ASSESSING CHILDRENS VISUAL ACUITY WITH STEADY STATE EVOKED POTENTIALS

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The material contained in the Thesis is the work of the author apart from the following: Michael Bradnam implemented the part of the system that collects data on the DSP card then passes it to the main program for analysis (section 5.4), and designed the study in section 5.3.2 to compare the speed and sensitivity of detection statistics. Ruth Hamilton performed ssVEP recordings on the 80 children investigated in chapter 4, and assisted in the collection of patient data for clinical evaluation of the step_VEP (chapter 7).

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...you rock!

Abstract

The majority of children attending ophthalmology clinics require a visual acuity assessment. The optimal technique depends on age as well as the ability to cooperate with testing. Most acuity assessments are performed subjectively by an orthoptist. Objective acuity assessment by Visual Evoked Potential (VEP) provides a complementary assessment in those subjects who cannot complete subjective tests. The aim of this study was to develop and evaluate a rapid, objective visual acuity assessment.

The technique was named the step_VEP and is based on the real-time analysis of steady-state VEPs (ssVEP). It presents high contrast checkerboard stimuli of sizes 0.4 to 3.0 LogMAR with a successive approximation algorithm. Speed of response detection, specificity and sensitivity were optimised by investigation of recording montage and analysis techniques in a group of normal children and adults (N=102). The success, duration and outcome of step_VEP acuity assessment was compared to transient VEP (t-VEP) acuity assessment and subjective acuity assessment in a group of paediatric patients (N=218).

1-D Laplacian analysis of three occipital electrodes was significantly faster than conventional recording and analysis (O_z-F_z) at detecting ssVEP responses near visual acuity threshold (3' checks) from three years upwards, and at detecting responses to 6' and 9' checks in the 7-9 year age group. A lateral electrode site at 15% of the half-head circumference was fastest most often in adults. Step_VEPs were 16% more successful than t-VEPs and 9% more successful than subjective tests in providing a complete acuity assessment. Subjective acuity scores were systematically higher than VEP acuity scores in subjects who successfully completed both assessments. A closer agreement with subjective acuity scores was found for step_VEPs than t-VEPs. The disparity between step_VEP acuity score and subjective acuity score was shown to reduce with age.

Visual system maturation continues throughout childhood affecting the time benefits of applying 1-D Laplacian analysis to VEP recording. A smaller or later extrastriate ssVEP response component in younger subjects and increasing noise coherence between electrodes with age most likely resulted in increased signal preservation and noise cancellation respectively. This twofold improvement in signal to noise ratio (SNR) resulted in a significant reduction in time to detection for responses to 6' and 9' checks in 7-9 year old children using the 1-D Laplacian analysis. In the patient group, the higher success rate of test completion for step_VEPs compared to t-VEPs was partly due the assessment being 67% faster, and partly due to the stimulus presentation algorithm designed to maintain attention. The greater the developmental delay in the patient group, the greater the improvement in success rate of test completion by employing the step_VEP. The closer agreement between subjective and step_VEP acuity scores implied that a faster stimulation rate results in a higher acuity score.

Contents

List of figures

List of Tables

List of abbreviations

LGN-Lateral Geniculate Nucleus

VEP-Visual Evoked Potential

t-VEP-Transient Visual Evoked Potential

ssVEP-Steady state Visual Evoked Potential

GAC-Glasgow Acuity Cards

CC-Cardiff Acuity Cards

LogMAR- Log of the Minimum Angle of Resolution

SNR-Signal to Noise Ratio

DT-Response Detection Time

1-D-One Dimensional

DPI- Dots per Inch

ADC-Analogue to Digital Converter Card

DSP-Digital signal Processing Card

VGA-Video Graphics Adapter Card

DOS-Disk Operating System

Chapter 1 The visual system and its assessment

1.1 Introduction

Visual acuity describes an individual's capacity for spatial resolution at maximum contrast: the ability to resolve fine detail (Teller 1981). The size of text in books and other learning materials that an individual can both see and comprehend is, in part, determined by their visual acuity. Acuity is measured clinically using a number of subjective techniques such as reading letters from a chart or shifting gaze to observe a stimulus presented randomly to the left or right. However, neurological impairment or learning difficulties can make such verbal and physical responses impossible. In cases where subjective assessment is not possible, objective assessment of acuity can be attempted by recording electrical responses to specific stimuli from the visual part of the brain.

The majority of children attending ophthalmology clinics require a visual acuity assessment. The optimal technique depends on age as well as the ability to cooperate with testing. Most of these acuity assessments are performed subjectively by an orthoptist. Objective acuity assessment can be used in all age groups, although the necessary preparation is relatively time consuming. Rather than being used in every patient requiring acuity assessment, objective assessment is either complementary to subjective assessment, or it provides the only estimation of visual acuity.

The aims of this chapter are threefold.

1) To introduce the basic anatomy and physiology of the visual system pertaining to visual acuity and to describe their developmental course.
2) To review current methods of visual acuity assessment and to describe their developmental rates in relation to visual system development.
3) To outline the topics to be investigated in this thesis.

1.2 Anatomy of the Visual System

1.2.1 Introduction

The brain receives information from the eye via the retina, an extension of the brain linked to it by the optic nerve. The optics of the eye comprise (figure 1.1) the cornea, aqueous humour, lens and vitreous humour. They ensure that light is collected and directed onto the retina where the optical information is converted into neural activity.

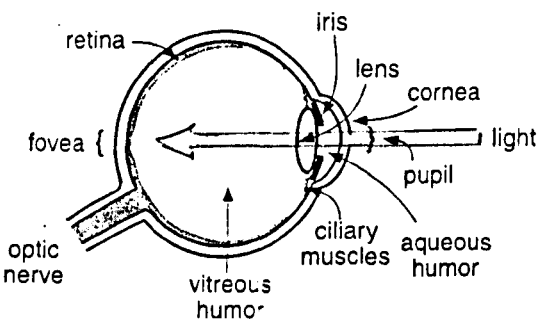


Figure 1.1: The optics of the eye.

1.2.2 The Retina

Figure 1.2 shows the variety of cells present in the retina and also the path taken by light after hitting the surface. The photoreceptors are sensors for incoming light, which they convert into neural activity. Photoreceptors are present in two types, cones and rods. The rods outnumber the cones, typical values are 120 million and eight million respectively (Curcio and Allen 1990). Rods are very sensitive to light and are used for vision in

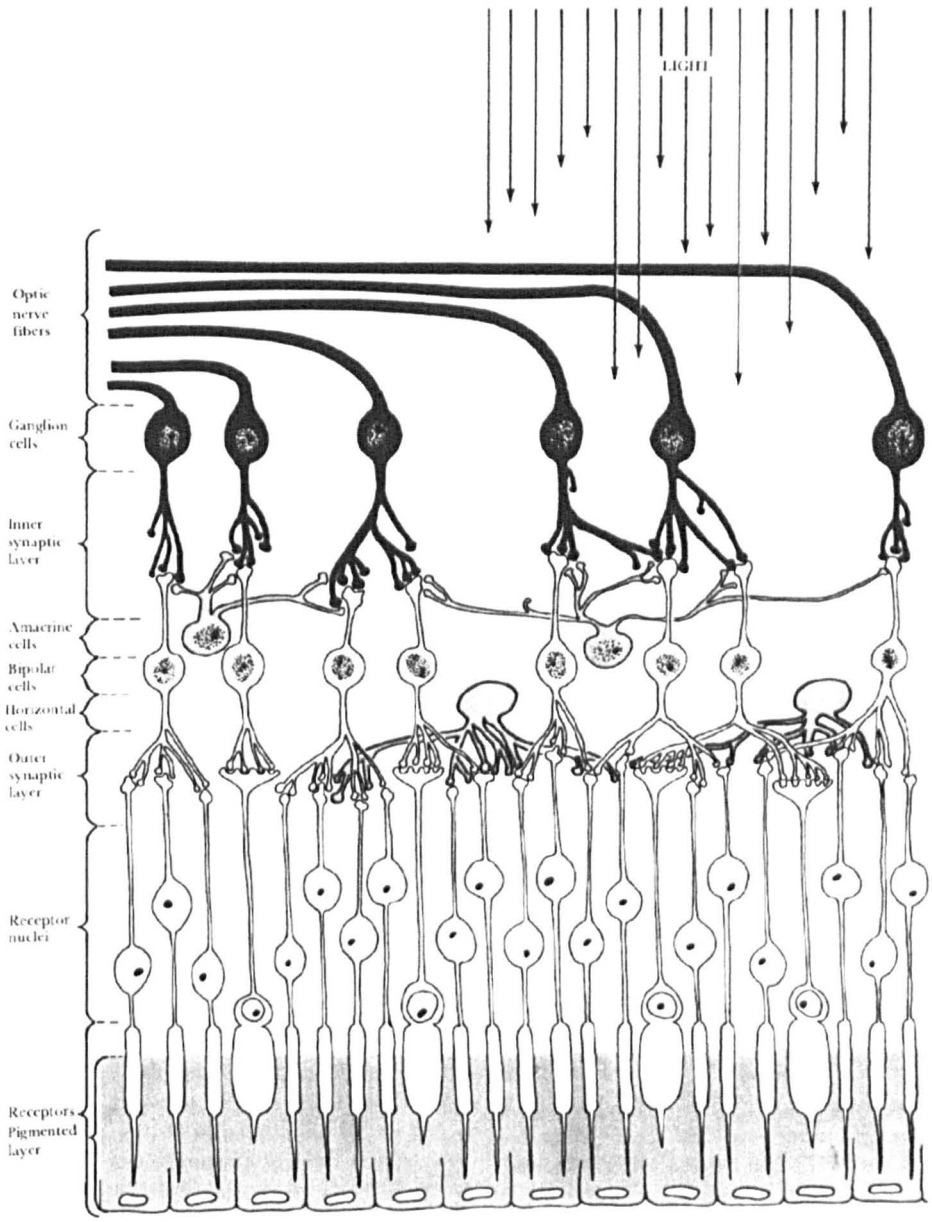


Figure 1.2: Organisation of cells in the retina. (Palmer S. (1999). Vision Science; from photons to phenomenology. MIT press, London. Reproduced with permission of the publisher).

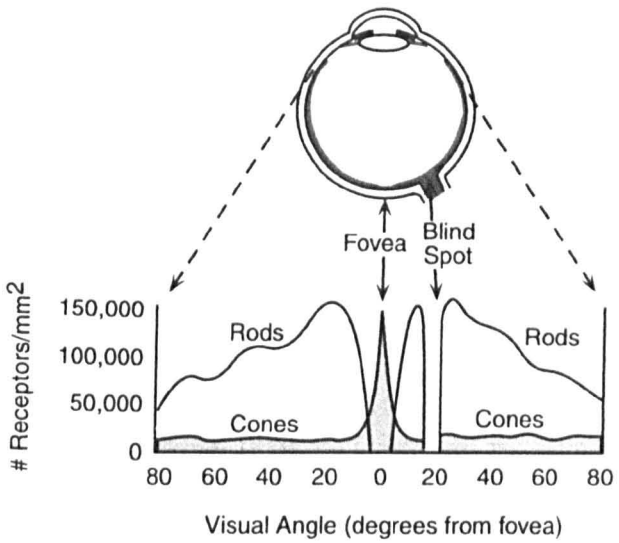


Figure 1.3: Density of rod and cone photoreceptors across the retina.

scotopic conditions (low light levels). The density of rods peaks at 15° from the centre of the retina (ibid.). Cones are less sensitive to light and more concentrated in the centre of the retina. The distribution of rods and cones in the retina is shown in figure1.3. Light absorbed by the pigment of a photoreceptor produces electrical changes in its outer membrane; this propagates to the cells synaptic region ready to communicate with the neurones in the retina; the horizontal, bipolar, amacrine and ganglion cells. There are around one million ganglion cells and they too are concentrated in the central retina.

The visual field is the space in which objects are simultaneously visible to the steadily fixating eye (Harrington and Drake 1990). The macula is a disc in the centre of the retina 4.5mm in diameter (Ogden 1994) where the ganglion cells are two deep or more (Palmer 1999). The fovea, a shallow rounded pit at the centre of the macula due to the displacement of inner retinal layers, is 1.5mm in diameter which corresponds to an angle of 1-2° in the visual field (Sigelman 1989). The central 0.25° of the fovea is called the foveola, which lies directly over the optic axis and contains only cone photoreceptors. The absence of overlying cells and blood vessels in this area, in addition to the high density of cones, contributes to a high level of visual acuity. Perfect visual acuity describes a visual system by which two points as close as 0.5 minutes of arc can be discriminated (Hubel and Wiesel 1988). This angle corresponds to a circle of diameter 2.5μm on the retina, which is the diameter and centre to centre spacing of cones in the foveola. Bipolar cells receive input from the photoreceptors and pass their output onto the ganglion cells (figure 1.1). This process occurs directly or after modulation by the horizontal and amacrine cells. Horizontal cells provide links between some photoreceptor and bipolar cells with the amacrine cells providing some bipolar-ganglion cell links.

Figure 1.4 illustrates the concept of a receptive field (Hubel and Wiesel 1988), used to describe the output characteristic of a ganglion cell (Kuffler 1952) whose input comes from one or more photoreceptors. In the fovea there is a ganglion cell for each photoreceptor, but as eccentricity increases each ganglion cell receives input originating from an increasing number of photoreceptors. The field has a circular central portion that responds to either the onset or offset of light and a surrounding annulus shaped portion that responds

antagonistically. There are two types of ganglion cell receptive fields; the on centre-off surround cell, and the off centre- on surround cell. On centre-off surround cells discharge at an increased rate when light is incident on the area of the retina corresponding to the centre of its receptive field. Stimulating the surrounding region with light inhibits the cell firing due to stimulation of the central region. These two effects can cancel each other out completely. An off-centre, on surround cell exhibits the opposite behaviour; its response is largest when its outer region only is stimulated.

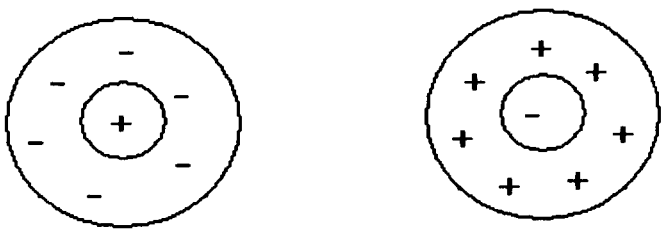


Figure 1.4: On centre and off centre responses of receptive fields.

A further dichotomy occurs in both on-centre and off-centre ganglion cells. Magnocellular (M) ganglion cells receive input from both cones and rods, whilst parvocellular (P) ganglion cells receive input from cones only. M and P cells have different behaviour; M cells have high contrast sensitivity and fast temporal resolution whereas P cells exhibit high spatial resolution and colour sensitivity (Shapley and Perry 1986). The signals from M and P cells are fed separately through the visual system forming the magnocellular (M) and parvocellular (P) pathways respectively.

1.2.3 Optic Nerves

The nerve axons of the ganglion cells form the optic nerves. At the optic chiasm (figure 1.5) fibres from the nasal portion of each retina crosses over to the opposite side of the brain resulting in each half of the brain receiving information from one half of the visual field only. A myelin sheath covering each axon speeds the conduction of signals (Palmer1999). The path of the optic tract on leaving the optic chiasm is also shown in the diagram. A small number of the nerves on each side go to the superior colliculus, a nucleus in the brain stem that processes information about location and plays a part in the control of eye movements (Sterling and Wicklegren 1969). The optic tract terminates at the Lateral Geniculate Nucleus (LGN).

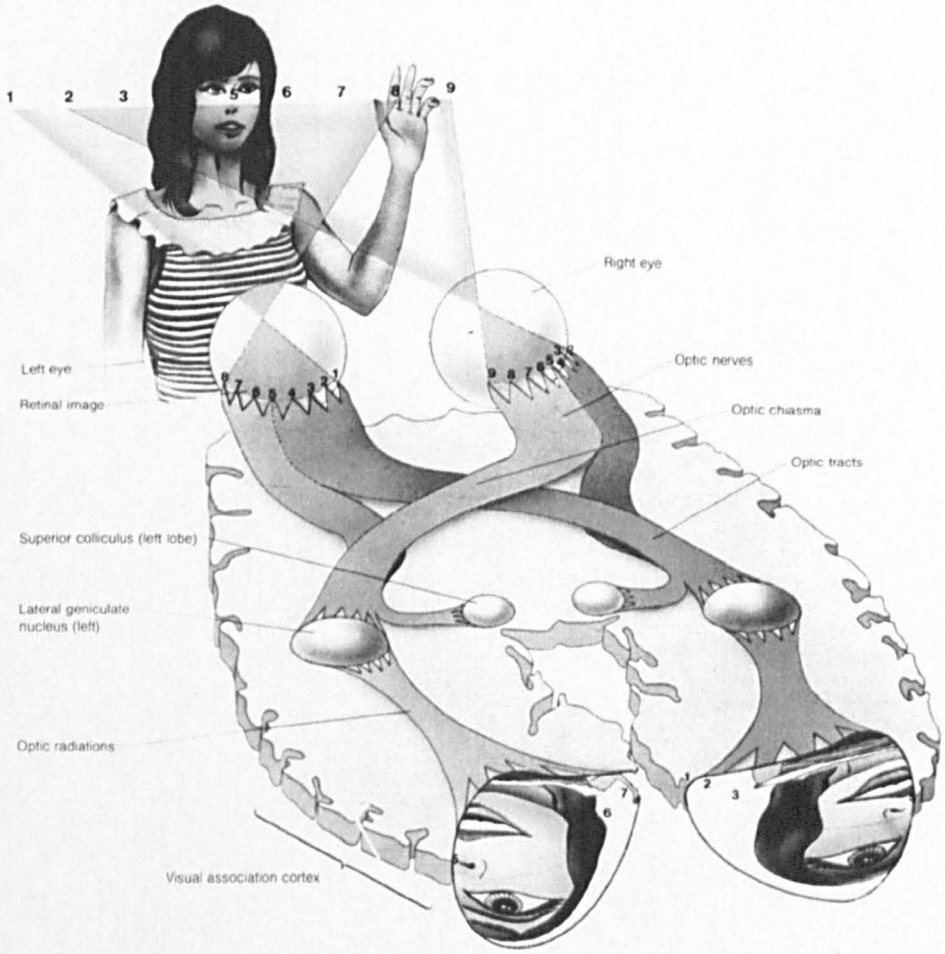


Figure 1.5: Visual pathways and the representation of the retinal response in the visual cortex. (Palmer S. (1999). Vision Science; from photons to phenomenology. MIT press, London. Reproduced with permission of the publisher).

1.2.4 Lateral Geniculate Nucleus (LGN)

The LGN is composed of six layers. Its cells receive input from the optic nerve fibres of both eyes with contributions from left and right eyes arranged into alternate layers. Each layer is spatially laid out like the retina of the eye providing its input (Zeki 1993). The lower two layers are called the magnocellular layers; the upper four are the parvocellular layers. The input to the M and P layers of the LGN comes from the respective type of retinal ganglion cell (Shapley and Perry 1986). Each LGN cell receives input from several ganglion cells, defining its receptive field. However, the inhibitory surround of an LGN cell receptive field is greater than in the receptive field of a ganglion cell. The P cells receive input from fewer ganglion cells, have smaller cell bodies, and smaller receptive fields than M cells. The LGN cells send axons to the visual cortex; this bundle of fibres forms the optic radiation.

1.2.5 The Visual Cortex

The visual cortex refers to the part of the brain which primarily processes visual information. Visual function is spread throughout the visual cortex but is predominantly concentrated in the occipital lobes. Each part of the retina is represented in the primary visual cortex (V1) (Zeki 1990), and the subsequent visual centres utilised in visual processing. The proportion of different cortical cells underlies the architecture and specific functional characteristics of each area in the visual cortex.

Cortical cells can be described as simple, complex or hypercomplex. The simple cells have excitatory and inhibitory regions as do ganglion and LGN cells. Complex cells are said to be responsive to motion but not position, and make up 75% of V1. Complex cells have relatively large receptive fields, and in receiving input from several simple cells provide the line and edge detection properties characteristic of area V1 (Hubel and Wiesel 1963; Hubel and Wiesel 1968). Hypercomplex cells (or end stopped cells) are also present in V1 and respond better to lines of a shorter length (Hubel and Wiesel 1988). The spatial frequency theory provides an alternative view of processing in V1. It suggests that processing is performed by a number of overlapping spatial frequency and orientation channels (Blakemore and Campbell 1969). Single unit recordings from simple and complex cells found different cells sharply tuned for different spatial frequencies, which supports the spatial frequency theory (De Valois *et al.* 1982). The optimum spatial frequency of a channel depends on the receptive field size of the neurones that form the channel (Maffei and Fiorentini 1977).

1.2.6 Functional specialisation of the Visual Cortex

Functional specialisation in the visual cortex was first demonstrated with single cell recordings on the rhesus monkey (Zeki 1978). More recently, this specialisation has been shown in humans using functional Magnetic Resonance Imaging (MRI) (Dubowitz *et al.* 1998).

The visual cortex can be divided into at least 5 areas whose topography is shown in figure 1.6. The striate cortex, area V1, receives its input from the ipsilateral LGN, which has layers of cells representing both retinae. Area V1 has output to areas V2-V5 known as the extra striate cortex. The receptive fields of cells in V1 are smaller than the receptive fields in V2, which are smaller than the receptive fields in V3 and so on. Receptive fields also become more functionally selective at higher levels of the visual pathway. The striate cortex has a unique organisation of its input from the left and right eyes which, in addition to its relatively small receptive fields, result in a higher precision retinal image in V1 than the other areas.

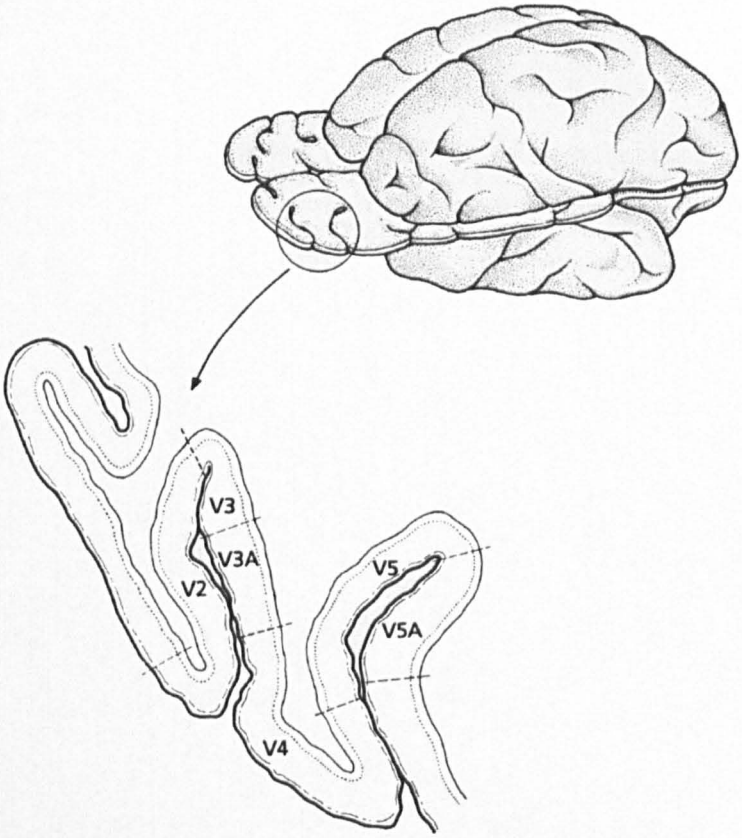


Figure 1.6: The organisation of the visual cortex. (From Zeki S. (1993) A vision of the brain. Blackwell scientific publications, Oxford. Reproduced with permission of the publisher).

1.3 Assessment of Visual Acuity

1.3.1 Introduction

Large patterns with high contrast are easier to see than small patterns with low contrast. The contrast sensitivity function summarises the level of contrast at which patterns of various sizes become visible (Blakemore and Campbell1969), and will differ between adults and babies (Atkinson *et al.* 1977). The largest differences are observed for the smallest patterns. This function provides an extensive description of visual performance, which is useful in the assessment of visual development and visual disorders. However, a single high contrast test of spatial resolution (visual acuity) is adequate to provide useful information to the parents, teachers and carers of those with visual impairment.

Functional assessment of vision can be carried out with both eyes open (Dutton 1998). Visual acuity can be subdivided into detection, resolution and recognition all of which have a different functional significance. Detection acuity estimates the minimum size visible, resolution acuity is the minimum separation which allows discrimination, and recognition acuity is the minimum size which facilitates identification (Dutton1998). There are numerous subjective techniques for assessing visual acuity. The most appropriate will depend on the age and developmental level of the subject.

Crowding is a clinical manifestation of a simultaneous visual processing problem (Pike *et al.* 1994) which causes a delay when the affected patient is asked to process information

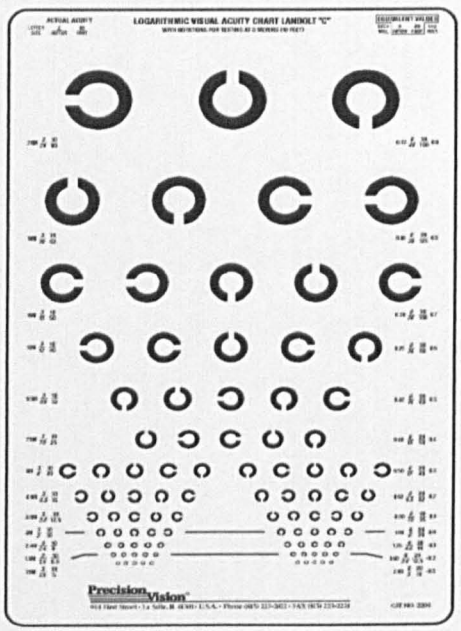
from a complex visual scene(Jacobsen *et al.* 1996). The age and diagnosis of a patient should determine whether a crowded or uncrowded assessment is most suitable.

The tests designed for infants' use a simple stimulus such as high contrast black and white stripes. The stimulus is presented in such a way that it is obvious if the child has seen it or not without requiring a verbal response. An optotype is a picture or letter that the subject is required to identify physically or verbally. For pre-school children simple pictures of familiar objects such as trains or houses can be presented with outlines of different widths. The child completes the assessment by matching the picture to one of his or her own set of pictures or by naming the object if he or she is verbal. In older children optotypes may be letters that they will be asked to read out. Age, lack of co-operation, and developmental delay can prevent the use of subjective methods for assessing visual acuity. In these situations an objective assessment using electrical activity recorded from the brain warrants consideration.

1.3.2 Subjective Acuity assessments

The Landolt-C test (Landolt 1909) is considered the 'gold standard' test for visual acuity (Colenbrander 1988). The test consists of circles with a section missing (like very round C's) oriented at random. Landolt-C optototypes are presented with a defined space between symbols (Figure 1.7a) to control for the effect of crowding on visual acuity (Haas 1982). Theoretically, Landolt C rings are superior to pictures because the subtended angle of contrast recognition is very precise. The tumbling E's (Precision Vision, La Salle, Illinois)chart is also based on this premise (figure 1.7b).

a



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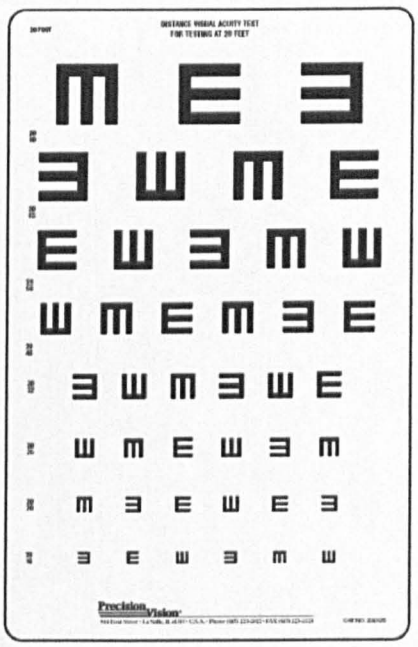


Figure 1.7: a) Landolt C rings b) tumbling E's

The Landolt-C test is not widely used clinically as patients, particularly children, find it more difficult to describe the position of the gap in the ring than identifying a letter or number (ibid.). The test outcome can also be affected by the orientation of the gap (Schrauf and Stern 2001). It has been recommended (Colenbrander1988) that all other psychophysical measures of acuity should be compared to Landolt-C acuity before being used in clincal practice. The subjective tests used most often in local Glasgow practice are given in table 1.1.

Table 1.1: Most Frequently used Visual acuity tests by age group.

AGE (years)	< 1	1-2	2-3	3-4	>4
Keeler Cards	X				
Cardiff Cards		X			
Kay Pictures			X		
Sheridan-Gardiner				X	
Snellen or Bailey-Lovie					X

Infants will prefer to look at a striped target in preference to a blank target of equal luminance when both are presented simultaneously (Fantz 1958). This is called preferential looking (PL). If an infant consistently fixates on a target with greater than chance probability (1/2) then the examiner concludes that it can be seen. The finest striped target fulfilling these criteria provides an estimate of grating acuity. The examiner should be

unaware of the position of the fixation target on presentation, and makes a forced choice judgement of its position by assessing the infant's fixation preference.

The targets can be presented randomly or with a staircase strategy. The latter dictates that the examiner presents targets of increasing spatial frequency until an incorrect judgement occurs (Mayer and Dobson 1982). The card representing the last correct response followed by the next, higher spatial frequency target, are re-presented until a 75% preference can be established. Operant Preferential Looking (OPL) follows the same procedure but offers positive reinforcement, such as food or a toy, when a correct response was achieved (Mayer and Dobson1982; Dobson *et al.* 1985). The two preferential looking tests have been shown to compare well with each other and have high repeatability (Mayer and Dobson1982; Birch *et al.* 1983). McDonald *et al* (1985) used a further adaptation of the preferential looking technique where the speed and continuance of fixation preference was considered when determining acuity. The success of preferential looking acuity assessment is dependent on the child's level of neurological impairment. Success rates of 92% (Adams and Courage 1990) and 99% (Hertz and Rosenberg 1992) have been reported in children with mild neurological impairment, with this rate dropping to 74% in a study of patients with more severe neurological impairment (Mackie 1995). Test cards for all preferential looking assessments may need to be presented vertically if hemianopia (blindness in half of the visual field) is suspected or horizontal nystagmus (uncontrolled horizontal eye movements) is present (Dutton1998).

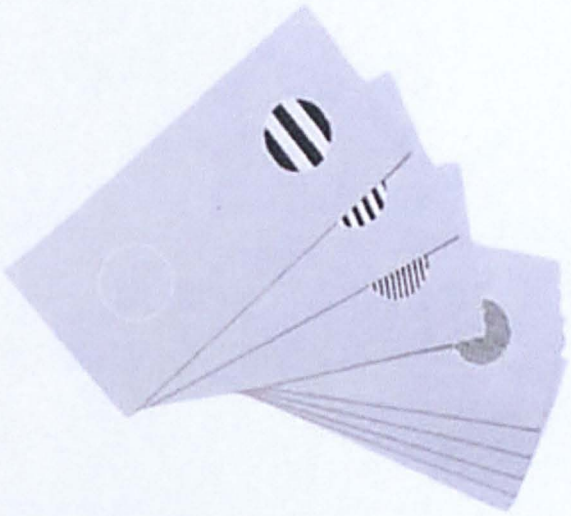
The acuity card was developed to give quicker but agreeable results to the tests described above(Mcdonald *et al.* 1985) and with similar variability. There are different sets of cards

for different age groups. Keeler Cards (Keeler, Windsor, Berkshire) are inserted into the centre of a screen. On each card there is one circular black and white grating and one isoluminant grey circle. The examiner should be unaware of the position of the grating. Each card has a small peephole in the centre through which the infant can be observed. A standard set consists of eight cards of decreasing spatial frequency, presented at 38cm, with the final card having two grey circles as a control. The short test distance and the peephole and screen make the procedure suitable for neonates and all infants. Teller cards are the same but with a square aperture, and were used to examine 77 children, 49 with strabismus, 9 with anisometropia and 19 with various organic ocular diseases (Katz and Sireteanu 1989). The vision of some of these children was also tested with the Landolt C and fixation preference tests. A comparison of the three tests showed that Teller Acuity Cards were insensitive to inter-ocular differences in strabismic amblyopia but a sensitive detector of acuity loss due to ocular diseases.

Cardiff cards (Vistech Consultants, Dayton, Ohio)(Adoh and Woodhouse 1994; Adoh *et al.* 1992; Woodhouse *et al.* 1992) present pictures on an isoluminant grey background as their targets. The pictures are outlined by a white band surrounded by two black bands (with half the width of the white band). These targets are all of the same size but the width of white and black bands decrease until the target can no longer be seen. The narrowest white band for which the target is visible gives a measure of acuity. The use of familiar shapes instead of gratings such as PL targets improves co-operation in children between 12 and 36 months (Graf *et al.* 1996). Cardiff cards are an example of stimuli that equalise detection and resolution acuity in the fovea by setting the mean luminance of the stimulus equal to that of

its background (Frisen 1986). Figure 1.8 gives an example of Keeler, Teller and Cardiff acuity cards.

a



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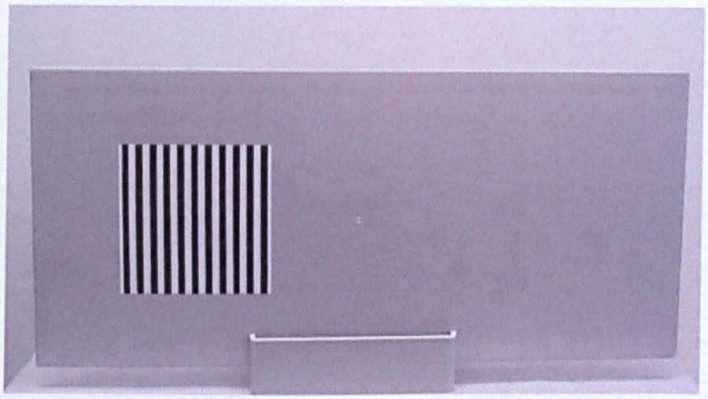

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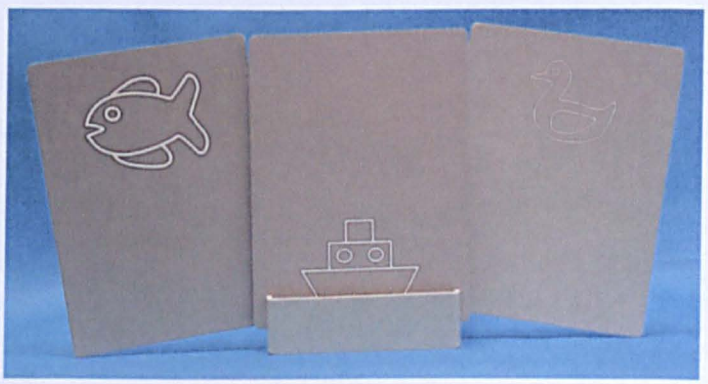


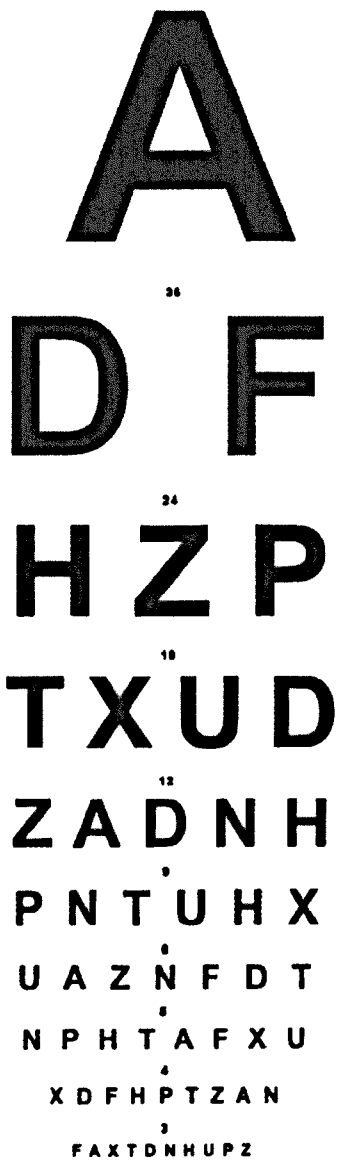
Figure 1.8: a) Keeler Cards, b) Teller cards and c) Cardiff Cards

An example of Kay pictures (Kay Pictures, Tring, Hertforshire) is included as figure 1.9. The test requires the patient to be able to recognise a single drawing and then point to the matching picture on their sheet; literacy is not required. An older or more able child can be asked to name the pictures when they are shown, this introduces a recognition component. For example a child may not respond to a picture of a boat purely because he or she may never have seen one before.

Figure 1.9: Kay Pictures

Crowding is present in letter charts and as a result the acuity measured is often poorer than visual acuity measured by a simpler test of detection or resolution (Dutton1998). Testing with letters becomes appropriate over the age of three years in normal children (Egan and Brown 1984). A Snellen chart (Snellen 1862) has a series of letters reducing in size as one reads down the chart (figure 1.10a). The test is conducted at six metres in order to elicit myopia.

a


A
36
D F
24
H Z P
18
T X U D
12
Z A D N H
9
P N T U H X
6
U A Z N F D T
5
N P H T A F X U
4
X D F H P T Z A N
3
F A X T D N H U P Z

b

c

P U H D F

F P U N R

N P D F T

H D R E P

E R N F U

R H T U P

T F R D E

d

Figure 1.10: a) Snellen Chart b) Sheridan-Gardiner test c) Bailey-Lovie Chart and d) Glasgow Acuity Card.

The Sheridan-Gardiner test (Sheridan and Gardiner 1970)(Keeler, Windsor, Berkshire) is a version of the Snellen test without crowding for very young children or illiterate patients. The patient is shown letters individually at a distance of six metres and responds by pointing to the matching letter on a chart in his/her lap (figure 1.10b). This matching card makes the test easier to perform than other letter charts making it particularly suitable for those who are illiterate. However, the snellen chart has an irregular progression of letter sizes and unequal numbers of letters per line.

The Bailey-Lovie Chart (Bailey and Lovie 1976; Bailey and Lovie 1980) standardised the legibility of letters, the number of letters per row, between row spacing and between letter spacing (figure 1.10c). The same number of letters per row means crowding is consistent between cards, and logarithmic progression of letter sizes is used to simplify the adjustment of acuity score when non-standard test distances are used. LogMAR (log of the minimum angle of resolution) is a unit for visual acuity calculated by taking the log of the visual angle of the smallest optotype a patient can resolve (Johnston 1985).

A shorter test distance has been shown to provide more rapid and successful assessments of children's vision (Sheridan and Gardiner1970). Glasgow acuity Cards (GAC's) (McGraw and Winn 1993) were designed specifically for children and present four letters at a time with the same logarithmic increments in letter size as the Bailey-Lovie chart. The rows of letters are surrounded by a black rectangle (figure 1.10d). Each target is a 0.025 increment on the logmar scale of acuity therefore an exact acuity can be defined for partial success in

reading the final target. These small scoring increments also make the test particularly sensitive to changes in acuity after amblyopia treatment (McGraw *et al.* 2000).

1.3.3 Objective Acuity assessments

The assessment of visual acuity in young children and those with communication problems can be difficult if they cannot respond verbally to the presentation of letters or pictures. Children with cerebral palsy may also have impaired physical responses such as head turn and abnormal eye-movements which make even specially designed preferential looking tests of limited use.

Visual Evoked Potentials (VEPs) provide a measure of the electrical activity in the visual cortex in response to a specific stimulus. The use of visual evoked potentials (VEPs) to estimate visual acuity eliminates the need for either physical or verbal responses and therefore has the potential to be useful in young children and those with communication problems. A cortical response to a flash of light can be used as a crude indicator of visual function, however for a more detailed assessment, a high contrast stimulus that changes periodically can be presented on a computer monitor. This is repeated for decreasing stimulus sizes, and the smallest stimulus size evoking a measurable, reproducible response is used to describe VEP acuity. A physiological amplifier and custom designed software are used to filter the response and analyse whether it is significantly larger than the background noise also present in the recording.

The most commonly used stimulus for VEP recording is one of pattern reversal. Its response characteristically appears as in figure 1.11a. The main positive peak, P100, has the most consistent latency across subjects and is used to identify a normal response. Transient stimuli evoke responses about once every second. In adults, around one hundred transient VEP responses are averaged before the electrophysiologist determines whether a reproducible response is present or not. VEP recording is repeated for stimuli reducing in size until the spatial resolution threshold is found. For the transient VEP method, the identification of responses is subjective and therefore subject to inter-individual variation.

Stimulation patterns can be sinusoidal gratings, square wave gratings or checkerboards. When a stimulus pattern and an isoluminant grey screen are alternately presented for similar lengths of time, the response (figure 1.11b) is quite different to that evoked by a pattern reversal stimulus. This type of stimulus is known as pattern-onset and its response waveform takes longer to mature than the pattern reversal VEP (Apkarian 1994).

Children suffering from nystagmus have continuous involuntary eye movements. A transient stimulus reverses once every second with subsequent averages accumulating each second. One second is a relatively long presentation time and results in the stimulus being blurred due to the patients eye movements, often resulting in recordings with no reproducible responses. The shorter presentation time of the pattern onset stimulus avoids

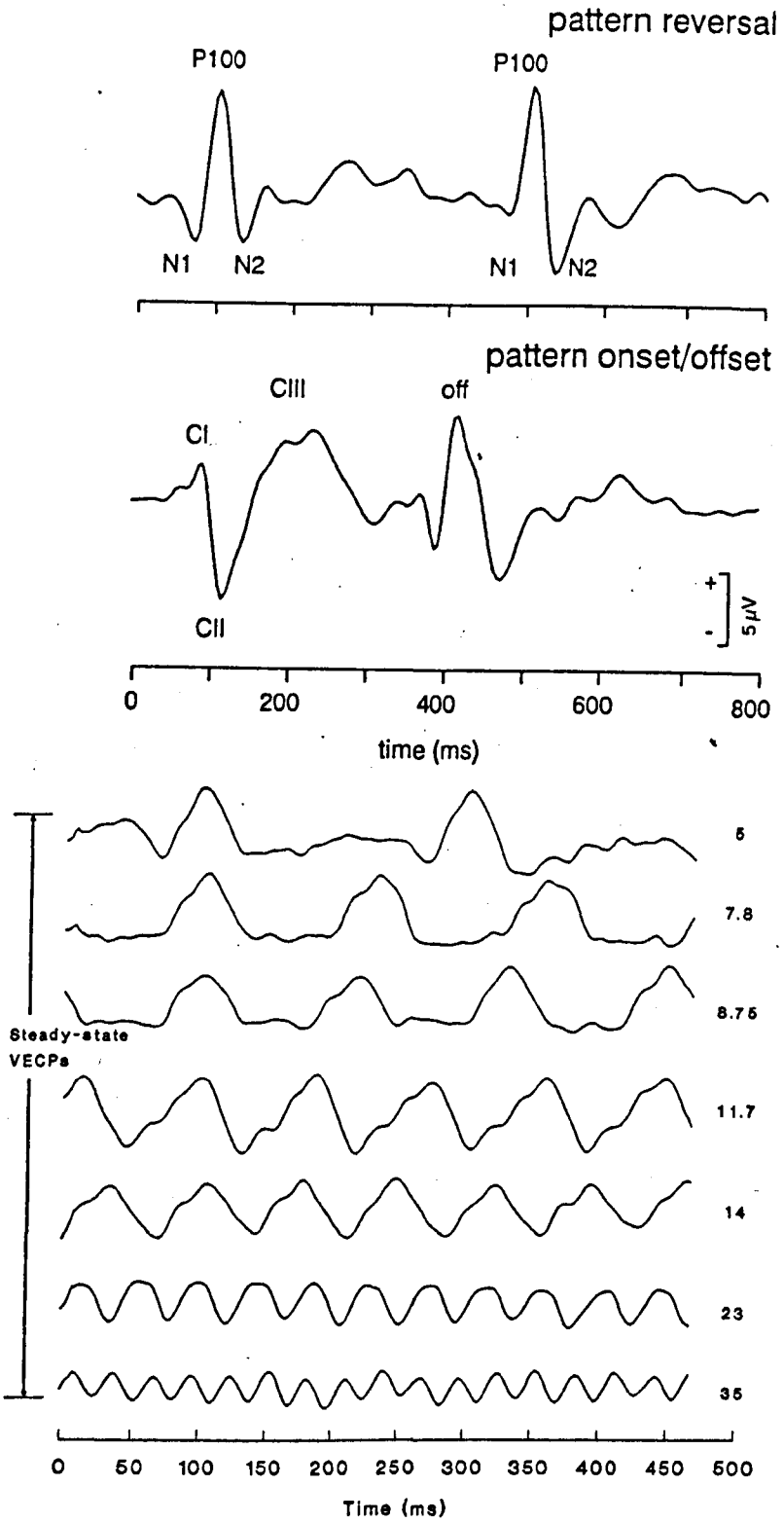


Figure 1.11: VEP waveforms recorded in response to a) transient pattern reversal stimulation b) transient pattern onset stimulation and c) steady-state pattern reversal stimulation.

this blurring and has proved to be more successful in achieving good quality results in patients with nystagmus (Saunders, Brown, and Mcculloch 1997).

Steady-state stimulation refers to rapid stimulation rates that generate a steady-state response with frequency components that remain constant in amplitude and phase (Regan 1966). This happens at rates of around five stimuli per second (Van der Tweel 1965). This allows rapid accumulation of response data, and the periodic nature of ssVEP responses (figure 1.11c) allows for objective analysis in the frequency domain. Spatial resolution is derived from the smallest stimulus evoking a statistically significant response (Skalka 1980), or the intercept of linear regression of the spatial frequency-amplitude function with a preset noise level (Sokol S 1983). This is explained in more detail in chapter two.

VEP response amplitude plotted against stimulus size forms a characteristic spatial frequency-amplitude function. In sweep VEP recording (Regan 1977) several steady state pattern reversal stimuli are presented in rapid succession while responses are simultaneously recorded. An electronic version of the sweep presents ten different stimulus sizes over ten seconds (Tyler *et al.* 1979). The sweep is repeated as often as is necessary for a clear picture of the spatial frequency-amplitude function to be identified from the cumulative average. This usually takes at least one minute. Linear regression is performed on the descending limb of this function to determine the acuity threshold. The system is extremely successful in assessing the vision of normal children from preterm upwards, (Skoczenski AM 1999; Allen, Tyler, and Norcia 1996; Norcia and Tyler 1985; Norcia *et al.* 1999) (Norcia *et al.* 1987; Riddell *et al.* 1997) and clinically assessing vision in a variety of

pathologies (Katsumi *et al.* 1997). Success rates of 100% and 80% have also been reported in assessing the visual acuity of children with cerebral palsy (Costa *et al.* 2002) and Downs Syndrome (John *et al.* 2002) respectively. These success rates seem excessively high after experience in Glasgow with similar groups of patients. It should be noted that the sweep VEP does not require a reproducible threshold, and the studies outlined did not use an alternative technique (e.g. PL) to validate the test outcome in any of the subjects.

1.3.4 EEG and its effect on VEP recording

Signal averaging, filtering and statistical techniques are used to distinguish the VEP response from background noise. Although electrical equipment in a laboratory can add noise to VEP recordings, the background noise is mainly caused by ongoing electrical activity in the brain called the electroencephalogram (EEG). The EEG can be summarised by several different components (Berger 1929; Jasper and Andrews 1938; Walter 1936) that are classified by their peak frequency, topographical distribution and conditions of registration. Alpha activity is measured in the occipital region at frequencies of 8-12Hz and relates to any visual input to the brain. As VEPs are also measured from the occipital cortex, much of the noise present during VEP recording is likely to be due to the alpha component of the EEG. VEP responses reach steady state at around five reversals per second(Van der Tweel 1965). However, assessments must avoid stimulation in the same frequency region as EEG alpha activity.

1.4 Anatomical and functional maturation of the visual system

Postnatal development of spatial vision is affected by foveal maturation (Banks, Geisler, and Bennett 1987). Although the number of neurones in both retina and visual cortex is adult like by seven months post-conceptual age, the arrangement of photoreceptors in the central retina may still be changing at four years (Abramov *et al.* 1982; Yuodelis C 1986). In primates, postnatal increases in spatial resolution are greater than can be explained by retinal cone packing (Jacobs and Blakemore 1988). The increase in spatial resolution measured behaviourally, mirrors the increase in spatial resolution of LGN neurones (ibid.). Cortical neurones undergo similar improvements towards the theoretical maximum provided by foveal cone spacing. Although the visual cortex develops more slowly than other parts of the visual pathway (Cleary 2002), the primary visual cortex (V1), responsible for fine pattern vision, develops faster than other cortical areas in the first year of life. Myelination of the optic nerve and tract begins before birth and carries on until about two years of age (Magoon and Robb 1981) with foveal fibres developing first.

A synapse describes the connection between dendrites of two neurones. In the first year of life the number of these connections in the visual cortex reaches its lifetime peak (Michel and Garey LJ 1984). These intra-cortical connections reduce to adult numbers over the next 10 years (Huttenlocher PR 1982; Huttenlocher and de Courten 1987). As the number of short range connections is reducing, the number of long range, or inter-cortical connections, is increasing (Yakolov and Lecours 1967; Holland *et al.* 1986).

The development of EEG alpha activity is reported to be dependant on extrauterine visual experience and has been shown to change considerably in terms of both peak frequency and topography in the first years of life (Srinivasan R. 1999; Stroganova, Orekhova, and Posikera 1999). These changes are probably related to those that occur in the primary visual cortex over the same period. Yordanova and Kolev (Yordanova and Kolev 1997;Yordanova and Kolev 1996) compared the EEG alpha component of children and adults. EEG alpha activity was not adult like in amplitude (it was larger), topography or phase consistency until 10-11 years. These gradual functional changes that occur during childhood may be related to further maturation of the occipital cortex.

The morphology of the transient VEP waveform reflects maturation of the visual pathway and is selectively sensitive to disease processes (Apkarian1994). Transient VEP acuity correlates well with Snellen acuity in adults (Regan and Richards 1971). Although the pattern onset response waveform does not have adult-like properties until puberty, a reasonable estimate of acuity can be made by six months using the smallest stimulus to which a reproducible VEP is recorded (Spekreijse 1983). The maturational information reflected by changes in wave shape is largely lost in steady state VEP recording; during which responses are simply quantified by their amplitude and phase. The ssVEP spatial frequency amplitude function is adult-like by six months of age (Sokol S 1978) leading to extrapolated sweep VEP acuities that are close to adult values during the first year of life (Norcia and Tyler 1985; Skoczenski AM1999).

Subjective measures of acuity take until puberty to reach their adult values. In childhood, higher spatial resolution estimates for age are obtained by pattern reversal VEPs than subjective techniques (Dobson and Teller 1978). Due to its temporal component, the VEP stimulus may be processed differently to stationary stimuli by the visual system. Higher values of spatial resolution for higher stimulus rates have been observed during the first year of life(Sokol *et al.* 1988) but not after two years of age (Sokol, Moskowitz, and McCormack 1992).

Chapter 2: Existing VEP systems and technical aspects of recording

2.1 Introduction

The aims of this chapter are to review the current technology available for stimulating, recording and analysing VEPs and to produce a design specification for a new paediatric visual acuity assessment based on the real-time analysis of ssVEPs. Local, academic and commercial systems will be evaluated in terms of their suitability for acuity assessment and different methods of expressing assessment outcomes will be considered.

Figure 2.1 represents the system currently in use clinically at the Royal Hospital for Sick Children in Glasgow (Bradnam 1994a). The system is used for flash, transient pattern reversal, transient pattern onset and steady-state pattern reversal stimulation and recording. It also has software to analyse recordings off-line. The main components of the system are described in the following sections.

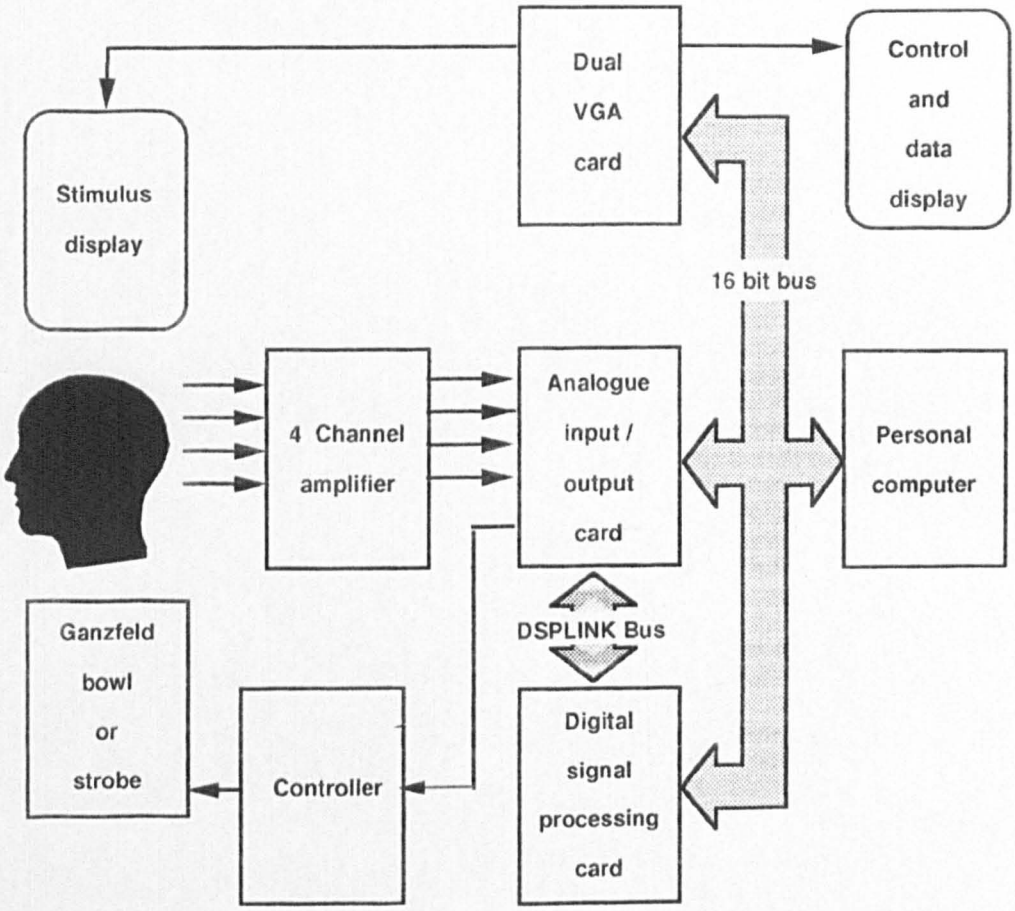
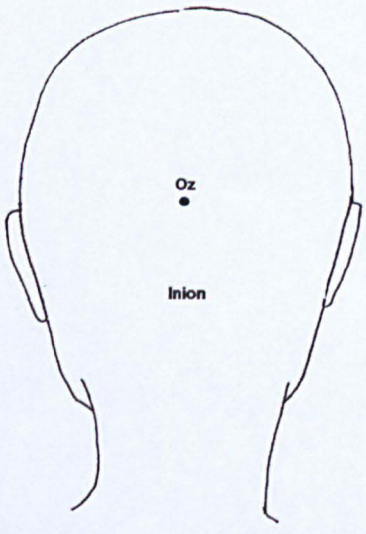


Figure 2.1: Existing VEP stimulation and recording system (Bradnam 1994).



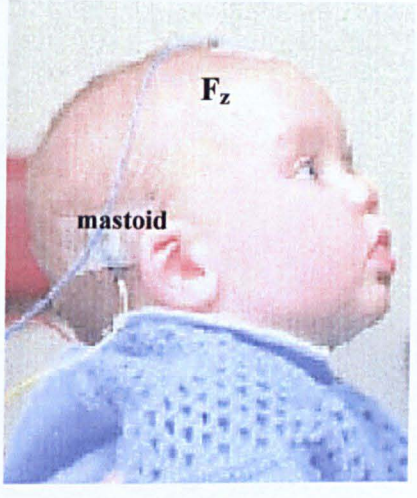


Figure 2.2: Electrodes are placed at Oz, Fz and a mastoid for VEP recording

2.2 Hardware Currently in use

2.2.1 Recording the VEP

It is possible to record a VEP with three electrodes placed at O_z, F_z and a mastoid (figure 2.2). The potential difference measured between O_z and F_z provides the data for analysis. The use of active (O_z) and reference (F_z) electrodes eliminates the component of the signal that is common to both electrodes. The ground electrode connects anelectrically inactive area to the ground terminal of the equipment .

2.2.2 Physiological Amplifier

Data is first filtered and amplified by a physiological amplifier built by the Clinical Physics and Bioengineering department in Glasgow. It has four channels with which to amplify the potential difference between two electrodes. Its specification is given in table 2.1. As physiological signals are very small compared to mains interference, an amplifier with a high common mode rejection ratio (CMRR) is essential to minimise measurement noise. The CMRR is optimised during recording by an amplifier with high input impedance coupled with low, matched recording electrode impedance.

Table 2.1: Physiological amplifier specification.

Parameter	Range (increments)
Gain	1-800000 (32)
Output	±500mVd.c.
Input Impedance	100MΩ
High Pass Filter	d.c.-100Hz (8)
High Pass Filter Roll Off	12dB/octave
Low Pass Filter	10-3000Hz (8)
Low Pass Filter Roll Off	12dB/octave
Common Mode Rejection Ratio	>125dB
Noise	1uV (0.1-100Hz)

The high pass filter cut off is set to 1Hz to eliminate any DC offset and low frequency drift in the signal. If the cut-off was higher it would distort the relative component amplitudes of the signal or introduce spurious peaks. A low pass filter cut off of 100Hz allows all the important components of the waveform to be recorded and prevents artificial delays in the main peak latency and the loss of fine details in morphology. No filter has a perfect cut-off and there will be a gradual 'roll off' that may affect the frequency region of interest. Again, to ensure no relevant information is discarded and no delays or peaks are introduced there is a limit to how steep this roll off can be. The International Society for the Clinical Electrophysiology of Vision (ISCEV) standard states that Analogue high pass and low pass filters should be set at ≤ 1 Hz and ≥100 Hz respectively (Harding *et al.* 1996), and that the filter roll-off should be <12 dB per octave for low frequencies and < 24 dB per octave for the high frequencies (ibid).

The patient is optically isolated from the electricity used to power the amplifier, and an isolation transformer is included in the system between the mains supply and the amplifier (International Electrotechnical Commission 1988).

2.2.3 Personal Computer (PC) and monitors

Two monitors are required by the system. One displays a stimulus to the patient, while the other allows the tester to control stimulation and monitor response waveforms. A special IBM monitor (model 14XG) was used for the stimulus display. It was chosen for its luminance uniformity and range as well as its electromagnetic screening properties.

2.2.4 Analogue-to-Digital Converter (ADC) Card

The sampling (or digitisation) rate of the ADC card refers to the number of times a response waveform is sampled every second, creating a discrete array of values to describe the waveform. The nyquist frequency (f_N) is defined as being half the sampling frequency (Jervis *et al.* 1989) and must exceed the highest frequency component of the VEP to prevent aliasing. Aliasing is distortion of the lower frequency half of the spectrum, which occurs when the sampling rate is too low. A Loughborough Sound Images four-channel input/output card (Loughborough, England.) digitises the output of the physiological amplifier at a rate of up to 5KHz. It provides a linear output for an input voltage range of ±2.5V.

2.2.5 Digital signal processing (DSP) Card

This is a board made by Loughborough Sound Images (Loughborough, England) which is used to process the output of the ADC card. The PC can access the DSP card memory while it is operating, and while the DSP card is liasing with the ADC card, the PC is free to perform other tasks. The card used a Texas instruments TMS 320C processor (superdual VGA) operating at 50 MHz.

2.2.6 Video Graphics Adapter (VGA) Card

A dual Video Graphics Adapter (VGA) card by Colorgraphics communications (Atlanta Georgia) drives the two monitors required by this system. This was compatible with the standard IBM VGA.

2.3 Software currently in use

2.3.1 Languages

The programming languages used within the system are:

1) Pascal version 3.3 for the main system control.

2) TMS320C40 assembly language to control the DSP card.

3) 80286 assembly language to control the VGA card and provide communication between the P.C and the DSP card.

4) DOS macros to call the programs

2.3.2 Operating system

The PC uses Microsoft Disk Operating System (DOS). DOS is a single-user operating system from Microsoft that controls the operation of IBM and IBM-compatible PCs. Since the 1990s PC's have commonly been controlled by the Windows operating system. As the main objective of this project was to accurately collect data, analyse data and present results simultaneously in real-time it was important to consider how each operating system prioritises different tasks. A DOS program can be set up to respond to interrupts, which in turn can be prioritised by the programmer. Similarly the DSP card responds to interrupts from a timer to control data acquisition through the ADC. Early versions of Windows do not allow interrupts to be set up to control priorities. It is possible to perform time critical operations in more recent versions of windows, although this is unstable (Parks 2000. Personal communication). It was concluded that the development work for this program should be carried out in DOS as

development work on the use of interrupts in Windows was beyond the scope of this study.

2.3.3 Transient VEP

Several minutes of recording may be necessary for the observer to identify a VEP in the averaged waveform. Two averaged waveforms are built up in the analysis software by adding raw data into alternate averages as it is collected. This allows reproducibility to be assessed visually by observing the waveforms, and objectively by calculation of the cross correlation coefficient. The cross-correlation method compares corresponding data points from each waveform in the time domain and establishes a coefficient between zero and one. The cross correlation coefficient will be equal to one if the two waveforms are identical. The raw t-VEP waveforms are also displayed so that the tester can check the quality of the raw data being acquired.

When performing a transient VEP (t-VEP) visual acuity assessment, the tester will not move on to a different stimulus size until a response to the present stimulus is confirmed to be present or absent. The tester is aware of the patient's progress and can make decisions on the order and size of subsequent stimuli based on this information. A medium sized stimulus (120') is usually chosen as a starting point rather than displaying stimuli from largest (480') to smallest (3'). If reproducible responses are recorded to this initial stimulus then a smaller subsequent stimulus is presented (60'). If no response is identified, then a larger (240') is presented. This is likely to reduce the number of stimulation periods necessary to find acuity threshold, and will therefore reduce the overall test duration.

2.3.4 Steady-State VEP

The existing steady-state VEP (ssVEP) system (Bradnam 1994) provides observation of raw data but does not perform real-time analysis. Instead a separate analysis program performs post-hoc analysis of the recordings. The rapid collection of data allowed by the fast reversal rate of ssVEPs enables responses to be rapidly detected. Applying maths and statistics rather than identifying the response by eye is objective and can also reduce ssVEP detection time (DT) compared to t-VEPS.

DT reductions through the use of ssVEPs are currently hypothetical as the presence or absence of a response is not calculated in real-time using the current system. A fixed stimulation time of up to 60 seconds per stimulus is typically used. As no analyses are carried out until all recording is completed, recording responses to a large range of stimulus sizes is necessary to ensure the visual acuity threshold region is spanned in all subjects.

2.4 Optimising steady-state VEP recording

2.4.1 Introduction

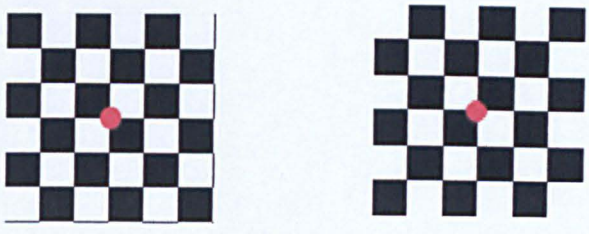
ssVEP stimulation and recording has been outlined. The type of stimulus used and the location of recording electrodes can be varied with a view to providing the best possible quality of recordings. Once good quality recordings have been made, mathematical analysis and statistical techniques (collectively known as signal processing) can be applied to further eliminate unrelated electrical activity from the recording and to define whether a response to stimulation is present or absent. In the current ssVEP system, the signal processing is performed by computer software. The analysis parameters of this program could be varied in order to achieve the fastest possible detection of responses.

2.4.2 Stimulation Parameters

The screen refresh rate describes how often the stimulation monitor updates its display. Figure 2.3 shows the two states of a reversing checkerboard. The time it takes to display both states and return to the first one is called the stimulation period. The time period that each state is displayed for is therefore half the stimulation period, and the number of times the display switches between states every second is called the reversal rate.

The sampling (or digitisation) rate of the ADC card refers to the number of times the response waveform is sampled every second to create a discrete array of values describing the waveform. There must be an exact number of data samples per checkerboard stimulus state to ensure all response power is confined to one bin in the frequency domain representation of the recording (described in more detail in section

2.4.4). Response power spread across several frequency bins is called spectral leakage and leads to a reduction in signal to noise ratio (SNR).



State 1 **State 2**

Figure 2.3: The two states of a reversing checkerboard.

The epoch used for analysis should have an integer number of stimulation periods. This means that when raw data segments are averaged, the response timings correspond resulting in signal maintenance and noise cancellation. More than ten stimulation periods per epoch will allow recording artefacts to be observed (Bach & Meigen 1999). For example, low frequency muscle noise could add to the amplitude of the response and may go unnoticed if responses are analysed in isolation. Observing ten responses at a time would allow comparison of several response amplitudes and enable identification and removal of a low frequency or DC noise level. However, in practice, this may be time consuming and can add subjectivity to the analysis technique.

2.4.3 Electrode montage

The 10-20 system is a map of electrode placement for the recording of the electroencephalogram (EEG). It was devised to standardise EEG recordings by using percentages of total head circumference to space the electrodes (Jasper 1958). VEP recording is concerned only with the occipital region of the brain and therefore only the O_z, O1 and O2 sites of the 10-20 system are located in the area of interest. The Queens square system (Blumhardt *et al.* 1977) was designed specifically for VEP recording with more sites over the visual cortex. It uses a fixed electrode spacing of 3cm and 5cm for children and adults respectively. Figure 2.4 illustrates the placement of electrodes in the 10-20 system.

Analysis of the potential difference between O_z and F_z is an example of monopolar recording. Monopolar recording uses a electrode site distant from the active site as its noise reference, such as F_z in VEP recording whose position means that it is as distant as possible from activity in the visual cortex. This results in signal preservation and some noise cancellation.

Bipolar recording uses an additional active site that is also compared to a distant reference electrode. The difference between these two channels provides the data for analysis, which effectively brings the noise reference closer to the active site. The noise

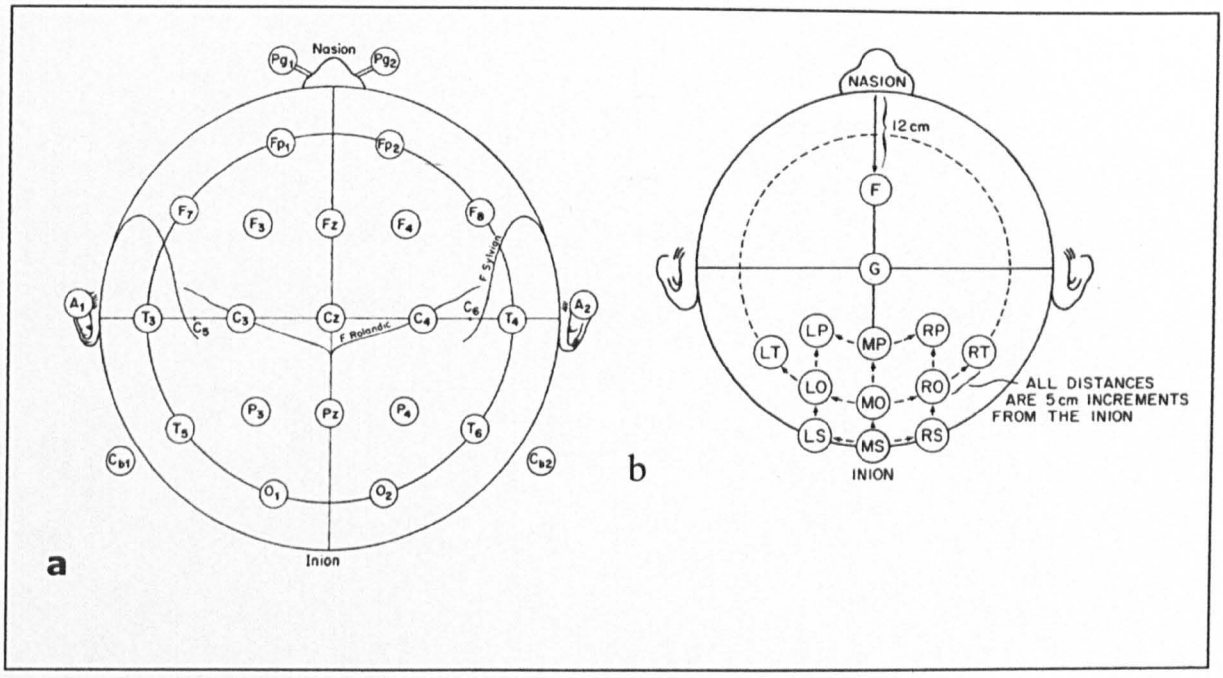


Figure 2.4: a) the 10-20 map of electrode placement for EEG recording and b) the adapted Queens square map for VEP recording.

measured by this additional local electrode will have greater coherence with noise measured at the active site compared to the noise measured by distant electrode site, and therefore more noise will be cancelled. In VEP recording, for example, O1 and O_z will have greater noise coherence than F_z and O_z.

An alternative montage makes use of the Laplacian analysis. In Laplacian analysis several local reference electrodes are used to measure current density at a central site. It is based on the premise that the tangential current around a central point should be equal, by current conservation, to the radial current from the area on the cortical surface under this central point (Nunez 1981). This gives a different picture to standard referential recording and is used to locate the source of cerebral potentials. The Laplacian analysis is best described generally as a spatial filter that emphasises local sources and reduces the contribution of distant sources. (ibid.).

Taking the second spatial derivation of electric potential measured by a two dimensional, symmetrical array of electrodes, as illustrated in figure 2.5 performs the Laplacian analysis.

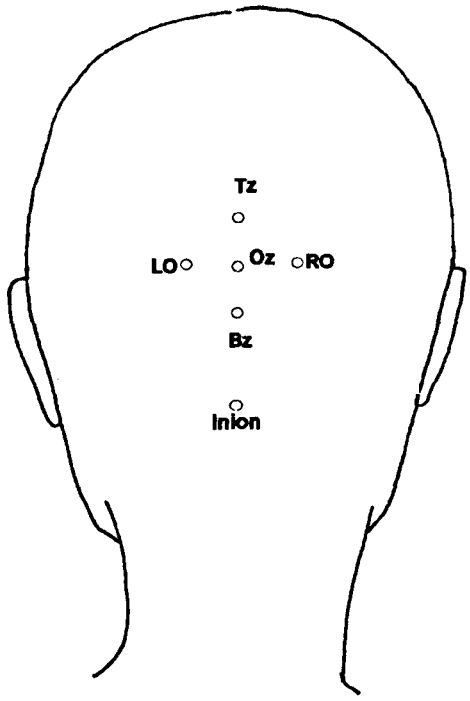


Figure 2.5: Typical active electrode array used in a Laplacian analysis.

The measured quantity is proportional to the current emerging from the scalp (Nunez 1981). A negative value corresponds to the convergence of current into the scalp and therefore a current sink. If there is a lot of measurement noise (from external sources) present in the recording rather than physiological noise this analysis is not recommended (Bradshaw & Wikswo 2001). For example, a faulty central electrode would result in noise being amplified rather than cancelled which would cause the SNR of the recording to be reduced

The use of multiple active occipital sites referenced to the same place (F_z for example) is known as common reference recording (Harding & Rubinstein 1980). The ISCEV standard recommends monopolar recording from O_z-F_z and additional active recording sites to investigate the lateralisation of the VEP (Harding *et al.* 1996). O1 and O2 are placed laterally, 10% of the half-head circumference from O_z, and analysed in common reference mode. It is possible that these electrodes, which are recommended to investigate the spread of the VEP with time, could also be used to describe the VEPs instantaneous distribution in space. This will be discussed further in chapter three.

2.4.4 Signal processing

After data samples are filtered and amplified, mathematical analysis is performed by computer software. The fourier transform can be used to characterise a linear system by identifying its frequency components (Bracewell 1965). The inverse fourier transform reverses this process by expressing frequency information in the time domain. To perform a fourier transform computationally, continuous waveforms are sampled using a discrete fourier transform. The Fast Fourier Transform (FFT) (Cooley & Tukey 1965)

is an optimised version of the discrete fourier transform which reduces the amount of computation by cancelling unnecessary terms. A mathematical derivation of the FFT equations can be found in the paper by Bergland (1969). If the stimulus rate is known, as it is in ssVEP recording, then the bin in the frequency spectrum that contains any response power is known. The relative power contained in this bin is used to decide if a response is present or absent. The analysis epoch must contain N^2 data points (Jervis *et al.* 1989) for FFT analysis, where N data samples in the time domain contain a finite number of stimulation periods. Other constraints are placed on the analysis epoch depending on the signal detection criteria used.

The display period will include an integer number of screen refreshes, and ideally the screen refresh rate and the sampling rate of the ADC card should have an integer relationship (Bach & Meigen 1999) to avoid spectral leakage. The sampling rate (f_s) must also be higher than twice the nyquist frequency, f_N, to prevent aliasing (section 2.2.4). Even if the analysis is only concerned with low frequency components, these can still be affected by the presence of high frequency components when digitisation is performed below twice the nyquist frequency. The sampling rate, f_s, and analysis epoch determine the number of points per analysis segment. The number of data points per analysis segment (N) and the time between data samples ($T_s = 1/f_s$) determines the spectral resolution of the FFT output. Each frequency component is separated from its neighbour by $1/(N-1)T_s$. The sampling rate should be set so that the spectral resolution of the FFT output is conducive to the response power being present in a single bin only (Bergland 1969). This will improve SNR when the recording is analysed in the frequency domain and result in reduced detection times.

An alternative definition of response detection is provided by circular T squared statistics (T^2_{CIRC}) (Victor and Mast 1991). It is applied to the output at the stimulation frequency after performing fourier analysis on un-averaged data. A circular confidence interval in polar co-ordinates illustrates the variance of response amplitude and phase across data samples. The radius of this circle also depends on the pre-set statistical significance level. A response detection is declared when the area of the circle is independent of the origin which indicates that the response magnitude is unlikely to be equal to zero.

Adaptive filtering (AF) provides an alternative technique to separate the response signal from the background noise during ssVEP recording (Cluckie *et al.* 1994; Tang & Norcia 1995). This method uses a least squares algorithm to determine the presence of a response, comparing the EEG to a sinusoidal reference at the stimulation frequency. The filter adapts over time, as often as once per data sample if desired, using the error between reference and real signals. In theory, adaptive filtering would provide the closest thing to real-time analysis of ssVEP recordings. However the minimum appropriate analysis epoch is constrained by the statistical techniques used to determine response detection. These constraints are outlined in the following sections.

2.4.5 Signal to noise ratio

The FFT quantifies the response power present at the stimulation frequency. Further calculation is necessary to determine if this is larger than the EEG in general in each individual. As the frequency of stimulation is known in ssVEP recording, the representation of the EEG in the frequency domain (after transformation by FFT) can be

used to calculate response magnitude and the magnitude of background electrical noise. The noise measurement comes from neighbouring bins in the frequency domain to the bin that contains signal power. The bin at the stimulus frequency in a frequency domain representation of an unstimulated control recording can also be used to provide a noise measurement, however this was shown to give a less statistically significant SNR (Meigen & Bach 1999). Empirical relationships between signal and noise (Norcia & Tyler 1985a; Norcia *et al.* 1987) have been used to set SNR detection criteria. A 0.3% false detection rate (or specificity of 0.997) was reported in 100 control samples when the SNR required for signal detection was set to three. The more rigorous mathematical treatment of Meigen and Bach (1999) confirms that the analysis epoch of one second and a stimulation frequency of 12Hz provided adequate spectral resolution for analysis. It was also calculated that an SNR of 3 ensures the response is statistically larger than noise with $p=0.04$, which can alternatively be expressed as a false detection rate of 4%. The 0.3% false detection rate in Norcia's study was calculated from the average noise measurement of 100 different 10 second EEG samples. However, this is not the same technique used to quantify noise in VEP SNR calculation in his study (thus forming the inclusion criteria for amplitude extrapolation). During sweep VEP recording, the noise measurement is taken from bins in the frequency domain either side of the stimulus frequency. The latter noise measurement is likely to be more variable between and within individuals than the average of 100 samples. This should result in an experimental false detection rate closer to 4%.

As well as expressing a quantity calculated in the frequency domain, the term signal to noise ratio can also be used to describe the quality of the VEP recording in the time domain. Figure 2.4 shows several active occipital electrodes that can be used to record

the ssVEP. At any instant in time during stimulation there will be differing proportions of response signal and unrelated noise recorded by each electrode. The further the electrode is from the site of neural activity, the less response signal will be present in relation to the noise and therefore the poorer the SNR in the time domain will be.

2.4.6 Statistical techniques

As the ssVEP is of a similar magnitude to background EEG, the SNR of one sample of ssVEP recording is likely to be no more than one. However, as in t-VEP recording, signal averaging can rapidly eliminate noise during ssVEP recording. Signal averaging followed by FFT analysis and SNR calculation can identify a ssVEP response in a matter of seconds. The SNR required to declare response detection depends on the statistical significance required.

If an FFT is performed on un-averaged data then phase sensitive statistics can be applied to the real and imaginary output at the stimulation frequency. Phase sensitive statistics can also be applied to the bivariate output of adaptive filtering. Magnitude Squared coherence (Dobie & Wilson 1989) was shown to be more sensitive than either T^2_{circ} statistics (Victor & Mast 1991) or Hotellings T^2 statistics (Hotelling 1951), however it proved to have a poorer specificity than T^2_{circ} statistics (Bradnam & Hamilton 1997). All three tests used both amplitude and phase information, and were better than the phase coherence technique, which ignores amplitude information. They were also better than the central limit theorem that assumes the distribution of the two estimates in a rectangular co-ordinate system are independent (ibid.).

2.5 Alternative Systems

2.5.1 The Sweep VEP

The sweep VEP acuity assessment was introduced in section 1.3.3 (Regan 1977; Tyler *et al.* 1979). It was designed specifically for the assessment of acuity in children and its primary goal is rapidity. It typically presents 20 different steady-state stimuli over ten seconds after which an estimate of acuity can be made. However, the statistical significance of this estimate is improved if several sweeps are averaged. In practice a typical assessment comprises eight to ten sweeps (Candy 2001. Personal Communication). The sweep VEP was evaluated by Norcia & Tyler (1985a;1985b) in infants. The range of stimulus sizes can be varied depending on the age and diagnosis of the subject, and the range typically spans either 20:1 or 30:1 in 20 linear or logarithmic spatial frequency steps respectively (Norcia & Tyler 1985a; Norcia & Tyler 1985b, Piecuch *et al.*1987). Fourier analysis is performed on twenty one-second data segments after each sweep, and the resulting amplitude is plotted against spatial frequency. The one-second analysis 'window' spans two stimulation epochs but only moves forward by 0.5 seconds at a time. This provides some smoothing of the spatial frequency-amplitude function. To be considered significant, the response amplitude must be sufficiently larger than the noise measured at a nearby frequency bin and response phase must be equal to or gradually lagging the phase of responses to larger pattern sizes. The requisite value of SNR can be varied depending on the specificity and sensitivity required.

It is also possible to apply statistics to the analysis of sweep VEPs (Zemon *et al.* 1997). As the technique requires at least two data samples to perform analysis, the minimum

sweep length would be 20 seconds for 20 different stimuli. Data samples to each stimuli would be collected ten seconds apart, which ensures the independence of EEG samples (Victor & Mast 1991) demanded by T^2_{circ} statistics. Although this increases single sweep duration, less sweeps may be necessary to identify statistically significant responses. A sweep VEP system has been adapted in specific research studies to present each stimulus for eight seconds (Ridder *et al.* 1998).

If the co-operation of a patient is poor during sweep VEP assessment then few sweeps may be possible. One sweep, for example, may not identify any statistically significant responses. By using a fixed range of stimulus sizes; the sweep VEP paradigm may be spending time stimulating away from an individuals acuity threshold. Some stimuli presented in the sweep may be substantially larger than the patient's spatial resolution threshold and thus time will be wasted gathering data that will not be included in the amplitude extrapolation. If there appears to be nothing on the screen, then loss of attention is probable. If many of the stimuli are smaller than the patient's spatial resolution threshold then little information will be gathered and/or attention may be lost.

2.5.2 Review of commercial systems

Table 2.2 summarises the stimulus and amplifier specification of several commercial visual electrophysiology systems. The in house system of the RHSC in Glasgow is also included for comparison. All the commercial systems are capable of presenting checkerboards, square wave gratings and sine wave gratings in pattern onset or pattern reversal mode. The amplifier filter specifications adhere to the ISCEV standard

(Harding *et al.*1996) which is described in more detail in section 2.2.2. The stimulus parameters included in table 2.2 are those relevant to the assessment of visual acuity.

It is recommended that the stimulated field size is 15 degrees or more for VEP recording to all stimulus sizes to ensure that response morphology is preserved (Harding *et al.*1996). However, no specific standard for VEP acuity estimation exists and it is postulated that preservation of response morphology is irrelevant to acuity estimation; this will be discussed further in section 5.4.3. For now, the maximum viewing distance specified in the table refers to the distance at which the given stimulus monitor subtends a field of 15 degrees. The minimum stimulus size given refers to a check width presented at the maximum viewing distance, which is limited by the resolution of each stimulus monitor, expressed in dots per inch (dpi). Normal adults may have detectable VEPs for stimulus sizes as small as 1.5'(Mackay 2001). It is important to exceed the capabilities of a patient in order to establish the threshold of spatial resolution. A system with small minimum check size and a large number of increments in spatial frequency is capable of determining accurate thresholds in patients with a wide range of visual acuities. As the aim of the project is to develop a paediatric acuity assessment, it should be noted that the minimum stimulus size necessary to establish threshold in children may be larger than 1.5'required in normal adults.

The number of recording channels and amplifier common mode rejection ratio are also included in table 2.2 for comparison. The common mode rejection ratio should be as large as possible to maximise the SNR in the time domain on each channel. The number of recording channels is also relevant to the SNR and will be investigated in chapter three.

Table 2.2 Specification of commercial electrophysiology systems for acuity assessment. The maximum distance refers to the maximum viewing distance that maintains a field size of 15°.

System	Monitor Size	dpi	Max distance	Min Stimulus	Max Contrast	Max Luminance	Max Reversal Rate	Channels	CMRR
RHSC	13"	56	77cm	1.8'	100%	100cd/m^2	70	4	>125
Espion	19"	52	111cm	1.25'	100%	>100cd/m^2	30	5	>100
LKC	15"	85	88cm	1.1'	100%	80cd/m^2	30	8	>120
Roland	15"	85	88cm	1.1'	100%	80cd/m^2	30	8	

2.6 Visual Acuity Estimation

Visual acuity can be expressed as the fundamental spatial frequency of the smallest checkerboard, sinusoidal or square wave grating to which a response is detected. The spatial frequency of a square wave grating or checkerboard can alternatively be expressed as the visual angle corresponding to one period of its fundamental spatial frequency component. For square wave gratings this will be equal to two bar widths, for checkerboards this is equal to one check diagonal. The term subjective acuity is used in this study to describe the outcome of acuity cards and letter charts. Although different units are used by different tests to express acuity, these are interchangeable. Converting test scores into common units allows comparison of test outcomes in the same subject.
The formula for conversion between units and a table of equivalent values is included in appendix A.

If intra-cellular recordings could be made in normal adults, it is postulated that VEP acuity will be systematically higher than subjective acuity measurements. The reason being that VEP detection requires a response in the primary visual cortex (V1) only, whereas subjective tests require varying degrees of additional cortical processing. However, VEPs are attenuated on their journey through cortical tissue and the skull. VEP acuity determined by recordings from a scalp electrode therefore tend to be poorer than subjective acuity measured in the same subject. The relationship with subjective acuity may also be different for t-VEPs and ssVEPs due

to the presence of different pathways for different stimulus temporal and spatial combinations.

The relationship between VEP and subjective acuity is also likely to be affected by visual pathway maturity and general cortical maturity. If post-V1 damage is present, then hypothetically a reduced subjective acuity could occur when VEP acuity is normal. The degree of disparity between t-VEP and subjective test results has been shown to vary with different pathologies (Westall *et al.* 2000).

Estimation of visual acuity derived from VEP recordings can be expressed in three ways:

1) The smallest stimulus (in angle or LogMAR) that evokes a response statistically larger than background noise. This is called either smallest check size(Skalka 1980) or critical check size(Katsumi *et al.* 1994)and has been applied to both t-VEPs and ssVEPs.

2) The point of interception with noise after extrapolation of the spatial frequency-amplitude function. Linear regression (extrapolation) is only valid if there are enough statistically significant responses to identify a descending limb on the spatial frequency amplitude function. This technique has been applied to both t-VEPs (Sokol 1978) and sweep VEPs (Tyler *et al.* 1979).

3) The range of subjective acuities that VEP critical check size corresponds to in a normative study or particular patient group(Katsumi *et al.*1994).

Clinically, VEP acuities could be compared to a set of normal values for age, or they can be used to estimate subjective acuity and thus can be compared to normal indirectly. The disparity between VEP and subjective acuities in specific patients may provide the clinician with additional diagnostic information.

2.7 Discussion

ssVEP analysis is currently performed off-line, and more data than necessary is often collected for each stimulus in order to ensure statistical significance of any responses present. If analysis is performed post-hoc then more stimuli than necessary may be presented. A typical ssVEP acuity assessment typically requires six stimulation periods and therefore around six minutes of recording. Recording for six minutes can necessitate test durations of up to 45 minutes after periods of inattention have been accounted for. At present, the duration of ssVEP acuity test duration is likely to be longer than the duration of t-VEP acuity assessment.

Maximising the SNR during each recording will result in a reduction in DT. This may result in a significant reduction in test duration. Arranging the electrodes in such a way as to optimise recording signal to noise ratio is also an area for investigation.

If statistical analysis could be carried out during recording (in real-time) then only the necessary amount of data would be recorded for each stimulus before moving on to the next. This would substantially reduce recording time during ssVEP acuity assessment.

Real time analysis would allow the presence or absence of a response to a specific stimulus size to be known during recording. Therefore the computer could also be programmed to choose the most appropriate stimulus to show next. Reducing the number of stimulation periods would provide a reduction in overall test duration.

ssVEP analysis performed in real time would fully exploit the time improvements over t-VEPs offered by the rapid accumulation of data due to the fast reversing stimulus and the objective analysis by computer program that is facilitated by the periodic ssVEP waveform.

2.8 Aims of Study

The aim of this study is to update the ssVEP stimulation and recording software currently in use to allow online statistical analysis. Knowing when to stop recording and move on to a different stimulus will drastically reduce test duration. The study will attempt to further optimise test duration by:

1) Investigating which ssVEP recording electrode montage provides the highest SNR and therefore the fastest DTs.
2) Optimising signal processing parameters to obtain the fastest possible DTs.
3) Investigating stimulus presentation algorithms to find spatial resolution threshold with the minimum number of stimulation periods.

SsVEPs will be compared to subjective testing in the same patient and on a separate group of patients receiving a t-VEP acuity assessment. The tests will be evaluated in terms of success, test duration and test outcome on a group of real patients requiring visual acuity assessment.

Chapter 3: 1-D Laplacian analysis of ssVEPs in normal adults

3.1 Introduction

A typical VEP acuity assessment records responses to at least five differently sized stimuli. Within each of these stimulation periods, the time taken to detect a VEP can be reduced by optimising the signal to noise ratio (SNR) of the recording. The VEP SNR in the time domain is optimised when a response measured at O_z has most of its background noise cancelled by the reference electrode. The noise at both active and reference electrodes must be similar (coherent) for this to happen. A distant reference electrode is chosen in referential recording because the activity it measures is unlikely to be related to the active electrode, resulting in little or no signal cancellation. Conversely, the further the reference site is from the active site, the less coherent the recorded noise activity will be, resulting in little or no noise cancellation.

As the Laplacian procedure requires only a sample of the potentials surrounding the central point, hexagonal, square and triangular electrode arrays are all considered to be valid (Mackay 1983) with no loss of information from the 10-20 system (Wallin & Stalberg 1980). A 1D Laplacian analysis has been used to study the sources of potentials at various cortical depths (Petsche *et al.* 1984) and in the source derivation technique to attempt to identify the origin of responses to specific stimuli (Clement *et al.* 1985). However a valuable benefit of Laplacian analysis to rapid VEP

recording is the SNR improvement (Srebro 1992). We propose that a 1D Laplacian analysis adequately samples the potentials surrounding a central point (O_z), improves SNR thus allowing faster VEP detection and economises the number of electrodes required.

The rapid rate of data collection afforded by steady state stimulation is also ideally suited to rapid VEP acuity assessment. The clinical application of steady-state VEPs (ssVEPs) is supported by significantly small intra-subject variability of amplitude and phase (Tobimatsu *et al.* 1996). Further time benefits are predicted by increasing the SNR through applying a 1D Laplacian analysis to an electrode array centred on O_z. The purpose of this study was firstly to assess whether these improvements would reduce the duration of ssVEP recordings and secondly to determine where best to locate the Laplacian reference electrodes.

3.2 Methods

3.2.1 Subjects

The overall aim of the thesis is to develop a paediatric acuity assessment. However, it is preferable to use ophthalmologically normal, co-operative volunteers for many of the initial experiments as their attention span tends to be longer, facilitating a more in depth investigation. A paediatric patient group can then be studied based on the preliminary findings in adults (see chapter 4). Twenty-two volunteers were studied with ages ranging from 24 to 52 years. Optical correction was worn if required. Visual acuity was measured using Glasgow Acuity Cards (McGraw & Winn 1993) to confirm that optically corrected vision was normal; this ranged from LogMAR 1.00 to 1.20 (6/6 to 6/3.75 Snellen equivalent). The local ethics committee approved the study, and informed written consent was obtained from each subject.

3.2.2 Stimulation

Black and white checkerboards reversing at 7.78 Hz were presented by a custom-built VEP system (Bradnam 1994). The reasons for using this stimulation rate are discussed in section 5.2.3. Six different stimulus check sizes from 60' down to 1.5' were presented for 60 seconds each. The largest check size (60') was repeated to test for adaptation effects during the experiment: detection times showed no significant difference over the duration of the experiment, suggesting that responses were

unaffected by cortical adaptation effects. The mean luminance of was 60 cd/m^2 and the contrast was 100%. The stimulus field size was 30°×24°, except for the 1.5' checks where the field size was 15°×12°. An isoluminant grey screen was presented for 25 seconds between each recording epoch to prevent cortical adaptation to a stimulus contaminating subsequent responses (Ho & Berkley. 1988). Figure 3.1 illustrates the order of stimulus presentation.

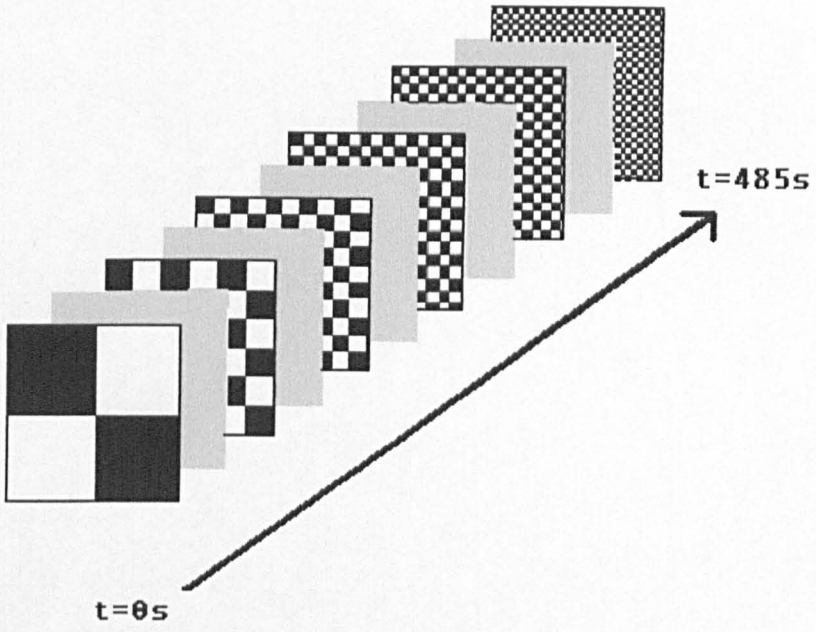


Figure 3.1: Stimuli were presented from large (60') to small (1.5') checks for 60 seconds each with an isoluminant grey screen presented for 25 seconds between each stimulus. This protocol was repeated for all five lateral electrode positions.

3.2.3 Recording

The electrode montage used for each recording is shown in Figure 3.2a. This comprised electrodes at O_z, and horizontally either side of O_z, denoted by LO and RO. All three electrodes were referenced to F_z. Five different positions for the LO and RO electrodes were investigated, positioned at 5% increments of the half-head circumference, 5%, 10%, 15%, 20% and 25% (Figure 3.2b). The 10% positions coincided with O_1 and O_2 of the 10-20 system (Jasper H).

3.2.4 Spatial structure of the ssVEP

The method of Spitzer *et al* (Spitzer *et al.* 1989) was used to ensure the electrodes were appropriately spaced by describing the instantaneous spatial bandwidth of typical responses to near-threshold (3') and supra-threshold (12') stimuli. The potential measured across the occiput in response to each stimulus was Fourier transformed and presented in the spatial frequency domain allowing the spatial bandwidth (B) of the evoked response to be calculated. The Nyquist distance, 1/2B, describes the minimum spacing of electrodes required fully to describe the evoked response.

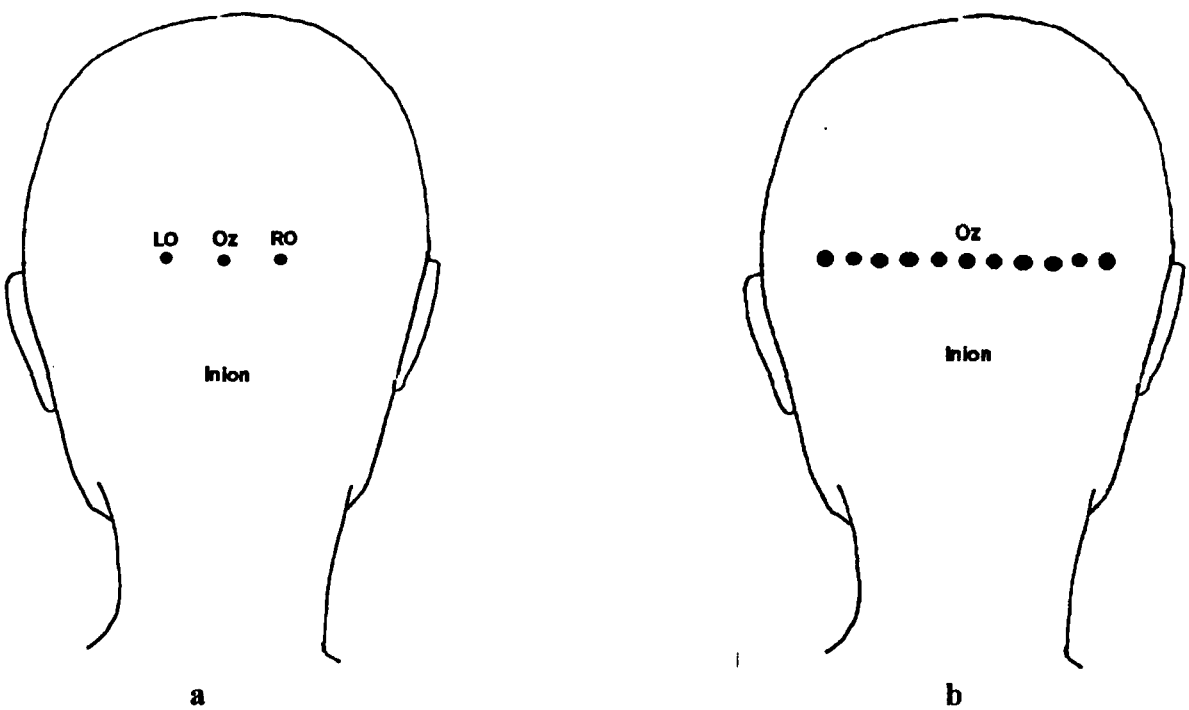


Figure 3.2: a) Standard analysis used O_z-F_z. Laplacian analysis is applied off-line to the transformation $2O_z$-(RO+LO). b) Five different positions for the lateral electrodes RO and LO were investigated for use in a 1D Laplacian analysis. The O_z-LO/RO distance was varied in increments of 5% of the half-head circumference.

3.2.5 Analysis

Analysis was carried out offline. Standard analysis used data from O_z-F_z; the 1D Laplacian analysed $2O_z$-(RO+LO), where RO and LO refer to the potentials measured by the pair of lateral electrodes. Four-second data epochs were analysed by Fast Fourier Transform (FFT), followed by a circular t^2 statistical test for significance (Victor & Mast 1991). Statistical significance (α) was set to 0.005 and if a ssVEP was detected, response amplitude, phase and SNR were calculated and DT defined.

For all recordings where responses were detected both on O_z-F_z and the 1D Laplacian channel being investigated, repeated one-way ANOVAs and Kruskal-Wallis tests were used to compare DTs as a function of lateral electrode position, stimulus check size and subject. Common reference analysis was also applied to this set of recordings and ANOVAs and Kruskal-Wallis tests were used to compare DTs and mean VEP phase at DT on O_z-F_z with each of the five left[Ψ] occipital channels referenced to F_z.

[Ψ]A Comparison of equivalently lateral right and left hand channels showed no significant differences with the exception of the 60' response at 25%. In this instance the left hand channel took a median of 4 seconds longer than the right hand channel to detect a response ($p=0.033$)

3.3 Results

3.3.1 Spatial structure of the ssVEP

Figure 3.3a illustrates typical differences in the instantaneous distribution of potentials in response to near-threshold (3') and supra-threshold (12') check sizes. The responses to the smaller checks were confined to a much smaller area than the responses to the larger checks, and had a different composition, with a peak at the midline (O_z) which typically fell off to zero volts by 15% of the half-head circumference around O_z. The 12' responses also had a peak at the midline (O_z) but had additional peaks around 15% of the half-head circumference either side of the midline. The responses extended to at least 25% of the half-head circumference around O_z, which was much further than responses to the smaller checks. Representation of these responses in the frequency domain (Figures 3b and 3c) allow this distribution to be quantified by spatial bandwidth (B). For 12' stimulation, $B=0.19cm^{-1}$, giving a Nyquist distance of 2.63cm. For 3' stimulation, $B=0.29cm^{-1}$, leading to a Nyquist distance of 1.72cm. The average head circumference in this study was 56cm (range: 53-62cm) giving an average 5% of half-head circumference of 1.40cm (range: 1.33-1.55cm). As the calculated Nyquist distances are greater than this range it is reasonable to assume that all the responses measured in this study are adequately spatially represented.

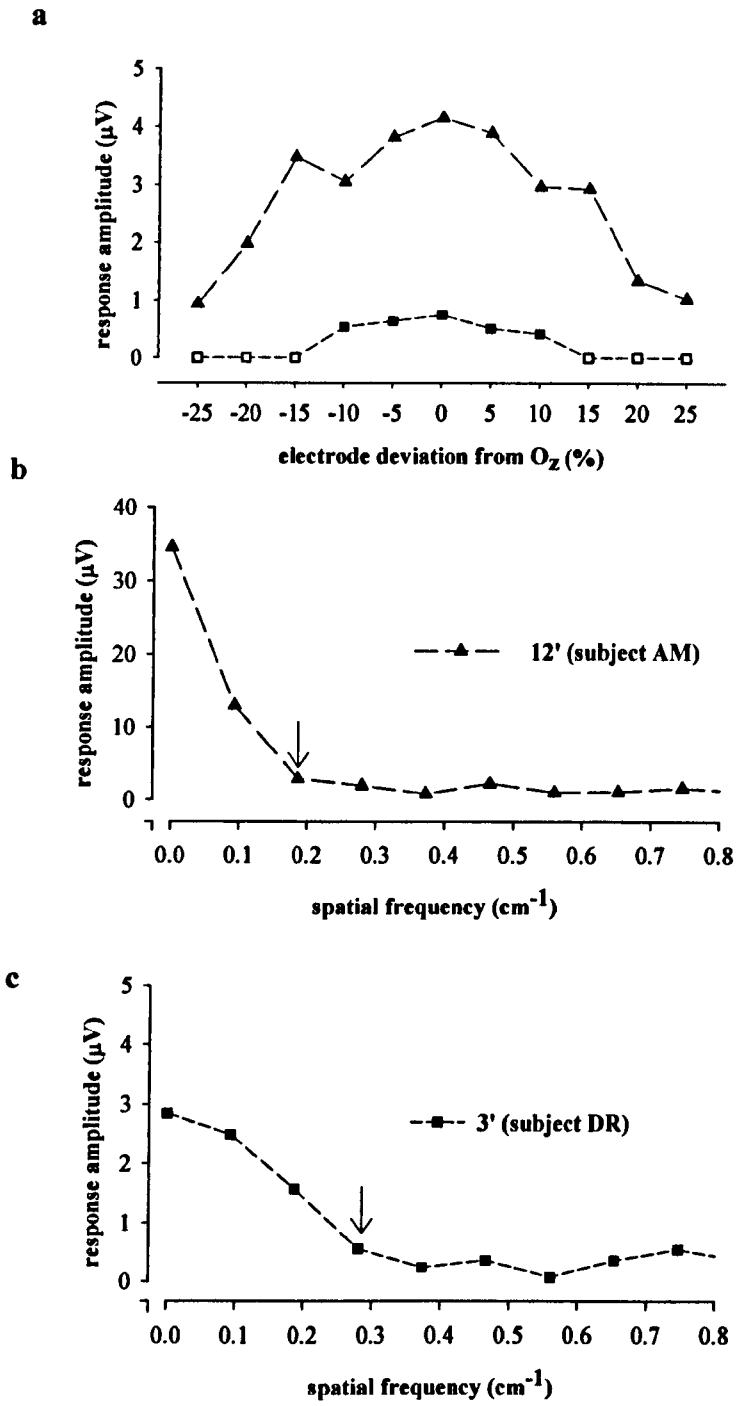


Figure 3.3: a) Typical examples of the instantaneous distribution of potential in steady-state VEPs. The potentials are plotted against the % of the half-head circumference of each subject to allow comparison. Triangles represent responses to 12' checks; filled squares represent responses to 3' checks; empty squares represent absent responses to 3' checks. b) Frequency domain representation of 12' response data and c) 3' response data. The arrows show the 'knee' in the spectrum which was used to define the bandwidth of the response.

3.3.2 1D Laplacian analysis vs O_z-F_z

Table 3.1 illustrates the number of responses detected and length of recording required to detect a ssVEP response to each check size, recorded by the O_z-F_z montage and by each of the five 1D Laplacian analyses. If both O_z-F_z and 1-D Laplacian analysis detected a response during the same recording, the difference between the two DTs was used for further analysis; these DT differences are shown in Table 3.2.

A repeated one-way ANOVA to test for effects of stimulus size, lateral electrode site and subject on the DT difference between recording montages showed that both stimulus size and subject were related to faster 1D Laplacian detections ($p<0.000$). A Kruskal-Wallis test showed that lateral electrode position was also likely to have an effect ($p=0.068$) (Table 3.3). For all the subjects and electrode sites combined, the 1D Laplacian analysis was significantly faster than O_z-F_z analysis for 3' checks but not for larger check sizes (Figure 3.4).

For all the subjects and stimulus sizes combined, no electrode site provides faster detections with a 1D Laplacian analysis (Figure 3.5a). However, if the 3' check size is considered alone, the 1D Laplacian is significantly faster (by 12.3 seconds on average) for lateral electrodes at 15% of the half-head circumference and shows a tendency to be faster (by 4.1 seconds on average) for lateral electrodes at 20% (Figure 3.5b). Each subject was considered individually for the 3' check size in

Figure 3.5c. A 1D Laplacian analysis of a montage with lateral electrodes at 15% was fastest more often than any other montage, although in around half of the subjects, there was no DT difference between 1D Laplacian and O_z-F_z analysis.

3.3.3 Response lateralisation: speed of detection

In common reference recording, the median difference in DTs between O_z-F_z and LO-F_z montages are shown in Table 3.4. A repeated one-way ANOVA to test for effects of stimulus size, lateral electrode site and subject on the DT difference between O_z-F_z and LO-F_z recording montages showed that both electrode site and subject were related to slower LO-F_z detections ($p=0.020$, $p=0.039$) (Table 3.5). For all subjects and electrode sites combined, it took longer on average for a ssVEP to be detected at LO-F_z than at O_z-F_z for each check size (Figure 3.6). For all the subjects and stimulus sizes combined, the two outermost electrode sites (20% and 25%) for LO-F_z provide significantly slower detections O_z-F_z (Figure 3.7).

3.3.4 Response lateralisation: phase

Differences in the response phase for the common reference (monopolar) recordings (Table 3.6) were investigated by a repeated one-way ANOVA to test for effects of stimulus size, lateral electrode site and subject on the phase lag between recording montages, which showed no significant effect. However, a Kruskal-Wallis test showed that stimulus size did affect the phase lag at LO (any electrode site) with respect to O_z-F_z ($p=0.014$) (Table 3.7). Phase differences between LO-F_z and O_z-F_z for responses grouped by stimulus size and electrode site were investigated. This showed that there was a significant phase lag at any lateral electrode sites to 3' checks (Figure 3.8). However, comparison of median phase lag with respect to O_z-F_z for ssVEPs to 3' checks across the five different lateral electrode sites suggests that the lag gradually increases as the electrode site moves further away from O_z (Figure 3.9).

Table 3.1: Time to detect a statistically significant ssVEP to six differently-sized checks, recorded and analysed by six different electrode montages.

	DT (seconds). Median (95% confidence interval)					
	60'	**12'**	**9'**	**6'**	**3'**	**1.5'**
O_z-F_z	12.3 (12.3-16.4) N=22	12.3 (12.3-12.3) N=20	12.3 (12.3-16.4) N=20	16.4 (16.4-16.4) N=19	16.4 (12.3-45.2) N=15	20.6 (20.6-49.4) N=3
Laplacian (5%)	12.3 (12.3-16.4) N=22	12.3 (12.3-12.3) N=20	16.4 (12.3-16.4) N=20	20.6 (12.3-24.7) N=19	20.6 (16.5-45.2) N=15	37.1 (20.6-53.6) N=2
Laplacian (10%)	14.4 (12.3-16.4) N=20	12.3 (12.3-16.4) N=19	12.3 (12.3-16.4) N=18	16.4 (12.3-24.7) N=13	24.7 (12.3-49.3) N=12	- - N=0
Laplacian (15%)	14.4 (12.3-20.6) N=22	16.4 (12.3-20.6) N=20	14.4 (12.3-24.7) N=20	16.4 (12.3-20.6) N=18	20.6 (12.3-28.8) N=11	16.4 (12.3-24.7) N=4
Laplacian (20%)	12.3 (8.2-12.3) N=16	12.3 (12.3-16.4) N=20	12.3 (12.3-20.6) N=18	16.4 (12.3-28.8) N=12	16.4 (12.3-24.7) N=7	20.6 - N=1
Laplacian (25%)	12.3 (8.2-16.4) N=20	12.3 (8.2-16.4) N=20	12.3 (8.2-16.4) N=17	12.3 (12.3-32.9) N=12	16.4 (12.3-28.8) N=12	- - N=0

Table 3.2: Difference in time to detect a statistically significant ssVEP between Oz-Fz and Laplacian montages in the same recording. Results are shown for all six check sizes, recorded and analysed by six different electrode montages.

	O_z-F_z DT minus Laplacian DT (seconds). Median (95% confidence interval)					
	60'	**12'**	**9'**	**6'**	**3'**	**1.5'**
Laplacian (5%)	0 (0-0) N=22	0 (-4.1-0) N=20	0 (0-0) N=20	0 (-8.2-0) N=19	0 (-16.4-0) N=15	-4.1 - N=1
Laplacian (10%)	0 (-4.1-4.1) N=20	0 (-4.1-0) N=20	0 (-4.10-0) N=18	0 (-8.2-0) N=13	0 (-8.2-0) N=12	- - N=0
Laplacian (15%)	0 (-4.1-4.1) N=22	0 (-4.1-0) N=20	0 (-4.1-0) N=20	0 (-4.1-4.1) N=18	12.3 (8.2-24.7) N=11	8.2 - N=1
Laplacian (20%)	0 (0-8.22) N=16	0 (0-4.1) N=20	0 (-8.2-0) N=18	-2.1 (-8.2-8.2) N=12	4.1 (-4.1-20.6) N=7	- - N=0
Laplacian (25%)	0 (-4.1-4.1) N=20	0 (-4.1-4.1) N=21	0 (-4.1-4.1) N=17	0 (-4.1-4.1) N=11	0 (-8.2-4.1) N=11	- - N=0

Table 3.3: Results of statistical comparison of DTs etween conventional and 1D Laplacian channels.

		ANOVA		Kruskal-Wallis	
Parameter	**Degrees of freedom**	**F**	***P***	χ^2	***P***
Stimulus size	4	6.007	0.000***	11.51	0.021**
Lateral electrode site	4	1.392	0.236	8.724	0.068*
Subject	20	3.077	0.000***	67.90	0.000***

* P<0.1

** P<0.05

*** P<0.01

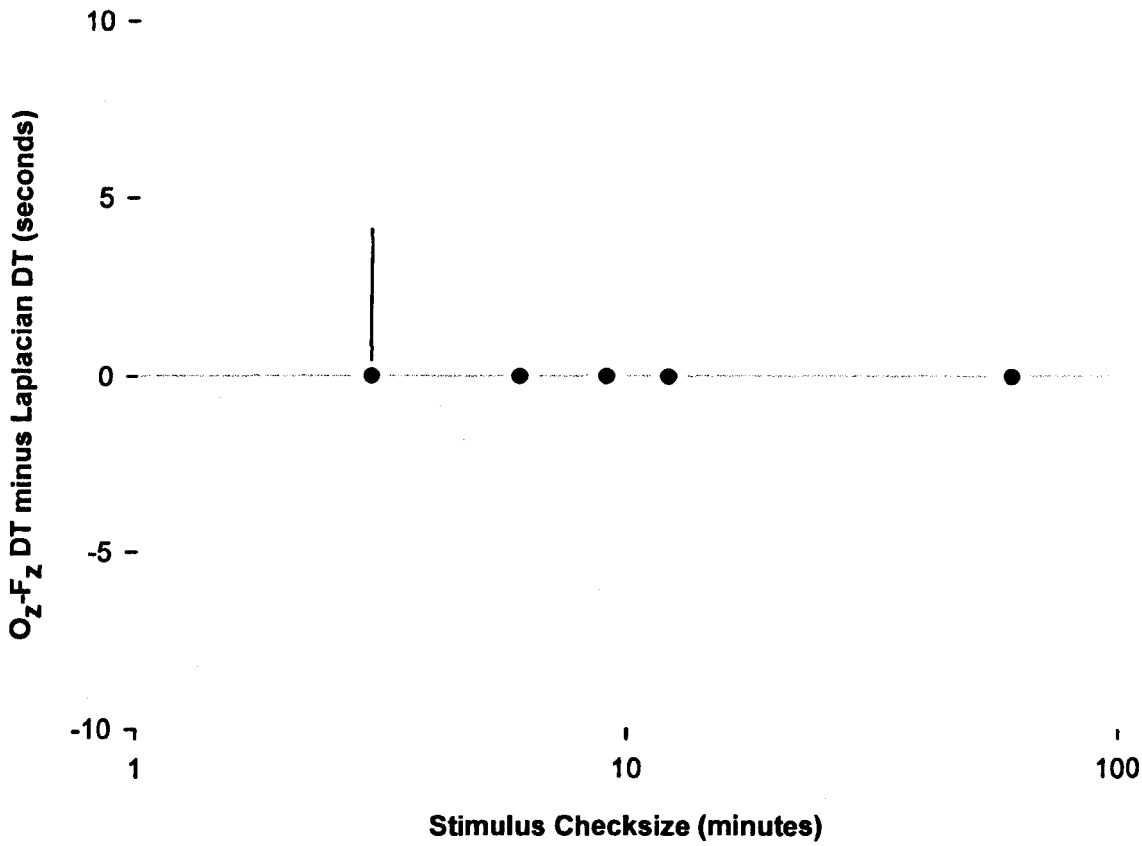
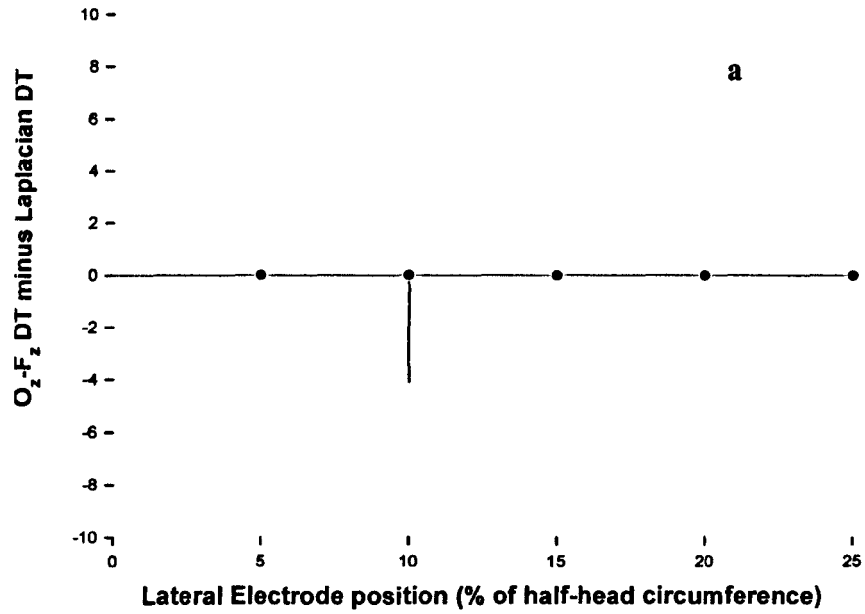
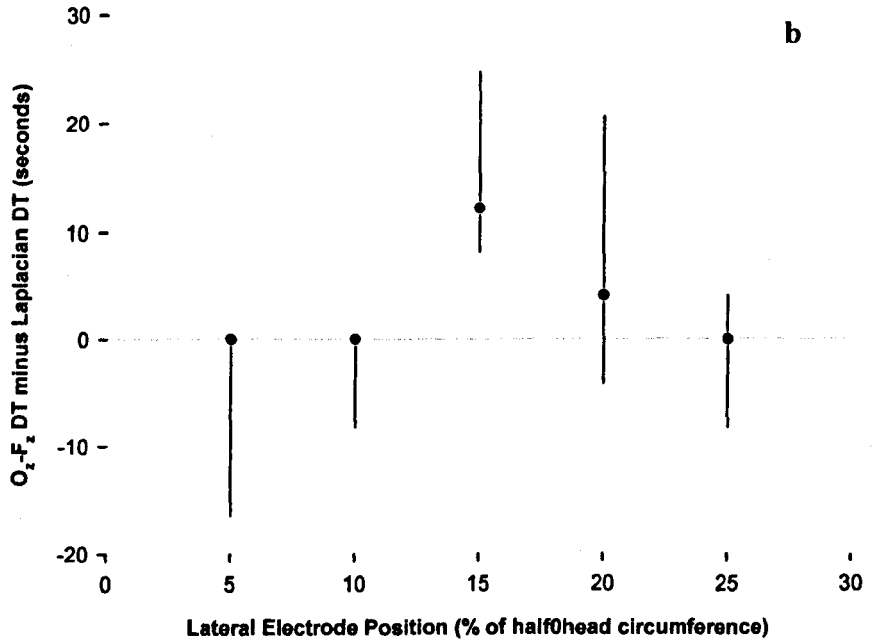


Figure 3.4: 95% confidence intervals of median differences in DT between O_z-F_z and all Laplacian analyses as a function of each stimulus check size.


a
10
8
6
4
2
0
-2
-4
-6
-8
-10
0
5
10
15
20
25
O_z-F_z DT minus Laplacian DT
Lateral Electrode position (% of half-head circumference)


b
30
20
10
0
-10
-20
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25
30
O_z-F_z DT minus Laplacian DT (seconds)
Lateral Electrode Position (% of half0head circumference)

c

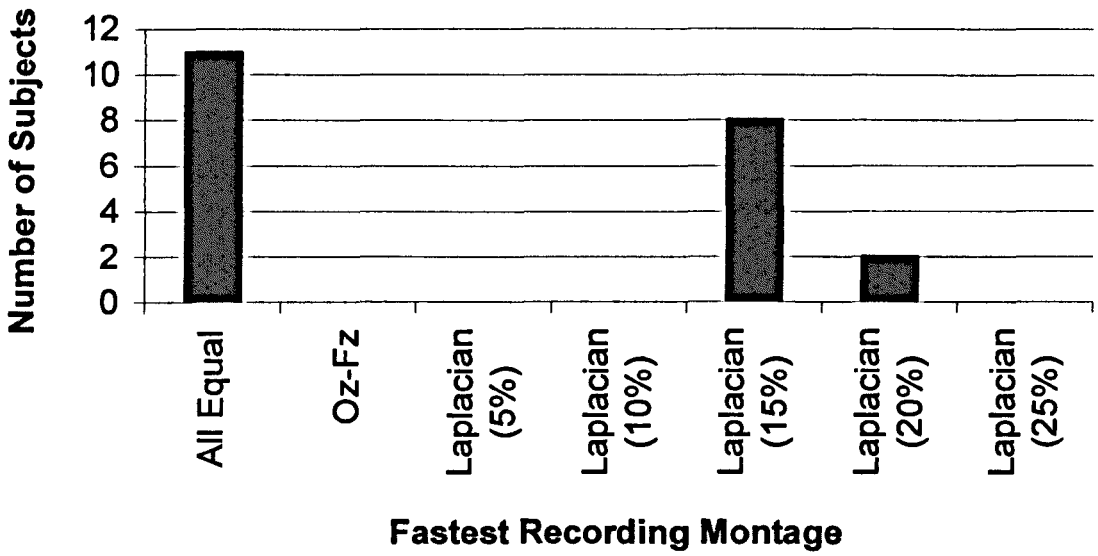


Figure 3.5: 95% confidence intervals of median differences in DT between O_z-F_z and Laplacian analysis as a function of each lateral electrode position for a) all check sizes and b) 3' checks. c) Histogram showing the frequency of fastest detection of VEPs to 3' checks in each subject for each electrode montage.

Table 3.4: Difference in time to detect a statistically significant ssVEP between O_z-F_z and LO-F_z in the same recording. Results are shown for five check sizes and five lateral electrode sites.

	LO-F_z DT minus O_z-F_z DT (seconds). Median (95 % confidence interval)				
	60'	**12'**	**9'**	**6'**	**3'**
5%	0 (0-4.1) N=15	0 (-4.1-0) N=12	0 (-4.1-0) N=18	0 (-4.1-0) N=18	0 (-4.1-4.1) N=6
10%	0 (-8.2-4.1) N=13	0 (-4.1-4.1) N=9	0 (0-16.4) N=11	4.1 (-8.2-16.4) N=2	0 (0-4.1) N=3
15%	0 (-8.2-12.3) N=13	0 (-8.2-4.1) N=13	0 (-4.1-4.1) N=11	0 (-16.4-4.1) N=11	8.2 (-12.3-16.4) N=3
20%	4.1 (-8.2-12.3) N=10	0 (-8.2-4.1) N=14	-4.1 (-16.4-4.1) N=10	0 (0-8.2) N=6	0 - N=1
25%	4.1 (0-32.9) N=7	-4.1 (-16.4-4.1) N=10	0 (-8.2-12.3) N=13	4.1 (0-37.0) N=5	4.1 (-12.3-28.8) N=5

Table 3.5: Statistical test results describing DT lag at lateral monopolar recording sites with respect to O_z-F_z

		ANOVA		Kruskal-Wallis	
Parameter	**Degrees of freedom**	**F**	***P***	χ^2	***P***
Stimulus size	4	0.583	0.676	3.976	0.416
Lateral electrode site	4	2.974	0.020**	6.656	0.155
Subject	20	1.702	0.039**	32.33	0.020**

** P<0.05

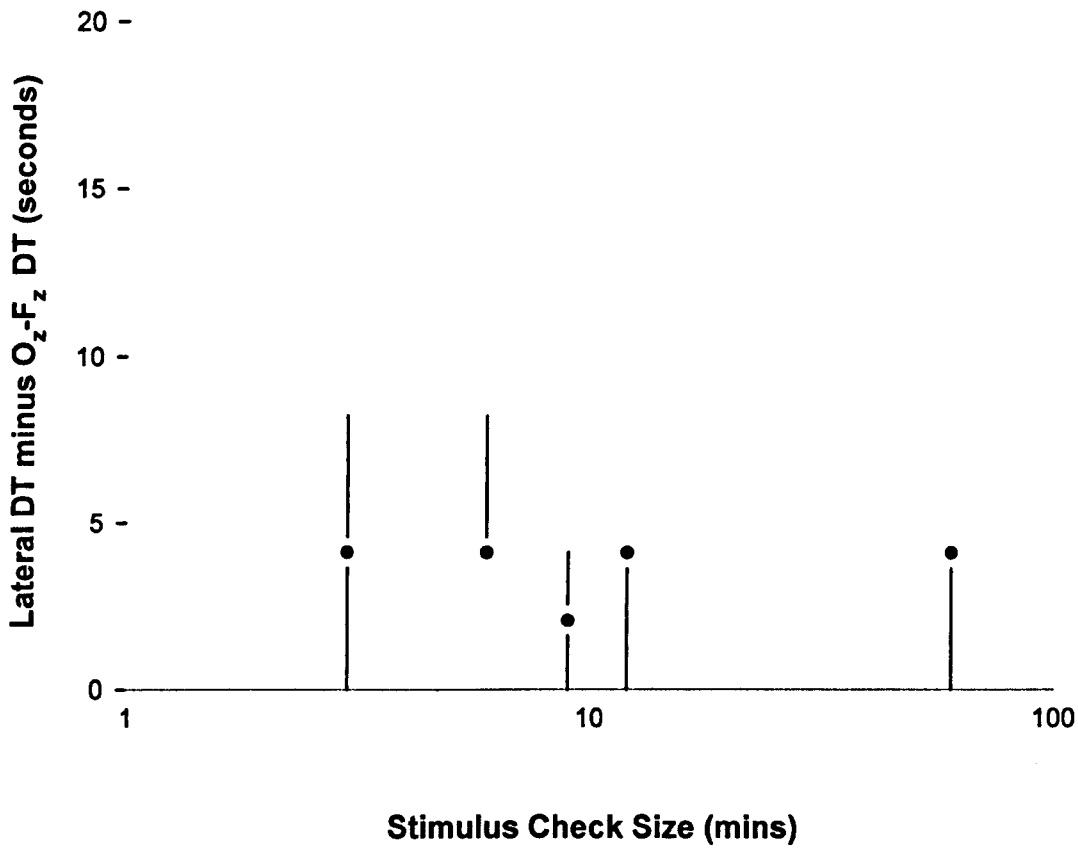


Figure 3.6: 95% confidence intervals of median lag in DT at each lateral monopolar recording sites as a function of check size.

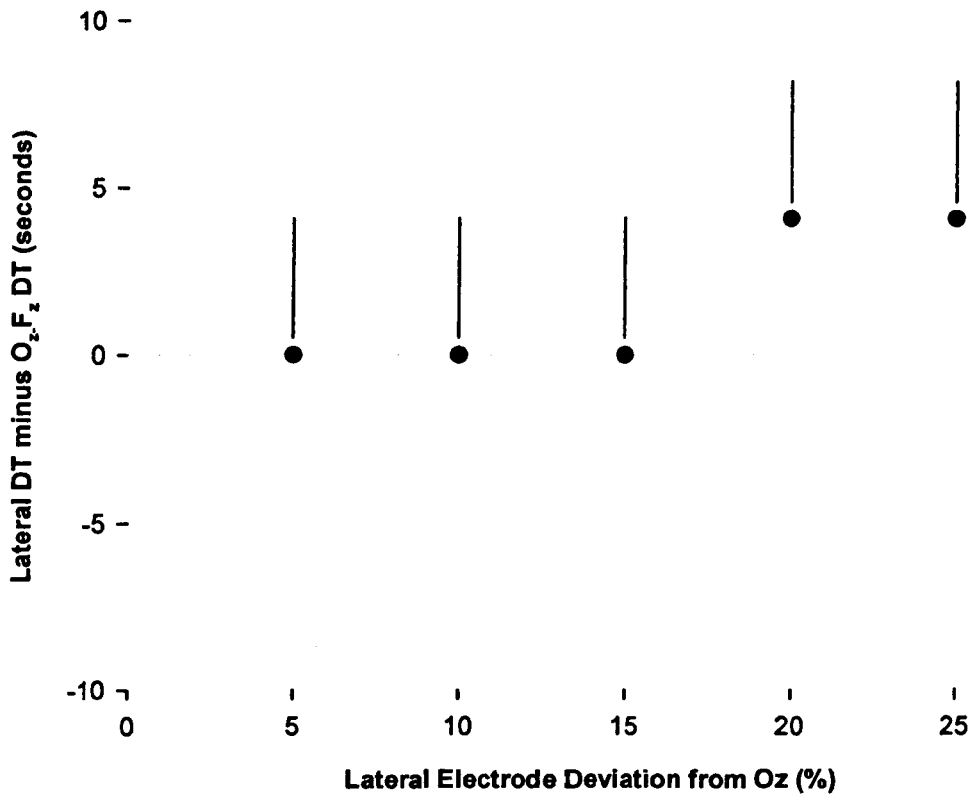


Figure 3.7: 95% confidence intervals of median lag in DT at each lateral monopolar recording sites for all check sizes as a function of lateral electrode deviation from O_z.

Table 3.6: The difference in response phase at DT between O_z-F_z and LO-F_z in the same recording. This is described for five differently sized checks and five lateral electrode positions.

	LO-F_z phase minus O_z-F_z phase (degrees). Median (95% confidence interval)				
	60'	**12'**	**9'**	**6'**	**3'**
5%	-0.6 (-20.8-18.1) N=15	3.2 (-8.3-12.8) N=12	6.8 (-15.7-21.1) N=18	10.4 (-14.3-24.0) N=18	13.7 (5.6-125.2) N=6
10%	2.7 (0.9-29.4) N=13	1.8 (-12.6-9.0) N=9	1.0 (-20.8-8.0) N=11	-7.0 (-18.9-10.0) N=2	12.4 (2.0-18.2) N=3
15%	28.2 (8.6-35.9) N=13	-1.4 (-11.6-14.7) N=13	-0.7 (-24.0-15.2) N=11	13.7 (-15.7-38.2) N=11	21.4 (-35.2-89.4) N=3
20%	7.8 (-29.8-28.7) N=10	1.5 (-27.0-38.0) N=14	-5.6 (-42.9-14.4) N=10	17.3 (-47.4-81.6) N=6	35.5 - N=1
25%	12.2 (-50.4-59.0) N=7	-4.9 (-24.7-31.1) N=10	8.0 (-36.5-126) N=13	1.9 (-48.3-68.4) N=5	28.2 (-0.5-33.4) N=5

NB. Negative values indicate a phase lead on the lateral channel

Table 3.7: Statistical test output describing phase lag at lateral monopolar recording sites with respect to O_z-F_z.

		ANOVA		Kruskal-Wallis	
Parameter	**Degrees of freedom**	**F**	***P***	χ^2	***P***
Stimulus size	4	0.714	0.565	12.47	0.014**
Lateral electrode site	4	0.792	0.531	3.235	0.519
Subject	20	0.182	1.000	11.44	0.875

** $P<0.05$

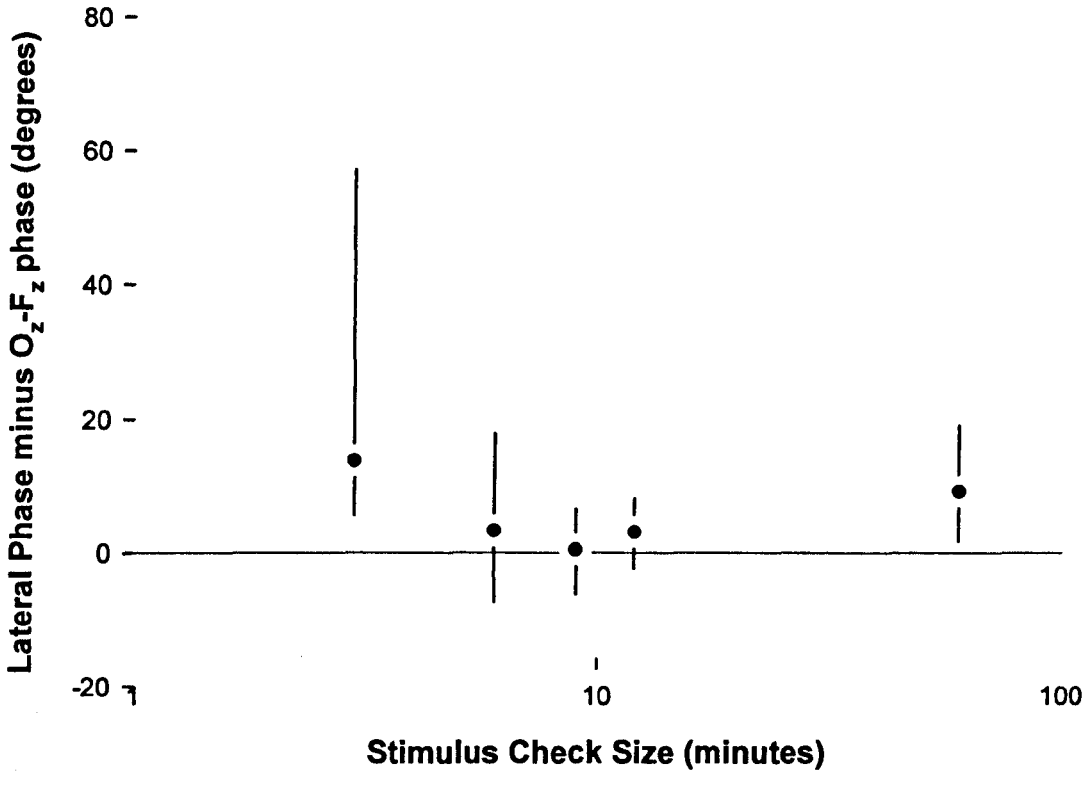


Figure 3.8: 95% confidence intervals of median phase lag at each lateral monopolar recording sites as a function of check size.

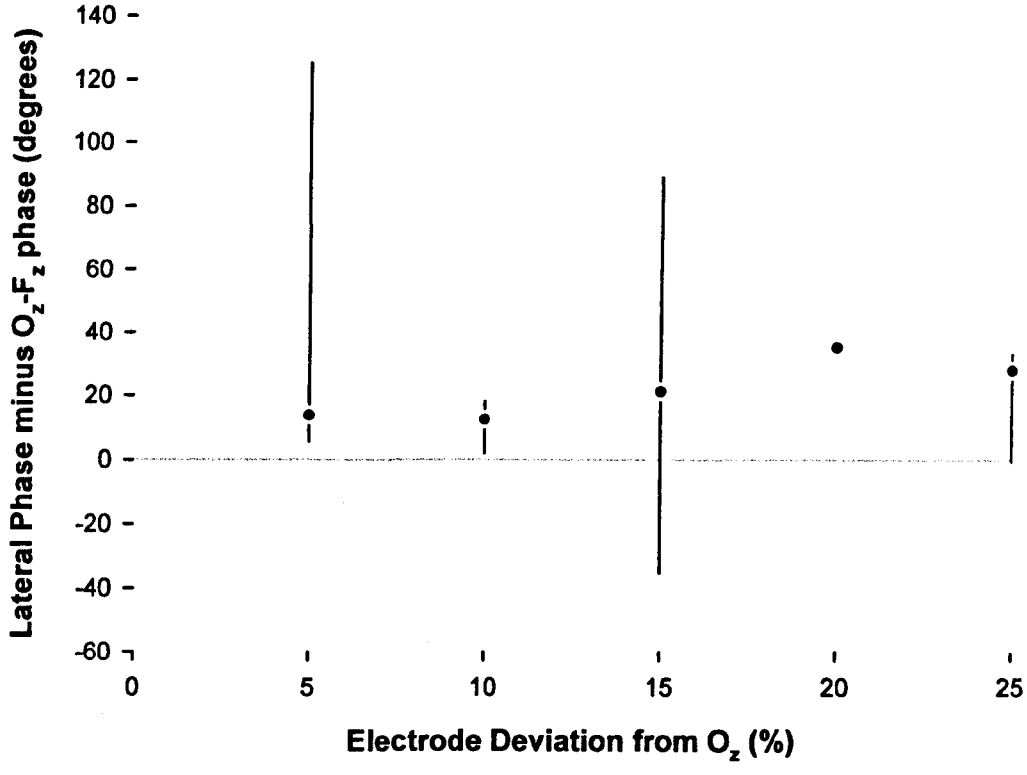


Figure 3.9: 95% confidence intervals of median phase lags of VEPs to 3' checks at each lateral monopolar recording sites as a function of lateral electrode deviation from O_z.

3.4 Discussion

3.4.1 Optimum Electrode Montage

The main finding of this study was that a 1D Laplacian analysis detects ssVEPs faster than O_z-F_z for small (3') pattern-reversal stimulation. A 3' checkerboard was close to the acuity threshold of all the subjects in this study. Patterns of this size are known to provoke a predominantly striate cortex response for both onset and reversal stimulation (Harding & Rubinstein 1980; Proverbio 2002; Maier 1987). For increasingly large pattern-onset checks, the extrastriate component of the response is reported to increase in size (Manahilov *et al.* 1992; Beers *et al.* 1992). In the current study, responses to 12' checks show a large central peak at O_z and additional peaks at around 15% of the half-head circumference, suggestive of an extrastriate response. In contrast, responses to 3' checks show only a central peak without side peaks, implying the absence of an extrastriate response (Figure 3.3a). When 3' responses were recorded at lateral electrode sites, there was a significant phase lag compared to O_z-F_z (Figure 3.8). In contrast, no significant phase lag was observed for laterally recorded responses to larger checks, corroborating the idea of a larger instantaneous distribution due to extrastriate components compared with responses to 3' checks. Responses to 3' checks can be detected at lateral electrode sites, but their significant phase lag with respect to O_z-F_z indicate that these detections may be the result of striate response lateralisation, or possibly a delayed extrastriate response.

The absence of a simultaneous, laterally measured, extrastriate response to small stimuli would mean little or no signal cancellation, preserving the striate response in a Laplacian analysis (an effect not seen for larger checksizes). 1D Laplacian analysis applied in this study was faster than conventional O_z-F_z recording at detecting VEPs to 3' checks; this suggests an improvement in SNR that is therefore probably due to improved noise cancellation. The cancellation of non-visual noise is common to 1D Laplacian analysis of responses to all stimulus sizes; however, response amplitudes are smaller for 3' stimuli than for larger stimuli (Mackay *et al.* 2003), meaning the effect of any noise cancellation is likely to be more pronounced.

For all responses recorded to 3' check stimulation, a reduction in DT through applying a 1D Laplacian analysis was only likely for the 15% and 20% reference electrode sites (Figures 3.5b and 3.5c). The instantaneous distribution of the 3' response (Figure 3a) means that much of the signal amplitude recorded at O_z will be cancelled by the signal measured laterally at the 5% and 10% electrode sites. 1D Laplacian analysis with lateral electrode sites at 15% show bigger time improvements than at 20%, and no improvement was observed at 25%. As the reference electrode site moves further from the active electrode site, the noise coherence between active and reference electrodes becomes poorer (Srinivasan 1999). Lateral electrodes at 15% of the half-head circumference therefore offer the best compromise between maximum noise cancellation and minimum signal cancellation, and therefore the fastest ssVEP detections.

It is interesting to observe that the 95% confidence intervals around the median DT for VEPs to 3' checks are smaller for 1D Laplacian analysis with 15%, 20% and 25% montages than O_z-F_z recording (Table 3.1). This is consistent with the study of Hjorth (1980) which reported less inter-subject variability in response amplitude for source derivation compared to bipolar recording. It is possible that this is due to cancellation of non-visual EEG from the VEP signal in a 1D Laplacian analysis.

Figure 3.7 shows some significant differences in DT between lateral electrode sites and O_z-F_z for all stimulus sizes combined. The small number of detections possible at the lateral channels for the 3' stimulus (Tables 3.4 and 3.6) suggests any extrastriate response component is small or absent. A lack of extrastriate component means that a VEP response detected to this stimulus and recorded laterally may have traveled from the midline, being attenuated by brain tissue on the way. Such a small signal will take longer to achieve the SNR for detection. The journey from the midline may also explain the significant and gradually increasing phase lag with respect to O_z-F_z observed for lateral responses to 3' checks (Table 3.6, Figure 3.10). This phase lag was not observed for laterally detected responses to 6' checks, possibly due to a simultaneously occurring extrastriate response component to this check size. The resulting signal cancellation in a 1D Laplacian analysis may explain why it offered no time improvements over O_z-F_z. Assuming the degree of noise cancellation is the same at a given electrode site for responses recorded to both 3' and 6' checks, the significantly larger amplitude of 6' responses (Mackay *et al.*

2003) results in less pronounced noise cancellation. This may also have reduced the time improvements possible through applying a 1D Laplacian analysis to recordings of 6'check responses.

3.4.2 Wave phenomena

In addition to the electrode montage used and the stimulus presented, the current study reported that individual subject was a significant factor in the effectiveness of a 1D Laplacian analysis (Table 3.3). Burkitt *et al.* (2000) reported two different wave phenomena dependent both on the stimulus presented and the cortical architecture of an individual. For flash stimulation, most responses were in the form of a standing wave: they occurred simultaneously at several different recording sites. For steady-state reversing checkerboards (11') the response was most often a travelling wave; a source at O_z spreading across the scalp at a certain phase velocity. Taking cortical folding into account, they found a mean phase velocity of 8.7±1.4 m/s for 14 normal subjects. In the current study, the median phase lag of laterally recorded responses to 3' checkerboard reversals compared to O_z-F_z and the median head circumference of 56cm resulted in an estimated phase velocity of approximately 7m/s for our subject group, agreeing reasonably well with Burkitt's work.

The gradual increase in phase lag for the smallest stimuli as the recording site became more lateral fits the model of a single source at O_z and lateralisation of the

signal in the form of a travelling wave. No significant differences in phase for the larger check sizes were seen, analogous to a standing wave model. As the stimulus becomes larger, the VEP is more likely to have simultaneously occurring components from both striate and extrastriate cortices. This finding (typical of responses to all check sizes larger than 3' in our subject group) is at odds with the conclusion of Burkitt *et al* (2000) that an 11' stimulus generally evokes a travelling wave. Although this difference may be due to differences in the cortical architecture of our subject group, a direct comparison is not possible since their study stimulated at the peak alpha frequency of each individual.

The level of noise coherence between the central and lateral electrodes depends on cortico-cortical connections and the speed of electrical signals through the cortex, neither of which are related to the head circumference. A fixed distance for lateral electrode placement, similar to the Queen's square system (Blumhardt & Halliday 1979), may be more appropriate and should be investigated. This distance may, however, be dependent on age.

For individuals with displaced visual cortices, due to hydrocephalus for example, a three-electrode montage and 1D Laplacian derivation could also be beneficial. However, the whole array should be displaced by an appropriate amount guided by anatomical imaging.

3.5 Conclusions

The current study shows that when recording responses to steady-state pattern reversal stimulation, a 1D Laplacian analysis can reduce the time to statistical detection of VEPs compared to the traditional O_z-F_z recording for stimuli near the normal spatial resolution threshold. This in turn could be used to minimise the length of a VEP acuity assessment. Lateral electrodes placed at 15% of the half-head circumference optimised this time improvement in adults.

Chapter 4: Faster and more sensitive VEP recording in children.

4.1 Introduction

1-D Laplacian analysis improved the DTs of ssVEP recordings made near visual acuity threshold in normal adults (section 3. 3). A lateral electrode position of 15% of the half-head circumference from O_z provided the quickest ssVEP detection most often in the study group. The purpose of the current study was to investigate whether the improved ssVEP DTs found in adults is also found in children and whether these improvements vary with age.

4.2 Methods

4.2.1 Subjects

80 normal children aged from one month to 13 years and a group of 19 normal adults were studied. Acuity assessment was performed using Cardiff Cards and Glasgow acuity cards to confirm that visual acuity was normal for age. The local ethics committee approved the study, and informed written consent was obtained from the parents of each child. The data from the adults was collected for a previous study (section 3.3) and included in this section for comparison.

4.2.2 Stimulation

Checkerboards reversing at 7.78 rev/s were presented by a custom-built VEP system (Bradnam M.S 1994). The reasons for choosing this stimulation rate are discussed in section 5.2.2. Checksizes of 60', 12', 9', 6' and 3' were presented for up to 60 seconds each in descending size order as part of a study collecting normative ssVEP data. The number of recordings completed by age group and checksize is shown in Table 4. 1 and

depended on a subject's attention span. The mean luminance was 60 cd/m^2 and the contrast was 100%. The stimulus field size was 30°x24°. Between each stimulus size a cartoon was presented (isoluminant grey screen for adults).

Table 4. 1. Total number of recordings completed by group.

Age Group (years)	Checksize				
	3'	6'	9'	12'	60'
1-3	26	26	32	30	30
3-5	9	11	11	12	12
5-7	11	9	10	10	10
7-9	8	10	10	7	7
9-13	14	14	13	12	12
Adults (>21)	19	19	19	19	19

4.2.3 Recording

Active occipital electrodes were placed at O_z and at 15% of the half-head circumference symmetrically either side of O_z, referred to as RO and LO (right occipital and left occipital). Reference and ground electrodes were placed at F_z and a mastoid respectively. The placement of the three active recording electrodes is illustrated in Figure 4. 1.

4.2.4 Analysis

Analysis was performed off-line after all data were collected. The 1-D Laplacian analysis 'channel' used the mathematical derivation of the three occipital electrodes, $2O_z$-(RO+LO), and was analysed in the same way as O_z-F_z (conventional channel). A Fast Fourier Transform (FFT) was performed on four-second data segments from each channel and used to estimate the signal amplitude and phase at the stimulus frequency. The circular T^2 statistic (CT^2) (Victor & Mast 1991) was used to test the significance of the estimated signal. Detection time (DT) was defined as the length of recording until

detection of a statistically significant VEP signal. Only those recordings where a signal was detected with 99.5% significance on both 1-D Laplacian and conventional analysis channels were used for further analysis.

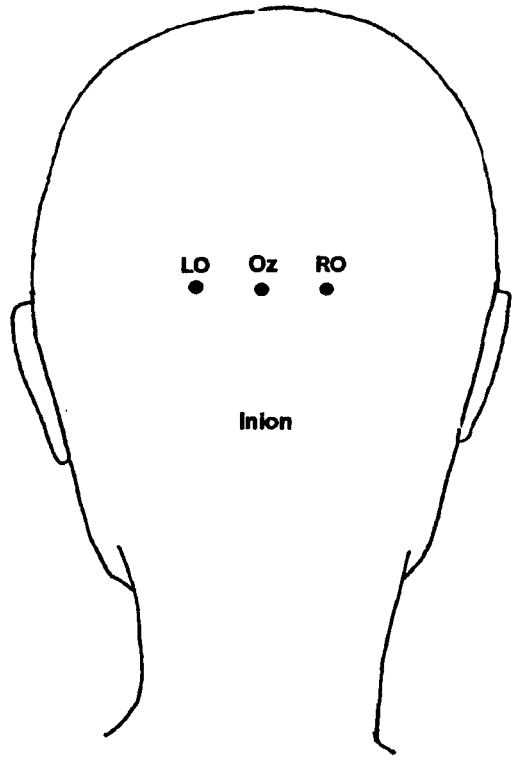


Figure 4.1: Active electrode recording sites. Lateral electrodes RO and LO are placed at 15% of the half-head circumference. Standard analysis uses O_z referenced to the forehead (F_z), 1-D Laplacian analysis uses $2O_z$-(RO+LO).

The proportions of VEP detections made by each channel in the children's age groups were compared using McNemar's non-parametric test. The sub-set of VEPs that were detected by both channels were then examined. The effect of age group and of checksize on the difference between DT (conventional O_z-F_z DT minus 1-D Laplacian DT) were examined using repeated Kruskal-Wallis tests. The 1-3 year old group (3' checksize) which had only one result was excluded from this analysis. Median and 95% confidence intervals for DT differences were calculated for age groups by checksize, and for checksizes by age group. For VEPs detected on the conventional (O_z-F_z) channel, some amplitudes were compared across and within age groups using the Mann-Whitney U-test and Wilcoxon's paired signed ranks test respectively.

4.3 Results

4.3.1 Frequency of detections (children's age groups only)

Over all checksizes, a total of 362 recordings were completed in children. A VEP signal was detected in 222 (61.3%) of these by either the 1-D Laplacian channel, the conventional (O_z-F_z) channel or both. In some cases, subjects were watching stimuli below their spatial frequency threshold, or had poor attention.

When a VEP was detected, it was usually detected by both channels (176/222, 79.3%). On 11 (5.0%) occasions, only the conventional channel detected a VEP and on 35 (15.8%) occasions, only the 1-D Laplacian channel detected a VEP. The 1-D Laplacian channel therefore detected significantly more VEPs under the same conditions than the conventional channel (211 (95.0%) versus 187 (84.0%) detections, McNemar's test: χ^2=11.5, df=1, p=0.001). These results are illustrated in Figure 4. 2.

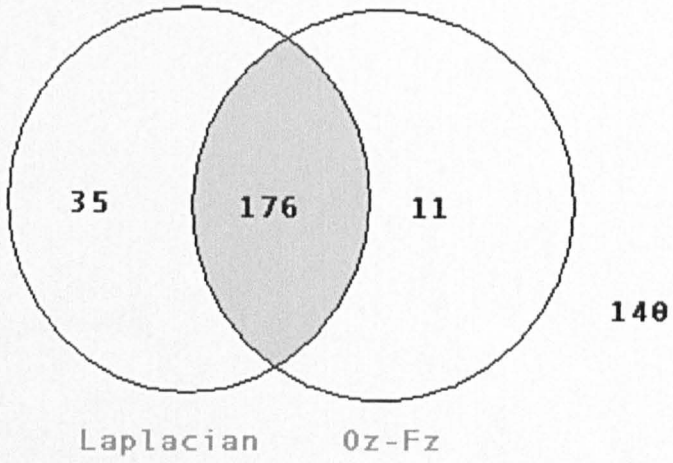


Figure 4.2: Venn diagram illustrating the number of VEPs detected by each recording channel during all the ssVEP recordings in children (excludes adult data). The number in the overlapping section describes recordings with both O_z-F_z and 1-D Laplacian channels detecting a VEP. The number outside the circles describes recordings with no VEP detected by either channel.

The number of VEPs detected by each channel, and the median DT varied across age groups and stimulus size. As expected, VEPs were detected more quickly in older age groups and to larger checksizes (Table 4. 2).

4.3.2 1-D Laplacian versus conventional channels: effect of checksize

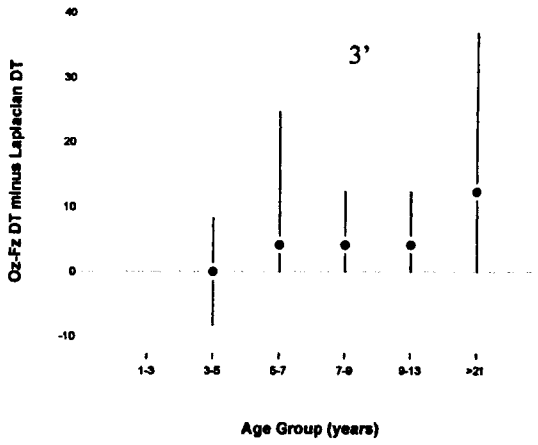
Considering both children and adult data, there were 256 recordings where a VEP was detected by both channels. Comparing the DT differences across the five checksizes showed that significant inter-group differences existed (Table 4. 3). Specifically, the detection time differences (1-D Laplacian faster) to 3' checks were significantly larger than the differences to other checksizes. More detailed inspection of the effect of checksize by age group shows this effect (Figure 4.3), with the 1-D Laplacian channel faster on average than the conventional channel to 3' (all children over 5 years old), 6' (7-9 year olds) and 9' (7-9 year olds).

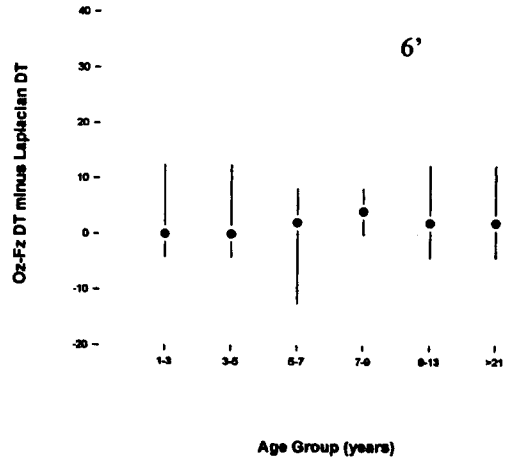
4.3.3 1-D Laplacian versus conventional channels: effect of age group

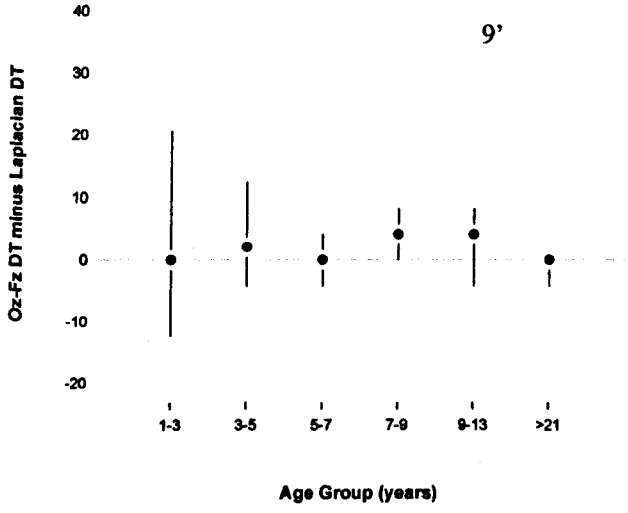
Comparing the DT differences across the six age groups for the same 256 recordings showed that some inter-group differences existed (Table 4. 3). Specifically, the detection time differences (1-D Laplacian faster) in the adult age-groups were larger than the differences in the other age groups, with small differences for children aged 5-13, and no difference for children under 5. More detailed inspection of the effect of age group by checksize shows this effect (Figure 4.4), with the 1-D Laplacian channel faster on average than the conventional channel for 5-7 year olds (3' checks), 7-9 year olds (3', 6' and 9' checks), 9-13 year olds (3' checks) and adults (3' checks)

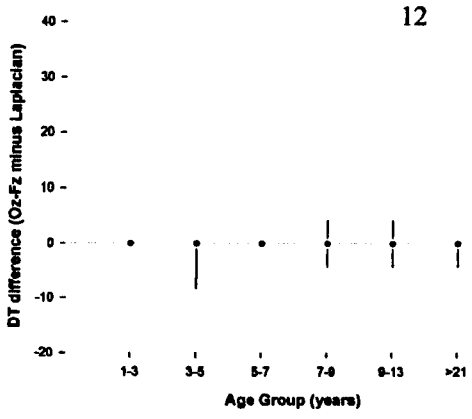
Table 4.2: Detection times (DTs) in seconds for recordings where a ssVEP was detected by either conventional (O_z) or 1-D Laplacian (L) channels. DTs are described by the median and range for each recording channel for each age-group and checksize combination. The number of responses detected by each channel is also indicated.

Age (years)	Stimulus check size									
	3'		6'		9'		12'		60'	
	O_z	L	O_z	L	O_z	L	O_z	L	O_z	L
1-3	16.5 - N=1	16.5 - N=1	24.6 20.6-45.2 N=9	20.6 12.3-49.3 N=7	24.6 16.5-41.1 N=9	26.7 16.5-49.3 N=8	16.5 8.2-20.6 N=7	16.5 12.3-20.6 N=7	16.5 12.3-28.8 N=9	16.5 8.2-41.1 N=8
3-5	16.5 8.2-37.0 N=4	28.8 8.2-49.3 N=7	32.8 12.3-45.2 N=8	26.7 16.5-49.0 N=8	20.6 12.3-24.7 N=11	16.5 12.3-20.6 N=10	16.5 12.3-20.6 N=4	16.5 16.4-20.5 N=5	12.3 8.2-28.8 N=6	16.5 12.3-16.5 N=9
5-7	22.6 12.3-53.3 N=6	18.5 12.3-61.6 N=6	26.7 12.3-37.0 N=9	28.8 12.3-45.2 N=9	12.3 12.3-16.5 N=9	12.3 12.3-20.6 N=9	16.5 12.3-20.6 N=5	16.5 12.3-20.6 N=6	12.3 8.2-16.5 N=5	12.3 12.3-16.5 N=7
7-9	37.0 12.3-49.0 N=7	28.8 12.3-49.0 N=7	16.5 12.3-20.6 N=9	14.4 12.3-20.6 N=10	16.5 16.5-20.6 N=10	12.3 8.2-16.5 N=10	12.3 12.3-16.5 N=9	12.3 12.3-12.3 N=8	14.4 8.2-16.5 N=4	12.3 12.3-12.3 N=6
9-13	22.6 16.5-45.2 N=8	20.6 12.3-24.6 N=13	16.5 12.3-28.8 N=12	16.5 16.5-28.8 N=14	16.5 12.3-20.6 N=11	12.3 12.3-20.6 N=13	12.3 12.3-16.5 N=7	12.3 12.5-16.5 N=12	12.3 12.3-16.5 N=9	12.3 8.2-12.3 N=11
Adults (>21)	20.6 8.2-12.3 N=13	20.6 8.2-45.2 N=11	16.5 8.2-53.5 N=18	16.5 8.2-49.3 N=18	12.3 8.2-41.4 N=19	14.4 12.3-49.3 N=18	12.3 8.2-28.8 N=17	16.4 8.2-28.8 N=17	12.3 8.2-32.9 N=19	12.3 8.2-41.1 N=19









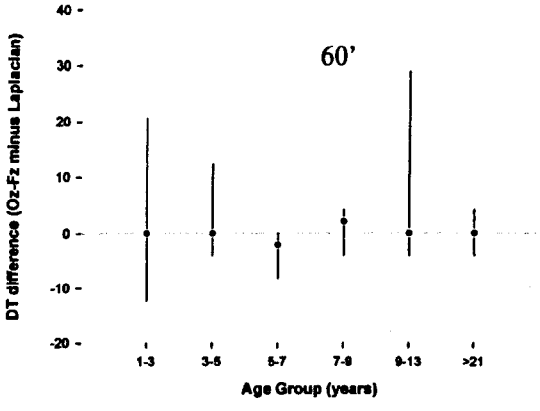


Figure 4.3: 95% Confidence intervals around the median DT difference between O_z-F_z and 1-D Laplacian analysis for checksizes of a)3'; b)6'; c)9'; d)12';e)60'. Positive values represent faster detections on the 1-D Laplacian channel than on the conventional channel.

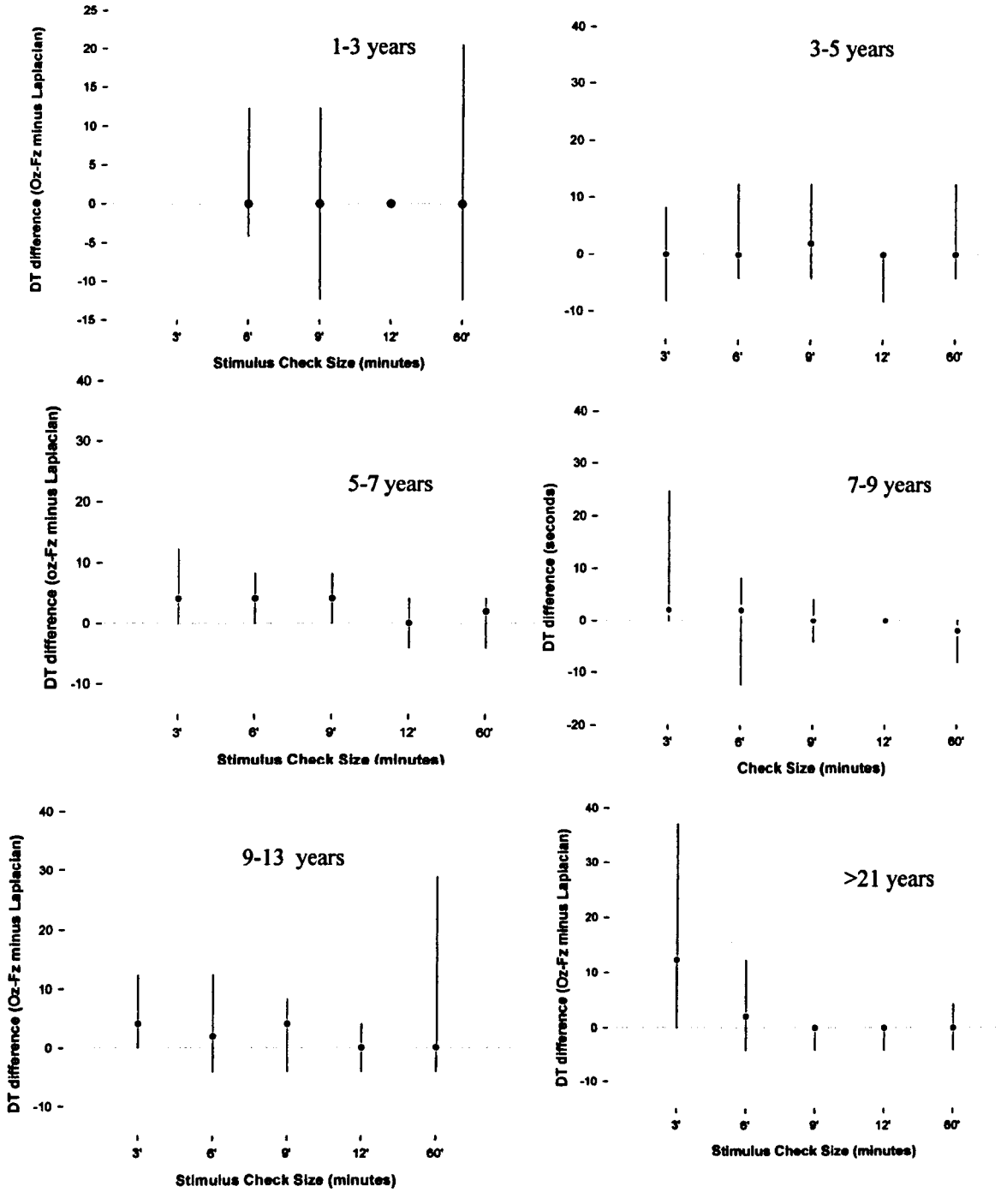


Figure 4.4: 95% Confidence intervals around the median DT difference between O_z-F_z and 1-D Laplacian channels for age groups a)1-3 years; b)3-5 years; c)5-7 years; d)7-9 years; e)9-13 years; f)adults (>21 years). Positive values represent faster detections on the 1-D Laplacian channel than on the conventional channel.

Table 4. 3. Kruskal-Wallis test results for the effect of parameter of the difference between O_z-F_z and 1-D Laplacian DTs.

Parameter	Degrees of Freedom	H value	P-value
Stimulus Size	4	23.410	0.000
Age Group	5	9.246	0.100

4.3.4 Response amplitudes (conventional (O_z-F_z) channel only)

The amplitudes of the VEP responses recorded on the conventional channel are largest in the 3-5 year age group (median amplitudes across checksizes range from 3.8-6.1μV) and reduce gradually with age to adult values (median amplitudes across checksizes range from 1.5-3.8μV) (Table 4. 4).

Selective amplitude comparisons were performed. A comparison of adult response amplitudes for 3' and 6' checks showed that 6' responses were larger on average by 1.1μV (95%CI 0.3-2.0μV; p=0.020). Comparing between groups, amplitudes of VEPs to 9' checks were 2.0μV (95%CI 0.3-3.7μV) larger on average in the 7-9 years old group than in adults (p=0.015).

Table 4.4. ssVEP response amplitudes for a range of checksizes. Amplitudes (μV) are described by the median and 95% confidence interval for the O_z-F_z recording channel for each age-group and checksize combination. The number of responses within each group are also indicated.

	Stimulus Check Size (')				
Age (years)	3'	6'	9'	12'	60'
1-3	1.12 - N=1	2.9 1.5-3.7 N=9	3.9 2.1-8.4 N=9	4.2 1.2-8.2 N=7	4.1 1.5-8.2 N=9
3-5	5.5 1.9-8.0 N=4	6.1 4.1-11.5 N=8	5.6 2.5-8.2 N=11	5.0 3.4-6.5 N=4	3.8 2.7-8.6 N=6
5-7	2.9 1.3-12.9 N=6	3.8 1.6-6.9 N=8	4.5 3.4-7.6 N=9	4.7 4.3-9.5 N=5	5.9 3.6-11.9 N=5
7-9	3.3 1.8-6.1 N=7	4.4 2.5-9.1 N=9	4.9 2.0-13.4 N=10	5.8 4.6-9.1 N=9	4.5 4.3-6.6 N=4
9-13	2.8 2.1-3.9 N=8	3.5 2.6-4.2 N=12	3.6 2.4-5.0 N=11	5.8 1.3-7.5 N=7	3.8 3.0-5.5 N=9
Adults	1.5 1.2-2.8 N=13	1.9 1.3-2.4 N=18	2.8 1.0-5.5 N=19	3.8 2.2-6.0 N=18	2.8 1.3-6.8 N=19

4.4 Discussion

4.4.1 Noise and signal cancellation in a 1-D Laplacian analysis

The SNR of a ssVEP recording is optimised when a response measured at O_z is preserved yet has most of its background noise cancelled by the reference electrode. The noise at both active and reference electrodes must be similar (coherent) for effective noise

cancellation. In this study, the lateral electrodes used in the 1-D Laplacian analysis act as local noise references. Any lateralisation of the VEP to the reference electrodes of the 1-D Laplacian montage can also adversely cause a proportion of signal to be cancelled as well as noise.

A larger SNR (and reduced DT) using a 1-D Laplacian analysis is a result of either increased noise cancellation or decreased signal cancellation. Decreased signal cancellation (signal preservation) is likely when the extrastriate response component is small or delayed with respect to the striate component. Increased noise cancellation, effected by a 1-D Laplacian analysis, is most evident when the response amplitude is small (1-D Laplacian analysis reduced DT during ssVEP recording near threshold (3') in adults (chapter 3). Lateral electrodes placed at 15% of the half-head circumference around O_z most frequently provide the best compromise between noise cancellation and signal preservation (Chapter 3). An example of the effect of 1-D Laplacian analysis on noise cancellation is shown in Figure 4.5, which illustrates a near-threshold ssVEP recording made in this study.

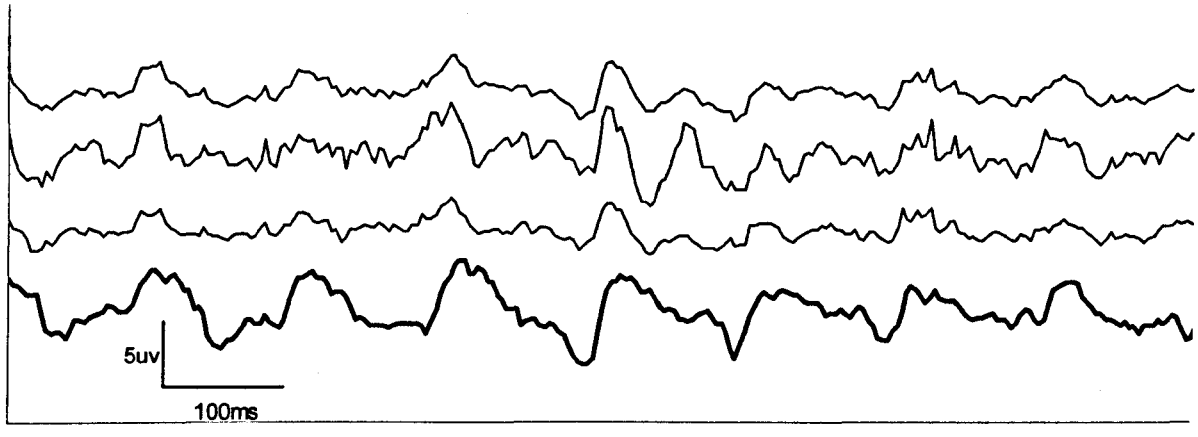


Figure 4.5: The noise cancelling effect of a 1-D Laplacian analysis on un-averaged ssVEP responses displayed in the time domain. The top three tracings are made from O_z-F_z, RO- F_z and LO- F_z respectively. The bottom trace is the 1-D Laplacian transformation of $2O_z$-(RO+LO).

4.4.2 3' checks

The 1-D Laplacian channel was faster at detecting responses to 3' checks in subjects from five years old to adults, possibly reflecting the more mature fovea and its representation in the visual cortex (Huttenlocher *et al.* 1982; Garey 1984; Youdelis & Hendrickson 1986; Candy *et al.* 1998) . This effect was not seen in the younger 3-5 year old age group (Figure 4.3a), which had relatively large response amplitudes (Table 4. 5), possibly reducing the noise cancellation effect of the 1-D Laplacian. The pruning of synapses within the visual cortex (intra-cortical connections) between one and 11 years (Huttenlocher *et al.*1982; Garey 1984) causes a gradual reduction of VEP amplitude (Norcia & Tyler 1985a). As the improved noise cancellation of 1-D Laplacian analysis has a more pronounced effect on small response amplitudes, this may also explain why the 1-D Laplacian was faster in adults for 3' checks but not for larger checksizes. Small amplitude responses can be associated with more benefit from a 1-D Laplacian analysis. In adults, the 1-D Laplacian channel was significantly faster than the conventional channel for 3' but not for larger checks. A comparison of adult response amplitudes for 3' and 6' checks showed that 3' responses were smaller on average by 1.1μV ($p=0.020$).

4.4.3 6' and 9' checks

The 1-D Laplacian channel was faster at detecting responses to 6' and 9' checks only in the 7-9 year old group (Figure 4.3b and c). 1-D Laplacian analysis can be faster because of enhanced noise cancellation when response amplitudes are small. However, in this

case, significant time improvements were observed in a group (7-9 years) whose amplitudes were larger than in the adult group (by 2.3μV on average, p=0.003) where the 1-D Laplacian was not faster. In adults, it is postulated that extrastriate and straite responses to checks larger than 3' generally occur simultaneously. In children, supra-threshold stimuli may evoke either a smaller or a later extrastriate response. With a 1-D Laplacian analysis, this would reduce signal cancellation. This signal preservation results in larger SNR and therefore reduced DT.

4.4.4 Changes in noise cancellation

Decreasing amplitudes with age are observed for VEPs to 3' checks. The confidence intervals in Figure 4.3a suggest that 1-D Laplacian benefits are larger in adults than in children, which may be simply a result of these smaller response amplitudes. However, the noise coherence between recording electrodes is also likely to change with age. At the same time as intra-cortical connections are pruned, longer distance (inter-cortical) connections are being made (Srinivasan 1999). It has been reported in humans that these long distance inter-cortical connections govern global noise correlation (ibid.). Consequently, in the current study, the noise measured at RO and LO will become more correlated with the noise measured at O_z as the subjects get older, leading to further noise cancellation by a 1-D Laplacian analysis. Greater benefits of the 1-D Laplacian in adults than in children for very small checksizes are therefore probably due both to improved noise cancellation because of increasing inter-cortical connections and the enhanced effect of a 1-D Laplacian analysis because of decreasing signal amplitudes. Other studies

which used transient pattern onset stimulation for acuity estimation have also found a 1-D Laplacian analysis more reliable (Beers *et al.* 1992) and more highly correlated with Snellen acuity (Apkarian & Bour 2000).

4.5 Conclusions

This study has shown that a 1-D Laplacian analysis can detect significantly more ssVEPs than a conventional O_z-F_z montage in children from three years of age. The increased noise cancellation offered by 1-D Laplacian analysis allows smaller responses to be distinguished from the background noise and therefore be detected more often.

The 1-D Laplacian analysis also significantly reduces the time taken to detect a ssVEP, particularly to threshold-sized checks and in subjects from five years old to adults. The time improvements observed are typically four seconds per stimuli. This gives the potential for faster VEP acuity estimates in these age groups. VEP acuity estimated by extrapolation of steady-state response amplitudes to reversing sinusoids and checkerboards approaches maturity within the first year of life (Sokol 1978; Norcia & Tyler 1985; Skoczenski 1999; Allen, Tyler, & Norcia 1996). Maturation of the visual system continues throughout childhood and we can postulate that this maturation affects the benefits of applying a 1-D Laplacian analysis to ssVEP recording in different age groups.

In children, supra-threshold stimuli may evoke either a smaller or a later extrastriate response. With a 1-D Laplacian analysis, this would reduce signal cancellation. This signal preservation results in larger SNR and therefore reduced DT.

Simultaneous use of both a conventional (O_z-F_z) VEP recording channel and a 1-D Laplacian channel is likely to offer not only faster overall VEP detections, but also to increase the likelihood of detecting small-amplitude VEPs. In combination, this is likely to give faster, more accurate VEP assessments.

Chapter 5: Software Development

5.1 Introduction

Detection time (DT) reductions have been shown through the use of additional electrodes (chapter 3 and 4). More substantial reductions in test duration could potentially be made by ongoing analysis of ssVEP recordings. Real-time analysis would allow the program to make stimulation decisions based on the information gathered so far. If the program provided feedback periodically during analysis then each stimulus need only be displayed for as long as it takes to detect a response. As feedback on responses to several stimulus sizes is accumulated, the program could make objective decisions about which stimulus size to present next. Investigation of stimulation parameters, analysis parameters and detection statistics would further optimise the reduction in test duration. The most appropriate technique for estimating visual acuity from ssVEP recordings also needs to be established.

An important aspect of the test software is its user friendliness. An automated test with a graphical display of results would require no specific scientific knowledge to perform the test and interpretation of the results could also be done objectively by the software. This chapter aims to describe the software development work in creating such a test. The flow diagram in figure 5.1 outlines the software development process. The corresponding paragraphs in the text describe how each aspect of the program was optimised by experiment.

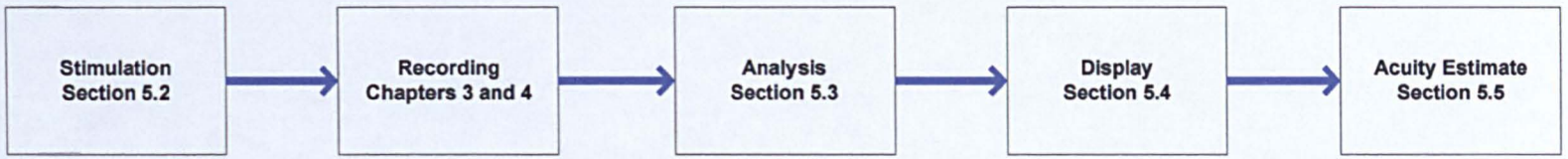


Figure 5.1: Development of a user-friendly acuity assessment based on the real-time analysis of ssVEPs.

5.2 Stimulation Parameters

5.2.1 Introduction

The screen refresh rate, stimulation period, ADC sampling rate and analysis epoch are co-dependant for reasons described in section 2.2. The main program is written in Microsoft Pascal, but also needs to communicate with the hardware control cards (section 2.2.4-2.2.6) using additional low-level languages. For example, the analysis procedures in the main program need to receive data in segments of the correct length for analysis. The aim of this section is to choose an appropriate stimulus pattern and rate of stimulation for recording ssVEPs in children with varying degrees of visual and neurological impairment. As a result, an appropriate sampling rate for the ADC card will be chosen.

5.2.2 Stimulus pattern

If a sine wave grating of spatial frequency f is fourier analysed, the frequency spectrum is made up of one component at frequency f. Analysing a checkerboard of fundamental spatial frequency f in the same way would have additional higher harmonic components at 3f, 5f and so on. The theory of edge detection implies that the edges of a checkerboard evoke responses in the primary visual cortex. However, there has been much recent evidence support spatial frequency theory, which describes the visual system as being made up of numerous channels tuned to different spatial frequencies (section 1.2.5). If a stimulus has more than one component of spatial frequency, the component at the fundamental frequency determines visual acuity threshold (Graham & Nachmias 1971). The amplitude and phase of responses to steady-state pattern reversals at high spatial frequencies show no

difference for sinusoidal, square wave or checkerboard stimulation with the same fundamental components (Tobimatsu *et al.* 1993). This supports the hypothesis that at threshold, only the fundamental spatial frequency component of a checkerboard is visible. However, at low to medium spatial frequencies, the responses to checkerboard stimulation were shown to be significantly larger than responses to square wave and sinusoidal gratings (ibid.). Large amplitude responses provide large SNRs and in turn, fast response DTs (Tables 4.1 and 4.2). While the stimulus pattern has no effect on the visual acuity outcome, it could have an effect on the overall duration of the test. ssVEP assessment stimulates at a variety of spatial frequencies before finding threshold and therefore checkerboards are likely to provide the fastest total test duration

5.2.3 Stimulation and sampling rates

As the refresh rate of the stimulus monitor is fixed at 70.11Hz, the sampling rate, stimulation rate and analysis epoch length must be compatible within their own constraints (section 2.2). All possible combinations of reversal rate and ADC sampling rates are shown in Table 5.1. Steady-state responses can be measured from stimulation rates of around five per second (Van der Tweel 1965), which provides the lowest stimulation rate included in the table. The fastest stimulation rate is limited by the fact that one complete screen refresh must be completed before the pattern can be reversed.

Table 5.1: All possible combinations of ssVEP reversal rate and sampling rate.

Monitor refreshes/stimulus state	Reversal Rate	ADC sampling rate (Hz)	Samples/ stimulus state
1	70.11	2243.52	32
2	35.06	1121.76	32
3	23.37	747.84	32
4	17.53	560.88	32
5	14.02	448.70	32
6	11.69	373.92	32
7	10.02	320.50	32
8	8.76	280.44	32
9	7.79	249.28	32
10	7.01	224.35	32
11	6.37	203.96	32
12	5.84	373.92	64
13	5.39	350.56	64
14	5.01	320.5	64
15	4.67	299.14	64
16	4.38	280.44	64
17	4.12	263.94	64
18	3.90	249.28	64
19	3.69	236.16	64
20	3.51	224.36	64
21	3.34	213.66	64
22	3.19	203.96	64
23	3.05	390.16	128
24	2.92	373.92	128
25	2.80	358.96	128
26	2.70	345.16	128
27	2.60	332.36	128
28	2.50	320.52	128

All the parameters in table 5.1 are within the specification of the ADC. The low pass filter cut off is set to 100Hz and therefore the nyquist frequency must exceed this frequency (section 2.2.4).

5.2.4 EEG components and their effects on recording

The standard classification of frequency grouping in EEG recordings, their topography, and their conditions of registration were introduced in section 1.3.4. In normal adults, alpha activity occurs between 8-12Hz at occipital sites. As VEP recording sites are always occipital (Harding *et al.* 1996), a reversal rate coinciding with the EEG alpha band of 8-12Hz may result in responses being contaminated by noise. There is also the possibility that a large transient spike of alpha activity could be mistaken for a VEP.

In the first year of life, the peak alpha frequency is normally observed between 6.0 and 8.8 Hz with the peak moving to higher frequencies with age (Stroganova *et al.* 1999). It has been shown that normal infants between 2 and 10 months of age respond better to gratings reversing 7.5 or 14 times a second than 2.5 or 23 rev/sec gratings (Sokol *et al.* 1988). A reversal frequency just above or just below the 8-12Hz alpha band would therefore be appropriate in normal children and adults.

The temporal processing capabilities of a neurologically impaired child may be slower than normal and it is postulated that a stimulation rate above 12 Hz may be too fast for the visual system to respond. The test conditions must be appropriate for children of all ages with a

variety of pathologies. A reversal rate just below the alpha EEG band has been shown to be successful, even in immature subjects. Such a stimulus rate would therefore allow rapid collection of response data while avoiding noise contamination of occipital recording sites.

5.2.5 Conclusions

A compromise between noise reduction, temporal tuning in infancy and the possible temporal limitations of an impaired visual system is a reversal rate of 7.78/sec, which requires a digitisation rate of 249Hz (Table 5.1). The pre-alpha EEG reported during the first year of life (Stroganova *et al.* 1999) did not significantly affect the findings of Sokol *et al.* (1988) for checkerboards reversing 7.5 times every second . However, an alternative reversal rate of 5.84/sec, requiring digitisation at 186.96 Hz (Table 5.1), could be considered for ssVEP recording in infants.

5.3 Analysis Parameters

5.3.1 Introduction

The stimulation parameters (section 5.2) and recording electrode positions (chapters 3 and 4) have been optimized for high SNR and therefore fast DTs. The techniques for EEG analysis and the statistical detection of responses can also be optimised. This section aims to compare speed of detection, specificity and sensitivity between different analysis and statistical techniques for the detection of ssVEPs.

5.3.2 Experimental comparison of detection statistics

Introduction

A comparison of signal detection methods was carried out for a previous study in the Clinical Physics department in Glasgow (Bradnam & Hamilton 1997). T^2_{circ} statistics were found to provide the highest detection specificity with good sensitivity. Fourier analysis (FFT) and adaptive filtering (AF) are the two most common methods of analysis for ssVEP recordings and will be discussed in more detail in the next section. Although T^2_{circ} statistics can be applied to the output of either FFT or AF, the SNR technique is only applicable to fourier analysis. As the aim of this study is to compare T^2_{circ} statistics and SNR, the FFT technique was chosen for ssVEP analysis.

Methods

The subjects were 23 normal adults wearing any required optical correction. The stimulus was a 100% contrast checkerboard reversing at 7.78 reversals/sec with a mean luminance of 60cd/m^2 and a field size of 25° (reduced to 12.5° for the smallest stimulus). Stimuli of check sizes 60', 12, 9, 6, 3'and 1.5' were presented for one minute each. Recordings were made from O_z, RO, LO and F_z with a ground electrode placed at a mastoid. Two channels, O_z-F_z and 2 O_z-(RO+LO) (1-D Laplacian analysis), were analysed off-line by the two analysis methods. The first applied an FFT to un-averaged data followed by T^2_{circ} statistical analysis of the FFT output at the stimulation frequency. The second applied an FFT to cumulatively averaged data, then calculated SNR using the frequency bin at the stimulus reversal rate and its two neighbouring frequency bins (Meigen & Bach 1999).

A four-second analysis epoch provided adequate spectral resolution for SNR calculation in the frequency domain and ensured statistical independence between data samples for T^2_{circ} statistics. The level of statistical significance was set to 0.005 for both techniques to declare detection, at which point DT was defined. The DT difference between analyses methods in each subject was evaluated using 95% confidence intervals. Control recordings were made in 20 subjects by occluding the stimulus screen with black card and recording EEG for one minute. False detection rate expressed the rate of statistical detection during these 20 control recordings. Sensitivity was expressed as the rate of statistical detection during the 138 stimulated recordings. The sensitivity of each analysis technique was compared using a sign and binomial test.

Results

The median DT for each analysis technique and the O_z-F_z recording and analysis channel is shown in Figure 5.2a. The median DTs for each analysis technique on the 1-D Laplacian analysis channel are shown in Figure 5.2b. Both montages and both analysis techniques show that DTs increase as the stimulus check size gets smaller. This effect is more pronounced for the SNR analysis technique.

The DT differences between the two analysis methods for each stimulus is illustrated in figure 5.3. The confidence intervals suggest that as the stimulus check size is reduced, T^2_{circ} statistics tend to be faster than SNR, with both analysis channels in agreement. Figure 5.3b also shows T^2_{circ} statistics are significantly slower than SNR for the largest two stimulus sizes (60' and 12').

The T^2_{circ} statistics detected responses in 83% (115/138) of the stimulated recordings compared to SNR detections in 76% (105/138) of recordings. The sign and binomial test proved that this difference was significant ($p=0.014$). Both techniques had a false detection rate of 5% (1/20).

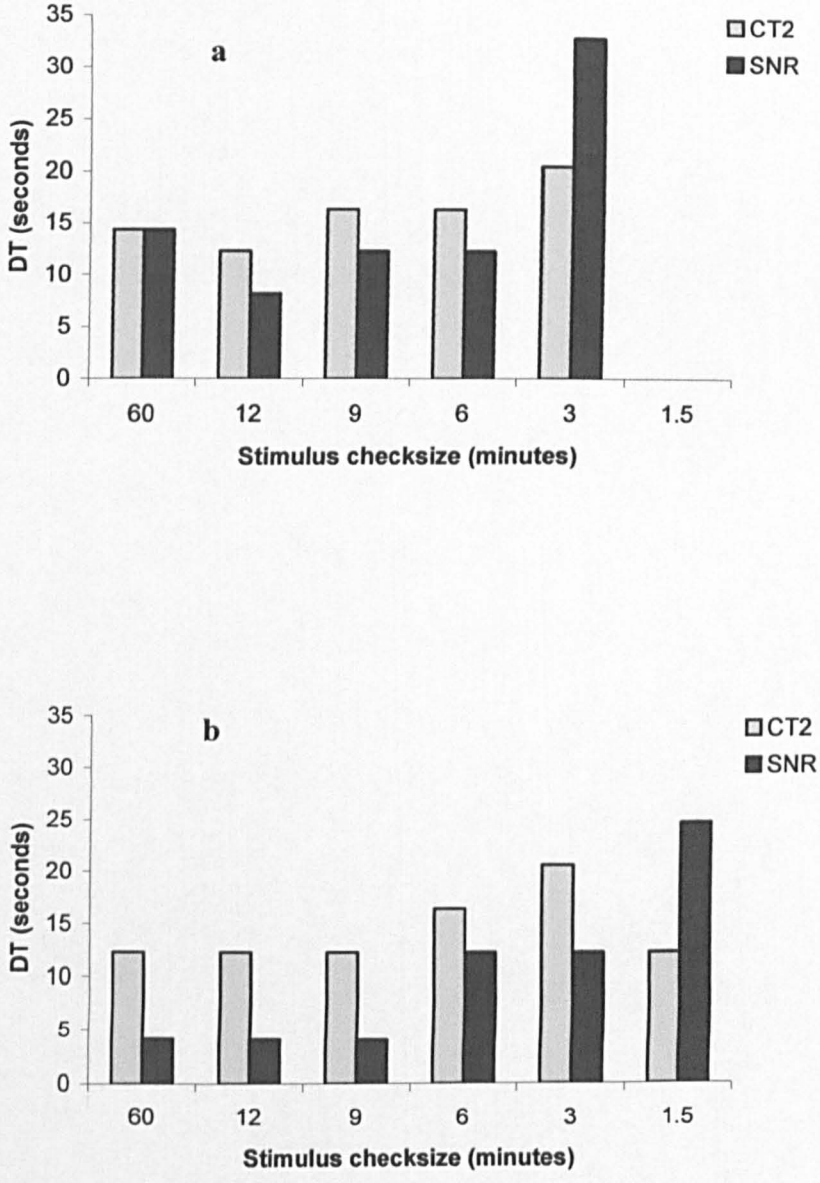


Figure 5.2: a) DTs for both detection statistics on O_z-F_z channel.

b) DTs for both detection statistics on 1-D Laplacian channel.

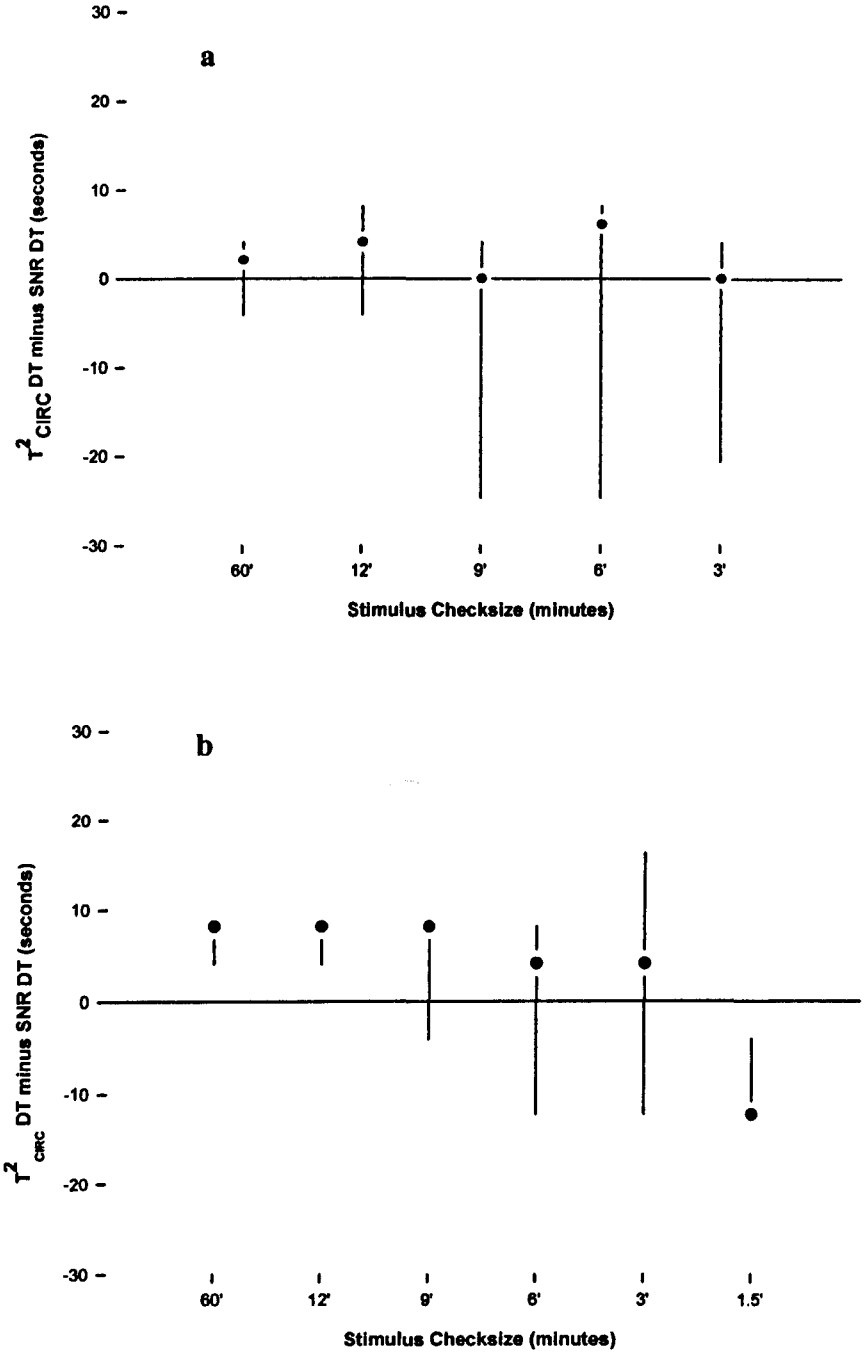


Figure 5.3: a) DT difference between detection statistics on O_z-F_z channel.

b) DT difference between detection statistics on 1-D Laplacian channel.

Discussion

T^2_{circ} statistics use both response amplitude and phase information, whereas the SNR technique depends solely on response amplitude. The amplitude of responses to small stimulus sizes are smaller than the amplitude of responses to large stimulus sizes (table 4.4). Small response amplitude resulted in small SNR and slow DT for both statistical techniques. The phase of ssVEPs are known to be more stable than the amplitude (Tobimatsu *et al.* 1996) which results in the increase in DT for small stimuli being less dramatic for the phase sensitive T^2_{circ} statistics than the SNR technique.

For large amplitude responses to 60' and 12' stimulation (table 4.2), detection was often made in as little as four seconds using the SNR technique. The T^2_{circ} method required a minimum of two data epochs to perform analysis meaning the minimum DT for this method was eight seconds. This explains why DT was significantly slower using T^2_{circ} statistics rather than SNR for the two largest check size stimuli in this study

T^2_{circ} statistics detected 7% more responses than the SNR technique. Detection of small amplitude responses is likely to be quicker using T^2_{circ} statistics than SNR analysis as they take both response phase and amplitude. This explains why T^2_{circ} statistics detected significantly more responses overall than the SNR calculation, as well as explaining why T^2_{circ} statistics were significantly faster than the SNR method for the smallest stimulus size.

False detection arises when the EEG is mistaken for a genuine signal. Through investigation it was found that the false detection using T^2_{circ} analysis was made was made due to an EEG peak that coincided with the stimulation frequency and was stationary across two data segments. The false detection using the SNR technique was found to be a result of a large amplitude EEG component coinciding with the stimulation frequency.

As SNR detects responses to large stimuli faster and T^2_{circ} statistics detect responses to small stimuli faster and more often, the techniques are complementary for use in a rapid assessment of vision. In patients with reduced acuity, small amplitude responses should occur at larger stimulus sizes corresponding to their resolution threshold. It is postulated that T^2_{circ} statistics will detect responses more quickly at threshold even for elevated thresholds if the response amplitude is small. As the false detection rates are identical and low, the estimation of visual acuity derived from ssVEP recordings using either technique should be equally accurate.

5.3.3 Experimental comparison of objective analysis methods

Introduction

The adaptive filter (AF) and fourier transform (FFT) methods were introduced in chapter 2 and are the most common methods used to analyse ssVEP recordings. Cluckie *et al* (1994) used an adaptive noise canceller (ANC) to evaluate the detectability of real physiological signals and sinusoids of known amplitude added to EEG noise. The ANC showed a higher detectability than a DFT for the synthesised signals (Tang & Norcia 1995; Cluckie *et al*, 1994) and for real ssVEPs (Tang & Norcia1995). T^2_{circ} statistics were not used for either of these studies but have since been shown (section 5.3.2) to be faster and more sensitive than the SNR technique for near threshold recordings. T^2_{circ} statistics can be applied to the output of both AF and FFT analysis techniques which is not possible using the SNR method. The purpose of the current experiment was to compare DTs, specificity and sensitivity of ssVEP recordings analysed by AF and FFT.

Methods

ssVEPs were recorded in 10 normal adults wearing any required optical correction. The stimulus was a 100% contrast checkerboard reversing at 7.78 reversals/sec with mean luminance of 60cd/m^2 and a field size of 25° (reduced to 12.5° for the smallest stimulus). Stimuli of check size 60', 12, 9, 6 and 3' were presented for one minute each. Recordings were made from O_z-F_z with a ground electrode placed at a mastoid. Each recording was analysed off-line using both AF and FFT analysis techniques. T^2_{circ} statistics were applied

to the output at the stimulation frequency of each analysis method to calculate the statistical significance (α) of any responses. When α reached 0.005 a DT was defined. T^2_{circ} statistics demand that the analysis epoch is at least three seconds to ensure independence of background EEG between data samples (Victor & Mast 1991). Each recording was therefore analysed in epochs of four seconds before applying T^2_{circ} statistics.

Control recordings were made in all subjects by occluding the stimulus screen with black card and recording EEG for one minute. False detection rate expressed the rate of statistical detection during these control recordings. Sensitivity was expressed as the rate of ssVEP detection during the 60 stimulated recordings.

Results

Both analysis techniques show an increase in median DT for the smallest stimulus size (Figure 5.4a). This is likely to be a direct result of the relatively small amplitude of ssVEP responses to 3' checkerboards (table 4.4). The difference in DT between analysis methods is summarised as a median and 95% confidence interval for each stimulus check size in Figure 5.4b. As none of the confidence intervals are distinct from zero no significant difference between the techniques can be reported. However, the trend of the DT differences suggests that for the smallest stimulus size (and therefore the smallest response amplitudes) the AF tends to be quicker than the FFT.

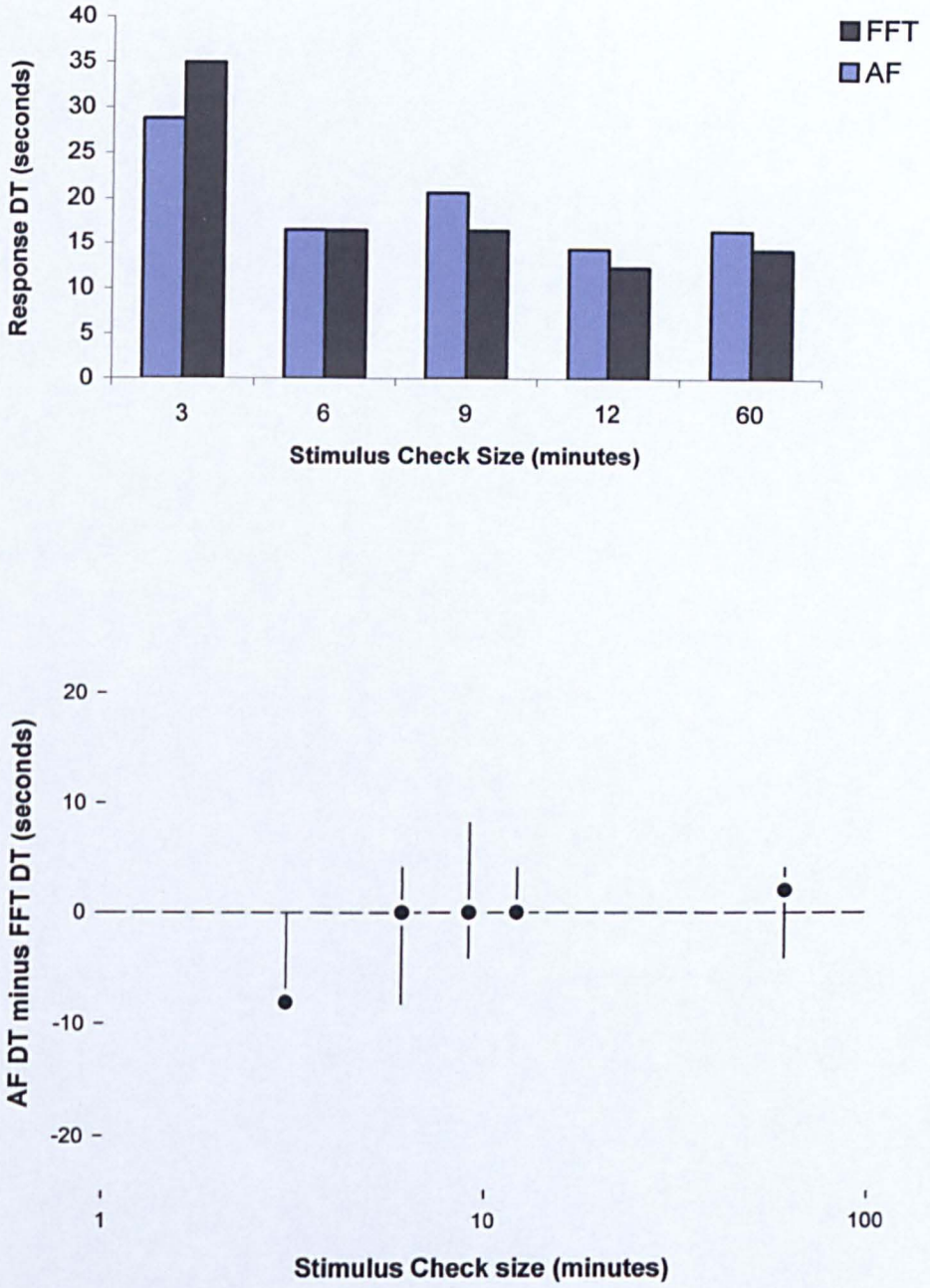


Figure 5.4:a) Median DTs for AF and FFT analysis of ssVEP responses to five different stimulus check sizes. b) 95% confidence intervals showing the difference in DT between analysis techniques.

Response detectability was 82% (49/60) for AF analysis and 83% (50/60) for FFT analysis. There is obviously no significant difference between the two.

Discussion

The AF requires one analysis epoch for its output to settle to within 99% of its input. This means that statistical analysis cannot be started until the second data epoch. T^2_{circ} statistics require at least two data samples before they can estimate the statistical significance of the response at the stimulation frequency. This means the minimum DT is 12 seconds (3 epochs) for the AF compared to eight seconds for the FFT. However this did not result in the FFT detecting responses significantly faster in this study.

The study of Tang and Norcia (1995) also compared AF and FFT. As the same criteria for response detection was applied to both FFT and AF in each study, the relationship between the outcome of these analysis methods should not be affected. This study did not find any significant difference in detectability between techniques, whereas the study of Tang and Norcia (1995) found the adaptive filter to have a higher detectability. However, the FFT is easier to compute than the AF, and displaying its output graphically provides a more intuitive illustration of the ongoing results than the AF output. The FFT is therefore the most suitable technique for the current application of real-time analysis of ssVEPs.

5.3.4 Effects of varying the analysis epoch length

Introduction

The previous two sections were primarily concerned with identifying the analysis technique providing the fastest DTs in ssVEP recording. All experiments performed so far in this thesis have used an analysis epoch length of four seconds and a statistical significance, α, of 0.005 to declare response detection. Reducing the analysis epoch length theoretically increases the risk of false detection (section 5.3.2). However, as it would result in more chances for signal detection, it is postulated that a shorter analysis epoch would reduce DTs and increase sensitivity over a one-minute recording period. The aim of this study was to quantify the trade off between test duration, sensitivity and specificity when the analysis epoch length was varied.

Methods

The subjects were 10 normal adults wearing any required optical correction. The stimulus was a 100% contrast checkerboard reversing at 7.78 reversals/sec with mean luminance of 60cd/m^2 and a field size of 25°. Stimuli of check size 60', 12, 9, 6, and 3' were presented for one minute each. Occluding the stimulus screen with black card and recording EEG for one minute made a control recording in each subject.

Recordings were made from O_z, RO, LO and F_z with a ground electrode placed at a mastoid. Two channels, O_z-F_z and 2 O_z-(RO+LO) (1-D Laplacian analysis), were analysed

off-line. Analysis was performed with epoch lengths of one second, two seconds and four seconds. As the techniques have been found to be complementary, both T^2_{circ} statistics and SNR calculations were used to calculate the response significance at the stimulation frequency.

When the statistical significance of either data channel analysed by either analysis method reached 0.005 response detection was declared. Theoretical total test duration for each subject and for each analysis epoch length was calculated by adding together the response DTs for all five stimulus sizes. An additional theoretical total test duration for each subject and for each analysis epoch length was calculated by adding the duration of a repeated 3' stimulation period to the previous total test duration. This attempted to mimic what might happen clinically, where thresholds are reproduced for validation.

Specificity was calculated using the number of false detections made in the set of control recordings. Detectability was calculated using the total number of response detections out of all 50 recordings.

Results

As the analysis epoch is reduced from four seconds to one second, the total test duration is halved (table 5.2). However, the specificity drops from 0.98 to 0.9 or one false detection in every ten recording periods, which is unacceptably high. Repeating stimulation at the

smallest check size significantly increased specificity without adding much to the test duration. Sensitivity decreased as analysis epoch increased.

Table 5.2: The relationship between analysis epoch, test duration and specificity. r represents a repeated recording at threshold .

Analysis Epoch (s)	Test Duration (s)	Specificity	Sensitivity
1	25.90	0.904	0.8
2	43.18	0.952	0.7
4	52.22	0.977	0.6
1r	36.44	0.991	
2r	51.60	0.998	
4r	88.00	0.999	

Exponential regression line confirms that the correlation between specificity and total test duration is significant (r^2 =0.74, p=0.02) (Figure 5.5).

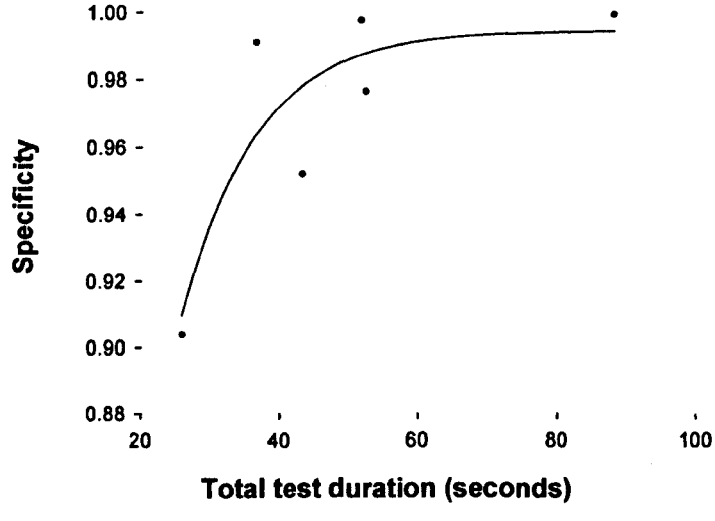


Figure 5.5: The trade off between specificity and test duration of ssVEP testing.

Discussion

The shortest analysis epoch used in this study was shown to give the fastest theoretical test duration, although specificity was compromised. Using a one-second analysis epoch with a repeat recording at threshold would maintain a rapid assessment while giving an adequate specificity. However, on 10% of occasions this threshold will have been defined by a false detection and repeating stimulation of this size will result in a long period where the patient is effectively observing a blank screen. Even if the stimulus can be seen, it is the same as the previous one and therefore a young patient may find it boring. The attention of a child may be lost in both situations.

A four-second analysis epoch provides a high specificity without the need for repeat stimulation at threshold, and total test duration is still less than one minute. In this analysis, the child would be required to attend to the screen for at least four seconds at a time to avoid that data segment being omitted from analysis. Clinical experience tells us that although some children may look at the screen for long periods without losing concentration, for many, recording of responses needs to be made a couple of seconds at a time.

An analysis epoch of two seconds without a repeat provides a good compromise between a short total test duration, adequate specificity, maintaining the child's attention by not repeating stimuli, and collecting data in short enough segments that a child with sporadic, short periods of concentration can still be assessed.

The value of α required to declare detection was set to 0.005 (0.5%) for all recordings in this study. This refers to a 0.5% chance of false detection per analysis epoch. Specificity is usually reported as the rate of false detection per recording period and therefore tends to be greater than 0.5%, as it is in this study. Calculating the rate of false detection per data analysis epoch gave a false detection rate (0.003%) much closer to the pre-defined statistical significance in a previous study (Norcia & Tyler 1985a).

As the pre-requisite statistical significance (α=0.005) describes the chance of false detection per analysis epoch, over a one-minute recording and an analysis epoch of two seconds, this is increased to $1-(1-0.005)^n$ or 0.13. (Bland & Altman 1995; Greenhalgh 1997). The Bonferroni method makes a small adjustment to α for individual analysis epochs in order to reduce statistical significance of the whole recording to the desired value. Such a correction is difficult to calculate and would reduce sensitivity. Therefore a qualitative explanation of results using traditional statistics is preferable (Perneger 1998).

The improvement in sensitivity after reducing the analysis epoch length is likely to be smaller than the improvement offered by a 1-D Laplacian analysis (section 4.3.1). Also, as both Oz-Fz and 1-D Laplacian analysis channels are used for signal detection, sensitivity is already likely to be near optimum whichever length of analysis epoch is chosen. The trade off between specificity and test duration should therefore determine the analysis epoch chosen. A two-second epoch without repeating any stimulation periods provides a good trade off.

5.3.5 Conclusions

As T^2_{circ} statistics and SNR detection techniques are complementary a response detection defined by either statistic should be accepted by the program. As there are no DT differences between analysis techniques, so the FFT should be used rather than AF as it is easier to compute and it will be easier to present the output graphically for the user interface. The level of α to define a detection should remain at 0.005 so as not to compromise test sensitivity. Theoretically, the analysis epoch should be three to four seconds long to satisfy the requirements of the detection statistics. However, investigation showed that a two-second analysis epoch length maintained adequate specificity whilst reducing the overall test duration.

5.4 Real-time analysis of ssVEPs

5.4.1 Introduction

The reduction in test duration offered by optimisation of the analysis parameters will only be realised if responses are analysed in real-time. In theory, fourier analysis can be performed by the PC after two seconds, as soon as the first epoch of data has been collected. Further analysis can be performed after every two-second data epoch. The use of interrupt service routines allows data to be analysed and the results displayed while the next data segment is being collected

Stimulating below the acuity threshold of an individual risks loss of attention in paediatric patients, as well as prolonging the test procedure. Stimulating too far above threshold wouldn't provide useful information, and may use up a valuable proportion of a child's limited concentration span. These points have already been raised in relation to the sweep VEP (section 2.5.1). The aim of this section is to develop an assessment that rapidly identifies the near-threshold region by using large increments in stimulus size, then reduces these increments to find more accurate visual acuity threshold.

5.4.2 Stimulation Period

Introduction

Up to this point in this study, ssVEP stimulation periods have been one minute long with analysis performed off-line when all recording was completed. A typical ssVEP response DT is 12 seconds (table 3.1). Real-time analysis of EEG recordings would need to stimulate for at least 12 seconds at each stimulus before detecting most responses. The aim of this study is to establish the maximum stimulation period required that ensures responses are detected as often as possible when they are present. The study will also establish if this stimulation period varies with stimulus size, particularly near the acuity threshold of an individual.

Method

The subjects were 23 normal adults. The stimulus was a 100% contrast checkerboard reversing at 7.78 reversals/sec with mean luminance of 60cd/m^2 and a field size of 25° (reduced to 12.5° for the smallest stimulus). Stimuli of check sizes 60', 12, 9, 6, 3'and 1.5' were presented for one minute each. Recordings were made from O_z, F_z, RO and LO with a ground electrode placed at a mastoid. O_z-F_z and $2O_z$-(RO+LO) (1-D Laplacian) were analysed using an analysis epoch of two seconds, and both SNR and T^2_{circ} statistics to determine the statistical significance of the signal power at the stimulation frequency. When this significance reached 0.005 using either analysis method detection was declared

and a DT established. Individual threshold check size referred to the size of the smallest stimulus that evoked a statistically significant ssVEP. Dividing the suprathreshold check sizes by this value for each individual enabled DTs to be plotted as a function of 'octaves above threshold'. The detection times in each of these groups were compared with a Wilcoxon signed ranks test.

Results

If a response within five octaves of threshold is present then it was detected within 53 seconds of stimulation in all subjects (figure 5.6). 98% (100/102) of these responses were detected within 22.6 seconds. The wilcoxon test did not establish any significant DT differences between stimulus sizes expressed as visual angles or octaves above threshold, this is also the case for normal children of all ages (table 4.2).

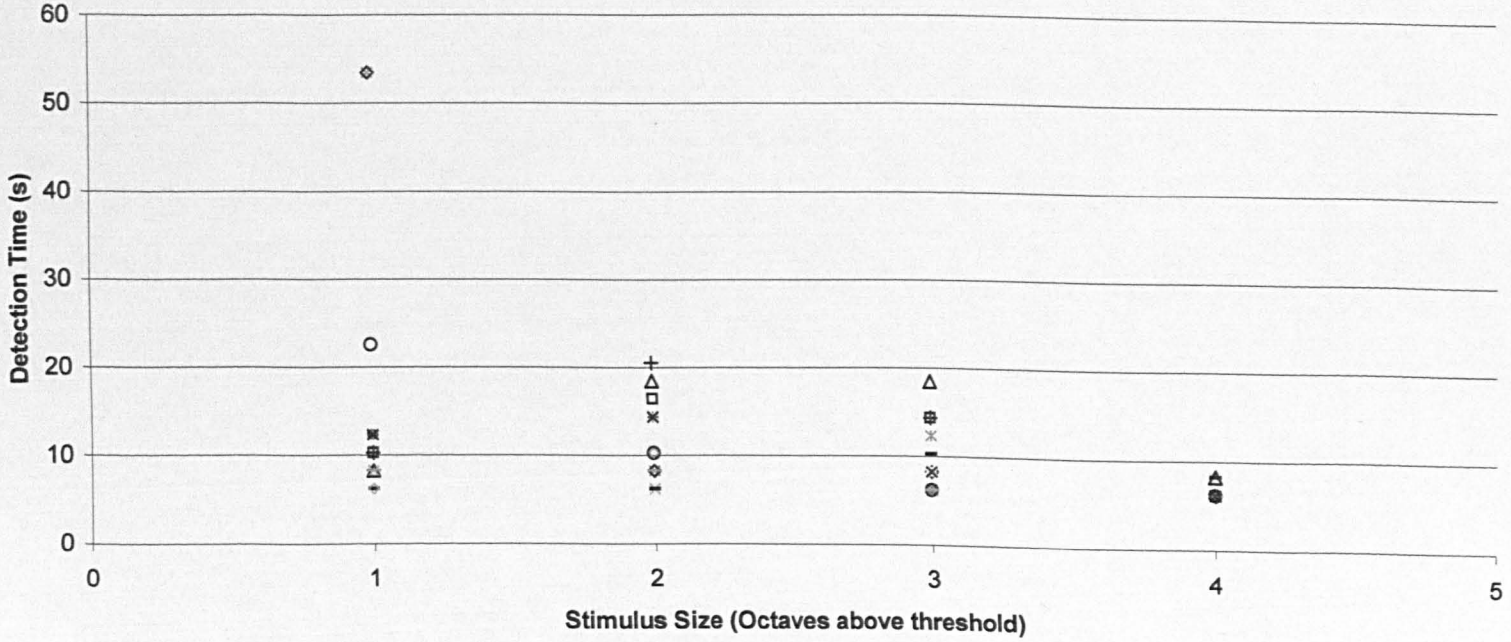


Figure 5.6: Scatter plot of response detection times plotted as a function of Octaves above threshold.

Discussion

All stimuli should be displayed until response detection or 22.6 seconds have elapsed as this will enable response detection in 98% of subjects during the initial stimulation period. There were two occasions where detection took around 50 seconds. It has already been concluded that stimuli should not be repeated if a response had already been detected to a specific stimulus checkerboard (section 5.3.4). In the interests of maintaining a child's attention, it would also be preferable not to repeat presentation of a stimulus that failed to elicit a response. Varying stimulus size in small increments after the first failure and demanding two consecutive response detections to define threshold would adequately validate thresholds without any repeat stimulation.

5.4.3 Calculating stimulus size range and increments

Introduction

The octave increments of transient (t-VEP) and ssVEP stimulation performed so far are equivalent to steps of 0.2-0.3 LogMAR. Glasgow acuity cards (GACs) and Cardiff Cards (CCs) both have increments of 0.1 LogMAR. At their standard test distance of 3 metres, GACs and CCs measure acuity in the range of 0.8 to –0.3 and 1.3 to 0.0 LogMAR respectively. Subjective testing therefore has a range of at least –0.3 to 1.3 LogMAR, corresponding to visual angles of 0.5' to 20' The geometric progression of GAC and CC stimulus sizes allows them to be used at non-standard test distances to increase this range. For example displaying the largest GAC stimulus at 1 metre is equivalent to a visual angle of 80 minutes, and reducing this test distance further to 50 cm equates to an angle of 160'.

It is important for the resolution and range of VEP assessment to be at least as good as subjective testing if it is to be complementary. For evaluation of the accuracy of any newly developed acuity test it is important that its spatial resolution matches that of the test to which it is being compared . This ensures that the outcome of two different assessments performed in the same subject can be accurately compared. Patients with cortical visual impairment (CVI) may have other developmental problems that make VEPs particularly useful in assessment of their visual acuity. As this patient group tends to have significantly reduced acuity, the range of test stimulus sizes needs to be as large as possible, and requires

spatial resolution of 0.1 LogMAR. The aim of this study is to create a set stimulus checkerboards for VEP acuity assessment matching the increments of commonly used subjective assessments and to extend the upper range to suit the range of abilities of our patient group.

Methods

LogMAR values of 0.0 up to 3.0 were converted to visual angles. This angle corresponds the diagonal period of a checkerboard, which is 1.4 times as large as the horizontal and vertical dimensions of the checks. The resolution of the stimulus monitor was 56 dpi (table 2.2). This resolution limits how small the stimulus can get and how small increments between stimuli can be. Increments of 0.1 LogMAR between stimuli can be maintained if the viewing distance is increased from the current distance of 45cm. This in turn reduces the stimulated field size. Resolving stimuli as small as possible is paramount in the assessment of visual acuity, for which the foveal vision only is used. The field size and the number of pattern elements were also calculated for each stimulus created.

Results

The stimulus sizes created are given in table 5.3. The smallest check size created was 1.8 minutes, which converts to 0.4 LogMAR. The monitor resolution also made it impossible to create each medium check-size increment at our standard viewing distance of 45cm. To

address this, 5 stimuli were presented at 90cm and 2 stimuli were presented at 180cm. It was not possible to create checks smaller than 1.8' without further increasing the viewing distance from 180cm, which also reduced the field size below 5°. Check sizes corresponding to 0.0-0.3 LogMAR were not included in this system although they are included in table 5.3.

Table 5.3: Check widths equivalent to 0.4 to 3.0 LogMAR in 0.1 LogMAR steps.

Stimulus	LogMAR	Visual Angle (')	Viewing Distance (cm)	Field Size (°)	Check Width (')	Pattern elements
1	3	1000.0	45	25	714.3	4
2	2.9	794.3	45	25	567.4	4
3	2.8	631.0	45	25	450.7	4
4	2.7	501.2	45	25	358.0	4
5	2.6	398.1	45	25	284.4	16
6	2.5	316.2	45	25	225.9	36
7	2.4	251.2	45	25	179.4	36
8	2.3	199.5	45	25	142.5	64
9	2.2	158.5	45	25	113.2	100
10	2.1	125.9	45	25	89.9	196
11	2	100.0	45	25	71.4	324
12	1.9	79.4	45	25	56.7	484
13	1.8	63.1	45	25	45.1	784
14	1.7	50.1	45	25	35.8	1296
15	1.6	39.8	45	25	28.4	2116
16	1.5	31.6	45	25	22.6	3364
17	1.4	25.1	45	25	17.9	5476

Stimulus	LogMAR	Visual Angle (')	Viewing Distance (cm)	Field Size (°)	Check Width (')	Pattern elements
18	1.3	20.0	45	25	14.3	8100
19	1.2	15.8	45	25	11.3	13456
20	1.1	12.6	45	25	9.0	21316
21	1	10.0	90	12.5	7.1	9216
22	0.9	7.9	90	12.5	5.7	13924
23	0.8	6.3	90	12.5	4.5	22500
24	0.7	5.0	180	6.75	3.6	8836
25	0.6	4.0	180	6.75	2.8	14884
26	0.5	3.2	90	12.5	2.3	87616
27	0.4	2.5	90	12.5	1.8	142884
28	0.3	2.0			1.4	
29	0.2	1.6			1.1	
30	0.1	1.3			0.9	

Discussion

Although standards for VEP recording recommend a stimulated field size of at least 15° (Harding *et al.*1996) these guidelines do not specifically apply to visual acuity assessment. Acuity assessment is concerned whether a response is present or absent rather than if every morphological feature of the waveform are preserved. Katsumi *et al.* (1988) found that when the number of pattern elements in a stimulus exceeded about 300 there was no further increase in response amplitude. It has also been shown that for check sizes of 15' up to

180', the stimulated field size has to drop to around 5° before any reduction in response amplitude is observed (Bradnam 1994). As the minimum field size of checkerboard presentation in this assessment is 6.75°, response amplitude and acuity outcome should not be affected by varying the test distance.

It is known from clinical experience that the further the stimulus monitor is placed from a young subject, the less likely it is that attention will be maintained. Although the standard test distance for GACs and CCs is 3 metres, in subject with learning difficulties or neurological impairment, the test would normally be attempted at a much shorter distance. The same applies to viewing distance for VEPs. The test distance had to exceed one metre on two occasions to maintain the 0.1 LogMAR spatial resolution between check sizes.

The smallest stimulus size presented in this study has a diagonal angle of 2.5' which converts to 0.4 LogMAR, a decimal acuity of 0.4 or 6/15 snellen equivalent (see Appendix A). However, the functional relationship between VEP and subjective acuity is likely to differ from this. ssVEP stimulation at 3' provided the threshold of spatial resolution for most normal adults (table 3.1), which suggests that empirically, responses to checks of 2.5' indicates a much better visual acuity than 6/15. The range of test stimuli created here therefore includes stimuli small enough to establish the presence of normal visual acuity.

5.4.4 Stimulus Control

Introduction

Real-time analysis of ssVEPs would allow stimulus presentation decisions to be based on the information collected up to that point. If a response is detected to the initial stimulus then a smaller stimulus should be presented. If the first stimulus fails to evoke a response then a larger stimulus should be presented. This would overcome the problem of the fixed range of stimulus sizes presented during the sweep VEP, many of which may be too small for the patient, whose level of vision is unknown, to see. Presenting stimuli that cannot be seen probably results in loss of attention.

Conversely, stimulating too far above the patients threshold may lead to a very long test procedure that in turn may result in loss of attention. This is also inevitable during the sweep VEP assessment of a patient with unknown acuity. It would also lead to much of the data being discarded as it cannot be used in amplitude extrapolation. Novel stimulation paradigms for subjective acuity assessment reduce the time presenting stimuli above threshold and concentrate on pertinent near threshold recordings (Camparini *et al.* 2001a; Macaluso *et al.* 2001; Camparini *et al.* 2001b). Large initial increments in stimulus check size during the ssVEP assessment should allow the acuity threshold region to be identified fairly quickly. A subsequent reduction in check size increment will allow an accurate acuity threshold to be established in as few steps as possible.

The aim of this study is to use the set of ssVEP stimuli developed in the previous section to establish acuity threshold in a group of clinical subjects using as few stimulation periods as possible.

Methods

The subjects were 44 children referred to ophthalmology clinics with a range of visual problems. Acuity assessment using real-time analysis of ssVEPs was successfully completed. A protoype stimulus presentation algorithm was used. The initial stimulus size was 45' and the protocol moved forward by three stimulus size increments if a response detection was made. The step size remained at three size increments until the first stimulation period that failed to elicit a response, after which the protocol moved back by two stimulus sizes. The step size was one stimulus size increment forward after subsequent response detection, and one stimulus size increment backward after subsequent detection failure. Repeat stimulation periods were avoided and if two response detections followed by a detection failure occurred for any three consecutive stimuli then the program ended. Threshold was defined as the smallest stimulus check size to which a response was detected, provided it was preceded by response detection and followed by a detection failure.

Results

The capability of the subject group is quantified by the detectability of each of the 27 stimulus sizes (Figure 5.7). 50% (22/44) of the patients responded to a stimulus of 22.6' or larger. 75% (33/44) of subjects responded to a stimulus of 56.7' or larger. 95% (42/44) of subjects responded to a stimulus of 284' or larger.

The new stimulus presentation algorithm is illustrated in figure 5.8. The algorithm starts at the fifth largest stimulus size of 284' and steps through the stimulus sizes in increments of four, two and one following 100% response detection, one detection failure, and more than one detection failure respectively. The number in the bottom right corner of each box represents the stimulus number assigned in table 5.3.

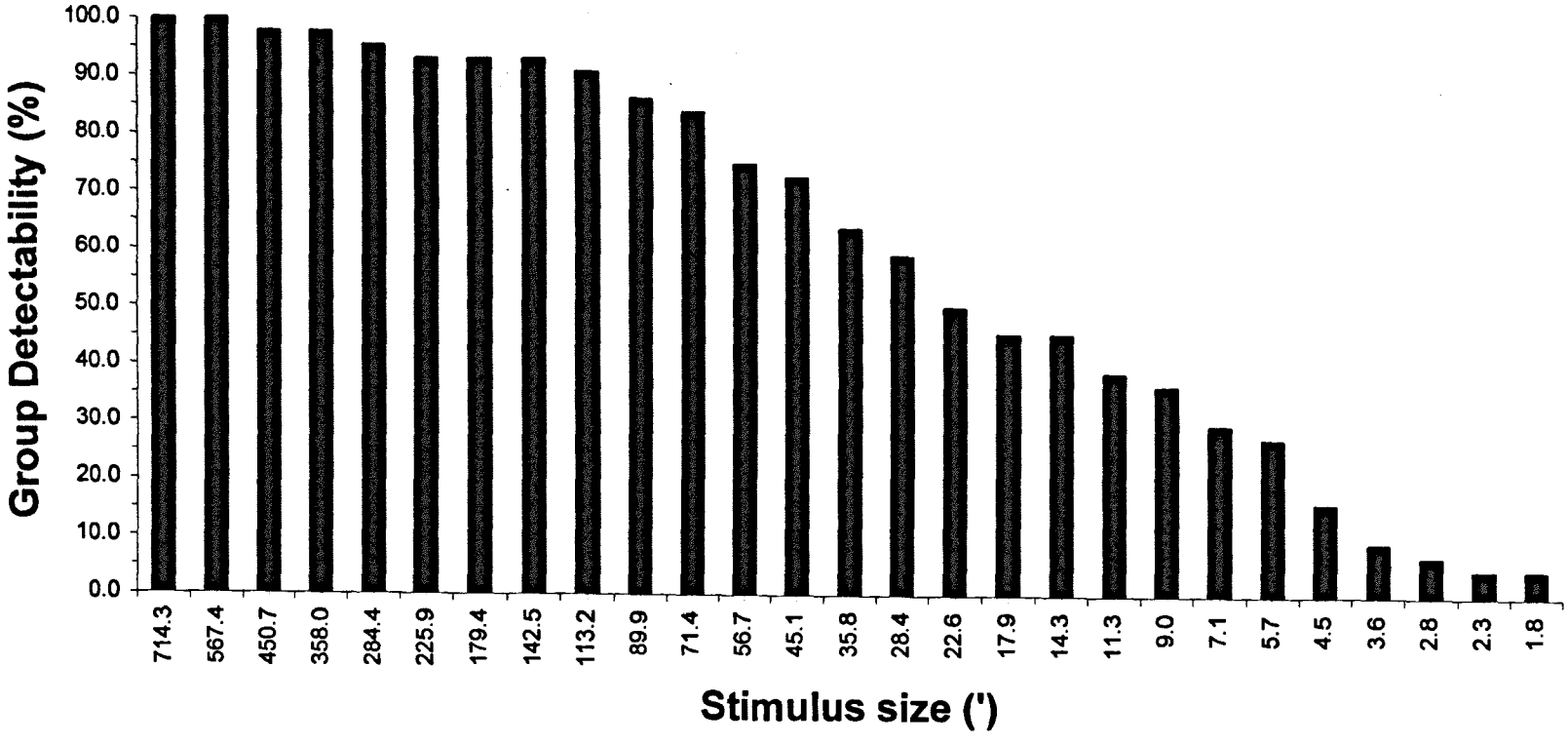


Figure 5.7: The proportion of the clinical group capable of responding to each stimulus check size.

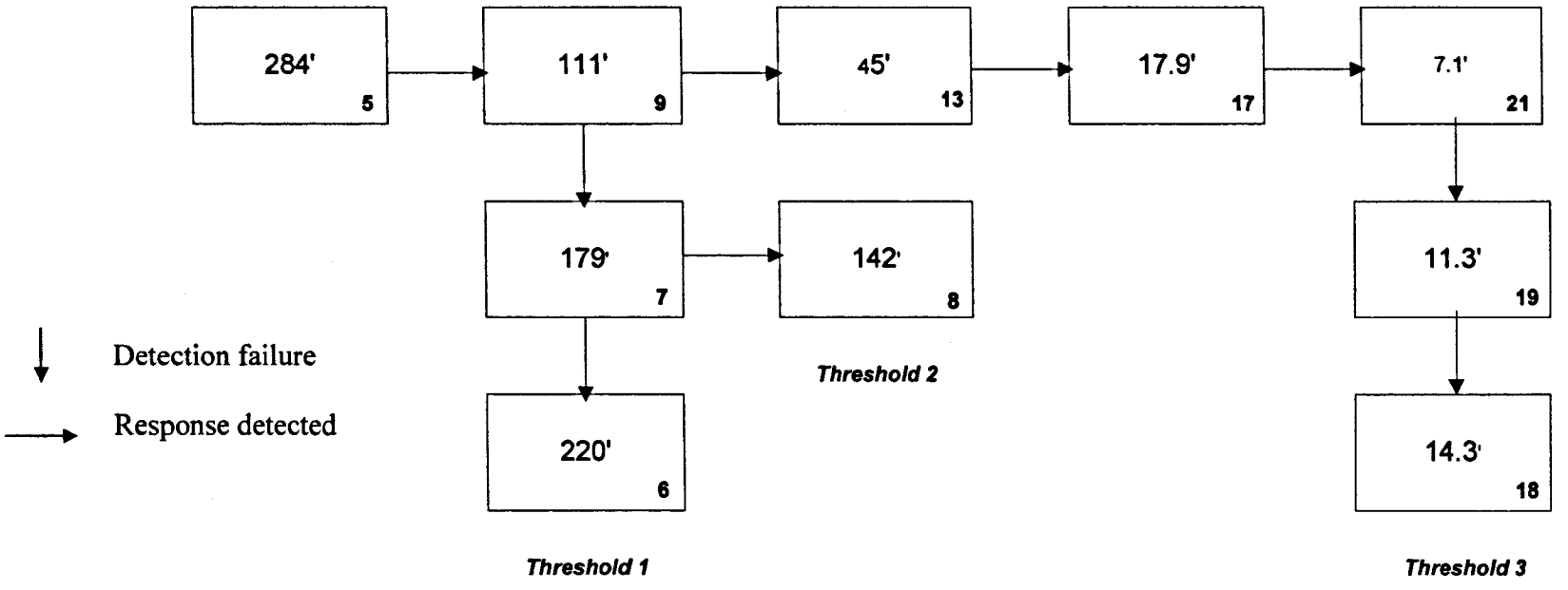


Figure 5.8: The final stimulus presentation algorithm indicating the typical stimulation order and determination of threshold for three different levels of vision.

Discussion

If this patient group is typical of patients referred for VEP acuity assessment then presentation of a stimulus checksize of 284' (number 5) means that straight away 95% of the patient group would be shown something they could see. If no detection were made then an initial increment of four stimulus sizes back would make stimulus number 1 the subsequent stimulus size. Presentation of a stimulus check size of 714' means that 100% of the patient group would be shown something they could see within 30 seconds of beginning the test. If no response detection is made at 714', then the acuity level is presumed to be light perception at best and the test would terminate. As long as response detections are being made, increments of four stimulus sizes ensure that stimulation reaches the threshold region as soon as possible. For clarity, the newly developed assessment will be called the step_VEP from now on.

5.4.5 Acuity Estimation

Introduction

VEP acuity test results have been described in terms of the visual angle of the smallest stimulus evoking a measurable response so far in this thesis. An alternative method of estimating visual acuity from VEP recordings is extrapolation of the spatial-frequency amplitude function (section 2.6). Comparison of the step_VEP acuity assessment with subjective acuity assessment in the same subject across a large group will allow step_VEP acuity to be described in terms of its subjective equivalent eventually. This is the most meaningful way of describing test results to other clinicians and parents. The aim of this study is to establish whether last check size acuity or extrapolated acuity agrees more closely with subjective testing in a group of normal adults.

Methods

The subjects were 9 normal adults. The stimulus was a 100% contrast checkerboard with mean luminance of 60cd/m^2 and a field size of 25° (reduced to 12.5° for the smallest stimulus). The reversal rate was 7.78 reversals/sec and stimuli of check sizes 60', 12', 9', 6', 3'and 1.5' were presented for one minute each. Recordings were made from O_z, F_z, RO and LO with a ground electrode placed at a mastoid. O_z-F_z and $2O_z$-(RO+LO) were analysed by fourier transform using an analysis epoch of four seconds. T^2_{circ} statistics were applied to the output of the FFT at the stimulation frequency to determine the statistical significance of the signal power. When this significance reached 99.5% using either

analysis method detection was declared. For each subject and each analysis channel visual acuity was estimated using 1) the smallest check size technique and 2) extrapolation of the amplitudes of statistically significant responses to 0uV. An additional criterium demanded that phase was stable or gradually lagging as the stimulus checkerboard got smaller.

Results

The agreement between subjective and VEP measurements of acuity in are similar for all four analysis techniques (figure 5.9). The 95% confidence limits of agreement overlap (figure 5.10) meaning that no technique was shown to be significantly different from any other in this patient group. The narrowest confidence intervals occur for the smallest check size technique and O_z-F_z analysis channel. The 95% confidence intervals are wider for the agreement with smallest check size and a 1-D Laplacian analysis channel.

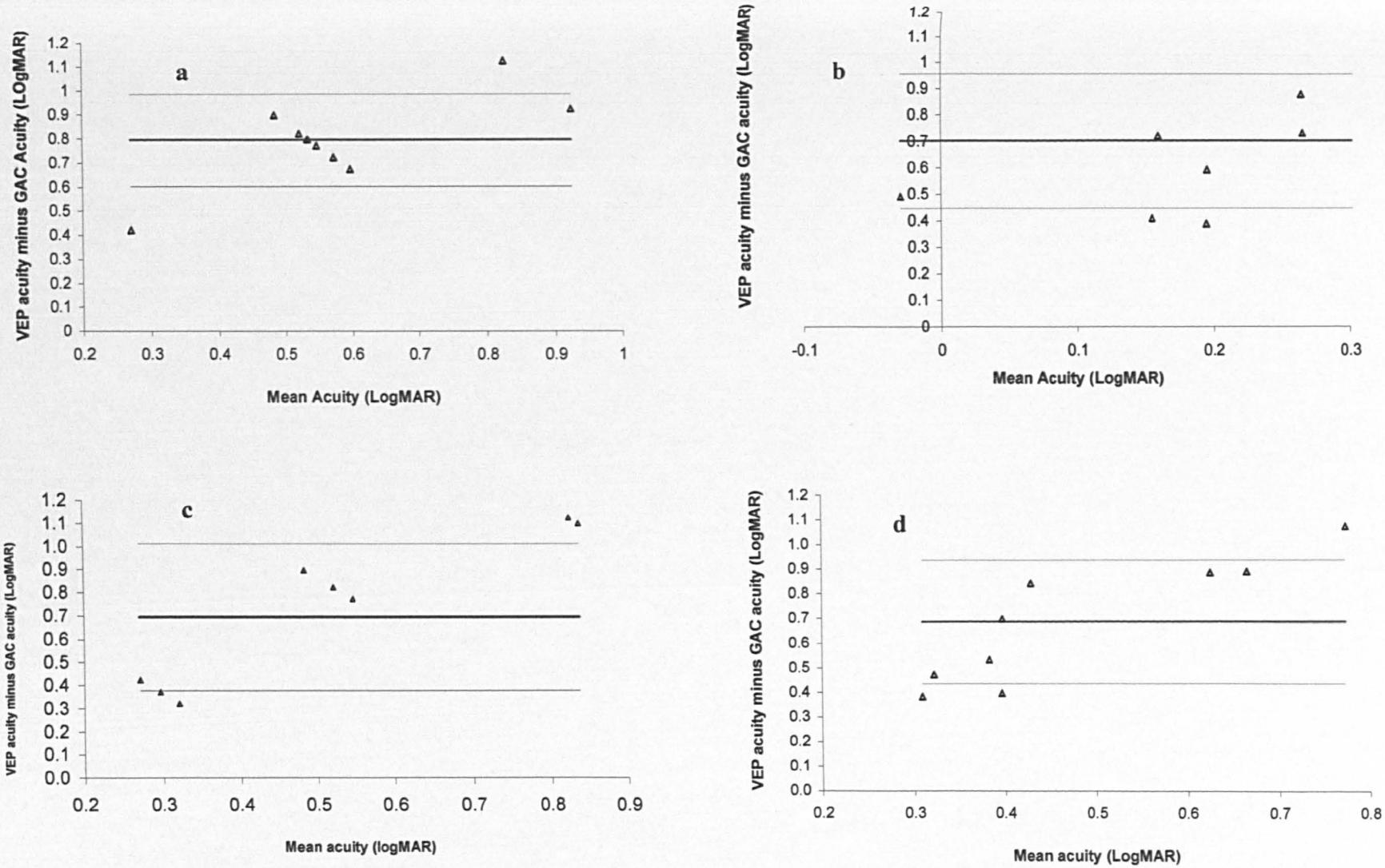


Figure 5.9: Agreement between subjective acuity and VEP acuity determined by a) the smallest check response detected by O_z-F_z. b) extrapolated O_z-F_z response amplitudes. c) the smallest check response detected by a 1-D Laplacian. d) extrapolated 1-D Laplacian response amplitudes.

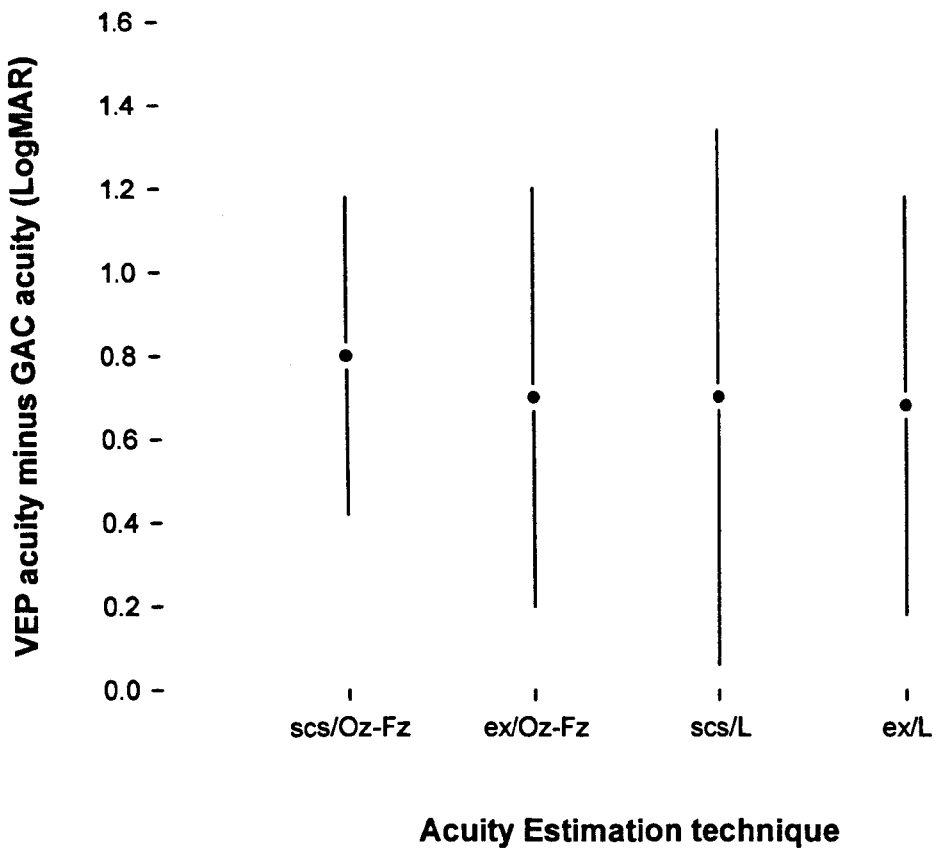


Figure 5.10: 95% confidence intervals of agreement between subjective acuity and four different VEP acuity techniques. scs refers to the smallest check size technique and ex refers to extrapolation. L denotes the 1-D Laplacian analysis channel.

Discussion

The results presented here show that extrapolation of ssVEP response does not provide significantly different limits of agreement with subjective acuity than using the smallest checksize seen. As it would be relatively difficult to compute a real-time amplitude extrapolation, the smallest checksize technique alone would provide sufficiently accurate acuities. In addition, the successive approximation presentation paradigm employed by the step_VEP (section 5.4.4) means that as few as two responses could be measured on the descending limb of the spatial frequency amplitude function. This would make extrapolation invalid as it requires several data points (section 2.6).

1-D Laplacian analysis has been shown to reduce DTs and increase sensitivity without compromising specificity (section 4.3). These time benefits should be exploited by the real-time assessment by accepting response detections from both O_z-F_z and 1-D Laplacian analysis channels.

5.4.7 User Display

There are eight chances for response detection for every two seconds of data that are recorded due to the four analysis channels and two statistical detection methods. Figure 5.11 illustrates the appearance of the display screen close to the end of a step_VEP acuity assessment. Although the test is fully automated, the tester can use keys F1 to F6 to override the program control.

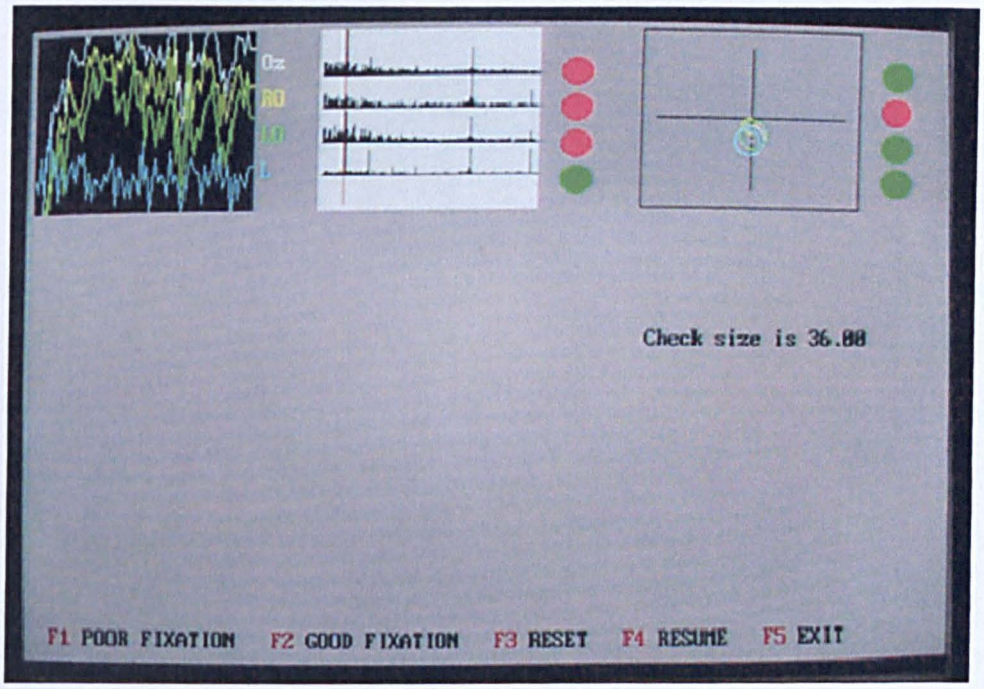


Figure 5.11: The user screen provides ongoing information on current recordings and options to override the automated analysis and stimulus presentation of the program

If the patient momentarily looks away then pressing F1 will pause analysis while allowing the program to carry on acquiring data. When the patient looks back at the screen, key F2 will restart analysis.

Although recording is ongoing, F3 allows the analysis period (23 seconds) for the current stimulus size to be reset while F4 instructs the program to re-start analysis.

F5 allows the current stimulus to be skipped. If F5 is pressed before a response is detected then the stimulus presentation algorithm (figure 5.8) will automatically present a larger check size as it will presume that a response was absent.

Pressing F6 will exit the program completely, which may be necessary if a patient loses attention before the program has found a threshold.

Responses to check reversal stimulation recorded from three occipital channels, O_z-F_z, LO-F_z and RO-F_z are shown in white, yellow and green respectively in the left hand window. LO and RO are located at 15% of the half-head circumference left and right of O_z respectively. The fourth trace coloured in blue is 1-D Laplacian transformation of these three recordings, $2O_z$-(LO+RO). If one of the recording electrodes falls off accidentally or one of the recording channels is contaminated with background noise, then this can be observed in this window.

Recordings from all four channels are averaged every two seconds in the time domain. The middle window displays the output of the subsequent FFT. The vertical red line highlights the bin stimulation frequency of 7.78Hz used in SNR calculation along with the two neighbouring bins. If the amplitude at the stimulation frequency bin here is five times larger than its neighbours then a response is defined as being present (Meigen and Bach 1999).

The output of a second FFT performed on un-averaged EEG data every two seconds is displayed on the polar plot in the right hand window. There is a coloured dot for each analysis channel showing the on-going average of response amplitude and phase. The colours match those of the raw EEG channels drawn in the first window. Correspondingly coloured circles illustrate the confidence interval around the mean, determined by the T^2_{circ} statistic. The T^2_{circ} statistic uses the spread of response amplitude and phase and the pre-defined statistical significance to calculate the radius of this circle.

If the signal at the stimulation frequency is significantly larger than noise (α=0.005) on any of the eight analysis channels, then the corresponding traffic light changes from red to green and the stimulus control algorithm will present a smaller check size. If the significance reaches level α reaches 0.01 then the traffic light turns amber to indicate that response detection may be imminent. However, stimulation continues at the current check size.

After at least one stimulation period has been completed, a chart of response amplitude and phase appears on the user screen. The response chart has a circular marker and a square marker representing each of the 27 stimulus sizes. If a stimulus has been presented for 22.6 seconds, but no response detected then the corresponding circle will be coloured red and its vertical position on the chart will represent the amplitude of EEG noise. If detection is made then the corresponding circle is coloured green and its vertical position represents the response amplitude. The vertical position of the aligned black square represents the response phase. The circular and square markers representing response amplitude and phase

for stimuli that have not yet been attempted are coloured black and remain at 0μV and 0 degrees respectively.

After each stimulation period, information about response DT, amplitude and phase recorded by each channels is saved to a data file as well as being displayed on the screen. This can be used to formulate a report at the end of the assessment. Every four seconds (two analysis segments) the raw data is also written to file allowing re-analysis of the data file off-line. This is useful for research purposes.

Chapter 6: Evaluation of step_VEP acuity assessment in normal adults

6.1 Introduction

The step_VEP test described in chapter five was designed to provide a rapid assessment of patients with a range of visual acuities. As ophthalmologists and orthoptists are more familiar with LogMAR and Snellen units than visual angles, the VEP test results should be converted accordingly (Appendix A). Expressing step_VEP acuity score as its equivalent subjective acuity score or range of subjective acuities is more likely to reflect functional visual acuity than direct conversion from the visual angle (section 2.6)

The relationship between VEP acuity score and subjective acuity score is known to vary with pathology (Westall *et al.* 2000). Some conditions result in larger disparity in VEP and subjective acuity score than others. The relationship between VEP and subjective acuity scores may also change during normal maturation of the visual system. As the step_VEP assessment is designed for paediatric patients this must be taken into consideration when comparing test results. A group of normal adult volunteers tested with both step_VEPs and subjective tests would allow collection of normative data free from pathological and developmental factors. A relationship between assessments at various levels of vision could be established by testing at various levels of artificially degraded vision. Repeating the step_VEP assessment at each different level will allow quantification of reproducibility and repeatability across a range of acuities.

Investigating the spatial frequency amplitude function would determine whether interindividual variability in the shape of the spatial frequency amplitude function has an on the acuity score of step_VEP assessment.

6. 2 Comparison of step_VEP acuity score and subjective acuity score.

6.2.1 Introduction

The Bailey-Lovie chart has become a gold standard in clinical research and clinical trials (Ferris & Bailey 1996). Glasgow Acuity Cards are a child friendly version of the Bailey-Lovie chart that can be used from a younger age. Although testing with letters becomes appropriate over the age of three years (Egan & Brown 1984), our study sample has a preponderance of children with learning and motor difficulties, which means that optotype tests like Cardiff Cards are often used in older patients than usual. However, even Cardiff cards are not possible to use for children with severe neurological or motor impairment and VEPs become the only option. Before subjective and VEP acuity scores are compared in the clinical group, it would be useful to establish the correlation between step_VEP acuity score and subjective acuity score in a neurologically normal control group.

6.2.2 Methods

The step_VEP program was adapted to present all 27 stimuli (table 5.3) from largest to smallest. This was named the staircase VEP. Staircase VEPs were also analysed in real time so that the typical length of the staircase VEP assessment was as short as possible at about ten minutes. Each checkerboard had a mean luminance of $60cdm^{-2}$ and a contrast of 100%. Recordings were made from four channels, O_z-F_z, LO-F_z, RO-F_z and $2O_z$-(RO+LO). The software accepted signal detection from any of these four channels. Step_VEPs, Cardiff cards and Glasgow cards were also used to assess the visual acuity

of each subject. Bangerter filters (Ryser Optic, St. Gallen, Switzerland) provide a robust method of degrading vision. A pilot study on two subjects showed that the 0.1, 0.6, 0.8 and 1.0 filters (arbitrary units), along with unfiltered vision provided an even spread of visual acuities between 6/3 and 6/60. The 0.1 filter degraded vision only slightly and the 1.0 filter degraded vision significantly. The filters were subsequently used to artificially degrade the vision of 16 optically corrected adult volunteers. Acuity was estimated by four methods for five levels of vision in each subject.

All acuity scores were converted to LogMAR units for comparison. Comparisons between assessments were made using three different techniques. Regression analysis was performed to quantify the correlation of test outcomes. Bland-Altman analysis was performed to quantify the agreement between methods. The range of subjective acuity scores (in LogMAR units) corresponding to each ssVEP critical check size (Katsumi *et al.* 1994)(section 2.6) was also expressed to provide a meaningful result to clinicians, patients and parents.

6.2.3 Results

A good agreement between Glasgow Cards and Cardiff Cards can be observed in figure 6.1. There is no bias across the range of acuity levels. There is also a good agreement between ssVEP stimuli presented in staircase (from smallest to biggest) or step algorithms (figure 6.2). The 95% confidence limits of agreement are also narrow at $\pm$0.5 LogMAR for each comparison.

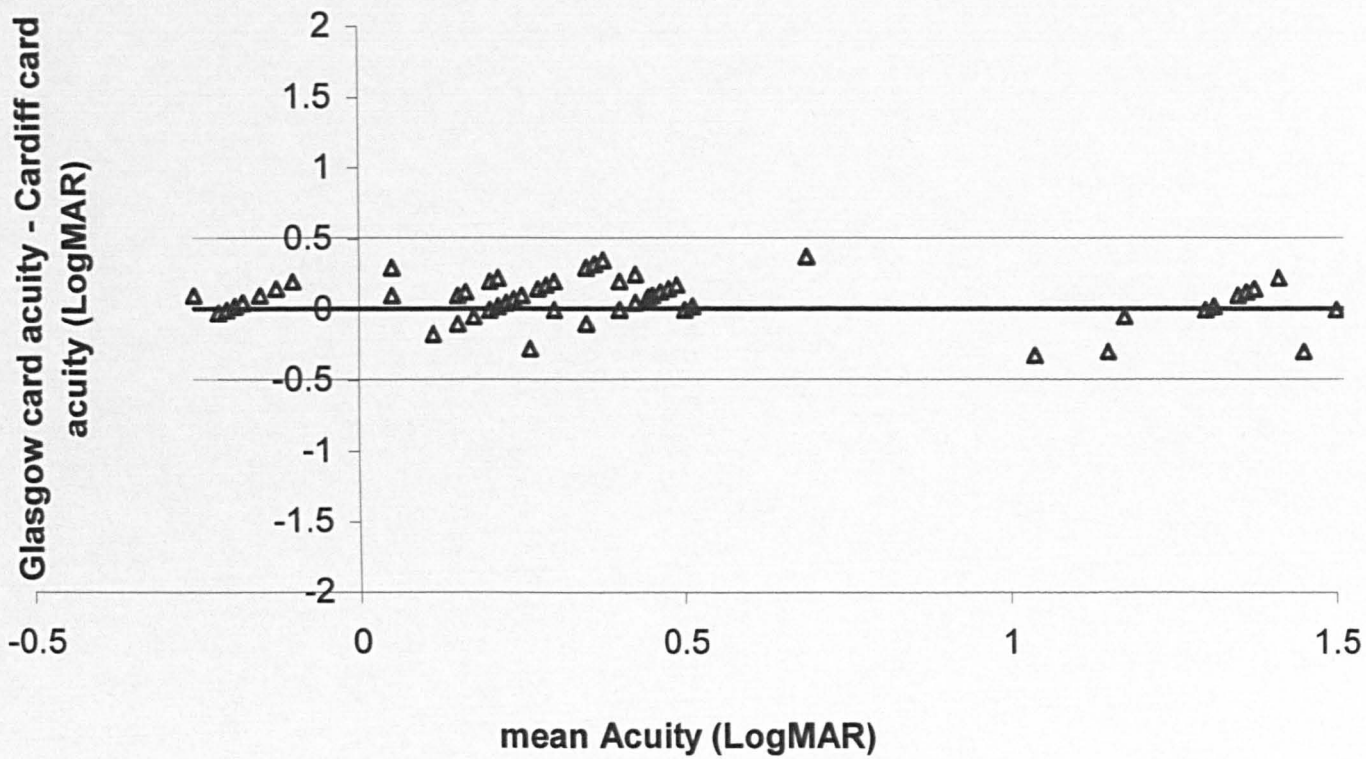


Figure 6.1: Mean and 95% confidence intervals of agreement between Glasgow card and Cardiff card acuity scores in neurologically normal adults tested at five different levels of vision.

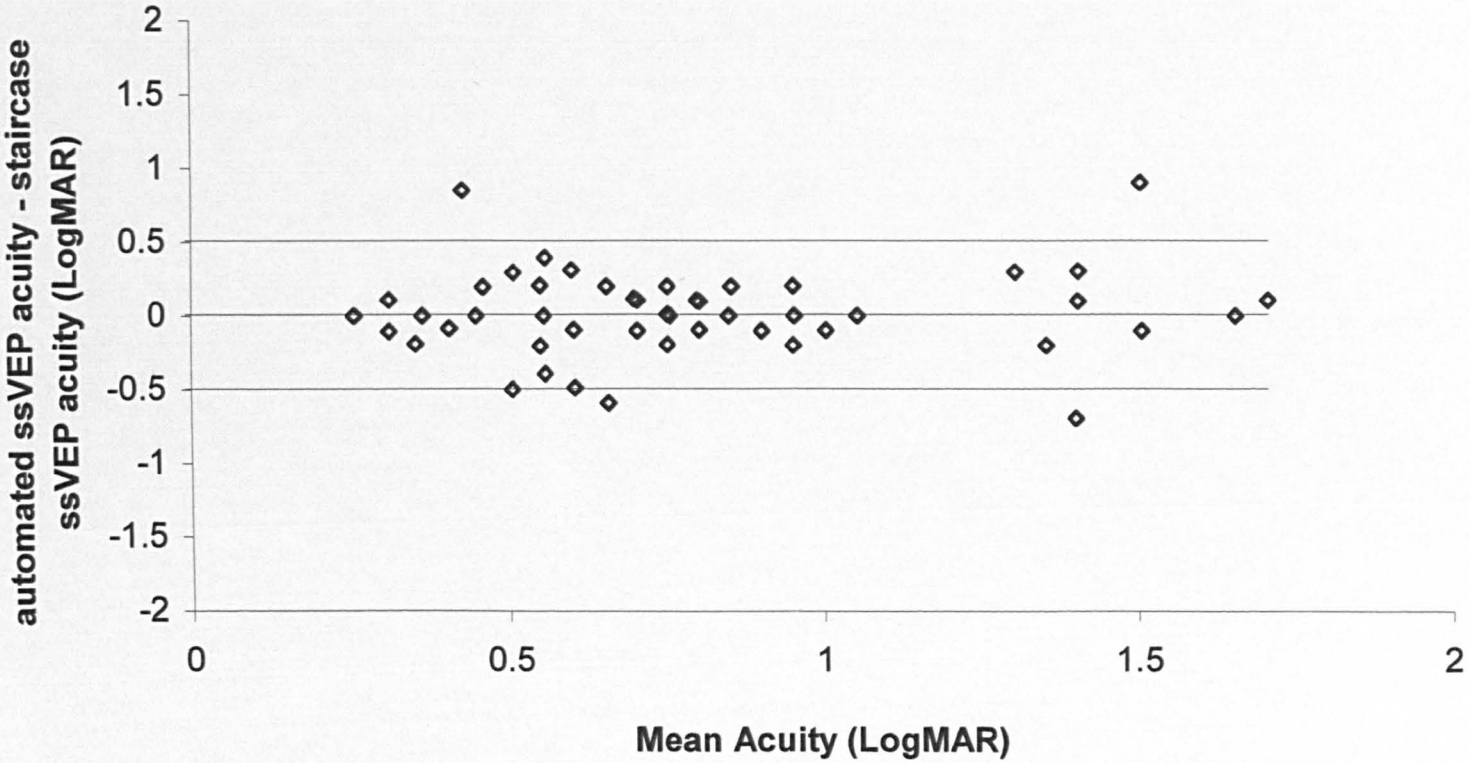


Figure 6.2: Mean and 95% confidence intervals of agreement between staircase VEP and step_VEP test outcomes in neurologically normal adults.

Linear regression (figure 6.3) of Glasgow card acuity score against step_VEP acuity score showed a significant correlation (r^2=0.60, df=1, p=0.000). A Bland-Altman plot (figure 6.4) showed a mean difference in acuity score of 0.42 LogMAR (95% confidence limit of –0.4 to1.0 LogMAR) between the two tests. The mean difference is equivalent to four stimulus size increments in the step_VEP assessement, or snellen scores of 6/6 to 6/15. A t-test also shows that the difference between acuity scores for the two techniques is significant (t=13.191, df=74, p=0.000). Figure 6.5 illustrates the range of Glasgow card acuities corresponding to each step_VEP critical check size for all the levels of vision investigated in this study. There is a large range of subjective acuities for each ssVEP critical check size and the results are summarized by the linear regression line and its 95% confidence intervals.

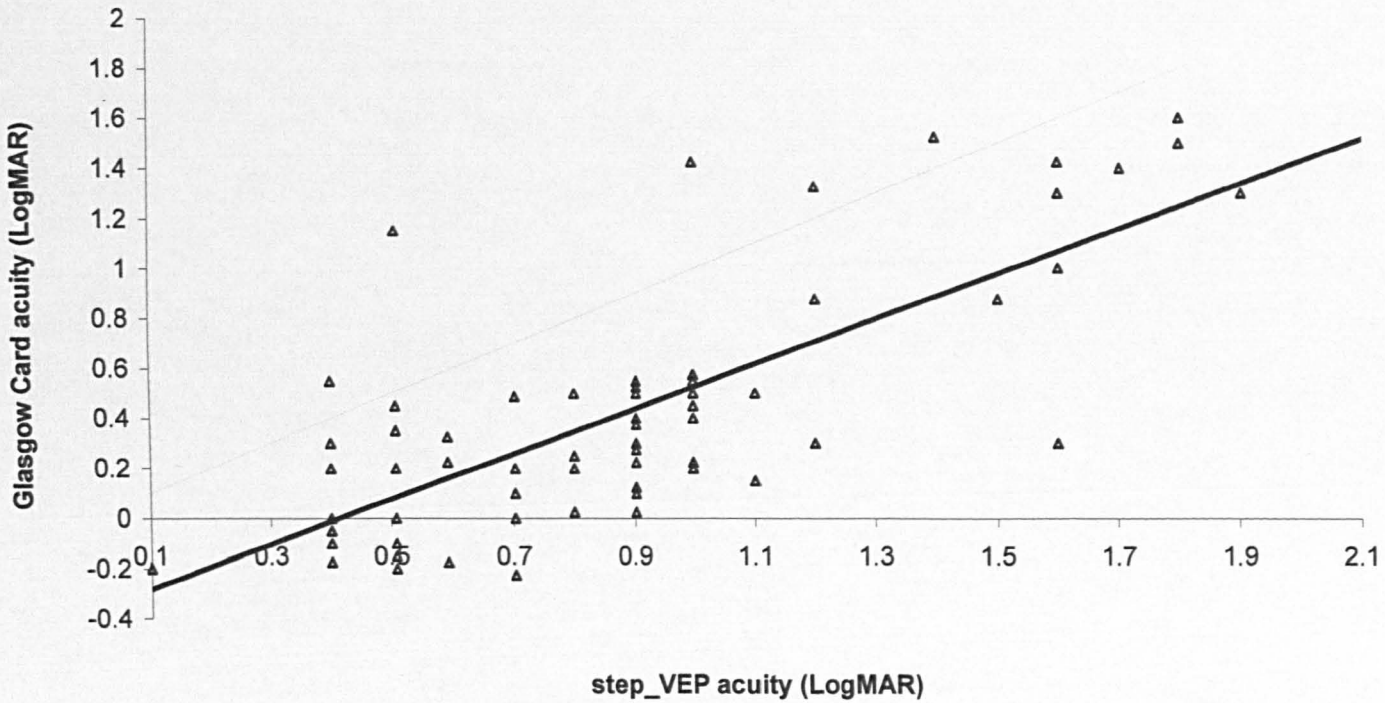


Figure 6.3: The bold line showed linear regression of Glasgow card acuity score against step_VEP acuity score. The grey line indicated the ideal of perfect agreement between the two tests.

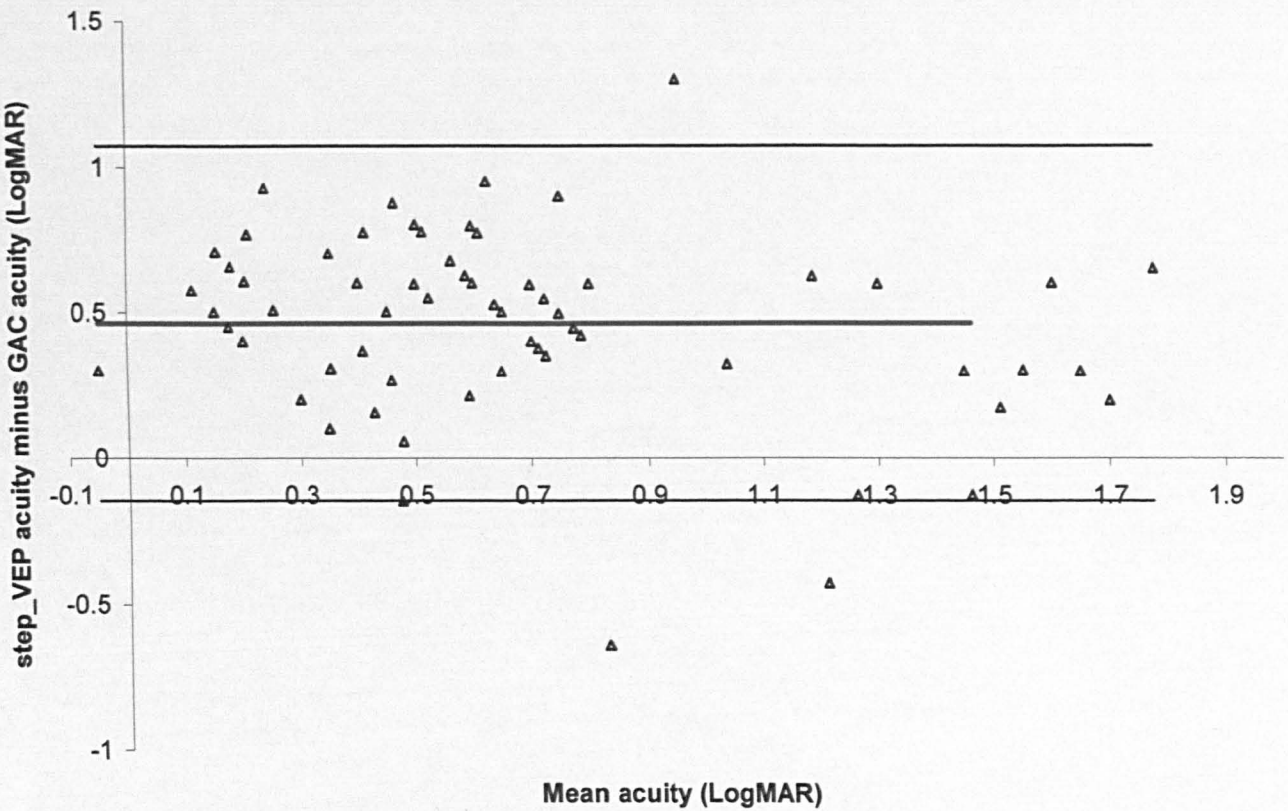


Figure 6.4: Acuity score agreement between assessment techniques. The bold line indicates the mean difference between the tests and the finer lines represent the 95% confidence limits of the difference.

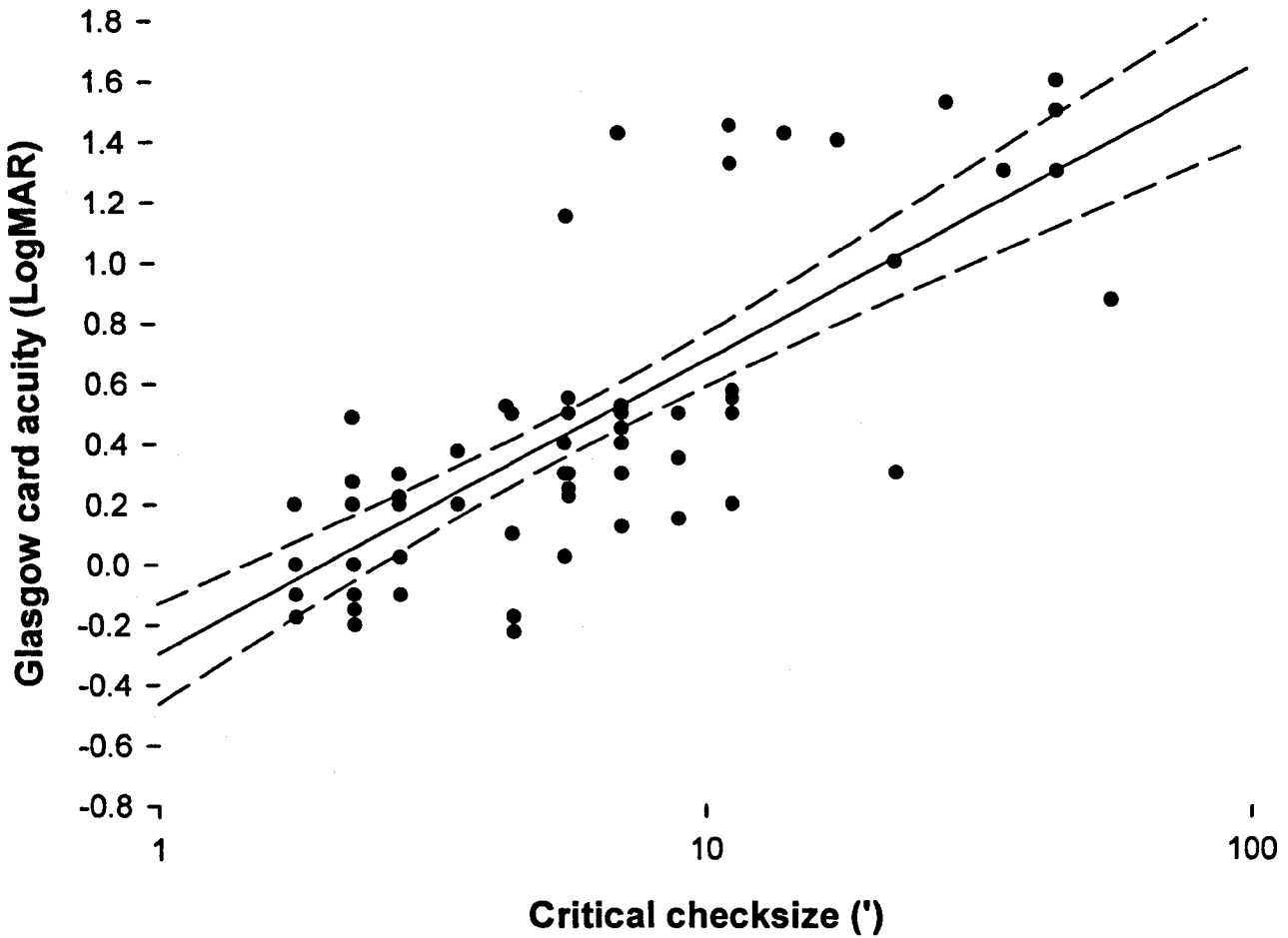


Figure 6.5: The range of subjective acuities corresponding to each step_VEP critical check size. The bold line shows a linear regression between the two. The dotted lines show the 95% confidence intervals of the regression line.

6.2.4 Discussion

Such good agreements in results mean that Glasgow cards and Cardiff cards can be considered interchangeable in this subject group. The excellent agreement between test outcomes for the staircase VEP and step_VEP presentation modes means that these tests can also be considered interchangeable.

A previous clinical comparison of t-VEP acuity score and subjective acuity score gave a mean difference of 0.76±0.85 LogMAR (Mackie 1995). The mean difference between step_VEP and subjective acuity scores in this study is 0.32±0.7 LogMAR. The difference between step_VEP and subjective acuity scores is not affected by the level of acuity of the patients in this study. However, the patient group of Mackie et al. (1995) had a high incidence of neurological impairment, which may affect the agreement of VEP and subjective acuity scores compared to this group. When sweep VEPs and t-VEPs were performed in the same subject, the sweep VEP gave a significantly better acuity score (Panton *et al.* 2003). This implies that a higher stimulus rate for VEPs results in a better acuity score. Subjective acuity scores are systematically better than all VEP scores. Better acuity scores obtained by the faster stimulus rate of step_VEPs than t-VEP scores obviously agree more closely with subjective acuity scores.

The range of subjective acuity scores corresponding to several ssVEP critical check sizes in a previous study (Katsumi *et al.*1994) is given in Appendix B. Comparing figure 6.5 to

Appendix B, subjective acuity scores for the same critical check size were systematically better for the stimulus rate of 12 reversals/second used by Katsumi *et al.* (1994) than they were for the 7.78 reversals/second used in this study.

6.3 Repeatability and reproducibility of step_VEP acuity

6.3.1 Introduction

Repeatability describes the closeness of agreement between acuity score measured by the same technique under the same conditions. Reproducibility describes the agreement between scores of the same assessment performed under different conditions. Repeatability of acuity score was investigated in normal adults to quantify the inherent variability of the step_VEP technique. Reproducibility of acuity score was investigated in normal adults to quantify the effect of electrode application when the step_VEP test was performed during a second session on a different day. Both repeatability and reproducibility were investigated at several levels of artificially degraded vision as it was important to establish the robustness of the test over a wide range of acuity levels.

6.3.2 Methods

Subjects comprised seven neurologically and ophthalmologically normal adults wearing their required optical correction. In addition to normal vision, four different Bangerter filters (Ryser Optic, St. Gallen, Switzerland) were used for each subject to artificially

degrade vision. The subjects viewed the step_VEP stimulus monocularly, and the test was performed 10 times, twice each for five different levels of vision. Six of the subjects returned for repeat testing, when one step_VEP assessment was performed for each of the five levels of vision. Each checkerboard had a mean luminance of $60cdm^{-2}$ and a contrast of 100%. Recordings were made from four channels, O_z-F_z, LO-F_z, RO-F_z and $2O_z$-(RO+LO). The software accepted signal detection from any of these four channels. Bland-Altman analysis was performed to quantify the agreement of acuity scores in each subject at each level of vision.

6.3.3 Results

The average agreement between acuity scores for step_VEPs performed on the same day under the same conditions was 0.15 LogMAR with 95% confidence limits of –0.21-0.51 LogMAR (figure 6.6). The average agreement between step_VEPs performed on different days was 0.26 LogMAR with 95% confidence limits of –0.31-0.82 LogMAR (figure 6.7).

6.3.4 Discussion

The 95% confidence limit of agreement for acuity scores during the same session was 0.7 LogMAR wide, which is the equivalent of seven stimulus size increments. This reflects inter-individual variability in VEP and EEG as well as the inherent variability of the test. The 95% confidence limit of agreement for acuity scores obtained under the same conditions on different days is 1.1 LogMAR, which is the equivalent of 11 stimulus size

increments. The extra variability must be introduced by variability in electrode application, as all other conditions are held constant. This measurement error is part of the inherent variability of the test. In a subjective study of normal children using acuity cards, 95% confidence limits of agreement for repeat testing was 0.36 LogMAR for single letter acuity and 0.125 LogMAR for Glasgow acuity cards (McGraw *et al.* 2000). The group size of Mcgraw *et al.* (2000) was 119, which is much larger then the group of seven tested in this study. Testing a much larger group would have reduced the width of the 95% confidence intervals in this study.

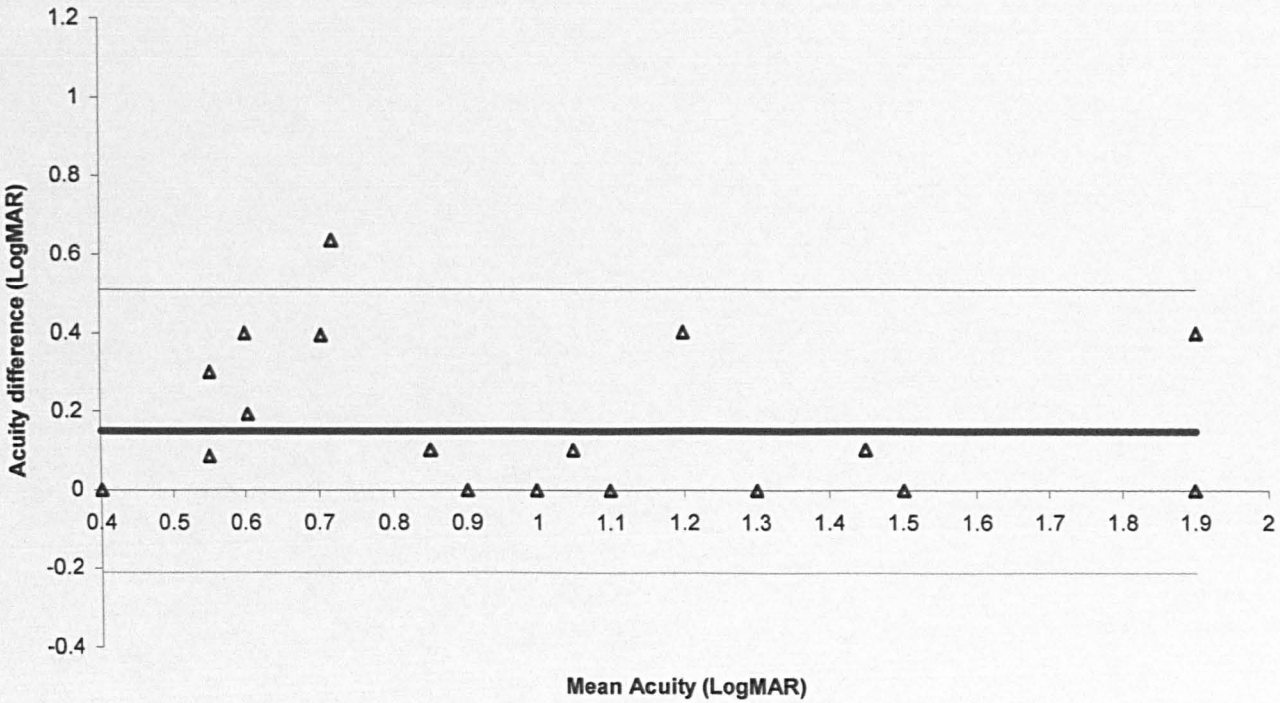


Figure 6.6: Repeatability of step_VEP acuity scores.

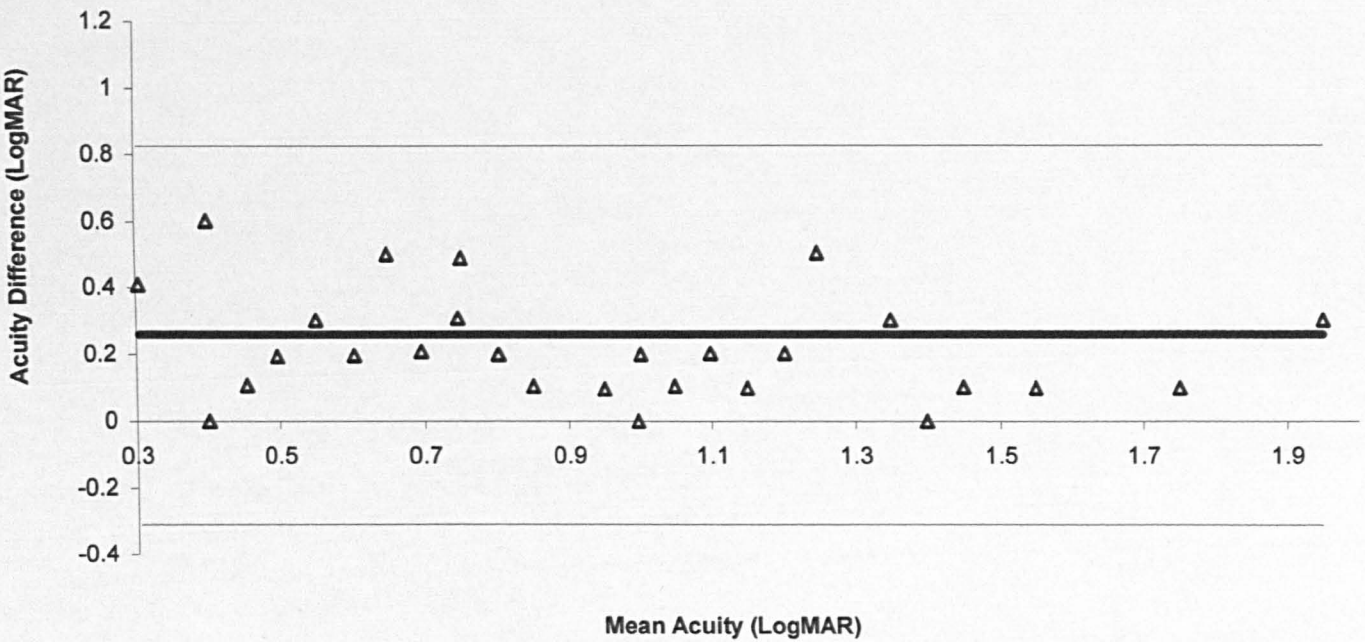


Figure 6.7: Reproducibility of step_VEP acuity scores.

6.4 Effect of spatial-frequency-amplitude notch on acuity outcome

6.4.1 Introduction

Repeatability and reproducibility of acuity score quantify the inherent variablity of the step_VEP technique. The amplitude and SNR of VEP recording varies between individuals which affects the detectability of responses. The 95% confidence limit of agreement between step_VEP acuity score and subjective acuity score (section 6.3) is partly explained by this inter-individual variability. The use of checkerboard stimuli is justified due to larger response amplitudes overall (section 5.2.2). When sinusoidal stimulation is used for ssVEP assessment, the spatial frequency amplitude function is a smooth curve with a peak medium sized stimulus. When checkerboards are presented, the function has the same overall curve but often features a low amplitude notch somewhere between maximum amplitude and acuity threshold where the response amplitude is not distinguishable from noise (Candy 2002. Personal communication; Meigen 2002. Personal communication). This may result in the underestimation of acuity using the successive approximation paradigm of the step_VEP. This relatively complex response tuning curve may be a result of the multiple frequency components of a checkerboard stimulus. There is no difference between extrapolated acuity scores for checkerboard, square wave or sine wave stimuli (section 5.2.2). This suggests that the extrapolation method is not affected by the presence of a notch in the spatial frequency amplitude function. However, the step_VEP uses the smallest checksize technique rather than extrapolation to estimate acuity and it is postulated that a

notch in the spatial frequency amplitude function may affect step_VEP acuity score. The aim of this study is establish if the presence of a notch in an individuals spatial frequency amplitude function affects the agreement between step_VEP and subjective acuity scores.

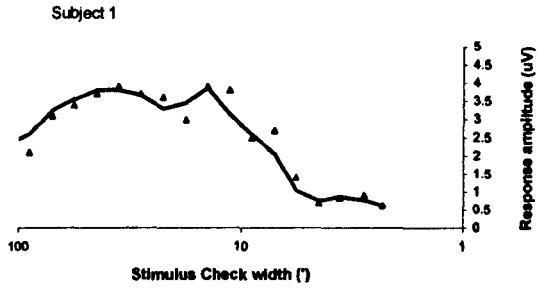
6.4.2 Methods

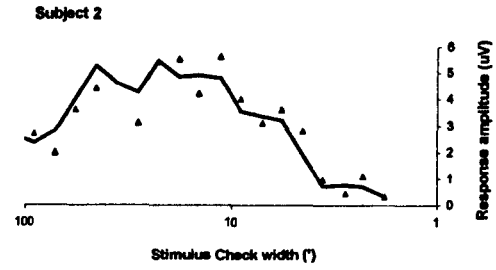
The subjects were 14 neurologically and ophthalmologically normal adults wearing their required optical correction. The staircase VEP was used to measure response amplitude to all 27 stimuli (table 5.3) in each subject. Each checkerboard had a mean luminance of $60cdm^{-2}$ and a contrast of 100%. Recordings were made from four channels, O_z-F_z, LO-F_z, RO-F_z and $2O_z$-(RO+LO). The software accepted signal detection from any of these four channels. Step_VEPs and Glasgow acuity cards were also performed to estimate visual acuity in each subject.

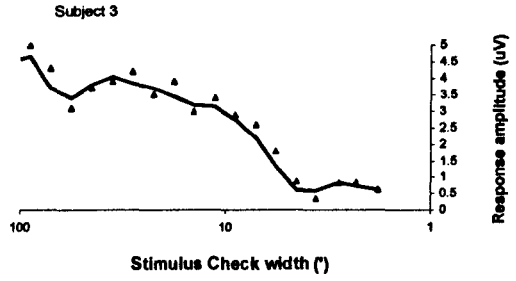
The spatial frequency amplitude functions were plotted and a qualitative analysis determined whether a notch was present between the peak amplitude of the function and spatial resolution threshold. The group was divided into two for further analysis; those whose spatial frequency amplitude functions showed a notch and those that did not. For each group, the median and 95% confidence intervals of the difference between step_VEP acuity score and Glasgow Card acuity score were calculated. This comparison effectively uses Glasgow acuity cards as the gold standard for comparison in this subject group.

6.4.3 Results

The results of qualitative analysis of the spatial frequency amplitude functions (figure 6.8) are given in table 6.2. The agreement between step_VEPs and subjective tests in the resultant groups is described in figure 6.9. Suprisingly, the mean agreement between step_VEPs and subjective testing is slightly better for the subjects whose spatial frequency amplitude functions showed a notch rather than poorer due to the predicted underestimation of acuity. However, no significant difference between the groups can be concluded as the 95% confidence intervals overlap.


Subject 1
Response amplitude (uV)
Stimulus Check width (')
100
10
1


Subject 2
Response amplitude (uV)
Stimulus Check width (')
100
10
1


Subject 3
Response amplitude (uV)
Stimulus Check width (')
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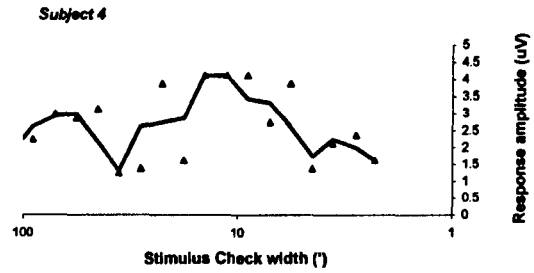
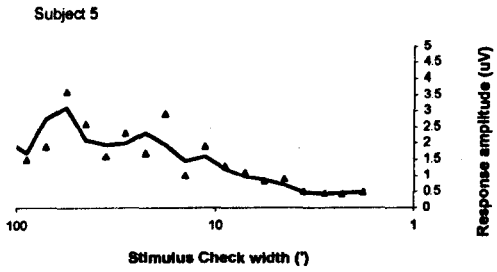
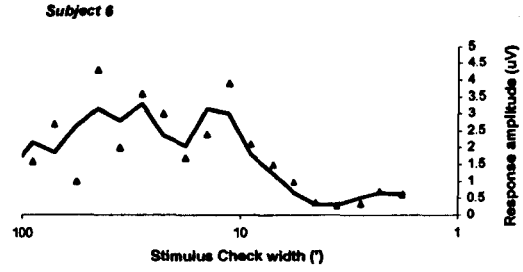
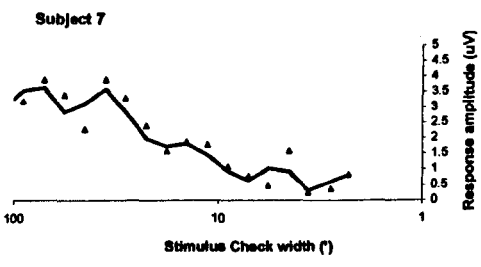
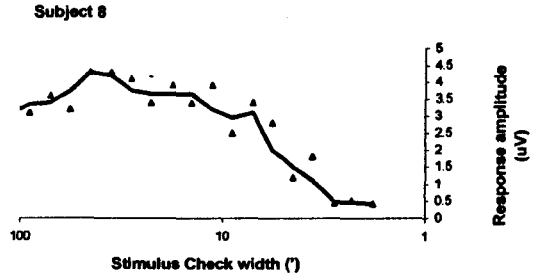
10
1


Subject 4
Response amplitude (uV)
Stimulus Check width (')
100
10
1


Subject 5
Response amplitude (uV)
Stimulus Check width (')
100
10
1


Subject 6
Response amplitude (uV)
Stimulus Check width (')
100
10
1


Subject 7
Response amplitude (uV)
Stimulus Check width (')
100
10
1


Subject 8
Response amplitude (uV)
Stimulus Check width (')
100
10
1

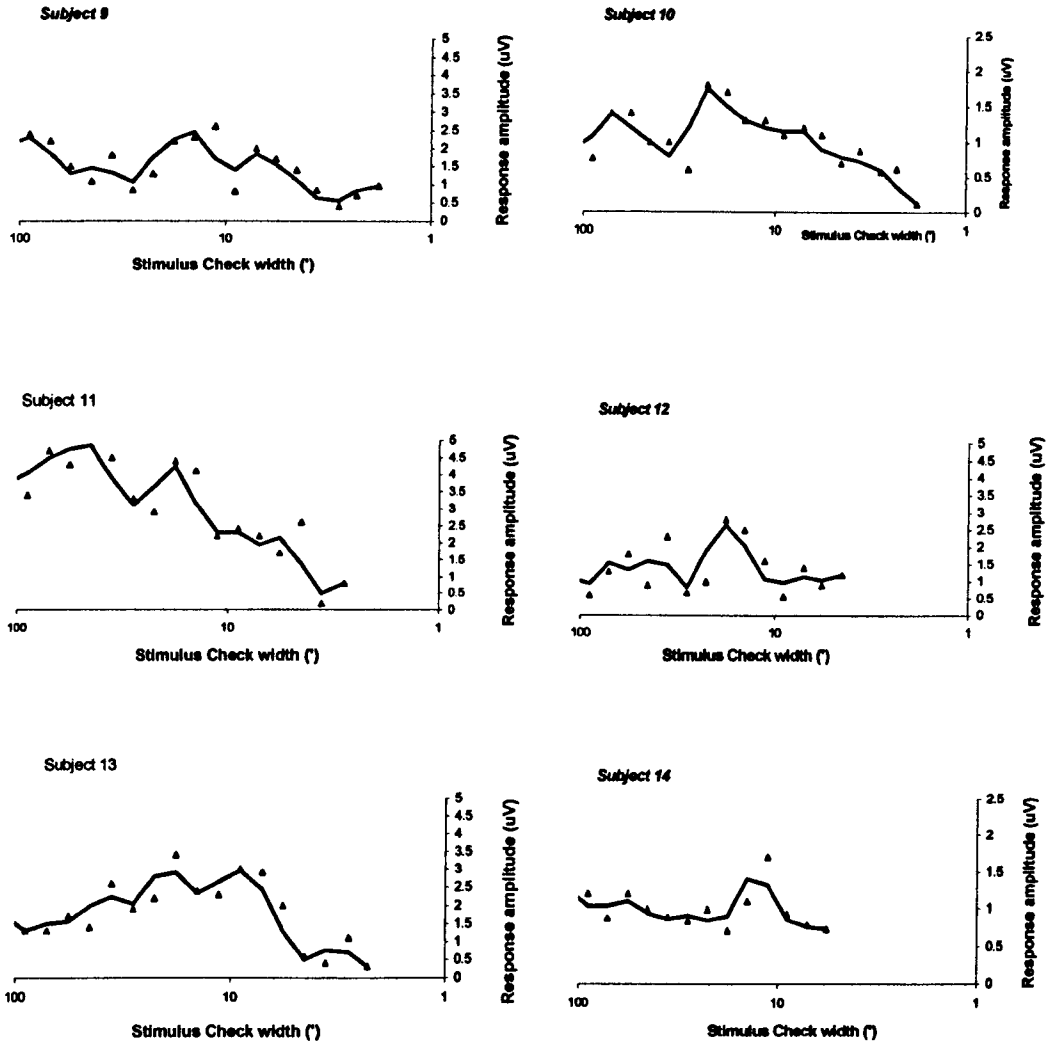


Figure 6.8: Individual spatial frequency amplitude functions of normal adults with good acuity. The trend line provides some smoothing so the overall similarity in shape between individuals can be observed. Those functions defined as containing a clear notch are labelled in bold italics.

Table 6.1: Difference in acuity scores between techniques for spatial frequency-amplitude functions with and without a notch.

Subject	step_VEP acuity-GAC acuity	Notch Present
1	0.3	No
2	0.6	No
3	0.6	No
4	0.7	Yes
5	0.78	No
6	0.38	Yes
7	0.21	No
8	0.3	No
9	0.2	Yes
10	0.1	Yes
11	0.37	No
12	0.45	Yes
13	0.8	No
14	0.77	Yes

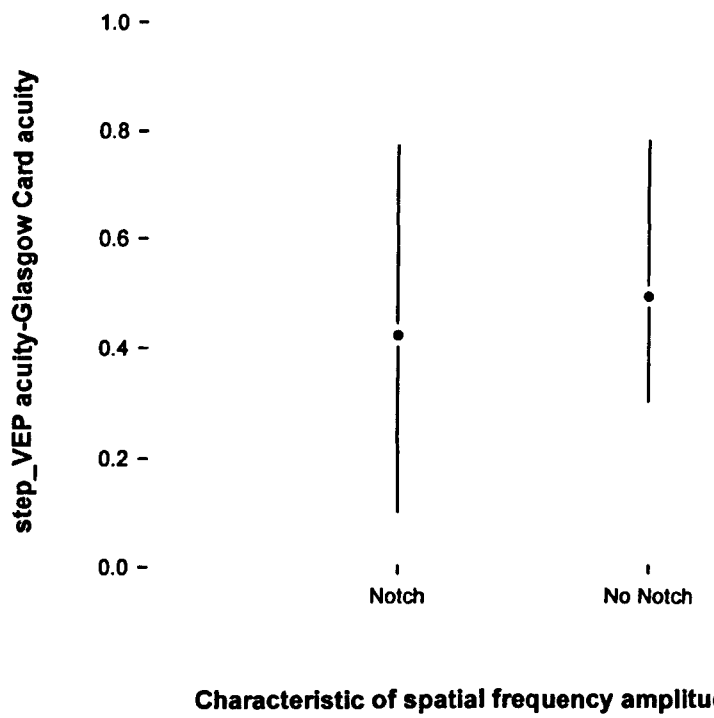


Figure 6.9: The difference in step_VEP and subjective acuity scores in subjects whose spatial frequency-amplitude functions do and do not show a low amplitude notch.

6.4.4 Discussion

The presence of a notch in the spatial frequency amplitude function did not result in a systematic underestimation of acuity in this study. As the spatial frequency-amplitude function of all individuals contain a notch to a greater or lesser degree it was quite difficult to divide the study group into two. A study of selected subjects with strongly defined notches in their spatial frequency function compared to those with a very smooth function may have shown a difference. A pilot study (section 5.4.5) showed similar agreement between ssVEP and subjective acuities for smallest check size and extrapolation techniques. The smallest check size technique was chosen because it required less stimulation periods and therefore provided a quicker assessment, and also because it was easier to compute. This study supports the hypothesis that the technique provides accurate acuity estimations in individual subjects, despite inter-individual differences in the shape of the spatial frequency amplitude function.

6.5 Conclusions

A previous study showed that in the same subject VEP acuity scores are better for a higher stimulus rate (Panton *et al.* 2002). As subjective acuity scores are systematically better than VEP acuity scores, this results in better agreements between subjective and VEP acuity scores as stimulus rate increases. The results of this study compared to the work of Mackie (1995) and Katsumi (1994) support this conclusion.

The inherent variability of step_VEP acuity score is 0.15 LogMAR (95% confidence interval –0.21 to 0.51 LogMAR). Assessments should agree to within 0.26 LogMAR (95% confidence interval –0.31 to 0.82 LogMAR) when performed on the same subject on different days.

Inter-individual differences in the shape of the spatial frequency amplitude function are unlikely to systematically affect the accuracy of the step_VEP acuity score.

Chapter 7 Clinical Evaluation

7.1 Introduction

The step_VEP was developed with the aim of facilitating objective measurement of visual acuity in visually impaired children. The aim of this chapter is to clinically evaluate the step_VEP. Independent groups of children tested with subjective, t-VEP and step_VEP assessments can be used to compare the success rate of each technique in providing a complete acuity assessment. Children in whom acuity was measured successfully by both t-VEP and subjective tests are used to compare their acuity scores. A similar comparison an be made for children in whom step_VEP and subjective assessment were successfully completed.

A subgroup of patients receiving acuity assessment by both subjective and VEP methods attended a multi-disciplinary vision clinic. These children also underwent assessment by a developmental paediatrician, facilitating investigation of the influence of developmental factors on the success of acuity assessment techniques and their outcomes.

7.2 Success rate and test duration of transient VEP acuity estimates: Retrospective audit and prospective study design

7.2.1 Introduction

Transient VEPs (t-VEPs) have been used as the electrophysiological method of estimating visual acuity at the Royal Hospital for Sick Children in Glasgow since 1993. The method is described in more detail in section 1.3.3. It was proposed that the step_VEP would be more successful than t-VEPs in achieving a complete acuity assessment for a number of different reasons. The shorter test duration of the step_VEP should be within the attention span of a greater proportion of children and the successive approximation algorithm used to present stimuli should prevent loss of attention part way through the test by minimising the time spent presenting stimuli that cannot be seen (section 5.4). Quantifying the success rate in completing an acuity assessment using t-VEPs was required to enable the clinicians to indicate what they would consider to be a significant percentage improvement in the success rate after introducing the step_VEP. These figures were required in turn to calculate the size of the prospective study group required to prove a difference in success rate between tests. It can be postulated that a success rate improvement is related to a reduction in test duration. Quantifying the average test duration of the t-VEP assessment would enable the clinician to indicate what they would consider to be a significant reduction.

7.2.2 Methods

An audit identified the children who attended ophthalmology clinics in 1999 and received a t-VEP assessment of acuity. Test results and laboratory notes were used to grade each assessment for success in completion. Stimuli were chosen from a set of black and white checkerboards with check widths of 480', 240', 120', 60', 48', 30', 24', 12', 9' and 6'. Each checkerboard had mean luminance of $60cdm^{-2}$ and a contrast of 100%. All stimuli were viewed at a distance of 45cm and with a field size of 25°. Recordings were made from O_z-F_z with ground at a mastoid. Each stimulus was presented until around 100 averages had been recorded. 120' checks were presented first and if a response was successfully detected then the stimulus was gradually reduced in size. If a response was not detected here then the stimulus size was gradually increased. Assessments that included two recordings with response detection followed by a recording with response absence indicated that the threshold of spatial resolution had been found and the assessment was classified as successful (Grade three). Assessments that included one or more recordings but found no reproducible threshold were classified as incomplete (Grade two). Assessments where no complete recordings were obtained were classified as a failure (Grade one). The success rate across the whole group was calculated using the grade three results only. Based on this success rate, the ophthalmologists were able to state the minimum improvement required to affect the service.

The statistical significance of a comparison describes the likelihood of an observed difference being down to chance. This figure should therefore be as low as possible. The statistical power of a comparison describes the likelihood of observing a significant

difference between two quantities if it is present. This figure should therefore be as high as possible. Significance (α) and power (β) were set to values of 0.05 and 0.8 respectively (Fleiss 1981) to allow a prospective sample size calculation to be performed. The equations required for the calculation are included in appendix C.

The test duration was determined from those t-VEP assessments classified as successful. This was achieved adding the duration of the first recording to the difference in time between saving the first file and the last file of the assessment on the computer hard drive.

7.2.3 Results

A t-VEP assessment was attempted in 49 patients in 1999. The assessment was successful in 37 of these patients. The mean test duration was 10 minutes 17 seconds with a standard deviation of three minutes 34 seconds. Given that 75% (37/49) of patients sent for acuity assessment by t-VEP received a successful assessment, a total study group of 494 patients would be required to show a 10% improvement on a success rate of 75% in a prospective study (Appendix C). For an improvement as large as 15% to be proved, the total group size could be reduced to 194. A reduction of about one third of the average test duration of 10 minutes 17 seconds was set as a target by the electrophysiologists. This was a qualitative decision based on previous experience.

7.2.4 Discussion

Comparison of the acuity outcome of VEP and subjective tests performed on the same day can only be appropriate when the testers are sure that each assessment has successfully been completed. For example if the VEP assessment is abandoned half-way through due to the child being tired and inattentive, then the outcome is likely to be poorer than a subjective assessment successfully performed half an hour earlier in the same subject. Sub-division of the prospective study group based on the success of VEP and subjective acuity assessments performed on the same day would identify subjects for use in the comparison of test success, test duration and test outcome.

The total sample size calculated for the success rate comparison can be used only as a guide. The actual power and significance of the comparison is also be dependent on the differences in success rate and test duration observed during the prospective study.

7.3 Comparison of the success rates of acuity assessments

7.3.1 Introduction

Children with cerebral visual impairment, infants and very young children present a challenge when trying to estimate visual acuity. Recording whether an acuity assessment is successful or not is important for two reasons. Firstly, it allows the suitability of different techniques to be compared in specific subject groups. Secondly, it allows the clinician to interpret the result of the test appropriately. For example if a VEP assessment is only partially successful, then the test result is likely to underestimate the acuity of the patient. The purpose of this section is to investigate the success rates of different acuity assessment techniques in all patients referred for electrophysiological assessment of visual acuity.

7.3.2 Methods

t-VEPs

Recordings were made using the method described in section 2.2.2. Assessments that included two recordings with response detection followed by a recording with response absence indicated that threshold had been identified and the assessment was classified as successful (Grade three). Assessments that included one or more recordings but no threshold recordings were classified as incomplete (Grade two). Assessments where no complete recordings were obtained were classified as a failure (Grade one).

Step_VEPs

The stimulus sizes in table 5.3 were presented using the algorithm described in section 5.4.4. Viewing distance varied from 45cm to 180cm depending on the stimulus, which is described fully in section 5.4.3. Each checkerboard had a mean luminance of 60cdm^{-2} and a contrast of 100%. Recordings were made from four channels, O_z-F_z, LO-F_z, RO-F_z and $2O_z$-(RO+LO). The software accepted signal detection from any of these four channels. If acuity threshold was found during testing then the software indicated this and the assessment was classified as successful (Grade three). Assessments that included one or more recordings but no threshold were classified as incomplete (Grade two). Assessments where no complete recordings were obtained were classified as a failure (Grade one).

Subjective tests

If the child was cooperative and the tester was satisfied that a threshold had been found (the criterion for threshold depended on the test itself) then assessment was classified as successful (Grade three). If a child completed part of the test but no threshold was established then it was classified as incomplete (Grade two). If the child did not complete any part of the test then it was classified as a failure (Grade one). The breakdown of subjective techniques used is listed in table 7.1. A description of each test and its protocol is given in section 1.3.2.

Only grade three results were counted as successful for these three types of acuity assessment. The questionnaire shown in figure 7.1 was completed for 218 patients who underwent acuity assessment by VEP. The t-VEPs were attempted on approximately half

the group (N=107) and the step_VEP were attempted on the other half (N=111), figure 7.2. The majority of patients (183/218) also underwent subjective acuity assessment on the same day.

The results of the 183 subjective tests were included in a single group to establish the success rate of subjective acuity tests in the clinical group as a whole. A z-test for combined proportions was used to describe the difference in the proportion of successful acuity assessments using each technique. The z-test for combined independent proportions (Bland 2000) uses a confidence interval around the median difference in test success rate to quantify significance. This has a higher power than a comparison of the proportions of two independent groups as it uses the total group size to calculate it's confidence interval.

98 of the 107 patients undergoing t-VEP assessment also underwent subjective acuity assessment on the same day. A McNemar test allowed us to describe whether success in one assessment was linked to success in the other, or whether failure in one test was linked to failure in the other. The same comparison was applied to the 85 patients who underwent subjective acuity assessment on the same day as the step_VEP.

Table 7.1: Subjective visual acuity assessment in t-VEP and step_VEP groups.

Subjective Test	% of patients tested with each technique	
	t-VEPs group	step_VEP group
Cardiff Cards	41	48
Keeler Cards	28	28
Snellen	22	21
Glasgow	5	0
Sheridan-Gardiner	2	3
OKN	2	0

ROYAL HOSPITAL FOR SICK CHILDREN
YORKHILL NHS TRUST

OPHTHALMOLOGY

Visual Electrophysiology Service

Date of Test:

Referring Consultant:

Electrophysiology: Desirable ☐ Essential ☐

Visual Acuity Threshold: Desirable ☐ Essential ☐

Visual Acuity threshold not attempted due to time limits of clinic ☐

Acuity Estimate by VEP	Done	Success 1	2	3	Acuity Estimate	Recording time
T-VEP	☐	☐	☐	☐		
Step_VEP	☐	☐	☐	☐		
Pattern Onset VEP	☐	☐	☐	☐		

Classification of Success: 1=No Data, 2=Some Data, 3=Data leading to an Acuity estimate

Other Visual Acuity Estimates	Done	Success 1	2	3	Acuity Estimate
Keeler	☐	☐	☐	☐	
Cardiff	☐	☐	☐	☐	
Glasgow	☐	☐	☐	☐	
Snellen	☐	☐	☐	☐	
Optokinetic Nystagmus	☐	☐	☐	☐	
Kay Pictures	☐	☐	☐	☐	
Other (Specify)	☐	☐	☐	☐	

Figure 7.1: The questionnaire designed to collect acuity test outcomes.

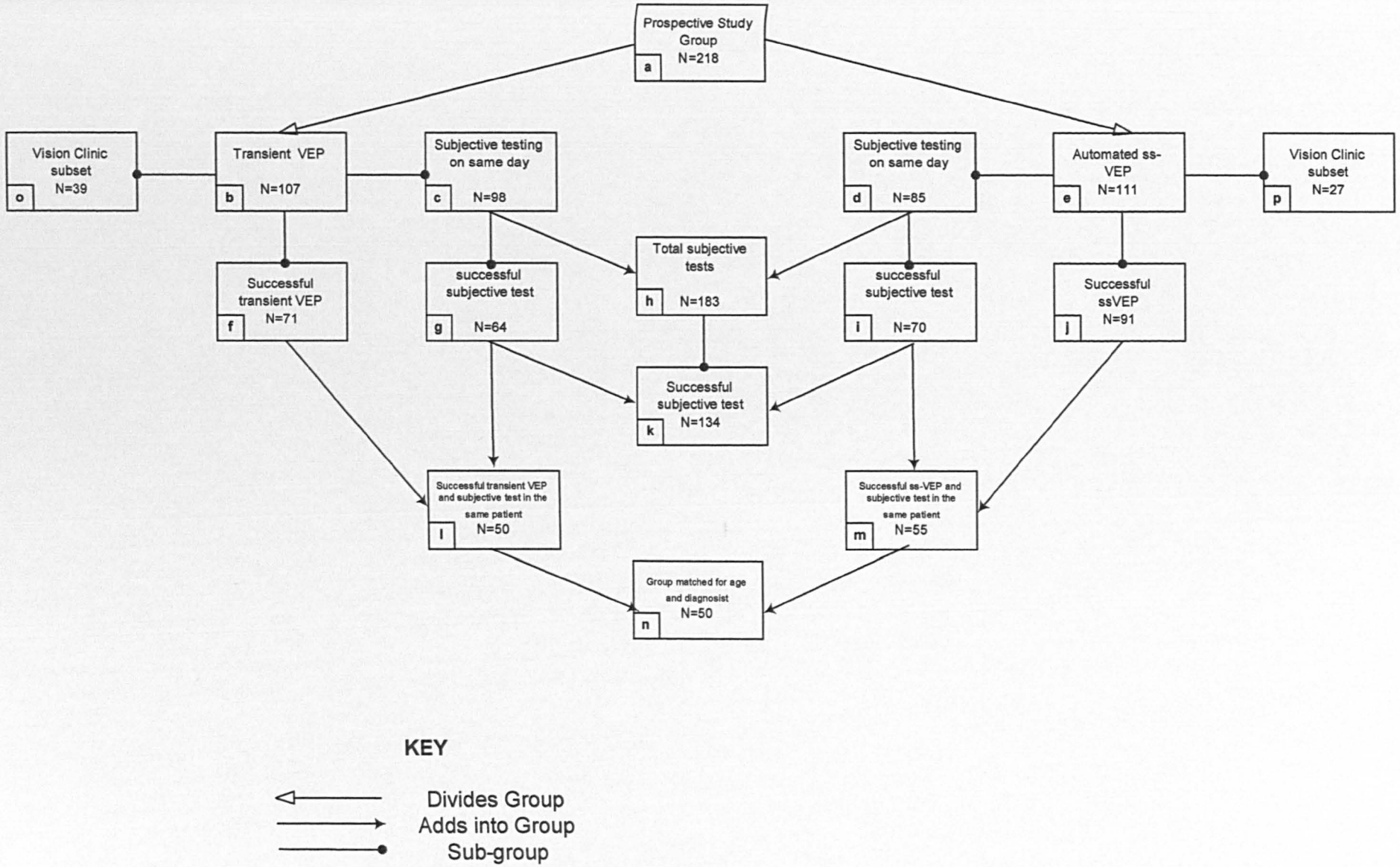


Figure 7.2 Breakdown of patient group for the various comparisons made in chapter 7.

7.3.3 Results

The success rate for t-VEP assessment was 9% poorer than subjective acuity assessments (figure 7.3). Although the results of a z-test for combined proportions did not indicate statistical significance (p=0.17) the 95% confidence interval shows that a difference is fairly likely (figure 7.4).

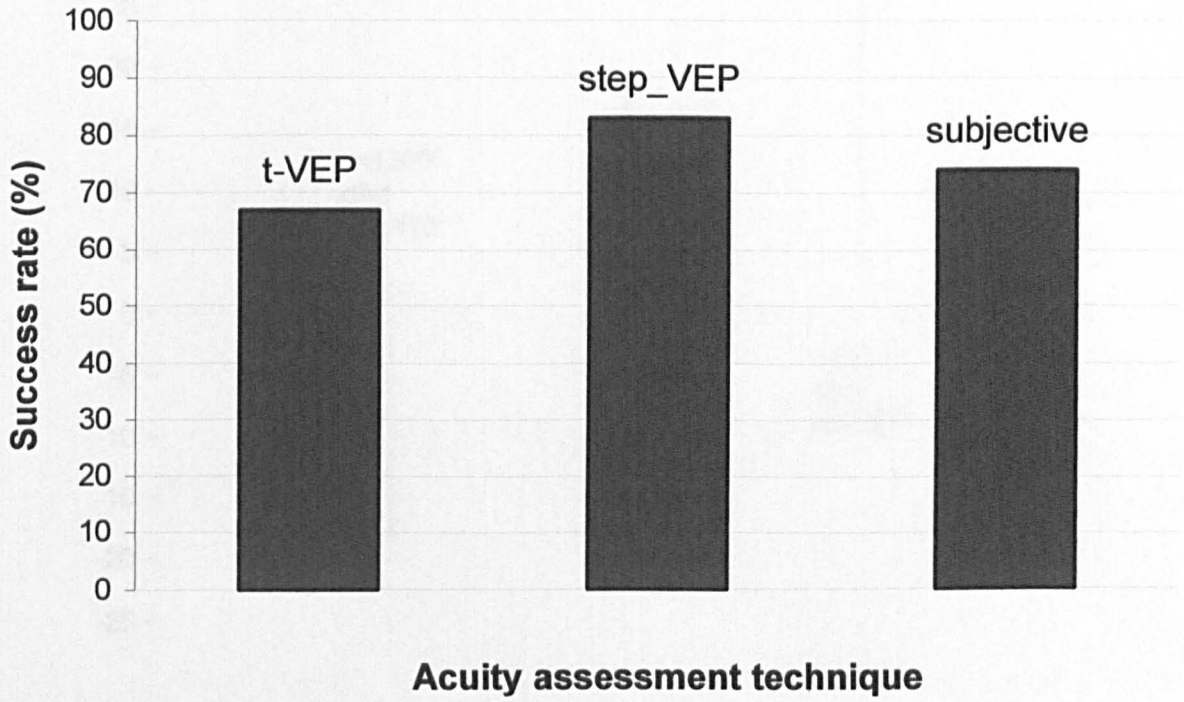


Figure 7.3: The success rate of three different acuity assessments techniques.

The step_VEPs were 9% more successful than subjective tests and 16% more successful than t-VEPs in completing an acuity assessment.

The 95% confidence intervals and the results of a z-test indicated these differences had a high statistical significance (p=0.000 and p=0.007).

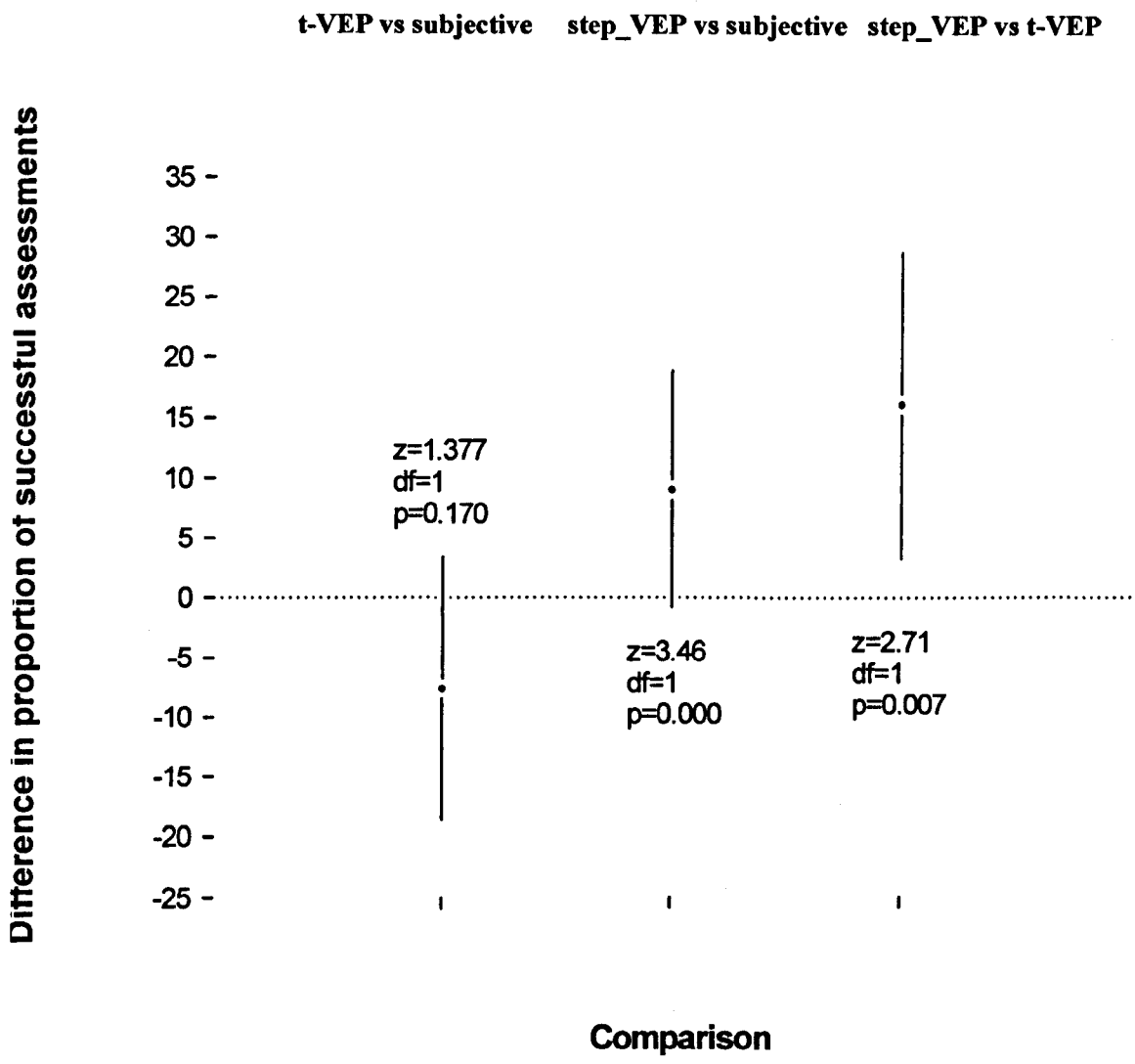


Figure 7.4: 95% confidence intervals of the difference in technique success rate.

Figure 7.5 shows the number of cases in the group where both were tested on the same day. A Mcnemar test showed no significant difference in test success for comparison of subjective assessments with t-VEPs or the step-VEP.

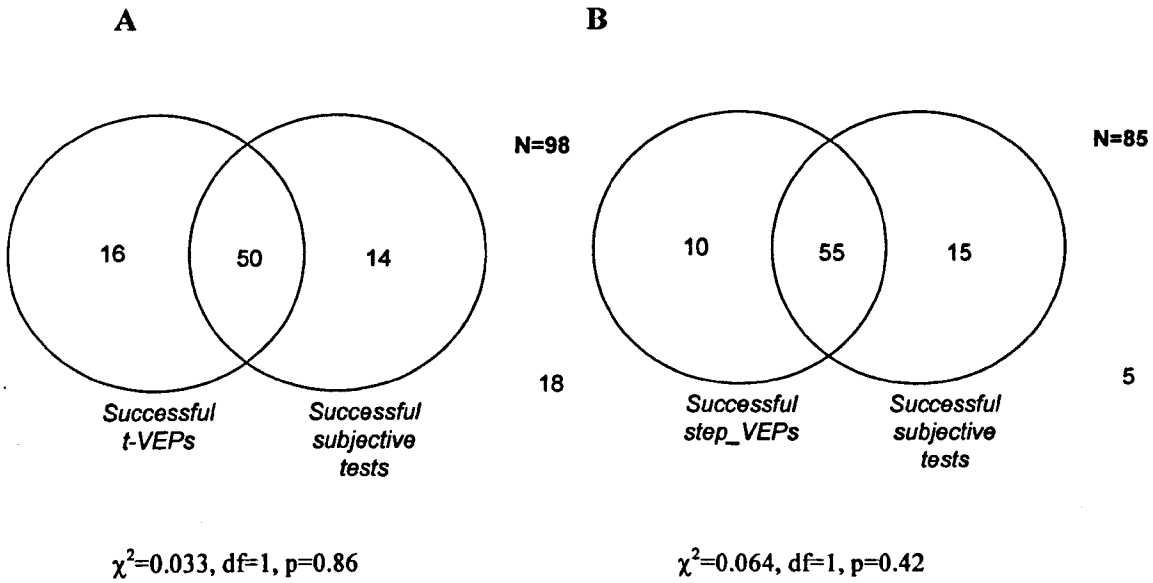


Figure 7.5: The success of VEP and subjective acuity assessments and how they overlapped for each VEP test modality. McNemar test statistics are also included.

7.3.4 Discussion

This study showed success rates of 67% and 74 % for t-VEP and subjective acuity testing respectively. A previous study of t-VEPs as an acuity test found 88% of assessments were successful (Mackie 1995). However, its inclusion criteria and definition of success were different. 18 of the 137 patients tested in their study had a response to flash stimulation only, which would have excluded them from the current study. 10 partially successful assessments, where no reproducible threshold was found, were also deemed successful in their study. When the success rate of Mackie (1995) is corrected for these differences, it is reduced to 78% which is similar to the 75% success rate found in the retrospective audit (section 7.2) although still higher than the 67% success rate found in this prospective study. Mackie (1995) reported a success rate of 86% (101/118) for randomly chosen acuity card tests. The successful group included 23 assessments where patients cooperated with testing but no reproducible threshold could be found, these assessments would have been graded as partially successful in the current study. When the success rate of Mackie (1995) is corrected for this difference, it is reduced to 66% which is fairly close to the 75% success rate for subjective testing in the current study.

Sokol (1983) reported a t-VEP success rate of 77% in the first year of life. This was maintained over the next five years. However, he reported a 25% success rate for preferential looking assessment in the first year of life, which gradually rose to over 80% by six years. This t-VEP success rate is comparable to the study of Mackie (1995) and the current study. However his subjective success rate is much better than these studies once

age ceases to be a limiting factor. The current study group, and that of Mackie (1995) included a large number of patients with profound neurological impairment. The group tested by Sokol (1983) included normal subjects and patients with various ocular pathologies who probably had a greater ability to co-operate with subjective testing once they understood the protocol. These studies show that subjective techniques are more likely to be affected by age and neurological impairment than t-VEP assessment.

Bane and Birch (1992) assessed a patient group aged from four months to nine years, who had mild to severe visual impairment. As the aetiology in many of these subjects was cortical, the group was comparable to the one investigated in the current study. t-VEPs were recorded to a series of five checkerboard stimuli and analysis on up to 100 responses per stimuli was performed off-line. A success rate of 64% compares well with our t-VEP success rate of 67%. Preferential looking tests were also performed, and their 98% success rate was much better than the 74% recorded here for all subjective tests combined. As the ability of the patient group is similar, this must be a result of a pre-test training or an older more cooperative group.

Success rates of 100% and 80% have been reported for sweep VEP acuity assessment of normal children (Costa *et al.* 2002) and children with Downs syndrome respectively (John 2002). A sweep VEP study of children with cerebral palsy (CP) also claimed to have a 100% success rate (Costa *et al.* 2002). The empirically derived SNR criterion of three used by the sweep VEP in these studies is likely to provide poorer specificity than the step_VEP (section 2.4.5) which demands an SNR of 5.1 or more. This would result in more erroneous

response detections being made by the sweep VEP and therefore a higher rate of test completion assumed. Also, it is possible to extrapolate acuity from an incomplete sweep VEP assessment. Many tests that would have been considered unsuccessful in the current study may have been classified as successful in these two sweep VEP studies. Without a comparison of sweep VEP acuity outcome with a gold standard clinical acuity assessment, it is impossible to verify the reliability of the acuity thresholds it estimates. The 83% success rate of step_VEPs on the mixed patient group investigated in this study is better than the success of sweep VEPs in a Downs syndrome group but poorer than normal and CP groups. A comparison of acuity outcome will be possible for the 55 patients (figure 7.2) who successfully completed both step_VEP and subjective acuity assessments on the same day.

7.4 Comparison of t-VEP and step-VEP acuity test duration

7.4.1 Introduction

It is postulated that an improvement in success rate after introduction of the step_VEP assessment is partly due to the test being quicker on average than the t-VEP test. This results in a greater proportion of tests performed being within the attention span of a child. Considering only those patients in whom VEP acuity assessment was successfully completed allows us to quantify the difference in test duration between t-VEP and step_VEP assessments. Using an age matched and diagnosis matched group ensures that each test is performed in the same patient population.

7.4.2 Methods

A prototype version of the step_VEP assessment used checkerboard reversal stimuli ranging from 480' down to 6' in octave increments. This matched the stimulus sizes used in the t-VEP assessment. Step_VEP acuity assessment with this prototype was successful completed in ten subjects. An observer who was masked to the duration of assessments matched these 10 subjects in terms of age and subjective acuity to 10 subjects on whom t-VEPs were successfully completed. The details of the t-VEP and step_VEP groups are given in tables 7.2 and 7.3 respectively. A Mann-Whitney U test for unpaired groups was performed to investigate the differences in prospectively logged test duration between t-VEPs and step_VEPs

Table 7.2: Patient details of the t-VEP group

Patient	Age	VEP Threshold	Subjective Acuity
1	0.3	30'	Not Possible
2	0.3	24'	6/24
3	4.4	6'	6/6
4	4.8	6'	6/9
5	5.6	240'	6/12
6	6.0	24'	5/5
7	6.5	240'	2/18
8	8.8	6'	6/6
9	11.6	6'	6/12
10	7.0	45'	5/9

Table 7.3: Patient details of the step_VEP group

Patient	Age	VEP Threshold	Subjective Acuity
1	0.2	9'	Not Possible
2	0.3	6'	6/96
3	2.2	180'	Not Possible
4	4.4	45'	5/36
5	4.5	6'	6/6
6	6.4	6'	6/4
7	9.4	6'	6/24
8	12.0	6'	Not Possible
9	12.2	30'	5/12
10	13	6'	Not Possible

7.4.3 Results

The median test duration for groups assessed by t-VEPs and the step_VEP respectively were seven minutes 34s and two minutes 29 seconds. The 95% confidence intervals of test duration for each technique (figure 7.6) were distinct which confirmed a difference between

the two groups. A Mann-Whitney U test showed that this difference was significant (Mann Whitney U=11 p=0.003).

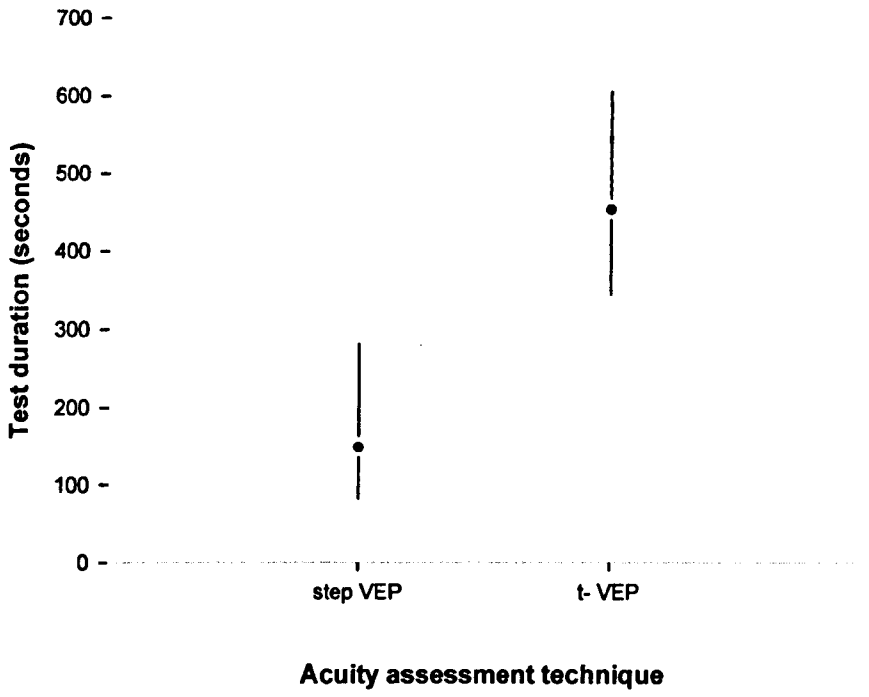


Figure 7.6: 95% Confidence Intervals of test duration for VEP acuity assessments.

7.4.4 Discussion

The considerable reduction in test duration seen after the introduction of the step_VEP in this study is part of the explanation why it was significantly more successful than the t-VEPs test in achieving a complete acuity assessment (section 7.3.3). The sweep VEP acuity assessment typically lasts for one minute (Panton *et al.* 2002) and the high success rates reported are likely to be a result of the rapid test procedure.

The average duration of t-VEP assessment was seven minutes 34 seconds in this study and 15 minutes in the study of Panton (2002). Although other t-VEP studies (Bane & Birch 2002; Sokol 1983; Mackie *et al.* 1995) have not reported test duration, similar presentation protocols imply that their typical duration lay within this range. Only the study of Sokol (1983) had a notably higher success rate than the current study, which was explained by a more able patient group (section 7.3.4).

The real-time analysis of the step_VEP assessment enabled rapid detection of any response that was present. This saved time collecting more data than necessary for any one stimulus. It is also proposed that rapidly identifying when a response is absent is as important as rapidly identifying when a response is present in order to maintain a child's attention. The maximum length of presentation of each stimulus in the step_VEP protocol takes this into account (section 5.4.2). Further work is necessary to identify how much of the success rate improvement of the step_VEP is explained by a shorter test procedure, and how much is explained by a stimulus presentation algorithm that maintains attention.

7.5 Comparison of VEP acuity and subjective acuity

7.5.1 Introduction

VEPs and subjective testing were compared in terms of their success rate in section 7.3. The purpose of this section was to compare the acuity estimates obtained from the two VEP measurement techniques with those measured subjectively. The t-VEP and step_VEP assessments were analysed separately as it was hypothesised that different neurological pathways would be preferentially stimulated due to the differences in stimulus reversal rate. A range of subjective tests was used according to each patient's ability. For the purposes of this study the subjective methods were assumed to give equivalent acuity estimates as justified in section 6.2 and the literature (Mackie 1995a; Mackie *et al.* 1996; Kushner *et al.* 1995).

7.5.2 Methods

The patient group was split into those undergoing t-VEPs and those undergoing the step_VEP. Each child was also assessed subjectively, the breakdown of subjective techniques in each patient group is given in table 7.1. t-VEPs were stimulated, recorded and analysed using the method of section 7.2.2. Step_VEPs were stimulated, recorded and analysed as described in section 7.3.2. For each technique, only assessments graded three for success (section 7.3.2) were considered for acuity comparison with subjective testing.

Group one comprised 50 children who successfully completed both t-VEP and subjective acuity assessment on the same day. Group two comprised 55 children who successfully

completed both step_VEPs and subjective acuity assessment on the same day. The following analyses were performed for each group.

The smallest check size observed in VEP assessment provided the acuity used in the comparison; this is referred to as the critical checksize (Katsumi *et al.* 1994). All scores were converted to LogMAR for ease of comparison (Appendix A). The range of subjectively established acuities for each critical check size were presented to allow VEP test results to be expressed in terms of their subjective equivalent.

Linear regression established if any correlation was present between two acuities measured in the same subject. Bland-Altman analysis investigated the agreement between VEP acuity score and subjective acuity score by plotting the difference in each patient's score against the mean in their scores (Bland & Altman 1986). Section 6.2 compared step_VEP acuity and subjective acuity in normal adults with various levels of artificially degraded vision. The 95% limits of agreement of the adult study are compared with the 95% limits of agreement established in this study.

7.5.3 Results

Figure 7.7 shows subjective acuity score plotted against t-VEP acuity score. The dotted line indicates the ideal of a perfect agreement between the two measurements. The bold line is a linear regression line through the data. It has a slope of 0.63 and its correlation coefficient, r^2, is 0.39 (p=0.000). Figure 7.8 presents the same data in Bland-Altman format. It shows

the mean difference in acuity measurement between the techniques is 1.04 LogMAR with 95% confidence limits (roughly equal to twice the standard deviation) of 0.02-2.10 LogMAR. A regression line fitted through the data had a slope that was indifferent from zero (r^2=0.081, p=0.06) indicating that the agreement between the techniques was consistent across the range of acuities. Table 7.4 shows the range of subjective acuitie scores corresponding to each critical check size.

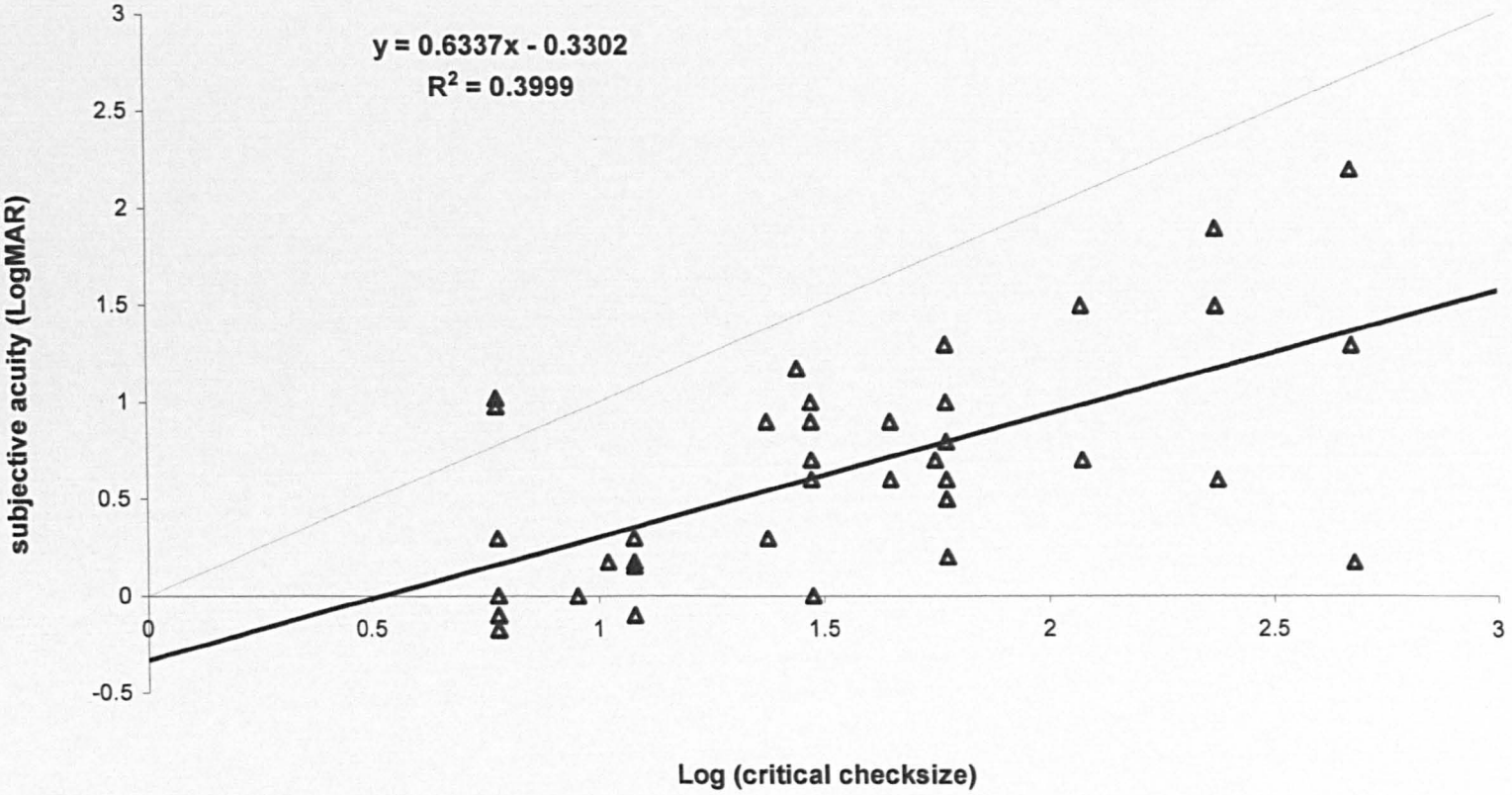


Figure 7.7: A scatter plot of subjective against t-VEP acuity.

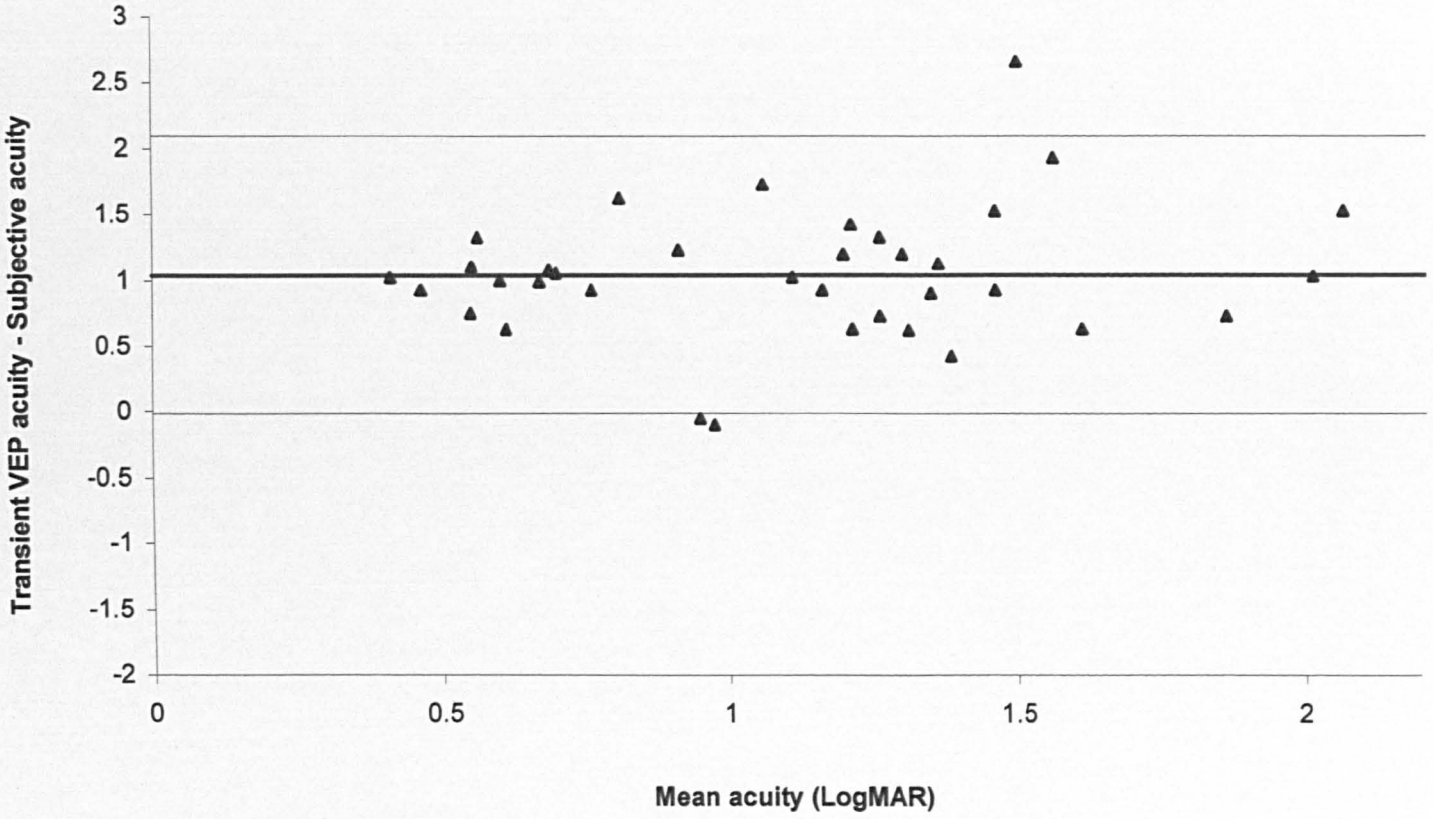


Figure 7.8: The mean and 95% confidence intervals of the difference between t-VEP and subjective acuity scores plotted against their mean.

Table: 7.4 The range of subjective acuity corresponding to each t-VEP critical check size.

	Subjective acuity (LogMAR)			Subjective acuity (Snellen equivalent)		
Critical Check Size (minutes of arc)	**median**	**minimum**	**maximum**	**median**	**minimum**	**maximum**
6	0.038	-0.10	1.025	6/6.5	6/5	6/60
9	0.100	0.00	0.175	6/7.5	6/6	6/9
12	0.163	-0.10	0.300	6/8.7	6/5	6/12
24	0.600	0.30	0.900	6/24	6/12	6/48
30	0.650	0.00	1.175	6/27	6/6	6/90
45	0.750	0.60	0.900	6/34	6/24	6/48
60	0.700	0.20	1.300	6/30	6/9.5	6/120
120	1.100	0.70	1.500	6/75	6/30	6/190
240	1.500	0.60	1.900	6/190	6/24	6/480
480	1.300	0.175	2.200	6/120	6/9	6/950

Figure 7.9 shows subjective acuity plotted against step_VEP acuity. The dotted line indicates the ideal of a perfect agreement between the two measurements. The linear regression is drawn in bold and has a slope 0.51. Figure 7.10 presents the same data in Bland-Altman format. It showed a mean difference of 0.41 LogMAR, with a 95% confidence limit of –0.09 –0.92 LogMAR. A regression line fitted through the data showed a slope that was indifferent from zero (r^2=0.0043, p=0.00) indicating that the agreement between techniques is consistent across a range of acuities.

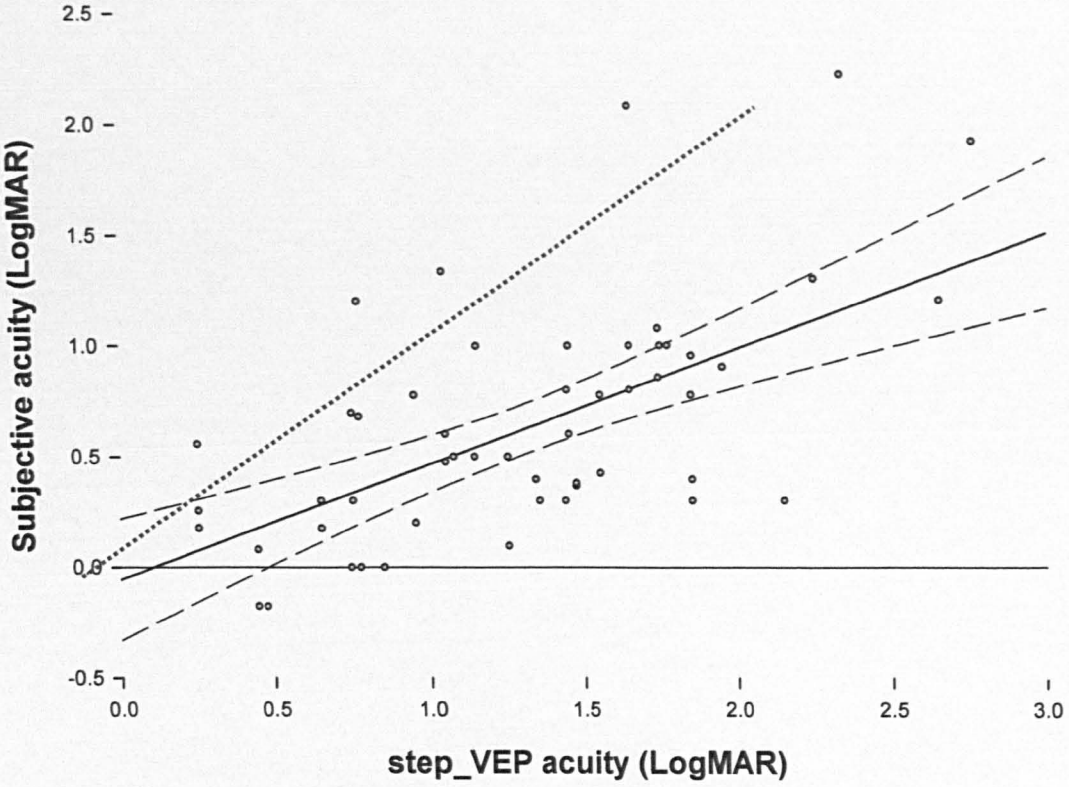


Figure 7.9: A scatter plot of subjective against step_VEP acuity. The dashed lines are the 95% confidence interval of the linear regression (solid) line. The dotted line indicates the ideal of perfect agreement between the two tests.

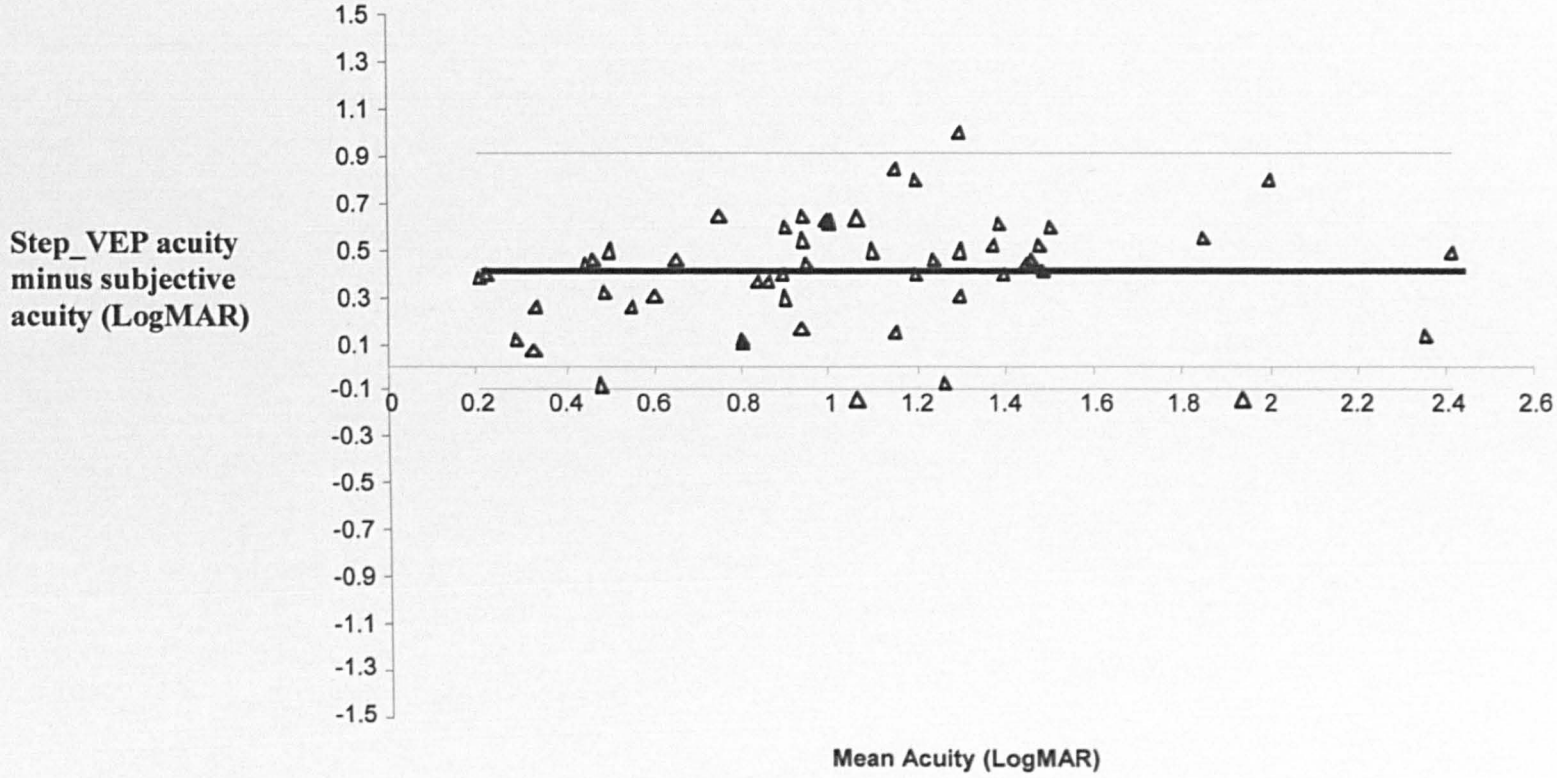


Figure 7.10: The difference between step-VEP and subjective acuity test outcomes plotted against mean acuity

Table 7.5 shows the range of subjective acuity scores corresponding to each step_VEP critical check size. Figure 7.11 compares the 95% limits of agreement between acuity scores for comparison of the t-VEP and subjective tests, step_VEP and subjective tests in the clinical group and step_VEP and subjective tests in the adult group. More details on the adult study can be found in section 6.3.

Table 7.5: The range of subjective acuities corresponding to step_VEP critical check size.

	Subjective acuity (LogMAR)			Subjective acuity (Snellen equivalent)		
Critical Check Size (minutes of arc)	median	minimum	maximum	median	minimum	maximum
1.8	0.26	0.18	0.56	6/11	6/9	6/22
2.8	-0.18	-0.18	0.08	6/4	6/4	6/7
4.5	0.24	0.18	0.30	6/10	6/9	6/12
5.6	0.3	0.00	1.20	6/12	6/6	6/95
7.1	0.0	0.00	0.00	6/6	6/6	6/6
9.0	0.49	0.20	0.78	6/19	6/9.5	6/36
11.2	0.55	0.48	1.34	6/21	6/18	6/130
14.0	0.75	0.50	1.00	6/34	6/20	6/60
17.9	0.30	0.10	0.50	6/12	6/7.5	6/20
22.0	0.35	0.30	0.40	6/13	6/12	6/15
28.0	0.49	0.30	0.80	6/19	6/12	6/38
45.0	2.08	2.08	2.08	6/720	6/720	6/720
56.0	1.0	0.86	1.08	6/60	6/43	6/72
71.0	0.59	0.30	0.95	6/23	6/12	6/53
90.0	0.90	0.90	0.90	6/48	6/48	6/48
142.5	0.30	0.30	0.30	6/12	6/12	6/12
179.0	1.30	1.30	1.30	6/120	6/120	6/120
220.0	2.22	2.22	2.22	6/1000	6/1000	6/1000
450.0	1.20	1.20	1.20	6/95	6/95	6/95
579.0	1.92	1.92	1.92	6/500	6/500	6/500

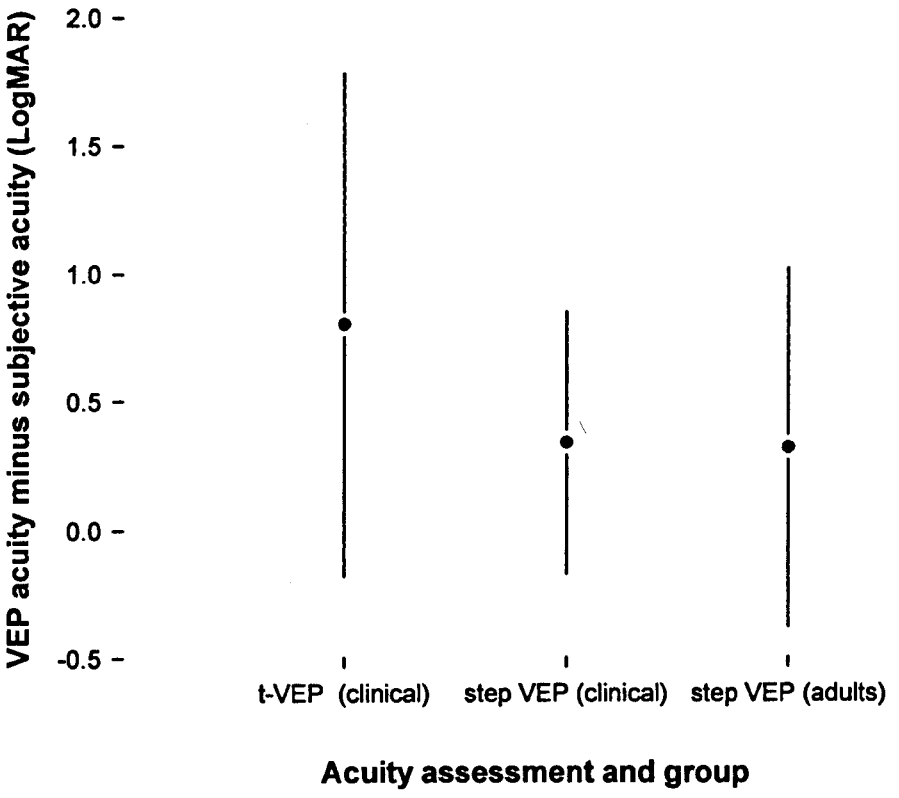


Figure 7.11: 95% confidence limits of agreement between acuity tests.

7.5.4 Discussion

Regression analysis showed a similar degree of correlation between t-VEP and subjective acuity and the step_VEP and subjective acuity. The coefficient of correlation for t-VEP and subjective acuity was higher than a previous study (Mackie 1995; Mackie *et al.* 1995). The overall ability of the patient group in the current study was likely to have been slightly better than the group investigated by Mackie (1995), which may explain the difference.

Bland-Altman analysis shows that both t-VEP and step_VEP acuity scores were poorer than subjective acuity scores independent of the level of acuity being measured. Step_VEP acuity agrees more closely with subjective testing than t-VEP acuity and had narrower 95% confidence intervals. As both groups were equally large, the wider confidence intervals suggest that there may have been greater inter-individual variability in the t-VEP group. This could be explained by the octave increments (0.3 LogMAR) between stimulus sizes in the t-VEP assessment compared to 0.1 LogMAR increments in the step_VEP and most subjective tests. There may have been changes in EEG amplitude and frequency distribution over the longer t-VEP test procedure affecting the ability of the test to detect small amplitude responses near threshold. It is also possible that the step_VEP test itself may be better than the t-VEP test with a smaller inherent inter-individual range. Across the whole group the mean difference between step_VEP acuity and subjective acuity was 0.6 LogMAR smaller than the mean difference between t-VEP and subjective acuity (0.4 LogmAR compared to 1.0 LogMAR). This suggests that t-VEP acuity scores are poorer than step_VEP acuity scores which agrees with the finding of Panton *et al.* (2002) that t-VEPs gave poorer acuity scores than sweep VEPs when both tests are performed on the

same subject. As the regression line between VEP and subjective acuity score and the line of perfect agreement are roughly parallel in each case, it can be concluded that there is a systematic difference between VEP acuity score than subjective acuity score. This must be caused by attenuation of the brains electrical responses by cortical tissue and the skull. The difference between the regression line and the line of perfect agreement between subjective and VEP testing (Figures 7.7 and 7.9) could be used to re-calibrate the VEP test scores to account for this attenuation.

The 95% confidence limits of agreement between step_VEP and subjective acuity scores were larger for normal adults with artificially degraded vision than for the clinical group, although the mean difference was the same. This is no doubt explained by the use of bangerter filters to degrade vision, which cannot recreate organic visual impairment. However regression analysis showed a higher correlation between step_VEP and subjective acuity scores in adults than t-VEP or step_VEP and subjective acuity scores in the patient group.

In paediatric patients with ocular pathologies, and artificially optically degraded normal adults, the sweep VEP resulted in poorer acuity scores than subjective assessments for subjects with good acuity. Better acuity scores for sweep VEPs than subjective tests were reported when the level of acuity was poor (Arai *et al* 1997; Katsumi *et al.* 1996; Katsumi *et al.* 1997). Riddell *et al* (1997) found that sweep VEP acuity scores were better than Teller card acuities in normal infants, which agrees with the studies of Katsumi's group if immature acuity is regarded as equivalent to reduced acuity. Sweep VEP and subjective

acuity scores generally reach agreement by one year of age in normal subjects (Sokol *et al.* 1992; Riddell *et al.* 1997). When patients with cortical visual impairment were investigated, sweep VEP acuity scores were better than Teller card scores for the children with particularly low vision (Good 2001). Relatively poor subjective acuity scores in cortically visually impaired patients may be related to immature or abnormal motor responses.

In a patient group up to 10 years of age with various ocular pathologies, t-VEP acuity scores were almost always better than Preferential looking acuity scores (Sokol 1983). Bane and Birch (1992) used t-VEPs to assess a patient group similar to the current study, i.e. mixed pathology with a high incidence of cortical visual impairment. They found VEP acuity scores were poorer than preferential looking acuity scores in the visually impaired but better than preferential looking in a group of normal children. This was corroborated by Mackie (1995) who found than t-VEP acuity score was poorer than subjective acuity score in a group of neurologically impaired children. The disagreement of these studies with Sokol (1983) suggests that the nature of visual impairment may affect the agreement between t-VEP and subjective acuity scores.

The median subjective acuity score corresponding to each t-VEP critical check size was systematically better than the subjective acuity score corresponding to the same step_VEP critical check size, corroborating the hypothesis that t-VEP acuity scores are poorer than step_VEP acuities. Appendix B gives the equivalent relationship for critical check size and snellen acuity established in the study of Katsumi (1994). The ranges of Snellen acuity scores for each check size were lower and larger those reported in this study. The

differences may be partly explained by the variation in rate of stimulus reversal; checkerboards reversing 12 times every second established poorer subjective acuity ranges than those reversing 7.8 times a second (step_VEP) which in turn had systematically poorer ranges than those reversing at 1.1 reversals per second (t-VEP). Katsumi used a Snellen chart to measure acuity subjectively whereas this study used a range of subjective techniques. There is a larger inherent variability in the Snellen task than acuity card tasks (Wiener *et al.* 1985) which may explain the larger acuity ranges he found for each critical check size.

Conclusion

In those with reduced acuity, the sweep VEP reports better acuity than subjective techniques whether the deficit is due to age, ocular pathology or cortical pathology. Both step_VEPs and sweep VEPs give better visual acuity scores than t-VEPs, regardless of the type of patient or the level of visual acuity deficit. The slower the reversal of checkerboard stimulation, the poorer the VEP acuity is likely to be.

The difference between the regression line and the line of perfect agreement between subjective and VEP testing (Figures 7.5 and 7.7) could be used quantify the degree of attenuation caused by cortical tissue, the skull and the scalp and therefore re-calibrate the VEP test scores. However, the clinician should be aware that the disparity between test scores may be affected by age in a paediatric patient group, and is known to vary with aetiology (Westall *et al.* 1997).

7.6 The effect of age and patient factors on the success and outcome of acuity assessment

7.6.1 Introduction

It has been shown that the faster step_VEP acuity assessment has a higher overall success rate than the t-VEP acuity assessment. It is hypothesised that the step_VEP test will also be more successful than t-VEP acuity assessment across a range of diagnoses and developmental levels. A subset of the total patient group attended a multidisciplinary vision clinic. Patients attending the clinic were assessed by a developmental paediatrician as well as an orthoptist, electrophysiologist, occupational therapist and ophthalmologist. Consequently it was possible to study the effect of diagnosis and development on the success and outcome of acuity assessment in this group.

7.6.2 Methods

The questionnaire shown in figure 7.12 was completed for 66 patients in addition to completion of the questionnaire recording acuity assessment result and success (figure 7.2). The acuity assessments were graded as '1' for an unsuccessful of incomplete assessment, or '2' for an assessment leading to acuity estimation

To facilitate statistical analysis, the developmental factors were graded as follows:

Motor development: 1=normal, 2=walks independently, 3=walks with aids, 4=sits independently, 5=sits with support, 6=not sitting, 7= no head control.

VISION CLINIC

DATE OF ATTENDANCE:.....

NAME:.....DOB.....

ADDRESS:.....

.....

AGE: .....

ATTENDED WITH CHILD:

MAIN DIAGNOSIS:

Cerebral Palsy/learning disability/other .....

VISUAL HANDICAP - site of disorder globe retina nerve cortex

aetiology of disorder/diagnosis

refraction

HEARING: normal/mild/moderate/severe loss/not known

SPECIFIC MOTOR DISORDER: - Spastic: diplegia, hemiplegia, quadriplegia, Dyskinetic, Other

MOTOR DEVELOPMENT:

N/ walks indep/ walks with aids/ sits indep/ sits with support/ not sitting/ no head control

HAND FUNCTION: (in best hand) L. R

N/ crude grasp / no sustained grasp / significant asymmetry

INTELLECTUAL DEVELOPMENT:

N /Impaired due to VH / Doubtful for VH-/ Mod Impairment / Severe impairment

SOCIAL DEVELOPMENT:

Normal / doubtful / withdrawn / significant behavioural diff / other

OTHER HANDICAP / MALFORMATION:

AETIOLOGY OF HANDICAP:

FAMILY HISTORY:

INVESTIGATIONS DONE:

EXAMINATION (comments) HC:

MATERNITY HOSPITAL: Where born

Figure 7.12: The Vision Clinic Questionnaire to assess developmental factors and details on diagnosis and aetiology.

Intellectual development: 1=normal, 2=some impairment, 3=severe impairment.
Social development: 1=normal, 2=withdrawn or doubtful development, 3=significant behavioural difficulties.

Table 7.6 presents the questionnaire results in all 66 patients. 39 of the group received a t-VEP acuity assessment and the other 27 received a step_VEP acuity assessment. All 66 received a subjective assessment of acuity. The success rates of these three independent groups were compared as a function of diagnosis and developmental factors using a sign and binomial test. A McNemar test was used to comparetest success in patients who received both VEP and subjective assessments on the same day. This was performed separately for patients receiving t-VEP and step_VEP acuity assessments. Within each of these groups the test was repeated for patients grouped by diagnosis and developmental factors.

Repeated Kruskal-Wallis tests were used to investigate the effect of these developmental factors on VEP success, subjective success and disparity between VEP and subjective test results. Linear regression was also performed to see if age had any effect on the outcome of acuity testing.

Table 7.6a: Summary of Vision Clinic patient group

Main Diagnosis	N
Learning Difficulty (LD)	35
Cerebral Palsy (CP)	14
Developmental Delay (DD)	2
Functional Visual Loss (FVL)	1
Optic Nerve Hypoplasia (ONH)	1
Unclassified	13
Total	**66**

Table 7.6b: Patient details collected by questionnaire in the vision clinic subgroup.

Patient	Age (years)	VEP Stimulus	VEP Acuity	VEP success	Subjective Acuity (LogMAR)	Subjective success	Motor development	Intellectual development	Social development	Category of diagnosis
1	1.92	Transient		1		1	4	3	1	Learning Difficulty
2	16.81	Transient	2.38	2	1.48	2	3	3	1	Learning Difficulty
3	3.19	Transient	1.78	2	0.20	2	2	2	3	Learning Difficulty
4	0.79	Transient	2.38	1		1	6	1	1	Learning Difficulty
5	2.66	Transient	2.38	2		1	6	3	1	Cerebral Palsy
6	4.76	Transient	0.78	2	0.18	2	1	1	1	Unclassified
7	1.05	Transient	3.00	2	2.20	2	4	1	1	Unclassified
8	8.89	Transient	1.78	2		1	7	3	1	Learning Difficulty
9	3.98	Transient		1	0.20	2	2	2	1	Developmental Delay
10	2.47	Transient	2.08	1	1.00	2	2	1	1	Cerebral Palsy
11	3.76	Transient		1	0.70	2	3	3	1	Learning Difficulty
12	1.46	Transient	1.48	2	0.90	2	7	3	1	Learning Difficulty
13	2.75	Transient	2.08	1		1	6	3	1	Learning Difficulty
14	4.77	Transient	2.08	1		1	4	3	1	Learning Difficulty
15	0.67	Transient	2.38	2	1.90	2	6	1	1	Developmental Delay
16	12.53	Transient	1.78	1	0.60	2	4	3	1	Learning Difficulty
17	4.41	Transient	0.78	2	0.00	2	1	1	1	Unclassified
18	0.84	Transient	1.48	2	0.60	2	1	1	1	Unclassified
19	4.99	Transient	1.08	2	0.18	2	3	3	1	Unclassified
20	6.17	Transient	2.08	1		1	6	3	2	Learning Difficulty
21	1.17	Transient	2.08	2		1	1	3	1	Learning Difficulty
22	3.10	Transient	3.00	2	2.22	2	6	3	2	Learning Difficulty
23	1.05	Transient	2.38	2		1	7	3	1	Learning Difficulty
24	14.18	Transient	1.08	2	0.30	2	7	2	1	Cerebral Palsy
25	19.63	Transient		1	1.20	2	3	3	1	Learning Difficulty
26	0.87	Transient	3.00	2	1.30	2	7	2	1	Cerebral Palsy
27	6.93	Transient	3.00	1	0.84	2	1	1	1	Unclassified
28	0.30	Transient		1		1	1	1	1	Unclassified
29	6.51	Transient	2.38	1	-0.95	2	1	1	1	Unclassified
30	15.64	Transient	0.78	2	0.00	2	1	1	1	Functional Visual Loss
31	14.25	Transient	1.48	1	0.18	2	2	3	1	Learning Difficulty
32	1.55	Transient	1.08	2		1	4	2	2	Learning Difficulty
33	5.89	Transient	2.08	1	0	1	5	2	1	Cerebral Palsy
34	11.89	Transient		1		1	6	3	1	Learning Difficulty

Table 7.6b continued: Patient details collected by questionnaire in the vision clinic

Patient	Age (years)	VEP Stimulus	VEP Acuity	VEP success	Subjective Acuity (LogMAR)	Subjective success	Motor development	Intellectual development	Social development	Category of diagnosis
35	2.91	Transient		1		1	1	1	1	Unclassified
36	8.79	Transient		1		1	1	2	1	Cerebral Palsy
37	1.15	Transient	1.48	2	1.00	2	7	3	1	Learning Difficulty
38	2.39	Transient	1.08	2	1.20	2	6	3	1	Learning Difficulty
39	14.79	Transient		1		1	1	3	2	Learning Difficulty
40	6.39	Step	0.45	2	-0.17	2	2	2	1	Cerebral Palsy
41	4.52	Step	0.75	2	0.00	2	2	2	1	Unclassified
42	0.16	Step	0.95	2	0.98	2	1	1	1	Unclassified
43	7.24	Step	1.75	2	1.08	2	1	2	3	Learning Difficulty
44	3.52	Step		1	0.30	2	4	3	1	Cerebral Palsy
45	5.38	Step	2.76	2	1.92	2	5	3	2	Learning Difficulty
46	3.82	Step	1.45	2	0.80	2	5	3	1	Cerebral Palsy
47	1.19	Step	2.45	2		1	1	1	1	Learning Difficulty
48	12.49	Step	0.65	2	0.18	2	1	2	1	Unclassified
49	2.86	Step		1	0.40	2	7	3	1	Cerebral Palsy
50	6.34	Step	1.45	2	1.00	2	1	1	1	Unclassified
51	1.42	Step	2.81	2		1	6	3	1	Learning Difficulty
52	16.17	Step	1.65	2	2.08	2	1	1	1	Optic Nerve Hypoplasia
53	2.63	Step	1.05	2		1	6	3	1	Learning Difficulty
54	4.30	Step	1.45	2	0.7	2	4	3	1	Learning Difficulty
55	5.86	Step	1.05	2	0.48	2	2	3	2	Learning Difficulty
56	1.83	Step	1.54	2		1	4	3	3	Learning Difficulty
57	1.33	Step	1.45	2	0.60	2	2	2	2	Learning Difficulty
58	0.90	Step	1.56	2	0.43	2	4	3	1	Learning Difficulty
59	0.59	Step		1	1.00	2	7	3	1	Unclassified
60	10.11	Step		1	0.78	2	6	3	1	Cerebral Palsy
61	3.40	Step	1.34	2	0.40	2	6	2	3	Cerebral Palsy
62	1.46	Step	3.00	2		1	7	3	2	Learning Difficulty
63	1.99	Step	3.00	2	3.0	2	4	3	1	Cerebral Palsy
64	1.37	Step		1		1	3	3	1	Learning Difficulty
65	0.64	Step	3.00	2		1	6	3	1	Cerebral Palsy
66	8.58	Step		1	1.00	2	6	1	1	Learning Difficulty

7.6.3 Results

Success rates

The success of VEP and subjective acuity assessment are summarised and compared in tables 7.7, 7.8 and 7.9. The numbers in the totals column (table 7.9) showed how many of the whole group were classified as having the given diagnosis or developmental problem. As it is possible that an individual patient had more than one of the problems listed many of these groups overlapped.

Umpaired tests

The statistical test results in table 7.8 indicate which groups were more successfully assessed by VEP than subjective testing. T-VEPs were never more successful than subjective tests and were actually significantly less successful than subjective tests when the vision clinic group was considered as a whole. Step_VEPs were significantly more successful than subjective tests in those with moderate to severe intellectual impairment, motor developmental delay and patients diagnosed with a learning difficulty as well as the whole vision clinic group. When t-VEPs and step_VEPs were compared (table 7.8) a significant improvement in success rate of the step_VEP was observed in those with moderate to severe intellectual impairment, those diagnosed with a learning difficulty and across the whole vision clinic group.

Paired tests

Table 7.9 presents the results of the paired tests. When VEPs and subjective testing were performed on the same day, no difference in the success of the two tests could be found. This applies to those receiving both t-VEP assessment and step_VEP assessment.

Table 7.7: Comparison of t-VEP and step_VEP success rates in the vision clinic sub-group. As only one type of VEP test was attempted in any patient, statistical test results for independent groups are given. * indicates statistical significance, ** indicates high statistical significance.

	step_VEPs	t-VEPs			
Patient Category	Successful assessments	Successful assessments	Statistical test	df	P-value
All vision clinic patients	78% (21/27)	51% (20/39)	Binomial and sign	1	0.003**
Severe intellectual impairment	67% (10/15)	52% (11/21)	Binomial and sign	1	0.12
Moderate to severe intellectual impairment	76% (16/21)	54% (15/28)	Binomial and sign	1	0.02*
Learning difficulty	80% (8/10)	52% (11/21)	Binomial and sign	1	0.06*
Cerebral palsy	70% (7/10)	50% (3/6)	Binomial and sign	1	0.17
Motor development delay	69% (11/16)	60% (12/20)	Binomial and sign	1	0.16

Table 7.8 Comparison of VEP and subjective test success rates in the vision clinic sub-group. Statistical test results for independent groups are given. * indicates statistical significance, ** indicates high statistical significance.

	Subjective tests		Compared to t-VEPs (table 7.7)			Compared to Step_VEPs (table 7.7)		
Patient Category	Success rate		Statistical Test	df	p-value	Statistical Test	df	p-value
All vision clinic patients	59%	(39/66)	Binomial	1	0.04	Binomial and sign	1	0.00**
Severe intellectual impairment	56%	(20/36)	Binomial	1	0.12	Binomial and sign	1	0.05*
Moderate to severe intellectual impairment	59%	(29/49)	Binomial	1	0.08	Binomial and sign	1	0.00**
Learning difficulty	55%	(17/31)	Binomial	1	0.13	Binomial and sign	1	0.00**
Cerebral palsy	63%	(10/16)	Binomial	1	0.23	Binomial and sign	1	0.16
Motor development delay	58%	(21/36)	Binomial	1	0.23	Binomial and sign	1	0.05*

Table 7.9: Comparison of VEPs and subjective tests performed in the same patient. Statistical test results for paired groups are given.

		Successful assessments							Successful assessments					
Patient Category	N	step_VEP	Sub	Statistical Test	Test statistic	df	P-value	N	t-VEP	Subj	Statistical Test	Test statistic	df	P-value
All vision Clinic patients	27	21	15	McNemar	χ^2=0.0	1	1.0	39	20	24	McNemar	χ^2=0.56	1	0.45
Severe intellectual impairment	15	10	10	McNemar	χ^2=0.125	1	0.72	21	11	10	McNemar	χ^2=0.0	1	1.0
Moderate to severe intellectual impairment	21	16	15	McNemar	χ^2=0.0	1	1.0	28	15	14	McNemar	χ^2=0.0	1	1.0
Learning difficulty	10	8	7	McNemar	χ^2=0.0	1	1.0	21	11	10	McNemar	χ^2=0.0	1	1.0
Cerebral palsy	10	7	7	McNemar	χ^2=0.167	1	0.68	6	3	3	McNemar	χ^2=0.25	1	0.62
Motor development delay	16	11	11	McNemar	χ^2=0.1	1	0.75	20	13	10	Mcnemar	χ^2=0.57	1	0.45

Changes with age

The peak latency of the transient VEP matures over the first 20 weeks of life, taking slightly longer for small stimulus sizes compared to large stimulus sizes (McCulloch *et al.* 1999). This small study of acuity only recorded t-VEPs from children older than one year and did not show any effect of age on the difference between t-VEP subjective acuity scores (Table 7.10 and Table 7.11). The difference was constant at 0.8 LogMAR. The study did show that the difference between step_VEP acuity and subjective acuity scores reduces with age and is statistically significant (Figure 7.13 and table 7.10). However, a t-test failed to show that the regression lines for t-VEPs and step_VEPs were significantly different from each other.

Table 7.10 Correlation between age and the disparity of acuity test outcomes.

Group	r	Test Statistic	df	p-value
All VEPs	0.36	F=4.60	1	0.04*
t-VEPs	0.04	F=0.17	1	0.9
Step_VEP	0.65	F=11.7	1	0.00**

Effect of developmental factors

Kruskal-Wallis tests showed that motor development and intellectual development both affected the success of subjective acuity testing (table 7.11). VEP success and the acuity difference between VEPs and subjective tests were not significantly influenced by the developmental factors investigated.

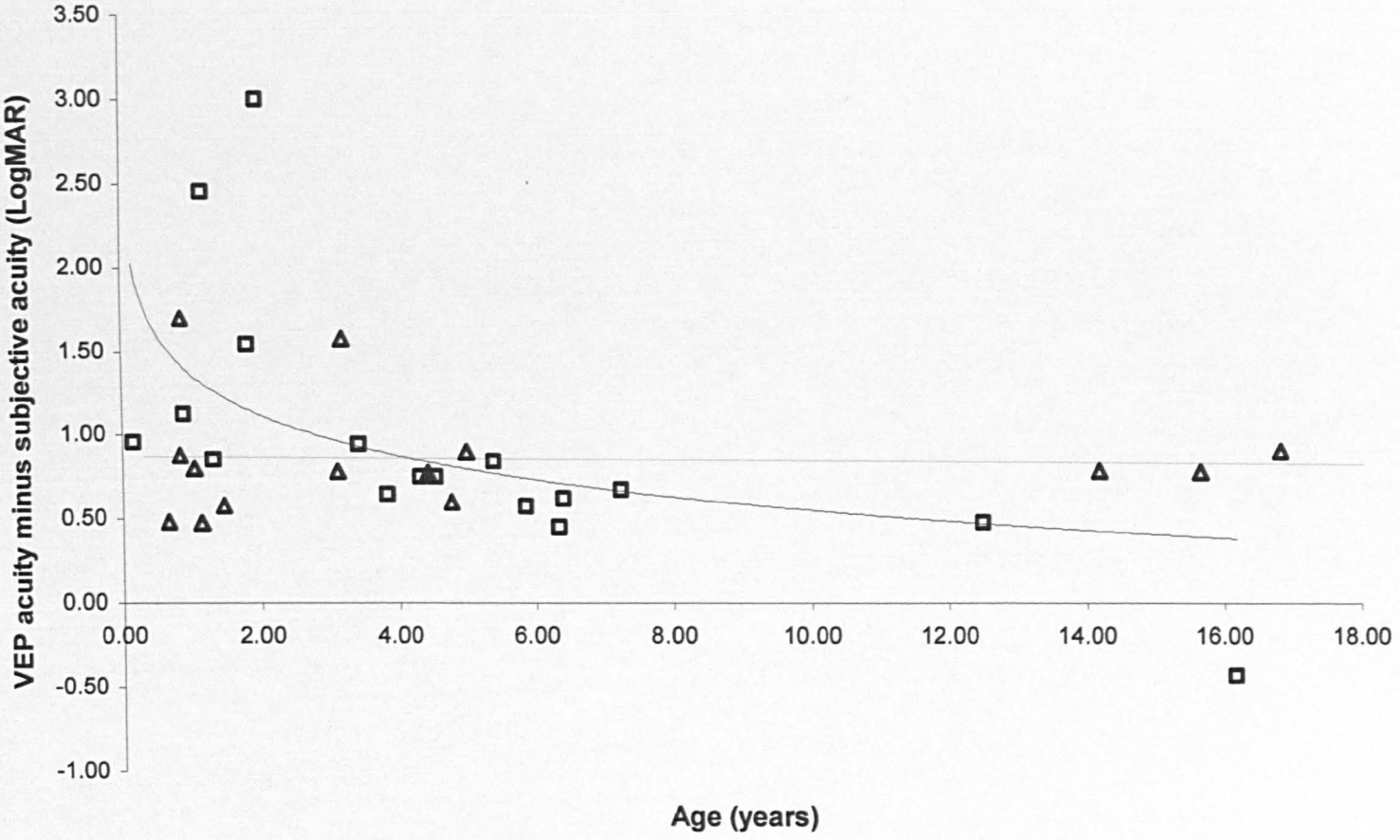


Figure 7.13: The effect of age on the disparity in outcome between VEP and subjective acuity assessments in vision clinic subjects. The triangles and dotted regression line represent t-VEPs, the squares and solid regression line represent step_VEPs

Table 7.11 Repeated Kruskal-Wallis of the influence of developmental factors on acuity test success and disparity in their outcomes.

Factor	Independent variable								
	VEP success			Subjective success			Acuity difference		
	Test statistic	*df*	*p-value*	*Test statistic*	*df*	*p-value*	*Test statistic*	*df*	*p-value*
Motor development	χ^2=3.25	6	0.78	χ^2=12.52	6	0.05*	χ^2=8.83	6	0.18
Intellectual development	χ^2=0.44	2	0.80	χ^2=7.71	2	0.03*	χ^2=0.78	2	0.68
Social development	χ^2=2.94	2	0.23	χ^2=1.13	2	0.57	χ^2=3.46	2	0.18

7.6.4 Discussion

Success rates

For children attending the Vision Clinic the success of completing a step_VEP assessment ranged from 67% to 80% depending on the degree of developmental delay; these results being slightly poorer than 83% (92/111) found in the study of the whole group (section 7.2). The success rate of t-VEPs ranged from 50% to 60% in the vision clinic patients, which is also poorer than the 67% (72/107) found in the whole group study. Subjective tests had a success rate of 74% (134/183) in the main study yet success rates in the vision clinic range from 55% to 63%. As these success rates are systematically poorer than the main study, it can be concluded that the vision clinic group was a different patient population who tended to find all types of acuity assessment more difficult. Tables 7.8 to 7.10 show that some of the group sizes are as small as ten or less. Although the statistical tests used are designed for small groups, they may have been left slightly under powered to show a difference between tests on some occasions.

When all the vision clinic patients were considered, step_VEPs were significantly more successful than subjective tests which in turn were significantly more successful than t-VEPs. This agrees with the main study in section 7.2. The 18% difference between step_VEPs and subjective testing was much greater than the 9% improvement reported for the whole patient group. Across the whole vision clinic group the step_VEP assessment was 26% more successful than t-VEPs. Again, this is much greater than the 16% improvement observed in the whole patient group in section 7.2. The results suggest that the greater the developmental delay present in a patient, the greater the chance of success by employing the step_VEP compared to other assessments.

Changes with age and development

The difference between t-VEP subjective acuity scores is not affected by age and is approximately 0.8 LogMAR. This agrees well with the larger study presented in section 7.5, which reports that the mean difference between t_VEP and subjective acuity scores was 0.8 LogMAR. The difference between step_VEP and subjective acuity scores reduces with age. The small size of this subject group must be taken into account as must the wide range of neurological pathologies within the group. A larger study of normal development of step_VEP acuity would establish the changes that are due to maturity and those explained by disease aetiology.

The range of subjective assessments used in addition to the VEP tests were evenly distributed across both t-VEP and step_VEP groups, and were considered to provide

interchangeable assessments. The increments of the step_VEP test were smaller than the t-VEP test as discussed in section 7.5. This was the case across all ages and so shouldn't have biased the agreement with subjective testing in older patients. One explanation is that the step_VEP assessment is testing a different neural substrate than t-VEP assessment, the developmental course of which is different to both t-VEPs and standard subjective tests.

7.7 Conclusion

The step_VEP assessment is more successful than t_VEPs in the patient group investigated. This is largely explained by a significantly shorter test procedure assisted by a stimulus presentation algorithm that maintains attention.

Subjective tests tend to give better acuity scores that VEP tests in patients with reduced acuity. Step_VEPs result in better acuity scores than t-VEPs and therefore a closer agreement with subjective test scores.

The greater the developmental delay in the patient, the greater the chance of success through employing the step_VEP compared to other tests. The disparity between step_VEP acuity score and subjective acuity score reduces with age.

Chapter 8: General conclusions and further work

8.1 Introduction

The overall aim of the study was to develop an objective method of paediatric visual acuity assessment based on the real-time analysis of ssVEPs. The specific areas for investigation are outlined in section 2.8, and the development work is described in chapters three to five. After development, the new step_VEP assessment was evaluated in a group of normal adults, and children attending opthalmology clinics at the Royal Hospital for Sick Children in Glasgow (chapters 6 and 7).

8.2 1-D Laplacian analysis of ssVEPs in children and adults

Two lateral occipital electrodes are recommended in addition to O_z to investigate the lateralisation of the VEP (Harding *et al.* 1996). These electrodes were utilised in a 1-D Laplacian analysis of ssVEPs, which measures the instantaneous potential distribution at three occipital electrode sites.

1-D Laplacian analysis was never significantly slower than conventional O_z-F_z analysis at detecting ssVEP responses. Near visual acuity threshold (3' checks) it was shown to be significantly faster than conventional analysis in children from three years of age upwards and in adults. A lateral electrode site at 15% of the half-

head circumference from O_z-F_z provided the fastest response detection times (DT) most often in adults.

The DT improvement offered by a 1-D Laplacian analysis is explained by increased noise cancellation; lateral, occipital electrode sites cancelled more noise than the F_z reference site as the noise they measured was more coherent with that measured at O_z. The increased noise cancellation offered by 1-D Laplacian analysis allowed smaller responses to be distinguished from the background noise and therefore they were also detected more often.

ssVEP acuity approaches maturity within the first year of life (Sokol 1978; Norcia & Tyler 1985; Skoczenski 1999; Allen *et al.* 1996). Maturation of the visual system continues throughout childhood and it is postulated that this maturation affects the benefits of applying a 1-D Laplacian analysis to ssVEP recording in different age groups. In children, DT reductions were observed for responses to supra-threshold stimuli (6' and 9' checks). In children, suprathreshold stimuli may evoke either a smaller or a later extrastriate response than in adults. This would result in less signal cancellation when a 1-D Laplacian analysis is used to analyse ssVEP recordings. Signal preservation results in a larger SNR and partly explains the reduced DTs observed in some age groups for suprathreshold stimuli. The noise coherence between recording electrodes also improves with age (Srinivasan 1999), which results in a larger SNR and therefore a further reduction in DT when a 1-D Laplacian analysis is used to analyse ssVEP recordings.

Simultaneous use of both a conventional (O_z-F_z) VEP recording and analysis channel and a 1-D Laplacian analysis channel is likely to offer faster overall ssVEP detection and increase the likelihood of detecting small-amplitude ssVEPs. This is likely to give more accurate ssVEP assessments, and to provide the potential for a reduction in overall test duration.

8.3 Development of step_VEP acuity assessment

T^2_{circ} statistics and SNR detection techniques were shown to be complementary and the response detection is accepted from either statistic by the step_VEP program. As there was no DT difference between them, the FFT analysis technique was used rather than AF as it was easier to compute and its output provided a more intuitive graphical illustration of results for the user interface. The level of α to define a detection was set at 0.005 so test sensitivity was not compromised. In theory, T^2_{circ} statistics required an analysis epoch of at least three seconds to maintain the independence of data samples (Victor & Mast . 1991). However, investigation of the effect of analysis epoch length showed that a two-second epoch maintained adequate specificity and reduced the (theoretical) test duration.

Stimuli displayed until response detection or 22.6 seconds had elapsed enabled response detection in 98% of patients during the initial stimulation period. Subsequent presentation of a stimulus check size of 714' meant that almost all

patients were shown something they could see within 30 seconds of beginning the assessment. To maintain attention, stimuli were not repeated for a stimulus that had already provided response detection, or for a stimulus that failed to elicit a response. The stimulus size was varied in small increments after the first failure, and response detection was demanded at two consecutive stimulus sizes to define threshold. Extrapolation of ssVEP response amplitudes did not provide significantly different limits of agreement with subjective acuity than using the smallest check size seen. As it would be relatively difficult to compute a real-time amplitude extrapolation, the smallest check size technique alone should provide sufficiently accurate acuities.

The stimulated field size has to drop to around 5° before any reduction in response amplitude is observed (Bradnam 1994). As the minimum field size of checkerboard presentation in this assessment is 6.75°, response amplitude and acuity outcome were not though to be affected by varying the test distance.

8.4 Evaluation of the step_VEP acuity assessment

The step_VEP assessment was 16% more successful than t_VEPs (83% compared to 67%) and 9% more successful than subjective tests (83% compared to 75%) at providing a complete acuity assessment in the patient group investigated. The increase in success rate is partly explained by the average step_VEP test duration (two minutes 29 seconds) being 67% faster than average t_VEP test duration (seven

minutes 34 seconds). It is also a result of a stimulus presentation algorithm specifically designed to maintain attention.

The greater the developmental delay in the patient group was, the greater the observed improvement in success rate by employing the step_VEP. The disparity between the outcome of step_VEP and subjective acuity assessments was shown to reduce with age.

Subjective tests were shown to give higher acuity scores than VEP tests in subjects with normal and reduced acuity in this study. VEP acuity score improves as stimulus rate increases. This results in a closer agreement between step_VEPs and subjective acuity scores than t_VEPs and subjective acuity scores. The presence of a notch in the spatial frequency amplitude function does not affect the agreement between step_VEP acuity and subjective acuity estimations in individual subjects.

The acuity scores of VEP tests can be corrected to account for the degree of attenuation caused by cortical tissue, the skull and the scalp. However, the clinician should be aware that the difference between test scores may be affected by age in a paediatric patient group, and is known to vary with aetiology (Westall *et al.* 1997).

8.5 Further work

The level of noise coherence between the central and lateral electrodes is dependent on individual cortical architecture, as this is not related to head circumference.

A fixed distance for the lateral electrodes may be more appropriate and should be investigated, as should the dependence of this distance on age.

Although increasing the viewing distance, and therefore reducing the stimulated field size, does not affect the ssVEP response amplitude, it is known from clinical experience that the further the stimulus monitor is placed from a young subject, the less likely it is that attention will be maintained. A stimulus monitor with higher resolution would allow a large range of stimulus sizes to be presented at a relatively short viewing distance. In addition to maintaining attention this would eliminate any extra time spent moving the stimulus monitor during the test.

The disparity between the outcome of step_VEP and subjective acuity assessments was shown to reduce with age in the Vision Clinic group. Testing a group of normal subjects would allow quantification of the effect of maturation alone on this disparity, independent of neurological impairment. Although the disparity between step_VEP and subjective acuity assessments was not shown to vary with patient factors in this study, testing larger groups of patients with specific aetiologies may provide some conclusive results.

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Appendix A

LogMAR=-Log (decimal acuity)

Decimal acuity=$10^{-LogMAR}$

LogMAR=Log(check diagonal or period of grating)

Line Number	Snellen Equivalent	Decimal Equivalent	Visual Angle (minutes)	LogMAR Equivalent
-3	6/3	2.0	0.5	-0.3
-2	6/3.75	1.6	0.63	-0.2
-1	6/4.8	1.25	0.8	-0.1
0	6/6	1.0	1.0	0.0
1	6/7.5	0.8	1.25	0.1
2	6/9.4	0.63	1.6	0.2
3	6/12	0.5	2.0	0.3
4	6/15	0.4	2.5	0.4
5	6/18.9	0.32	3.15	0.5
6	6/24	0.25	4.0	0.6
7	6/30	0.20	5.0	0.7
8	6/37.5	0.16	6.25	0.8
9	6/48	0.13	8.0	0.9
10	6/60	0.1	10.0	1.0
11	6/75	0.08	12.5	1.1
12	6/96	0.06	16.0	1.2
13	6/120	0.05	20.0	1.3
20	6/600	0.01	100.0	2.0
30	6/6000	0.001	1000.0	3.0

(Holladay 1997)

Appendix B

The Snellen acuities corresponding to each critical check size in the study of Katsumi (1994) in patients of all ages. Steady state stimuli were presented serially and analysis performed off-line. The LogMAR acuity equivalents are also included to allow comparison with other studies.

Critical Check	**Corresponding Subjective Acuity**					
size (minutes)	**LogMAR**			**Snellen**		
	mean	*min*	*max*	*mean*	*min*	*max*
10	0.26	-0.12	1.6	6/11	6/4.5	6/240
20	0.67	-0.12	1.6	6/28	6/4.5	6/240
40	0.88	0	1.9	6/46	6/6	6/480
80	1.20	0.40	1.9	6/93	6/15	6/480
160	1.25	0.40	1.9	6/106	6/15	6/480
Not recordable	1.60	0.54	2.2	6/244	6/21	6/960

Appendix C

For groups of unequal size:

$$(p_1-p_2)^2=f(\alpha,P)x(p_1(1-p_1)/n_1+p_2(1-p_2)/n_2).....1$$

For the special case of groups of equal size:

$$(p_1-p_2)^2=f(\alpha,P)x(p_1(1-p_1)+p_2(1-p_2)/n).....2$$

p_1 =the success rate in group 1, in this case those tested with t-VEPs

p_2=the success rate in group 2, in this case those tested by with step_VEPs

$f(\alpha,P)$=Power and significance level multiplication factor=7.85 for α=0.05 and P=80%

n_1=number of patients required in group 1

n_2=number of patients required in group 2

n=number of patients required in each group when group sizes are equal.

(Fleiss 1981)

Appendix D

Published abstracts

Mackay A, Bradnam MS, Hamilton R. A Laplacian analysis provides faster detection times than conventional recording for steady-state Visual evoked potentials (ssVEPs). *Investigative ophthalmology and visual science.* 2001.

Mackay A, Bradnam MS, Hamilton R. A Laplacian electrode montage detects Steady-state Visual evoked potentials (ssVEPs) faster than a conventional montage (Oz-Fz) in children over three years old.
ISCEV Annual symposium programme. 2001

Bradnam MS, Mackay A, Hamilton R. Objective detection of Steady-state Visual evoked potentials (ssVEPs): the circular T^2 statistic and signal-to-noise ratio are complementary.
ISCEV Annual symposium programme. 2001

Bradnam MS, Mackay A, Hamilton R. Rapid Paediatric acuity assessment: a new electrophysiological test.
Investigative ophthalmology and Visual science. 2002

Mackay A, Bradnam MS, Hamilton R. Improved success in paediatric acuity assessment.
ISCEV Annual Symposium programme. 2003.

Papers in Press

Mackay A, Hamilton R, Bradnam MS.
Faster and more sensitive VEP recording in children
Doc. Ophthalmol. 2003.

Mackay A, Bradnam MS, Hamilton R.
Rapid detection of threshold VEPs.
Clin. Neurophysiol. 2003.

Presentations

Estimating visual acuity with Visual evoked potentials.
Research Workers meeting. Tennant Institute of Ophthalmology, University of Glasgow.

A Laplacian electrode montage detects Steady-state Visual evoked potentials (ssVEPs) faster than a conventional montage (Oz-Fz) in children over three years old.
ISCEV Annual symposium 2001. Mont Orford, Quebec, Canada*.

A new, rapid paediatric visual acuity assessment.
Department of Clinical Physics and Bioengineering, NHS,Glasgow.

Improved success in paediatric acuity assessment.
ISCEV Annual Symposium 2003. Nagoya, Japan.

*Awarded the Eberhardt Dodt award for the best presentation by a young scientist at the ISCEV Annual symposium.