups. A consistent latency increase with age can also be seen, increasing with decreasing check size. Such a relationship was not observed for the CII component (Table 6.1.6) although in this case the sample size was rather small to draw any definite conclusions. An increasing latency trend with age was observed for the 56 minute and 19 minute checks ($p < 0.025$) (Figure 6.1.14). Neither component showed any significant amplitude differences between the groups. (It must be noted that the 10-19 year group, which showed such large amplitude differences for other components, were not included in these comparisons). Tables 6.1.7 and 6.1.8 show that the standard errors of the CIII and offset responses are fairly large, due to the uncertainty in differentiation of the later VEP waves on the traces. As before, the 10-19 year group showed a much larger amplitude than the other groups for the offset response.

Figure 6.1.9 Showing number of control subjects in which pattern VEP components could be identified. For each age group left columns represent 56 min, middle columns 19 min and right columns 13 minute check



	Check (min)	10-19 yr	20-29 yr	30-39 yr	40-49 yr	50-59 yr	60-69 yr	70-79 yr	Variance Ratio	df n/d	Significance Level	
LATENCY (m.sec)	56	108.56 ± 10.9 SE 3.63	101.78 ± 7.64 SE 2.55	106.78 ± 4.91 SE 1.64	104.6 ± 5.15 SE 1.72	102.89 ± 6.75 SE 2.25	109.22 ± 10.45 SE 3.48	111 ± 8.7 SE 2.9	Age Groups: 3.147	6/56	p<0.01	* *
	19	106.72 ± 4.17 SE 1.39	101.83 ± 4.24 SE 1.41	110.28 ± 10.5 SE 3.5	105.61 ± 3.30 SE 1.10	105.61 ± 7.37 SE 2.46	106.11 ± 4.54 SE 1.51	108.61 ± 9.39 SE 3.13	Check Sizes: 2.4	2/112	Not Sig	
	13	106.5 ± 8.19 SE 2.73	106.44 ± 7.84 SE 2.61	105 ± 8.52 SE 2.84	108.14 ± 10.4 SE 3.47	106.61 ± 10.32 SE 3.44	108.61 ± 7.23 SE 2.41	118.44 ± 9.52 SE 3.17	Age Groups: 3.115	6/56	p<0.05	*
	0 13	106 ± 10.48 SE 3.49	105.44 ± 6.67 SE 2.22	103.56 ± 8.8 SE 2.93	107.11 ± 7.59 SE 2.53	107.22 ± 6.57 SE 2.19	107.44 ± 10.37 SE 3.46	118.44 ± 10.31 SE 3.44	Electrodes: 2.34	1/56	Not Sig	
AMPLITUDE (uV)	56	11.85 ± 3.44 SE 1.09	4.54 ± 1.98 SE 0.63	5.1 ± 1.82 SE 0.58	6.73 ± 5.95 SE 1.88	6.07 ± 4.13 SE 1.31	6.13 ± 7.18 SE 2.27	6.20 ± 4.18 SE 1.32	Age Groups: 2.256	6/63	p<0.05	*
	19	11.49 ± 6.44 SE 2.07	4.58 ± 2.14 SE 0.68	5.06 ± 2.70 SE 0.85	7.01 ± 4.69 SE 1.48	7.65 ± 7.18 SE 2.27	8.81 ± 6.53 SE 2.07	5.5 ± 2.71 SE 0.86	Check Sizes: 0.39	1/63	Not Sig	
	13	4.58 ± 2.79 SE 0.93	2.78 ± 1.28 SE 0.43	3.47 ± 2.03 SE 0.68	3.22 ± 1.54 SE 0.51	3.75 ± 2.79 SE 0.93	4.11 ± 2.42 SE 0.81	4.36 ± 2.09 SE 0.7	Age Groups: 0.657	6/56	Not Sig.	
	0 13	4.51 ± 2.91 SE 0.97	2.62 ± 1.49 SE 0.50	3.32 ± 2.00 SE 0.67	2.88 ± 1.69 SE 0.56	3.9 ± 1.97 SE 0.66	4.77 ± 3.04 SE 1.01	4.12 ± 4.14 SE 1.38	Electrodes: 0.037	1/56	Not Sig	

TABLE 6.1.4 Effect of age on the major positive component of the pattern reversal VEP

Figure 6.1.10 Effect of age on the latency of the pattern reversal VEP showing mean ± 1 standard error of the mean

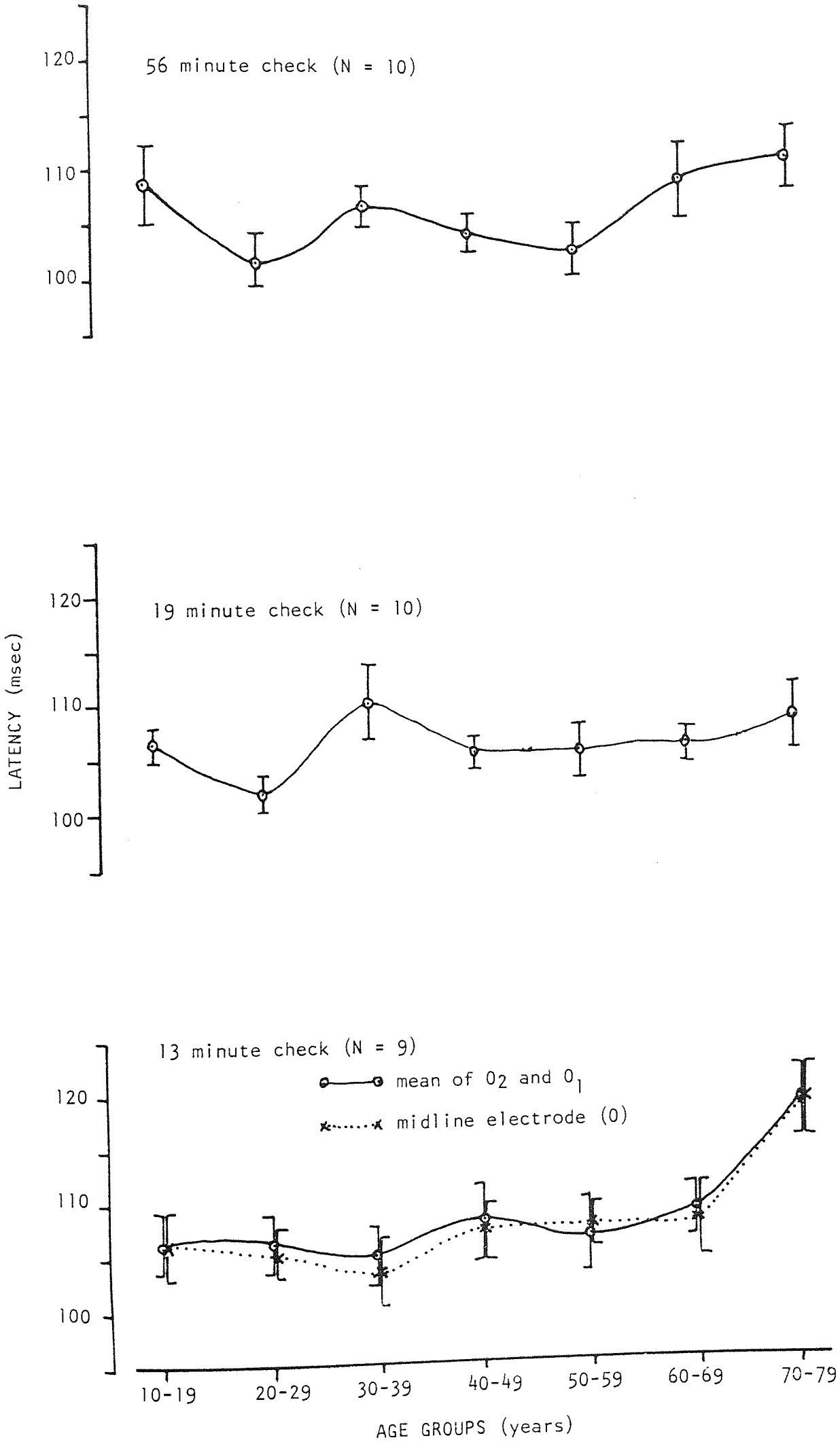
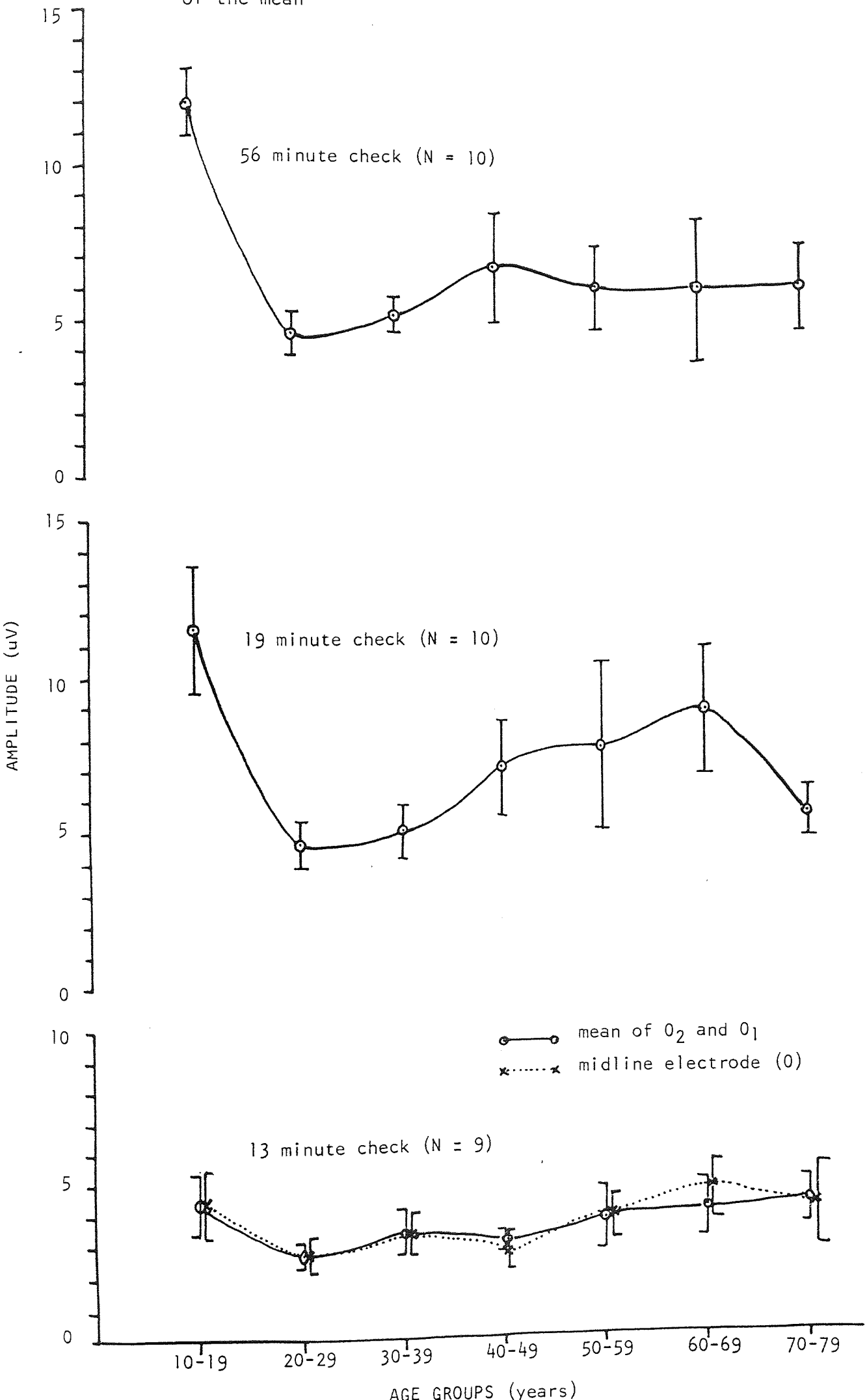


Figure 6.1.11 Effect of age on the amplitude of the pattern reversal VEP showing mean ± 1 standard error of the mean



Subject L.G. Age 13 years Left eye

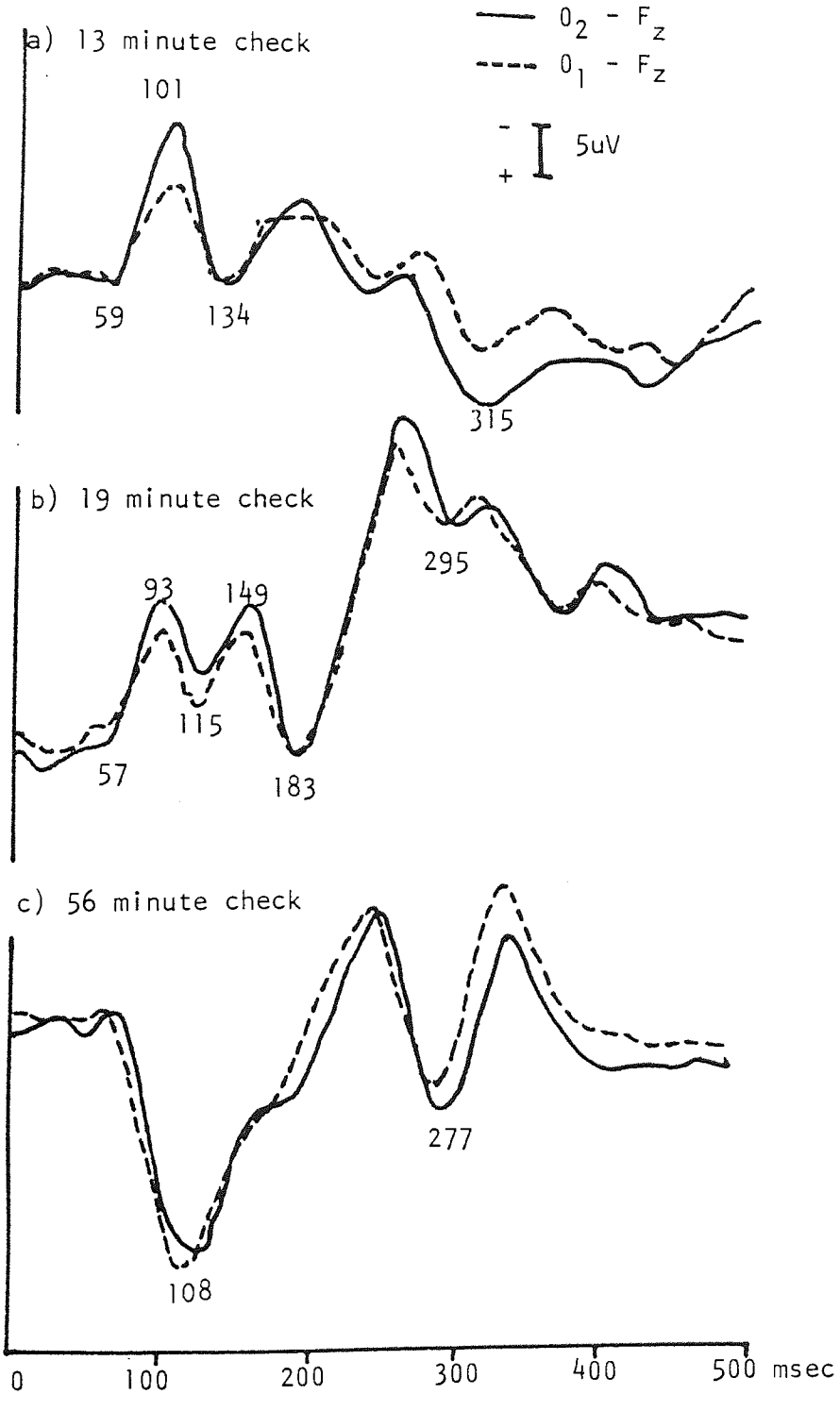
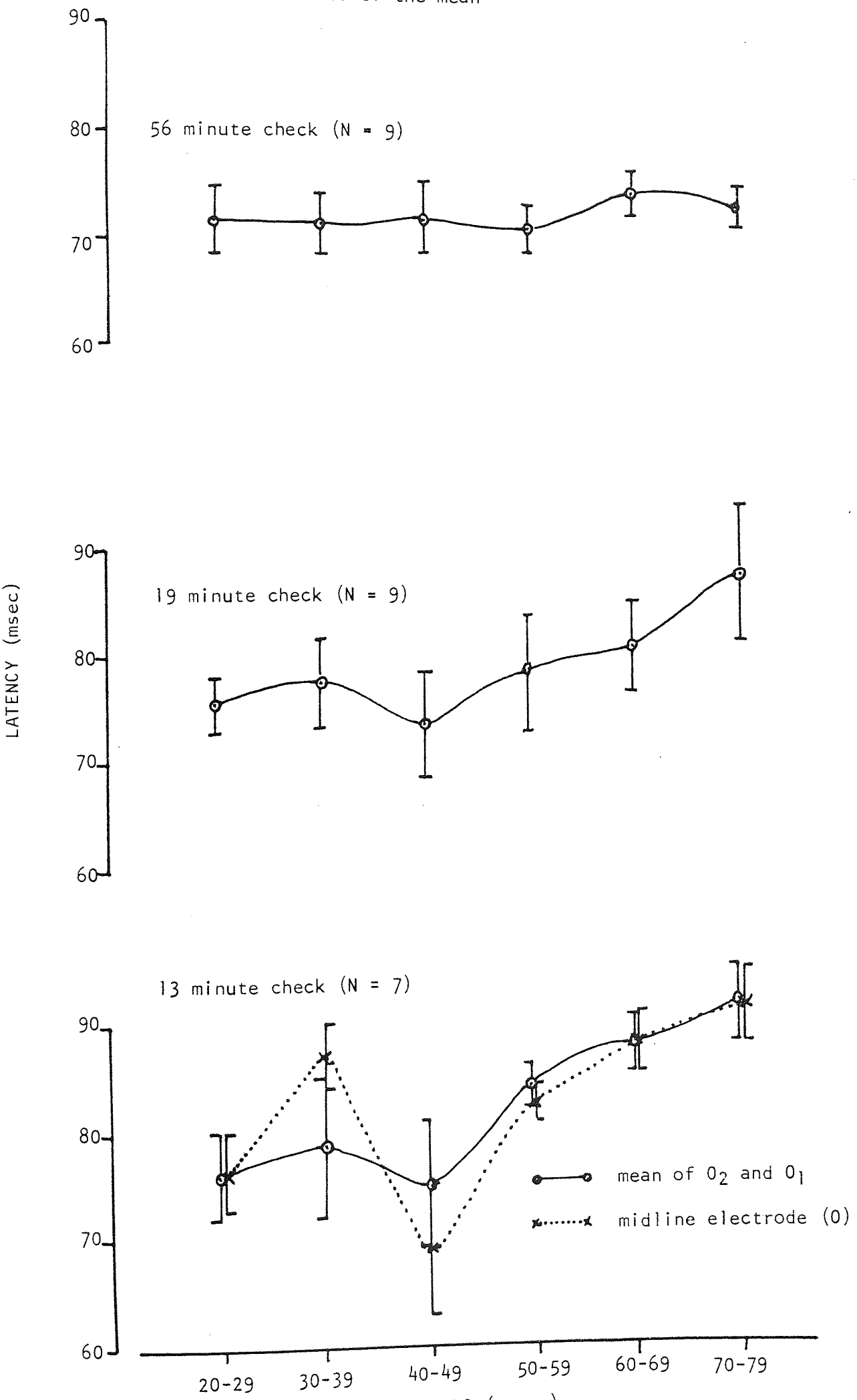


Figure 6.1.12 Ambiguous pattern onset-offset waveforms showing the difficulties encountered in the measurement of such VEPs a) shows a standard waveform with CII at 101 msec. b) can be interpreted either as two negative components or a single negative split in two by a positive wave at 115 msec. c) CII is completely obscured by a large positive wave which could be either CI or CIII or a combination of the two.

Check (min)		10-19 yr	20-29 yr	30-39 yr	40-49 yr	50-59 yr	60-69 yr	70-79 yr	Variance Ratio	df n/d	Significance Level	
LATENCY (m.sec)	56	-	71.39 ± 9.18 SE 3.06	71.06 ± 7.18 SE 2.39	71.61 ± 9.61 SE 3.20	70.72 ± 5.47 SE 1.82	74.08 ± 5.98 SE 1.99	72.56 ± 4.98 SE 1.66	Age Groups: 1.483	5/48	Not Sig.	
	19	-	75.67 ± 4.08 SE 1.36	77.62 ± 7.03 SE 2.34	73.39 ± 14.34 SE 4.78	78.33 ± 10.92 SE 3.64	80.5 ± 5.75 SE 1.92	87.31 ± 8.60 SE 2.87	Check Sizes: 29.11	1/48	p<0.01	**
	13	-	76.07 ± 10.65 SE 4.02	78.71 ± 15.26 SE 5.77	74.71 ± 14.57 SE 5.5	83.93 ± 4.12 SE 1.56	87.32 ± 6.02 SE 2.27	90.57 ± 9.52 SE 3.6	Age Groups: 4.419	5/36	p<0.01	**
	0 13	-	76.29 ± 9.23 SE 3.49	87.14 ± 8.47 SE 3.2	68.86 ± 15.7 SE 5.93	82.29 ± 4.19 SE 1.58	87.64 ± 7.05 SE 2.67	90.71 ± 4.86 SE 1.84	Electrodes: 0.046	1/36	Not Sig	
AMPLITUDE (uV)	56	-	4.76 ± 2.18 SE 0.73	3.63 ± 2.28 SE 0.76	5.34 ± 6.31 SE 2.10	5.73 ± 7.74 SE 2.58	6.34 ± 4.32 SE 1.44	5.44 ± 4.72 SE 1.57	Age Groups: 0.506	5/48	Not Sig	
	19	-	3.17 ± 2.22 SE 0.74	2.73 ± 6.31 SE 2.10	4.22 ± 4.88 SE 1.63	8.55 ± 14.2 SE 4.74	5.28 ± 4.14 SE 1.38	5.32 ± 6.26 SE 2.09	Check Sizes: 0.395	1/48	Not Sig	
	13	-	1.66 ± 0.59 SE 0.24	2.07 ± 1.08 SE 0.44	2.37 ± 1.16 SE 0.48	4.53 ± 3.81 SE 1.56	4.63 ± 2.90 SE 1.18	5.17 ± 5.94 SE 2.43	Age Groups: 1.393	5/30	Not Sig	
	0 13	-	1.13 ± 0.63 SE 0.26	2.43 ± 2.26 SE 0.92	1.58 ± 0.77 SE 0.31	2.68 ± 1.92 SE 0.79	4.1 ± 3.2 SE 1.3	4.15 ± 4.69 SE 1.92	Electrodes: 6.62	1/30	p<0.05	*

TABLE 6.1.5 Effect of age on the C1 component of the pattern onset VEP.

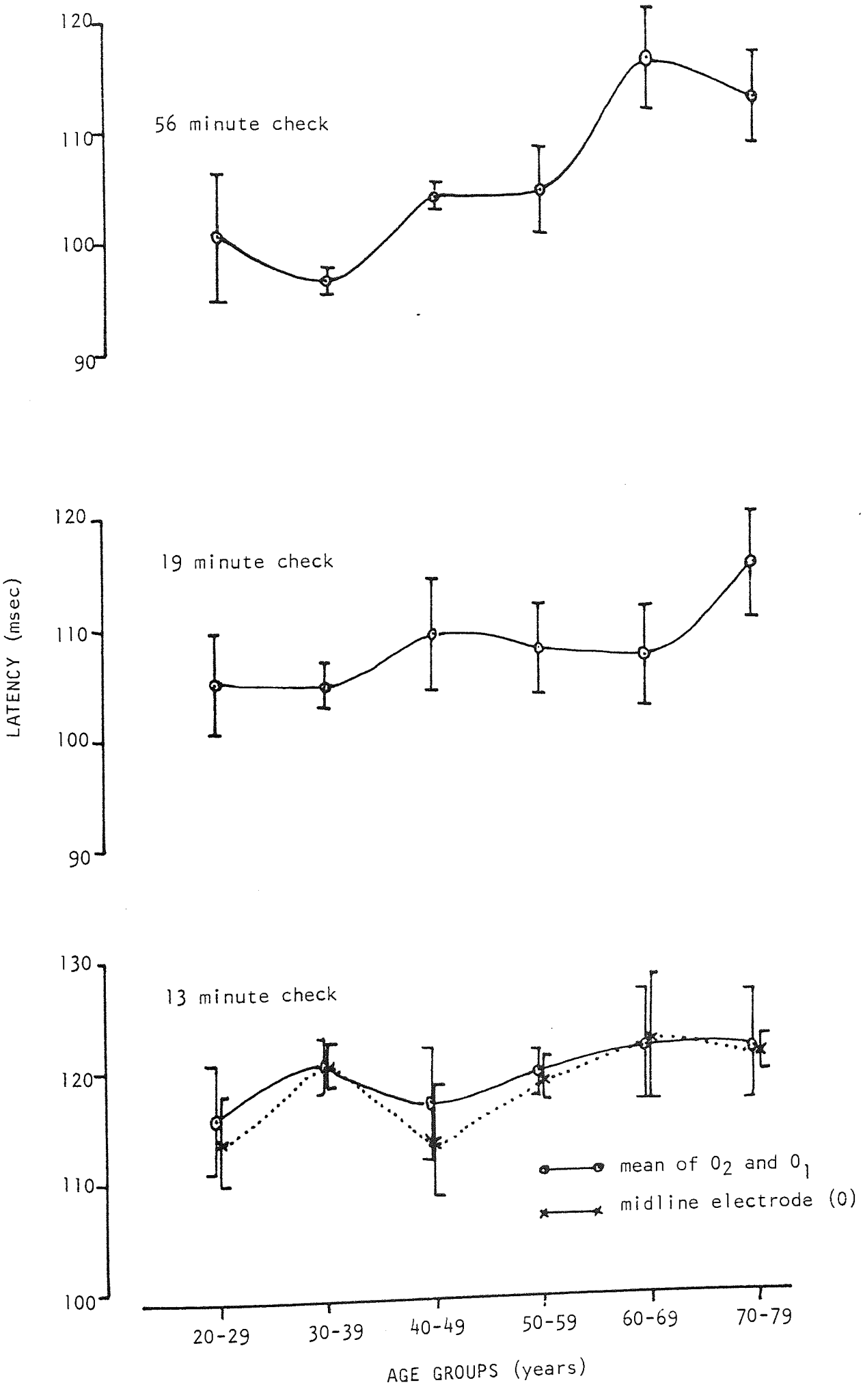
Figure 6.1.13 Effect of age on the latency of the C1 component of the pattern onset VEP showing mean ± 1 standard error of the mean



Check (Min)	10-19 yr	20-29 yr	30-39 yr	40-49 yr	50-59 yr	60-69 yr	70-79 yr	Variance Ratio	df n/d	Significance Level
LATENCY 56 (msec)	—	100.2 ± 12.57 SE 5.62	96.86 ± 1.86 SE 0.83	104.4 ± 2.36 SE 1.05	105.2 ± 8.7 SE 3.89	117 ± 10.02 SE 4.48	113.7 ± 9.16 SE 4.10	Age Groups: 3.42	5/24	p<0.025 *
19	—	105.2 ± 10.26 SE 4.59	105 ± 4.83 SE 2.16	109.6 ± 10.02 SE 4.48	108.2 ± 8.86 SE 3.96	107.5 ± 10.37 SE 4.64	116 ± 10.81 SE 4.83	Check Sizes: 1.30	1/24	Not Sig
13	—	115.4 ± 10.77 SE 4.82	121.2 ± 5.73 SE 2.56	117.1 ± 10.99 SE 4.92	119.4 ± 4.45 SE 1.99	121.8 ± 12.35 SE 5.52	121.5 ± 11.02 SE 4.93	Age Groups: 0.661	5/24	Not Sig
0 13	—	113.8 ± 10.38 SE 4.64	120.8 ± 4.66 SE 2.08	113.2 ± 10.64 SE 4.76	118.8 ± 4.49 SE 2.01	122.4 ± 12.93 SE 5.78	120.4 ± 3.65 SE 1.63	Electrodes: 2.593	1/24	Not Sig
AMPLITUDE 56 (uV)	—	3.16 ± 0.85 SE 0.38	3.49 ± 1.81 SE 0.81	8.91 ± 12.19 SE 5.45	6.78 ± 2.60 SE 1.16	12.66 ± 9.33 SE 4.17	11.5 ± 3.47 SE 1.55	Age Groups: 1.446	5/24	Not Sig
19	—	3.99 ± 1.76 SE 0.79	3.77 ± 2.56 SE 1.14	9.99 ± 11.17 SE 4.99	5.79 ± 3.84 SE 1.72	10.61 ± 7.64 SE 3.42	13.01 ± 3.61 SE 1.61	Check Sizes: 0.009	1/24	Not Sig
13	—	3.85 ± 4.08 SE 1.82	3.83 ± 3.56 SE 1.59	5.48 ± 3.45 SE 1.54	10.76 ± 9.15 SE 4.09	10.49 ± 7.30 SE 3.26	10.11 ± 11.98 SE 5.36	Age Groups: 0.964	5/24	Not Sig
0 13	—	4.48 ± 4.42 SE 1.98	4.14 ± 3.68 SE 1.65	5.22 ± 3.22 SE 1.44	9.02 ± 3.00 SE 1.34	10.13 ± 6.85 SE 3.06	9.1 ± 10.5 SE 4.7	Electrodes: 2.201	1/24	Not Sig

TABLE 6.1.6 Effect of age on the CII component of the pattern onset VEP.

Figure 6.1.14 Effect of age on the latency of the C11 component of the pattern onset VEP showing mean ± 1 standard error (N = 5)



Check (min)	10-19 yr	20-29 yr	30-39 yr	40-49 yr	50-59 yr	60-69 yr	70-79 yr	Variance Ratio	df n/d	Signif-icance
LATENCY 56' (m.sec)	-	146.4 ± 18.45 SE 8.25	141.4 ± 8.17 SE 3.66	149.4 ± 15.7 SE 7.02	153.9 ± 25.8 SE 11.56	159.6 ± 8.86 SE 3.96	177.9 ± 22.35 SE 10.00	2.643	5/24	p<0.05
19'	-	153.6 ± 39.44 SE 17.64	145 ± 6.75 SE 3.02	155.3 ± 21.96 SE 4.39	158.6 ± 33.13 SE 14.81	174.7 ± 33.24 SE 14.86	177.4 ± 31.35 SE 14.02	0.917	5/24	Not Sig
13'	-	148.2 ± 7.16 SE 3.2	146.2 ± 19.58 SE 8.75	164.8 ± 15.87 SE 7.10	176.2 ± 27.66 SE 12.37	161 ± 28.75 SE 12.86	174.2 ± 29.37 SE 13.13			
0 13'	-	151.8 ± 6.83 SE 3.06	148.6 ± 18.65 SE 8.34	165 ± 15.23 SE 6.81	174.4 ± 13.21 SE 5.91	170.8 ± 17.28 SE 7.73	174.2 ± 31.02 SE 13.87	1.502	5/24	Not Sig
								No significant difference between electrodes		
AMPLITUDE 56' (uV)	-	5.87 ± 2.49 SE 1.02	7.71 ± 7.03 SE 2.87	5.74 ± 3.33 SE 1.36	6.68 ± 4.86 SE 1.99	11.13 ± 11.24 SE 4.59	9.43 ± 5.32 SE 2.17	0.676	5/30	Not Sig
19'	-	3.65 ± 2.66 SE 1.08	4.93 ± 4.09 SE 1.67	7.21 ± 6.64 SE 2.71	7.99 ± 8.20 SE 3.35	7.50 ± 7.46 SE 3.04	9.98 ± 6.14 SE 2.51	0.806	5/30	Not Sig
13'	-	1.95 ± 1.16 SE 0.52	2.72 ± 3.20 SE 1.43	3.41 ± 1.85 SE 0.83	5.13 ± 3.41 SE 1.53	6.13 ± 8.27 SE 3.70	6.35 ± 4.14 SE 1.85	1.085	5/24	Not Sig
0 13'	-	3.02 ± 1.28 SE 0.57	2.5 ± 2.15 SE 0.96	4.12 ± 2.75 SE 1.23	5.06 ± 3.58 SE 1.60	6.86 ± 8.38 SE 3.75	8.7 ± 5.79 SE 2.59	(Between electrodes) (9.39	1/24	p<0.01)

Table 6.1.7 Effect of age on the CIII Component of the pattern onset VEP

	Check (min)	10-19 yr	20-29 yr	30-39 yr	40-49 yr	50-59 yr	60-69 yr	70-79 yr	Variance Ratio	df n/d	Signif-icance
LATENCY (m.sec)	56	263.06 ± 16.22 SE 5.73	265.13 ± 10.64 SE 3.76	256.56 ± 18.63 SE 6.59	247.94 ± 12.29 SE 4.35	248.88 ± 44.36 SE 15.69	260.94 ± 22.60 SE 7.99	254.63 ± 29.55 SE 10.43	0.779	6/49	Not Sig
	19	268.31 ± 16.59 SE 5.87	250 ± 14.73 SE 5.21	259.81 ± 7.81 SE 2.76	252.88 ± 13.28 SE 4.70	250.44 ± 24.34 SE 8.61	246.75 ± 29.62 SE 10.47	244.63 ± 23.54 SE 8.32			
	13	255.07 ± 21.3 SE 8.06	259.44 ± 19.76 SE 6.99	253.93 ± 20.6 SE 7.28	255.95 ± 14.05 SE 4.97	256.63 ± 16.02 SE 5.66	247.13 ± 28.11 SE 9.94	248.63 ± 22.97 SE 8.12	0.831	6/42	Not Sig
	0 13	255.86 ± 18.69 SE 2.65	261.75 ± 21.19 SE 6.71	256.13 ± 20.25 SE 7.16	254.75 ± 14.95 SE 5.29	262.13 ± 27.59 SE 9.75	248.13 ± 27.72 SE 9.80	245.25 ± 20.33 SE 7.19	No difference between electrodes		
AMPLITUDE (uV)	56	12.54 ± 10.54 SE 3.73	5.88 ± 3.64 SE 1.29	4.98 ± 2.62 SE 0.92	4.9 ± 3.31 SE 1.17	4.56 ± 3.46 SE 1.22	5.36 ± 4.61 SE 1.63	2.89 ± 2.67 SE 0.94	2.537	6/49	p<0.05
	19	9.47 ± 6.02 SE 2.13	4.16 ± 3 58 SE 1.27	4.04 ± 3.20 SE 1.13	4.05 ± 3.22 SE 1.14	5.18 ± 4.61 SE 1.63	4.76 ± 4.69 SE 1.66	4.76 ± 4.24 SE 1.50			
	13	9.46 ± 5.31 SE 2.00	5.51 ± 3.82 SE 1.35	3.57 ± 2.01 SE 0.71	2.93 ± 1.93 SE 0.68	3.69 ± 1.92 SE 0.68	3.12 ± 1.92 SE 0.68	3.5 ± 2.32 SE 0.32	2.839	6/42	p<0.025
	0 13	8.39 ± 6.03 SE 2.28	5.86 ± 4.05 SE 1.43	3.41 ± 2.15 SE 0.76	3.28 ± 2.28 SE 0.8	3.85 ± 4.46 SE 1.58	2.89 ± 1.70 SE 0.60	2.81 ± 1.95 SE 0.69	No difference between electrodes.		

Table 6.1.8 Effect of age on latency and amplitude of pattern offset component

Discussion - This study provides a unique opportunity to compare the effect of age on different psychophysical and electrophysiological measures. Such a comparative study has not previously been reported, nor has the effect of age on the de Lange curve or the pattern onset VEP.

The most marked age variation found for the psychophysical measures is the reduction in sensitivity at high spatial and temporal frequencies. It has previously been found that reduction in mean luminance level reduces sensitivity at high frequencies more than low frequencies for both CSF (190) and de Lange curves (226). The reduction in retinal illuminance caused by the decrease in pupil size with age must therefore be taken into account. The mean pupil diameter in our study decreases from 4.9mm in the 10-19 age group to 3.15mm in the 70-79 age group, representing a reduction in pupil area, and hence retinal illumination, of 0.38 log units.

The contrast sensitivity data of Kulikowski (190) for a 10 c/deg grating shows that, within the linear section of his graph (which includes the mean luminance level of our apparatus), a mean luminance reduction of 2 log units causes a contrast sensitivity reduction of 1 log unit. Applying this to our data, a contrast sensitivity reduction of 0.19 log units would be expected to be due to the decrease in pupil size alone. This accounts for $^{2}/_{3}$ of the measured 0.31 log attenuation at 12 c/deg in our study.

The decrease in pupil size with age would not be expected to produce a deterioration in the optical quality of the image, as in fact the pupil diameter of the older age group is the closest to the 2.4mm pupil

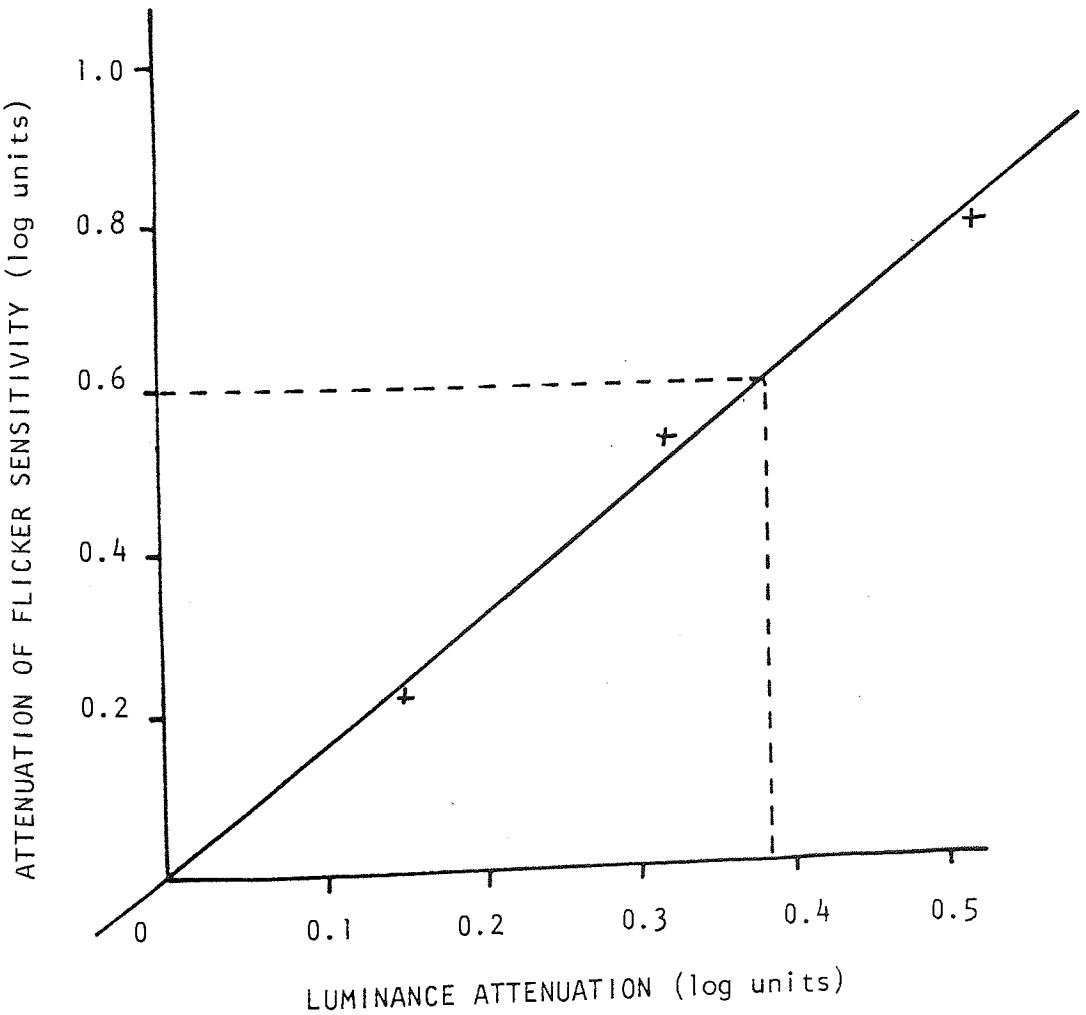
diameter shown by Campbell and Gubisch (276) to represent the best optical image quality due to the minimum combined effects of peripheral aberrations and diffraction. Another factor which causes a deterioration of the image in the ageing eye and could account for the remainder of the contrast sensitivity attenuation found in our study, is the increase in the light absorption of the lens with age which decreases the optical transmission and increases light scatter in the eye (360).

The effect of 0.38 log luminance attenuation on flicker sensitivity at 30Hz was measured on our apparatus using neutral density filters (Figure 6.1.15). An 0.38 log luminance attenuation was found to produce an attenuation in flicker sensitivity of 0.6 log units, almost totally accounting for the 0.68 log unit decrease with age found in our study.

The overall decrease in luminance due to pupil size would also be sufficient to account for the latency increases found for the pattern reversal VEP in the older age groups. Halliday (111) found a luminance decrease of 1 log unit produced a 15 msec increase in the latency of the pattern reversal VEP to 50 minute checks. A 0.38 log luminance decrease would therefore produce an increase of about 5.7 msec, which is consistent with the results for the 56 minute pattern reversal VEP in our study (Figure 6.1.10). Our results also show a larger latency increase for small checks consistent with other age studies (reviewed in Section 2C). Comparative studies on the effect of luminance on the VEP at different check sizes are not known, but it is presumed that the effect would be more pronounced at small check sizes, analogous to the psychophysical findings. The study of luminance and the pattern onset VEP of Van der Tweel, Estevez and Cavonius (110) also used large

Figure 6.1.15 Showing the relationship between flicker sensitivity at 30Hz and the mean luminance of the stimulus. Dashed line marks the 0.38 log unit attenuation of retinal illuminance produced by the decrease of pupil area between the 10-19 and 70-79 year age groups

Mean of 2 subjects aged 27 and 28 years



checks, of 40-60 minutes. They reported a larger latency increase, of the order of 30 msec per log unit luminance reduction, which would indicate an expected increase of 11.4 msec for the pattern onset CII component to the 56 minute checks in our study. The measured results would be consistent with this, although the small numbers involved and the variability of the results do not permit a more detailed analysis. From the amplitude measurements of Halliday (70), who found a decrease of the order of 15% per log unit luminance reduction, a luminance decrease of 0.38 log units would only cause an amplitude reduction of the order of 5%. Taking into account the normal variability of amplitude measurement, this effect would be negligible in our study.

The most consistent effect of increasing age on the flash VEP was the progressive increase in the latency of the P2 component. The effect of luminance reduction on P2 latency has been reported to be of the order of an 8-12 msec increase in latency per log unit (51, 52). An 0.38 log luminance reduction would therefore cause an increase of the order of 3 - 4.5 msec. The 20 msec overall P2 latency increase found in our study and other studies (44, 47, 48) must therefore be mainly due to neural factors. This result shows that P2 latency is the most sensitive indicator of the neural factors associated with ageing of the psychophysical and electrophysiological measures investigated in this study.

At the other end of the age scale, the 10-19 year age group shows VEP results which are markedly different from the other groups. Both the flash and pattern onset VEPs show a replacement of the early components by a single large component. A connection between these two observations was also indicated by the observation that the one subject (PG) who showed a flash VEP of standard configuration was also

one of the two who showed a 56 minute onset VEP of standard configuration. The apparent replacement of the onset VEP by a large positive wave of latency between that of CI and CIII is similar to the waveform described by de Vries-Khoe and Spekreijse (91) for the developing onset-offset VEP in children up to about 8 years of age. However, it seems unlikely that in this case this waveform is reflecting an absence or underdevelopment of foveal contrast mechanism as suggested by the above authors for children, as psychophysical results indicate that spatial and temporal mechanisms have developed fully to adult levels in this age group. In addition, the VEP evoked by the foveal stimulus shows a greater similarity to that obtained in other adult age groups with respect to both pattern onset waveform (Figure 6.1.12) and pattern reversal amplitude (Figure 6.1.11). It is suggested that, rather than being absent, the early components of the flash VEP and the foveal pattern onset VEP are obscured by the extremely high amplitude of signals from extrafoveal retinal areas. The reason for the high amplitudes of the components of the flash VEP and the pattern reversal and onset VEP to medium and large checks is not known, but one possibility is that it reflects hormonal changes connected with puberty.

TABLE 6.2.1 AMBLYOPES - CLINICAL DETAILS

	Age	AMBLYOPIC EYE		GOOD EYE		REFRACTION (Rx)	STRABISMUS	TREATMENT
		Right or Left	VA	VA	Optical Blur			
DE	32	L	0.1	1.0	0.1	R +7.75/-1.75x170 L +7.75/-1.50x170	Left Divergent 25° Distance 14° Near	Occl - 4 yrs of age for 12-18 months. Op - None. Rx - Worn constantly since 5½ yrs of age.
CVE	20	R	0.25	1.2	0.25	R -1.25DS 6Δ B.IN L +1.25/-0.25x180 6Δ B.IN	Right Divergent 14° Distance 3-4° Near	Occl.- on specs 2 years of age for 5 years. Op. - 3, at 2, 15 & 16 yrs. Rx - worn with blurring lens to prevent diplopia.
NP	68	R	0.25	1.0	0.25	R +6.00 DS L +4.50/-1.50x10	Right Convergent 14° Distance and Near	Occl. - None Op. - at 19 yrs of age Unsuccessful. Rx - worn constantly.
DS	59	R	0.26	1.2	0.26	R + 2.75 DS L + 2.75 DS	Right Convergent 6° Distance 8° Near	Occl.- None Op. - None Rx - worn constantly since 7 years of age.
HO	15	L	0.33	1.0	0.33	R +0.50 DS L +3.50/-1.00x20	No Deviation	No treatment or Rx prescribed.
MB	17	L	0.33	1.2	0.33	R + 1.25 DS L + 3.50/-1.00x75	Left Convergent 14° Distance and Near	Occl. - Total at 4 years of age for a few weeks, orthoptic treatment until 12 or 13 years. Op.-18 months of age. Rx - worn constantly.

CONTINUED/.....

AMBLYOPES - CLINICAL DETAILS (Continued)

RM	16	R	0.40	1.5	0.40	R Plano/-0.50x25 L +0.25/-0.50x170	Right Convergent 3-4° Distance and Near ECCENTRIC FIXATION	Occl.- Total for 1 month. Patch on glasses for 3 weeks. Orthoptic treatment from 5 to 8 years.
DB	35	R	0.43	1.2	0.43	R +2.00/-0.75x90 L +0.50/-0.25x70	Right Convergent 7° Distance and Near ECCENTRIC FIXATION	Occl. - on specs 8 years of age for a few months, then intermittent. Op. - None. Rx. - worn from 8 - 13 years.
SH	24	L	0.50	1.2	0.50	R -3.00 DS L -3.00/-2.00x30	No deviation	Occl. - 11 years for a few months. Op. - None. Rx. - worn constantly since 9 years of age.
AR	22	R	0.53	1.2	0.56	R +2.75 DS L +0.25 DS	Right Convergent 7° Distance and Near	Occl. 5 or 6 years of age for a couple of months. Op. - None. Rx. - Worn from 5-11 years of age.

Abbreviations:

Occl.- Occlusion
Op. - Operation
Rx - Optical prescription.

6.2 Amblyopia and optical blur study

This study of ten amblyopes offered a unique opportunity to study the effect of neural and optical blur and to compare them with normal clear vision in the same subject. The comparison of the amblyopic and clear conditions are reported in study 6.2A and the comparison of the optically blurred and clear conditions are reported in study 62B, with appropriate discussion.

62A Amblyopia study

Psychophysical results - The 10 volunteers were selected on the criterion of VA of $^{6}/_{12}$ or less in the amblyopic ey e and $^{6}/_{6}$ or better in the non-amblyopic eye (to avoid confusion of terms this eye will be referred to as the "good" eye). To establish that the good eye was unaffected, the psychophysical spatial results from the 10 good eyes were compared with the equivalent monocular results from 10 age and sex matched normal controls. There were no significant differences between these two groups for both VA (variance ratio 1.069; df n = 1 d = 9) or contrast sensitivity (variance ratio 0.538; df n = 1 d = 9) measurements. The good eye was therefore used as the control to the amblyopic eye in all comparisons - an ideal situation as both eyes are linked to the same brain.

The sensitivity of VA measurements on the Snellen chart was increased by asking the subject to read every letter on each line (246) and extrapolating the decimal notation to include intermediate values corresponding to the number of letters correctly read (354). The clinical details in Table 6.2.1 are arranged in order of increasing VA. It can be seen that subjects HO and SH are purely anisometropic

amblyopes and subjects DE, DS and RM are purely strabismic. The remaining 5 have both strabismus and anisometropia.

Figure 6.2.1 shows the individual MTF results arranged in order of increasing VA. The results are plotted in the form of sensitivity ratios of amblyopic eye/good eye so that any point below the level corresponding to the 1.00 ratio level represents that the sensitivity in the amblyopic eye is worse than that from the good eye, and vice versa.

From the individual CSF results it can be seen that 8 out of the 10 patients showed an increasing contrast sensitivity defect with increasing spatial frequency. The relative size of the high frequency defect does not, however, parallel the increasing VA. Inspection of the medium frequency results shows that two subjects, HO and SH showed a greater relative defect at 4 c/deg. These are the two anisometropic amblyopes, and it is particularly interesting to note that the nature of this defect corresponds to the pattern of CSF defects found in the optical blur study (Section 6.3). Subject HO shows the greatest relative overall CSF defect of all the 10 subjects (particularly marked at low and medium frequencies). From Table 6.2.1 it can be seen that this is the only subject who has had no treatment or refractive correction at all. At the lowest frequency, 5 subjects show no difference between the eyes at all. Of the remainder, HO has the most marked low frequency defect, as observed above. Subjects RM and DB both show a small low frequency defect - the clinical similarities between these two cases being the presence of eccentric fixation. Lastly, it is interesting to note that one subject, MB, shows enhanced contrast sensitivity for the 1.3 c/deg 9^{o} field stimulus, similar to that reported for some

Figure 6.2.1 Showing ratio of amblyopic : good eye for spatial and temporal MTFs of amblyopic subjects

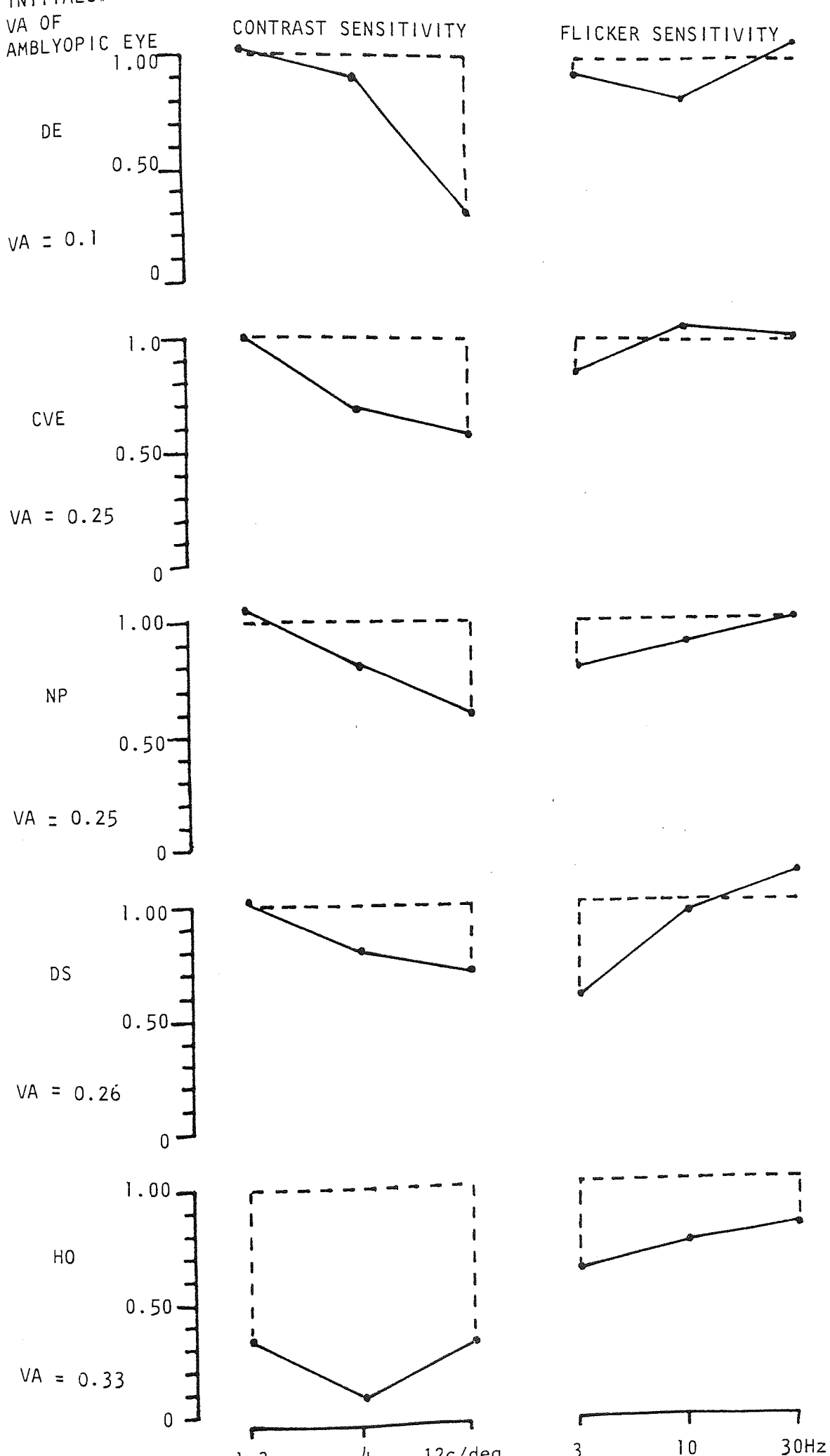
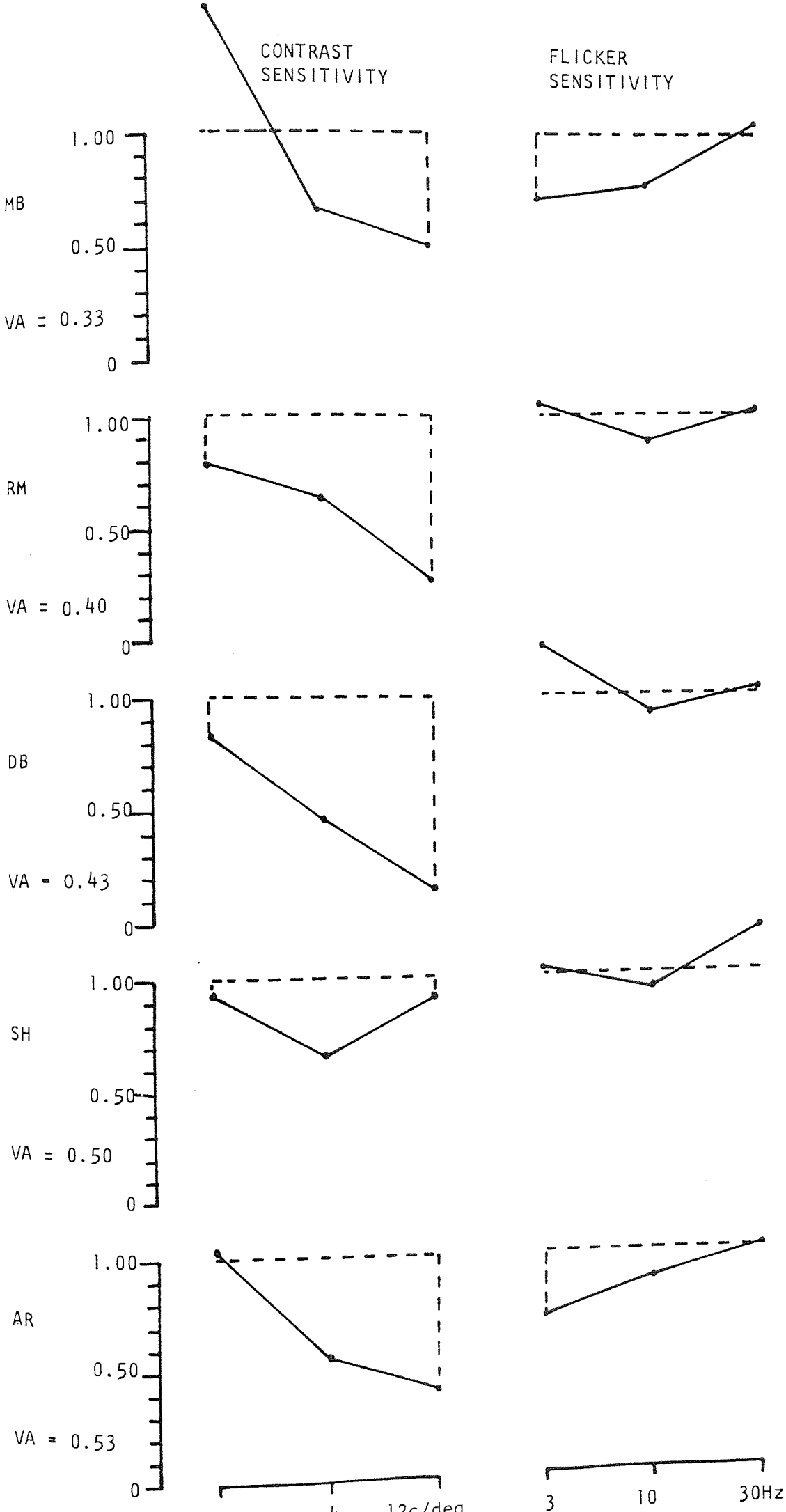


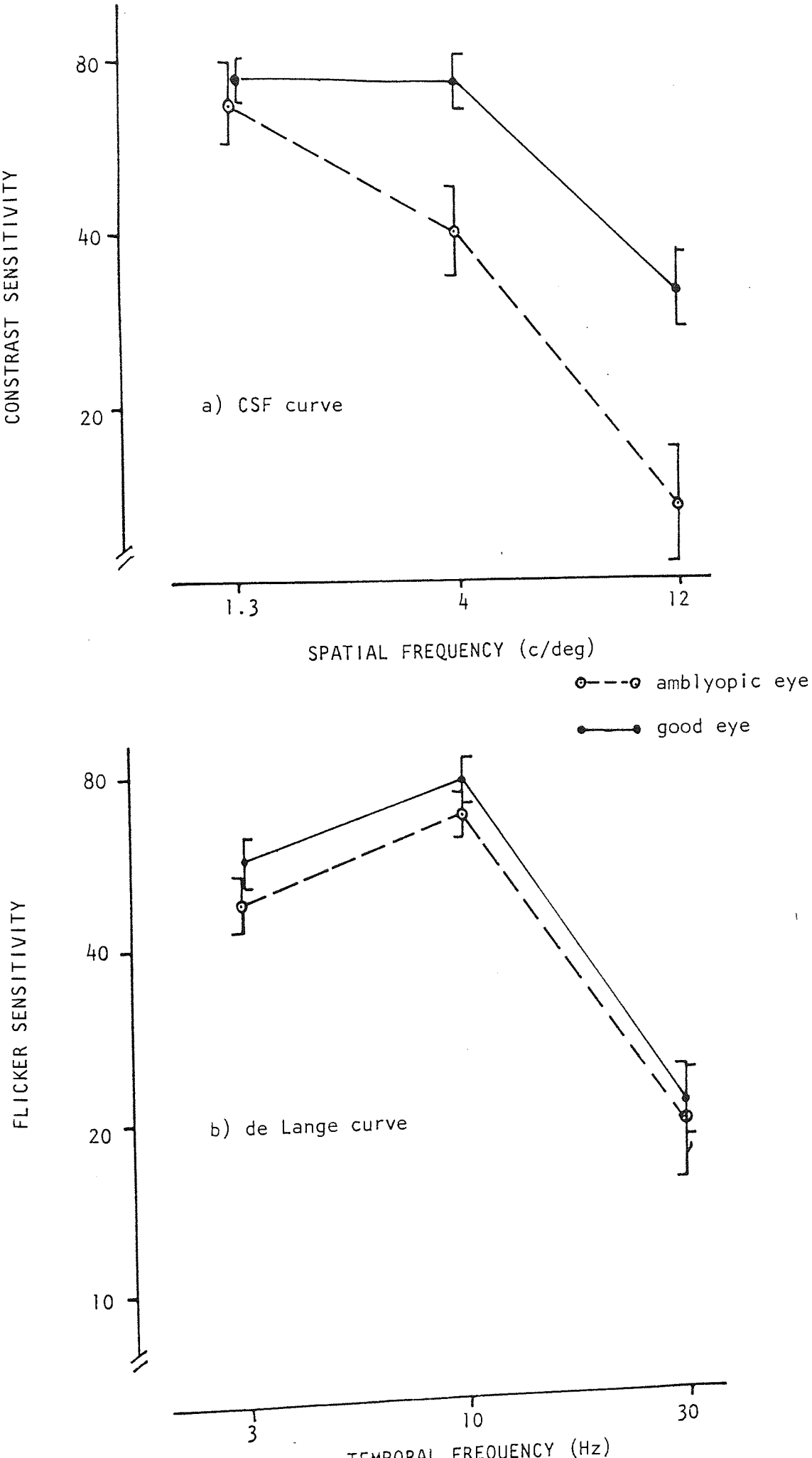
Figure 6.2.1 continued



		AMBLYOPIC EYE	GOOD EYE	Variance Ratio	df n/d	Significant Level	
VISUAL ACUITY		0.338 ± 0.131 SE 0.041	1.17 ± 0.149 SE 0.047	338.662	1/9	p<0.001	* *
LOG CONTRAST SENSITIVITY	1.3 c/deg	1.831 ± 0.224 SE 0.071	1.870 ± 0.134 SE 0.042				
	4 c/deg	1.614 ± 0.267 SE 0.084	1.872 ± 0.163 SE 0.052	13.973	1/9	p<0.01	* *
	12 c/deg	1.134 ± 0.305 SE 0.096	1.515 ± 0.212 SE 0.067	Interaction (10.396	2/18	p<0.001)	* *
LOG FLICKER SENSITIVITY	3 Hz	1.68 ± 0.148 SE 0.047	1.757 ± 0.135 SE 0.043				
	10 Hz	1.832 ± 0.137 SE 0.043	1.886 ± 0.132 SE 0.042	4.694	1/9	Not Sig.	
	30 Hz	1.282 ± 0.405 SE 0.128	1.319 ± 0.196 SE 0.062				

TABLE 6.2.2 Effect of amblyopia on psychophysical measures of vision.

Figure 6.2.2 Effect of amblyopia on the spatial and temporal MTF showing mean ± 1 standard error of the mean N = 10



subjects by Hagemans and Van de Wilt (249) with 4^{o} and 8^{o} fields.

These results are expressed for the whole group in statistical and graphical form in Table 6.2.2 and Figure 6.2.2. The difference in contrast sensitivity between the two eyes is highly significant ($p < 0.01$). The increase in the contrast sensitivity defect with increasing spatial frequency is seen clearly in Figure 6.2.2 and is shown statistically by the interaction ratio which is significant at the 0.001 level.

The de Lange curve was measured with a surround of equal luminance to that of the source which, according to Spekreijse, Khoe and Van der Tweel (227), should exaggerate the difference between the two eyes.

From the individual results in Figure 6.2.1 it can be seen that 7 subjects showed a relative temporal frequency defect at the lowest frequency (3Hz), 5 of these relative reductions also extending to include the medium temporal frequency (10Hz). However, when the group data is taken as a whole, the variance ratio of 4.694 (df n = 1 d = 9) is just below the 0.05 significance level, and therefore must be taken as not statistically significant.

Electrophysiological results - As expected, the flash P2 component does not show any difference between the amblyopic and good eye for either latency or amplitude (Table 6.2.3).

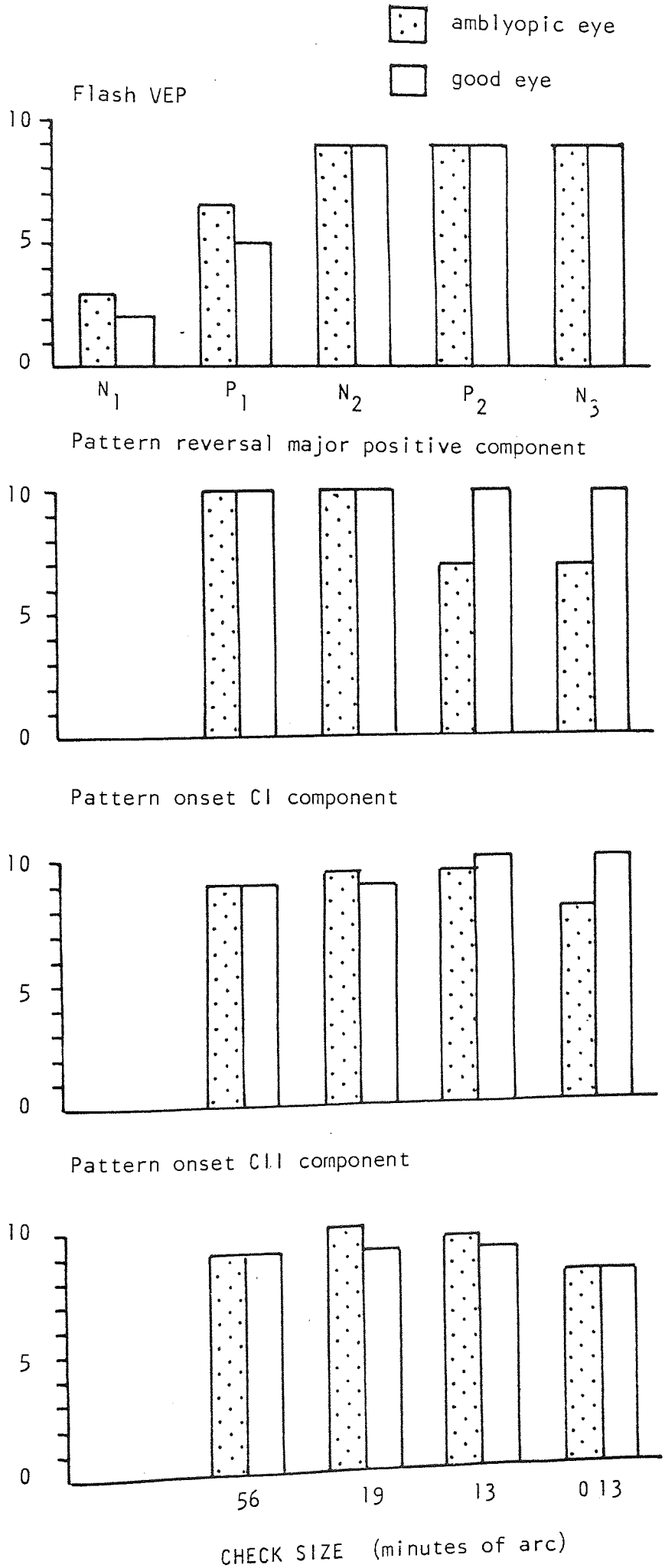
Inspection of Figure 6.2.3 shows the number of subjects in which each component of the pattern VEPs could be identified. It can be seen that the components of both pattern reversal and onset VEPs are equally

present in both eyes for the 56 minute and 19 minute checks. However, for the 13 minute check, 3^{o} field, the pattern reversal component is absent in the amblyopic eye of three subjects. The CI onset component is absent from the amblyopic eye in 2 subjects when the response is measured over the foveal representation of area 17 (0 electrode). Whether this latter observation indicates a greater sensitivity of the 0 electrode to amblyopic defects would require a much larger sample before any conclusions are drawn.

On these preliminary empirical observations, the pattern reversal VEP to a foveal stimulus appears to be more sensitive to the presence of amblyopia. The three subjects in which the pattern reversal component could not be identified are the two subjects with the worst VA, DE (VA = 0.1) and CVE (VA = 0.25), and subject RM (VA = 0.40).

Of the subjects in whom the components could be identified, analysis of variance was performed on the latency and amplitude values of the pattern reversal major positive component and the pattern onset CI and CII components to see if any intermediate effects could be identified. Of all these measures, the only one which showed a significant difference between the two eyes was the amplitude of the CI component to 19 minute checks (Table 6.2.4). This was significant at the 0.01 level - a marked contrast to all the other measures. The only other measure which showed a variance ratio just under the value corresponding to the lowest significance level was the 13 minute check pattern reversal amplitude (Table 3.2.3). Considered in conjunction with the previous observation that the 13 minute pattern reversal component was absent from the amblyopic response of three subjects (which could be considered as equivalent to zero amplitude) this VEP component seems to be reflecting the amblyopia to some degree.

Figure 6.2.3 Amblyopia study. Number of subjects in which each VEP component could be identified



	Check (min)	AMBLYOPIC EYE	GOOD EYE	Variance Ratio	df n/d	Significance Level
FLASH	Latency (ms)	114.72 ± 16.3 SE 5.43	114 ± 10.68 SE 3.56	0.405	1/8	Not Sig
	Amplitude (uV)	9.82 ± 7.47 SE 2.49	10.41 ± 3.23 SE 1.08	1.071	1/8	Not Sig
PATTERN REVERSAL	56'	106.95 ± 10.89 SE 3.44	106.5 ± 10.64 SE 3.37	3.255	1/9	Not Sig
	19'	113.7 ± 16.34 SE 5.17	107.1 ± 13.21 SE 4.18			
	13'	101.5 ± 8.95 SE 3.38	106.5 ± 5.81 SE 2.20	2.654	1/6	Not Sig +
	0 13'	101.72 ± 8.88 SE 3.36	107 ± 6.71 SE 2.54			
AMPLITUDE	56'	6.51 ± 5.48 SE 1.73	7.68 ± 5.69 SE 1.80	3.424	1/9	Not Sig
	19'	6.35 ± 6.35 SE 2.01	7.8 ± 6.39 SE 2.02			
	13'	3.16 ± 1.78 SE 0.67	4.89 ± 3.62 SE 1.37	5.539	1/6	Not Sig +
	0 13'	2.91 ± 2.33 SE 0.88	4.56 ± 3.56 SE 1.35			

+: no significant difference between electrodes.

TABLE 6.2.3 Effect of Amblyopia on the flash and pattern reversal VEP.

		Check (min.)	AMBLYOPIC EYE	GOOD EYE	Variance Ratio	df n/d	Significance Level
C1 COMPONENT	LATENCY (m.sec)	56	60.69 ±19.42 SE 6.86	64.88 ±16.11 SE 5.69	0.79	1/7	Not Sig.
		19	75.78 ±24.38 SE 8.13	72 ±18.53 SE 6.17	1.10	1/8	Not Sig.
		13	83.38 ±22.92 SE 8.10	79.31 ±21.30 SE 7.53	0.30	1/7	Not Sig.
		0 13	83.63 ±22.79 SE 8.06	79.5 ±21.51 SE 7.61			
	AMPLITUDE (uV)	56	2.86 ± 2.43 SE 0.86	5.15 ± 6.41 SE 2.27	2.01	1/7	Not Sig.
		19	1.41 ± 1.11 SE 0.37	3.22 ± 1.79 SE 0.60	19.59	1/8	$p < 0.01$ **
		13	1.89 ± 2.92 SE 1.03	3.67 ± 4.26 SE 1.51	4.94	1/7	Not Sig.
		0 13	1.81 ± 1.34 SE 0.48	3.11 ± 3.78 SE 1.34			
C11 COMPONENT	LATENCY (m.sec)	56	97.13 ±21.89 SE 7.74	97.75 ±22.52 SE 7.96	0.006	1/7	Not Sig.
		19	96.78 ±21.52 SE 7.17	98 ±16.53 SE 5.51	0.182	1/8	Not Sig.
		13	115.93 ±27.68 SE10.46	104.64 ±26.64 SE10.07	3.037	1/6	Not Sig.
		0 13	116.29 ±24.90 SE 9.41	105.43 ±25.95 SE 9.81			
	AMPLITUDE (uV)	56	4.83 ± 3.60 SE 1.27	3.93 ± 3.10 SE 1.10	0.594	1/7	Not Sig.
		19	3.08 ± 3.99 SE 1.33	3.87 ± 1.97 SE 0.66	1.074	1/8	Not Sig.
		13	2.69 ± 1.40 SE 0.53	3.59 ± 3.02 SE 1.14	1.211	1/6	Not Sig.
		0 13	2.56 ± 1.27 SE 0.48	2.61 ± 1.68 SE 0.63			

TABLE 6.2.4 Effect of amblyopia on the pattern onset VEP.

Discussion - The marked increase in contrast sensitivity attenuation found in the 8 amblyopes with strabismus indicates that only the foveal high frequency mechanisms which are producing diplopia are suppressed, while the lower spatial frequencies processed in the extrafoveal retina are unaffected. Thus, it appears that the brain makes use of all useful visual information, only suppressing the minimum necessary to eliminate undesired symptoms. The reason for the small reduction in low frequency sensitivity in the two subjects with eccentric fixation is not immediately evident. It appears that, in addition to the suppression of foveal mechanisms to eliminate diplopia as described above, the low spatial frequencies processed by the extrafoveal retina containing the point of eccentric fixation must also be suppressed to reduce confusion.

Strabismic subjects in this study do not show the overall CSF defects reported by other observers. An important factor is our experimental technique in which a 9^{o} field was used to maintain the same cortical projection at low as at high spatial frequencies. Thus, the amblyopic eye was able to make use of the extrafoveal retina, which apparently functions normally in amblyopia. Our technique, therefore, shows clearly the foveal nature of the defect in amblyopia.

The marked overall defect in subject HO shows clearly the importance of treatment. It must be assumed that the effect of an uncorrected +3D blur over many years in an eye with central fixation is very marked and would lead to a dense suppression. The overall pattern of CSF defect in the two anisometropic amblyopes is similar to the shape of CSF defect found in the optical blur studies (Section 62B and 6.3).

The co-existence of relative defects at high spatial and low temporal

frequencies observed in six strabismic amblyopes is consistent with the theory that amblyopia is a selective defect of the X cell or "pattern detector" system.

This study offers an interesting opportunity to study the VEP in a group with known psychophysical defects. From the selective spatial nature of the defects and their confinement to the foveal channels we would not expect the flash VEP recorded from a large area of retina to be affected. From the nature of the CSF defects one would expect the pattern VEP to be normal for the largest (56 minute) check size, and reduced in amplitude for the medium (19 minute) and small (13 minute) checks. The reduction in 'cut-off' frequency represented by the VA reduction would indicate that the VEP to very small checks would be absent in the amblyopic eye. As 13 minutes was the smallest check size used in our study, the VEP would only be absent in cases with a very large reduction in VA.

VEP research suggests that the pattern reversal and CI onset components reflect transient changes in contrast, while the CII onset component reflects 'contour detection' (39). It might be expected therefore, that the amplitude of the pattern reversal and CI components would reflect the contrast sensitivity defects at medium and high spatial frequencies, while the CII component would reflect the VA reduction at high frequencies.

It seems probable that the defects in amblyopia would have a greater effect on the amplitude than the latency of the VEP. A selective defect of the X cell system, which comprises the slower conducting fibres, would not be expected to produce an increase in the latency of

the VEP. Research which has drawn a connection between the CII of the onset VEP and the X cell, or sustained system (59, 10) suggests, as above, that the CII component would be reduced or absent in amblyopia.

The VEP results of this study partly concur with these theories. The P2 component of the flash VEP did not show any difference between the two eyes of the amblyopes, with respect to latency or amplitude. In addition, none of the pattern VEP components showed any significant change in latency with amblyopia.

The amplitude of the CI component was found to be significantly reduced in the amblyopic eye for the medium (19 minute) check size. The mean amplitudes of both the CI and pattern reversal components for (13 minute) checks are reduced in the amblyopic eye but these trends are not found to be significant due to the large variability of the results in both the good and amblyopic eye. The CII component does not reveal any significant differences between the two eyes, again partly due to the very large variability of the results. It is the pattern reversal component component which is absent in the amblyopic response to the smallest check of three subjects, including the two subjects with the worst VA.

In conclusion, psychophysical methods are clearly superior to clinical electrophysiological methods in revealing the selective visual defects which exist in amblyopia. The normal variability of the VEP is greatest in the areas of measurement which would be expected to be affected most by the amblyopic defect - amplitude measures, particularly at high spatial frequencies. This is the case even in studies such as

ours where inter-individual variations did not have to be taken into account due to the use of the fellow eye as a control. Due to all these factors it appears that the selective effects of amblyopia would be obscured in all but the most gross cases.

62B Comparison of amblyopia with the effect of optical blur

The good eye of each amblyope was blurred with positive spherical ophthalmic lenses to exactly the same VA as that of the amblyopic eye (using different charts to prevent memorisation of the letters).

Psychophysical results - The subjective comments of the subjects immediately showed a difference between the type of blur caused by the two conditions, even though the VA was identical in the two cases. Every subject considered that the vision with the optical blur seemed much worse. For example, one subject said that the vision in the amblyopic eye was "much clearer, but I still can't see what the letters are". In spite of this, most subjects found that determination of the contrast threshold was in fact easier in the optically blurred condition, as the vision through the amblypic eye appeared to be in a continuous state of change, with the grating "breaking up" at times.

Figure 6.2.4 shows the ratio of the blurred condition to the clear condition of the contrast and flicker sensitivities for each individual. The results are arranged in order of increasing VA, as in Figure 6.2.1. The relative low spatial frequency defect improves from 0.1 to 0.9 throughout the group, between VA values of 0.1 ($\frac{6}{60}$) to 0.53 ($\frac{6}{12+1}$). The medium to high spatial frequency defects, however, show no increasing trend with increasing VA. In fact, the ratio for the 4 c/deg grating is between 0.05 and 0.2 for all subjects. The shape of the

Figure 6.2.4 Showing ratio of blurred : clear vision in non-amblyopic eye for spatial and temporal MTFs

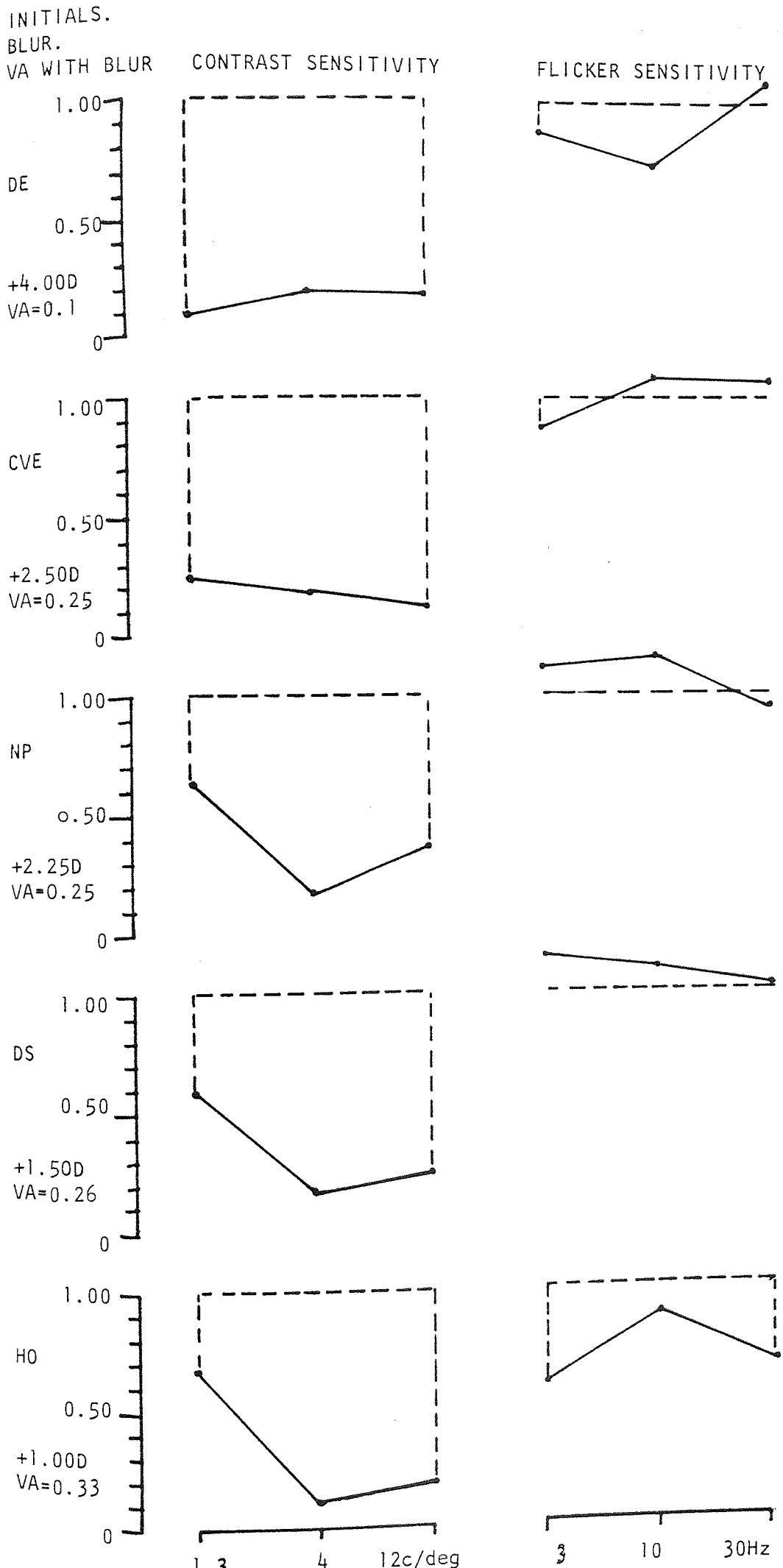
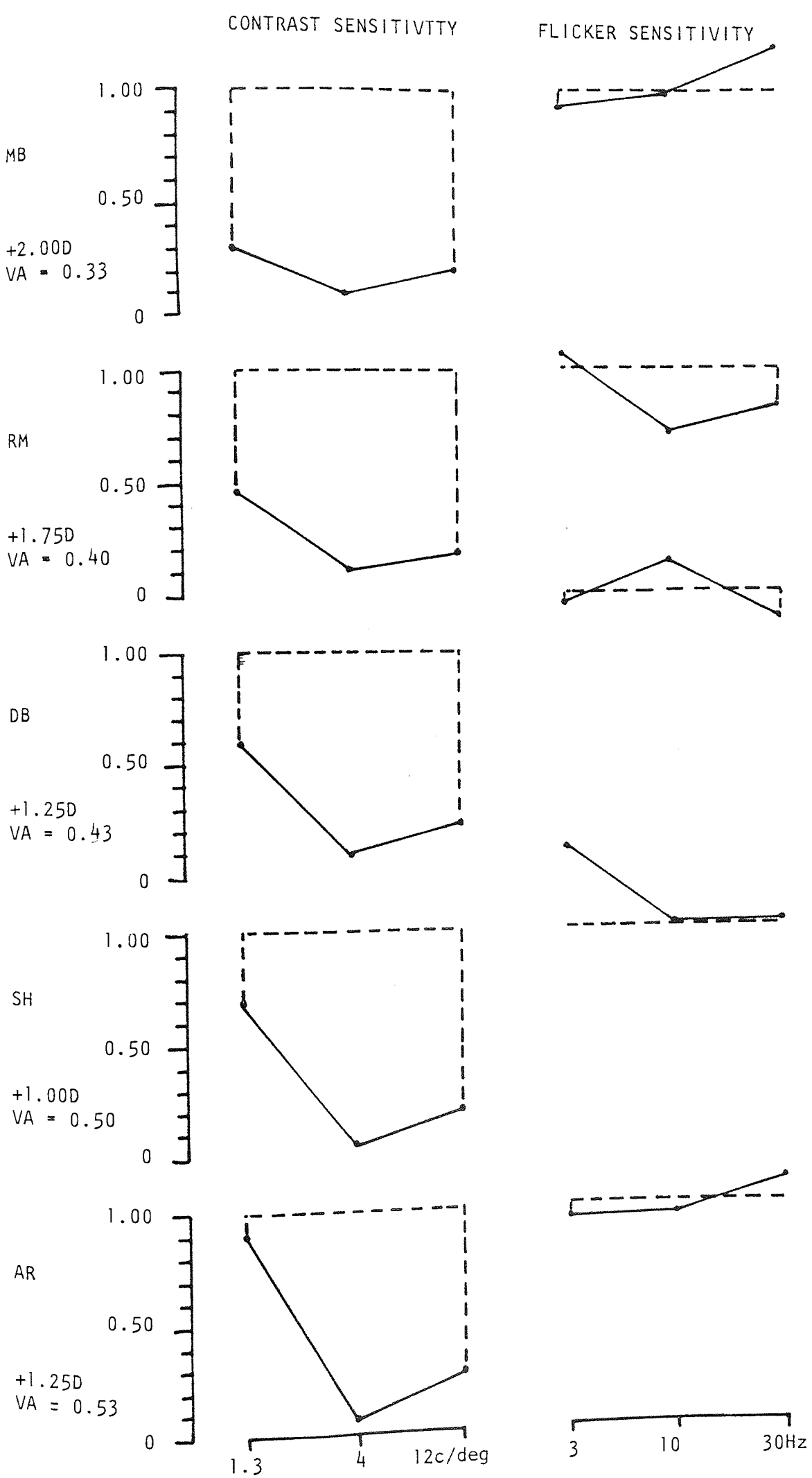


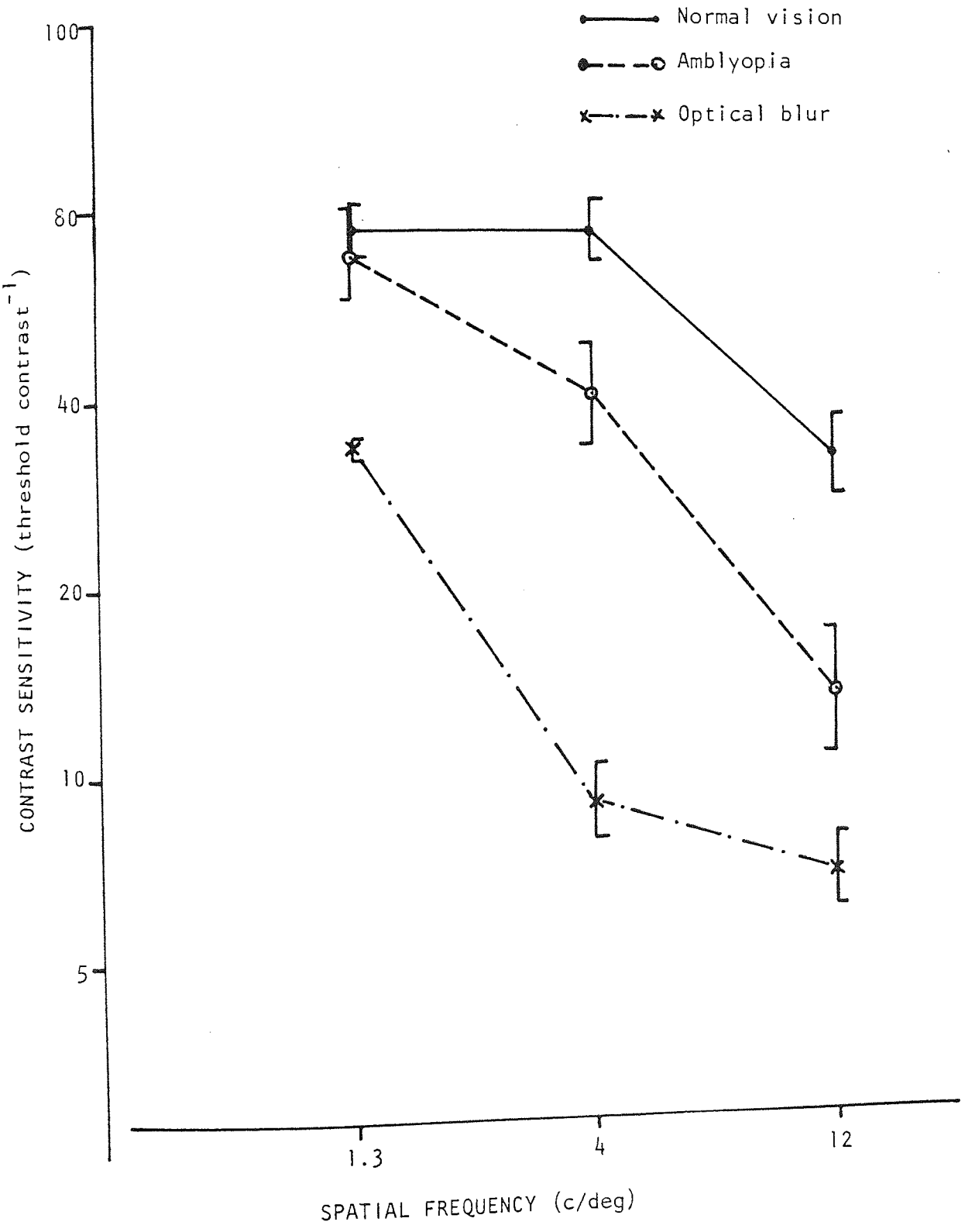
Figure 6.2.4 continued



		WITH BLUR	WITHOUT BLUR	Variance Ratio	df n/d	Significance Level	
VISUAL ACUITY		0.338 $\pm$ 0.131 SE 0.041	1.17 $\pm$ 0.149 SE 0.047	338.662	1/9	p<0.001	* *
LOG CONTRAST SENSITIVITY	1.3 c/deg	1.523 $\pm$ 0.397 SE 0.126	1.870 $\pm$ 0.134 SE 0.042	104.47	1/9	p<0.001	* *
	4 c/deg	1.025 $\pm$ 0.359 SE 0.113	1.872 $\pm$ 0.163 SE 0.052				
	12 c/deg	0.892 $\pm$ 0.944 SE 0.299	1.515 $\pm$ 0.212 SE 0.067				
LOG FLICKER SENSITIVITY	3 Hz	1.751 $\pm$ 0.132 SE 0.042	1.757 $\pm$ 0.135 SE 0.043	0.830	1/9	Not Sig	
	10 Hz	1.880 $\pm$ 0.167 SE 0.053	1.886 $\pm$ 0.132 SE 0.042				
	30Hz	1.262 $\pm$ 0.222 SE 0.070	1.319 $\pm$ 0.196 SE 0.062				

TABLE 6.2.5 Effect of blur on nonamblyopic eye - psychophysical measures

Figure 6.2.5 The effect of amblyopia and optical blur on the CSF curve showing mean values ± 1 standard error of the mean. N = 10



CSF defects in this group is similar to those found in the optical blur study (Section 6.3) with the greatest relative defect at 4 c/deg.

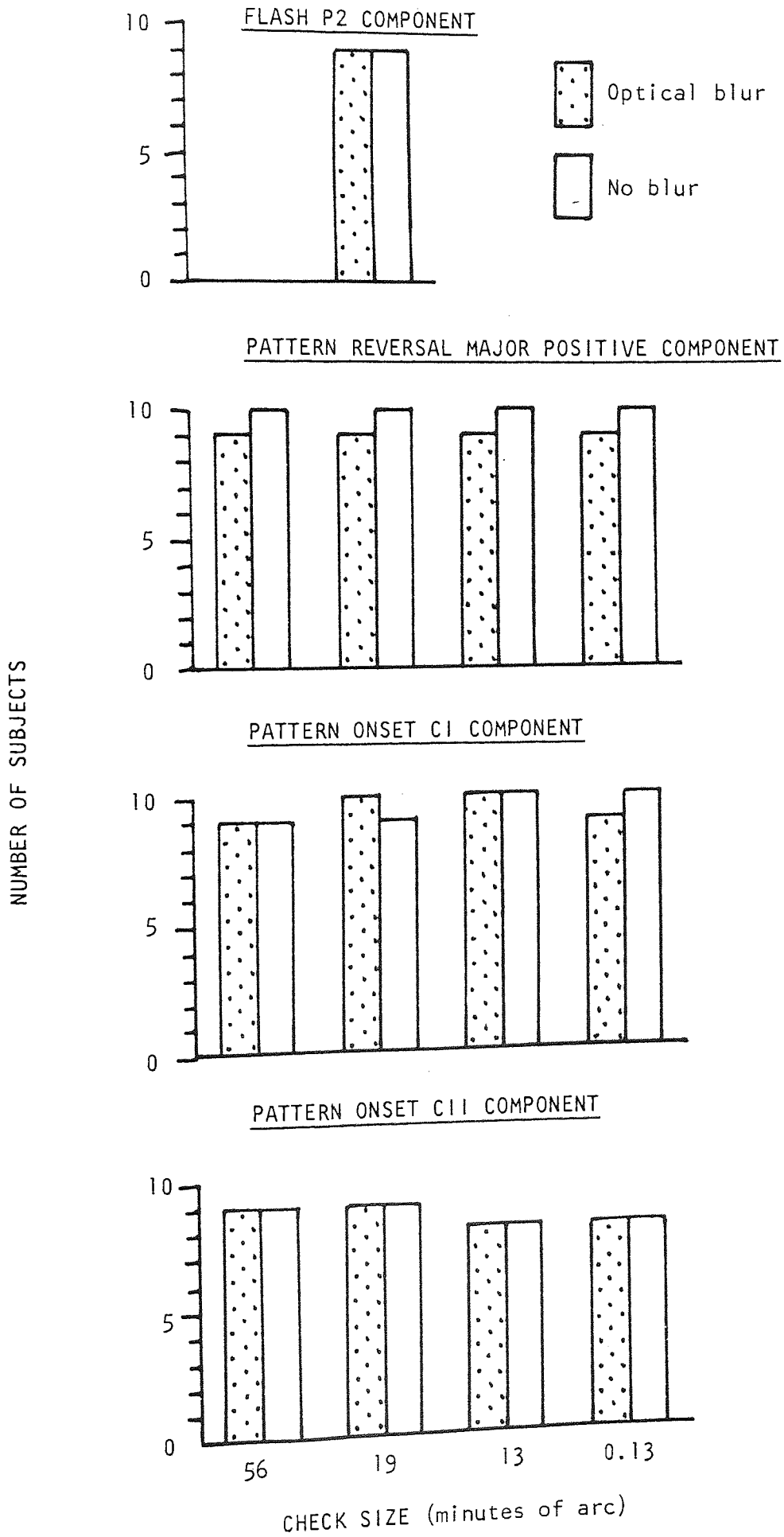
Comparison of the blurred : good eye ratios (Figure 6.2.4) with the amblyopic : good eye ratios (Figure 6.2.1) show that the effect of optical blur on contrast sensitivity is much more marked than the effect of amblyopia at medium and low spatial frequencies. The only subject in whom the CSF results are equivalent in the two cases is subject HO, the anisometropic amblyope previously discussed.

The group results (Table 6.2.5) show the magnitude of the contrast sensitivity defects are highly significant ($p<0.001$). The CSF curves in the amblyopic, optically blurred and normal conditions are shown in Figure 6.2.5. Comparison of the optical blur with the amblyopic contrast sensitivity results show that the difference is statistically significant at the 0.001 level (variance ratio 33.30 df n = 1 d = 9) which confirms the subjective impressions of the subject.

The individual flicker sensitivity results (Figure 6.2.4) do not show any consistent trends, and this is confirmed by the finding that the group differences are not significant (Table 6.2.5).

Electrophysiological results - Figure 6.2.6 shows that the incidence of pattern VEP components is not significantly different between the blurred and clear conditions for all check sizes. Tables 6.2.6 and 6.2.7 show that only two measures were significantly affected by the optical blur, at the 0.05 level. These were the pattern onset CI amplitude and CII latency for the 13 minute check.

Figure 6.2.6 Optical blur in the non-amblyopic eye showing the number of subjects in which each component can be identified



	Check (min)	WITH BLUR	WITHOUT BLUR	Variance Ratio	df n/d	Significance Level
FLASH (P_2) Latency (m.sec)		111.88 ± SE 10.19 / 3.6	110.41 ± SE 10.52 / 3.72	0.375	1/7	Not Sig
FLASH (P_2) Amplitude (uV)		11.33 ± SE 7.13 / 2.52	11.68 ± SE 7.63 / 2.70	0.619	1/7	Not Sig
PATTERN REVERSAL LATENCY (m.sec)	56'	108.2 ± SE 13.06 / 4.13	106.5 ± SE 10.64 / 3.37	0.261	1/9	Not Sig
	19'	111.7 ± SE 19.19 / 6.07	107.1 ± SE 13.21 / 4.18			
	13'	116 ± SE 18.38 / 6.13	112.44 ± SE 9.44 / 3.15	0.669	1/8	Not Sig+
	0 13'	115.89 ± SE 19.24 / 6.41	111.0 ± SE 8.26 / 2.75			
AMPLITUDE (uV)	56'	7.72 ± SE 5.83 / 1.84	7.68 ± SE 5.69 / 1.80	0.273	1/9	Not Sig
	19'	8.37 ± SE 7.67 / 2.43	7.8 ± SE 6.39 / 2.02			
	13'	3.73 ± SE 1.93 / 0.64	4.15 ± SE 3.47 / 1.16	0.211	1/8	Not Sig+
	0 13'	3.82 ± SE 4.68 / 1.56	3.98 ± SE 1.99 / 0.66			

Key: + - no significant difference between electrodes.

Table 6.2.6 Effect of blur on non amblyopic eye - flash and pattern reversal VEP

		Check (min)	WITH BLUR	WITHOUT BLUR	Variance Ratio	df n/d	Significance Level	
C1 COMPONENT	LATENCY (m.sec)	56	75.03 ± 13.84 SE 4.89	64.88 ± 16.11 SE 5.69	4.124	1/7	Not Sig	
		19	74.39 ± 25.59 SE 8.53	72.00 ± 18.53 SE 6.18	0.115	1/8	Not Sig	
		13	95.64 ± 34.93 SE 13.20	81.64 ± 21.87 SE 8.27	3.096	1/6	Not Sig+	
		0 13	95.61 ± 32.69 SE 12.36	82.00 ± 21.95 SE 8.30				
	AMPLITUDE (uV)	56	4.86 ± 2.20 SE 0.78	5.15 ± 6.41 SE 2.27	0.015	1/7	Not Sig	
		19	2.71 ± 1.05 SE 0.37	3.32 ± 1.53 SE 0.54	2.412	1/7	Not Sig	
		13	3.17 ± 4.57 SE 1.73	4.06 ± 4.44 SE 1.58	6.039	1/6	p<0.05+	*
		0 13	2.54 ± 3.63 SE 1.37	3.48 ± 3.92 SE 1.48				
C11 COMPONENT	LATENCY (m.sec)	56	99.99 ± 17.81 SE 6.30	97.75 ± 22.52 SE 7.96	1.003	1/7	Not Sig	
		19	101.97 ± 32.39 SE 10.80	98.00 ± 16.53 SE 5.51	0.356	1/8	Not Sig	
		13	125.54 ± 40.27 SE 15.22	104.64 ± 26.64 SE 10.07	7.913	1/6	p<0.05+	*
		0 13	126.14 ± 40.17 SE 15.18	105.43 ± 25.95 SE 9.81				
	AMPLITUDE (uV)	56	4.54 ± 3.73 SE 1.32	3.93 ± 1.98 SE 0.70	0.225	1/7	Not Sig	
		19	3.52 ± 3.71 SE 1.24	3.87 ± 3.81 SE 1.27	0.079	1/8	Not Sig	
		13	3.87 ± 3.91 SE 1.48	3.59 ± 3.02 SE 1.14	0.267	1/6	Not Sig+	
		0 13	3.02 ± 2.91 SE 1.10	2.61 ± 1.68 SE 0.63				

TABLE 6.2.7 Effect of blur on nonamblyopic eye - pattern onset VEP

+ No sig. difference between electrodes

Discussion - The psychophysical results show clearly that the differences between a reduction in VA caused by amblyopia and an equal VA caused by optical blur is that the overall contrast sensitivity reduction is much greater in the latter case. In optical blur, the pattern of the individual relative spatial and temporal frequency defects shown in Figure 6.2.4 do not suggest a selective defect in the functioning of the X cell system.

The psychophysical results show that optical blur has two major effects on vision - the reduction of VA due to the filtering out of high spatial frequencies, and the marked raising of contrast thresholds due to the reduction in the contrast of the image. In the interpretation of the VEP results it must be remembered that the visual defects are caused by a degradation of the image and not an impairment in the functioning of the visual pathways as in amblyopia.

From the reasoning outlined in the discussion of the VEP in the previous study, it is proposed that the amplitude reduction of the 13 minute CI 'contrast specific component' is reflecting the marked reduction in contrast of the stimulus while the increase in the latency of the 13 minute CII 'contour specific component' is reflecting the filtering of the high spatial frequencies and the consequent decrease in image sharpness. The increase in latency of CII could also be reflecting the reduction in contrast, as shown by Jeffreys and Musselwhite (115). This is the response of an intact visual pathway to an inferior visual stimulus. However, in amblyopia the defect lies in the visual pathways themselves, not in the stimulus. It has already been suggested that a selective defect of the X system would

not cause an increase in the latency of the VEP. The results from the amblyopic eye indicate that the neural visual defects are reflected either by amplitude reduction (19 minute CI component) or complete absence of the component (e.g. 13 minute pattern reversal).

These results show that optical and neural conditions producing equal VA reduction in the same subject can have very different effects on both CSF and VEP measures, showing that the overall reduction in vision and the brain's response to these visual defects is very different in the two cases.

6.3 Optical blur study

63A Pilot study - The original pilot study to establish the effect of optical blur on the VEP was carried out in the Ophthalmic Optics laboratory in 1980 before its amalgamation with the Clinical Neurophysiology Unit. Although the same types of VEP stimulation were used the techniques and apparatus were slightly different.

Methods - The subject rested on a couch with the head resting on pillows to minimise muscle tension and provide a relaxed position. The luminance of the room and surround was 60 cd/m^2. The stimulus was projected onto a transulcent screen from a slide projector, and the image of the screen was reflected to the subject by a surface silvered mirror. The image of the checkerboard was 133cm from the eyes of the subject, so a +0.75D lens was used in the experiments to relax the accommodation for this distance. The contrast of the checkerboard was 0.9 and the mean luminance 1400 cd/m^2. The diameter of the circular field was 2.5^{o}. In pattern onset-offset stimulation the checkerboard was presented for 150 msec, then replaced by a field of equal mean luminance for 400 msec by the movement of an electrically controlled diffusing shutter triggered from a Digitimer. The shutter moved mechanically in and out of the beam from the projector, inducing a delay of 24 msec between the trigger pulse and the onset of the pattern, for which allowance was made in the determination of latency. Reversal of the pattern twice per second was produced by oscillation of a small surface silvered mirror in the beam of the projector by a pen motor. The flash stimulus was produced by a flash gun and back projected on to a diffuse transulcent screen.

The VEP was recorded from an electrode 4% above the inion, corresponding

to the foveal projection of area 17 (10) referred to a mid frontal electrode (F_z). The responses were averaged on a Unimac averager. Filter settings were 50Hz with a 0.3 sec time constant. The VEP tracings represented a positive polarity by an upward deflection of the pen (the opposite convention to that used in the other studies).

The study - Preliminary investigations into the optimum check size for the study indicated that 14 minute and 7.75 minute checkerboards showed the best combination of a large well defined VEP to a clear image, followed by a large amplitude reduction when vision was blurred with a +1D lens.

Preliminary recordings showed that the latency of the CII onset component increased as positive lenses were introduced. As negative lenses were introduced the subject accommodated to keep the image in focus on the retina, and the latency remained approximately the same until the point was reached at which accommodation could no longer be maintained. It also appeared that the active accommodation was a factor in the large variability of the amplitude measures in these recordings. To investigate the effect of accommodation, the accommodation of the author was paralysed using 0.5% cyclopentolate HCL. The VEP results were found to be much more consistent, showing clearly the decrease in amplitude and increase in latency with optical blur. It was therefore decided to perform the study under cycloplegic conditions. All the volunteers were ophthalmic optics students who fully understood and were in agreement with the use of cycloplegic drops for the study.

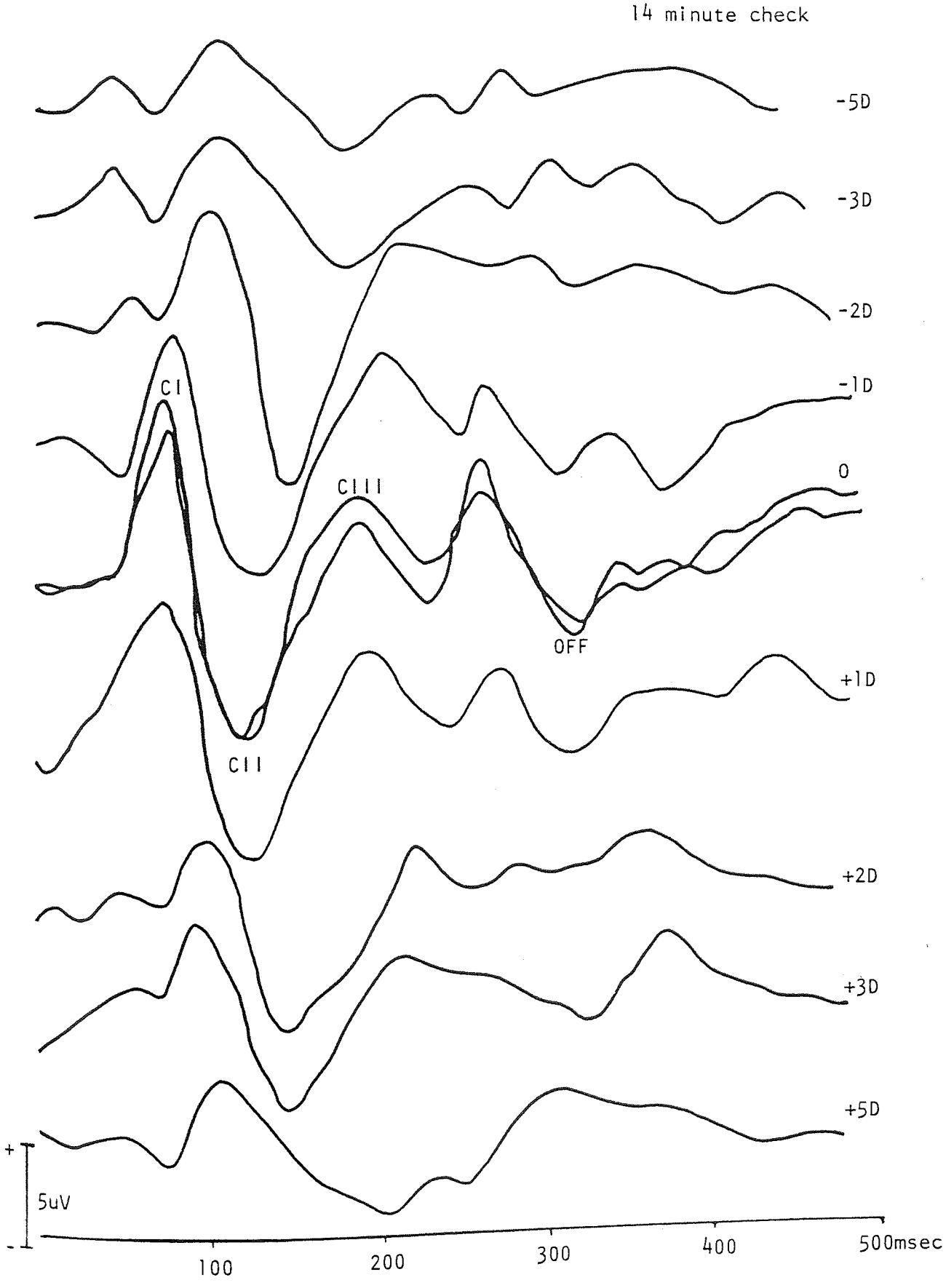
Ten volunteers were used for the study. VA was measured, with spectacles or contact lenses where appropriate, and a refractive check

ensured there was no residual refractive error. The cycloplegic drops were then administered. Cyclopentolate HCl takes about 30-40 minutes to take full effect, which gave ample time to affix the electrodes and to set up the equipment for VEP recording. The cyclopentolate also has a mydriatic effect - the mean pupil diameter of the group being 8.125 ± 0.54mm. The VEP was first recorded with no blur, under binocular conditions. Ophthalmic lenses were then introduced into the trial frame. The order in which the lenses were used was random, the only exception being that the low minus lenses were always introduced at the beginning of the experiment when the cycloplegia was at its maximum.

Examples of the effect of optical blur on individual VEP waveforms are shown in Figures 6.3.1, 6.3.2 and 6.3.3. The mean latency values for the group are shown in Table 6.3.1 and illustrated graphically in Figures 6.3.4 and 6.3.5. It can be seen that the optical blur causes a marked increase in the latency of the pattern components which is more pronounced for the smaller check size. The most noteable feature of these results is that the latency increase of the pattern onset CII component, which is of the order of 73 msec over the +5 dioptres of blur (7.8 min check), is much greater than that of the pattern reversal major positive component which is of the order of 40 msec for the equivalent amount of blur. An equivalent trend is seen for the negative lenses and for the larger check size. The P2 flash component does not show any consistent change in latency with optical blur, as would be expected.

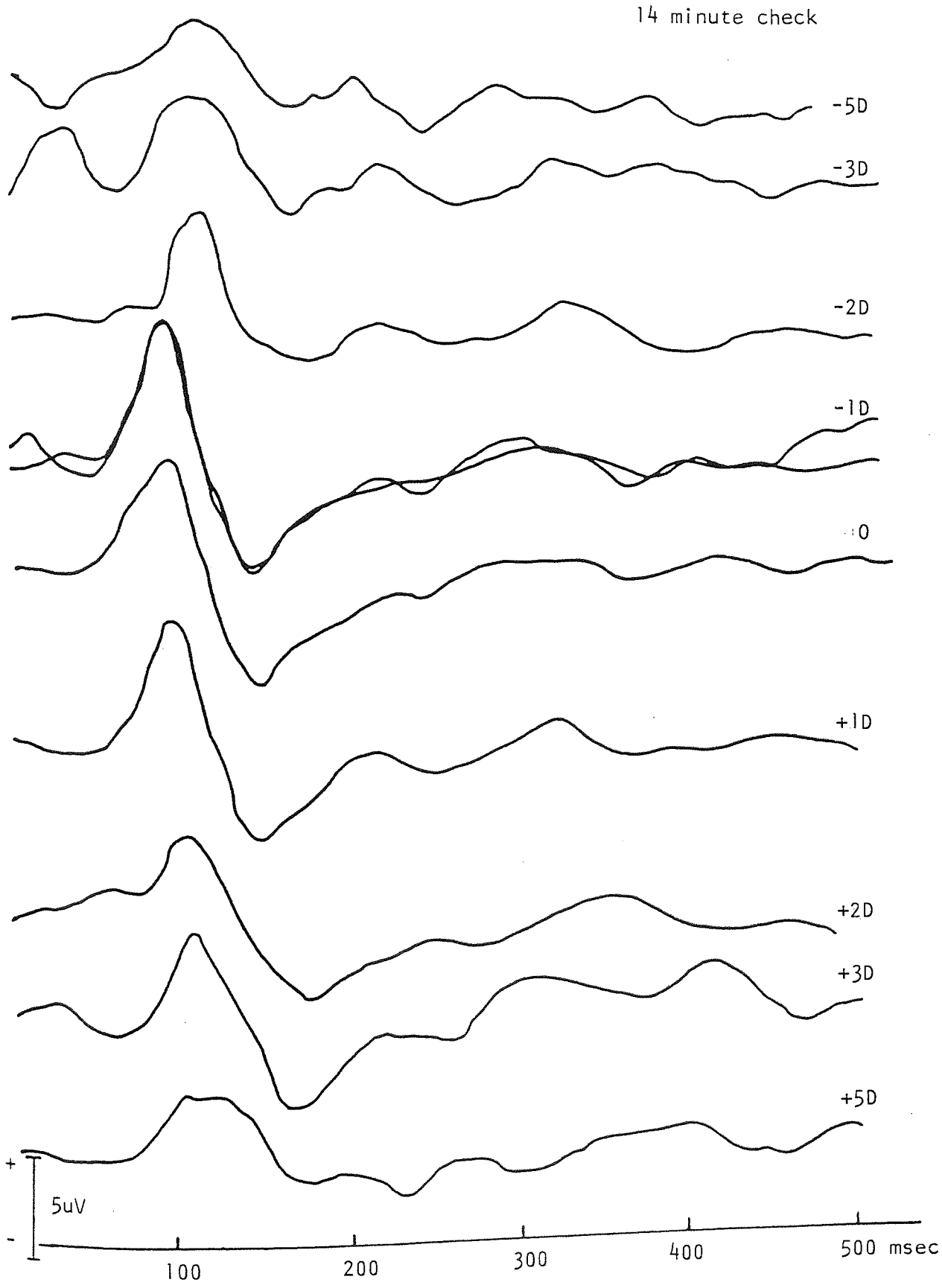
The amplitude of the flash N2-P2 configuration (Figure 6.3.7) is very variable, as shown by the large standard errors. The mean values vary

Figure 6.3.1 The effect of optical blur on the pattern onset-offset VEP - individual waveforms



Subject I.H.
with cycloplegia

Figure 6.3.2 The effect of optical blur on the pattern reversal VEP - individual waveforms

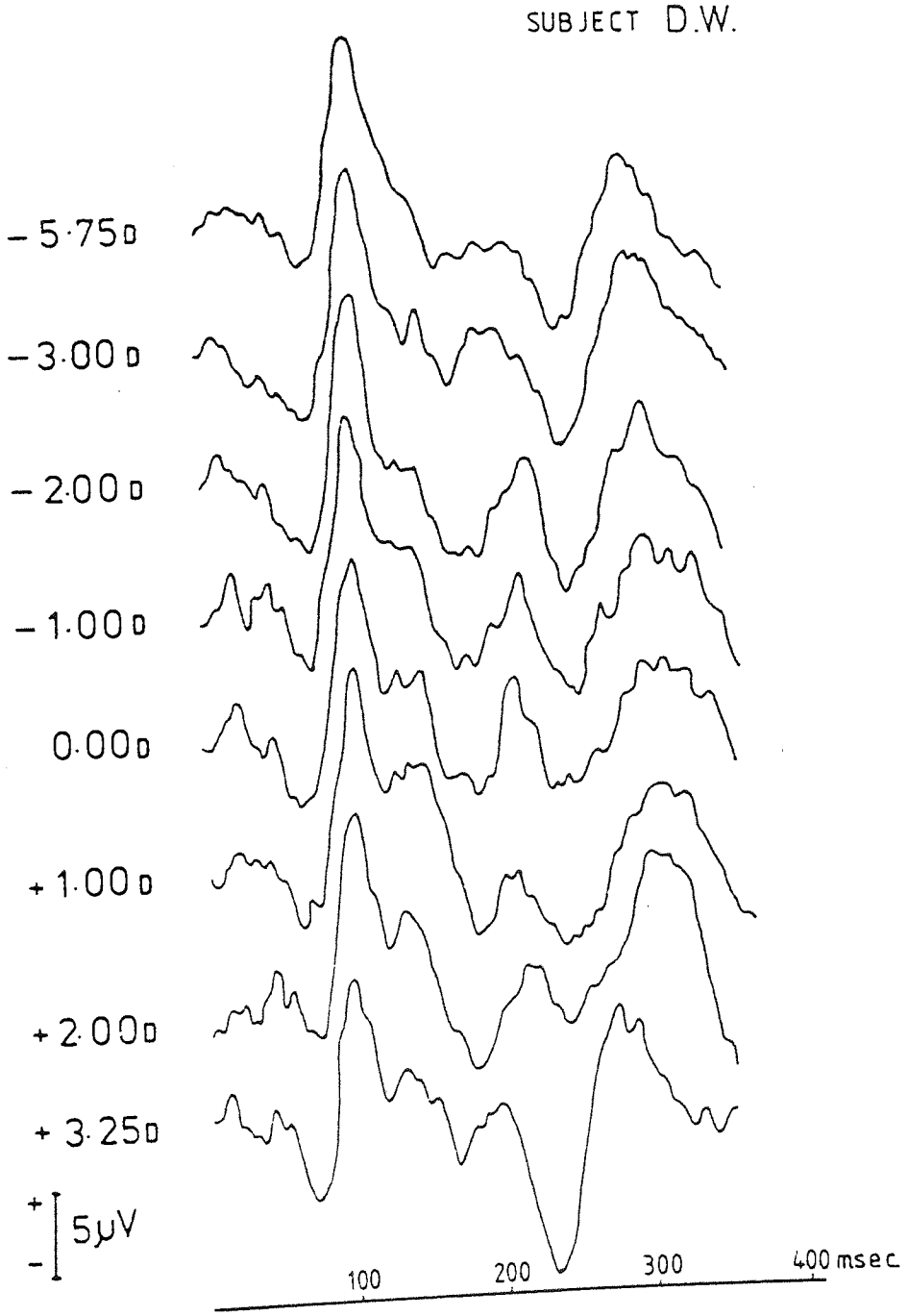


Subject I.H.
with cycloplegia

FIGURE 6.3.3

THE EFFECT OF OPTICAL BLUR ON THE VEP TO FLASH STIMULATION

INDIVIDUAL WAVEFORMS



Check Size (Min)	-5D	-3D	-2D	-1D	0	+1D	+2D	+3D	+5D
Pattern Onset CII Component 7.75	178.29	167.4	159.02	131.55	119.78	143.82	172.14	181.85	193.41
	± SE 21.83	± SE 19.80	± SE 20.56	± SE 17.44	± SE 10.75	± SE 13.70	± SE 20.48	± SE 12.88	± SE 25.75
	SE 7.28	SE 6.26	SE 6.50	SE 5.51	SE 3.40	SE 4.33	SE 6.48	SE 4.07	SE 9.10
14	185.3	168.08	142.27	124.17	122.05	137.77	156.43	174.87	194.24
	± SE 15.76	± SE 22.11	± SE 12.81	± SE 14.11	± SE 13.54	± SE 8.93	± SE 12.78	± SE 16.33	± SE 12.73
	SE 5.25	SE 6.99	SE 4.05	SE 4.46	SE 4.28	SE 2.82	SE 4.04	SE 5.17	SE 4.24
Pattern Reversal Major Positive Component 7.75	131.53	118.45	110.89	99.15	95.95	107.83	117.9	131.77	135.59
	± SE 10.18	± SE 9.76	± SE 12.46	± SE 8.28	± SE 9.80	± SE 9.06	± SE 11.44	± SE 17.66	± SE 15.75
	SE 3.60	SE 3.09	SE 3.94	SE 2.62	SE 3.10	SE 2.87	SE 3.62	SE 5.58	SE 5.25
14	114.49	109.72	99.73	91.46	91.24	95.52	105.22	112.96	118.66
	± SE 7.64	± SE 7.46	± SE 8.17	± SE 5.33	± SE 6.12	± SE 6.91	± SE 5.47	± SE 8.88	± SE 9.81
	SE 2.55	SE 2.36	SE 2.58	SE 1.69	SE 1.93	SE 2.18	SE 1.73	SE 2.81	SE 3.10
Flash P2 Component	109.38	109.6	111.9	108.58	106.9	107.52	108.57	108.98	110.42
	± SE 2.95	± SE 5.96	± SE 2.58	± SE 6.15	± SE 5.19	± SE 6.17	± SE 6.3	± SE 3.97	± SE 7.32
	SE 1.20	SE 2.43	SE 1.05	SE 2.51	SE 2.12	SE 2.52	SE 2.57	SE 1.62	SE 2.99

Table 6.3.1 Effect of optical blur on the latency (m.sec) of the VEP - Pilot study.

Figure 6.3.4 The effect of optical blur on the CII component of the pattern onset VEP - pilot study Mean values ± 1 standard error of the mean. N = 10
N.B. Latency axis displaced for clarity for 14 minute check

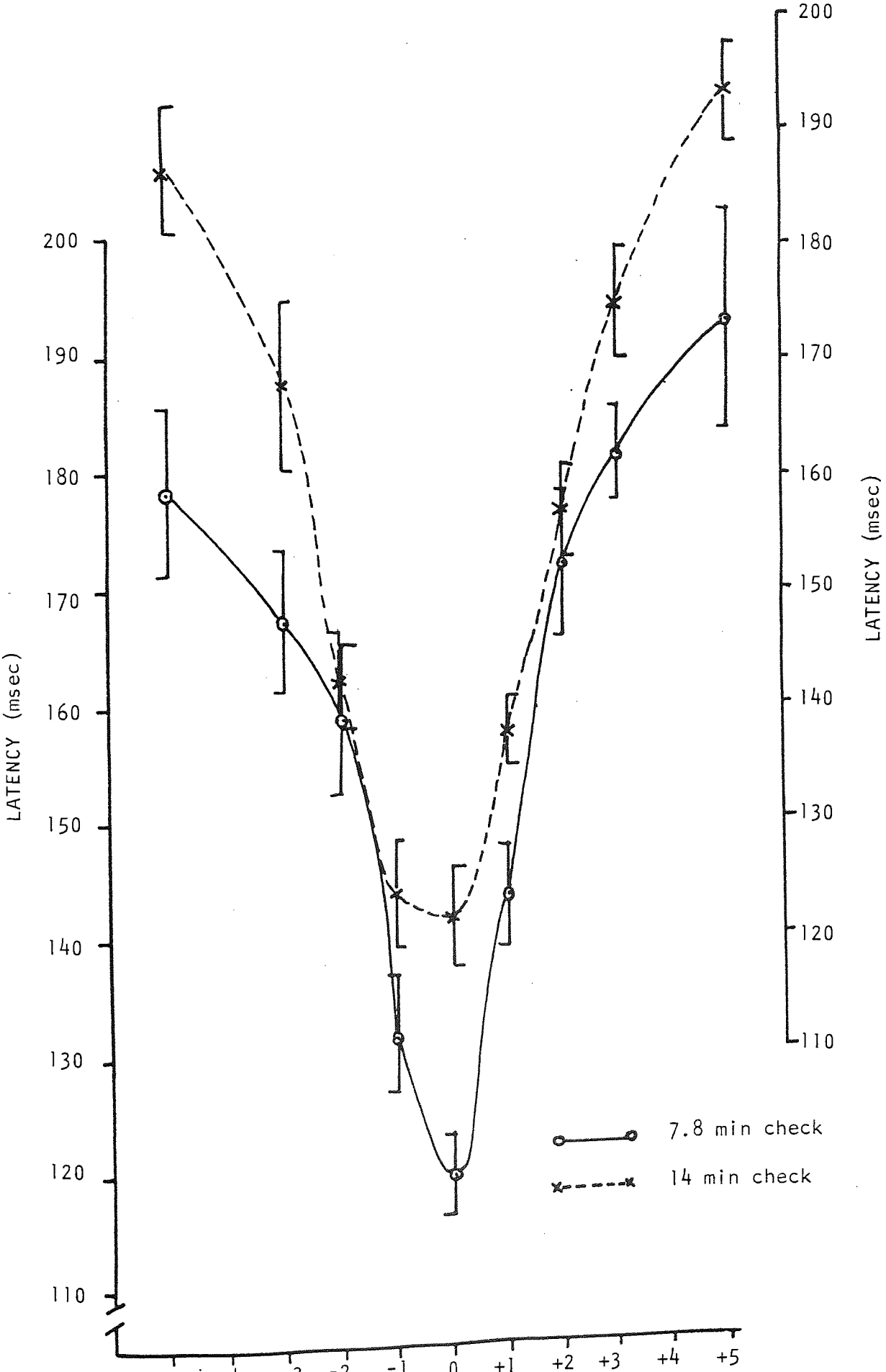
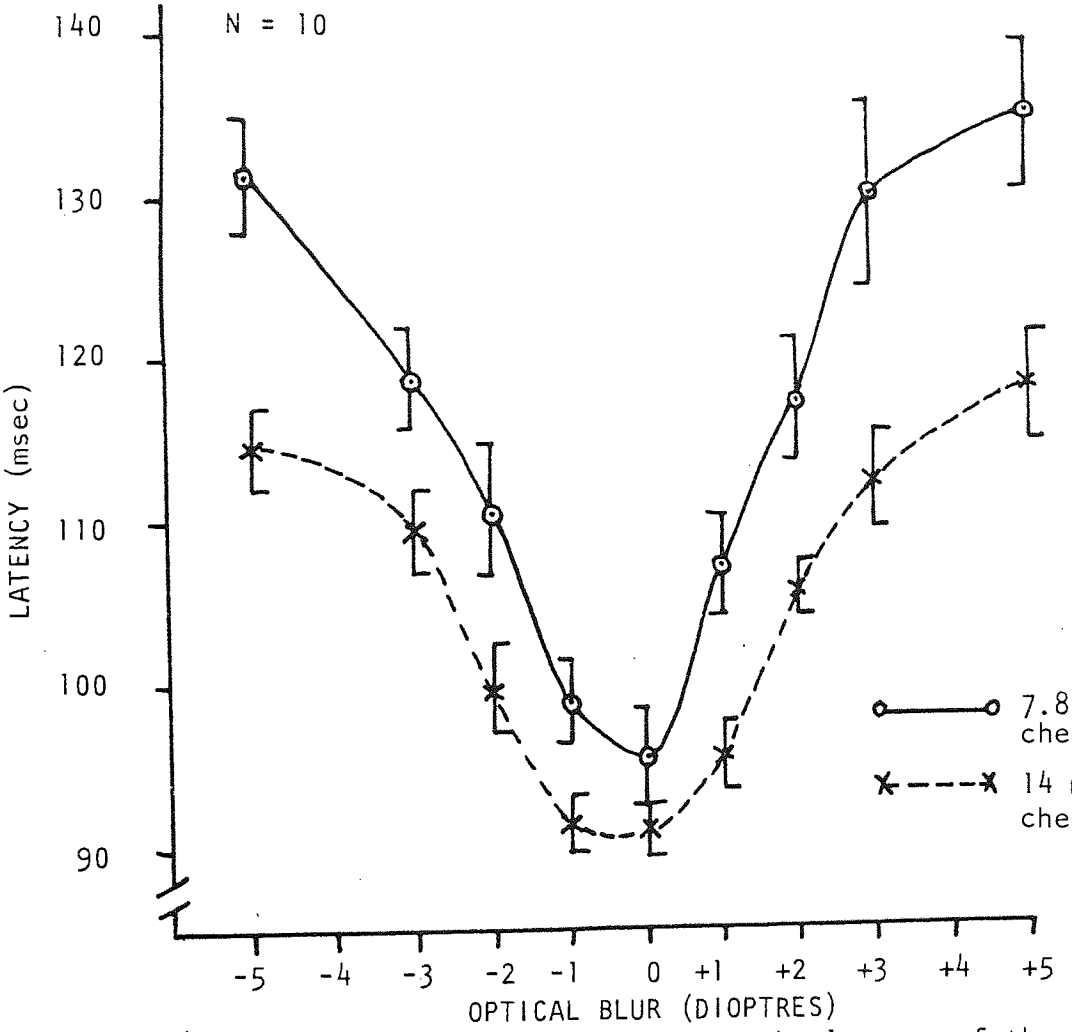
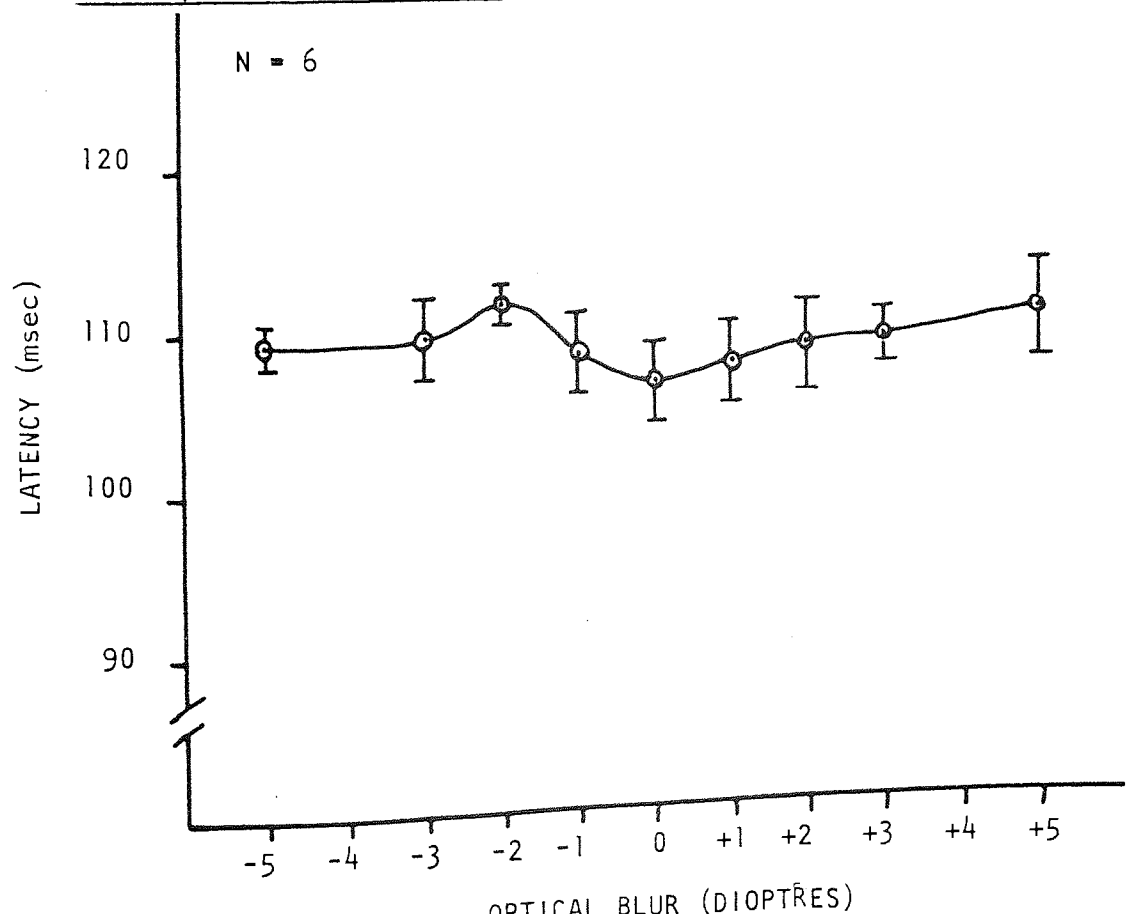


Figure 6.3.5a The effect of optical blur on the latency of the pattern reversal VEP - pilot study
Mean values ± 1 standard error of the mean



b) The effect of optical blur on the latency of the flash P2 component - pilot study Mean values ± 1 standard error of the mean



Check Size (min)	-5D	-3D	-2D	-1D	0	+1D	+2D	+3D	+5D
PATTERN 7.8 ONSET	8.11 + 3.58 SE 1.19	9.49 + 4.83 SE 1.53	10.05 + 4.13 SE 1.31	14.19 + 5.47 SE 1.73	14.87 + 4.70 SE 1.48	11.15 + 6.26 SE 1.98	10.77 + 5.24 SE 1.66	8.59 + 4.79 SE 1.52	8.62 + 4.36 SE 1.45
C1-C11 14 CONFIGURATION	9.24 + 4.86 SE 1.54	11.69 + 3.50 SE 1.11	15.19 + 4.87 SE 1.54	15.13 + 3.57 SE 1.13	15.7 + 5.43 SE 1.72	14.4 + 5.46 SE 1.73	14.76 + 6.08 SE 1.92	12.75 + 5.75 SE 1.82	10.76 + 4.13 SE 1.38
PATTERN 7.8 REVERSAL MAJOR POSITIVE COMPONENT 14	4.36 + 2.10 SE 0.70	4.74 + 2.02 SE 0.64	5.78 + 1.73 SE 0.55	5.98 + 3.76 SE 1.19	9.38 + 4.44 SE 1.40	7.58 + 3.53 SE 1.12	4.82 + 1.15 SE 0.36	5.52 + 3.48 SE 0.35	4.63 + 2.39 SE 0.80
	5.14 + 2.00 SE 0.67	5.58 + 2.41 SE 0.76	6.15 + 3.03 SE 0.64	8.56 + 3.44 SE 1.09	9.55 + 3.00 SE 0.95	7.18 + 3.74 SE 1.18	6.88 + 3.16 SE 1.00	6.48 + 2.59 SE 0.82	4.47 + 2.25 SE 0.71
FLASH N_2-P_2 CONFIGURATION	16.27 + 3.72 SE 1.52	16.9 + 3.57 SE 1.46	17.1 + 7.41 SE 3.03	16.2 + 6.34 SE 2.59	14.25 + 4.18 SE 1.71	12.8 + 4.45 SE 1.82	14.78 + 4.37 SE 1.78	15.32 + 4.30 SE 1.75	17.52 + 4.93 SE 2.01

Table 6.3.2 Effect of optical blur on the amplitude (uV) of the VEP - Pilot study.

Figure 6.3.6 The effect of optical blur on C1-C11 amplitude - pilot study N = 10

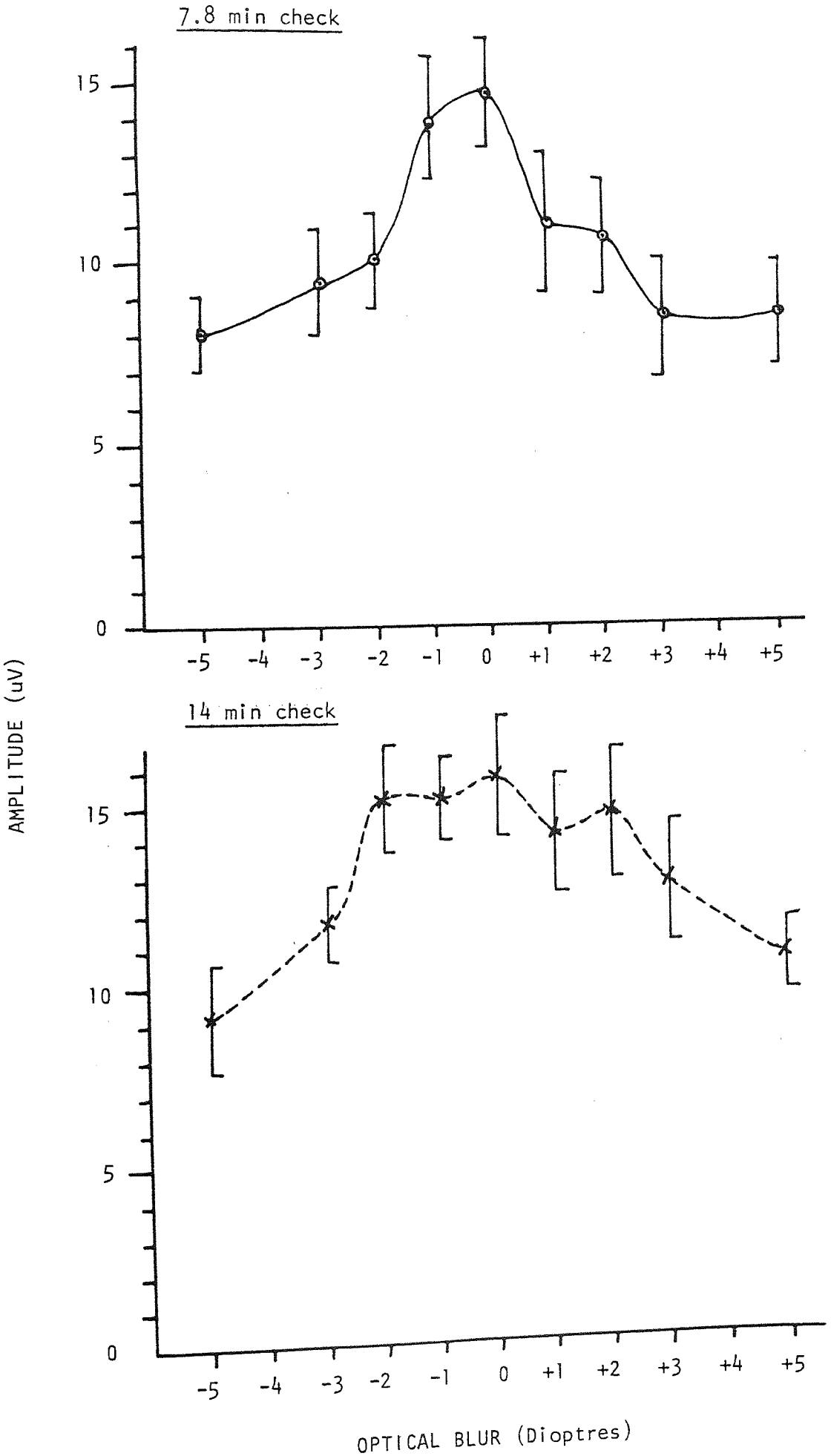
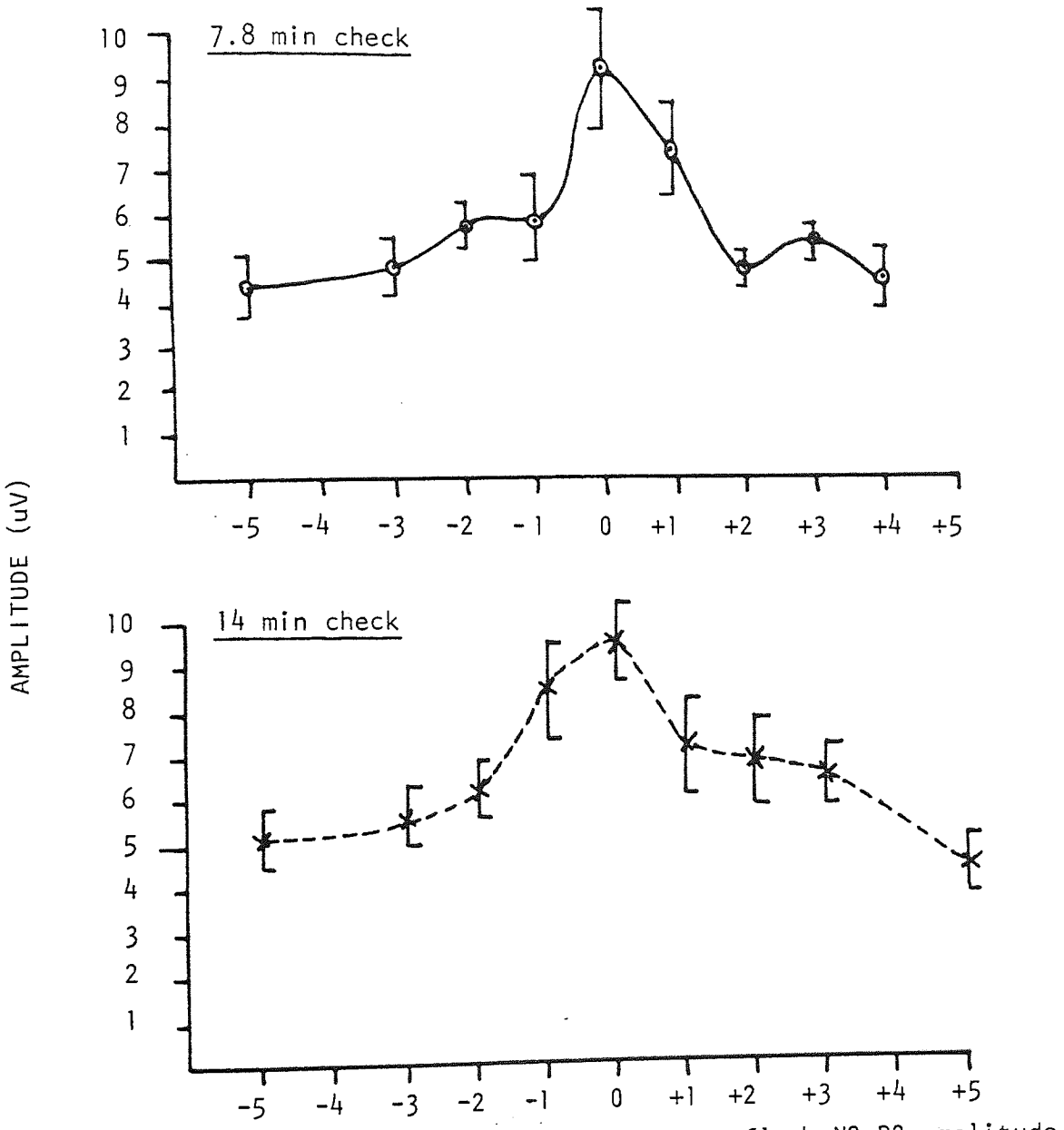
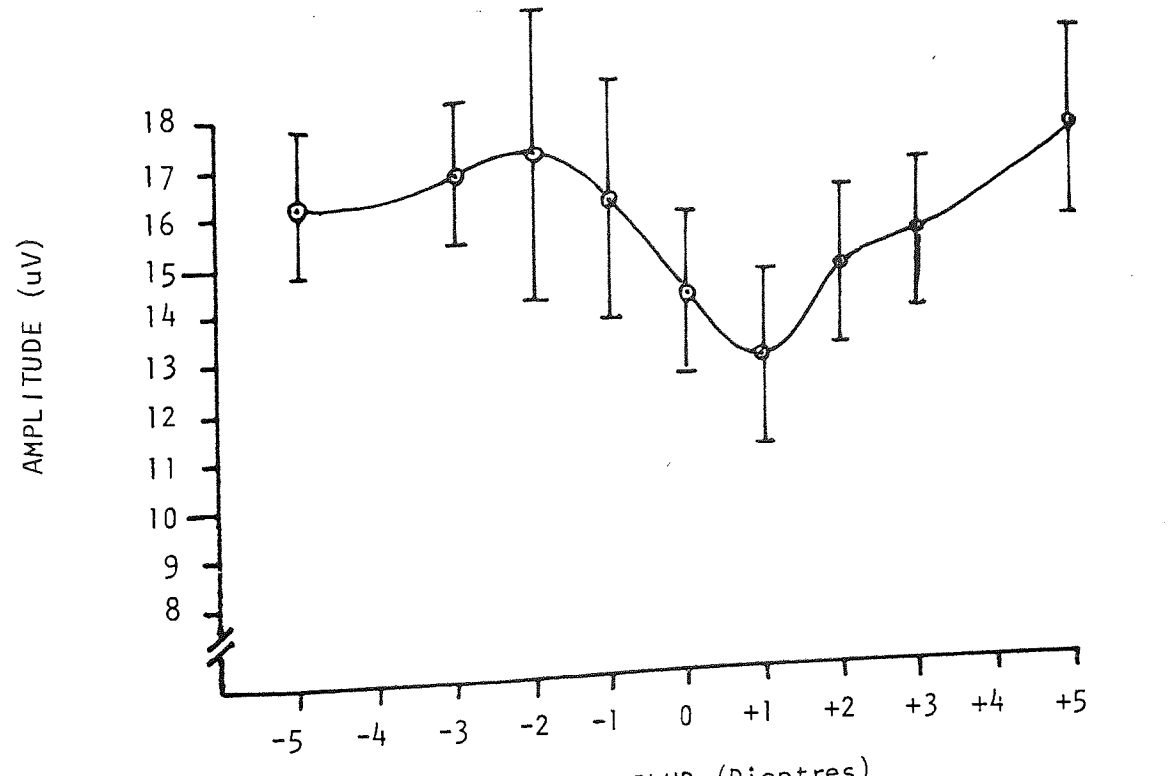


Figure 6.3.7a The effect of optical blur on pattern reversal amplitude - pilot study N = 10



b) The effect of optical blur on flash N2-P2 amplitude N = 6



with the different lenses, but show no consistent trend with increasing blur. The pattern components all show a peak amplitude with no blur, decreasing as positive and negative lenses are introduced (Figures 6.3.6 and 6.3.7). The precision of this effect is shown to be least for the CII component to the 14 minute checkerboard. For the 7.8 minute checkerboard the overall reduction of the CI-CII configuration is of the order of 45% for ± 5D. The corresponding reduction of the amplitude of the pattern reversal major positive component is of the order of 50% for both check sizes over ± 5D. The mean values are shown in Table 6.3.2.

These results clearly establish that optical blur has a selective effect on the VEP. The flash P2 component shows no consistent change in latency or amplitude with blur, while both the pattern reversal and pattern onset CII components show an increase in latency and decrease in amplitude with blur.

From these results the lenses selected for the subsequent comparisons of the effect of optical blur on the VEP and psychophysical measures of vision were +1, +2 and +3 dioptres. Three dioptres was sufficient blur to show a significant effect on the latency and amplitude of the VEP, while convex lenses were chosen so that accommodation would not come into play, and cycloplegia would not be necessary. The order in which the blur was introduced was random, so that a progressive effect could not be predicted.

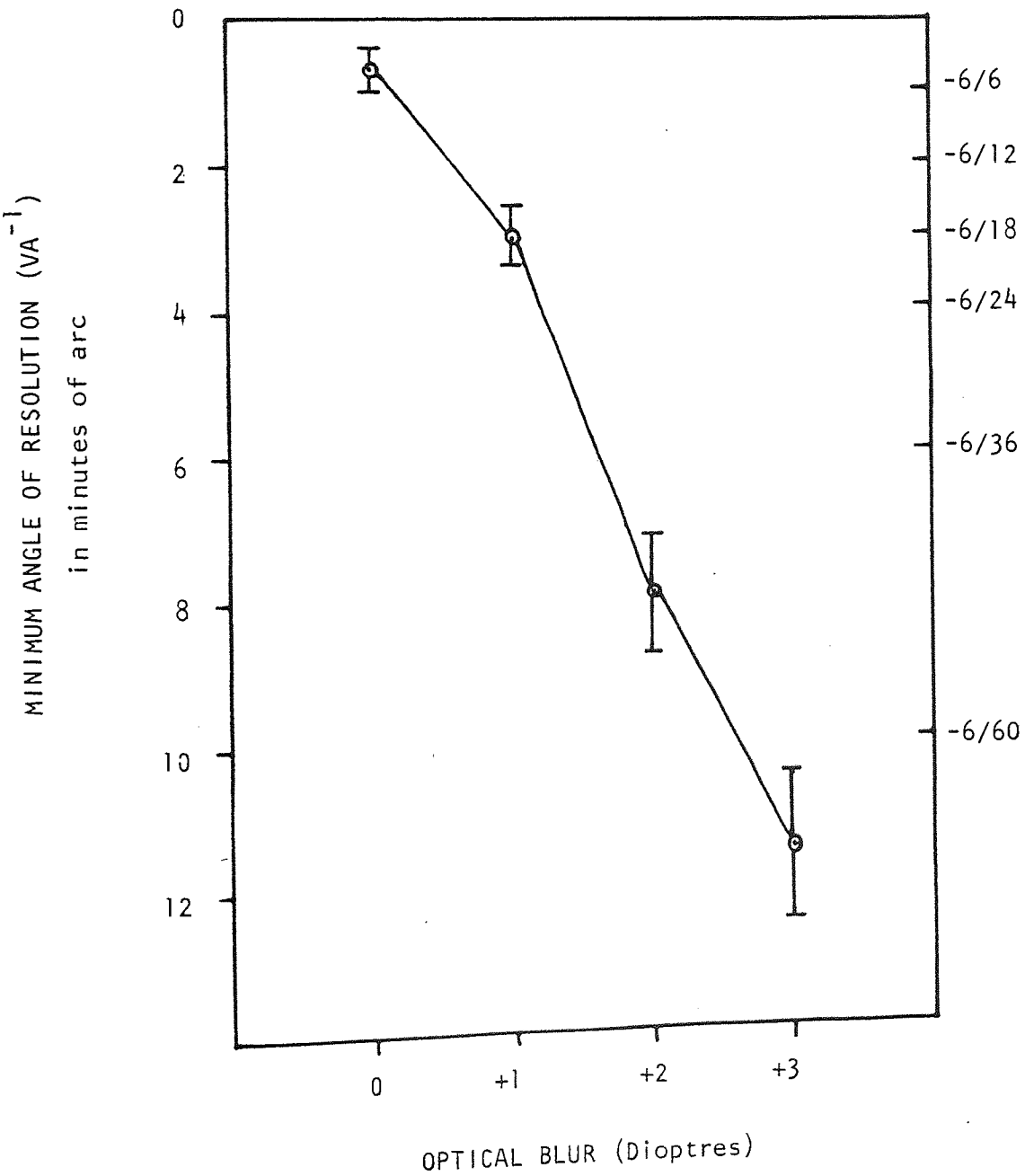
63B Psychophysical results - Figure 6.3.8 shows the effect of optical blur on VA expressed in terms of the minimum angle of resolution (MAR) in minutes of arc, the reciprocal of VA. The

Snellen chart is constructed so that the change in letter size between each line is small at the lower end of the chart, which represents the small letters, and large at the top of the chart, which represents the larger letters. The figure which relates to letter size is the denominator of the Snellen fraction which has the result that a scale of Snellen VA expressed in decimal form has the values relating to the lines of smaller letters spaced out at one end of the scale and the values relating to the lines of larger letters crowded at the other end. The reciprocal of decimal VA, or MAR scale therefore restores the VA values to their correct relative spacings. The use of a Snellen chart also means that VA is measured in discrete steps rather than on a continuous scale, although this was partly overcome in this study by the use of extrapolated intermediate values, as previously described (Table 5.1). Taking these factors into account it can be seen from Figure 6.3.8 that optical blur produces an approximately linear reduction in VA.

The contrast sensitivity results (Figure 6.3.9) show that optical blur has a marked effect on the shape of the CSF curve, changing the convex shape of the curve of contrast sensitivity with no blur to a concave shape with +1D blur. The curve approaches a linear decrease in contrast sensitivity with increasing spatial frequency at the higher levels of blur.

As these differences reflect differences in the effect of optical blur at each spatial frequency, the reduction in contrast sensitivity with optical blur was plotted for each spatial frequency separately (Figure 6.3.10). It must be noted that the contrast sensitivity for the 12 c/deg grating with +3D blur is underestimated, as 7 subjects could

Figure 6.3.8 The effect of optical blur on Visual Acuity showing mean ± 1 standard error of the mean



		0	+1D	+2D	+3D	Variance Ratio	df n/d	Significance Level	
VISUAL ACUITY		1.32 ± 0.1549 SE 0.0490	0.383 ± 0.1312 SE 0.0415	0.139 ± 0.0409 SE 0.0129	0.091 ± 0.0166 SE 0.0053	319.775	3/27	p <0.001	* *
LOG CONTRAST SENSITIVITY	1.3 c/deg	1.922 ± 0.160 SE 0.051	1.784 ± 0.153 SE 0.049	1.540 ± 0.172 SE 0.054	1.194 ± 0.210 SE 0.067	312.939	3/27	p <0.001	* *
	4 c/deg	1.909 ± 0.117 SE 0.037	1.153 ± 0.182 SE 0.058	0.927 ± 0.136 SE 0.043	0.766 ± 0.135 SE 0.043	Interaction (21.94	6/27	p <0.001)	* *
	12 c/deg	1.469 ± 0.146 SE 0.046	0.980 ± 0.231 SE 0.074	0.634 ± 0.120 SE 0.038	0.488 ± 0.053 SE 0.017				
LOG FLICKER SENSITIVITY	3 Hz	1.713 ± 0.161 SE 0.051	1.693 ± 0.146 SE 0.046	1.687 ± 0.153 SE 0.048	1.516 ± 0.549 SE 0.174	1.428	3/27	Not Sig.	
	10 Hz	1.879 ± 0.140 SE 0.044	1.839 ± 0.131 SE 0.042	1.855 ± 0.168 SE 0.053	1.859 ± 0.166 SE 0.053				
	30 Hz	1.396 ± 0.262 SE 0.083	1.376 ± 0.255 SE 0.081	1.393 ± 0.218 SE 0.069	1.336 ± 0.238 SE 0.075				

TABLE 6.3.3 Effect of optical blur on psychophysical measures of vision.

Figure 6.3.9 The effect of optical blur on the contrast sensitivity function showing the mean ± 1 standard error of the mean. N = 10

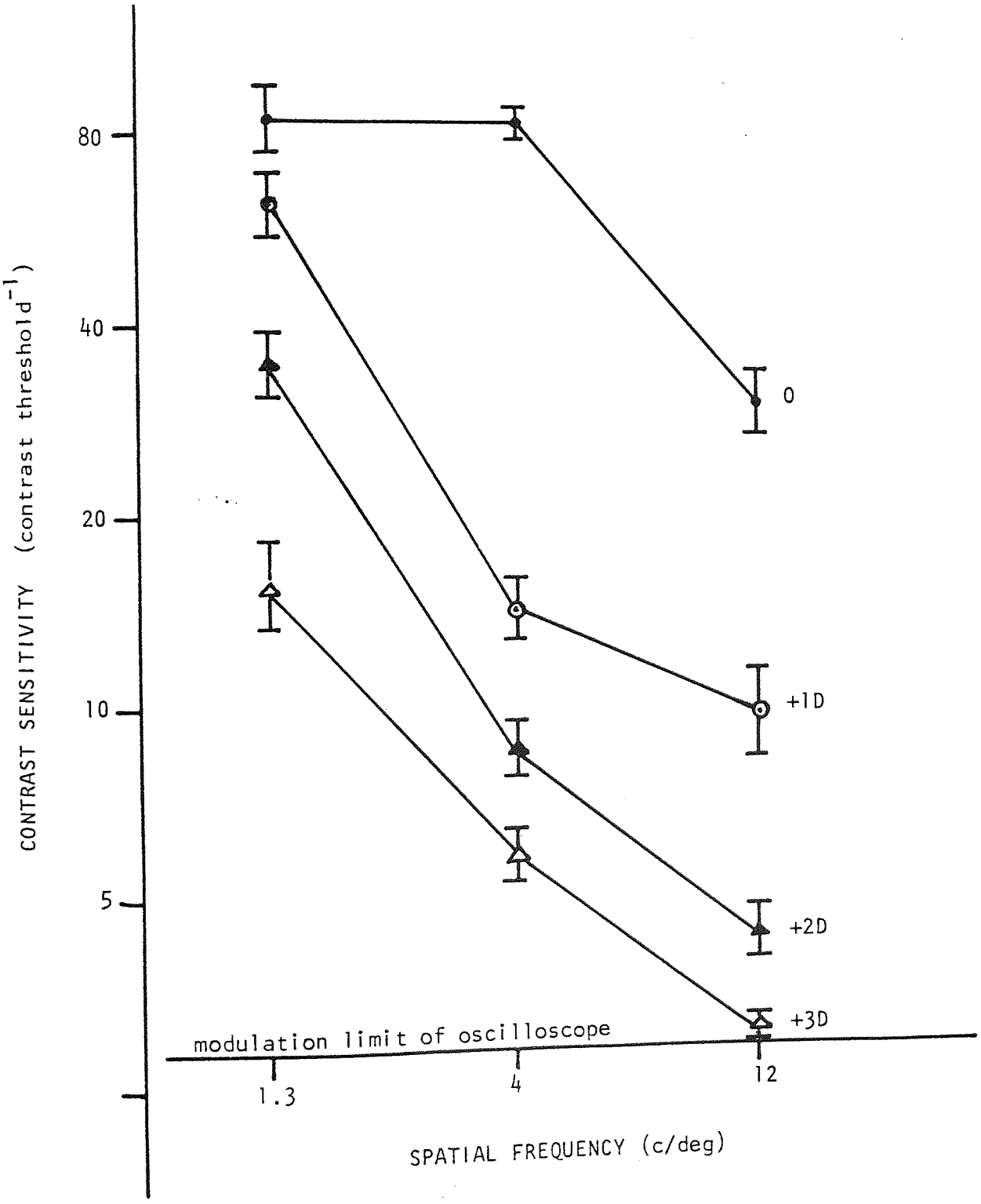
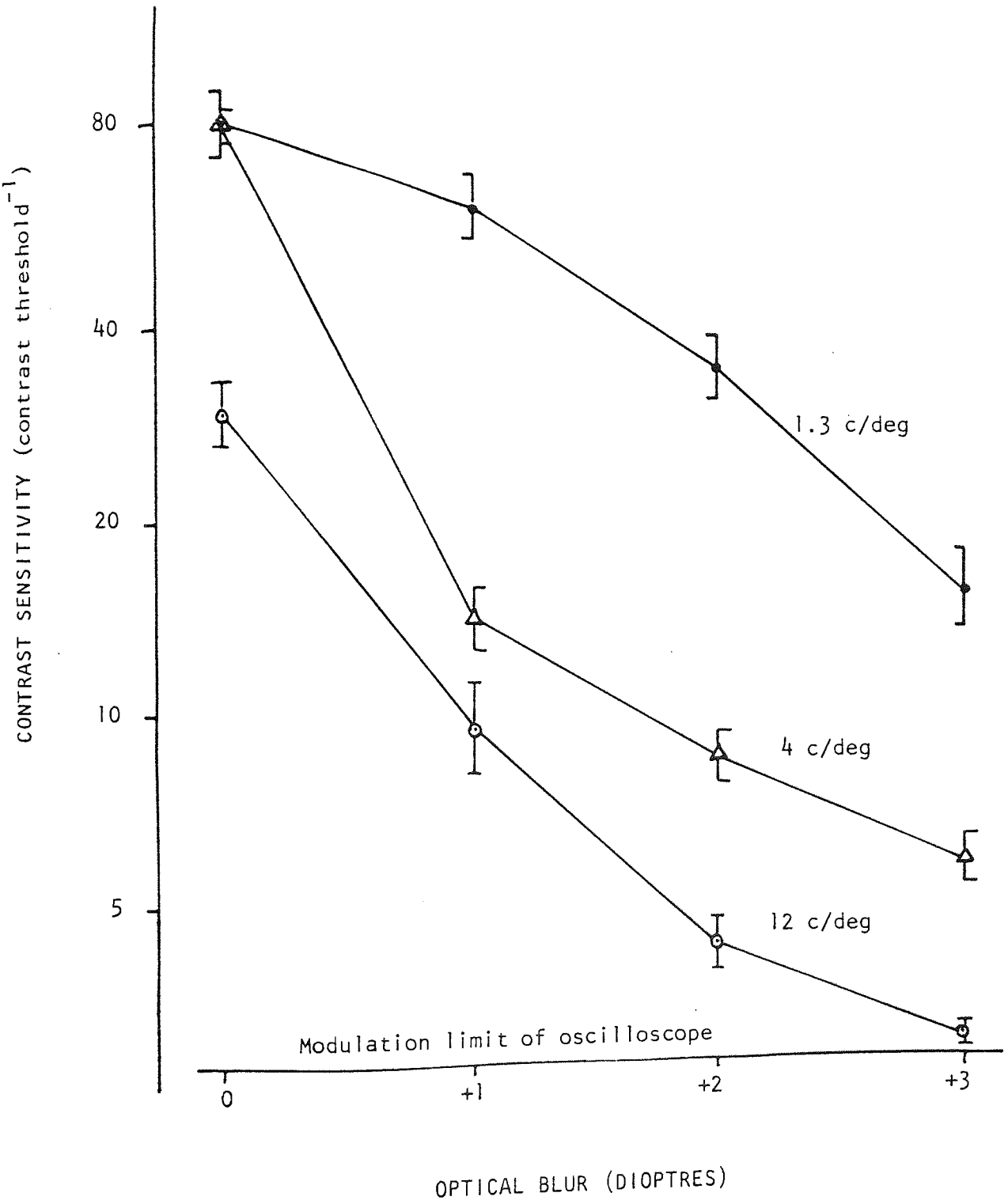


Figure 6.3.10 Effect of optical blur on contrast sensitivity at low, medium and high spatial frequencies showing the mean ± 1 standard error of the mean N = 10



not perceive the grating even with the modulation of the oscilloscope at the maximum contrast value of 0.35. The contrast threshold was therefore recorded as 0.35 though it would have been higher (and the contrast sensitivity therefore lower) if the range of the oscilloscope had been greater. It can be seen that the attenuation in contrast sensitivity caused by +1D of blur is greatest for the 4 c/deg grating, followed by the 12 c/deg and then the 1.3 c/deg grating. The overall attenuation for the 3 dioptres of blur is 0.67 log units for the 1.3 c/deg grating, 1.16 log units for the 4 c/deg grating and 0.98 log units for the 12 c/deg grating. Taking the underestimated +3D 12 c/deg value into account, it would appear that the overall attenuation for the 4 and 12 c/deg gratings is approximately equal.

No previous studies on the effect of optical blur on the de Lange curve are known. From the observations of Jennings and Charman (270) on the CFF and defocus, it would be expected that the effect of optical blur on the flicker sensitivity measured with the 2^{o} flickering source and equal luminance surround of our apparatus would be negligible. Table 6.3.3 shows that this is indeed the case.

It is interesting to note the subjective comments of the subjects during these temporal measurements. Due to the effect of the blur on the spatial details of the stimulus, most subjects were convinced that their performance with the higher degrees of blur was very poor, and expressed surprise when told afterwards that the modulation threshold had remained approximately the same throughout.

Electrophysiological results - Figure 6.3.11 shows that the components of the flash and pattern reversal VEPs could be identified in clear

and blurred conditions. The pattern onset components, however, were much less consistent. It can be seen, particularly for the 13 minute check size, that the difficulties in identification of the components were not due to the effect of optical blur degradating the waveform, but to interindividual differences in waveform, as described in study 6.1. This meant that the number of responses that could be included in the analysis of variance was greatly reduced.

Reference to Table 6.3.4 will show that, as expected, optical blur has no significant effect on the latency or amplitude of the P2 component of the flash VEP. However, the pattern reversal VEP shows a highly significant increase in latency and reduction in amplitude ($p<0.001$) with optical blur. Neither measure shows a significant interaction of variance ratios, presumably due to the variability of the results. However, Figure 6.3.12 shows that the overall increase in the mean latency is 20.5 msec for the smallest check, 12 msec for the medium check and 4.6 msec for the largest check. Similarly, the overall mean amplitude reduction is 43.3% for the 13 minute check (31.43% on the midline electrode), 27.7% for the 19 minute check, and 12.8% for the 56 minute check.

Tables 6.3.5 and 6.3.6 show the effect of optical blur on the CI and CII pattern onset components that could be identified. For ease of inspection, those components which showed a significant increase in latency or decrease in amplitude with blur are shown in Table 6.3.7:

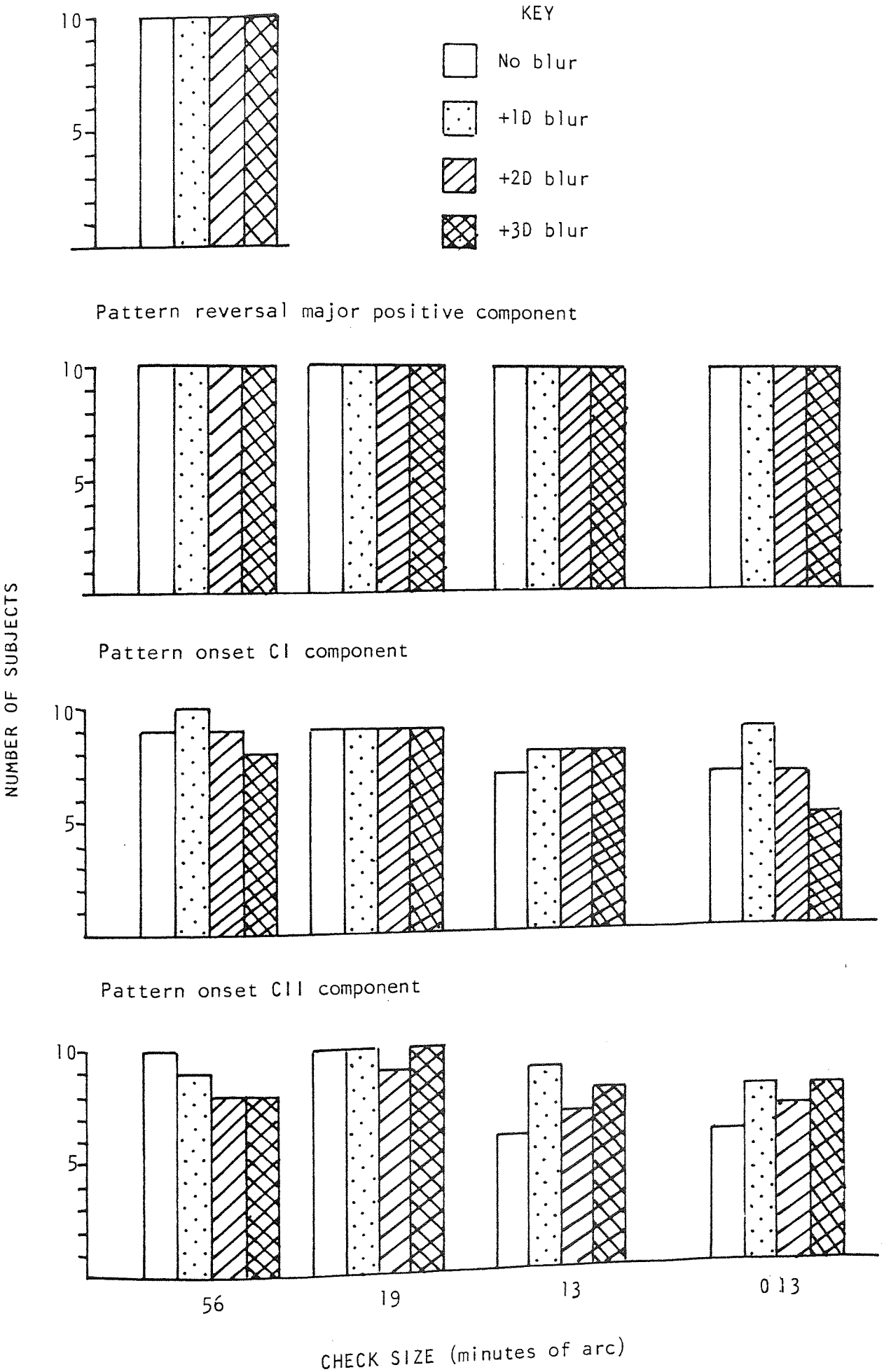
Table 6.3.7 Pattern onset measures which showed a significant change with blur

SIGNIFICANCE LEVEL	INCREASED LATENCY	DECREASED AMPLITUDE
0.001	CI 19 min CII 19 min	
0.01		CII 13 min
0.025		CII 56 min
0.05	CI 13 min 0	CII 13 min 0 CI 13 min

These results are also shown in more detail in Figures 6.3.12, 6.3.13, 6.3.14 and 6.3.15. It can be seen that the most significant effect of optical blur was on the latency of the CI and CII component to the 19 minute check. Figure 6.3.14 shows that this was a progressive effect, the overall increase in latency for the 3 dioptres of blur being 35 msec for the CI component and 40 msec for the CII component. The latency of the midline CI component to the 13 minute check increases at a similar rate with up to 2 dioptres of blur, but anomalous results in a couple of subjects for the +3D blur cause the mean latency to occur at an earlier value than would be expected.

The degree of overall reduction of mean amplitude is of the order of 50% for the 56 minute CII component, (58%) and the 13 minute CI and CII components (49% and 53% respectively). For the 13 minute CII component recorded from the midline electrode (0) the reduction was 68.3%.

Figure 6.3.11 Optical blur study. Number of subjects in which each VEP component could be identified



	Check (min)	0	+1D	+2D	+3D	Variance Ratio	df n/d	Significance Level	
FLASH (P_2)	Latency (m.sec)	117.38 ± 8.19 SE 2.59	119.59 ± 10.94 SE 3.46	119.82 ± 8.99 SE 2.84	120.71 ± 10.99 SE 3.48	1.33	3/27	Not Sig	
	Amplitude (uV)	9.13 ± 5.08 SE 1.61	11.45 ± 4.65 SE 1.47	9.8 ± 3.6 SE 1.14	10.27 ± 5.21 SE 1.65	1.924	3/27	Not Sig	
PATTERN REVERSAL LATENCY (msec)	56'	108.78 ± 10.57 SE 3.34	107.99 ± 11.96 SE 3.78	112.15 ± 12.15 SE 3.84	113.32 ± 17.17 SE 5.40				
	19'	99.32 ± 4.77 SE 1.51	101.38 ± 6.84 SE 2.16	110.98 ± 15.75 SE 4.97	112.13 ± 5.27 SE 1.67	8.979	3/27	p<0.001	**
	13'	106.47 ± 10.32 SE 3.26	113.77 ± 10.45 SE 3.31	119.65 ± 15.79 SE 4.99	126.97 ± 22.59 SE 7.14				
	0 13'	104.99 ± 5.79 SE 1.83	111.75 ± 10.57 SE 2.87	116.28 ± 12.74 SE 4.03	128.11 ± 22.05 SE 6.97	5.001	3/27	p<0.01 +	
AMPLITUDE (uV)	56'	8.36 ± 2.89 SE 0.91	7.29 ± 2.67 SE 0.85	7.22 ± 2.69 SE 0.85	7.29 ± 2.02 SE 0.64				
	19'	7.47 ± 3.21 SE 1.01	7.16 ± 2.82 SE 0.89	6.12 ± 1.84 SE 0.58	5.40 ± 2.40 SE 0.76	5.461	3/27	p<0.01	**
	13'	4.36 ± 2.09 SE 0.67	3.86 ± 2.47 SE 0.78	2.84 ± 1.81 SE 0.57	2.47 ± 1.57 SE 0.50				
	0 13'	3.55 ± 2.42 SE 0.77	2.85 ± 1.69 SE 0.53	2.16 ± 0.96 SE 0.30	2.45 ± 1.43 SE 0.45	2.833	3/27	Not Sig +	

Key: + - no significant difference between electrodes.

Table 6.3.4 Effect of optical blur on the flash and pattern reversal VEP.

Figure 6.3.12 The effect of optical blur on the latency of the pattern reversal VEP showing the mean ± 1 standard error of the mean (N = 10)

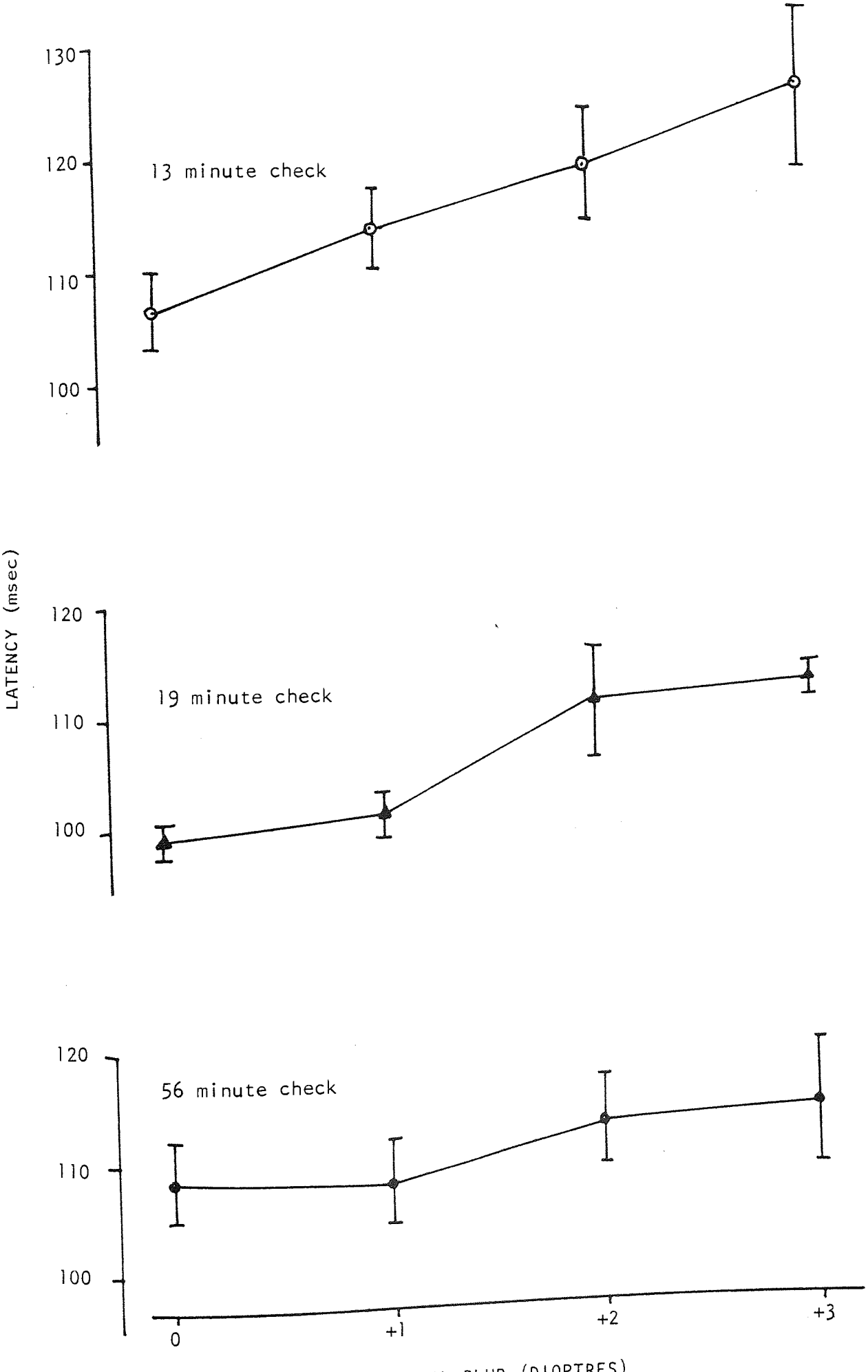
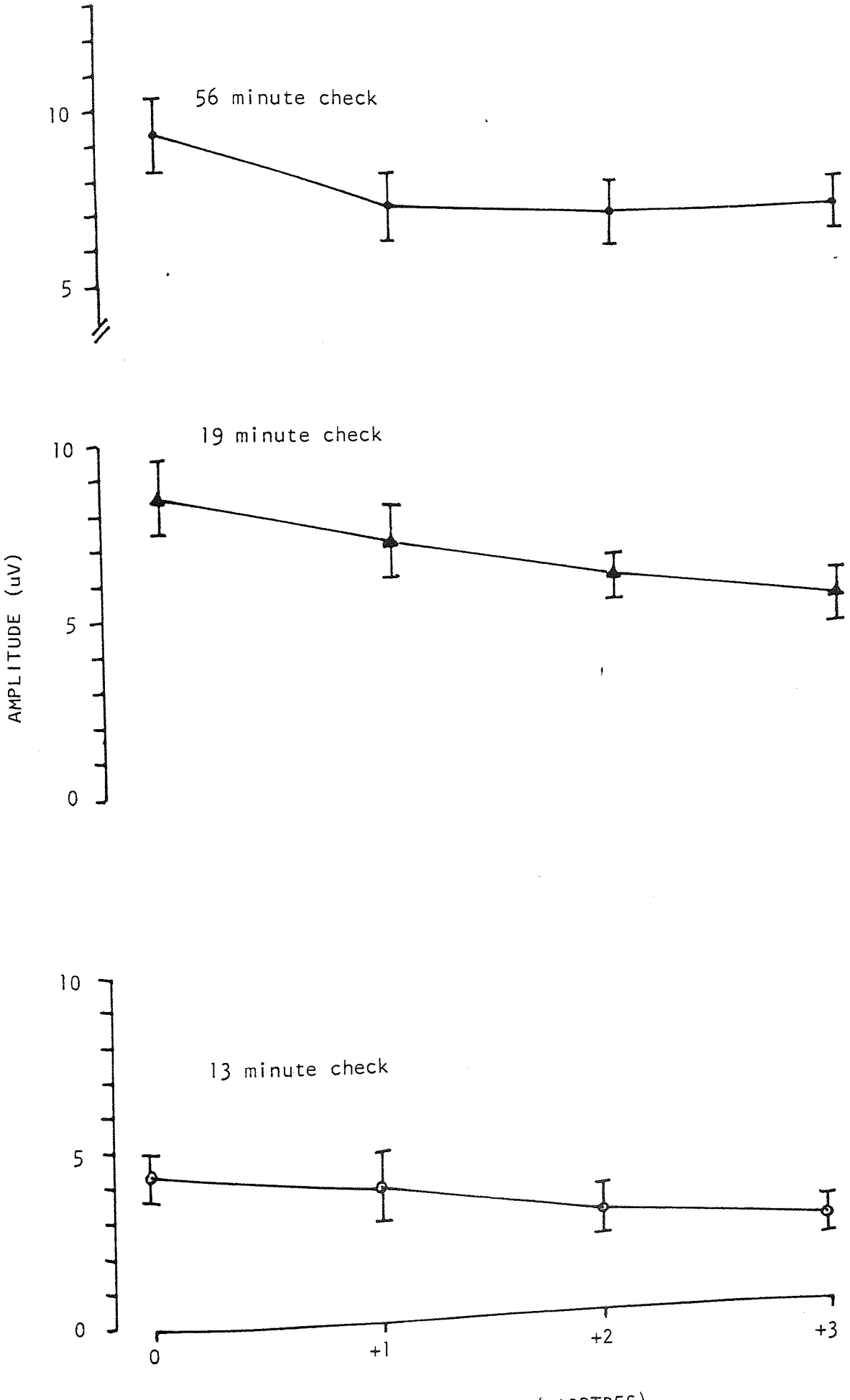


Figure 6.3.13 The effect of optical blur on the amplitude of the pattern reversal VEP showing the mean ± 1 standard error of the mean (N = 10)



Check (min)	0	+1D	+2D	+3D	Variance Ratio	df n/d	Significance Level	
LATENCY (m.sec) 56	76.06 ± 9.52 SE 3.36	82.59 ± 17.89 SE 6.33	79.57 ± 15.79 SE 5.58	74.92 ± 10.60 SE 3.75	0.945	3/21	Not Sig.	
19	71.25 ± 14.65 SE 5.54	81.98 ± 14.0 SE 5.29	96.94 ± 17.23 SE 6.51	106.35 ± 12.34 SE 4.66	12.46	3/18	p<0.001	* *
13	85.33 ± 5.2 SE 2.12	93.79 ± 13.2 SE 5.39	104.21 ± 26.3 SE 10.74	117.45 ± 10.84 SE 4.43	3.00	3/15	Not Sig.	
0 13	84.55 ± 7.16 SE 3.58	96.85 ± 18.58 SE 9.29	114.23 ± 10.69 SE 5.35	105.53 ± 16.21 SE 8.11	4.94	3/9	p<0.05	*
AMPLITUDE (uV). 56	4.91 ± 1.16 SE 0.52	6.25 ± 5.16 SE 2.31	6.42 ± 4.18 SE 1.87	2.75 ± 2.75 SE 1.23	1.97	3/12	Not Sig.	
19	5.0 ± 2.55 SE 0.96	3.90 ± 3.64 SE 1.38	3.92 ± 3.51 SE 1.33	4.43 ± 3.78 SE 1.43	0.37	3/18	Not Sig.	
13	4.39 ± 1.86 SE 0.76	3.01 ± 1.08 SE 0.44	3.78 ± 1.83 SE 0.75	2.24 ± 2.24 SE 0.91	3.92	3/15	p<0.05	*
0 13	3.24 ± 0.94 SE 0.42	2.48 ± 1.57 SE 0.70	2.87 ± 1.70 SE 0.76	1.69 ± 1.09 SE 0.49	1.81	3/12	Not Sig.	

TABLE 6.3.5 Effect of optical blur on the C1 component on the pattern onset VEP

	Check (min)	0	+1D	+2D	+3D	Variance Ratio	df n/d	Significance Level	
LATENCY (m.sec)	56	103.71 ± 13.88 SE 5.25	103.16 ± 16.02 SE 6.06	94.89 ± 14.13 SE 5.34	95.54 ± 13.95 SE 5.27	3.34	3/18	p<0.05	*
	19	95.77 ± 21.46 SE 7.15	108.35 ± 10.41 SE 3.47	117.63 ± 21.65 SE 7.22	135.22 ± 29.99 SE 10.0	7.67	3/24	p<0.001	* *
	13	148.83 ± 26.24 SE 11.74	158.48 ± 12.59 SE 5.63	160.4 ± 44.45 SE 19.88	172.75 ± 17.42 SE 7.79	0.705	3/12	Not Sig	
	0 13	129.06 ± 23.95 SE 10.71	143.74 ± 38.1 SE 17.04	146.86 ± 46.52 SE 10.8	165.08 ± 20.84 SE 9.32	1.486	3/12	Not Sig.	
AMPLITUDE (uV)	56	4.36 ± 2.49 SE 1.02	4.29 ± 2.46 SE 1.00	3.22 ± 3.51 SE 1.43	1.83 ± 1.35 SE 0.55	5.28	3/15	p<0.025	*
	19	4.28 ± 3.14 SE 1.11	3.94 ± 2.46 SE 0.87	2.63 ± 2.95 SE 1.04	2.86 ± 2.6 SE 0.92	1.63	3/21	Not Sig.	
	13	6.78 ± 1.56 SE 0.70	5.25 ± 2.76 SE 1.23	3.95 ± 2.07 SE 0.92	3.18 ± 1.27 SE 0.57	6.00	3/12	p<0.01	* *
	0.13	4.86 ± 1.34 SE 0.60	4.06 ± 2.47 SE 1.10	2.78 ± 2.24 SE 1.00	1.54 ± 1.42 SE 0.63	4.05	3/12	p<0.05	*

TABLE 6.3.6 Effect of optical blur on the C11 component of the pattern onset VEP

Figure 6.3.14 The effect of optical blur on the latency of the pattern onset VEP showing the mean ± 1 standard error of the mean

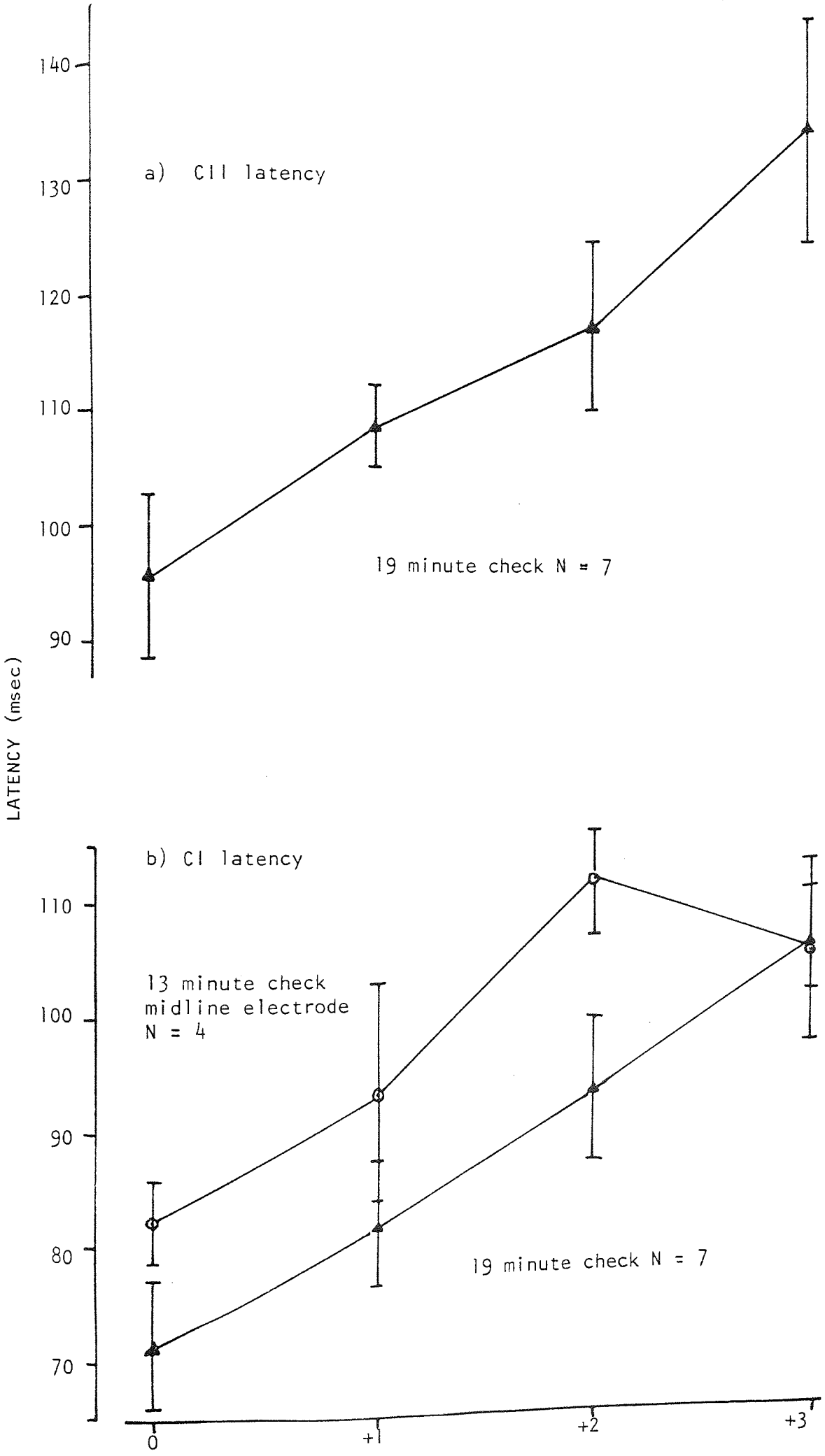
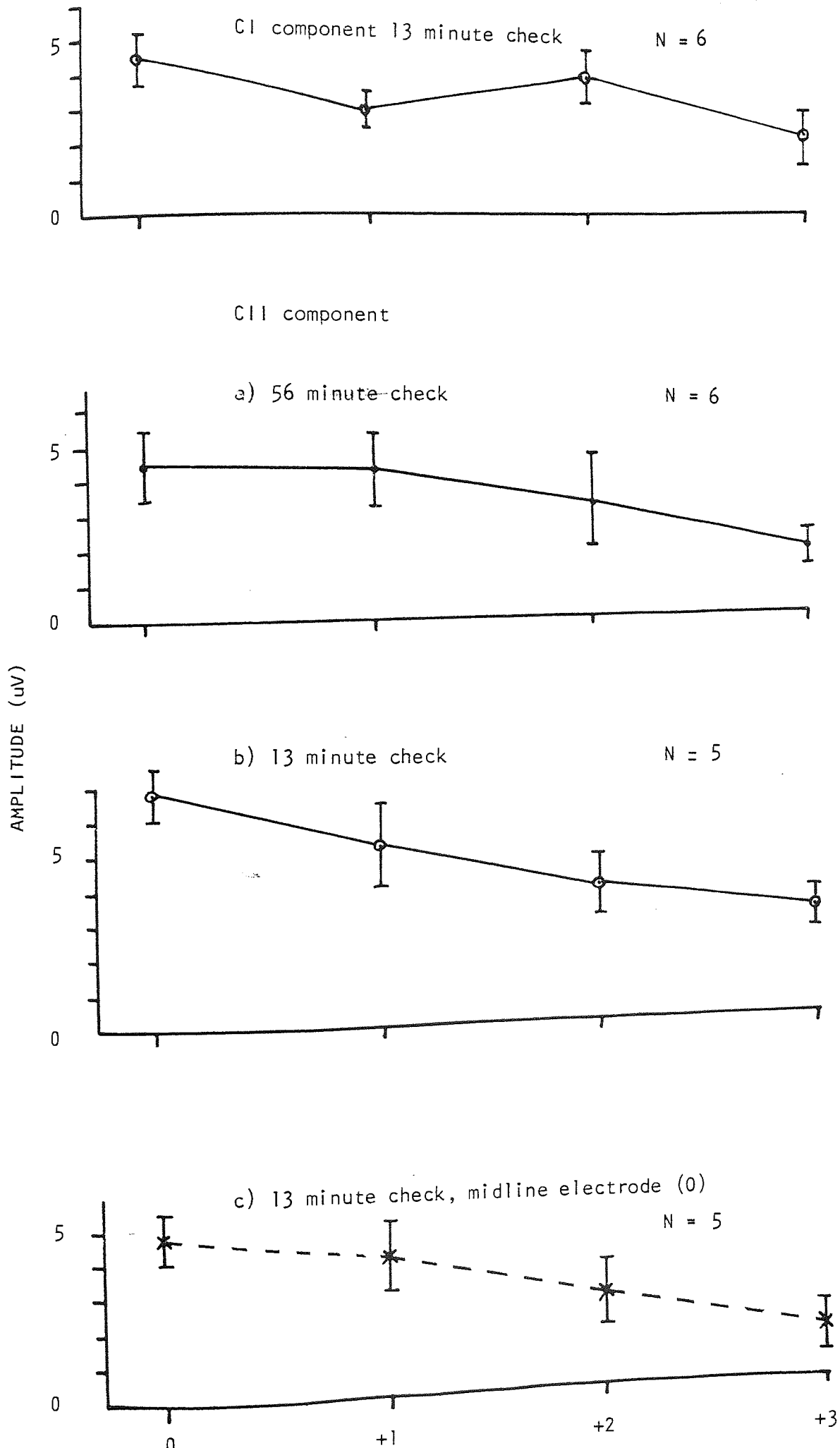


Figure 6.3.15 The effect of optical blur on the amplitude of the pattern onset VEP



Discussion - The results show that optical blur has no effect on the de Lange curve of the flash VEP, representing luminance and temporal processing.

The effect of optical blur on spatial processing is two-fold. The effect of the reduction of the high spatial frequency content of the stimulus is to reduce the visual acuity, while the effect of the light scatter and the consequent reduction in the contrast of the stimulus causes an elevation in contrast threshold, shown as a reduction in contrast sensitivity. Surprisingly, it was found in both this study and the study of optical blur in the good eye of the amblyopes (Section 62B) that the relative reduction in contrast sensitivity for the 4 c/deg grating is equal to or greater than the relative reduction for the 12 c/deg grating. This can also be seen in Figure 2 of Regan, Silver and Murray (180) which shows the effect of +1 dioptre blur on the mean CSF curve of 19 eyes. Of the 8 spatial frequencies investigated, the maximum reduction in contrast sensitivity was shown at 4 c/deg. The 'difference curve', representing the ratio of contrast sensitivities in blurred and sharp vision, showed that after the maximum difference at 4 c/deg, the difference declined with increasing spatial frequency up to about 12 c/deg, after which it increased again. A more detailed investigation of this effect is beyond the scope of this study, but it is suggested that it is related to the finding that the accuracy of accommodation for high contrast sinusoidal gratings was maximum for gratings of 3-5 c/deg, the peak of the CSF curve (361).

This effect might also account for the pattern onset VEP results, which show the effect of blur on the latency of both CI and CII to

be most highly significant for the medium, 19 minute, check size. The latency results for the smallest check showed an increase in the mean values, but this was not statistically significant, presumably due to the large variability of the responses.

An anomalous result was found for the latency of the 56 minute CII component which appeared to decrease by 8 msec between the clear and +1D blurred condition and between the +2 and +3D conditions. This is contrary to expectations and is probably due to an interactive effect with a particularly prominent CI component (as shown in the Table 6.3.5). The exact relationship between the components is complex, but highlights one of the problems of the interpretation of the pattern onset VEP in which each of the components of the response might be responding to the stimulus in a different way. This would particularly affect peak to peak amplitude measures. Apart from the 56 minute CII component mentioned above, all the other VEP components showing a significant amplitude reduction with optical blur were those evoked by the smallest checkerboard. The effect of optical blur on amplitude measures is not as pronounced as its effect on latency measures as clearly shown in the pilot study. VEP research has shown that reduction of the contrast of the image below saturation values can cause both a reduction in amplitude (38) and an increase in latency (115) of the transient VEP.

The most pronounced increase in latency with blur is shown by the CII component, which showed an increase of 52 msec with +3D blur in the cycloplegia study (14 minute check) and 40 msec in the second study (19 minute check). The pattern reversal component increased by 20 msec in the cycloplegia study and 23 msec in the second study

over +3D blur (14 and 13 minute checks). The latency of the CI component was only measured in the second study and showed an increase of 20 msec for the +3D of blur with the 13 minute checks which is practically identical to the pattern reversal value. This is entirely consistent with theoretical VEP studies (e.g.39) which suggest that the CI and pattern reversal components are 'contrast detectors' while the CII onset component also responds to 'contour', or the sharpness of pattern detail. A differential effect of optical blur on different pattern VEP components has not previously been reported. The results of these two studies indicate that the CI and pattern reversal components are reflecting the reduction in the contrast of the stimulus while the CII onset component is also reflecting the blurring of the fine detail of the stimulus, or filtering of high spatial frequencies caused by the optical blur.

TABLE 6.4.1 UNILATERAL OPTIC NEURITIS GROUP - CLINICAL DETAILS

		ONSET OF SYMPTOMS		APPOINTMENT AT NEUROPHYSIOLOGY UNIT			
	AGE	DATE	FIRST APPOINTMENT AT BMEH	DATE	MONTHS SINCE ONSET	MOST RECENT DETAILS FROM BMEH	DIAGNOSIS
1B	25	Oct. 1973	31.10.73. VA-RE 6/5 LE 6/12 P - Marcus Gunn Left side M - Full F - Paracentral scotoma (Amsler)	6.4.81.	90	18.3.81 VA-RE 6/5-2 LE 6/5-1 F - Relative baring of blind spot, both eyes. - Macular function normal (V.F.A.)	Left Optic Neuritis (3rd episode)
RR	52	June 1979	7.11.79 VA-RE 1/60 ($\bar{c}$P.H) LE 6/7.5+3 P - RE reactions slower than LE M - Full (gives discomfort) CV - No colour perception in RE F - Central scotoma (Goldmann)	18.3.81	21	25.3.81 VA-RE 6/5 LE 6/5 P - Reactions normal, sizes equal CV - Improved. Slight red deficit. F - No defect D - Right temporal pallor	Right RBN
FS	41	April 1980	2.5.80 VA-RE 6/6-2 LE6/6-3($\bar{c}$PH) Left eye proptosed CV - "Faint" F - No defect (Hamblin)	16.3.81.	11	30.5.81 VA-RE 6/5 LE 6/9+3 VA Worse after bath or hot meal. F - Relative central scotoma Thyroid function normal.	Left RBN Left antral polyp seen on X-ray.
BB	42	March 1981	9.3.81. VA-RE 6/5-3 LE 6/5 Loss of vision RE for 5 mins 2 days previously. M - full, but painful supra orbital tenderness CV - no colour perception in RE F - red patch nasally(Amsler)	14.7.81.	4	8.6.81 VA-RE 6/5+2 LE 6/4 P and M Normal F - Baring of blind spot RE (Goldmann) X-ray - no abnormality small irregularity of carotid-artery.	Right RBN or Vascular lesion.
JG	43	June 1981	12.6.81. VA-RE 5/36+1($\bar{c}$PH) LE 6/5 P - Afferent defect in RE M - Full but pain on adduction eye tender F - Central scotoma(confrontation) X-ray no abnormality	11.8.81.	2.5	22.6.81. VA-RE 6/6 LE 6/5 No other investigations-discharged	Right Optic Neuritis possible widespread demyelinating disorder (History of numbness in upper limbs)

CONTINUED/.....

UNILATERAL OPTIC NEURITIS GROUP - CLINICAL DETAILS (continued)

AP	39	Dec 1980	12.12.80 VA-RE 6/6 LE 6/5 Blurred vision in RE and bad headaches 2 days previously P - Reactions normal	9.2.81	2	13.1.81. VA-RE 6/9 LE 6/6 F- Uncertainty in paracentral areas of RE P - Marcus Gunn phenomenon	BMEH Right RBN Neurologist - Carpel tunnel syndrome. R L Decompression advised
PM	33	March 1981	3.3.81 VA-RE 6/24 ($\bar{c}$PH) LE 6/6 P - Afferent defect in RE M - Full but painful CV - Red Defect D - Slight papillary hyper-plasia	11.5.81.	2	31.3.81 VA-RE 6/12 ($\bar{c}$PH) LE 6/6 CV - "less sharp" RE D - "some pallor" RE 5.5.81. P - Brisk reaction RE	Right RBN
MW	42	April 1981	27.4.81 VA-RE 6/6 LE HM P - Afferent defect LE F - Upper nasal defect (confrontation) X-ray - No pathology D - Normal	24.6.81.	2	18.5.81. Vision "better" but still hazy in centre. No pain. D - Normal Has been taking ACTH for 2 wks	Left RBN
DW	31	Dec 1980	20.12.80 VA-RE 6/6 LE 6/24 P - Dilated CV - Normal	2.2.81.	1.5	19.1.81 VA-RE 6/6 LE 6/9 P - No defect F - Relative central scotoma	Neurological opinion Left Optic Neuritis
SB	25	March 1981	10.3.81 VA-RE 6/24+2 ($\bar{c}$PH) LE 6/5 Terrible occipital headaches P - Marked afferent defect RE F - No defect Reduced macular function RE (VFA)	14.4.81	1	31.3.81 VA-RE 6/6+2 LE 6/5 P - Slight afferent defect	Right RBN

Abbreviations:

P - Pupils
M - Motility
F - Fields
CV - Colour Vision
D - Optic Disc
VA - Visual Acuity

BMEH - Birmingham and Midland Eye Hospital
PH - Pinhole Disc
VFA - Visual Field Analyser
RBN - Retro Bulbar Neuritis
HM - Hand Movements only visible.

6.4 Unilateral optic neuritis study

The ten optic neuritis patients in this study were selected from those investigated at the Birmingham and Midland Eye Hospital (BMEH) on the basis of a known or probable unilaterally delayed pattern reversal VEP. Clinical details from the hospital are shown in Table 6.4.1, with the patients arranged in order of the months since the onset of symptoms. Two groups of details are shown : those relating to the first hospital appointment after the onset of symptoms, and those relating to the most recent appointment before the follow-up VEP investigation at our Neurophysiology Unit. It can be seen that the age range is 25 - 52 years which, according to Cogan (2), indicates that demyelination is the most likely cause of the optic neuritis. However, only one patient, JG, showed any indication of a more widespread demyelination. By the time they participated in this study, most patients had recovered from the acute symptoms.

In order to establish that there was no evidence of demyelination in the optic nerve of the apparently unaffected eye, the pattern reversal latency of the VEP recorded from this eye was compared with the appropriate monocular results from ten age and sex-matched controls. No significant latency difference was found for any of the three check sizes (variance ratio 0.540 df n = 1 d = 9). It was therefore considered valid to use this eye as a control in all subsequent comparisons. As observed in the amblyopia study, this provides the ideal control in that in both cases the VEP comes from the same visual cortex enabling the response from an optic nerve with inflammation and probable demyelination to be compared directly with the response from an intact nerve, without having to take any inter-individual variability into account.

The significance level of the group difference in pattern reversal latency between the two eyes is 0.001 as would be expected from the selection procedure (Table 6.4.2).

Figure 6.4.1 shows that the magnitude of the delay is very consistent, being between 36 and 40 msec for all check sizes. In addition, statistical analysis (Table 6.4.2) shows that there is a reduction in pattern reversal amplitude in the affected eye which is significant for the 56 and 19 minute check sizes ($p < 0.01$), but not for the 13 minute check size (Figure 6.4.2). The magnitude of the amplitude reduction is 20% for the 56 minute check VEP and 42% for the 19 minute check VEP.

The latency of the components of the pattern onset VEP also shows a marked delay in the affected eye (Table 6.4.3 and Figure 6.4.3). This is more significant for the CII latency values. The significance levels for the latency and amplitude measures for the different pattern VEP components are displayed for clarity in Table 6.4.4 below:

Table 6.4.4 Significance level of pattern VEP latency and amplitude differences in unilateral optic neuritis

CHECK SIZE	REVERSAL		CI		CII	
	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
56 min.	0.001	0.01	0.01	-	0.001	0.05
19 min.	0.001	0.01	0.05	-	0.01	0.05
13 min.	0.001	-	0.025	-	0.01	-

These results show a greater similarity between the reversal and CII

	Check (min)	AFFECTED EYE	UNAFFECTED EYE	Variance Ratio	df n/d	Significance Level	
FLASH (P_2)	Latency (m.sec)	131.45 ± 17.15 SE 5.43	124.75 ± 12.81 SE 4.05	1.304	1/9	Not Sig.	
	Amplitude (uV)	6.84 ± 5.13 SE 1.62	8.11 ± 6.13 SE 1.94	2.516	1/9	Not Sig.	
PATTERN REVERSAL LATENCY (m.sec)	56	141.6 ± 14.75 SE 4.66	105.2 ± 9.06 SE 2.87				
	19	143.1 ± 12.76 SE 4.04	103.45 ± 5.48 SE 1.73	100.314	1/9	p<0.001	* *
	13	142.55 ± 14.03 SE 4.44	104 ± 7.32 SE 2.31				
	0 13	140.8 ± 14.74 SE 4.66	104.7 ± 7.20 SE 2.28	82.84	1/9	p<0.001+	* *
AMPLITUDE (uV)	56	6.2 ± 3.39 SE 1.07	7.65 ± 3.16 SE 1.00				
	19	4.33 ± 2.37 SE 0.75	7.45 ± 4.68 SE 1.48	11.833	1/9	p<0.01	* *
	13	3.42 ± 2.01 SE 0.63	3.95 ± 2.35 SE 0.74	(Interaction 3.706	2/18	p<0.05)	* *
	0 13	3.32 ± 1.62 SE 0.51	3.76 ± 2.09 SE 0.66	1.926	1/9	Not Sig.+	

+ no significant difference between electrodes.

TABLE 6.4.2 Effect of optic neuritis on the flash and pattern reversal VEP.

Figure 6.4.1 Effect of optic neuritis on the latency of the pattern reversal VEP showing mean ± 1 standard error of the mean (N = 10)

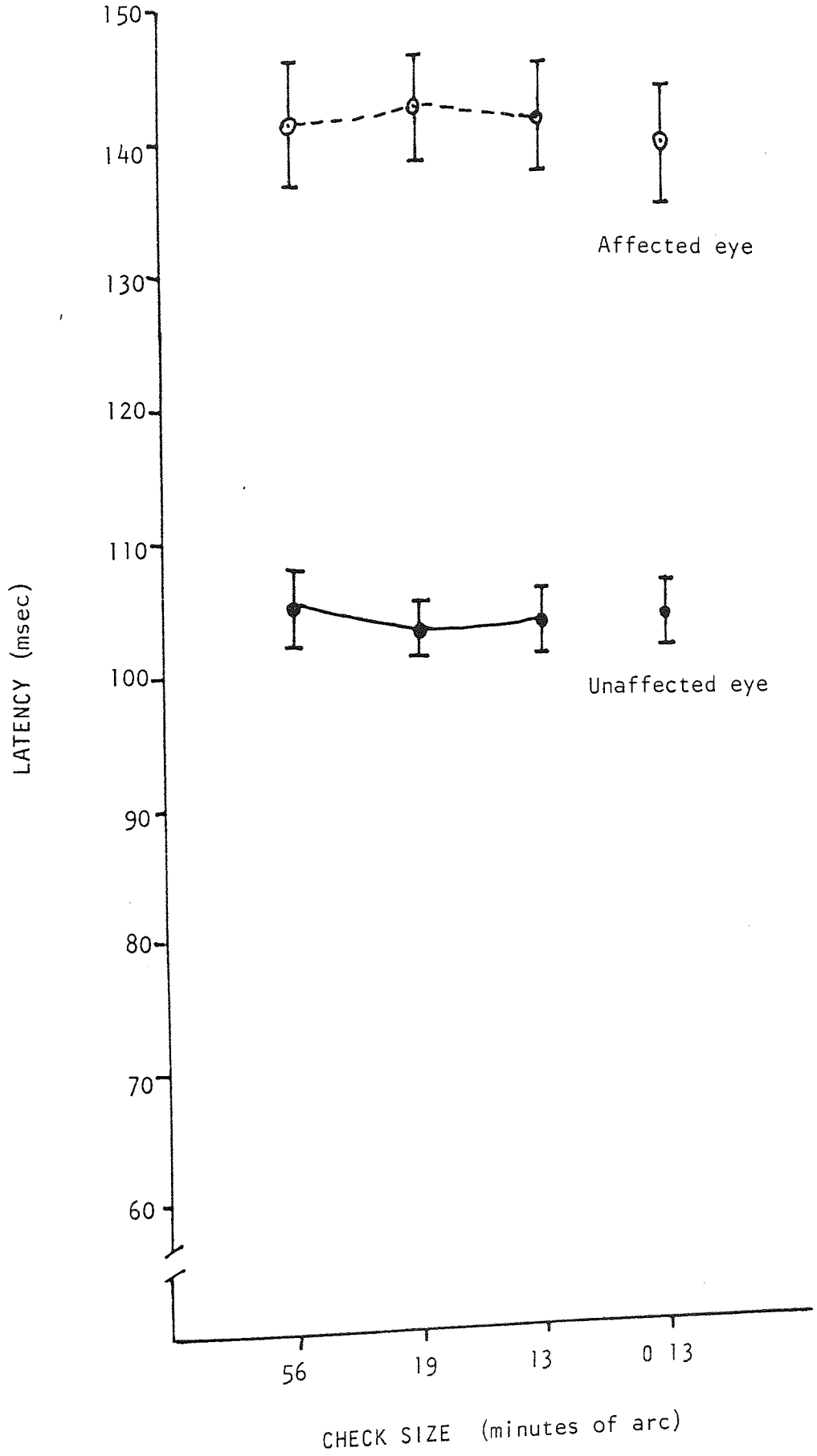
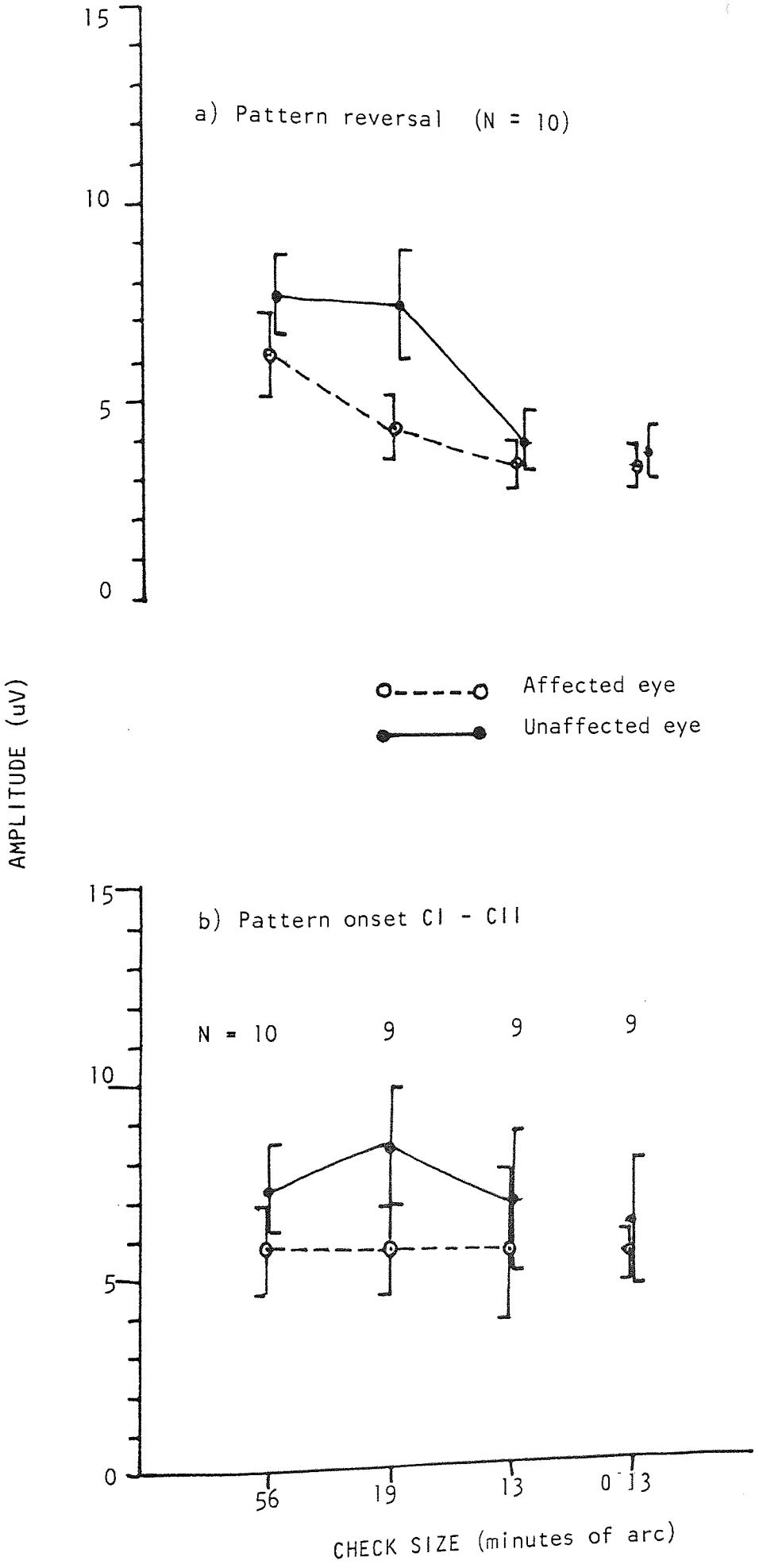


Figure 6.4.2 Effect of optic neuritis on the amplitude of the pattern VEP



		Check (min)	AFFECTED EYE	UNAFFECTED EYE	Variance Ratio	df n/d	Significance Level	
C I COMPONENT	LATENCY (m.sec)	56	98.1 ± 19.77 SE 6.25	68.15 ± 11.4 SE 3.61	18.488	1/9	p<0.01	* *
		19	101.22 ± 29.13 SE 9.71	71.39 ± 14.61 SE 4.87	7.189	1/8	p<0.05	*
		13	98.75 ± 27.41 SE 8.67	78.5 ± 17.48 SE 5.53	7.856	1/9	p<0.025 +	*
		0 13	99.5 ± 31.17 SE 9.86	74.3 ± 21.54 SE 6.81				
	AMPLITUDE (uV)	56	3.84 ± 2.09 SE 0.66	4.35 ± 2.49 SE 0.79	0.547	1/9	Not Sig	
		19	3.01 ± 2.34 SE 0.78	3.54 ± 2.28 SE 0.76	0.630	1/8	Not Sig	
		13	1.924 ± 1.10 SE 0.35	2.22 ± 1.25 SE 0.39	0.074	1/9	Not Sig +	
		0 13	1.71 ± 1.01 SE 0.20	1.30 ± 0.64 SE 0.20				
C II COMPONENT	LATENCY (m.sec)	56	137.75 ± 16.58 SE 3.24	102.15 ± 10.91 SE 3.45	27.472	1/9	p<0.001	* *
		19	144.94 ± 12.04 SE 4.01	105.56 ± 22.65 SE 7.55	14.831	1/8	p<0.01	* *
		13	146.89 ± 31.86 SE 10.62	120.11 ± 14.24 SE 4.75	14.294	1/8	p<0.01 +	* *
		0 13	145.89 ± 30.76 SE 10.25	118.67 ± 14.82 SE 4.94				
	AMPLITUDE (uV)	56	5.75 ± 3.51 SE 1.11	7.26 ± 3.63 SE 1.15	6.232	1/9	p<0.05	*
		19	5.62 ± 3.27 SE 1.09	8.33 ± 4.7 SE 1.57	5.846	1/8	p<0.05	*
		13	5.63 ± 5.76 SE 1.92	6.87 ± 5.55 SE 1.85	2.242	1/8	Not Sig +	
		0 13	5.34 ± 2.31 SE 0.77	6.28 ± 5.22 SE 1.74				

+: no significant difference between electrodes.

TABLE 6.4.3 Effect of optic neuritis on the pattern onset VEP.

Figure 6.4.3 Effect of optic neuritis on the latency of the pattern onset VEP mean ± 1 standard error

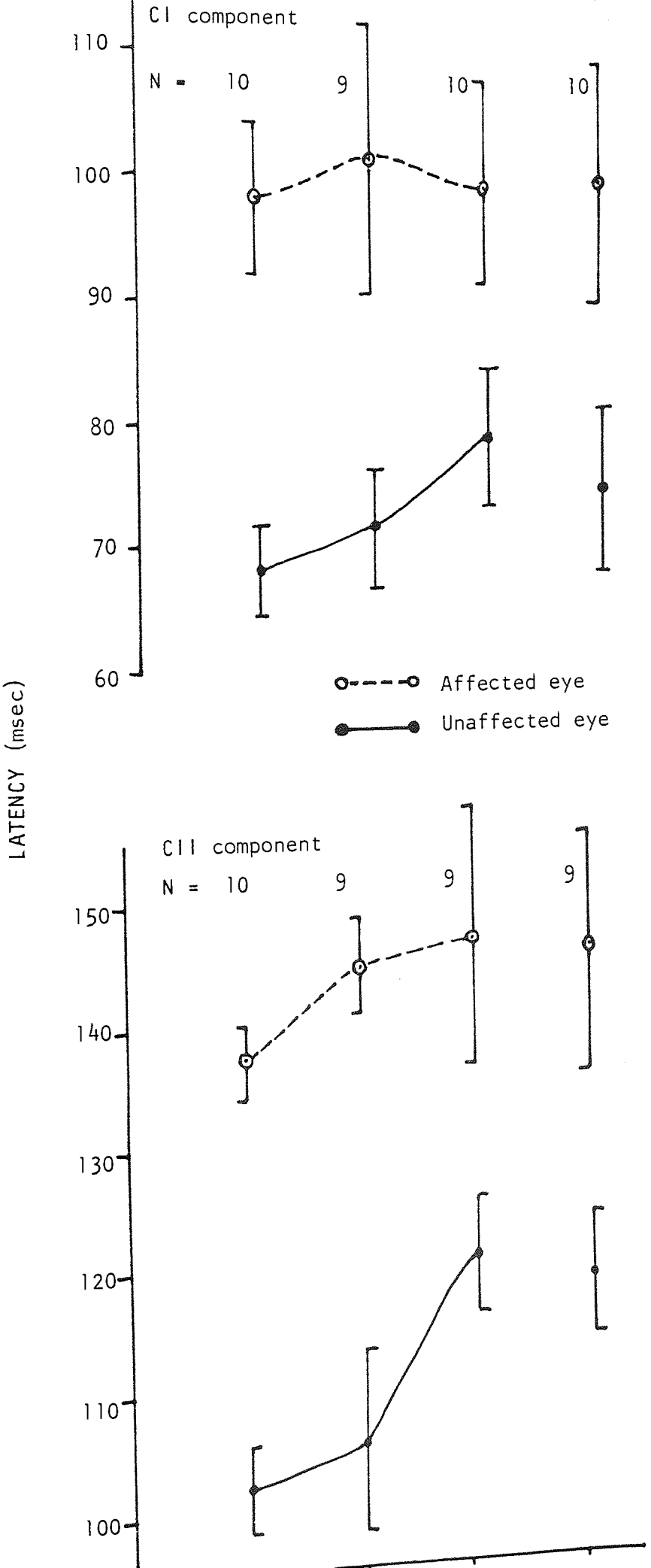


Figure 6.4.4 To show the range and overlap of the flash and pattern latencies of ten patients with optic neuritis

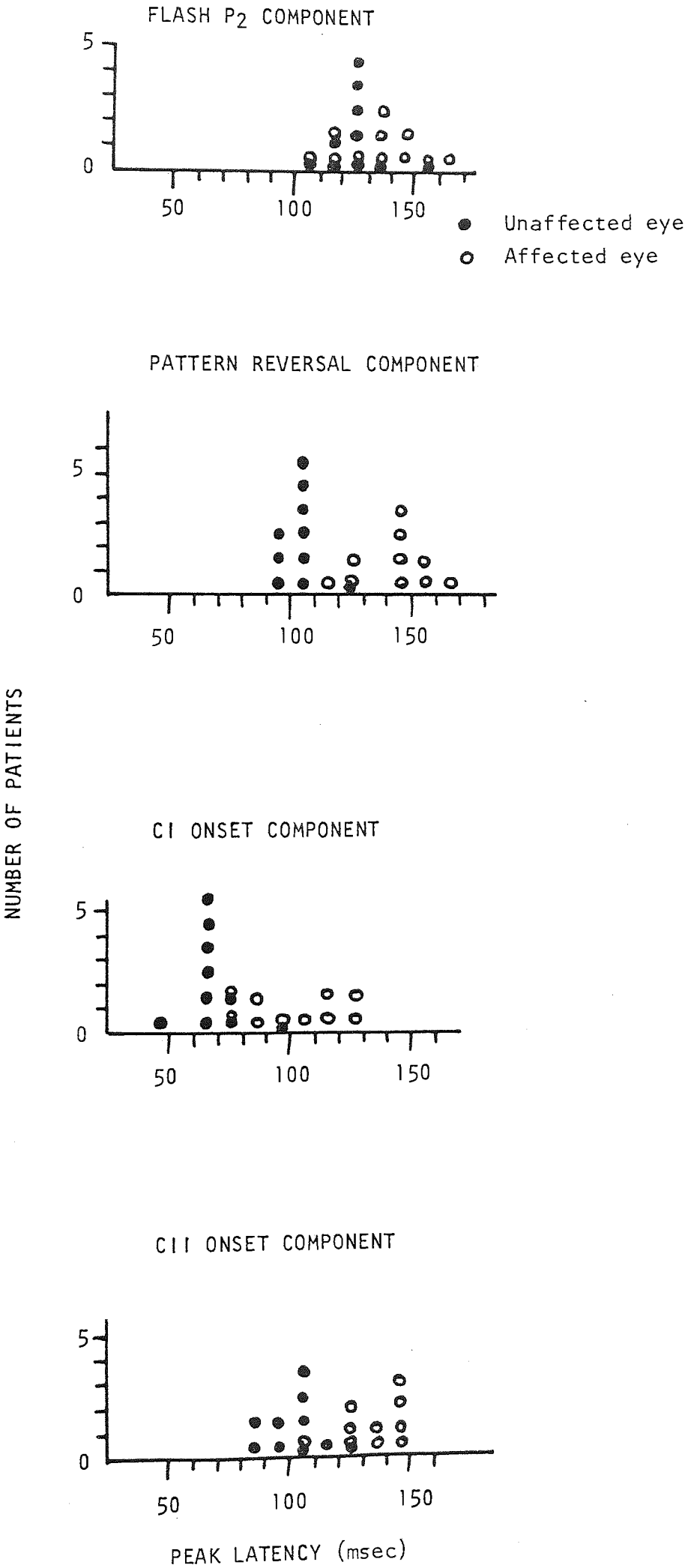


Figure 6.4.5 Flash and pattern VEPs in left optic neuritis

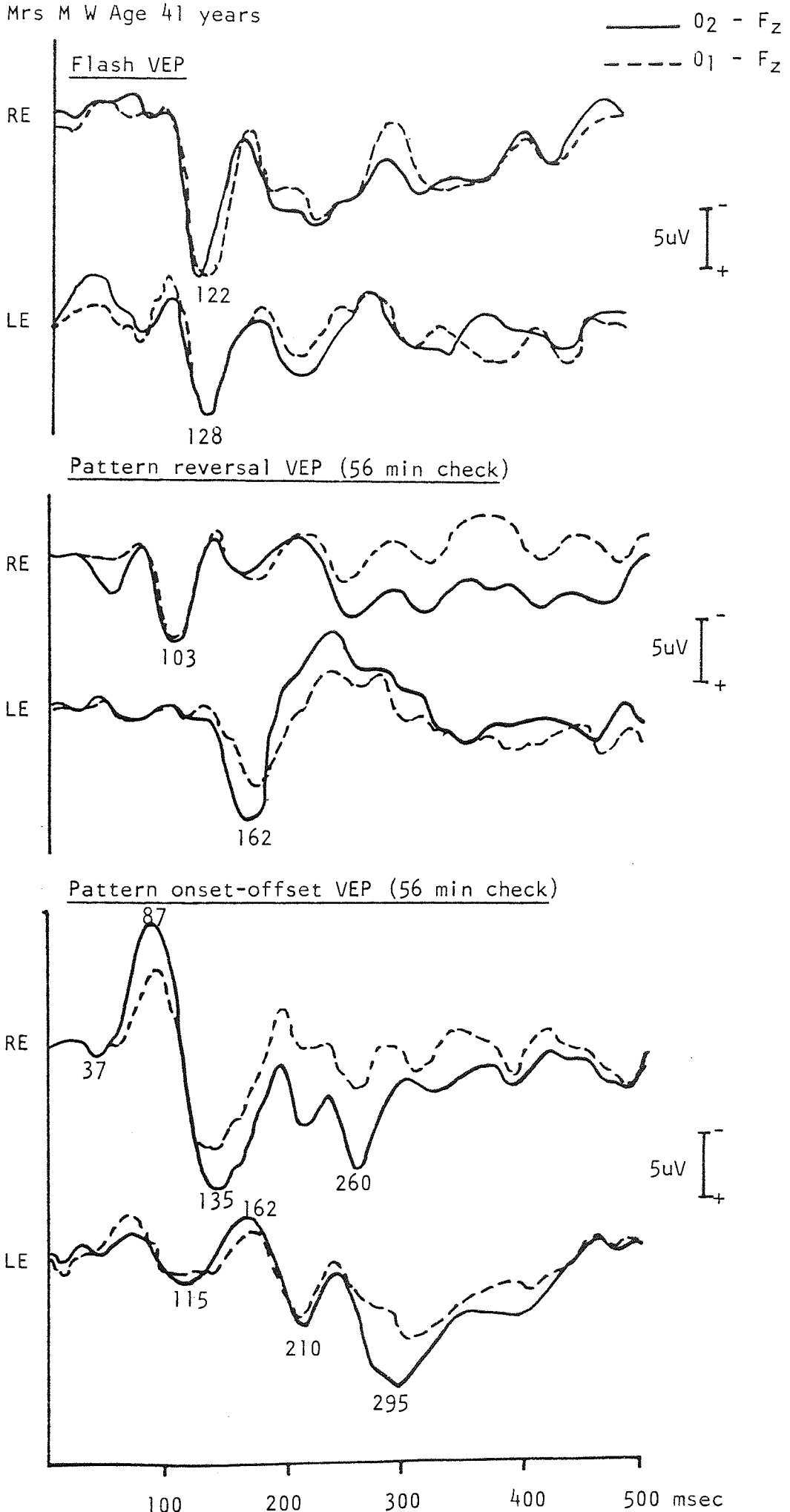
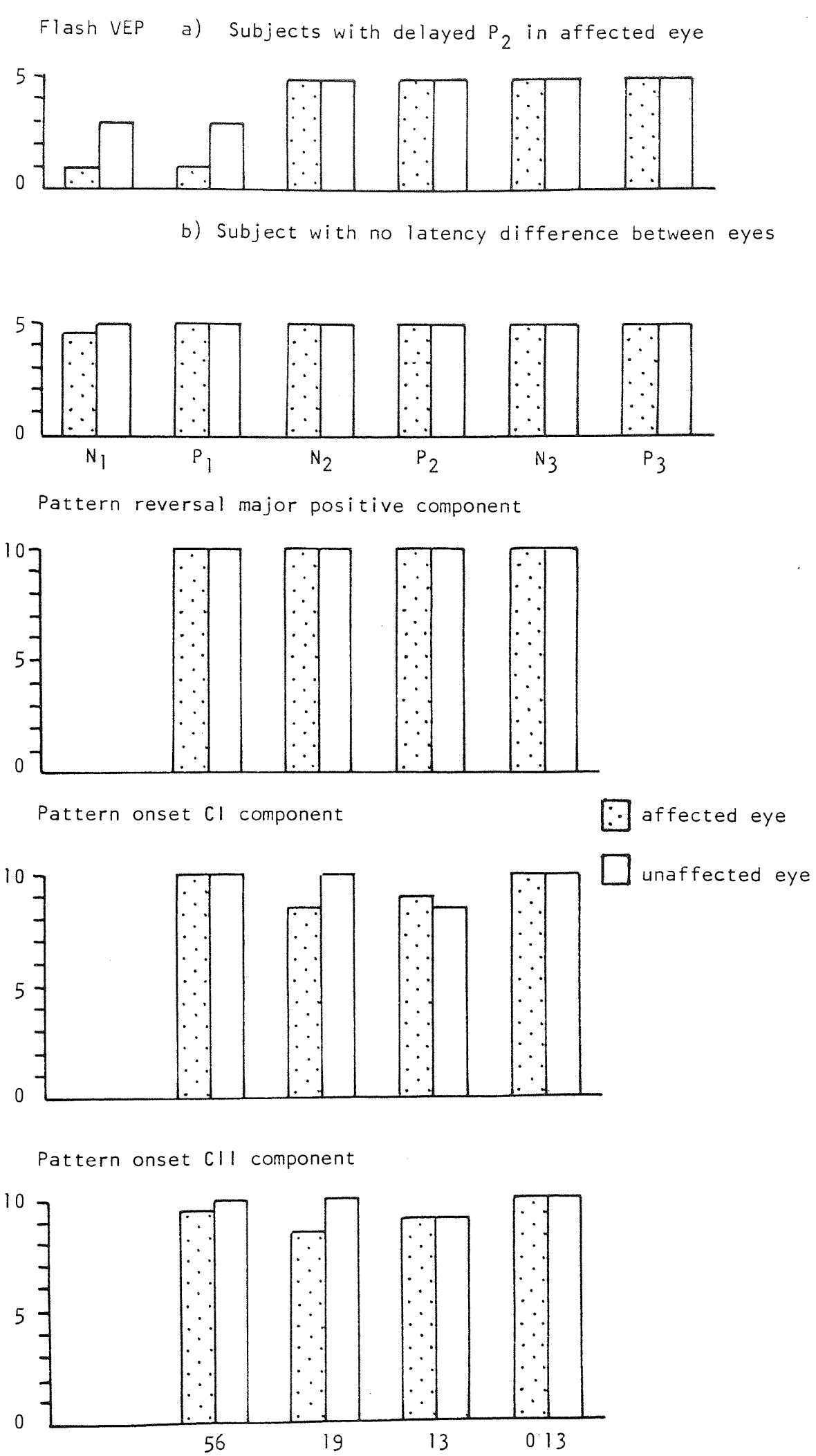


Figure 6.4.6 Unilateral optic neuritis study. Number of subjects in which each VEP component could be identified



measures with respect to both latency and amplitude. The C1 component does not show any significant reduction in amplitude for any check size. Tables 6.4.2 and 6.4.3 show that the differences between all these measures are very distinct.

The range of individual results are shown in Figure 6.4.4. It can clearly be seen that the latency difference between the eyes is much more marked for the pattern VEP components than the flash P2 component. This is also shown in the individual waveforms of subject MW in Figure 6.4.5.

Group analysis of the flash P2 latency and amplitude shows that there is no significant difference of the means between the two eyes. In fact, 5 subjects did show a relative P2 delay in the affected eye, but this was not reflected in the group as a whole due to the large overlap of results as shown in Figure 6.4.4 and previously observed by Halliday (70). Inspection of the P1 values to see if these showed a similar delay, revealed that only one subject, DW, had a P1 component which could be clearly identified. This also showed a relative delay. However, as shown in Figure 6.4.6, P1 could not be identified in the affected eye of the other four subjects with a relative P2 delay. This is particularly interesting in view of the fact that P1 could be identified in all of the five subjects with no relative P2 delay. A larger sample would be required before any definite conclusions could be drawn from these observations.

Psychophysical results - In view of the marked pattern VEP abnormalities found in optic neuritis it is of particular interest to investigate whether these are paralleled by equally marked psychophysical

defects.

VA measurements showed that in seven of the ten subjects, VA in the affected eye had returned to 'normal' levels of $^{6}/6$ or better. The mean VA of the ten affected eyes was 1.018 ± 0.18, or $^{6}/6 +1$. From the point of view of the patient this is a dramatic improvement after the marked loss of VA experienced during the acute attack of optic neuritis. However, more detailed analysis of the results show that in every case, the VA of the affected eye is still slightly less than that of the unaffected eye, and this relative difference between the eyes is shown to be statistically significant at the 0.01 level.

When asked about the vision of the affected eye before the investigation, the first response of all the patients was that it had returned to normal. However, some qualified this by saying that vision was still "hazy", "grey" or "washed-out" - one remarking that the vision was like "looking through water" and another that it was "like the TV with the contrast turned down". In view of these observations it was not surprising to find contrast sensitivity defects in the affected eye:

The individual ratios of the contrast and flicker sensitivities of the affected to the unaffected eye are shown in Figure 6.4.6. These are arranged in order corresponding to the time since the onset of symptoms. It can be seen that eight out of the ten patients show an overall relative CSF defect. The remaining two subjects, in whom the relative defect was confined to medium and high frequencies, are the two in which a large amount of time has elapsed since the onset of symptoms, implying that the contrast

Figure 6.4.7 Showing ratio of affected : unaffected eye for spatial and temporal MTFs in unilateral optic neuritis

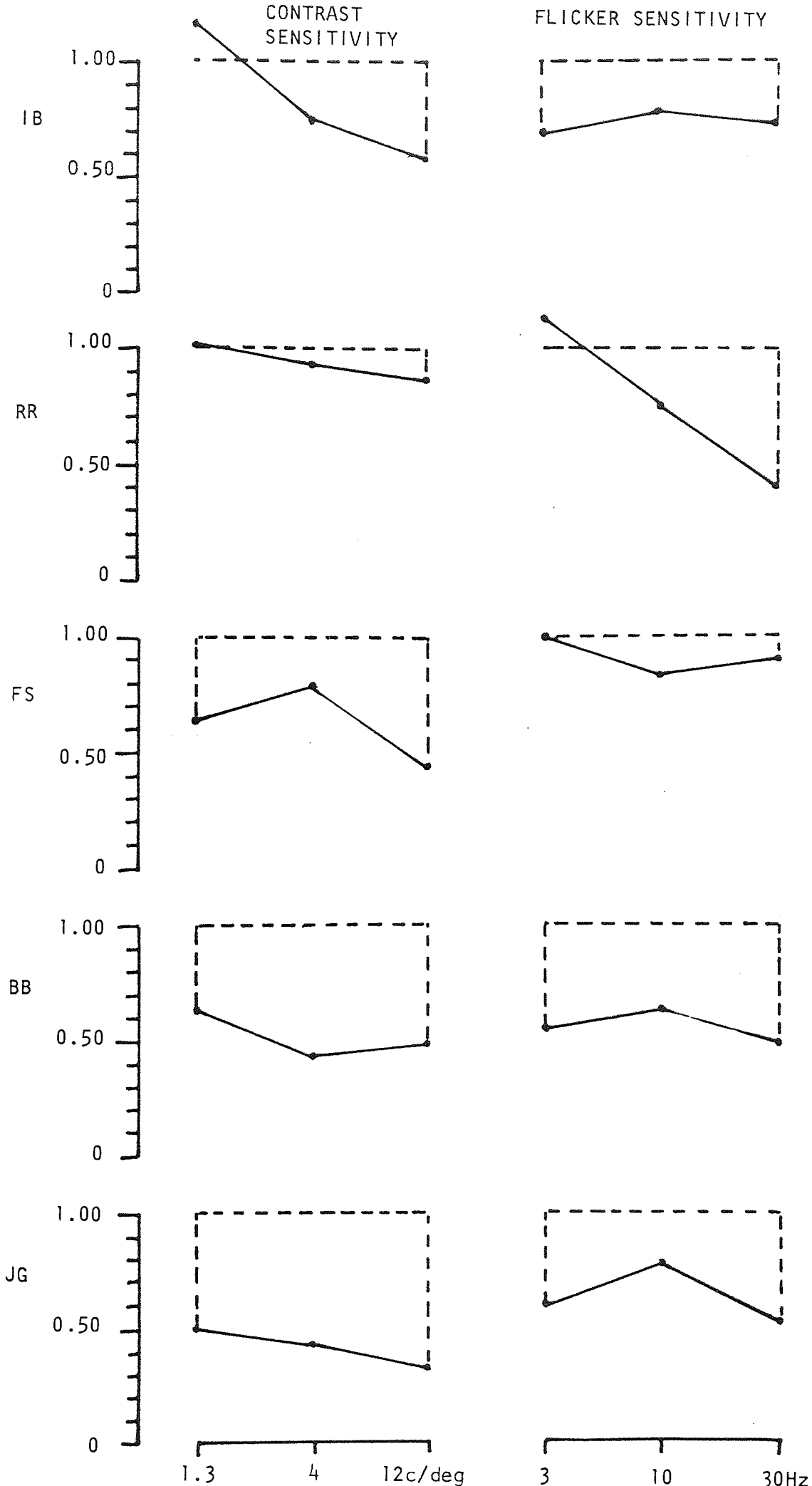
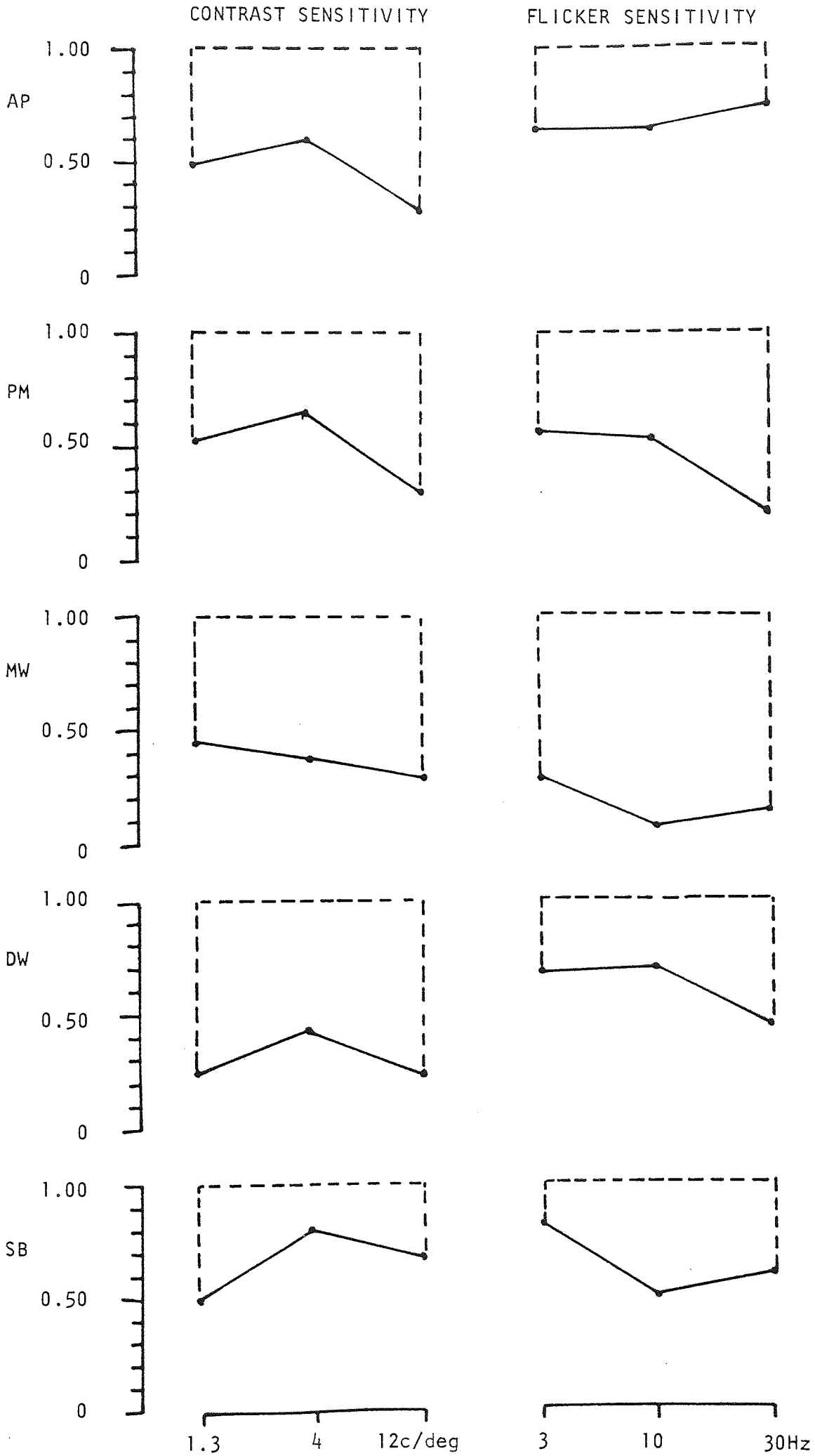


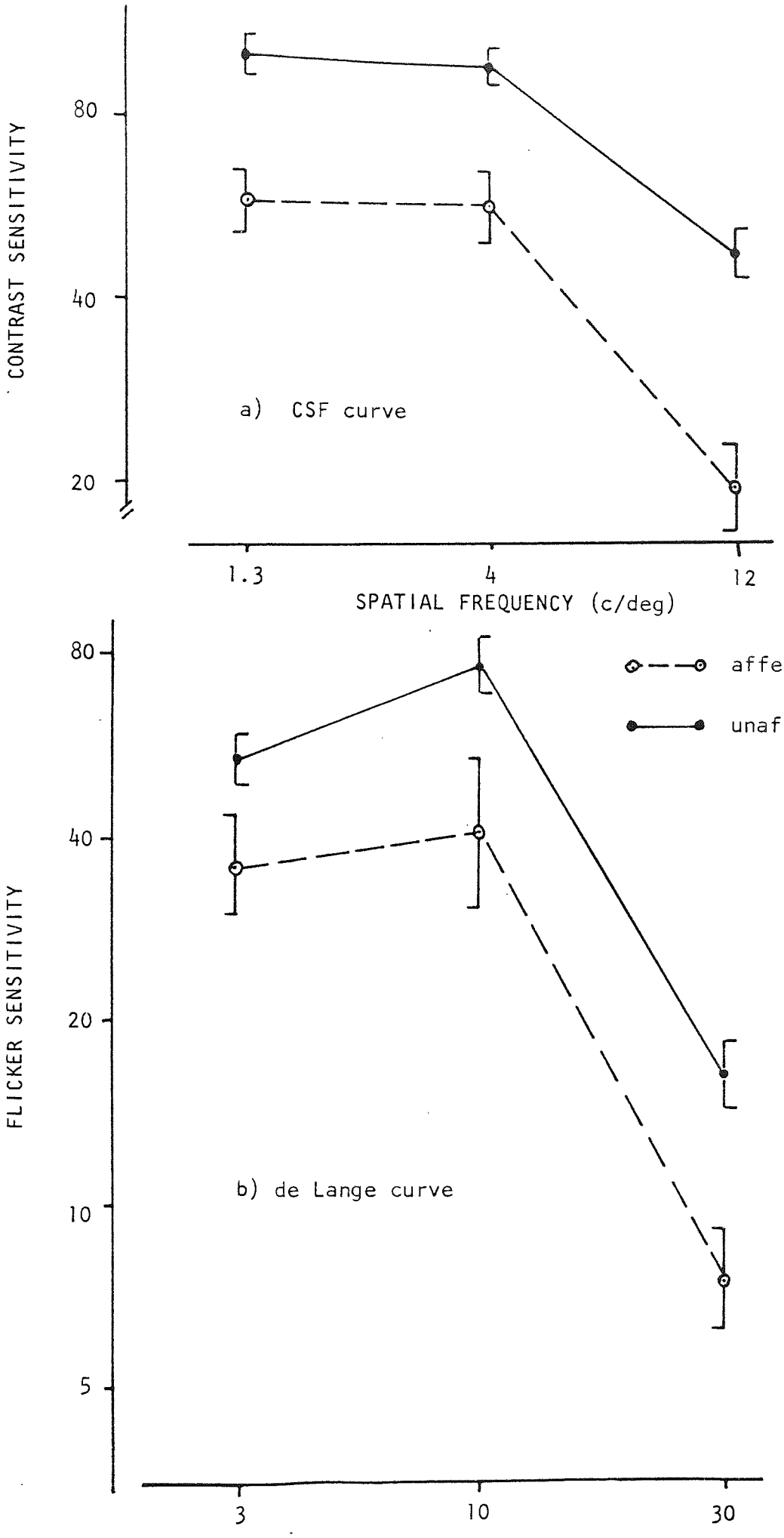
Figure 6.4.7 continued



		AFFECTED EYE	UNAFFECTED EYE	Variance Ratio	df n/d	Significance Level	
VISUAL ACUITY		1.018 ± 0.18 SE 0.06	1.19 ± 0.14 SE 0.04	11.19	1/9	p<0.01	* *
LOG CONTRAST SENSITIVITY	1.3 c/deg	1.700 ± 0.178 SE 0.056	1.943 ± 0.112 SE 0.035	33.78	1/9	p<0.001	* *
	4 c/deg	1.695 ± 0.186 SE 0.059	1.925 ± 0.088 SE 0.028				
	12 c/deg	1.237 ± 0.205 SE 0.065	1.613 ± 0.125 SE 0.04	(Interaction 8.17	2/18	p<0.01)	* *
LOG FLICKER SENSITIVITY	3Hz	1.559 SD 0.235 SE 0.074	1.736 SD 0.143 SE 0.045	13.97	2/18	p<0.001	* *
	10 Hz	1.628 SD 0.374 SE 0.118	1.891 SD 0.144 SE 0.045				
	30 Hz	0.878 SD 0.248 SE 0.078	1.211 SD 0.1772 SE 0.0580				

TABLE 6.4.5 Effect of optic neuritis on psychophysical measures of vision.

Figure 6.4.8 Effect of optic neuritis on the spatial and temporal MTF showing mean ± 1 standard error of the mean
N = 10



sensitivity (particularly at low frequencies) recovers with time.

Group analysis of the data (Table 6.4.5) show that the difference between the means is significant at the 0.001 level. Figure 6.4.8 shows that the contrast sensitivity attenuation in the affected eye is marked for all spatial frequencies but slightly more pronounced for the 12 c/deg stimulus.

The individual flicker sensitivity ratios showed an overall relative defect in eight of the ten patients. The other two subjects show a normal, or slightly enhanced sensitivity to low frequency flicker in the affected eye, subject RR showing a marked relative attenuation of flicker sensitivity with increasing temporal frequency. The group analysis of the de Lange curves shows a highly significant difference between the two eyes ($p < 0.01$, Table 6.4.5). Figure 6.4.8 shows the marked overall reduction of mean flicker sensitivity in the affected compared with the unaffected eye.

Discussion - The delay of the pattern reversal VEP in demyelination of the optic nerve is remarkable in its magnitude. This study shows that the delay is also shown by the CII component, and to a slightly lesser extent the CI component, of the pattern onset VEP. The flash VEP, however, did not show a similar delay.

It has been suggested (305, 77), that the high sensitivity of the pattern VEP is reflecting the particular vulnerability of the macular fibres to demyelination while the flash VEP reflects the integrity of fibres from a larger area of the retina. If the defects were specific to the macular, or foveal fibres, it would

be expected that they would be much more marked with the specifically foveal stimuli used in our study (as shown in the CSF results of the amblyopes in study 6.2). These were the 3^{o} field, 13 minute check VEP stimulus and the 1^{o} field, 12 c/deg grating used in the measurement of contrast sensitivity. Figures 6.4.1, 6.4.3 and 6.4.8 show that the pattern VEP delays and contrast sensitivity defects were approximately equal for low, medium and high spatial frequencies, and not more marked with the foveal stimuli. These results suggest that the defects exist in all the fibres transmitting spatial information, rather than the fibres from any specific retinal areas. Perhaps the specific vulnerability to demyelination is defined by the function, rather than the retinal location of the specific fibres. The CSF and de Lange curve results (Figures 6.4.7 and 6.4.8) do not suggest a specific defect of either the proposed X or Y system, but an overall defect of spatial and temporal processing.

The VEP amplitude results (Figure, 6.4.2, Tables 6.4.2. and 6.4.3) do not show a defect specific to the foveal area. On the contrary, there is no significant reduction in amplitude of any of the pattern components when the foveal stimulus (13 minute check, 3^{o} field) is used. Halliday (35) relates the amplitude of the 50 minute pattern reversal VEP to a psychophysical spatial measure, VA, showing that they parallel each other during recovery. It is suggested from the results of this study that the reduction in amplitude of the 56 and 19 minute pattern reversal and CII components are related to the psychophysical contrast sensitivity defects, while the normal amplitude of the components to foveal (13 minute) stimulation corresponds to the return of the VA of the affected eye to normal limits. However, it is surprising that the amplitude of the supposedly 'contrast

specific' CI component is not reduced in the affected eye for any of the check sizes.

Halliday (35) shows that the latency of the pattern reversal does not parallel the recovery of VA but remains delayed when vision has apparently returned to normal. The results of our study shown in Tables 6.4.2 and 6.4.3 also show that latency and amplitude measures appear to be independent of each other, an abnormality in one not necessarily corresponding to an abnormality of the other. The marked pattern latency delay is a stable phenomenon, believed to be related to the areas of demyelination slowing the transmission of impulses through the optic nerve (299). As such, it represents a temporal defect of the fibres transmitting spatial information.

A relationship was therefore sought between the magnitude of the relative VEP latency delays and psychophysical temporal defects measured in the study. This was done by determination of the correlation coefficient between the ratio of VEP latencies between the eyes and the ratio of flicker sensitivities (as previously shown in Figure 6.4.7). As evidence suggests that the de Lange curve represents two completely separate high and low frequency systems (226), the 3Hz and 30Hz were separately compared with the latencies of the three different pattern components to the 56 minute check.

Table 6.4.6 shows clearly that the relative defect at the high temporal frequency shows a very high correlation with the relative pattern VEP delay for all three components, particularly the pattern CI and CII components. This important finding indicates that the high temporal frequency psychophysical measures and the

Table 6.4.6 Correlation between VEP latency and psychophysical temporal measures

	LOW TEMPORAL FREQUENCY (3Hz)	HIGH TEMPORAL FREQUENCY (30Hz)
PATTERN REVERSAL	0.185	0.724
CI COMPONENT	0.506	0.892
CII COMPONENT	0.455	0.889
FLASH P2 COMPONENT	0.0026	0.198

pattern VEP latencies are reflecting the same processes in the optic nerve.

As the de Lange curve reflects luminance processing it was originally believed that it would relate closely with the flash latency results. However, Table 6.4.6 shows that this is not the case at all, with a negligible correlation between the two measures.

There have been very few investigations into the effect of demyelination on the de Lange curve (Section 4C23). The results of this study therefore provide an important contribution to this area of research. In particular, the discovery of a high correlation between the relative high temporal frequency defect and the relative pattern VEP delays has not previously been reported.

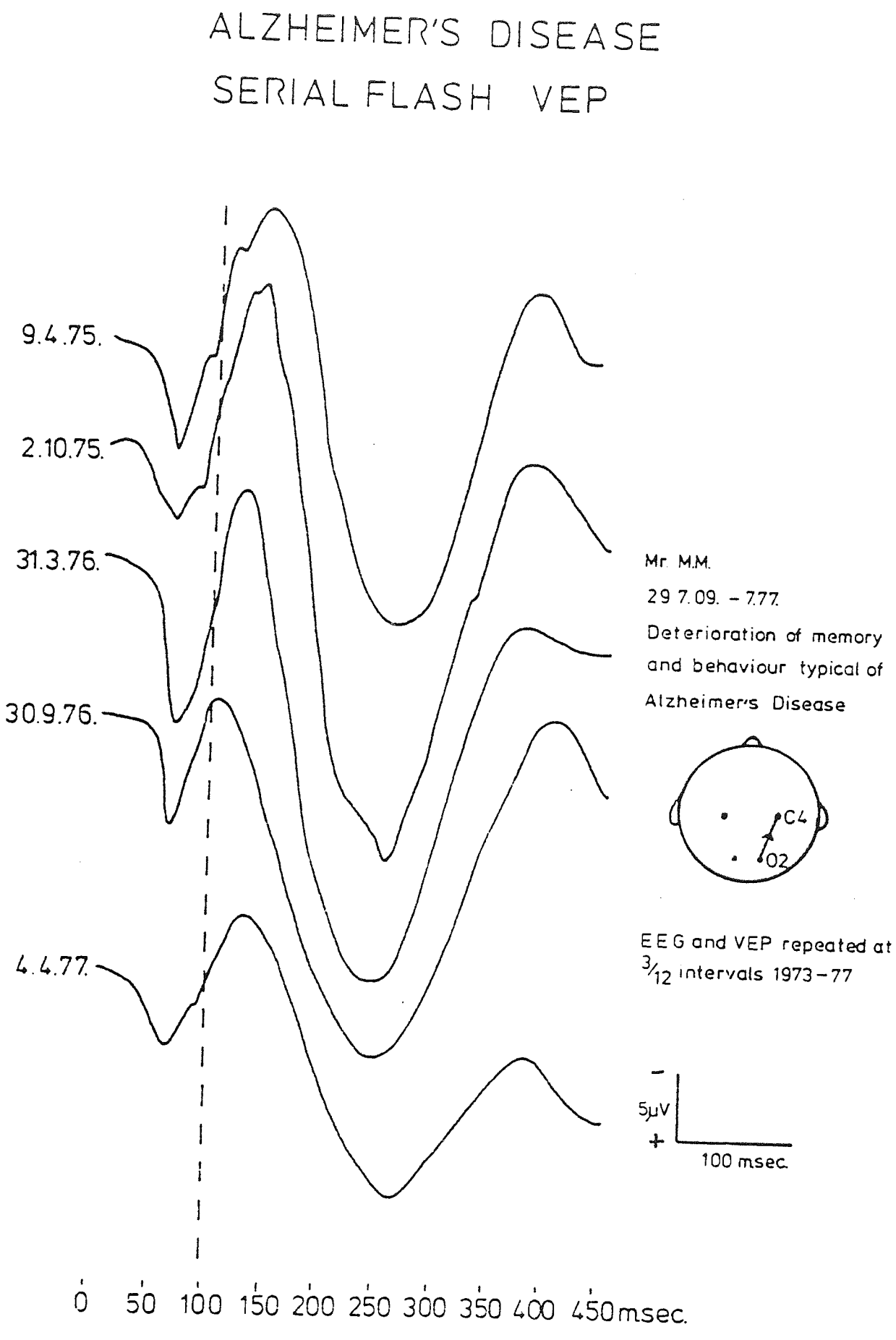
6.5 Dementia studies

65A Pilot studies - The interest of the Clinical Neurophysiology Unit in dementia began in the early 1970s when a Consultant at the Midland Nerve Hospital referred several patients with Alzheimer's disease for EEG and flash VEP recordings. One of these patients (MM) attended regularly every 3 months for 4 years until his death from the disease in 1977. This patient showed the EEG changes usually associated with Alzheimer's disease - diffuse theta activity and reduction of normal background alpha activity - and, in addition, a very delayed flash VEP (338). A selection of the serial flash VEPs recorded over this period up to 3 months before death are shown in Figure 6.5.1. A positive wave, presumably P_1, peaks at 60-70 msec, followed by a large positive component peaking at about 250 msec. Whether this component was an abnormally delayed P_2, or a P_3 component with a complete absence of P_2 was hard to determine, but the flash VEP was clearly markedly abnormal.

During one of the investigations, pattern reversal stimulation was attempted and, surprisingly, the VEP obtained was within normal latency limits. Similar results were observed in other patients with Alzheimer's disease attending the clinic, although the results were not investigated further at this stage.

This unusual co-existence of a markedly delayed flash VEP with a normal pattern reversal VEP has not previously been reported in any pathological condition. These findings therefore, once established, will provide a significant contribution to the use of the VEP in

Figure 6.5.1


ALZHEIMER'S DISEASE
SERIAL FLASH VEP
9.4.75.
2.10.75.
31.3.76.
30.9.76.
4.4.77.
Mr. M.M.
29 7.09. – 7.77.
Deterioration of memory and behaviour typical of Alzheimer's Disease
C4
O2
EEG and VEP repeated at 3/12 intervals 1973–77
5μV
100 msec.
0 50 100 150 200 250 300 350 400 450 msec.

PRE-SENILE DEMENTIA - CLINICAL DETAILS OF 12 PATIENTS

TABLE 6.5.1 INVESTIGATED BETWEEN APRIL 1971 AND MAY 1980

Initial	Age	E.E.G.	Visual Evoked Potential Latency of P2			Diagnosis	Other Clinical Indications.
			Flash	P.R.	Diff		
A.B.	69	Slow	150	-	-	Alzheimer's	
M.M.	66	Slow	250	120	130	Alzheimer's	Pneumoencephalography - lateral ventricles dilated. illusions, senile paranoia, incontinency.
E.S.	66	Slow	170	-	-	Alzheimer's	
E.G.	63	EMG Artifact	170	(EMG)	-	Alzheimer's	
B.K.	66	Slow low amp	170	100	70	Pre-Senile Dementia	Pneumoencephalography - Diffuse Atrophy.
K.T.	69	Normal	140	100	40	Arteriosclerotic Dementia	1977-Considerable Memory Deficit
W.C.	61	Normal Low amp.	130	105	25	Alzheimer's	Progressive deterioration of Alzheimer type. CAT Scan showed cerebral atrophy.
M.W.	57	Slow	150	108	42	Alzheimer's	Severely demented.
R.B.	57	Slow	150	100	50	Pre-Senile Dementia	Behaviour Changes. CAT-Scan-minimal cerebral atrophy.
L.V.	60	Normal	180	105	75	Pre-Senile Dementia	Forgetfulness
M.R.	53	Slow	130	95	35	Pre-Senile Dementia	Intellectual Impairment Forgetfulness.
G.W.	60	Slow	160	92	68	Alzheimer's	Severe cognitive impairment Preservation of personality
MEANS	62.25		162.5	102.7			

diagnosis. As they indicate a selective defect of the visual pathways they were of particular relevance to this project and so the author set out to establish the validity of these observations.

A retrospective study was carried out of the VEP records of the eight patients with a diagnosis of presenile dementia who had been investigated at the Unit over the previous eight years. These results were combined with those from four patients investigated by the author in 1980, and presented at the 18th ISCEV Conference in Amsterdam. The paper, which was subsequently published in the proceedings of the conference (362), (Appendix 4) compared the binocular flash VEP latency and the mean of the right and left eye 56 minute pattern reversal VEP latencies (mean of O_2 - C_4 and O_1 - C_3 derivations) (Table 6.5.1). The fact that most of these patients did not represent such an advanced stage of the disease as the original patient MM enabled a more reliable interpretation of the flash VEP waveform to be made. The P_2 component was delayed, compared with normal elderly controls, in ten of the twelve patients (mean latency 162.5 $\pm$ 31.9 msec). However, the pattern reversal latency was absolutely normal in all the nine patients in which it was recorded (mean latency 102.78 $\pm$ 8.17 msec) confirming our original observations.

The specificity of the unusual co-existence of a delayed flash P_2 component and normal latency pattern reversal major positive component can be characterised by subtracting the pattern value from the flash to give the difference between the two latencies (Table 6.5.1). A large flash-pattern latency difference value distinguishes a patient with presenile dementia from patients in which both latencies are normal (e.g. study 6.1), patients in which the flash latency is normal and pattern reversal is delayed (e.g. demyelination of the optic nerve

study 6.4 or refractive error - study 6.3) and those in which both latencies are delayed (e.g. acute optic neuritis (301)) as all these three possibilities would give a small, or even negative flash-pattern latency difference value.

The total number of demented patients investigated had increased to 18 when these results were reported at the scientific meeting of the EEG Society in May 1981 (363) (Appendix 4). Two control groups had been examined under identical conditions - a group of 17 normal controls of an equivalent age group and a group of 14 patients from the same psychiatric hospital who were suffering similar symptoms of forgetfulness, confusion and depression but did not show clinical signs of dementia. The mean flash P_2 latency and the mean flash-pattern latency difference value of the dementia group were shown to be significantly different from both of the control groups (statistical significance level $p < 0.01$) (Table 6.5.2) indicating these VEP abnormalities can be reliably attributed to the dementing process and not to associated factors such as confusion, depression, medication or hospitalisation. Preliminary observations also indicated that the CII pattern onset component was normal in latency in the dementia group, in common with the pattern reversal VEP.

These studies established the existence of the delay flash and normal pattern VEPs in known cases of dementia. However, for this unusual discovery to be of clinical use in the diagnosis of dementia it must be shown to be able to reflect the pathological changes in the early stages of the disease and to show a success rate that is equal to or better than existing diagnostic methods.

Table 6.5.2 Comparison of VEP latency results from dementia group with patient controls (P) and normal controls (N) - Pilot study

	DEMENTIA	CONTROLS	SIGNIFICANCE LEVEL (T test)
MEAN AGE (years)	61. 7 ± 5.7	P = 60. 4 ± 7.6 N = 61. 2 ± 4.4	
MEAN FLASH P2 LATENCY (msec)	153. 0 ± 27.9	P = 128. 8 ± 12.4 N = 129. 0 ± 6.9	$p < 0.01$ $p < 0.01$
MEAN PATTERN REVERSAL LATENCY (msec)	103. 8 ± 8.2	P = 105. 8 ± 8.5 N = 104 ± 5.8	Not sig Not sig
DIFFERENCE (msec)	47. 3 ± 27.1	P = 22. 3 ± 12.2 N = 24. 5 ± 8.3	$p < 0.01$ $p < 0.01$

The VEP results were presented in two groups - one containing the ten patients with well established dementia of 4-10 years duration, and the other containing the ten patients with presenile dementia of more recent diagnosis (Table 6.5.3). This classification was made by a Consultant Psychiatrist. A group of 20 "patient controls" with similar symptoms but diagnosed as suffering from depression, not dementia, was included as before (Table 6.5.4). The Tables show the VEP latency values alongside EEG and CT scan results. The latter results are categorised according to whether the results were consistent with a diagnosis of presenile dementia - an EEG showing diffuse theta activity and reduction of normal background alpha activity or a CT scan showing global atrophy - or whether the results were within normal limits. Non-specific abnormalities are also indicated. Table 6.5.5 shows the percentage of cases in which each test showed a positive result. A VEP result consistent with a

Table 6.5.3 Comparison of VEP, EEG and CT Scan Results in Patients with Pre-senile Dementia

GROUP 1 - Well established dementia of 4-10 years duration

Initial	Age	Flash P_2 (m.sec)	Diff.	EEG	CT Scan
AB	73	150		+	+
EG	69	170		+	
ES	66	170		+	
MM	67	250	130	+	+
BK	66	170	70	+	+
JT	62	163	51	+	+
GW	60	146	47	+	+
TK	62	145		+	+
JK	60	156	40	+	+
WC	61	130	25	NS	F
$\bar{X}$	64.6	165.0	60.5		
SD	4.3	32.3	37.1		

GROUP 2 - Pre-senile dementia of recent diagnosis

Initial	Age	Flash P_2 (m.sec)	Diff.	EEG	CT Scan
LV	60	160	60	NS	+
MW	57	150	42	+	-
RWo	67	166	57	NS	F
AS	67	150	41	+	
KT	68	140	40	NS	+
MR	53	144	47	+	+
ME	58	157	40	NS	F
MW	71	159	39	-	-
ER	59	129	33	NS	+
HG	67	132	30	-	F
$\bar{X}$	62.7	148.7	42.9		
SD	6.0	12.3	9.5		

Table 6.5.4 Comparison of VEP, EEG and CT Scan Results in Patients with Depression.

GROUP 3 - Patients with diagnosis of depression.

Initial	Age	Flash P_2 (m.sec)	Diff.	EEG	CT Scan
MC	42	130	21	Lateralised Abnormality	-
FC	52	132	27	NS	-
DC	62	123	21	NS	±
FC	61	139	24	-	
SC	66	140	25	-	-
TI	61	132	33	-	±
WJ	62	121	25	NS	
ML	51	126	23	NS	-
DL	64	138	28	NS	-
WL	60	136	36	-	-
EM	54	129	20	Focal Abnormality	-
EM	66	127	17	NS	-
HM	60	121	6	+	-
GP	56	134	32	-	-
GS	33	124	14	-	±
TS	59	123	20	-	-
MS	60	129	38	-	-
SS	60	126	6	NS	
CW	53	140	27	-	±
PB	51	140	44	+	-
$\bar{X}$	56.7	130.5	24.2		
SD	±7.5	±6.6	±9.2		

Key to Tables 6.5.3 and 6.5.4

EEG : + Diffuse theta activity & reduction of normal background alpha activity.
NS Non-specific abnormality
- No abnormality.

CT Scan : + Global atrophy
± Minimal atrophy
F Focal atrophy
- No abnormality

AGE RANGE	Flash (F) P2 COMPONENT (m.sec)	PATTERN REVERSAL (PR) major positive component (m.sec) 56' check	F - PR (Diff.)
70 - 79 (N = 10)	F 133 SD ± 8.15	PR 112.2 SD ± 8.1	+ 19.4 SD ± 5.9
60 - 69 (N = 10)	F 129.7 SD ± 7.5	PR 107.3 SD ± 9.4	+ 22.6 SD ± 9.2
50 - 59 (N = 10)	F 125.7 SD ± 5.15	PR 102.3 SD ± 6.2	+ 22.5 SD ± 4.1
40 - 49 (N = 10)	F 128.8 SD ± 6.45	PR 104.0 SD ± 5.5	+ 24.7 SD ± 9.0
30 - 39 (N = 10)	F 122.6 SD ± 11.05	PR 106.4 SD ± 5.7	+ 14.63 SD ± 10.6
20 - 29 (N = 10)	F 114.3 SD ± 11.45	PR 104.7 SD ± 7.8	+ 9.56 SD ± 8.1

Table 6.5.6 Mean flash and pattern reversal VEP latencies in normal adult controls

diagnosis of dementia consisted of a delayed flash P2 component with a large flash-pattern latency difference value. These were individually determined by comparison with the normal limits (mean $\pm$ 2 S.D) for the appropriate decade (Table 6.5.6). It must be noted that the VEP and EEG records were independently assessed by two observers, neither of whom knew the final clinical diagnosis. These results were presented in October 1982 at the 2nd Evoked Potentials Symposium in Cleveland, U.S.A. and have been accepted for publication in their proceedings (364).

Table 6.5.5 Comparison of VEP, EEG and CT scan results in patients with presenile -dementia. Showing percentage of cases in which the results were consistent with a diagnosis of dementia (non specific results in brackets)

	VEP	EEG	CT SCAN
1 WELL ESTABLISHED DEMENTIA (N = 10)	90% (-)	90% (10)	87.5% (12.5)
2 DEMENTIA OF RECENT ONSET (N = 10)	70% (-)	30% (50)	44.4% (33.3)
3 DEPRESSION (N = 20)	5% (5)	10% (40)	0% (20)

It can be seen that in well established dementia all tests show a positive detection rate of about 90%. However, in the detection of dementia of recent onset the VEP technique is clearly superior, with a positive detection rate of 70% compared with 30% for the EEG and 44.4% for the CT scan. In the patient control group with depression but no dementia, the CT scan was the most consistent as no patients showed global cortical atrophy, while 5% (1 patient) showed a VEP result outside the normal range. This patient (PB, Table 6.5.4) also showed an EEG abnormality consistent with presenile dementia and his clinical history is being followed with interest. Taking the incidence

of non specific abnormalities into account, the VEP technique appears to reflect the clinical diagnosis most accurately. The EEG appears to be sensitive to a wider variety of physiological disorders, as shown by the large number of reported non specific abnormalities in groups 2 and 3. One additional advantage of the VEP technique over the EEG and CT scan techniques is that the latter two require a subjective interpretation by a person experienced in the field. The VEP technique, however, provides a numerical result which, provided data on normal latency ranges is available, can be interpreted by any medical person.

The conclusion drawn from these pilot studies is that the co-existence of a delayed flash P2 latency with a normal pattern reversal latency (characterised by the flash-pattern latency difference value) indicates the presence of a dementing process in the brain. With respect to both early diagnosis and specificity this VEP abnormality is shown to be diagnostically superior to EEG and CT scan techniques.

6.5.B Main study

The 59 patients included in the main study were those investigated personally by the author. Of these, 17 were finally diagnosed by the Psychiatrists as suffering from dementia and their clinical details are shown in Table 6.5.7. Of the 42 who were eventually shown not to have dementia, on the basis of clinical diagnosis, four were excluded from the study because of ophthalmic pathology (cataract and glaucoma) and ten because of other cerebral pathology. From the remainder a patient control group of 17 was selected on the basis of age, attempting to match the two groups as closely as possible. The clinical details of this group are shown in Table 6.5.8. The patients excluded from

the patient control group are therefore mainly those under 52 years and those over 73 years of age. The normal control group of 17 was also selected on the basis of age. It was not possible to exactly age and sex match the dementia group with either the patient controls or normal controls because of the large predominance of females in the group with dementia and also the large number between 60 and 68 years. Details of all three groups are given in Table 6.5.9. The psychophysical tests in both the dementia and patient control groups were measured with one eye only (the eye with better VA if any difference existed) so the electrophysiological results also represent the values from the same eye. The results from the normal control subjects also matched those from the dementia group with respect to right or left eye.

Electrophysiological results - The monocular flash P2 latency of the 17 demented patients (mean 155.32 $\pm$ 24.87 msec) showed a delay which was significant at the 0.001 level when compared with both the normal and patient control groups (Table 6.5.10). The individual latencies are shown in Table 6.5.11 and it can be seen that the large standard deviation of the P2 latencies is partly due to patient LL who showed a large positive component at 241 msec. This patient has marked signs of dementia and was virtually mute at the investigation. She has been examined by psychiatrists in Birmingham and London, but the exact nature of the pathology causing her extreme symptoms has not been determined, although Alzheimer's disease is considered a strong possibility. Her VEP waveforms are shown in Figure 6.5.2 and it can be seen that the flash VEP is similar in configuration to that of the original patient investigated, MM. The VEP waveforms from a patient more typical of the dementia group, JK, are shown in Figure 6.5.3. The P2 component of the flash VEP is delayed, peaking at 167 msec.

TABLE 6.5.7 Dementia group - clinical details

P.P.D. = Primary presenile dementia

Aston University

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TABLE 6.5.8 Patient control group - clinical details

	DEMENTIA	NORMAL CONTROLS	PATIENT CONTROLS	
Psychophysics (N = 13)	11 females 2 males	9 females 4 males	6 females 7 males	
Mean Age (Years)	63.85 ± 6.47	62.23 ± 5.88	58.38 ± 4.89	
Range	52 - 73	50 - 71	51 - 66	
Electrophysiology (N = 17)	14 females 3 males	9 females 8 males	10 females 7 males	
Mean Age (Years)	63.06 ± 6.11	61.76 ± 5.41	58.53 ± 4.77	
Range	52 - 73	50 - 71	51 - 66	
Pupil Size (mm)	3.64 ± 0.75 SE 0.23	3.41 ± 0.77 SE 0.23	3.32 ± 0.90 SE 0.27	Variance ratio 0.452 (df 2/30) Not Sig

TABLE 6.5.9 Characteristics of dementia and control groups

		DEMENTIA		a) NORMAL CONTROLS b) PATIENT CONTROLS	Variance Ratio	df n/d	Signficance Level	
P1 COMPONENT	Latency (m.sec)	77.48 ± 13.01 SE 3.48	a)	69.86 ± 11.0 SE 2.94	2.805	1/26	Not Sig.	
			b)	74.11 ± 9.27 SE 2.48	0.625	1/26	Not Sig	
	Amplitude (uV)	8.81 ± 7.80 SE 2.16	a)	4.60 ± 4.15 SE 1.15	2.95	1/24	Not Sig	
			b)	6.06 ± 4.89 SE 1.35	1.167	1/24	Not Sig	
P2 COMPONENT	Latency (m.sec)	155.32 ± 24.87 SE 6.03	a)	127.41 ± 6.03 SE 1.46	20.222	1/32	p<0.001	* *
			b)	131.82 ± 6.83 SE 1.66	14.114	1/32	p<0.001	* *
	Amplitude (uV)	17.58 ± 11.09 SE 2.69	a)	10.12 ± 9.49 SE 2.30	4.447	1/32	p<0.05	*
			b)	11.81 ± 8.15 SE 1.98	2.993	1/32	Not Sig	
DIFFERENCE (m.sec) FLASH P_2 - 56 min P.REVERSAL		48.46 ± 27.35 SE 6.63	a)	21.16 ± 9.21 SE 2.23	15.21	1/32	p<0.001	* *
		51.12 ± 27.01 SE 6.55	b)	21.12 ± 11.28 SE 2.74	17.858	1/32	p<0.001	* *

TABLE 6.5.10 Effect of dementia on the flash VEP

TABLE 6.5.11 Dementia group - individual results

	AGE	VEP LATENCY (m.sec)			2-3	TYPE OF MEDICATION*
		1 FLASH P1	2 FLASH P2	3 56' P.REV		
ME	58	64.5	167	116	51	C1
JK	60	89.5	167	118.5	48.5	E, E, E, E
MR	54	66	155.9	102	53.9	C1, A, A
ER	58	72.5	139	96	43	A
JT	62	87.75	158.5	111	47.5	-
LV	60	102	155	99.5	55.5	E
RWo	65	82.5	147.5	102	45.5	A, E
GW	60	-	157.5	88.5	69	E
LL	57	53.5	241	98.5	142.5	B, E, E
HG	67	-	129	105	24	-
MB	71	72	124.5	109.5	15	-
RB	57	72.5	151	115.5	35.5	B
MN	71	88.5	155.5	114	41.5	-
EP	64	84.5	148.5	120	28.5	B
AS	67	-	146	106.5	39.5	D
RWe	73	65	154	106	48	C2, D, A, D2, E
LC	68	84	143.5	108	35.5	C1, D1, E
	63.06 ± 6.11	77.48 ± 13.01	155.32 ± 24.87	106.85 ± 8.56	48.46 ± 27.35	

* Key to Drug Groupings

A Sedatives/Tranquillisers

B Major tranquillisers

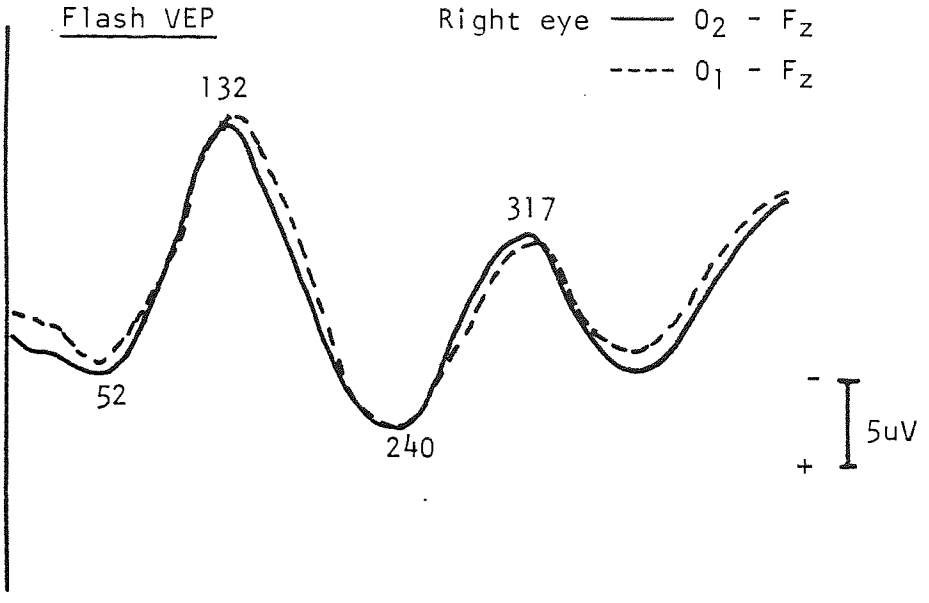
C Antidepressants 1. Tricyclic
2. Tetracyclic
3. Lithium

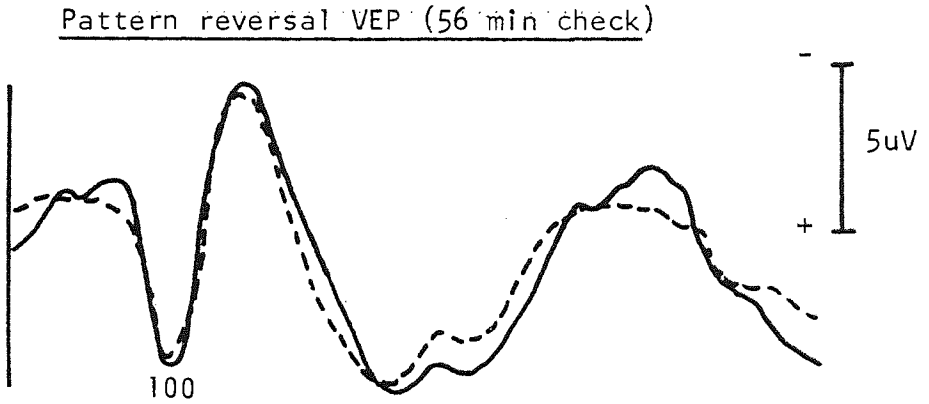
D 1. Drugs for Parkinsons disease
2. Drugs to combat Parkinson-like side effects ot other drugs.

E Miscellaneous

Figure 6.5.2 Showing the coexistence of a markedly abnormal flash VEP with normal pattern VEP in one patient

Mrs L L aged 57 years. Diagnosis of either primary presenile dementia or encephalopathy





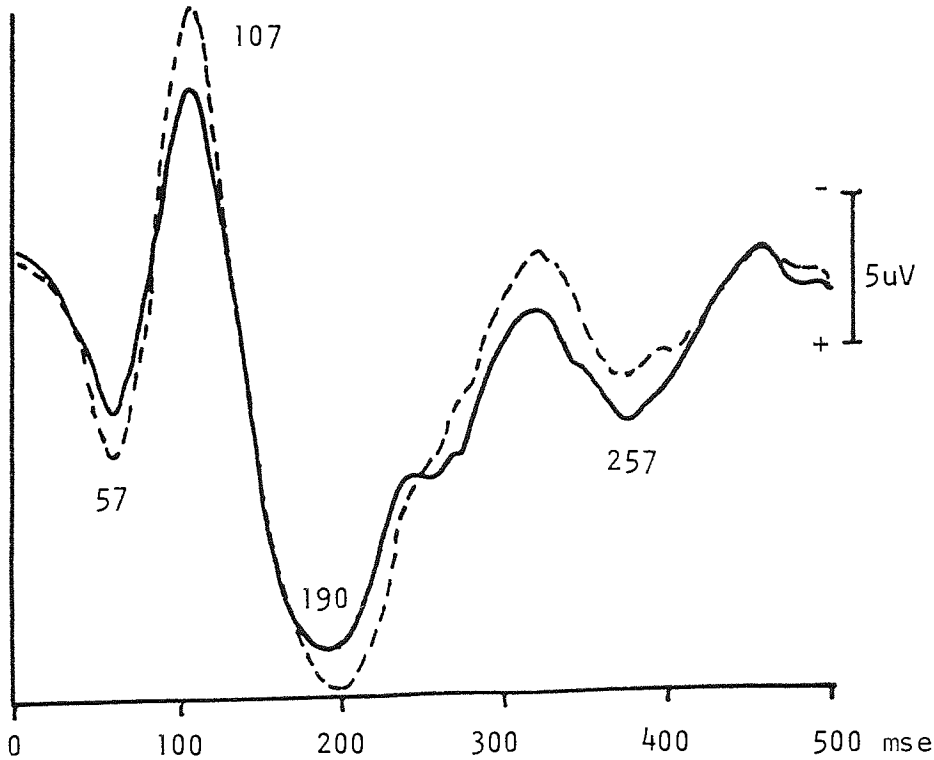
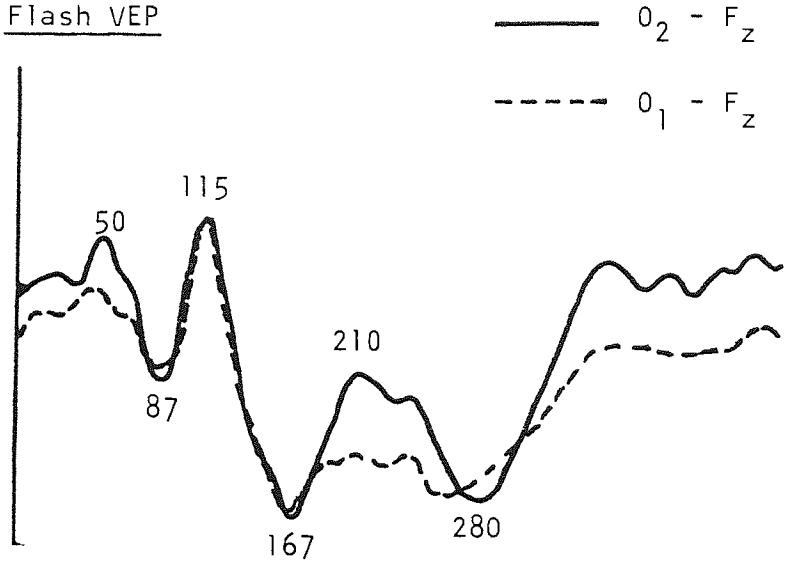


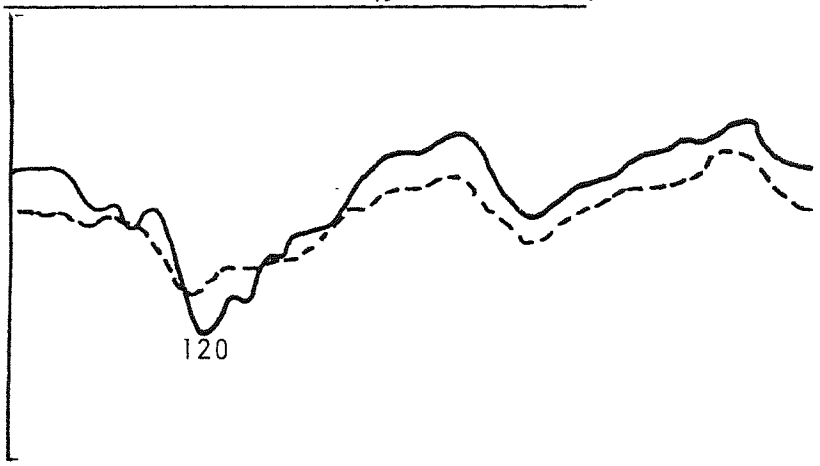
Figure 6.5.3 Flash and pattern VEPs in primary presenile dementia

Mrs J K Age 60 years Right eye

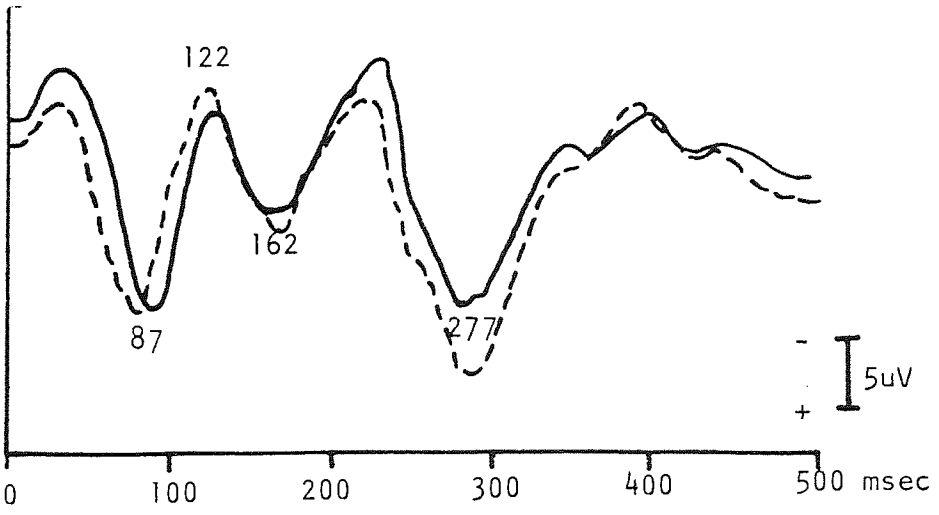
Flash VEP



Pattern reversal VEP (56 min check)



Pattern onset-offset VEP (56 min check)



These two figures clearly show the remarkable nature of the results, in that flash VEPs of such delayed P2 latency and, in the case of LL, abnormal waveform can coexist with such normal pattern VEPs. This study confirmed that the latency of the pattern reversal, and also the CI and CII onset components, for 56, 19 and 13 minute checks showed no significant difference between the dementia group and either the patient or normal controls. Table 6.5.12 only shows the comparison between the dementia group and normal controls for pattern reversal and CII onset components as a representative selection. Figure 6.5.4 clearly shows the large difference between the flash and pattern reversal latencies for the dementia group, compared with the two control groups.

The subtraction of the 56 minute pattern reversal latency, from the flash P2 latency, gives the flash-pattern latency difference value. Table 6.5.10 shows that the mean difference value of the dementia group is much larger than the mean values for both the normal and patient control groups - the results being significant at the 0.001 level in both cases. It has already been shown that it is the combination of the delayed flash and normal pattern latency, defined by the flash-pattern latency difference value, which characterises the abnormality specific to dementia. The use of the difference value in conjunction with the flash latency value therefore acts as a control in excluding the diagnostic possibility of other pathological conditions which might cause a flash delay associated with a pattern delay.

A further confirmation of the specificity of the VEP abnormalities described in dementia was provided by examination of the results from the patients who were not included in either the dementia or the

patient control groups due to clinical evidence of other cerebral conditions. Brief details of these ten cases are shown in Table 6.5.13. It can be seen that the group includes a variety of disorders including a high proportion of patients with cerebral atrophy shown by the CT scan. Comparisons of the results with ten normal controls show no significant difference between the groups for both flash P2 latency (mean for pathology group 138.05 $\pm$ 16.40 msec variance ratio 3.827 df 1/18) or for the flash-pattern latency difference value (mean for pathology group 21.2 $\pm$ 12.59 msec, variance ratio 0.014 df 1/18).

These results establish that the delayed flash and normal pattern latency findings described in this study are in some way specific to the dementing process and are not just reflecting the presence of cortical atrophy. The possibility that these VEP latency results are in some way connected with the medication being taken by the patients with dementia was excluded by comparison with the patient control group. The drugs being taken by the individual patients in both groups are shown in the clinical details in Table 6.5.7 and 6.5.8. The non-proprietry names are given, and the drugs are classified according to their mode of action under the following main headings:

A	Sedatives/Tranquillisers
B	Major Tranquillisers
C	Antidepressants
D	Drugs for Parkinsonism
E	Miscellaneous non-psychiatric drugs

Inspection of Tables 6.5.7 and 6.5.8 show that the drug groupings are

approximately balanced in the dementia and patient control groups. The only exception was the major tranquilliser Chlorpromazine (or Largactil) which was taken by patients LL, RB and EP in the dementia group, but none of the patient control group. Inspection of the results in Table 6.5.11 shows that the flash delay and large flash-pattern latency difference value is not specific to these patients. However, to conclusively establish this, the patient controls were compared with the dementia group excluding patients LL, RB and EP. The difference between the mean flash P2 latencies in the two groups was still significant at the 0.001 level (variance ratio 22.66 df n = 1 d = 26). Similarly, the mean flash-pattern latency difference values also showed a difference between the groups which was significant at the 0.001 level (variance ratio 26.623 df n = 1 d = 26) establishing that both these markedly abnormal latency results are not due to the effects of medication.

Table 6.5.10 shows that the N2-P2 amplitude is significantly higher in the dementia group than the normal controls ($p<0.05$). This is consistent with other published studies of the flash VEP in presenile dementia (352). However, the difference in mean amplitude is not significant when the dementia and patient controls are compared. This indicates that the increased N2-P2 amplitude is not specific to the dementing process and is related to associated factors common to both patients groups, such as the medication.

A final important point shown in Table 6.5.10 and Figure 6.5.4 is that the flash P1 component in the dementia group is normal with respect to both latency and amplitude when compared to both normal and patient control groups. The presence of a P1 of normal latency in a flash VEP

		Check (min)	DEMENTIA		NORMAL CONTROLS		Variance Ratio	df n/d	Significance Level
PATTERN REVERSAL	LATENCY (m.sec)	56	108.23	± 8.10 SE 2.44	107.41	± 9.08 SE 2.74	0.595	1/20	Not Sig.
		19	112.55	± 7.77 SE 2.34	108.77	± 9.37 SE 2.83			
		13	112.91	± 10.60 SE 3.20	111.46	± 11.73 SE 3.54			
	AMPLITUDE (uV)	56	9.70	± 8.17 SE 2.46	8.26	± 5.33 SE 1.61	0.110	1/20	Not Sig
		19	9.34	± 7.13 SE 2.15	12.54	± 8.86 SE 2.67			
		13	5.76	± 4.18 SE 1.26	6.64	± 2.58 SE 0.78			
CII PATTERN ONSET	LATENCY (m.sec)	56	108.91	± 10.44 SE 2.69	107.29	± 9.62 SE 2.48	0.120	1/28	Not Sig
		19	109.52	± 26.1 SE 7.53	110.38	± 9.55 SE 2.76	0.011	1/22	Not Sig
		13	130.5	± 14.89 SE 4.96	123.23	± 13.27 SE 4.42	0.729	1/16	Not Sig
	AMPLITUDE (uV)	56	14.15	± 6.34 SE 1.64	9.86	± 7.53 SE 1.94	2.849	1/28	Not Sig
		19	9.9	± 5.11 SE 1.48	18.42	± 19.85 SE 5.73	2.332	1/22	Not Sig
		13	9.71	± 5.70 SE 1.90	12.42	± 10.34 SE 3.45	0.331	1/16	Not Sig

TABLE 6.5.12 Effect of dementia on the pattern VEP

Figure 6.5.4 The effect of dementia on flash and pattern reversal latency

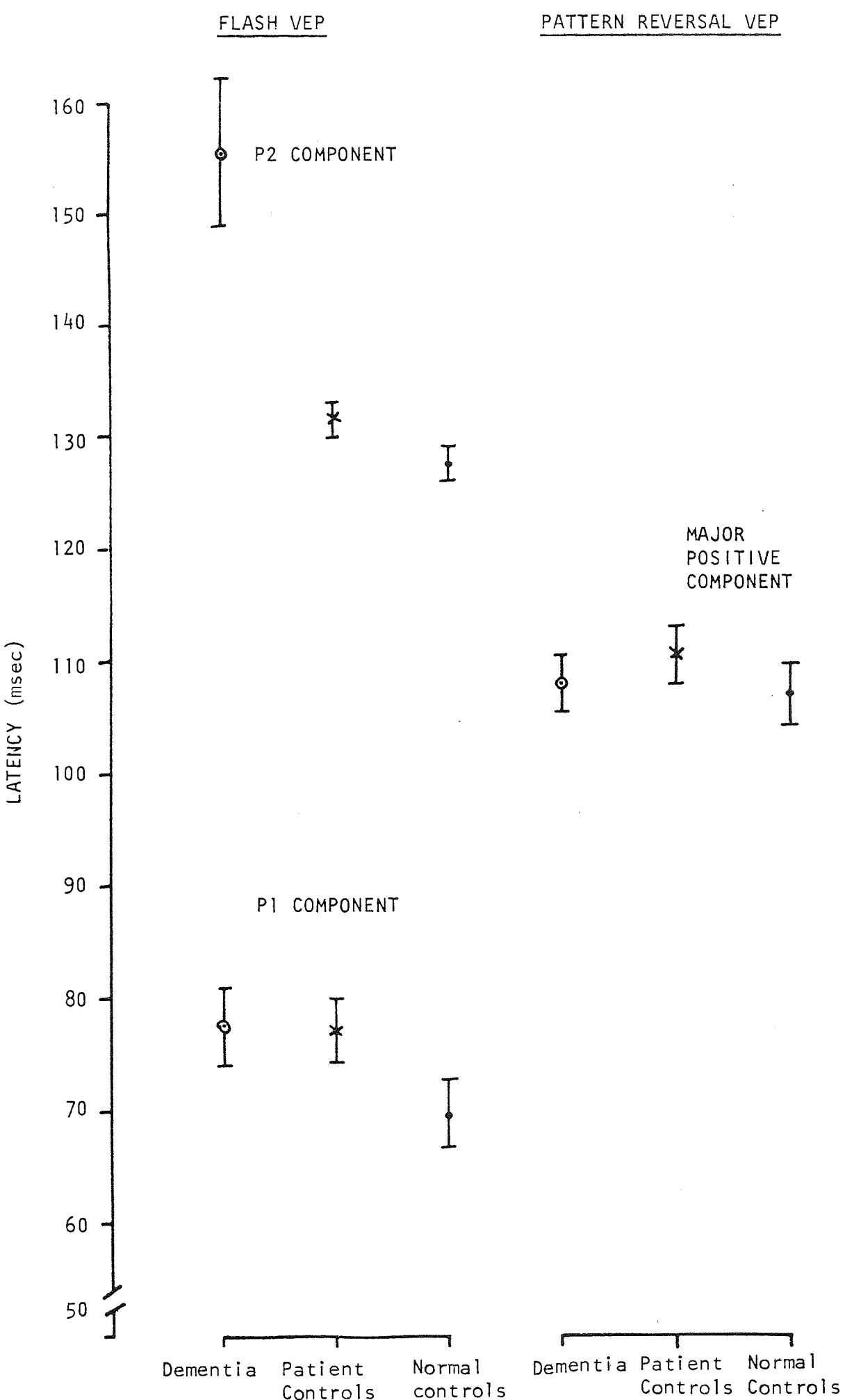


Table 6.5.13 Clinical details for patients with cerebral conditions other than dementia.

INITIALS	SEX	AGE	DIAGNOSIS	CT SCAN*
IB	F	61	Encephalopathy	
HC	M	61	Korsakoff's syndrome	++
RF	M	49	Meniere's disease and Depression	--
SH	M	59	Paranoia	++
GL	M	76	Cerebro vascular disease & Depression (now deceased)	+
LM	M	76	Folate deficiency and Depression	
AN	M	59	Folate deficiency and Anxiety Depression	--
GP	M	62	Korsakoff's syndrome	++
JS	M	64	Cerebro vascular disease/ Infarct	++ frontal
CW	F	65	Capgrass syndrome	±

* Key to CT Scan Results:-

++ : marked atrophy

+ : cerebral atrophy

± : minimal atrophy

- : no atrophy.

(NB. CT Scan not performed on patients IB and LM).

with markedly delayed P2 is extremely interesting and will be discussed in a later section.

Psychophysical results - There have been no known previous reports on the psychophysics of vision in dementia. In view of the gross abnormality of the flash VEP and the selective nature of the VEP abnormalities, the investigation of spatial and temporal measures of vision in these patients provides a very interesting area of study.

In general, the patients with presenile dementia of the Alzheimer type showed a preservation of personality and a willingness to cooperate in the psychophysical tests. However, two were too demented to be able to co-operate. Patient LL stared straight ahead throughout the entire investigation with no spoken communication, which made the recording of VEPs very easy, but the psychophysical measurements impossible. However, a whispered response to the familiar VA test was eventually obtained. The other severely demented patient, GW, was unable to respond to any of the psychophysical tests.

Of the remaining 15 patients with dementia, one, ME, had VAs of $^{6}/_{36}$ and $^{6}/_{18}$ due to cataracts and was therefore excluded from the psychophysical measurements. The CSF of EP was not measured due to malfunctioning of the oscilloscope, and HG was originally investigated before the flicker apparatus was completed and refused to attend for any of the subsequent follow-up appointments requested by the psychiatrist. This leaves a final total of 15 VA results, 13 CSF and 13 de Lange curve measurements.

Ofthose patients able to participate in the tests, many were apprehensive and initially slow to understand and respond. To a certain extent,

the ascending and descending method of limits cancelled out the effect of the slowness of response. The span of attention was also limited in many cases and much encouragement was necessary. It was therefore particularly important in the psychophysical measurements that a patient control group was used, as the same psychological difficulties were encountered in this group.

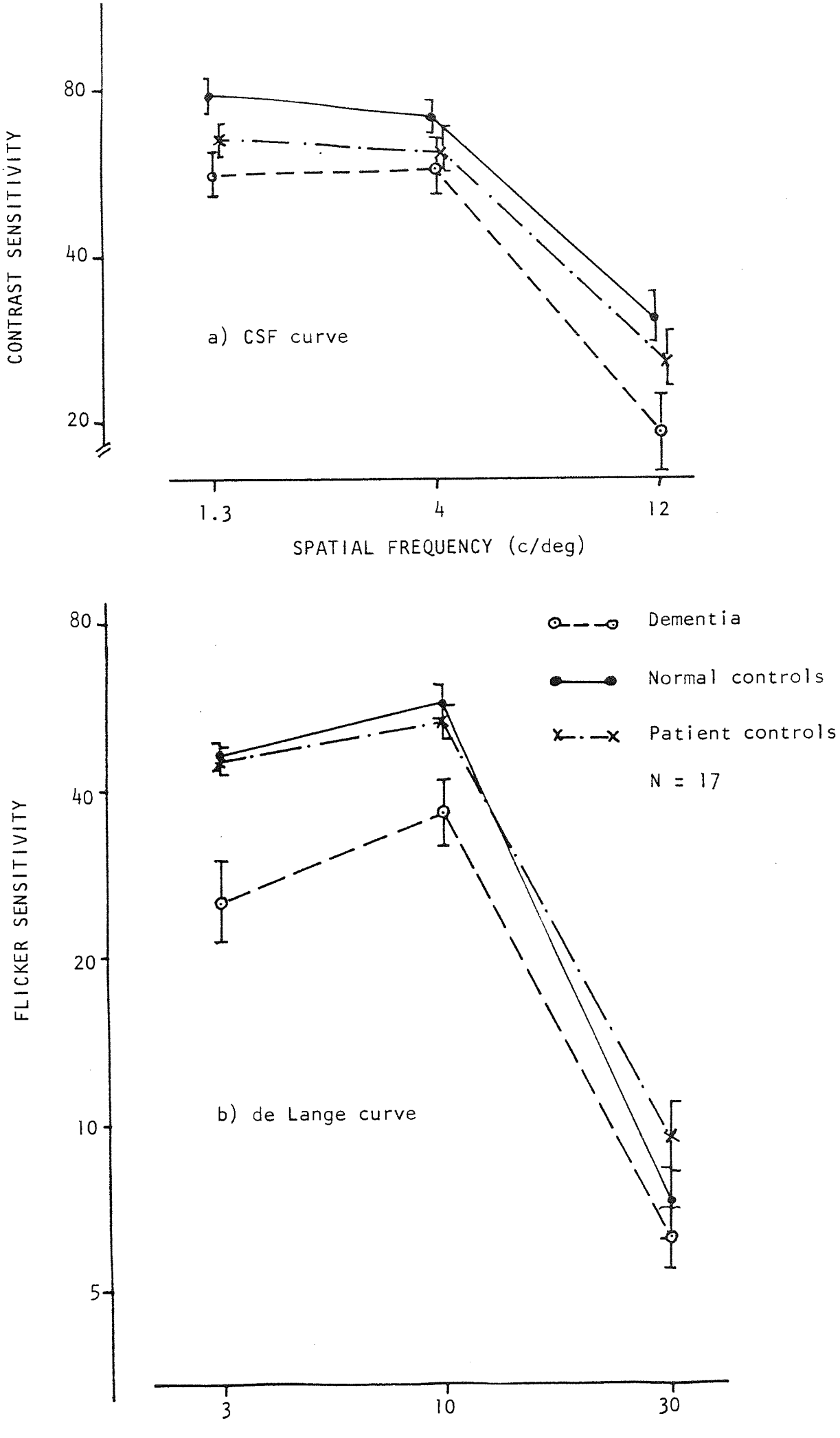
Examination of the mean psychophysical results for the three groups (Table 6.5.14) show this to be the case. When compared with the normal controls (mean VA $^{6}/_{5}^{-1}$) the VA of the dementia group (mean $^{6}/_{6}^{+1}$) is significantly lower ($p<0.01$). However, no significant VA difference is found when compared with the patient control group (mean VA $^{6}/_{6}^{+2}$), indicating that psychological factors are involved. In addition, the mental state of the patients meant that the optimum refractive correction could not be determined as accurately in the two patient groups as in the normal control group. Similarly, the CSF results of the dementia group appear to be reduced when compared with normal controls ($p<0.025$), but show no significant difference from the results of the patient control group (Figure 6.5.5). The conclusion that is drawn from these results is that they show no psychophysical defect of spatial processing that is specific to the group of patients with dementia.

The flicker sensitivity of the demented patients, however, was found to be significantly reduced when compared with both the normal and patient control groups ($p<0.01$) (Table 6.5.13). Figure 6.5.5 shows that this reduction in flicker sensitivity is particularly pronounced at low and medium temporal frequencies. This reduction is clearly specific to the demented patients, as shown by comparison with the

		DEMENTIA	a) NORMAL CONTROLS b) PATIENT CONTROLS	Variance Ratio	df n/d	Significance Level	
VISUAL ACUITY		1.029 ± 0.136 SE 0.035	1.173 ± 0.130 SE 0.034	a) 8.803	1/28	p<0.01	* *
			1.043 ± 0.238 SE 0.061	b) 0.043	1/28	Not Sig.	
LOG CONTRAST SENSITIVITY	a) 1.3 c/deg	1.756 ± 0.138 SE 0.038	1.893 ± 0.113 SE 0.03				
	4 c/deg	1.751 ± 0.178 SE 0.049	1.860 ± 0.113 SE 0.03	a) 7.314	1/24	p<0.025	*
	12 c/deg	1.284 ± 0.242 SE 0.067	1.494 ± 0.161 SE 0.045				
	b) 1.3 c/deg		1.808 ± 0.09 SE 0.025				
	4 c/deg		1.788 ± 0.128 SE 0.036	b) 1.848	1/24	Not Sig	
	12 c/deg		1.414 ± 0.16 SE 0.44				
LOG FLICKER SENSITIVITY	a) 3 Hz	1.406 ± 0.27 SE 0.075	1.663 ± 0.125 SE 0.035				
	10 Hz	1.565 ± 0.211 SE 0.059	1.763 ± 0.119 SE 0.033	a) 7.823	1/24	p<0.01	* *
	30 Hz	0.793 ± 0.199 SE 0.055	0.85 ± 0.231 SE 0.064				
	b) 3 Hz		1.650 ± 0.133 SE 0.037				
	10 Hz		1.717 ± 0.108 SE 0.030	b) 8.732	1/24	p<0.01	* *
	30 Hz		0.978 ± 0.234 SE 0.065				

TABLE 6.5.14 Effect of dementia on psychophysical measures of vision.

Figure 6.5.5 Effect of dementia on the spatial and temporal MTF showing mean ± 1 standard error of mean



patient controls. Luminance differences would not be expected to produce a low frequency defect, (226) and were excluded as there was no significant difference in pupil diameter between the three groups (Table 6.5.9).

Discussion - The work reported in this study firstly confirms the delay of the flash P2 component reported by other VEP studies of dementia (352, 47). However, the discovery of the co-existence of a normal pattern VEP in such cases has not previously been reported. Considered together, these results, specified by a large flash-pattern latency difference value give a type of VEP abnormality which appears to be specific to dementia. The studies show that the VEP abnormality is not shown in patients with depression, confusion and forgetfulness or other cerebral pathology which causes cerebral atrophy, and is not due to the medication taken by the patients with dementia. It has also been shown that this VEP diagnostic finding is superior to EEG and CT scan results with respect to specificity and early diagnosis.

The importance of research into the diagnosis of dementia has been emphasised by reports of the Medical Research Council (320) and Royal College of Physicians (319) and it is believed that the results of these studies make a significant contribution to this area of research. The clinical importance of these VEP techniques is confirmed by the fact that, since the preliminary results were reported in 1981 (362), over 100 patients have been referred by Birmingham Psychiatrists for investigation at our Unit. Applications for funding to employ the author to continue this research has been given scientific approval by the Board of the Mental Health Foundation and have been successful

in procuring funding for 3 years from the charity 'Age Research'.

As well as contributing to the problem of the clinical diagnosis of dementia, these results provide some insight into the brain processes reflected by the VEP.

Research into the biochemical enzyme reduction (331) and reduction in cerebral blood flow (340) in dementia of the Alzheimer type have shown that the pathological changes are most evident in the temporal-parietal-occipital areas (Figure 4D1) which includes the areas in which the VEP is generated. Of particular relevance to the delayed flash P2 latency and normal pattern reversal latency found in our studies are the findings of Gustafson's group (340) which showed, by measurements of the cerebral blood flow, that defects in Alzheimer's disease are found in the association areas, while the primary projection areas are comparatively spared. This corresponds to the clinical signs that dementia is a "global impairment of higher cortical function" (319).

These findings would explain the normal pattern VEP in dementia, as the pattern response is believed to be generated in the primary visual projection areas, as suggested by topographical studies (e.g. 13, 33, 9). This is confirmed by studies of the effect of cortical lesions on the pattern reversal VEP by Blumhardt and Halliday (365). One of their conclusions particularly relevant to our research is that:

> " a striking feature of the pattern reversal technique appears to be its insensitivity to even widespread cortical destruction provided that the geniculo-cortical pathways and occipital generator areas in the cortex are intact".

The implications of the completely normal pattern VEPs found in our study are therefore that the pathological processes in Alzheimer's disease have completely spared the geniculo-cortical pathways and primary projection areas. In addition, the psychophysical results indicate that spatial processing in these patients is unaffected up to the highest levels of visual processing. The review of the work of Blumhardt and Halliday (365) ends with the conclusion:

> " The pattern reversal technique provides a simple and reasonably sensitive method for the functional examination of the primary visual pathway and the cortical generators of the VER. Whether a further development of the technique or the discovery of an appropriate visual stimulus will allow the detection of lesions beyond the primary visual projection pathway remains a challenge for future investigation".

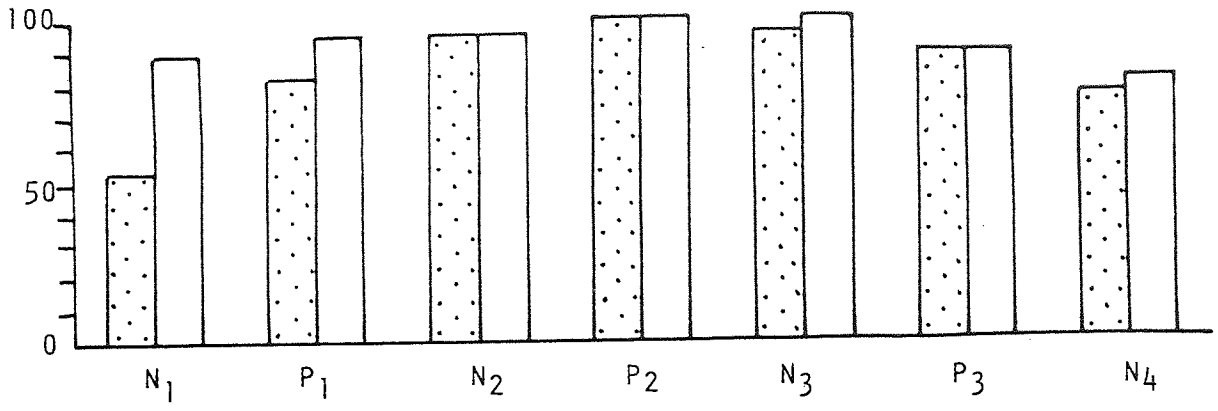
The VEP findings described in this study answer this challenge as they provide a diagnostic criterion for detection of lesions at a higher stage of cortical processing. Ironically, the "appropriate visual stimulus" which reveals these higher cortical abnormalities is the unstructured flash which has lost popularity since the introduction of patterned stimuli in the late 1960s and early 1970s.

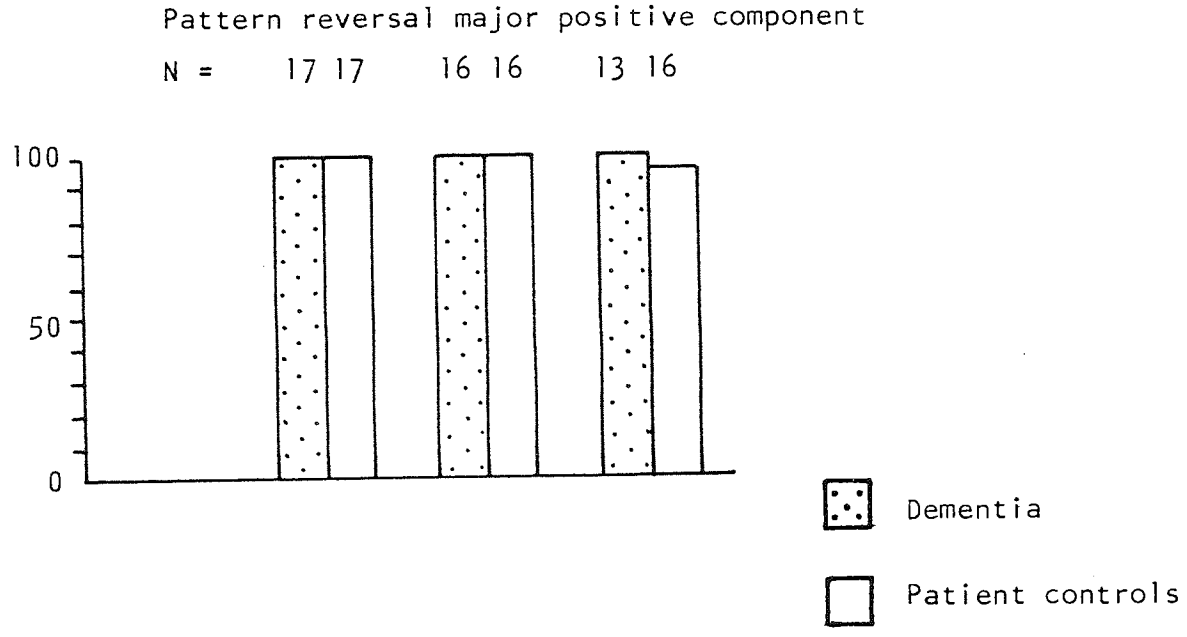
The delay of the P2 component of the flash VEP is in itself unusual, summaries of the diagnostic use of the flash VEP in neuroophthalmology showing that pathology affecting the flash VEP usually causes a reduction in amplitude, or absence of components (301, 366). The

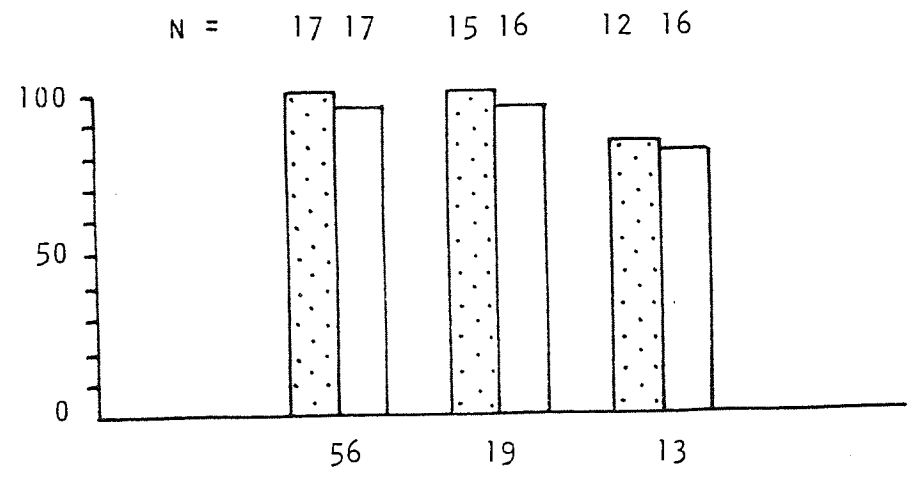
few cases in which the flash VEP is delayed represent such marked pathology of the visual pathways that the pattern VEP is completely abolished (301). Our results are remarkable in two respects, firstly, in that the waveforms of all the VEPs were not altered (with the exception of the flash VEP of LL shown in Figure 6.5.2) so that all the components could be easily identified (Figure 6.5.6) and secondly, in the magnitude of the flash P2 delay which is equivalent to the remarkable pattern delay found in demyelination of the optic nerve (Section 6.4). The VEP results in dementia, specified in our group by a mean flash-pattern latency difference value of about 50 msec (Table 6.5.10) could be described as an exaggerated ageing response. Section 6.1 shows that the latency of the P2 flash component increases with age, while the latency of the 56 minute pattern reversal major positive component is only slightly affected. This leads to an increase in the mean flash-pattern latency difference value from 1.77 $\pm$ 22.2 msec in the 10-19 year age group to 19.4 $\pm$ 11.8 msec in the 70-79 year age group. The clinical symptoms of presenile and senile dementia have often been described as similar to an exaggerated form of ageing.

The presence of a flash P2 delay has been shown by our study, and that of Cosi et al. (47) not to be directly connected with the presence of cortical atrophy. It appears that the two techniques reflect different aspects of the pathological process - the CT scan showing anatomical features, while the VEP reflects physiological functioning. From current research on the nature of the pathological processes in dementia it appears probable that the delay of the P2 flash component is caused by defects in neural transmission caused by reduction in the transmitter substance acetylcholine. This

Figure 6.5.6 Dementia study. Percentage of subjects in which each VEP component could be identified







CHECK SIZE (minutes of arc)

reduction has been shown to be greatest in the temporal and parietal cortex and hippocampus (331).

Research into the topographical distribution of the flash VEP has shown that it is more diffuse and widespread in distribution than the localised pattern VEP (51, 52, 64) and does not show results consistent with the retinotopic organisation of the visual cortex in studies of visual field defects caused by cortical damage (365). Ciganek (40) suggested that the early flash components (N1, P1 and N2) are generated in the primary visual cortex, while the later components (including P2) are generated in secondary visual cortex. Spekreijse, Estevez and Reits (92) also compared this to their study of steady state luminance VEPs in which they proposed that the high frequency response originates in the primary visual cortex, the medium frequency response in the secondary visual cortex, and that the low frequency response is not generated in a specific cortical region, but is distributed more widely over the scalp. Finally, Schwartz and Chaney are reported (170) as proposing that a high frequency processing system is located in the visual cortex and lateral geniculate body while the low frequency system is located in the tectal region.

Taking these theories into account, the normal latency of the P1 flash component in dementia, found in our study, is consistent with its proposed origin in the primary visual cortex (40), an area which has already been shown by the pattern VEP in our study to be unaffected in dementia. The psychophysical flicker results showed relatively little reduction at high temporal frequencies in dementia which, from the above theories and results of our studies, would be consistent with an unaffected geniculo-cortical

pathway and primary visual cortex.

The interpretation of a flash VEP with a P1 component of normal latency and a delayed P2 component could either be that it represents serial processing of the visual signals through unaffected lower to affected higher cortical areas or that it represents the combined effect of separate signals transmitted through separate pathways. Apart from the main geniculo-striate pathway, fibres from lower visual centres are known to innervate the visual cortex. For example, fibres from the pulvinar, an association nucleus in the thalamus, innervate the visual association areas 18 and 19 (367). The medium and low temporal frequency defects found in our psychophysical measures on patients with dementia indicate, from the theories described above, that the lower visual centres are affected by the dementing process, and raise the possibility that the fibres transmitting the P2 signals pass through these areas, rather than the geniculo-striate pathway. Alternatively, these results could be interpreted as showing that the higher visual processes responsible for the perception of low temporal frequency flicker are located in the association areas which are affected in dementia, and in which the flash P2 component is generated. A more detailed study of these possibilities would be very interesting but is beyond the scope of the present study.

CHAPTER 7 CONCLUSIONS

7 CONCLUSIONS

The study of conditions representing selective defects of vision and the visual pathways reported in Chapter 6 have led to the following conclusions about the visual processes reflected by the psychophysical and electrophysiological measures used in the clinical studies.

7.1 Psychophysical tests

Spatial measures - Measurement of visual acuity (VA) is universally understood and provides a result which can be directly compared with other research work, or hospital records. Its advantage in our study lay in its use as a quick screening test for the detection of ocular pathology or refractive error. However, the clinical studies showed that the measurement of the contrast sensitivity function (CSF) contributed a large amount of additional information on the spatial vision of the patients. It was found that measurement of the CSF was no more difficult for the patients to understand than VA measurement - of the 17 patients with dementia, only two were unable to respond to CSF measurement and one was unable to respond to measurement of VA.

Examples in which the CSF revealed information not shown by the VA are found in four of the clinical studies. Despite a VA of $^{6}/_{6}$ or better in all the control subjects in Study 6.1, measurement of the CSF was sensitive enough to reveal that there was a deterioration in the processing of high spatial frequencies with age, believed to be largely due to a deterioration in the quality of the retinal image. In Study 6.2, VA measurement indicated that the

quality of vision in the amblyopic eye and the optically blurred eye of each subject was identical. However, CSF measurement showed that the overall visual impairment was much greater in the optically blurred condition. The CSF results clearly showed that the visual defect in amblyopia is confined to high spatial frequencies. VA and CSF measurement proved to be superior to the VEP in revealing the visual defects in amblyopia. In the study of unilateral optic neuritis (6.4), VA testing alone would have indicated that the VA of the affected eye in individual cases was within normal limits (although statistical analysis of the group data showed that the VA of the affected eye was consistently lower than that of the unaffected eye). However, assessment of the CSF showed a marked overall visual impairment. These latter results showed that a marked contrast sensitivity reduction at high spatial frequencies can co-exist with a normal VA of $^{6}/_{6}$.

Temporal measures - The measurement of the de Lange curve in these clinical studies has provided new information not previously reported, which give an insight into the visual processes which transmit temporal information.

The measurement of flicker sensitivity at the highest temporal frequency (30Hz) proved very sensitive to the reduction in the luminance of the retinal image with age caused by the decrease in pupil area (Study 6.1). This reveals a substantial reduction in visual performance in normal subjects that is not usually recognised. As would be expected, the de Lange curve was not affected by optical blur (Studies 62B and 6.3). However, some amblyopic subjects in Study 62A showed a small relative decrease in flicker sensitivity at low temporal frequencies, consistent with the theory that amblyopia

represents a selective defect of the X system. Demyelination of the optic nerve, however (Study 6.4) appears to affect all spatial and temporal frequency mechanisms approximately equally and is not specific to either the X or Y system.

The de Lange curve results of studies 6.4 and 6.5 suggest that measures of high and low temporal frequency are reflecting completely separate systems. They also show that the transmission of temporal information is closely related to the latency of the VEP. The high correlations between pattern latency delays and flicker sensitivity defects in optic neuritis suggest that the high temporal frequency system is connected with the transmission of spatial information in the geniculo-striate pathway to the primary visual cortex. Low temporal frequency information, however, appears to be processed in a different part of the brain. The selective medium and low temporal frequency defects and flash P2 delay found in dementia indicate that the two measures reflect similar processes. As dementia particularly affects the higher association areas, it is possible that these areas are responsible for the perception of low temporal frequency flicker. Clearly, measurement of the de Lange curve in these studies has revealed valuable information about visual processing which is not shown by other psychophysical measures.

7.2 Visual evoked potential

These studies have shown that the pattern and flash VEP cannot be considered as independently reflecting spatial and temporal (or luminance) visual processing respectively. Psychophysical spatial measures are believed to be mainly related to pattern VEP amplitude, although changes in the spatial stimulus parameters can also produce latency changes, as shown by the optical blur study. Latency measures were found to be more informative in these cases. Psychophysical temporal measures have been shown to be related to the latency of both the pattern and the flash VEP. The amplitude of the flash VEP does not appear to relate to either of these concepts. The most significant amplitude changes of flash components found in our studies appeared to be related to developmental or hormonal factors in teenage controls and were also shown by the pattern reversal and the pattern onset-offset VEP.

VEP measures associated with spatial visual defects - In the amblyopia study (6.2) the only measure which showed any significant difference between the two eyes was the amplitude of the 19 minute Cl onset component. No significant latency differences were found. In optic neuritis (Study 6.4) amplitude reductions accompanied latency increases and are presumed to reflect the contrast sensitivity defects. However, in these two neural conditions, amplitude measures did not show a differentiation between 'contrast specific' and 'contour specific' processes or any consistent relationship with spatial psychophysical measures. For example, in optic neuritis, which represents a marked overall contrast sensitivity reduction but normal VA, the amplitudes of the CII onset and the pattern reversal major positive components were reduced but the Cl component

showed no amplitude reduction. However, in amblyopia, which represents a marked VA reduction but a CSF reduction which is limited to high spatial frequencies, the amplitude of CI is reduced. This is opposite to the effect that would be predicted from theoretical studies on the responses of the components to different stimulus variables which indicate that CII is a 'contour specific' component and CI and the pattern reversal major positive are 'contrast specific' components (39).

The optical blur study (6.3) which measured the response of an intact visual system to an optically degraded stimulus, showed latency results which were consistent with the above hypothesis, (although the reduction in amplitude with blur did not differentiate between the components). The increase in latency produced by optical blurring of the stimulus was found to be more marked for the CII onset component - which is believed to be reflecting both the reduction in contrast and the reduction insharpness of the image - than for the CI and reversal components - which are believed to reflect the reduction in contrast only.

These results suggest that theories derived from the study of spatial stimulus parameters in normal subjects can only be applied to similar conditions, and not necessarily to visual defects produced by neural defects of the visual pathways.

Throughout the clinical studies no significant differences were found between the results recorded from the 'foveal' midline electrode 4% above the inion, and the mean of $O_2 - O_1$ (F_z reference in both cases). This is probably due to individual variations in

cortical architecture between patients and shows that precise location of responses cannot be predicted in studies using large numbers of patients or subjects. This does not, however, prevent the use of such theories in studies of VEP topography in individuals with known localisation characteristics (e.g.10).

VEP measures associated with temporal visual defects - The results of these studies have shown that the visual mechanisms which transmit high and low temporal frequency information are connected with the latency of the pattern VEP and flash P2 components respectively. In these latency measures, no differentiation between the behaviour of the pattern reversal, CI and CII onset components was found.

The latency of the pattern VEP is accepted to be an extremely sensitive indicator of demyelination of the optic nerve. These marked latency increases shown in the optic neuritis study (6.4) and the normal latencies found in the study of dementia, which is believed to be a pathological process affecting the association areas, but not the primary projection areas, (Study 6.5) confirm that the pattern VEP reflects the integrity of the optic nerve, geniculo-striate pathways and the primary visual cortex.

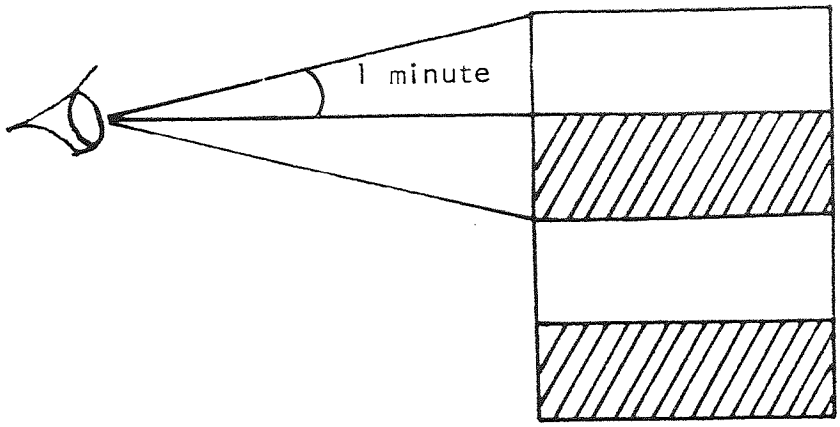
The P_1 and P_2 components of the flash VEP are found to show different characteristics, suggesting that they are generated in different areas of visual cortex. In the study of ageing in normal controls (Study 6.1) the latency of the P1 component did not significantly change with age, while the latency of the P2 component increased by 20 msec between the 10-19 and 70-79 year age groups. In the study

of dementia (6.5) the flash P_2 latency could show a delay of the order of 40 msec (and, in exceptional cases appeared to be delayed by 110-120 msec) while the latency of the P_1 component remained within normal limits. These results are interpreted as showing that the flash P2 component is generated in the higher association areas, while the P_1 component is generated in the primary visual cortex. Study 6.5 showed the flash P_2 component to be related to psychophysical low temporal frequency processing. The P_1 component, being generated in the same area as the pattern VEP, would be more closely related to high temporal frequency processing. A relationship between P_1 and high temporal processing, and P_2 and low temporal frequency processing is consistent with their respective latencies in the flash VEP.

The combination of a delayed flash P_2 and a normal latency P_1 and pattern VEP therefore reflects the pathology of the higher association areas and sparing of the primary projection areas which exists in dementia. This unique finding appears to be specific to dementia and therefore has an important diagnostic application. The author is now beginning full time research into the development and extension of these findings. It is intended that this research will include longitudinal studies monitoring the course of the disease and investigation of different forms of dementia and other related psychiatric conditions, with the aim of establishing a comprehensive diagnostic service for the West Midlands Psychiatric Hospitals.

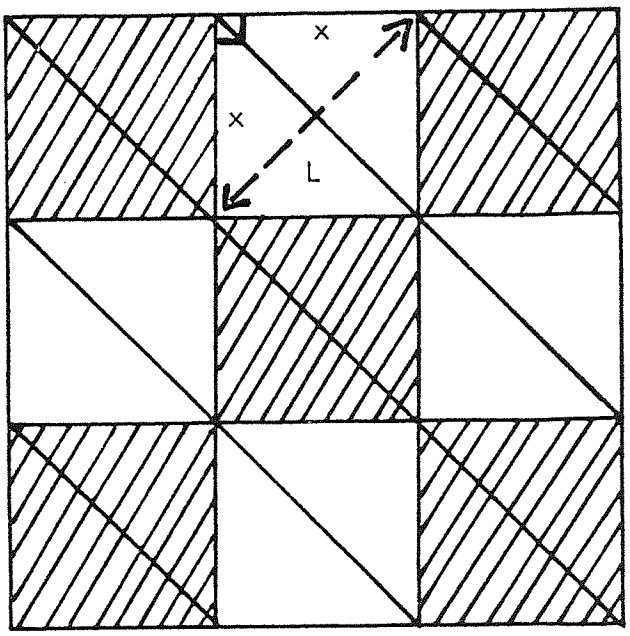
APPENDICES

APPENDIX 1 Relationship between VA measures and spatial frequency of grating and checkerboard stimuli



a) VA of $^{6}/_{6}$ is equivalent to a grating in which each bar subtends 1 minute of arc at the eye, representing a spatial frequency of 30 c/deg

b) Comparisons of the spatial frequency of gratings and checkerboards should consider the fundamental frequency. In a checkerboard the fundamentals are at 45 and 135° to the edges of the checks (98, 99, 287). The diagram shows that the wavelength (L) of the fundamental is equivalent to the side length of the check (x) in minutes of arc multiplied by $\sqrt{2}$. The spatial frequency is the reciprocal of this value



$$L^2 = 2x^2$$

$$L = \sqrt{2} \cdot x$$

56 minute check ≡ 0.76 c/deg
19 minute check ≡ 2.24 c/deg
13 minute check ≡ 3.37 c/deg

APPENDIX 2

TECHNIQUES USED IN THE DIAGNOSIS OF DEMENTIA (SECTION 4D)

i) MEASUREMENT OF CEREBRAL BLOOD FLOW

Briefly, 133 Xenon (a gamma-emitting insert and diffusible tracer) is introduced into the cerebral blood circulation either by inhalation or injection into one of the internal carotid arteries. The progress of the isotope is measured by multiple scintillation detectors over the labelled hemisphere.

ii) ASSESSMENT OF CORTICAL ATROPHY

Previous techniques for the assessment of cortical atrophy included Pneumoencephalography, in which air is inserted via a lumbar puncture into the cerebro spinal fluid, allowing outlining of the ventricles. Conventional X ray plates of the head had the disadvantage of being a 2 dimensional representation of a 3 dimensional object and so it was difficult to distinguish individual structures.

The Computerised Axial Tomograph (CT scan) overcame this problem by presenting a series of pictures of 'slices' of the cranium, each slice being unaffected by structures either side. This technique is about 100 times more sensitive than conventional methods in showing variations in the soft tissues of the brain and represented a major advance in the assessment of cortical atrophy. A detailed description of the technique can be found in the introductory article by the designer, Hounsfield (368) and the following brief summary is taken from that account:

A beam of X-rays is passed through the head and measured by a scintillation detector, from which the absorption value at the point on the head is calculated. 28,000 absorption measurements are taken to sample every point at every angle across the slice of head under examination. These absorption values are fed into a computer and the absorption value at every point within the slice is calculated. These values can be printed out, or the results can be displayed in the form of a picture in which the most dense structures are white, the least dense structures black, and intermediate values as shades of grey.

The structures of the head are identified and any abnormality in their shape, size or position are noted. Changes in tissue density are then identified. Increases in density could be due to blood clots, or calcium deposits in tumours or other lesions. Lowered tissue density could be caused by tissue necrosis, oedema, cyst formation or haemorrhage with no clotting (369).

The detection of tumours can be enhanced by intravenous injection of substances containing large atoms (eg Sodium Iothalamate) to artificially enhance the tissue density (369). Normal pressure hydrocephalus is not readily diagnosed by CT scan (341).

iii) THE ELECTROENCEPHALOGRAM

The electroencephalogram (EEG) is a record of the electrical activity of the brain. A detailed account of this technique can be found in the textbook by Cooper, Ossleton and Shaw (370).

In brief, the procedure is as follows: About 20 small disc electrodes

are attached to the scalp with glue and the potential difference between the electrodes is amplified and recorded with pen writers on continuously moving paper. The arrangement of the electrodes is designed to sample the different areas of the brain and is standardised according to the 10-20 system of Jasper (26). The area of brain under observation at any one time is determined by the settings on the EEG machine and the activity of up to 16 channels can be observed simultaneously, depending on the equipment available.

The rhythmical electrical EEG activity is classified on the basis of frequency (371). The alpha rhythm (8-13 c/sec) is recorded over the posterior parts of the head during wakefulness and is attenuated or abolished by visual attenuation. It is most evident when the eyes are closed. Slowing of the alpha rhythm can be due to ageing, clouding of consciousness, metabolic disorders or other cerebral pathology, or the effect of certain drugs, such as anticonvulsants. Activity greater than 13 c/sec is known as beta activity and is of generalised distribution over the scalp. Focal or lateralised beta activity can be indicative of cerebral pathology, while frequencies in excess of 20 c/sec can be due to the action of drugs such as barbiturates and benzodiazepine compounds.

Theta activity (4-7 c/sec) is conspicuous in children, becoming less prominent with maturation. It is less common in older subjects, except during drowsiness or hyperventilation, particularly in females. Focal or lateralised theta activity may be indicative of cerebral pathology, while diffusely distributed theta activity can be found in patients with many different neurological and metabolic disorders. Activity slower than 4 c/sec - delta activity - is an abnormal finding in the EEG of an awake adult, as it usually only occurs during sleep stages 3 and 4. It is the predominant rhythm in infants.

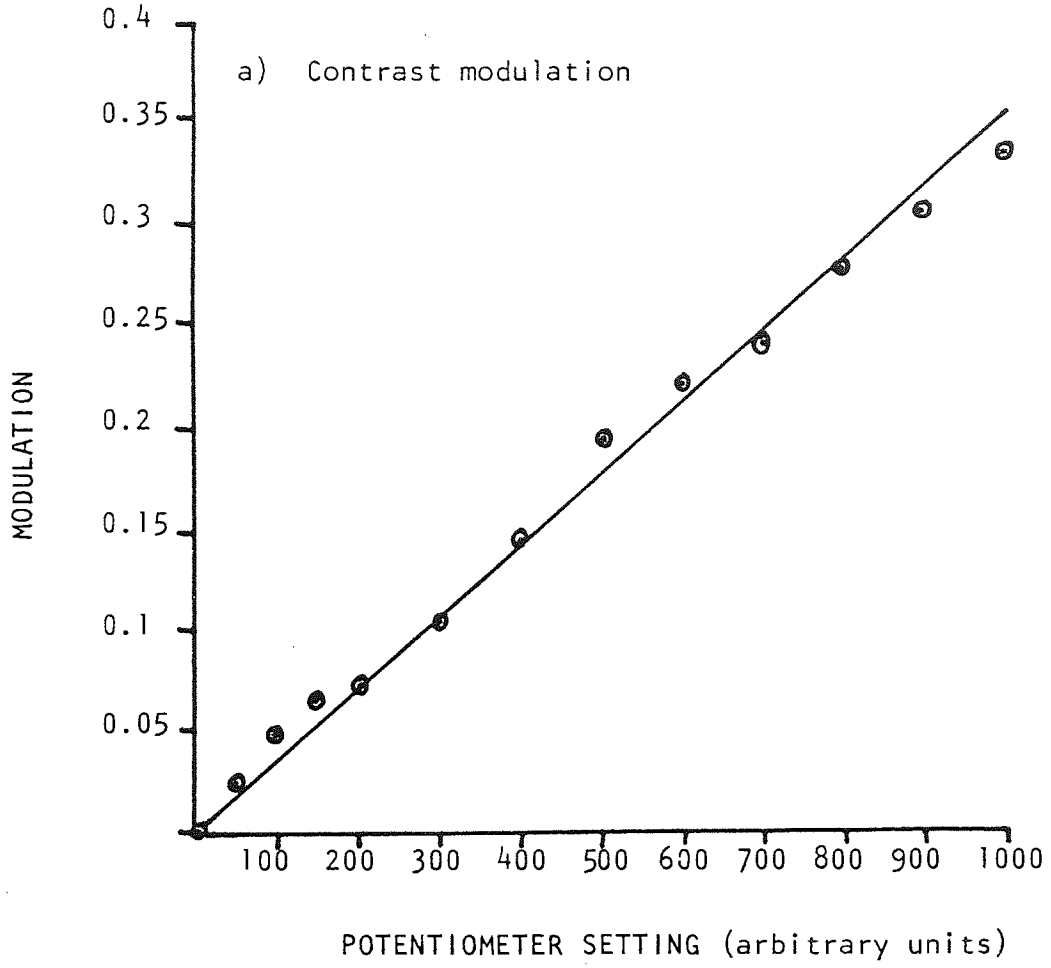
APPENDIX 3

Calibration of modulation values:

(i) Spatial MTF - The maximum and minimum luminance of the sinusoidal grating on the oscilloscope were measured at 13 potentiometer settings with a Spectra mini spot photometer. Contrast was calculated for each setting using the equation : contrast = L max - L min/ L max + L min. These values were plotted against potentiometer setting (Figure A31) and the slope of the best fit line drawn by eye through these points and zero was found to be 0.35×10^{-3} . This factor was used for the conversion of all other potentiometer settings to contrast values.

(ii) Temporal MTF - A similar method was used for the calibration of the sinusoidally modulated flicker source. A luminance profile of the sinusoidal modulation for 8 potentiometer settings was obtained using a photocell connected through an amplifier to an X-Y plotter (Figure A32). Maximum and minimum luminance values were determined by comparison with tracings obtained from luminances of known value, and contrast calculated from the equation: Modulation = L max - L min/ L max + L min. The slope of the best fit line drawn by eye through zero and the plots of these contrast values against potentiometer setting is 0.295×10^{-3} (Figure A31). This value was used in the conversion of all other potentiometer settings to modulation values.

Figure A3.1 Calibration of equipment used in the measurement of spatial and temporal modulation functions



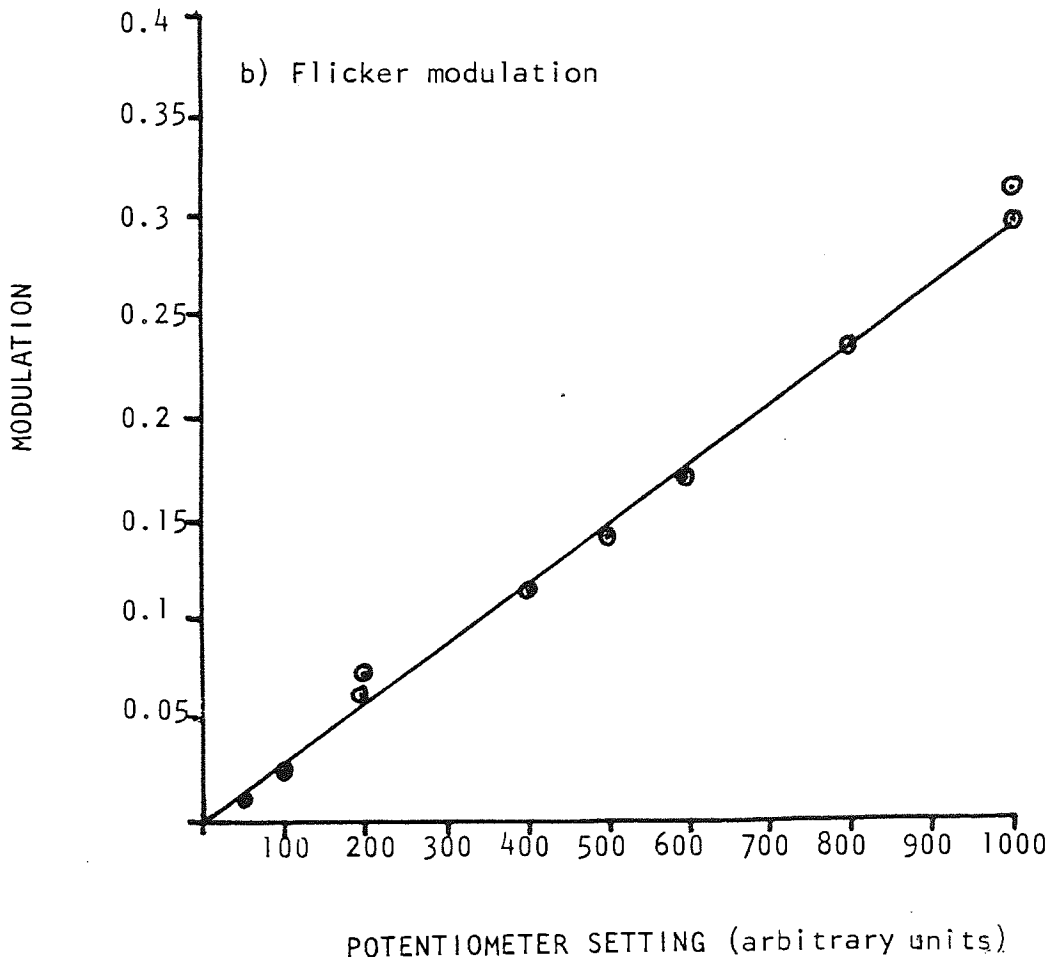


Figure A32 Luminance profiles of sinusoidal modulation of the 2° flicker source measured directly from apparatus with a photocell

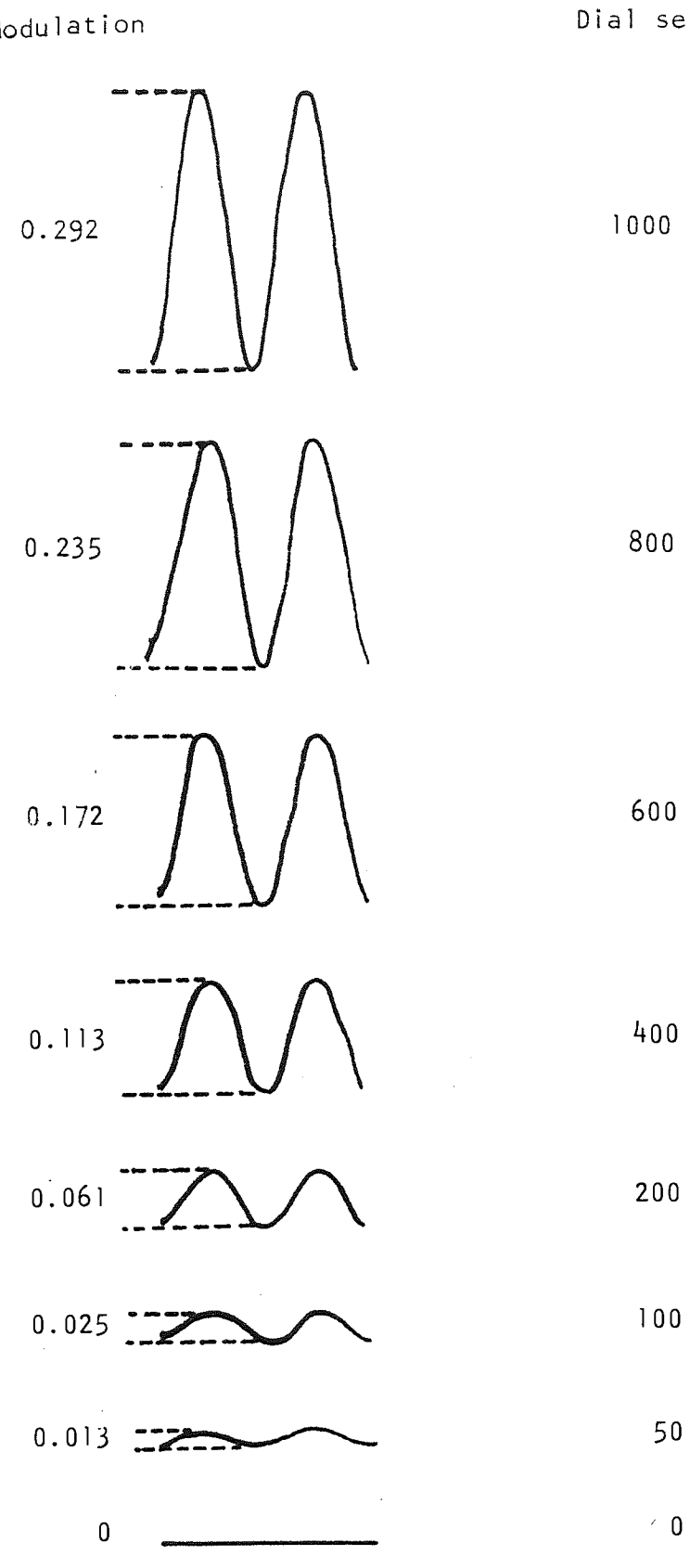


Figure A33 The full CSF curve measured with the method described in this project. Each point represents the mean ± 1 standard error of 10 normal subjects aged between 18 and 27 years. Dashed lines mark the spatial frequencies used in the clinical studies

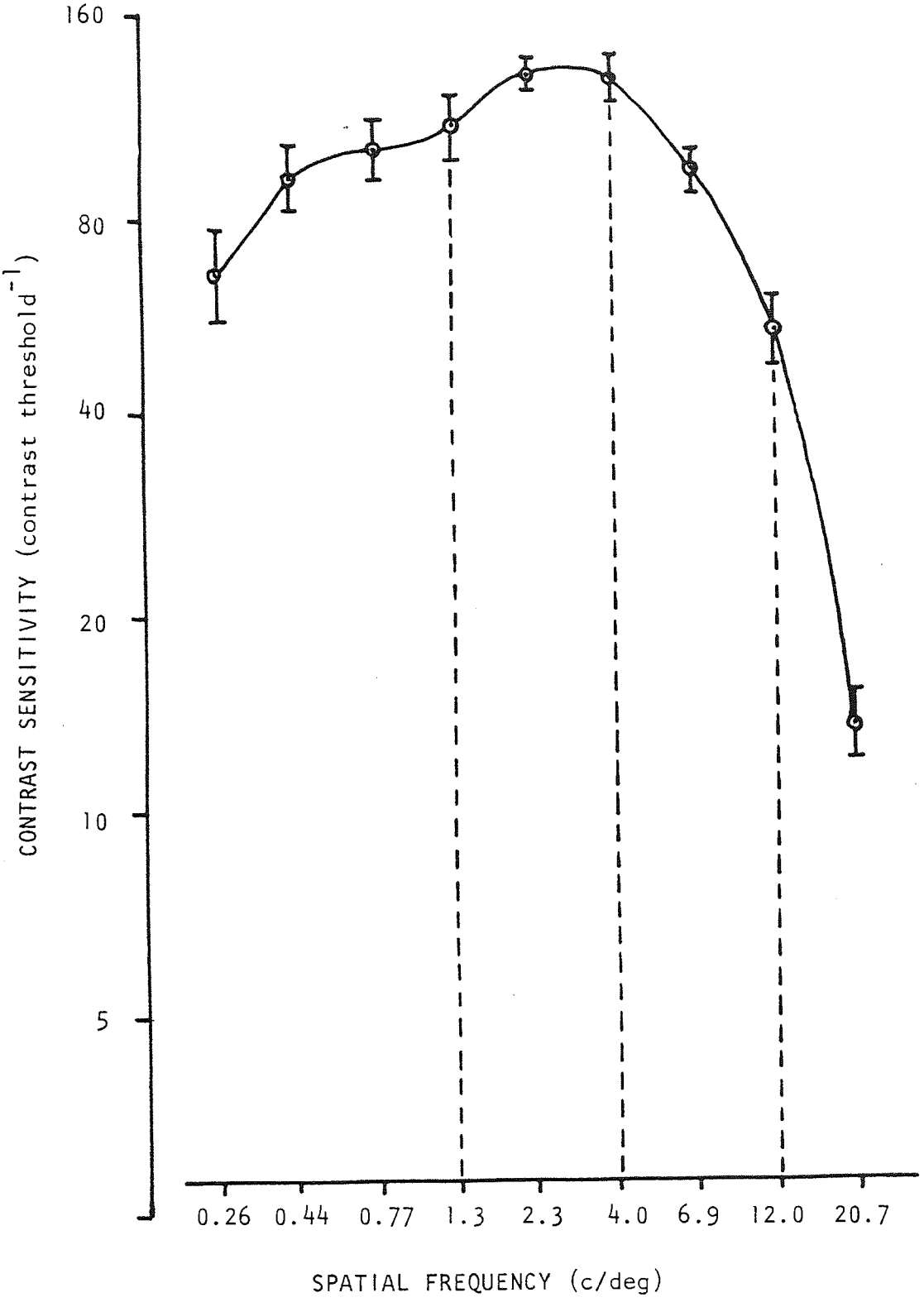
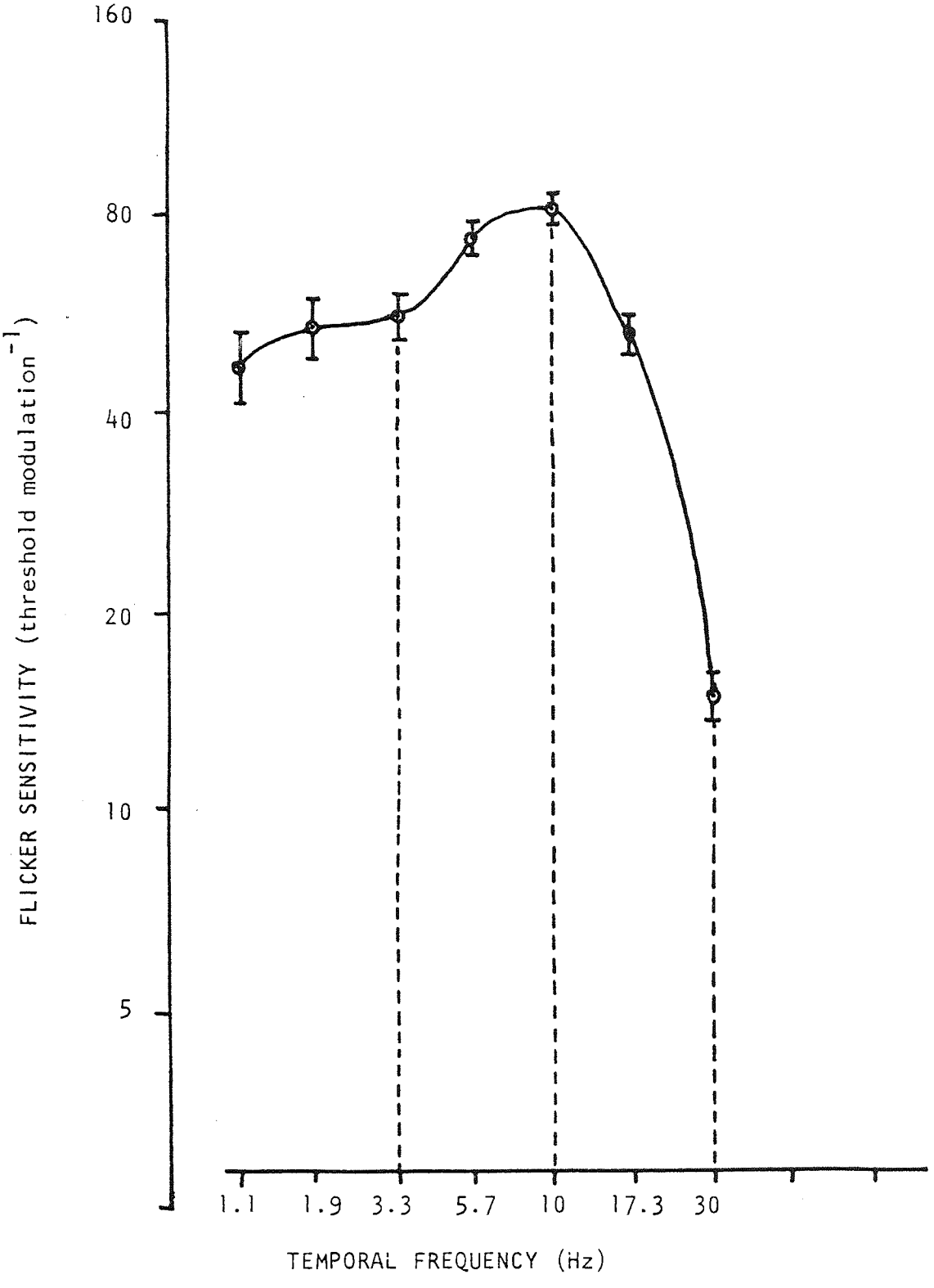


Figure A3.4 The full de Lange curve measured with the apparatus described in this project. Each point represents the mean ± 1 standard error of 10 normal subjects aged between 21 and 30 years. Dashed lines mark the temporal frequencies used in the clinical studies



APPENDIX 4 - PUBLICATIONS

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