THE EFFECTS OF CLICK REPETITION RATE ON THE AUDITORY BRAINSTEM RESPONSE

GUY RICHARD LIGHTFOOT

A thesis submitted in partial fulfilment of the
requirements of the Council for National Academic Awards
for the degree of Doctor of Philosophy

THE LIVERPOOL POLYTECHNIC
and
THE ROYAL LIVERPOOL HOSPITAL

APRIL 1991

CONTENTS

Continued

Continued

Continued

ACKNOWLEDGMENTS

I gratefully acknowledge the assistance and encouragement of the following, without whose support this study would not have been possible:

Director of Studies:

Dr.A.R.D.Thornton BSc, PhD, C.Eng., MIERE, MBCS.
Scientist in charge, MRC Institute of Hearing Research
Southampton Outstation
Royal South Hants Hospital, Southampton.

Internal Supervisor:

Dr.J.C.Goodchild BSc, PhD, M.Inst.P, MIOA, C.Phys.
Senior Lecturer, The Liverpool Polytechnic.
Visiting Lecturer, University of Liverpool.

Statistics Advisor:

Mr.J.Higgins BSc, MIS, FSS, AFIMA.
Principal Lecturer in Statistics, The Liverpool Polytechnic.

Thanks are also due to my Medical and Surgical colleagues at the Royal Liverpool Hospital and at Walton Hospital, Liverpool, for the referral of patients and for the provision of diagnostic information; to Drs.D.N.Brooks and R.R.A.Coles for their comments on the subject categorisation protocol; to Dr.A.Davies for the 4kHz asymmetry data from the MRC National Study of Hearing; to fellow scientist Gary Norman for his assistance in the testing of some subjects to my research protocol and for politely listening to my ramblings. Finally I thank the 36 normal volunteers who willingly gave their time for the benefit of this research study.

Guy Lightfoot, April 1991

Dedication

For Charlotte

(21 January 1981 - 12 May 1981)

THE EFFECTS OF CLICK REPETITION RATE ON THE AUDITORY BRAINSTEM RESPONSE

G.R.LIGHTFOOT

ABSTRACT

This study examines the effects of stimulus repetition rate (SRR) on the auditory brainstem response (ABR) in normal and otologically abnormal subjects. A total of 267 subjects were tested: 36 normal volunteers; 49 subjects with normal hearing but with tinnitus or vertigo; 135 with cochlear impairment; 16 with suspected but unconfirmed retrocochlear pathology; 31 with acoustic neuromata.

In normal subjects, the results of analysis revealed a genuinely linear prolongation in latency of ABR waves V, III & I with increasing SRR. Wave V amplitude was not affected by SRR whereas waves III & I showed an approximately linear reduction in amplitude with increasing SRR. Click train adaptation studies demonstrated that the latency adaptation of wave V, unlike waves III & I, is incomplete by the eighth click in a train of clicks. Recovery of this adaptation requires more than 90ms and less than 243ms for waves V & III. The recovery time for wave I was less clear.

A general finding was that, unlike other ABR measures, rate effect measures appear insensitive to the effects of gender and hearing loss and are only weakly influenced by age. Neither tinnitus nor vertigo had significant effects on SRR results. Using 95% confidence limits derived from non-tumour subjects, the 11.1/s - 88.8/s wave V latency shift was found to be a powerful index of retrocochlear dysfunction. For tumour ears with a sub-total hearing loss, the sensitivity and specificity of this measure was 84% and 94% respectively ($d' \approx 2.5$). As a by-product of the analysis, 2 appropriately corrected low-SRR measures were found to have a diagnostic performance superior to SRR and inter-peak latency measures. A diagnostic strategy employing a number of ABR measures is suggested for the optimum detection of acoustic neuromata.

CHAPTER 1

THE REASON FOR THE STUDY

1.1 INTRODUCTION

The auditory brainstem response (ABR) has several clinical applications, one of the most important being the detection of retrocochlear disorders. One such life-threatening disorder is the acoustic neuroma (more accurately termed vestibular schwannoma), the prevalence of which is thought to be between 5 and 10 cases per million population per year, making it the most common cerebellopontine angle tumour.

Patients with acoustic neuromata may present with a variety of symptoms, including unilateral hearing loss, unsteadiness or vertigo, tinnitus, headache, aural fullness, diplopia, dysdiadochokinesis, papilloedema, or facial weakness, pain or numbness. Turner *et al.* (1984) reviewed the performance of audiological, vestibular and radiological tests for retrocochlear pathology and concluded that the ABR is the best non-invasive test available and is particularly good at identifying small tumours.

A variety of analytical methods have been developed for this application of the ABR, yet none is without limitations of accuracy or applicability. This thesis investigates one such method, stimulus repetition rate (SRR) effects, rarely

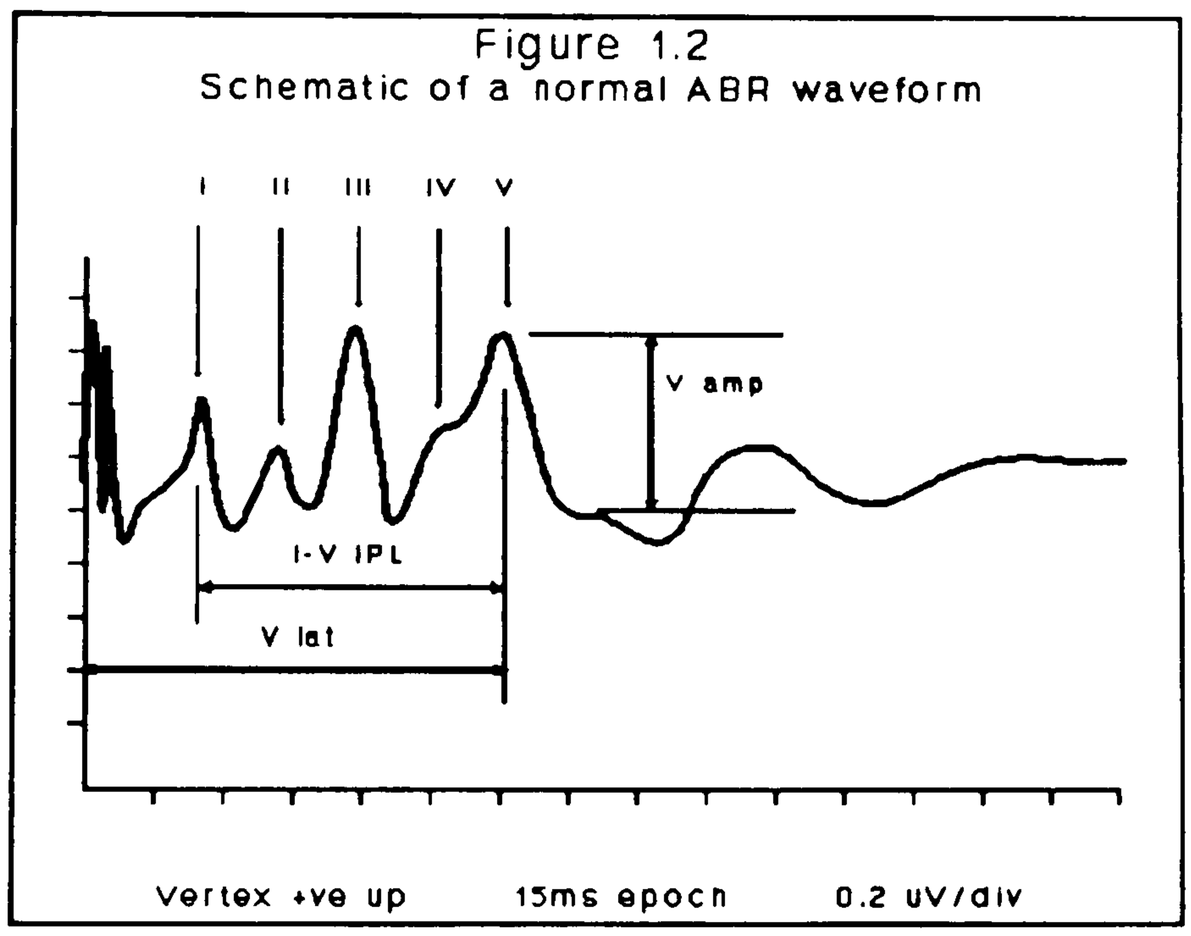
employed in the clinic, in an attempt to assess its utility, and in particular, determine whether it can "fill the gaps" exposed by more popular ABR techniques. A secondary aim of this study is to explore the temporal characteristics of ABR adaptation onset and recovery in normal and patient populations, to obtain a better insight of the responsible processes.

An ideal diagnostic test has 100% sensitivity (correctly identifies all cases of abnormality for which it is designed), 100% specificity (never gives an abnormal result in the absence of the abnormality) and can be applied to all patients requiring the test. Few real tests meet this ideal, and to explain why SRR effect measurements might augment existing ABR methods, it is first necessary to identify the limitations of popular ABR measurements and then to review the literature on rate effects.

1.2 POPULAR ABR MEASUREMENTS

This section introduces and reviews the performance of the popular ABR measurements used in otoneurological diagnosis. Important considerations are the sensitivity, the freedom from any subject or methodological factors and the applicability of the measures in the clinical population.

Figure 1.2 illustrates a classic, well-defined high intensity click-evoked ABR waveform obtained from a normal subject. Vertex positive peaks are labelled according to the Jewett Convention (Jewett and Williston, 1971). The latency of the peaks is measured from stimulus onset and amplitudes are measured from a given peak to the following trough. In cases of flat-topped peaks (quite often encountered with wave V), the rightmost edge of the peak is used.



Values of recorded latency and amplitude are influenced by both methodological and patient factors, especially stimulus intensity and hearing loss, respectively. As the following sections show, for waveform measurements to be used as a basis for neurological assessment, such factors need to be strictly controlled or accommodated.

1.2.1 Inter-peak latency measurements (IPLs)

Unlike peaks II and IV, which are sometimes absent or indistinct in normal subjects, peaks I, III and V can be recorded with reliability, both in normals and patients with modest degrees of sensorineural hearing loss. Three IPL measurements are therefore commonly made: the I-V, I-III and III-V intervals. These are usually about 4 ms, a little over 2 ms and a little under 2 ms respectively in subjects free from neurological disease.

Patients with neurological dysfunction of the auditory nerve or low brainstem classically exhibit a slowing of the neural propagation velocity, which may be recorded as an abnormally extended IPL. In cases of acoustic neuromata extended I-V and I-III intervals may be seen in 95% of cases where these peaks are recorded (Eggermont *et al.*, 1980). A large number of references now exist which demonstrate that this technique is highly sensitive for acoustic neuroma detection, provided that the ABR peaks can be recorded.

Although sensory hearing loss is known to influence the recorded values of IPLs (Coats & Martin, 1977), the effect is relatively slight, as are those due to the subject's age and sex, and so simple criteria can be applied with acceptable precision. Specificity is governed by the criterion employed and a mean plus two standard deviations is often used clinically. IPL measurement has accordingly become the method of choice, offering both good sensitivity and good specificity.

A major drawback, however, is one of applicability. Because an acoustic neuroma

is a variable pathology, its site, degree of granulation and size can cause various effects. These may include direct and indirect pressure effects not only on the nerve but also on the vascular supply to the cochlea and on CNS structures. As well as the pressure on the nerve creating asynchrony of the high frequency fibres necessary to generate a clear wave I, secondary cochlear damage can elevate the hearing thresholds, resulting in an absent wave I or even total absence of the ABR. Musiek & Gollegly (1985), Cashman & Rossman (1983), Selters & Brackmann (1977) and Josey (1985) reported that wave I is absent in about half of acoustic neuroma patients, whereas wave V is present in well over half.

Inter-peak latency measurements are therefore powerful but have low applicability in many acoustic neuroma patients. Nevertheless, the method is very good for *excluding* the likelihood of an acoustic neuroma in patients having only mild-to-moderate high-frequency hearing loss, when the likelihood of recording the peaks is high. One can reasonably speculate that IPL applicability would be higher if patients were referred at an earlier stage in the development of the tumour.

A wave I which is absent from the conventional surface-electrode recorded ABR can often be measured using transtympanic or extratympanic electrcochleography (ECochG), since this provides a much higher signal-to-noise ratio for wave I. This allows IPL measurements to be made even with a significant high frequency hearing loss (Coats, 1978; Eggermont *et al.*, 1980; Portmann *et al.*, 1980), thus improving the applicability of IPL measurements. Despite this, combined ABR/ECochG techniques have remained largely unpopular because of the discomfort to the patient, even with many types of extratympanic electrode.

1.2.2 Peak amplitude ratio measurements

Several authors (e.g. Hecox, 1980; Nodar, 1980) have noted that in some cases of retrocochlear pathology the ratio of the amplitudes of waves I and V (the I/V amplitude ratio) is abnormally great, e.g. wave I is larger than wave V, a ratio greater than unity, whereas in normal and cochlear-disordered subjects the reverse is usually true. One can accept that this might be so in conditions such as multiple sclerosis, where the cochlea is normal but there is neurological dysfunction within the brainstem, affecting the amplitudes of the later ABR waves.

It is possible to record abnormal I/V ratios in extracanalicular acoustic neuromas, where the cochlea and distal portions of the auditory nerve are largely intact, yet the size and site of the tumour in the cerebro-pontine angle (CPA) disrupts the normal physiology of the brainstem (Musiek & Gollegly, 1985). However, using this measure with a criterion of 1.0, Musiek & Gollegly (1985) obtained a sensitivity of <50% in retrocochlear lesions where both waves were present. Using a criterion of 2.0, Cashman & Rossman (1983) found that the measure could be applied to only 5 of their 35 acoustic neuroma cases and in none of these was the result abnormal.

In conclusion, both the sensitivity and applicability of the I/V amplitude ratio are very poor in detecting acoustic neuromas. If both waves I and V can be recorded, the I-V IPL would appear to be vastly superior.

1.2.3 Inter-aural latency differences

The wave V latencies recorded from stimulating a normal subject's right and left ears should be about the same. Selters and Brackmann (1977) confirmed this and further demonstrated that this holds true (the wave Vs being within 0.2 ms of each other) for patients with a unilateral cochlear loss of up to about 50dB at 4kHz, when using a click stimulus at 83dBnHL. However, greater cochlear losses at 4kHz tended to extend the wave V latency in the poorer ear.

In comparing their cochlear patients to audiometrically similar tumour patients (mostly with acoustic neuromas) they found that 46% failed to produce a wave V at all, and in a further 46% the inter-aural wave V latency difference (ILDV) was well over 0.2ms. The remaining 8% of tumour cases had an ILDV of less than 0.2ms and these either had bilateral tumours or tumours not affecting the auditory nerve. The only disadvantage of this test is that of greater ILDVs arising from severe unilateral cochlear hearing losses at 4kHz. They modified their criterion to be 0.3ms for losses of 55, 60 and 65dB and to 0.4ms for losses over 65dB in an attempt to maximise the test specificity.

It should be noted that they excluded all subjects having hearing thresholds at 2, 4 and 8kHz over 75dB from their study, since they did not expect to record an ABR waveform with a stimulus intensity of 83dBnHL (i.e. at a high frequency sensation level of <10dB). In tumour cases producing a wave V they noted a positive correlation between tumour size and ILDV.

The ILDV method has been validated by a number of studies (Clemis & McGee, 1979; Bauch *et al.*, 1982; Cashman & Rossman, 1983; Bauch & Olsen, 1989), each applying a static ILDV criterion (e.g. 0.2, 0.3 or 0.4ms) plus an additional correction (e.g. 0.1ms per 10dB of 4kHz hearing threshold over 50dBHL) to compensate for the effects of reduced effective stimulus intensity at high frequencies in cases of severe hearing loss.

The conclusions of those studies are broadly similar:

(i) An ABR cannot be identified in a high proportion of patients with acoustic neuromata.

(ii) For those in whom wave V can be identified the ILDV measure has very good sensitivity.

(iii) To maintain optimum specificity in patients having a significant high-frequency hearing loss, some correction to the ILDV criterion is necessary.

(iv) ILDV measures have greater applicability than those employing wave I, since wave V can be recorded at lower effective stimulus sensation levels - i.e in patients with greater hearing losses.

It is noteworthy that in all of the above studies the stimulus levels employed were in the range 80 to 90dBnHL (except Bauch *et al*, 1982, who used 95dBnHL when necessary). Many employed different intensities in the two ears without making an appropriate correction for the ILDV offset that this would be expected to induce. It is tempting to speculate whether the use of a higher (e.g. 100 or 105dBnHL) stimulus intensity would make the ILDV test applicable to a greater

number of patients with severe hearing loss.

It is also interesting that no study has explored the possibility of turning the problem of hearing loss compensation on its head: rather than making a latency correction for unequal sensation level stimuli, why not attempt to stimulate the ears at similar sensation levels by performing a loudness balance test at 4kHz prior to ABR testing and use the results to provide equally loud ABR stimuli in the two ears. The expectation would be that ILDV values would be tightly controlled in non-tumour patients, allowing a fixed criterion to be deployed. Significant ILDV values would then be directly attributable to a neurologically induced latency delay.

1.2.4 Absence of a recognisable ABR waveform

Most studies of the performance of ABR techniques in identifying acoustic neuromata have compared ABR results in tumour and non-tumour groups. A common finding is one of an absent or unrecognisable waveform and it is therefore worth examining whether such a negative finding has positive diagnostic value.

Before examining sensitivity it is important to establish the effects of cochlear hearing loss and stimulus intensity on the detectability of the ABR, since the cochlea must receive effective stimulation at some supra-threshold level before an ABR can be recorded. The question is this: what is the minimum sensation level (SL: stimulus intensity minus audiometric hearing threshold) required to reliably record an ABR, and over what frequency range?

The click-evoked ABR can be used with success to estimate hearing thresholds in the 1kHz - 4kHz range, and for audiograms which are flat in this range, ABR waveforms are usually present at only 5dBSL in cases of substantial cochlear loss, although for normal audiograms the stimulus may need to be at 10 or 20dBSL (Hyde, 1985). Selters & Brackmann (1977) recorded a wave V in 100% of non-tumour patients using an 83dBnHL click, but none of their patients had thresholds over 75dB at 2,4 and 8kHz. Campbell & Abbas (1987) did not appear to restrict their cochlear cases on the basis of hearing loss and they, too, recorded wave V in all cases, although they employed stimuli up to 105dBnHL. Bauch *et al.* (1982) employed intensities up to 95dBnHL and recorded an ABR in 94% of non-tumour

patients and noted that most of the other 6% had a severe-to-profound loss at 2kHz and 4kHz.

Other authors made generalised comments regarding ABR detectability, and to summarise, most considered that a stimulus intensity of at least 10dBSL is required in the range 2-4kHz for an ABR wave V to be obtained with any degree of reliability in cases of severe cochlear hearing loss. With this as a benchmark, an absent ABR does indeed appear to be a useful criterion for detecting acoustic neuromata, providing a stimulus intensity of at least 15dBSL can be delivered in this frequency range.

Compared to 100% ABR detectability in their non-tumour groups, Selters & Brackmann (1977) and Bauch & Olsen (1989) could obtain an ABR in only 54% and 41% of tumour patients respectively, and a figure of 67% was obtained by Campbell & Abbas (1987). Using a maximum intensity of 90dBnHL, Clemis & McGee (1979) were able to record an ABR in as many as 85% of tumour cases. However, Cashman & Rossman (1983) combined the presence of wave V with the requirement that its latency be within normal limits (after correction for hearing loss) and found that only 11% of results in tumour cases were normal when the 4kHz hearing threshold was below 70dBHL. The figure drops to only 4% for more severe losses, suggesting that this is a very sensitive criterion.

The absence of a recognisable ABR at only modest high frequency stimulus sensation levels therefore appears to have real diagnostic merit. Clearly, the effects of stimulus sensation level are important and what could be taken as a

firm abnormality at higher SLs will become softer as the SL approaches 10 or 15dB. Other factors affecting the recognisability of the ABR are bound to be influential, such as the patient's myogenic activity. Finally, if the presence of a low sensation wave V is to be used as a diagnostic measure, it should be possible to maximise test efficiency by lowering the high-pass filter setting to a value more commonly used in threshold estimation procedures (Mason, 1984).

1.2.5 ABR abnormalities from ears contralateral to tumours

The major neural generators responsible for ABR waves IV and V in man are thought to be the superior olivary complex and lateral lemniscus on the side of the brainstem contralateral to the stimulated ear (Moller & Jannetta, 1985) although there is still some disagreement in the literature. Selters & Brackmann (1977) examined the III-V IPL results of their study and found that a sub-group of patients with large acoustic neuromata (> 3cm) had significantly ($p<.01$) extended III-V IPL results from tests of their non-tumour ears. Radiological results convincingly confirmed their hypothesis that these findings correspond to brainstem displacement/compression caused by large tumours. Similar findings have been reported by Moffat *et al* (1989) with 6.3% of all tumour patients having an extended contralateral ear III-V IPL although they also found abnormal I-III IPLs in 8.9%. The incidence of such abnormalities was again related to tumour size.

Cashman & Rossman (1983) noted that 20% of their tumour patients had abnormal contralateral ABR results (extended absolute wave V latency or I-V or III-V IPLs) and such findings have been echoed by Josey (1985) and Musiek & Gollegly (1985), quoting cases where contralateral abnormalities may resolve following surgery and where brainstem compression may result in the selective abolition of the contralateral wave V.

Since these findings correspond to the compressive effects of only large tumours, the sensitivity of this "test" is relatively low in the general tumour population.

However, since the hearing sensitivity in ears opposite to acoustic neuromas is generally good, contralateral ABR tests have good specificity and applicability. They are particularly useful in cases where (as is often true with large tumours) a profound or total hearing loss on the suspect side results in an absent ABR.

Summary of section 1.2

The IPLs offer an impressive performance in otoneurological diagnosis and are largely immune from subject factors. Their downfall is that they cannot be measured in the majority of patients with an acoustic neuroma. Amplitude ratio measurements have a poor sensitivity. The ILDV is a useful adjunct to the IPLs and can be used when wave I is absent although it has two disadvantages. A correction is required for the effects of hearing loss and a reference ear is required. The absence of a recordable ABR is not diagnostically useful if the audiogram shows a profound or total hearing loss but for milder losses, this finding is a strong positive sign of retro-cochlear disease. Tests on the contralateral ear sometimes reveal the effects of tumour compression of the brainstem.

Because of the above limitations, a study of an alternitive form of ABR measurement involving rate effects was undertaken. Specific objectives will be stated in Section 1.4.2.

1.3 A REVIEW OF THE LITERATURE ON RATE EFFECTS

1.3.1 Introduction

The effects of altering the stimulus repetition rate (SRR) were first investigated in order to characterise the nature of the ABR (Thornton & Coleman (1975), Hyde *et al.* (1976), Stockard *et al.* (1978), Jewett & Williston (1971)) and from this work appropriate rates were established together with other methodological factors which allowed the ABR to be applied in a clinical environment. Despite attempts (Thornton 1983,1987) there has been no international agreement or standardisation of ABR methodology. Nevertheless, a rate of about 10/s is most often used in otoneurological applications and in threshold estimation work a higher rate, typically in the range 25/s to 50/s is usual.

Notwithstanding the evidence outlined in the following review of the literature, which suggests that varying the SRR as a test parameter is likely to yield valuable diagnostic information, it is unusual for most clinics to vary SRR as a test parameter, and for a given application a fixed rate is usually applied.

1.3.2 Stimulus rate effects in the normal population

1.3.2.1 *Absolute Latency*

Although a small number of studies (Jewett & Williston (1971), Klein & Teas (1978) and Pratt & Sohmer (1976)) failed to identify any change in latency in some or all of the ABR waves, most research has identified a definite and orderly relationship where both the latency of a given wave is progressively extended as SRR is increased and where progressively later waves are extended in latency more than preceding waves. Figure 1.3.2.1 (a),(b),(c) summarises this relationship from the literature. The lines shown are not regression lines. They are discussed later.

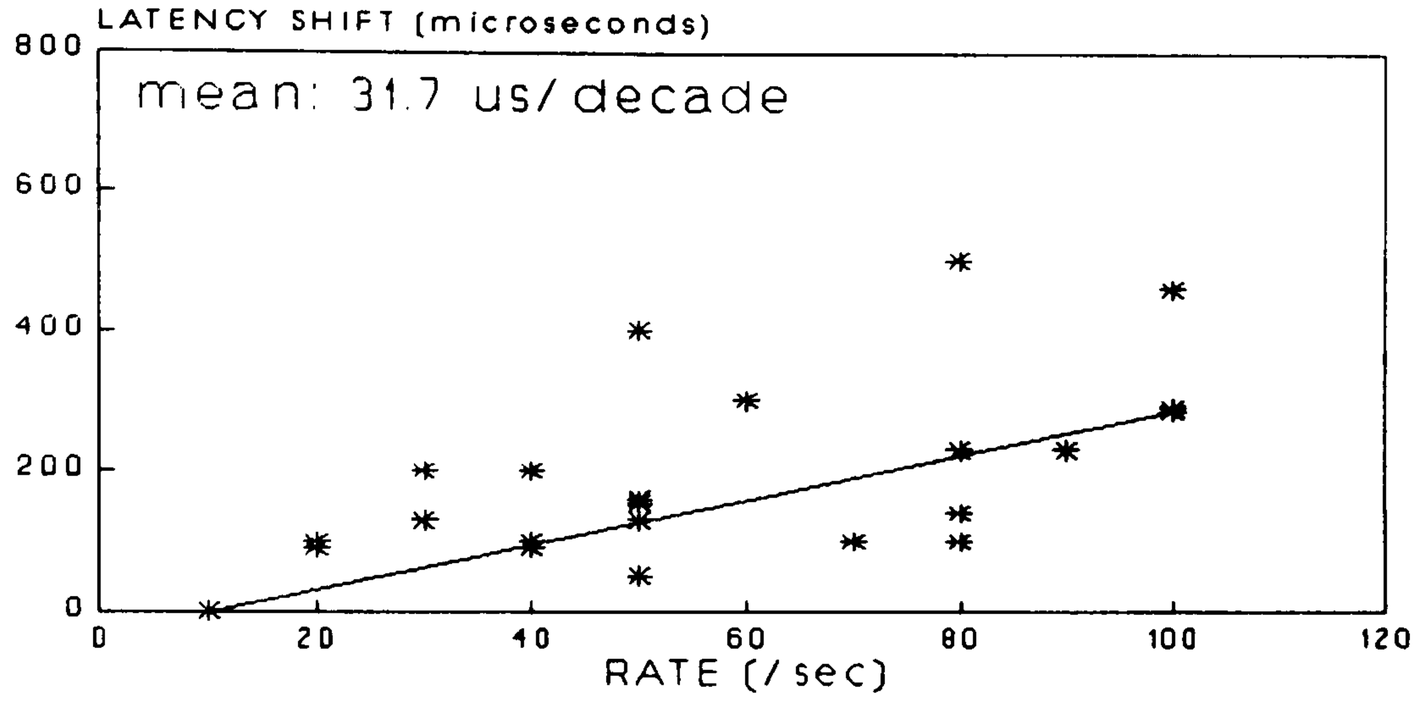
Data for Figure 1.3.2.1 originate from the following sources:

Authors	Fig.1.3.2.1 (a)	(b)	(c)
Chiappa *et al.* (1979)	+	+	+
Despland & Galambos (1980)			+
Don *et al.* (1977)			+
Fowler & Noffsinger (1983)	+	+	+
Fujikawa & Weber (1977)			+
Gerling & Finitzo-Hieber (1983)			+
Harkins *et al.* (1979)	+	+	+
Hecox *et al.* (1981)			+
Lasky (1984)	+	+	+
Mouney *et al.* (1978)	+		
Paludetti *et al.* (1983)	+	+	+
Picton *et al.* (1981)	+	+	+
Sand & Sulg (1984)	+	+	+
Terkildsen *et al.* (1975)	+		+
Tietze & Gobsch (1980)	+	+	+
Yagi & Kaga (1979)	+	+	+

FIGURE 1.3.2.1
Latency Shift of ABR Peaks - Summary from the Literature

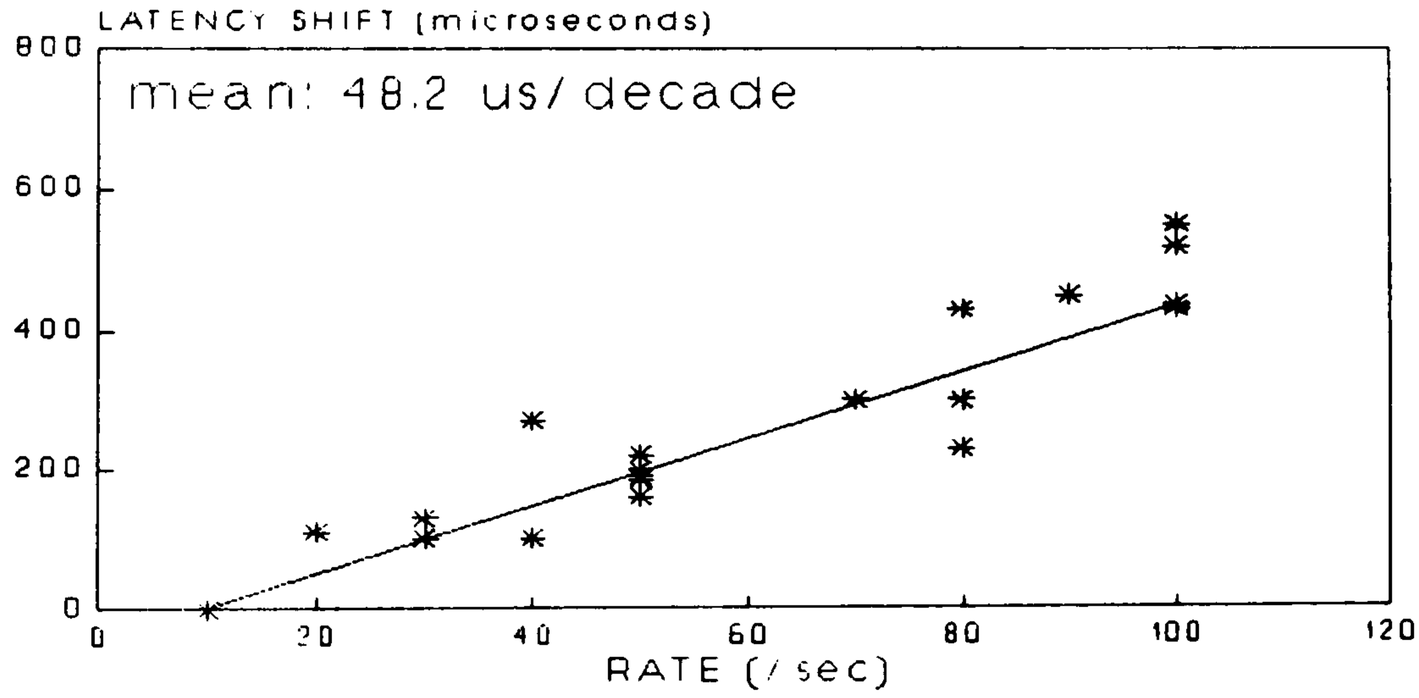
The magnitude of the latency shift was calculated using the lowest and highest rates quoted by each study and the mean value across studies was calculated for each wave. The mean is shown as the slope of the line in the figures below. The lines were artificially constrained to cross zero at 10/s since the majority of the studies used this as their lowest rate. The lines are therefore not regression lines.

WAVE I



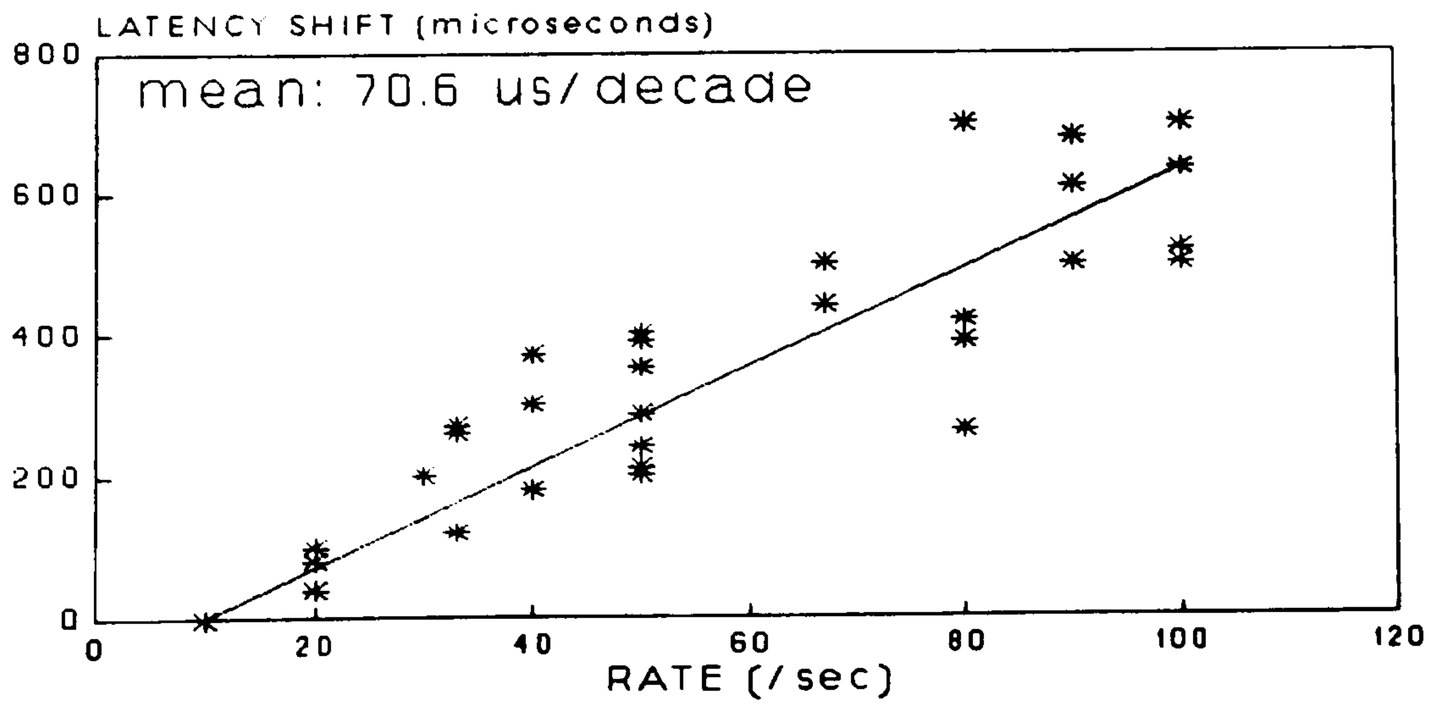
(a)

WAVE III



(b)

WAVE V



(c)

There is reasonably good agreement between studies considering the inevitable differences in test conditions. The data of Paludetti *et al.* (1983), Harkins *et al.* (1979), Tietze & Gobsch (1980), Fujikawa & Weber (1977), Don *et al.* (1977) and Lasky (1984) support the notion that the relationship between latency prolongation and SRR is approximately linear and that the slope of the function for a given wave can be expressed in terms of a given latency increase for every 10/s increase in SRR. The unit used to describe this is rather clumsy and the term "μs/decade" has been adopted by some. Although "decade" in engineering and physics represents a ten-fold (X10) change, there seems little point in introducing yet another term and so "μs/decade" will be used for simplicity in the rest of the text.

For the studies shown in Figure 1.3.2.1, the magnitude of this parameter was calculated using the lowest and highest rates quoted. For Wave I the mean value was 31.7 (SD=16.5) μs/decade; for Wave III the value was 48.2 (SD= 8.5) μs/decade and for Wave V the value was 70.6 (SD=21.4) μs/decade. Lines having these slopes are shown in the Figure for comparison. The lines were artificially constrained to cross zero at 10/s since the majority of the studies used this as their lowest rate. It is apparent that in absolute terms, the latency shift is greater for successive ABR waves. As a percentage of the latency of each wave, however, the latency shift is greatest for wave I, with the percentage shifts for waves III & V being less, and approximately equal.

For measures of latency shift with SRR to have an clinical utility, both the mean and *range* for normal values needs to be established. For Wave V ,

Musiek & Gollegly (1985) quoted a formula of 100μs/decade, plus a variance factor of 0.2 ms. Hecox (1980) uses 60μs/decade plus 0.4ms to define the upper limit of normality, whereas Gerling & Finitzo-Hieber (1983), using rates of 20/s and 90/s, deduced an upper limit of 1.04ms for Wave V latency shift based upon a mean (0.61ms) plus three Standard Deviations (0.14ms).

In a comprehensive analysis, Lasky (1984) found that at 70dBnHL, a linear relationship for Wave V latency in adults versus SRR was best described by the function : 5.7ms (SD=0.2ms) plus 86μs (SD=32μs)/decade. Similar functions were derived for Waves I and III, but these fitted the data less precisely.

1.3.2.2 *Inter-peak Latencies*

The clear differences between the susceptibility of Waves I,III and V to latency prolongation with increasing SRR indicates that there is an effect of increasing SRR on the inter-peak latencies (IPL): I-III, III-V and I-V. The effects of SRR on IPLs (particularly the I-V interval) has been the subject of a number of studies.

The following table compares the results of some studies of the rate effect on IPL expressed here in the form of IPL change in μs/decade.

TABLE 1.3.2.2

Rate Effects on Inter-Peak Latencies

Study	I-III (ms)	III-V (ms)	I-V (ms)	Polarity	SRR Range (/s)	Intensity (dBHL)
(a)			37.5	Alt	10-50	75
(b)			64	Rar	10-80	70
(c)	33.3	16.6	50	Rar	10-70	60
(d)	33.3	16.7	50	?	10-70	60
(e)	17.5	8.7	29	Rar+Con	10-50	50
Mean	28.0	14.0	46.1			

Key to Studies:

(a) : Pratt *et al.* (1981)

(b) : Stockard *et al.* (1979)

(c) : Stockard *et al.* (1978)

(d) : Chiappa *et al.* (1979)

(e) : Sand & Sulg (1984)

Whilst there are some quite large differences in these data across studies, a general trend is apparent. The III-V IPL exhibits the least rate dependency and the I-V the most. There is one apparent outlier however. Study (e) (Sand & Sulg, 1984) show smaller IPL/SRR effects than the other studies. Two aspects of their study are noteworthy: their rarefaction data is in close agreement with the other studies whereas their condensation results suggest

very little IPL/SRR effect, and the intensity they used is the lowest of the five studies being compared, perhaps revealing an intensity interaction.

1.3.2.3 *The effects of stimulus polarity on latency*

The variation in the IPL data may be in part attributable to some non-linearity in the IPL shift/SRR function, since the studies use differing upper SRR values, perhaps making the use of the "μs/decade" unit somewhat erroneous. Subject variables may also be a factor. A more promising explanation, however, concerns the interaction of stimulus polarity (phase) on the latency and IPL shifts with SRR.

Both Stockard *et al.* (1979) and Sand & Sulg (1984) examined the effects of polarity on SRR-induced latency shift and their conclusions were in complete agreement. Whilst condensation and rarefaction polarities appear to produce the same degree of SRR/latency shift effect for Wave V, the effect of stimulus polarity on Wave I is pronounced. There seems to be very little Wave I latency shift with SRR for rarefaction stimuli but a large shift was observed for condensation stimuli. This effect was so marked that Stockard *et al.* (1979) reported that Wave I at high stimulus rates is often indistinct with alternating (or summed rarefaction and condensation) polarity stimuli due to a cancellation of the components. The rather high value of 64μs/decade SRR change for the I-V IPL, as measured by Stockard *et al.* (1979), may be explained by their use of rarefaction stimuli only. It is unfortunate that typically half of the publications on rate effects omit to

identify the polarity of stimuli employed. Comparison of the data between those studies quoting stimulus polarities failed to reveal any significant polarity effect for rate-related latency changes in Waves III and V.

1.3.2.4 *The effect of stimulus intensity on latency.*

This has received less attention than other variables, particularly regarding the early ABR waves which cannot be readily identified at the lower stimulus intensities. However, for Wave V in normal adults Thornton & Coleman (1975), Gerling & Finitzo-Hieber (1983), Paludetti *et al.* (1983), Stockard *et al.* (1979). Don *et al.* (1977) and Zollner *et al.* (1976) all agree that the SRR effects on latency shift are independent of stimulus intensity over a convincingly large range of intensities and rates. One notable exception is the work of Tietze & Gobsch (1980) in which trains of four clicks (the inter-click rate being 80/s) were used to study latency changes within a click train. No statistical treatment was applied, but by inspection of their graphical data, the latency prolongation of Wave V to the fourth click compared to the first within a click train, shows a tendency to greater latency shift at lower intensities.

The picture appears different for Wave I, where the data of Stockard *et al.* (1979) and Zollner *et al.* (1976) suggest that SRR-related changes in Wave I latency are greater as stimulus intensity is reduced. As noted earlier in section 1.3.2.2, Sand & Sulg (1984) used a relatively low intensity and obtained different results from other studies of IPL/SRR effect, perhaps

suggesting an intensity interaction. Inspection of Thornton & Coleman's (1975) data suggests the opposite effect, however, and since none of these studies applied statistical analyses to this relation, it would be dangerous to draw any conclusions regarding the effect of stimulus intensity on rate-related changes in Wave I latency.

1.3.2.5 *The effects of age on latency*

The effect of subject age on the ABR latency/SRR interactions has been studied and found to have a strong influence, particularly at the extremes of the age spectrum. In developmental studies, Lasky (1984) and Despland & Galambos (1980) observed pronounced maturational effects of Wave V latency versus SRR in the pre-term and term neonate. Again, using the slope of the function in terms of μs/decade increase in stimulus rate, 32-week gestation neonates had values of 300 and 190 as measured by the above studies respectively. Full-term (40 week) neonates had values of 162 and 110, with adult values quoted at 86 and 35-40 for the two studies. Neither study reported the polarity of the click stimulus in use. Lasky (1984) also observed similar maturational changes for Waves I and III although, unlike Wave V, the earlier waves were close to complete maturity by 40 weeks gestational age.

Using alternating clicks, Picton *et al.* (1981) compared Wave V latency shifts with increasing SRR (from 10/s to 80/s) in newborns and adults and found an increase of 0.8ms (114μs/decade) and 0.4ms (57μs/decade) in the

two groups. In a similar study Hecox *et al.* (1981) identified values of 137μs/decade and 62.5μs/decade in neonates and adults respectively. Similarly, Fujikawa & Weber (1977) compared 7-8 week old infants with adults. Values of 149μs/decade and 83μs/decade were observed when rates of 10/s and 67/s were used. However, no difference between the two age groups was apparent at rates at or below 50/s.

Stockard *et al.* (1978), using rarefaction click stimuli, observed that the rate-dependent increase in IPL was greater in newborn infants than in adults. In children as old as 8-13 years, Pratt *et al.* (1981) noted that the I-V IPL rate-related changes are still greater than in adults (62.5 compared to 37.5 μs/decade), although no difference was apparent in the changes in the absolute Wave V latency by this age. No effect of subject sex on rate/latency interaction was noted in either children or adults.

Turning to the other end of the age spectrum, Fujikawa & Weber (1977) also investigated geriatric subjects (age range 69-81 years) and found them to have even greater Wave V latency shift functions than the neonates in their study. Unlike neonates, however, the elderly had rate/latency functions which departed from the young adult data at rates as low as 33/s (at this rate, the elderly adult function was 3.5 times that of the young adult value). Another study by Shanon *et al.* (1981) using alternating clicks compared the brainstem conduction time (unusually defined as the I-Vn interval) of young adults and the elderly (70-91 years) with rates of 10/s and 50/s. The shift in this value with rate was 0.31ms in the elderly compared

to 0.13ms in the young adults.

1.3.2.6 *Absolute amplitude.*

The amplitude of ABR Wave I (equivalent to the NI response recorded by electrocochleography at higher intensities) is well known to be highly susceptible to adaptation at even modest stimulus rates. In changing the SRR in normal adults from 10/s to 20/s, Mouney *et al.* (1978), Pratt & Sohmer (1976) and Zollner *et al.* (1976) recorded mean amplitude reductions of about 10%, 25% and 38% respectively (from their graphical data). The reduction in Wave I amplitude from 10/s to 50/s has been measured as 39%, 44% and 40-50% by Lasky (1984), Scott & Harkins (1978) and Hyde *et al.* (1976).

The amplitude adaptation of Wave III is somewhat less than that of Wave I. Scott & Harkins (1978), Hyde *et al.* (1976) and Robinson & Rudge (1977) recorded amplitude reductions of 25%, 30% and 38% respectively as the rate was changed from 10/s to 50/s.

Unlike Waves I and III which exhibit an orderly reduction in amplitude for increasing rate, Wave V is characterised by a maximum amplitude at a rate of around 40/s (Galambos *et al.* (1981), Scott & Harkins (1978), Pratt & Sohmer (1976) and Paludetti *et al.* (1983)) although some studies indicate that changes in Wave V amplitude do not reach statistical significance over a wide range of SRRs (Scott & Harkins (1978), Paludetti *et al.* (1983),

Zollner *et al.* (1976), Sand & Sulg (1984)), probably because of the large variability of this measure.

1.3.2.7 *The I/V amplitude ratio*

Because of the large inter-subject variability of the ABR amplitudes, the I/V amplitude ratio has been suggested as a diagnostic criterion, since it has less variability (See, for example, Stockard *et al.* (1978)). The effect of SRR on the I/V ratio has been studied. At 10, 30 and 70/s, Chiappa *et al.* (1979) obtained mean (and standard deviation - probably calculated inappropriately since the I/V ratio is not normally distributed) values of 73% (48%), 41% (23%) and 40% (31%) respectively at 60dBSL in normal adults. Sand & Sulg (1984), using 75dBSPL clicks, also noted a reduction of the I/V amplitude ratio as SRR was increased from 10/s to 50/s and observed that this reduction was significantly greater for condensation clicks than for rarefaction clicks.

1.3.2.8 *The effect of intensity on amplitude.*

This subject has received very little attention, but a perusal of the literature seems to suggest that there is little or no significant effect of intensity on rate-related amplitude changes in the ABR. One possible exception is that of Zollner *et al.* (1976), whose graphical data on Wave III would suggest a slight tendency to disproportionately greater amplitudes at high intensities as the SRR is reduced from 10/s to 5/s. The effect may

also be present for Wave I but to a lesser extent. In their adaptation study, Thornton & Coleman (1975) showed a greater degree of adaptation as intensity was reduced from 80dBSL to 60dBSL, a finding they attributed to the differential employment of the high and low threshold systems within the cochlea.

1.3.2.9 *The effect of age on amplitude.*

Only one paper could be found which investigated this. In comparing pre-term and term neonates with adults, Lasky (1984) was unable to draw any significant conclusions regarding developmental effects on the rate/amplitude function, mainly because of the large measurement variability.

1.3.2.10 *The time-course of the rate adaptation process.*

It is clear that the latencies of the ABR waves undergo an increase in normal subjects as the SRR is increased. In an effort to determine how rapidly these changes occur, three studies investigated the time-course of the Wave V latency change from the onset of the first stimulus in experiments which employed trains of stimuli. The experimental design of these experiments was such that the stimulus rate within a train was high and silent intervals between the trains were presumably long enough to allow complete recovery of the response mechanism prior to the onset of the next stimulus train.

Thornton & Coleman (1975) used trains of four clicks at a rate of 66.7/s with an inter-train interval of 90ms at 60,70 and 80dBSL. Tietze & Gobsch (1980) used trains of eight 4kHz tone pips at rates of 40/s and 80/s with an inter-train interval of 200ms at 20,40,60 and 80dBSL. Don *et al.* (1977) used trains of 20 clicks at a rate of 100/s with an inter-train interval of 500ms at 40dBSL. These three studies agreed to the extent that the SRR-induced latency prolongation of Wave V is complete (i.e., reaches the steady-state value) by the third to fifth stimulus. Thornton & Coleman (1975) showed that the amplitude adaptation process follows a similar time course to that for latency.

Tietze & Gobsch (1980) extended their study to include the earlier ABR waves which exhibited a similar time-course to that of Wave V. Whilst the three studies agree on the time-course for the onset of the latency prolongation process, it is interesting to note the considerable differences between investigators concerning the length of the silent inter-train interval deemed sufficiently long to ensure complete recovery. Since this recovery or "release time" is unknown, Don *et al.* (1977) compared the latencies of Wave V due to the first and last stimuli in the train to those produced at 10/s and 100/s and found them to be identical, suggesting their 500ms silent interval was more than adequate to ensure complete recovery. Tietze & Gobsch (1980) undertook a similar process (presumably to validate their 200ms inter-train interval) but, although their stimulus train study suggested complete latency prolongation after the fourth stimulus, continuous

stimulation resulted in greater latency shifts. This not only suggests that their 200ms silent interval was sufficiently long to allow complete recovery, but that the latency prolongation process was not, in fact, complete by the fourth stimulus. No explanation was given to this rather contradictory finding.

When these conclusions are applied to the context of the normal continuous averaging using 1000 or more stimuli, any effect of a blurring of the response due to an initially unadapted or unfatigued system is therefore insignificant.

1.3.2.11 *Summary of rate effects in the normal population.*

The reviewed literature reveals the following trends:

(i) Increasing SRR results in extended latencies of all ABR waves.

(ii) The earliest waves are extended the least, the latest waves the most (in terms of absolute, not % latency shift where wave I is extended the most).

(iii) Inter-peak latencies are correspondingly extended by increasing SRR.

(iv) The latency prolongation seems approximately linear with increasing SRR, especially for Wave V.

(v) Stimulus polarity has an effect on the Wave I latency/rate function but does not affect waves III or V.

(vi) Subject age has a strong influence on the SRR/latency relationship, especially in immature neonates and probably in the elderly.

(vii) There appears to be no unanimous link between intensity and SRR/latency prolongation or SRR/amplitude diminution.

(viii) For Waves I and III the latency prolongation is associated with a diminution of amplitude.

(ix) Wave V amplitude is largely unaffected by SRR.

(x) The I/V amplitude ratio is reduced by increasing SRR.

(xi) The latency and amplitude adaptation process is rapid, occurring by the third to fifth click after onset of a high rate click train.

The above points are valuable for setting the scene, but before the aims outlined in Section 1.2 can be addressed, pathological populations need to be considered.

1.3.3 Stimulus rate effects in pathological populations

1.3.3.1 *Cochlear pathology*

Whilst considerable attention has been paid to the effects of SRR on the ABR of normally hearing subjects, few investigators have sought to identify any dependence of these measures on the extent of hearing loss by including patients with known hearing losses of cochlear origin in their studies. Nevertheless, several reports (see below) have attempted to use rate-related ABR changes to aid the identification of patients with retrocochlear pathologies, many of whom also had a cochlear hearing loss. The work of Coats & Martin (1977) has clearly shown that cochlear dysfunction can result in a shortened I-V IPL. It is therefore unwise to assume that reference data obtained from normally hearing subjects can be applied with validity or optimum precision to patients with hearing loss.

In addition to their 48 normal adult controls, Gerling & Finitzo-Hieber (1983) studied 221 patients, 90 of whom had impaired hearing. When evaluating the Wave V latency shift caused by increasing the SRR from 20/s to 90/s, they identified no significant difference in the control and normally hearing patient distributions. However, the distributions of the hearing impaired and normally hearing patient groups were statistically different ($p < 0.001$) with the hearing impaired group tending to yield less Wave V latency shift with increasing SRR. Like Coats & Martin (1977), they therefore conclude that the use of normal control reference data is likely

to lead to a higher false negative error for the identification of retrocochlear dysfunction than if the effect of hearing loss were accounted for.

Conversely, Campbell & Abbas (1987) studied 20 patients with asymmetric cochlear function and could find no significant correlation ($p>.05$) between wave V latency shift (due to increasing the SRR from 9.7 to 59.7/s) and extent of hearing loss at either 2kHz or 4kHz. Stimulus intensity (85dBnHL and 105dBnHL) also had no effect on wave V latency shift in cochlear-impaired subjects.

Fowler & Noffsinger (1983) also studied normal, cochlear impaired and retrocochlear impaired subjects, but concluded that the cochlear group exhibited no significantly different rate/latency shift behaviour from the normal controls. However, their analysis did not compare the Wave V latency shift at the two rates employed (10/s and 50/s) but rather grouped the absolute Wave V latencies for each group for each rate. It is interesting to speculate whether the two groups would remain indistinguishable had the analysis compared intra-subject rate-related latency shifts.

Both Fujikawa & Weber (1977) and Shanon *et al.* (1981) identified "abnormal" ABR rate effects in elderly but otherwise normal subjects and attributed this finding to impaired neural function in this population. The effects of presbyacusis were not considered in their conclusions.

1.3.3.2 *Acoustic Neuroma.*

Given the interest in the use of ABR techniques to identify patients with acoustic neuromas, there are surprisingly few reports of the use of high stimulus rates in this group. In establishing normal data and evaluating 50 patients with a variety of retrocochlear abnormalities, Pratt *et al.* (1981) included inter-peak latency shifts due to increasing the stimulus rate from 10/s to 50/s. They concluded that rate effect studies do not enhance the detection of acoustic neuromas, unlike other retrocochlear lesions. Examination of their patients' case histories led them to conclude that abnormal rate effect results may be restricted to patients with impaired synaptic function.

Paludetti *et al.* (1983) presented one case of a patient with a confirmed acoustic neuroma. ABR tests at 10/s on the tumour side yielded an abnormal I-V interval. At 100/s Wave V disappeared.

In evaluating the use of the inter-aural wave V latency difference in the detection of acoustic neuromas, Thomsen *et al.* (1978) stated without justification that it was "advisable to use fast stimulus repetition rates".

Josey (1985) noted that in 18 consecutive cases, ears with acoustic tumours having wave V intact, 13 (72%) demonstrated an abnormal rate pattern using clicks at rates of 13.1, 33.1 and 63.1/s although the criterion for abnormal wave V latency shift was not given.

In discussing the utility of varying SRR, Musiek & Gollegly (1985) concluded "Those using ABR must await a major study on repetition rate and VIIIth nerve lesions to provide more definitive evidence for its use".

Since then, Campbell & Abbas (1987) have reported their study of 20 patients with asymmetrical cochlear hearing loss and 8 patients with acoustic neuromas. Using alternating polarity clicks at 85 or 105dBnHL at rates of 9.7, 39.7, 49.7 and 59.7/s, they observed significant differences in the wave V latency shift between the two groups ($p<.05$) between the slowest and two fastest rates, but not between 9.7 and 39.7/s. However, there was considerable overlap of results between subject groups and they concluded that the wave V latency shift method is poorer than conventional, low rate ABR measures such as ILDV. They considered that the optimum criterion for wave V latency shift with rate was the mean plus only one standard deviation and this yielded a sensitivity of 86% (but with an obviously poor specificity). Their study also concluded that using the amount of wave V latency shift in the better ear as a control did not enhance the performance of the test. They could establish no significant correlation between wave V shift and either stimulus intensity or hearing loss at 2kHz or 4kHz, in either cochlear or neuroma groups. Similarly, the incidence of wave V disappearing at higher rates (when present at 9.7/s) was similar in both groups and measures of wave V amplitude change with SRR also failed to differentiate the groups.

1.3.3.3 *Multiple Sclerosis.*

Unlike many neurological disorders, ABR test results on MS patients are not characterised by a restricted range of abnormal findings. In MS the findings may include abnormality of symmetry, latency delay, fragmented response, decreased amplitude or absence of peaks, poor test/retest repeatability, abnormal rate effects or abnormal latency-intensity function (Keith & Jacobson (1985)).

Probably the most well-known research on adaptation effects on MS is the early work of Robinson & Rudge (1977). Rather than varying SRR, they used 20/s single clicks or pairs of click stimuli, 5ms apart and looked for abnormalities in the amplitude and latency of Wave V evoked by the single click or by the *first* of the pairs of clicks. Using standard single clicks, they found that 76% of MS patients with evidence of a brainstem lesion exhibited an abnormal Wave V latency/amplitude characteristic. Of those who had a normal latency but reduced amplitude Wave V to single clicks, 57% developed an abnormal Wave V latency when using pairs of clicks. In their analysis they concluded that at 20/s, pairs of clicks stressed the auditory system and in MS patients increased the proportion of abnormalities detected.

Using a similar stimulation paradigm, Mogensen & Kristensen (1979) were unable to measure any advantage in double clicks over single clicks although they preferred the former because they found that double clicks provide a

better separation of Waves IV and V.

The effect on Wave V latency of increasing SRR in MS patients has also been studied. Fowler & Noffsinger (1983) tested six MS patients and in one recorded a normal Wave V latency at 10/s which extended to beyond normal limits at 50/s. Similarly, Paludetti *et al.* (1983) recorded a normal ABR at 10/s in an MS patient. However, the 10/s - 100/s latency shift of Wave V was abnormally prolonged bilaterally.

Antonelli *et al* (1986) tested 39 MS patients (16 of which were graded as definite MS) using conventional and various experimental ABR paradigms, one of which was to increase SRR from their standard 11/s to 51 and 81/s, using 70dBnHL alternating polarity clicks. They regarded a result as positive (ie abnormal) if there were "waveform and/or latency changes concerning wave III and/or wave V at 51/s" (presumably re 11/s). They did not specify their criteria for such changes, however. This technique yielded a sensitivity of 62.5% and a specificity of 93.7%. Eleven of their MS patients gave normal ABR results at 11/s but two of these had abnormalities appearing at higher SRRs. When MS patients were grouped according to the presence or absence of current neurological (brainstem) signs, SRR results were different in the two groups ($p<.01$), suggesting that the technique is poor in identifying sub-clinical MS.

Abnormal changes in the brainstem conduction time with increasing SRR have been identified in MS patients. Jacobson (1983) reported an abnormal

I-V IPL in 52.5% of 20 patients at a stimulus rate of 10/s. At rates of 67/s and 80/s abnormal IPLs were present in 65% of patients. Two studies used rates of 10/s, 50/s and 80/s, in which the I-Vn IPL was measured in MS patients. Shanon *et al.* (1981) compared their patients to young normal adults and elderly normal adults and found that both the MS group (mean age 32 years) and the elderly group (mean age 74 years) produced significantly longer IPLs to their young group (32 years). Conversely, Elidan *et al.* (1982) found that in a group of 51 MS patients, changes in SRR did not identify ABR abnormalities not already apparent at 10/s, although abnormalities were sometimes accentuated at the higher rates. Likewise, Chiappa (1980) found that increasing SRR from 10/s to 70/s did not assist in the identification of abnormality using a three standard deviation criterion.

Stockard & Rossiter (1977) noted that increasing the stimulus rate to 25 or 30/s appeared to enhance the sensitivity of the ABR tests, eliciting otherwise absent abnormalities.

Finally, Keith & Jacobson (1985) demonstrated that the response variability often associated in MS patients can be exacerbated by the use of higher stimulus rates.

1.3.3.4 *Other neurological pathologies*

Spasmodic dysphonia is a disease of unknown aetiology and variable symptomology affecting the nervous system. Schaefer *et al.* (1983) studied 12 patients with this disease using ABR methods and measured the I-V IPL, the I/V amplitude ratio and Wave V latency shift due to increasing the SRR from 20/s to 90/s. Their criteria for abnormality for these three parameters were >4.6ms, >2.0 and >1.04ms respectively. Nine patients (75%) were judged to have an abnormal ABR. Only three of these had an abnormal I-V IPL, none had an abnormal I/V ratio, but seven had a pathologically extended Wave V latency shift.

Hecox *et al.* (1981) also included Wave V latency shift measurements (using rates of 10/s, 30/s, 50/s and 90/s) in their ABR analysis of neonatal patients with a variety of neurological pathologies. In two premature babies with suspected intraventricular haemorrhage, clearly identifiable ABR waveforms were recorded at a rate of 10/s, but at 50/s no response could be seen. The babies died. A 6-year old patient with peripheral neuropathy had abnormal IPLs and a 1.00ms Wave V latency shift (10/s - 90/s). Other cases were presented where abnormal IPLs were accompanied by normal Wave V latency shifts with increasing SRR.

In changing the SRR from 20/s to 90/s, Gerling & Finitzo-Hieber (1983) identified 16 normally hearing patients with abnormal Wave V latency shifts (>1.04ms). Of these, nine were children with significant neurological

findings (spasticity, seizures and psychomotor retardation) in which the abnormal Wave V latency shift was the only test parameter indicative of brainstem involvement. They concluded with the recommendation that routine testing of all patients include a low and a high stimulus rate to aid in documenting intracranial pathology.

In addition to recording abnormally great Wave V latency at a rate of 50/s (compared to 10/s) in one patient with multiple sclerosis, Fowler & Noffsinger (1983) recorded a similarly abnormal result in a patient with an 8cm calcified intra-axial brainstem tumour. One of their conclusions was that a stimulus rate of 50/s as opposed to that of 10/s increases both the hit rate and the false positive rate in the identification of VIIIth nerve and brainstem lesions.

Despland & Galambos (1980) included high SRRs in their ABR analysis of neonates with known neurological problems and showed an example where a high rate (70/s) made ABR waveform abnormalities, including Wave V amplitude, more evident.

Finally, Yagi & Kaga (1979) presented one case in support of their application of stimulus rate tests in neurological diagnosis. The patient had a large tumour occupying the IVth ventricle which displaced the cerebellum laterally. Using rates of 10/s, 30/s and 90/s, they observed that the later ABR waves disappeared as the stimulus rate was increased.

1.3.3.5 *Summary of rate effects in pathological populations*

(i) There is disagreement whether SRR induced Wave V latency shifts are influenced by the effects of the cochlear pathology.

(ii) Rate effect measures on the Wave V latency shift, I-V IPL, I/V amplitude ratio and on waveform morphology appear to provide similar diagnostic information in identifying retrocochlear pathologies of various aetiologies.

(iii) In retrocochlear pathologies, rate effect abnormalities may be present with other abnormal ABR findings, although in some cases they are the only abnormality and in others the rate results are normal where conventional ABR results are abnormal. This might suggest subtly different pathophysiological mechanisms affecting the conventional fixed rate and variable rate ABR test results.

(iv) As with all other ABR test parameters, rate effect parameters have accuracy limitations, with finite false positive and negative findings.

(v) There seems to be no clear consensus regarding how best to utilise the diagnostic utility of SRR ABR effects. Probably the most common and, in terms of normal reference data the most valuable, is the Wave V latency shift.

These conclusions may be used as landmarks when planning the best way of addressing the broad aims of the study outlined in Section 1.2.

1.3.4 The mechanism responsible for rate-induced ABR changes in normal and abnormal populations

Many of the studies reviewed have referred to stimulus rate effects in terms of an increasing stimulus stress, capable of revealing or exacerbating the limitations of the auditory brainstem pathways for both normal and pathological subjects. There are a number of possible factors which might explain the observed changes in amplitude and latency of the ABR waves. With increasing stimulus rate, these include a lengthening of the neural refractory period, a decrease in the firing rate of nerve fibres, a decrease in the number of participating fibres, a reduction in the nerve conduction velocity, a reduction in the synchrony of the fibres or an increased synaptic delay. Many of these are, of course, interrelated.

In the normal adult, Don *et al.* (1977) observed that the neural refractory period is too rapid (1-2ms) to be the responsible mechanism and Thornton & Coleman (1975) concluded that for Wave I the effects are explained by a decrease in the firing rate, rather than a decrease in the number of participating fibres, whereas for Waves III and V, the opposite mechanism is at play (two mechanisms suggested by Sorensen, 1959).

ABR abnormalities associated with incomplete or abnormal myelination may be due to increased refractory period or reduced conduction velocity (Keith & Jacobson (1985)), although Zollner *et al.* (1976) was more cautious in explaining the reason for the observed effect in patients with multiple sclerosis. The abnormal ABR/SRR findings of Fujikawa & Weber (1977) in geriatric subjects was

attributed to a reduced number of nerve fibres (lower cell count) in that population.

Space-occupying lesions of the cerebro-pontine angle can cause pathophysiological changes by stretching or compressing the auditory nerve and cause a slowing of the conduction velocity (Musiek & Gollegly (1985)) or by a desynchronisation of the firing rate of neurones, together with a possible selective action on high and low frequency fibres (Eggermont *et al.* (1980)). However, it is not clear from these reports how SRR interacts with these effects.

It would appear, therefore, that a single independent mechanism may not account for the effects of stimulus rate on the ABR in normal and various pathological states. Whatever the underlying causes, there are definite and predictable rate effects on the ABR of normal subjects and these effects are clearly magnified in a number of auditory nerve and brainstem pathologies.

1.4 AN OUTLINE OF THE STUDY

1.4.1 The promise of stimulus rate effects

Section 1.2 considered the popular conventional ABR measurements, their strengths and weaknesses. IPL measurements appear to be the method of choice, but frequently cannot be applied in the target population. ILDV measurement has greater coverage but requires compensation for the effects of hearing loss. Being a test of asymmetry, it requires a neurologically normal reference ear (with reasonable hearing) or at least for there to be an asymmetry of neurological dysfunction.

Stimulus repetition rate effects, perhaps in the guise of the Wave V latency shift, appear promising since only Wave V needs to be recordable. Reference ear results may not be required (although it is possible that precision could be maximised if they were considered) and, importantly, corrections for the extent of hearing loss may not be required. The additional ABR waveforms necessary, being at a high SRR, should not extend the overall test time by a large extent. Waveform analysis and result interpretation should be straightforward.

Test simplicity and applicability are therefore the anticipated advantages of SRR tests. Not only does this need to be substantiated but the sensitivity and specificity of the tests need to be quantified.

1.4.2 Specific questions to answer

The various possible means of quantifying the effects of SRR on the ABR will be examined in section 1.4.4. below. Putting aside these details for the moment, this section identifies the questions posed by this study on SRR effects. They are:

(i) Do SRR tests provide additional or complementary diagnostic information to other ABR tests in the detection of retrocochlear pathology?

(ii) What is the performance of SRR tests in terms of sensitivity and specificity, and in what circumstances are they applicable?

(iii) Do any corrections need to be made to account for factors such as age, sex, hearing loss, etc.?

(iv) Can the magnitude of an abnormal SRR test result be related to the type or severity of retrocochlear disorder?

(v) Can more be learnt about the temporal characteristics of SRR effects in order to identify the mechanism which produces them, and if so, are there different mechanisms at work in normal and abnormal populations?

The remaining sections in this chapter describe the strategic means by which these questions are addressed and the next chapter (Methods) details how they are implemented.

1.4.3 Subject groups

The details for candidacy for the following groups are given in Chapter 2: Methods. A total of 268 subjects were tested (135 males, 133 females).

1.4.3.1 *Group A: normal subjects*

Although the primary goal of this study is to examine the clinical utility of SRR effects tests in delineating between cochlear and retrocochlear disorders, the effects of cochlear dysfunction itself need to be quantified and to do this a reference group of true normals is required. Since age is also likely to affect the results, the normal group needs to span the age range of patients likely to be referred for otoneurological ABR tests, i.e. from young adulthood to eighty years. Thirty-six subjects (3 males and 3 females in each of six decade bands) were recruited into this group, mean age 49.0 years, age range: 19-78 years.

Presbyacusis, the deterioration of hearing with age, is a confounding problem in such a normal group. Rather than using a fixed audiometric criterion for candidacy of this group (and thus reject many older subjects who had normal hearing for their age), age-related criteria were adopted which rejected only those who were probably unrepresentative of their age group. Full details will be given in Section 2.3.1. The normal sample is therefore designed to reflect the normal population, and thus, for the older ages particularly, it is impossible to distinguish between the effects of age *per se* and those of

age related hearing loss.

Unlike all other subject groups, who are NHS patients referred for investigations as part of their diagnostic work-up, Group A comprises non-patient volunteers.

1.4.3.2 Group B: subjects with normal hearing but with tinnitus and/or vertigo

Both tinnitus and vertigo are often associated with hearing loss. To test whether either influence the test results of subjects who had tinnitus and/or vertigo, together with hearing loss or retrocochlear dysfunction, a separate group was formed. The same criteria for entry into Group A was applied to this group, except for the requirement to be free from tinnitus or vertigo.

Group B comprises 50 subjects (20 males, 30 females), mean age 45.5 years, age range: 19-81 years.

1.4.3.3 Group C: subjects with cochlear dysfunction

This group includes all subjects who had abnormal hearing for their age in one or both ears and in whom retrocochlear pathology was effectively excluded by ABR (but not rate effect) tests, conventional diagnostic audiometry and radiology. All forms of cochlear pathology are included. Group C comprises 135 subjects (73 males, 62 females), mean age 50 years, age range: 13-71 years.

1.4.3.4 *Group D: subjects with suspected but unconfirmed retrocochlear dysfunction*

Ideally, this group should not exist. It comprises subjects who failed the entry criteria for Group C, usually on audiological/ABR results, but who could not be definitely diagnosed as having a retrocochlear disorder. The reasons for this varied, but frequently comprised a negative CT Scan or IAM tomography result where the clinician or radiologist could not be persuaded to proceed to more definitive radiology or magnetic resonance imaging (MRI). Group D comprises 16 subjects (9 males, 7 females) mean age 51 years, age range: 34-66 years.

1.4.3.5 *Groups E and F: subjects with confirmed acoustic neuromata*

The presence of an acoustic neuroma was the only requirement for candidacy of these groups. The difference between Groups E and F relates to the ear on which more comprehensive tests were conducted and the main criterion for this was the extent of hearing loss in the tumour ear (see Chapter 2 : Methods). Groups E & F comprise 18 & 13 subjects respectively, (15 males, 16 females), mean age 52 years, age range: 29-78 years.

1.5.3.6 *Group G: subjects with multiple sclerosis*

Subjects with definite MS and current clinical signs of brainstem involvement were to be the entrants for this Group. However, despite arranging for suitable and willing subjects to be referred by the neurologists at the Region's Centre for Medical and Surgical Neurology, none was obtained and so unfortunately this group had to be abandoned.

1.4.4 Assignment of "test" and "reference" ears

In a clinical setting most otoneurological ABR tests are conducted on patients having unilateral or asymmetrical signs or symptoms and although tests should be conducted on both ears, attention is usually focused on the poorer, or "suspect" ear.

The tests employed in this study are quite time-consuming and so the full range of ABR tests was conducted on one ear only: the "test ear". The other ear, the "reference ear", received only abbreviated tests. In Group A, by definition, no one ear was suspect, and so assignments of test and reference ears were made by tossing a coin. In Group B the assignment of the test ear was made according to the side of tinnitus, aural pressure or the side to which the subject tended to veer when dizzy. When the subject's symptoms were symmetrical, a coin was tossed. In all other groups, assignment of test ear was straightforward and almost always corresponded to the ear with the poorer pure tone thresholds.

1.4.5 Forms of rate effect and adaptation to be investigated

There are a number of ways in which adaptation of the ABR to rapidly repeated stimuli can be investigated, as is apparent from the review of previous work in section 1.3. The variety of experimental paradigms used range from pairs of closely spaced clicks, through bursts (or trains) of a number of clicks followed by a recovery period, to continuous stimulation at a number of SRRs. Different aspects of the adaptation process are thus revealed, although the simplest and most commonly used procedure is that of continuous stimulation, although this ignores any per-stimulatory changes in the ABR.

The test paradigms in this study were designed not only to provide data on the straightforward continuous stimulation rate effects, but also to give insights into the temporal characteristics of adaptation and recovery in periods ranging from milliseconds to several tens of seconds. The next chapter (Methods) gives full details of how this was done, but an outline is given here in order to explain the rationale.

Reference ear ABR tests were conducted first, and these comprised obtaining waveforms to clicks at rates of 11.1/s, 44.4/s and 88.8/s. This allowed conventional ABR results to be extracted from the 11.1/s waveform, together with the wave V latency shift from 11.1/s to 44.4/s and from 11.1/s to 88.8/s.

Test ear ABR tests followed, commencing with a conventional run at a rate of 11.1/s. Instead of conventional higher rate ABR tests (as on the reference ear),

a rather unconventional procedure was followed. Rates of 22.2/s, 44.4/s, 66.6/s and 88.8/s were employed. The choice of these rates allows the geometric 11.1 - 22.2 - 44.4 - 88.8 sequence to be analyzed. The inclusion of the 66.6/s was made to allow for linear steps of 22.2/s to be analyzed from 22.2/s to 88.8/s.

Instead of continuous stimulation and averaging for each of these rates, an automated procedure was designed in which any slow per-stimulatory changes in the ABR could be identified. This involved presentation of the stimulus and sequential averaging into a group of three memory blocks in the averaging computer, followed by a ten second stimulus-free recovery period. Repetitions of this sequence were made so that each memory block contained 1,000 averages, allowing latency measurements to be made with reasonable precision. The duration of averaging into each memory ranged from 9.0 seconds for rates of 22.2/s and 44.4/s to 4.5 seconds for rates of 66.6/s and 88.8/s. Latency differences between the first and third sequential waveform could be taken as evidence of slow per-stimulatory adaptation. Adaptation over such periods is known to exist for continuous pure tones and is often abnormally great in the presence of retrocochlear pathology, although such adaptation is reduced or abolished when interrupted or transient stimuli are used. Whether clicks presented at high rates constitute an interrupted or continuous stimulus is open to debate and this test paradigm was therefore designed to identify any such long range changes in normal, cochlear pathology and retrocochlear pathology populations. The equivalent of a "continuous" rate ABR series was obtained by summing all three ABR waveforms obtained for each rate on the basis that any such slow per-stimulatory changes at a given rate are likely to be small compared to the inter-

rate differences. Such an assumption is open to examination (for normal ears, at least) by comparing results of test and reference ear ABR tests in Group A.

The above test ear "rate series" was followed by a repeat of the initial 11.1/s test. The two 11.1/s waveforms were separated by at least 10 minutes of stimulation involved in the rate series and so very long time course changes could be identified.

The other end of the temporal spectrum was investigated on some subjects by deploying a test paradigm similar to that used by Thornton and Coleman (1975), Don *et al* (1977) and Tietze and Gobsch (1980). Trains of 8 clicks with an inter-stimulus interval of 11.3 milliseconds (chosen to be almost exactly equivalent to a rate of 88.8/s) were used with train repetition rates of either 3.1/s or 5.9/s (or both for subjects in Group A). The corresponding silent inter-train interval of these rates is 243.7 milliseconds and 90.7 milliseconds. The former is longer than that used by Tietze and Gobsch (1980) which was probably insufficient to allow complete recovery, and shorter than that used by Don *et al* (1977) which was more than sufficiently long. The latter silent inter-train interval not only corresponds to the inter-stimulus interval of a standard 11.1/s rate, but is also equivalent to that used by Thornton and Coleman (1975). By means of these "click train" tests, both the onset and recovery of the adaptation process can be investigated.

1.4.6 Conventional tests

As a precursor to entry to the study and subsequent ABR tests, pure tone audiometry, tympanometry and acoustic reflex threshold tests were performed. Additionally, acoustic reflex decay tests were performed where applicable (except for Group A subjects) and in most subjects an alternate binaural loudness balance (ABLB) test at 4kHz was undertaken (again, except for Group A subjects).

When conducted, the ABLB result was frequently used to allow the ABR tests to be conducted at intensities in the two ears corresponding to equal loudness (ie sensation level) at 4kHz. This forms part of a separate investigation into the efficiency of ILDV correction techniques, but is mentioned here in order to explain the rationale for the selection of ABR test intensities.

CHAPTER 2

METHOD

All subject groups underwent the same basic core investigations with further tests conditional upon group, test results or pathology. Data were recorded on a simple database (Lotus 1-2-3) and statistical analyses were performed using a proprietary statistics package (SPSS PC+ version 3.1) linked to a proprietary graphics package (Harvard Graphics) running on an IBM-AT compatible personal computer (Opus PC-V 286 with co-processor).

2.1 CORE INVESTIGATIONS

2.1.1 History

For the normal subjects (Group A) this comprised questions for the purposes of candidacy for the group. See Section 2.5.1 for details. These questions were presented in a consent form (see Appendix B) which the subject completed after first reading a description of the study and their completed form was reviewed by tester and subject immediately prior to testing.

For all other groups, a more general and thorough history was taken for diagnostic purposes. Any recent vertiginous episodes were graded as rotatory or non-rotatory

and their maximum duration categorized. Any tinnitus was categorized as being in the test ear only, reference ear only, either ear, simultaneous bilateral, or central. Tinnitus duration was also categorized. The duration categories for both vertigo and tinnitus were:-

0 = None

1 = <1 minute

2 = 1 to 5 minutes

3 = >5 to 60 minutes

4 = >1 hour to 1 day

5 = >1 day

2.1.2 Otoscopy

An otoscopic examination was performed prior to any testing, principally to ensure that the canals were not completely occluded by wax (if they were, the wax was removed) and to note any obvious abnormal features of the tympanic membrane. Normal subjects were required to be free from tympanic perforations or active middle ear disease.

2.1.3 Pure tone audiometry

Conventional manual pure tone audiometry was performed by BSA method A (British Society of Audiology, 1981), using masking where necessary (British Society of Audiology, 1986) on a Kamplex AC3 audiometer calibrated to BS2497 & BS6950 in a 10' x 11' IAC audiology cabin in which the maximum ambient noise

was 20 dBA.

2.1.4 Acoustic admittance tests

Standard tympanometry was performed (266Hz, Y) on all subjects (except those who clearly had a tympanic perforation) followed by measurement of the 1kHz ipsilateral acoustic reflex threshold (maximum available stimulus intensity: 110dBHL). These tests were conducted on a Grayson Stadler GSI 33 Instrument.

2.1.5 Auditory brainstem response tests

ABR tests were conducted with the subject in a comfortable fully-reclined chair housed in the test cabin used for pure tone audiometry. Both tester and equipment were sited outside the cabin with the subject under both visual (closed circuit TV) and auditory (intercom) surveillance. Instructions to the subject were to relax fully, paying particular attention to their neck, shoulder and jaw muscles. They were advised that they could sleep if desired and to tell the tester should any of the test signals become uncomfortably loud. No sedatives were administered. The electrode montage comprised four electrodes: at the subject's forehead (Fpz) as ground; vertex (Cz) as positive (non-inverting); and both mastoid processes (A1, A2) as references (inverting). A single recording channel (vertex and ipsilateral mastoid) was used in all ABR tests. Silver/silver chloride 9mm electrodes were used, attached with double-sided adhesive discs following skin preparation with cotton wool moistened with acetone. Inter-electrode impedances (at 20Hz) were reduced to less than 5kΩ (typically 3kΩ) and all pairs of electrodes

had impedances balanced to within 1kΩ in order to maximise rejection of common mode signals.

A Nicolet Pathfinder System was used with SM200 amplifiers and SM700 auditory stimulator, expanded memory, dual floppy discs and a 70MB hard disc. A fixed level of amplification was employed corresponding to an artefact rejection level of 49μV. Occasionally, in patients with persistently high levels of myogenic activity, the sensitivity (amplification) was halved (ie an artefact rejection threshold of 98μV) but this was done only as a last resort after repeated attempts to relax the subject. Analogue filter settings of 100Hz to 3kHz were employed (both 12dB per octave). The recording epoch was 15.36ms with 512 data points giving a cursor latency resolution of 0.03ms. The stimulus was presented at the start of the epoch (ie with no pre-stimulus analysis or post-stimulus delay).

Stimuli were 100μs unfiltered clicks delivered via 300Ω Telephonics TDH-39 earphones without noise-excluding mountings. Contralateral unfiltered wide-band noise was routinely delivered to the non-test ear at an effective masking level of 40dB below that of the stimulus, plus an amount corresponding to the average air-bone gap in the non-test ear at 1, 2 and 4 kHz, rounded to the nearest 10dB.

The stimulus intensity was frequently at a single level and 80dBnHL was the standard intensity, although a higher level was used if 80dBnHL yielded waveforms of poor morphology, indistinct or equivocal peaks or abnormal results. Whichever single intensity met the above criteria using an initial stimulus rate of 11.1/s, this intensity was used for that ear in the remainder of the tests. Data from only

one stimulus intensity per ear was used in the study although the intensities used in the two ears were often different because of hearing loss asymmetries.

Calibration of the click intensity was derived from a previous biological study using normally hearing volunteers to determine 0dBnHL. When measured on a B&K 4152 (NBS-9A) coupler and B&K 2209 sound level meter on "peak hold" setting, 80dBnHL equals 113dB peak SPL. The click intensity was objectively checked at regular intervals throughout the study and remained unchanged within the accuracy limits of the measuring equipment.

Special data acquisition and analysis programs were written in the Nicolet Pathfinder language MECOL, and listings of these appear in Appendix A.

The reference ear was tested first using clicks at 11.1/s with 1000 rarefaction clicks followed by 1000 condensation clicks. Repeat runs were performed at rates of 44.4/s and 88.8/s. This concluded the ABR tests on the reference ear.

More comprehensive ABR tests were then performed on the test ear. The aim again was to use a single intensity and 80dBnHL was tried, but higher intensities were used if 80dBnHL proved unsatisfactory (as above), or if the results of ABLB recruitment tests at 4kHz suggested that a higher intensity was more appropriate. Having decided on an intensity for the test ear, this level was used throughout the remainder of the ABR procedure. Following the 11.1/s ABR at the chosen intensity, a separate program was called which performed the following test sequence.

Test ear 22.2-88.8/s rate series

(a) Alternating polarity clicks at a rate of 22.2/s were introduced with the ABR resulting from the first 200 clicks being averaged into the first memory block.

(b) Without interrupting the stimulus a further 200 clicks (ie clicks 201 to 400) were averaged into the second memory block.

(c) Without interrupting the stimulus a further 200 clicks (ie clicks 401 to 600) were averaged into the third memory block.

(d) The stimulus was withdrawn (although contralateral masking continued) for a 10 second stimulus-free period.

(e) Steps (a) to (d) were repeated 4 times so that a total of 5 passes were made through the sequence resulting in a total of 1000 clicks being averaged into each memory block.

(f) Steps (a) to (e) were repeated with further groups of 3 memory blocks using stimulus rates of 44.4/s, 66.6/s and 88.8/s, there being a 10 second stimulus-free period between changes in stimulus rate.

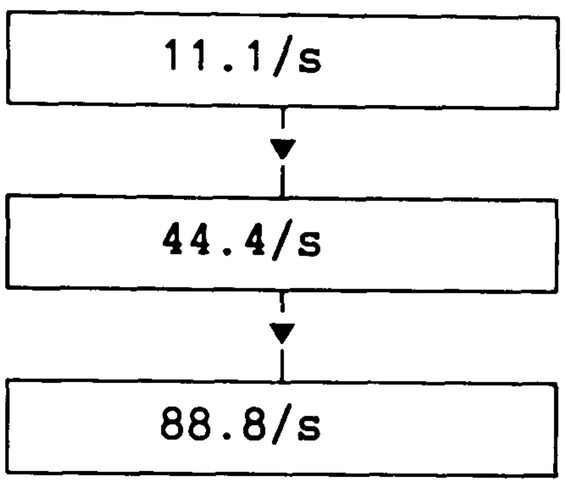
A repeat ABR at 11.1/s was finally performed in an identical fashion to the 11.1/s ABR performed prior to the 22.2 - 88.8/s rate series. The two test ear 11.1/s ABR runs were kept separate and designated as "start" and "end" respectively. All waveforms were stored to hard disc for off-line analysis for which a separate analysis program was written for the test ear results.

Figure 2.1.5 clarifies the sequence of core ABR tests on reference and test ears.

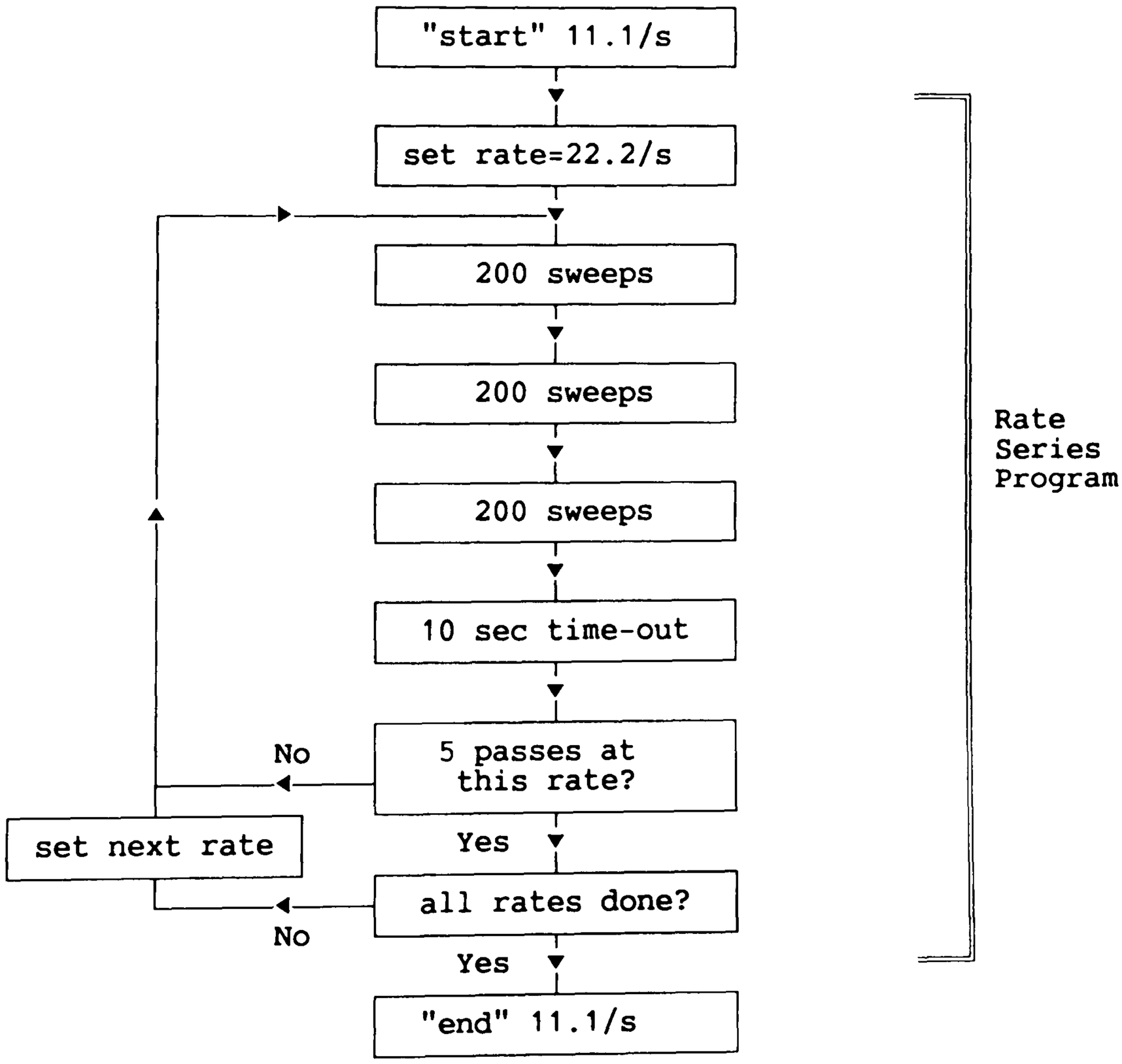
FIGURE 2.5.1

Core ABR test protocol - flow diagram

(i) Reference ear



(ii) Test ear



Notes on stimulus polarity and number of clicks delivered

All ABR tests at 11.1/s were conducted using 1000 rarefaction and 1000 condensation clicks, the waveforms being combined for measurement. Tests at 22.2 to 88.8/s used alternating clicks, the polarity of the first click in a sequence being randomised, with a total of 3 X 1000 clicks presented (plus any during artefact rejection) at each rate. For rates 22.2/s and 44.4/s this resulted in one click per epoch. However, for the rates 66.6/s and 88.8/s, using an epoch of 15.36 ms meant that every other click fell within the recording epoch associated with the preceding click and these were ignored by the averaging system sweep counter. So, for these rates, 400 rather than 200 clicks were presented to the subject for each memory block on each pass through the program in order to acquire the required 200 sweeps in each block.

This poses a potential problem regarding the use of alternating clicks, with a possibility of the resulting waveforms arising from a single stimulus polarity. However, the combined effects of randomisation of starting polarity on each pass through the loop of the program, together with "missed" epochs due to occasional artefact rejection during stimulation, served to effectively overcome this problem. Inspection of the magnitude and polarity of the stimulus artefact associated with individual memory blocks confirmed that approximately equal numbers of rarefaction and condensation clicks contributed to the averaged waveforms.

2.2 CONDITIONAL INVESTIGATIONS

2.2.1 Click train tests

Certain subjects additionally underwent a "click train" test in a designated test ear only, the purpose of which was to explore the temporal aspects of adaptation onset and recovery to an 8-click train of high SRR clicks. Two click train tests were used, both employing an inter-click SRR of 88.8/s (ie 11.3ms between clicks within a click train). The two tests differed only in the inter-train repetition rate. Train repetition rates (TRRs) of 3.1/s and 5.9/s were chosen for reasons outlined in section 1.4.5, allowing some control over the silent recovery period between trains of click stimuli.

In order to acquire averaged waveforms evoked by a train of 8 clicks 11.3ms apart, an averaging epoch of nominally 93 (actually 94.185) ms was chosen and the number of data points within the epoch was increased from 512 to 4096 in order to maintain appropriate waveform resolution (0.023ms). When applied, the click train test was conducted following the rate series tests, and prior to the repeat (ie "end") standard 11.1/s ABR test. The stimuli were clicks at the same intensity as used in the test ear rate series test. Two sequential runs were performed: 1000 rarefaction clicks and 1000 condensation clicks being the stimuli, with the two waveforms stored separately but combined prior to analysis. The click train test was applied to all Group A (normal) subjects at both 3.1/s *and* 5.9/s train

repetition rates. In all other groups the test was applied when:

(i) Sufficient time was available within the test session, and

(ii) Results of the rate series tests showed that wave V was unambiguously present at the 88.8/s rate.

Only one train rate was employed in such cases because of the constraints of test duration, with the rate being chosen by tossing a coin.

2.3 BASIC TEST RESULT CLASSIFICATION

2.3.1 Pure tone audiogram

One of the principle determinants for group candidacy was a classification of the subject's hearing threshold status as measured by two indices related to normal reference data for the subject's age and sex. The intention here was to broadly classify patients as having either "normal" or "abnormal" hearing by air conduction and the two indices were based upon average hearing thresholds (both ears combined) and right/left asymmetry. Both measures would be expected to impinge upon the ABR results or their analysis.

Average hearing thresholds

The subjects hearing thresholds averaged across 1,2 and 4 kHz in both ears was compared to the average of the 90th centiles of the normal distribution at these frequencies given in BS6951. The reference data were calculated in 5 year age increments with separate data for males and females. Table 2.3.1 and Figure 2.3.1 (a) illustrate these reference data. Combining three 90th centile values in an average does not strictly yield a 90th centile value for the average (Robinson 1988), yet this approach was used since the choice of 90% was essentially arbitrary and intended only as a gross measure of hearing status. If a subject's average hearing as measured in this way was worse than the reference value for their age and sex then they were classified as having abnormal hearing under this measure.

Right/left asymmetry

In addition to the above classification, the subject's hearing threshold asymmetry at 4kHz was calculated and compared to the 90th centile reference datum for this measure obtained from the MRC Institute of Hearing Research National Study of Hearing (Davis, 1988). Table 2.3.1 and Figure 2.3.1 (b) illustrate these reference data. The original data were in 10 year age increments but 5 year increments were calculated by linear interpolation.

TABLE 2.3.1

Hearing Threshold Reference Data Versus Age & Sex

(a): Mean of 1, 2 & 4kHz 90th centiles from BS6951
(b): 4kHz asymmetry 90th centiles from MRC IHR Study

AGE	(a) 1,2,4 Average, dB		(b) 4kHz Asymmetry, dB	
	male	female	male	female
≤30	11	10	15	11
31-35	13	12	16	11
36-40	16	14	18	12
41-45	20	16	20	14
46-50	24	19	21	15
51-55	28	22	22	16
56-60	34	26	23	16
61-65	40	31	24	16
66-70	48	36	25	16
71-75	58.5	43	25	17
76-80	68	50	25	18

A simple program, written in BASIC, was written to classify individual subjects from their age, sex and pure tone thresholds on the basis of the above reference data. A listing of the program appears in Appendix A.

FIGURE 2.3.1 (a)

Hearing Threshold Reference Data
Mean of 1, 2 & 4kHz 90th centiles
from BS 6951

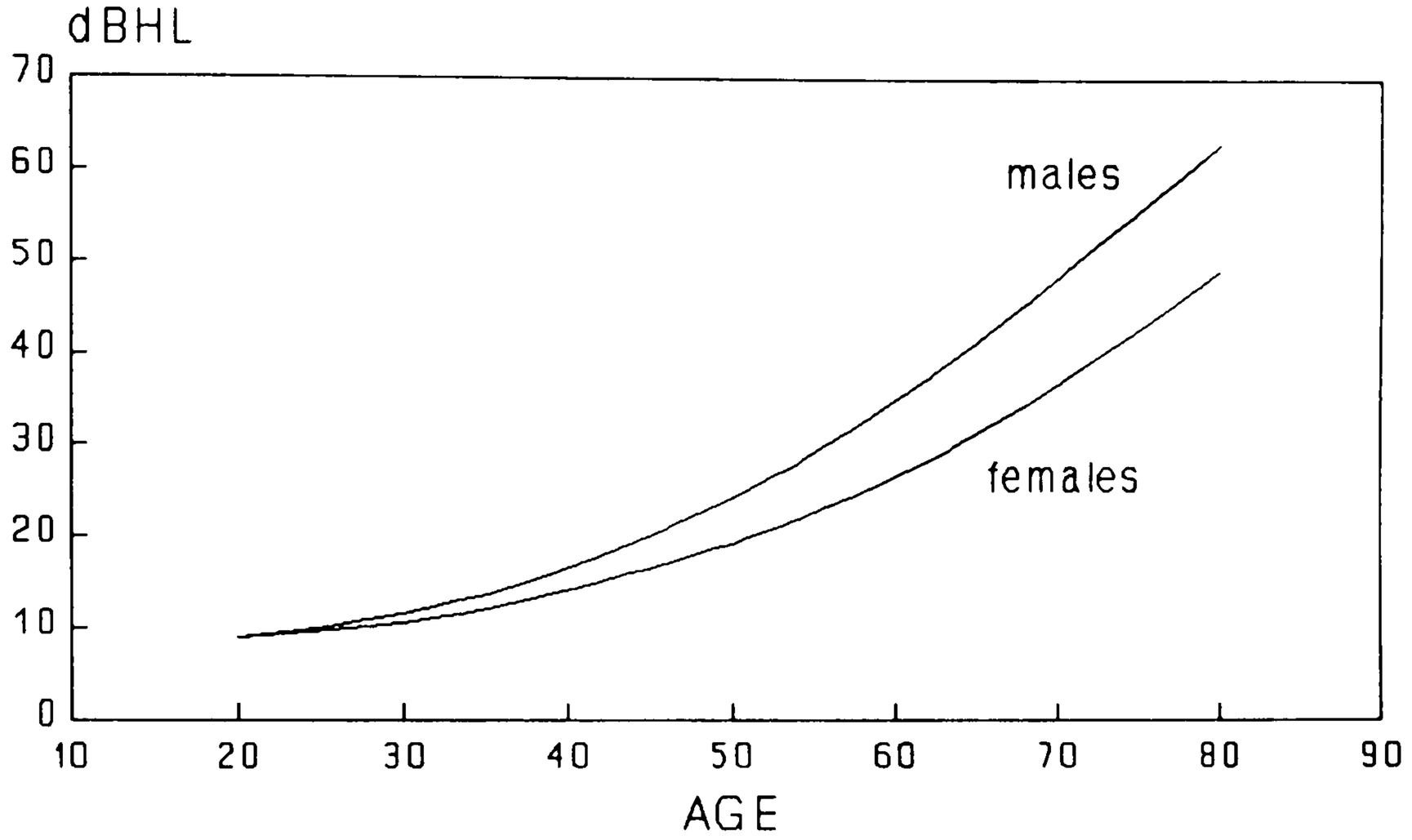
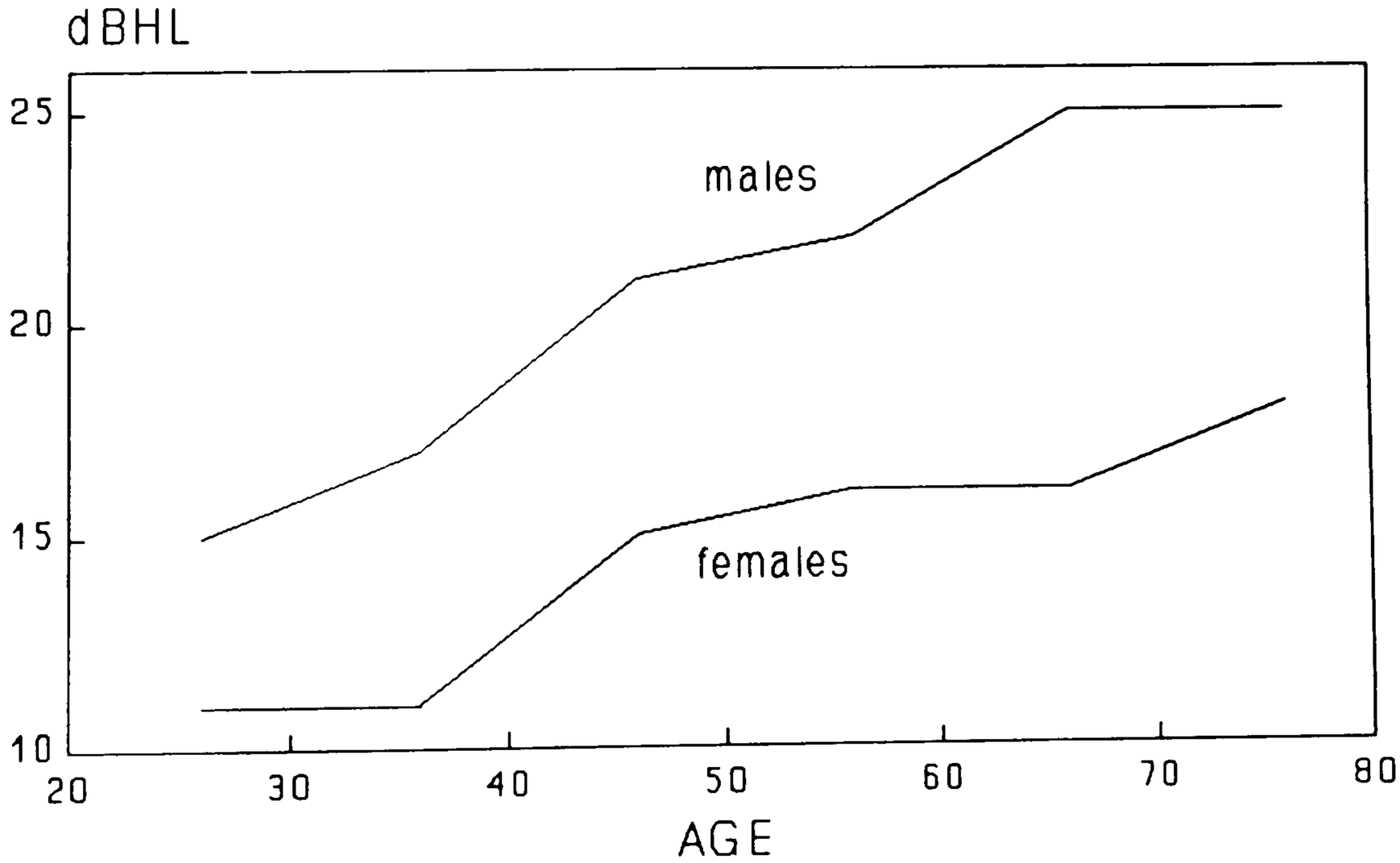


FIGURE 2.3.1 (b)

4kHz Asymmetry Reference Data
90th centiles - from MRC IHR
National Study of Hearing



2.3.2 Acoustic reflex threshold and decay

Acoustic reflex threshold (ART) measurements were made at 1kHz using an ipsilateral pulsed stimulus at a static probe pressure corresponding to the measured middle ear pressure. The ART was taken as the minimum intensity at which two consecutive presentations evoked two reflexes of at least 0.2ml. Acoustic reflex decay (ARD) was measured with a continuous (ie not pulsed) 1kHz ipsilateral tone at an intensity of ART + 10dB, presented for 10 seconds. Anderson's criterion was adopted (Anderson *et al* 1970).

There were, of course some patients who had no recordable reflex at all up to 110dBHL and there were some patients who had reflexes but upon whom ARD was not evaluated (eg in the case of very small reflexes).

2.3.3 Alternate binaural loudness balance

An ABLB test was performed (Priede & Coles, 1974) on most subjects (except Group A) at 4kHz (and occasionally also at 1kHz or 2kHz). The test was for two purposes and had two forms of interpretation:

(i) To provide a conventional assessment of degree of recruitment and so assist in cochlear (sensory) versus retrocochlear (neural) differentiation. Recruitment was classified as being complete, incomplete (sensory), incomplete (neural), no recruitment or derecruitment, after Priede & Coles (1974). Any air-bone gap in either ear was accounted for before applying the criteria for classification.

(ii) To assist in the selection of ABR test intensity in test and reference ears. A major (though not exclusive) consideration in selecting ABR test intensities was the 4kHz loudness balance point. Since 80dBnHL was usually employed in reference ear ABR tests, the intensity in the "worse" or (test) ear corresponding to 80dBHL in the "better" or (reference) ear was obtained from the ABLB chart.

The 4kHz ABLB test was conducted even when there was less than 20dB difference in the 4kHz pure tone thresholds (when curiously the test is often not considered appropriate even though a patient with a unilateral retrocochlear lesion and symmetrical audiogram can exhibit derecruitment) or conversely when the 4kHz asymmetry was so great as to cause cross hearing. In this latter case, a modified technique is required but is sometimes useful when a patient with

recruitment "uncrosses" at supra-threshold intensities.

2.4 ABR TEST INTERPRETATION

2.4.1 General

All ABR waveforms were subject to a 9-point centre weighted smoothing routine and baseline correction. Where separate waveforms were obtained for rarefaction and condensation stimuli, they were combined prior to analysis. Amplitude measurements were made from a given peak to the next (following) major trough. When a peak was apparent only as a point of inflection in an otherwise rising or falling portion of waveform (as is sometimes the case when myogenic evoked responses are superimposed at high SRRs), the latency was noted but the amplitude was taken as zero.

2.4.2 Reference ear results

The latency and amplitude of waves I, III and V were measured on the reference ear 11.1/s ABR waveform. The wave V latency shift between the 11.1/s and 44.4/s reference ear waveforms and between the 11.1/s and 88.8/s waveforms were measured. Figures 2.4.2 (a) & (b) show typical results.

2.4.3 Test ear results

Similar measurements of waves I, III and V were made on the test ear "start" and "end" 11.1/s waveforms, together with measurement of the combined ("mean") waveform. Figures 2.4.3 (a), (b) & (c) show typical results.

ANALYSIS	LATENCY		AMPLITUDE
I	1.560	I	0.25
II		II	
III	3.630	III	0.44
IV		IV	
V	5.340	V	0.71
I-III	2.070		
III-V	1.710		
I-V	3.780		

ms/div	uV/di
1.500	0.31

B1 RIGHT EAR. CON. 80 DBHL
A1 RIGHT EAR. RAR. 80 DBHL
X1 RIGHT EAR. 80DB RAR+CON

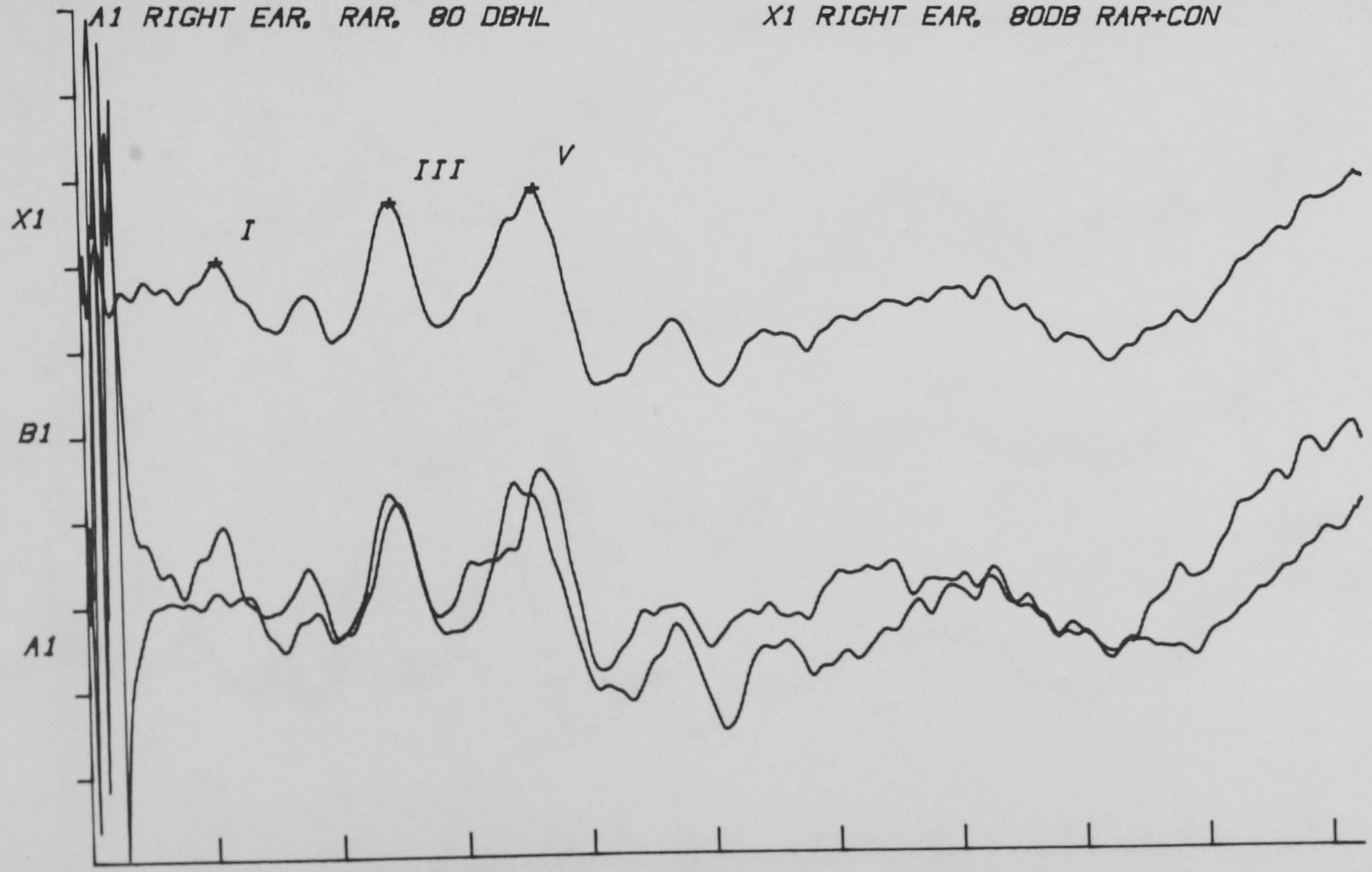


FIGURE 2.4.2 (a)

Example of a typical Reference Ear 11.1/s ABR

RATE	LAT		AMP
88.8	5.910		0.77
66.6			
44.4	5.670		0.79
22.2			
11.1	5.340		0.71
-DIFF-		-DIFF-	
88-11	0.570	44-11	0.330
66-11		22-11	

ms/div	uV/div
1.500	0.31

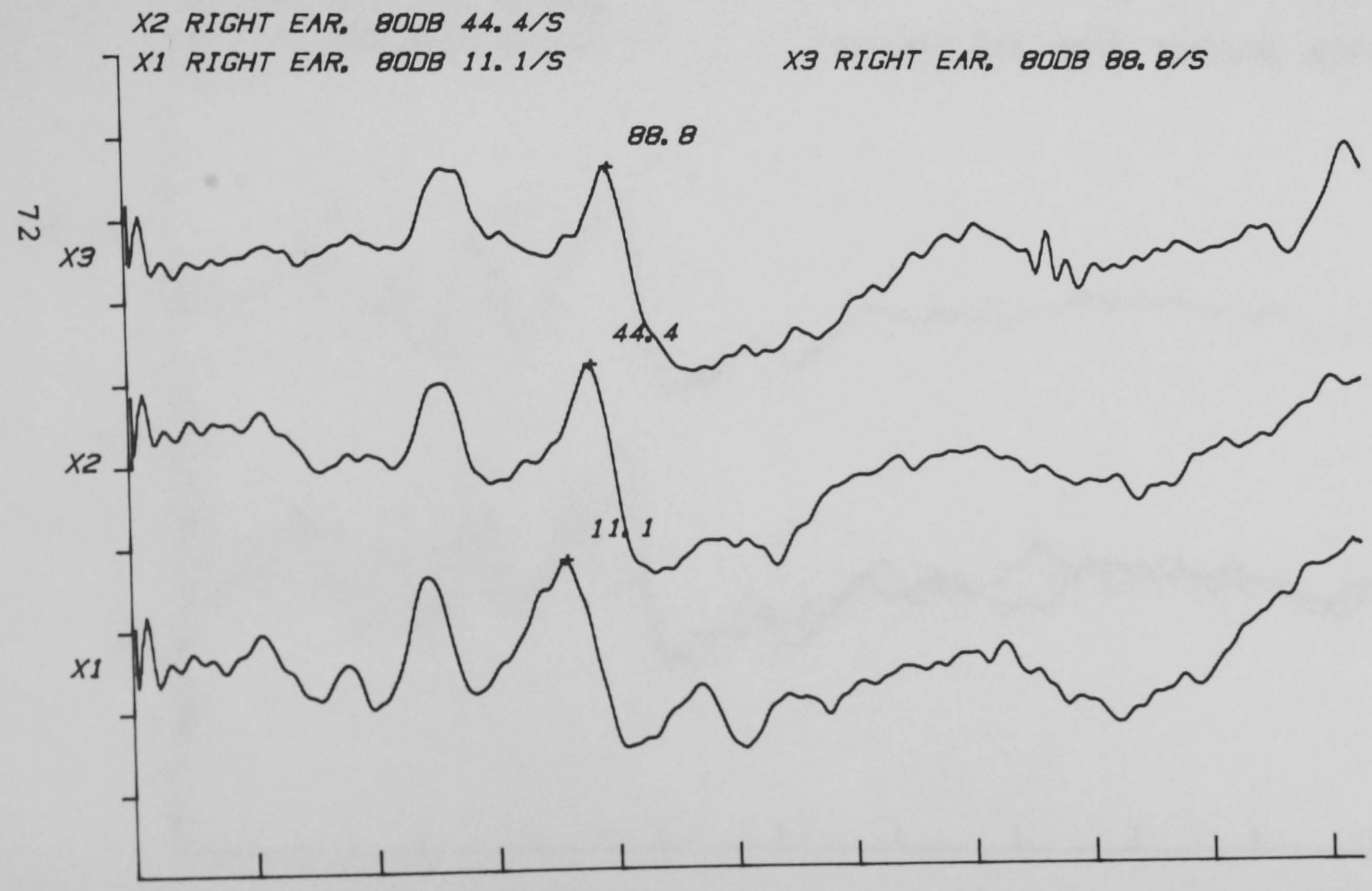


FIGURE 2.4.2 (b)

Example of a typical Reference Ear 11.1-44.4-88.8/s ABR series

ANALYSIS	LATENCY	AMPLITUDE
I	1.590	0.38
II		
III	3.630	0.35
IV		
V	5.460	0.76
I-III	2.040	
III-V	1.830	
I-V	3.870	

ms/div	uV/d
1.500	0.3

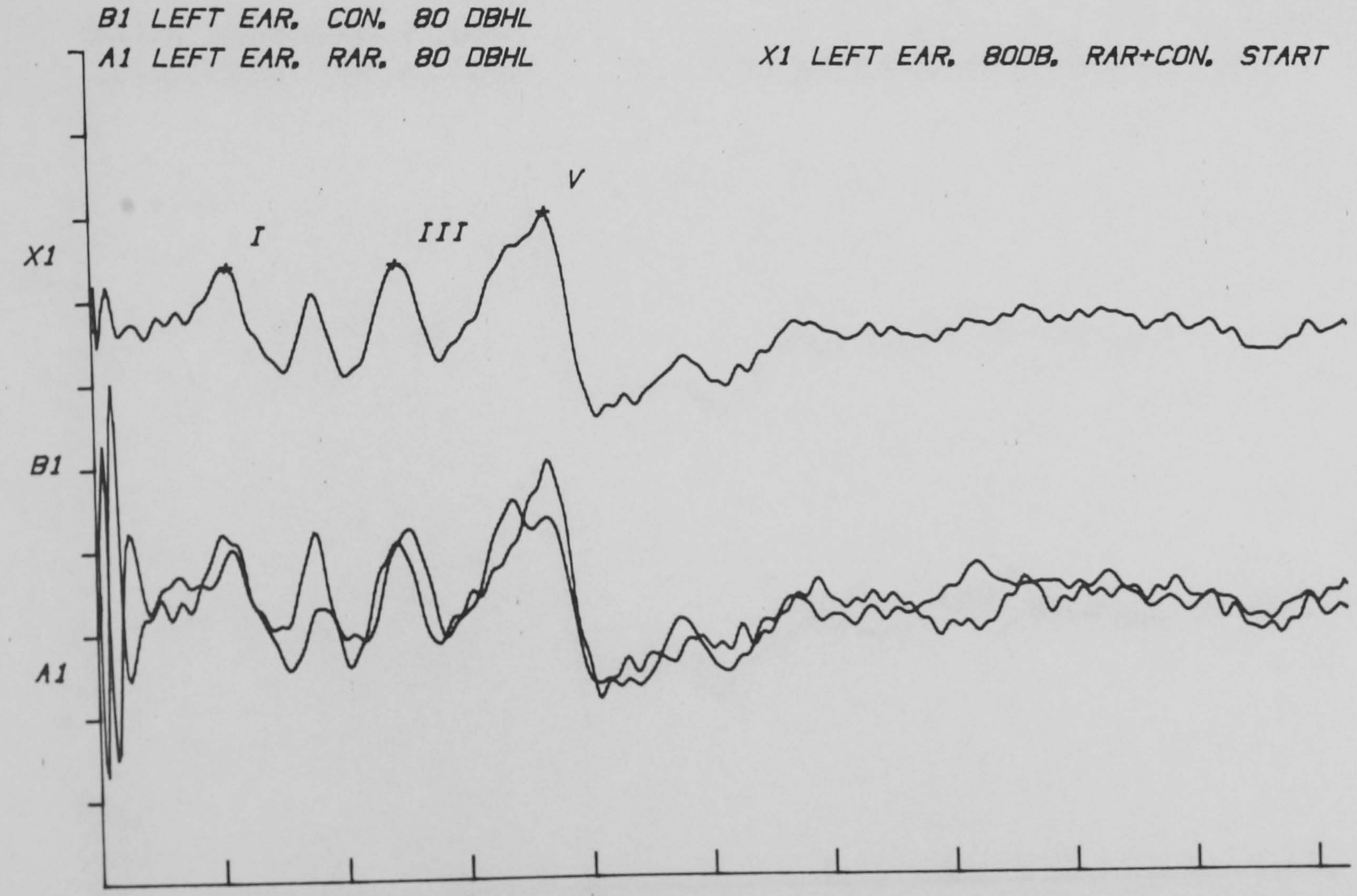


FIGURE 2.4.3 (a)

Example of a typical Test Ear "Start" 11.1/s ABR

ANALYSIS	LATENCY		AMPLITUDE
I	1.590	I	0.29
II		II	
III	3.660	III	0.31
IV		IV	
V	5.490	V	0.73
I-III	2.070		
III-V	1.830		
I-V	3.900		

ms/div	uV/di
1.500	0.31

B2 LEFT EAR. CON. 80 DBHL
A2 LEFT EAR. RAR. 80 DBHL

X2 LEFT EAR. 80DB. RAR+CON. END

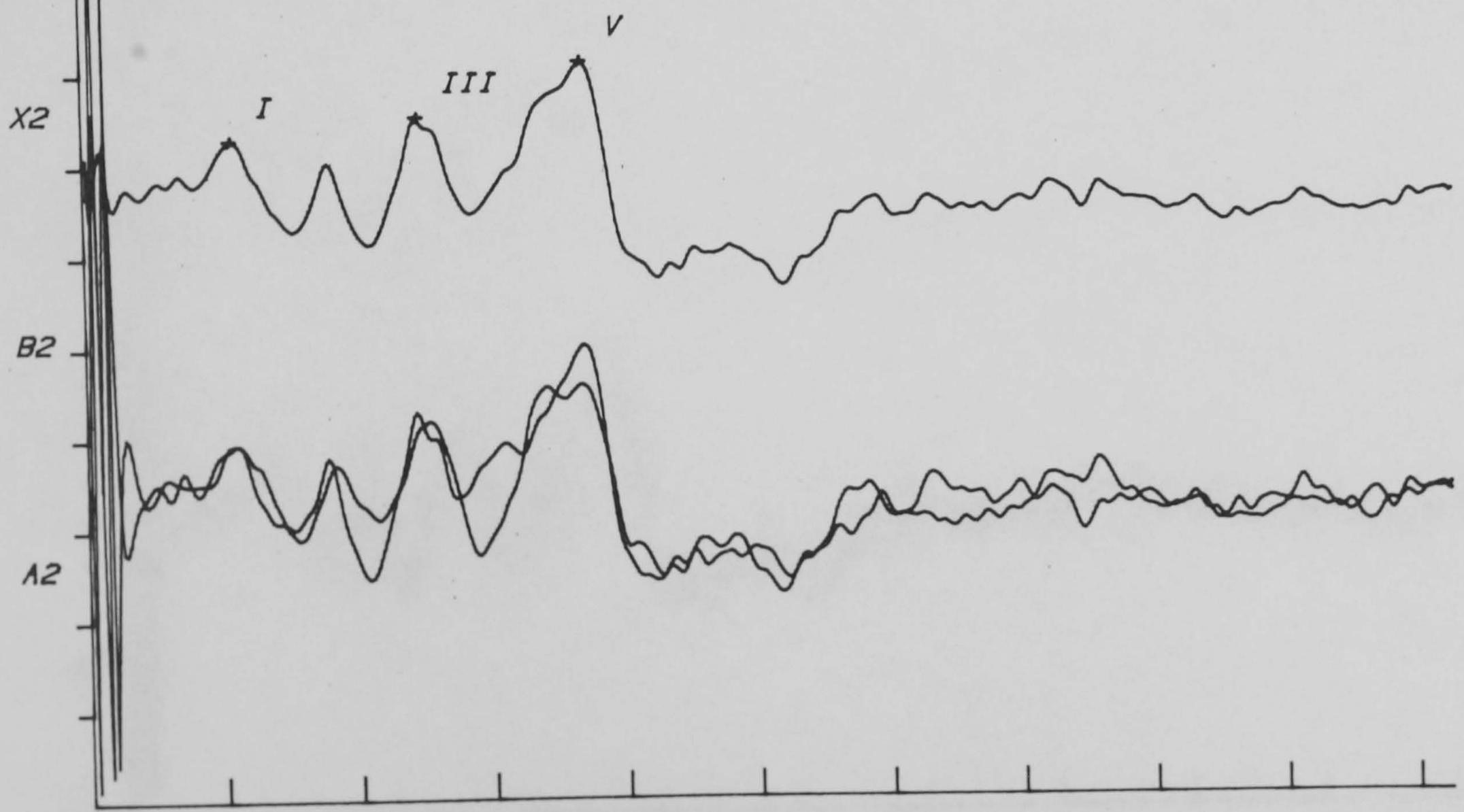


FIGURE 2.4.3 (b)

Example of a typical Test Ear "End" 11.1/s ABR

ANALYSIS	LATENCY		AMPLITUDE
I	1.590	I	0.33
II		II	
III	3.660	III	0.33
IV		IV	
V	5.490	V	0.72
I-III	2.070		
III-V	1.830		
I-V	3.900		

ms/div	uV/d
1.500	0.3

A3 LEFT EAR. CON. 80 DBHL
A4 LEFT EAR. RAR. 80 DBHL
A5 LEFT EAR. CON. 80 DBHL

A1 B80L 11.1/SEC MEAN
A2 LEFT EAR. RAR. 80 DBHL

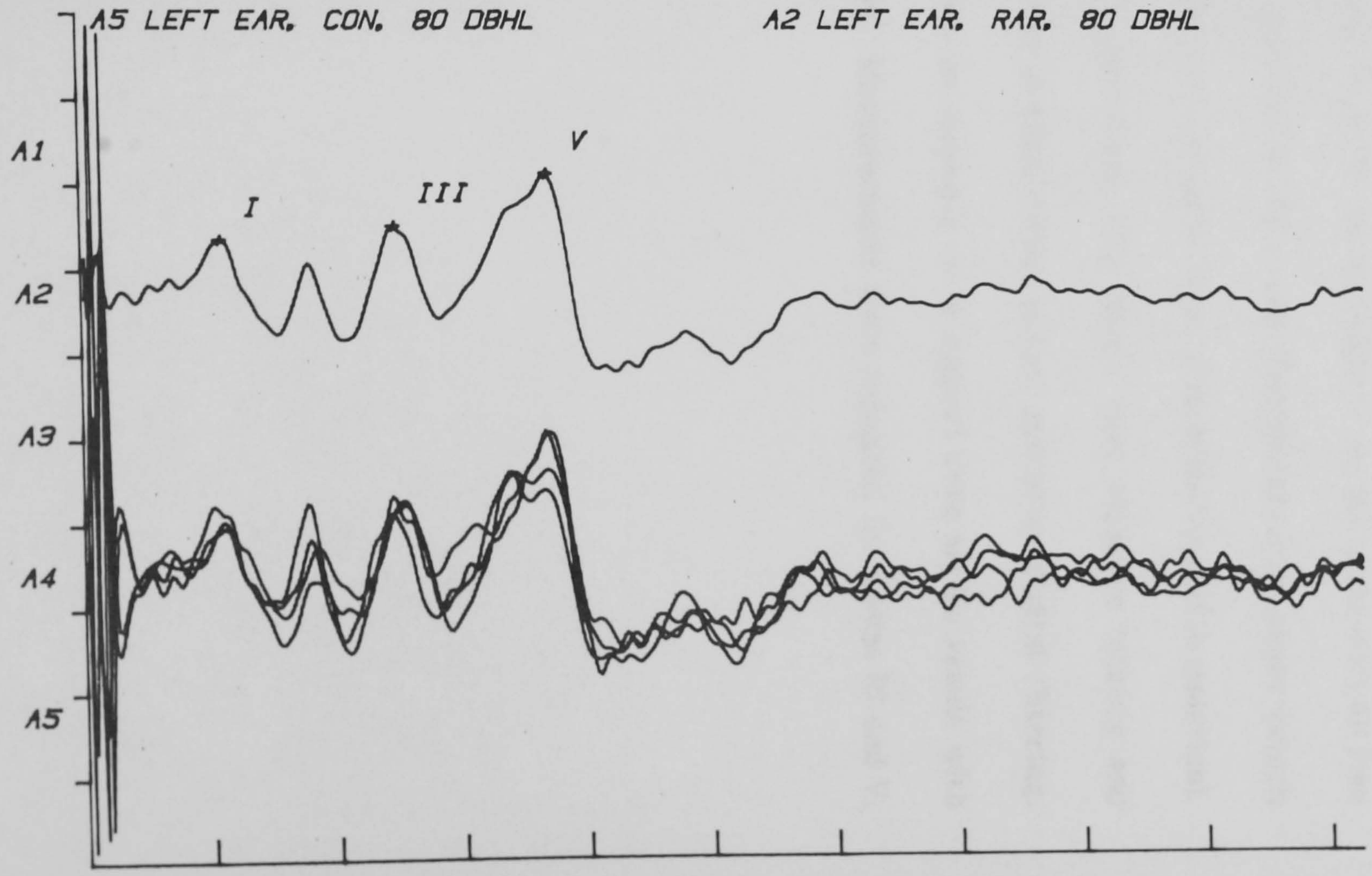


FIGURE 2.4.3 (c)

Example of a typical Test Ear "Mean" 11.1/s ABR

2.4.3.1 *Rate series analysis*

A special analysis program, ANAL.CMD, was written to analyse the test ear ABR rate series. The four 11.1/s waveforms were combined as were the three waveforms obtained at each of the four higher rates, producing five waveforms in all, one for each rate. These five waveforms were subject to a low pass 2kHz digital filter to minimise the residual effect of non-signal noise and so maximise the precision of latency measurements. The latency and amplitudes of waves I, III and V were measured across rates with all five waveforms displayed together to aid in the identification of peaks (which were sometimes indistinct or equivocal in location when viewed in isolation). For the "mean" 11.1/s waveform, this meant that separate latency and amplitude measures were available both before and after digital filtering. Figure 2.4.3.1 (a) shows an example of a typical rate series result with wave V being measured. Measurements were repeated for waves III and V.

RATE

LAT		AMP	
88.8	5.940		0.70
66.6	5.820		0.64
44.4	5.700		0.76
22.2	5.550		0.76
11.1	5.490		0.70
-DIFF-		-DIFF-	
88-11	0.450	44-11	0.210
66-11	0.330	22-11	0.060

ms/div	uV/d
1.500	0.3

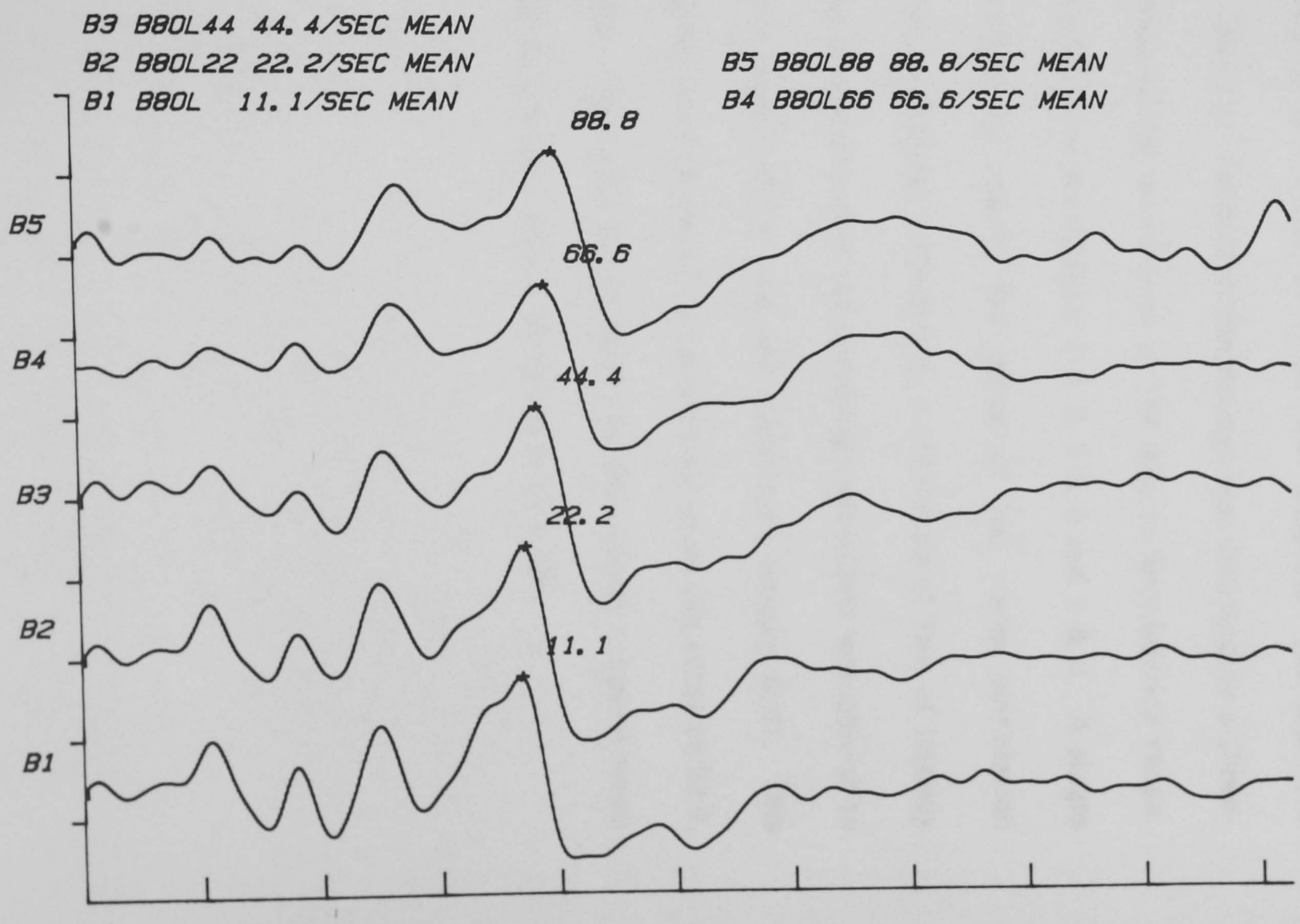


FIGURE 2.4.3.1 (a)

Example of a typical Test Ear full rate series ABR

The second part of the rate series analysis program recalled and displayed the three 1000-click waveforms for each rate (22.2, 44.4, 66.6 and 88.8/s) individually. For each rate, the latency difference (or "jitter") between the wave V in the first and third waveforms was measured - a positive value indicating an earlier initial wave V with a later wave V in the third waveform. The term "jitter" is potentially misleading but is being used here to represent any systematic perstimulatory latency shift rather than a random fluctuation with a zero mean. The author simply could not identify a more appropriate term, so jitter was adopted. An objective measure of repeatability of waveform morphology was obtained by a three-way cross correlation of the waveforms in the 4ms to 9ms latency range. That is, correlation between waveforms 1 & 2, 2 & 3 and 1 & 3. A single measure was obtained by taking the mean of the three correlation coefficients. In the correlation calculation, a maximum of 1ms of latency shift, (or "lag") was allowed so that the resulting coefficient was chosen to reflect both general repeatability and any significant latency shift. This procedure was applied to each set of three waveforms at the rates of 22.2, 44.4, 66.6 and 88.8/s. Figure 2.4.3.1 (b) shows an example of a typical result (in this case of the 22.2/s rate with a correlation of 0.93).

ABR ADAP	JV LAT	JV AMP
MEAN	5.520	0.77
RUN 1	5.490	0.81
RUN 2	5.490	0.74
RUN 3	5.550	0.78
2-1	0.000	
3-1	0.060	

ms/div	uV/
1.500	0.

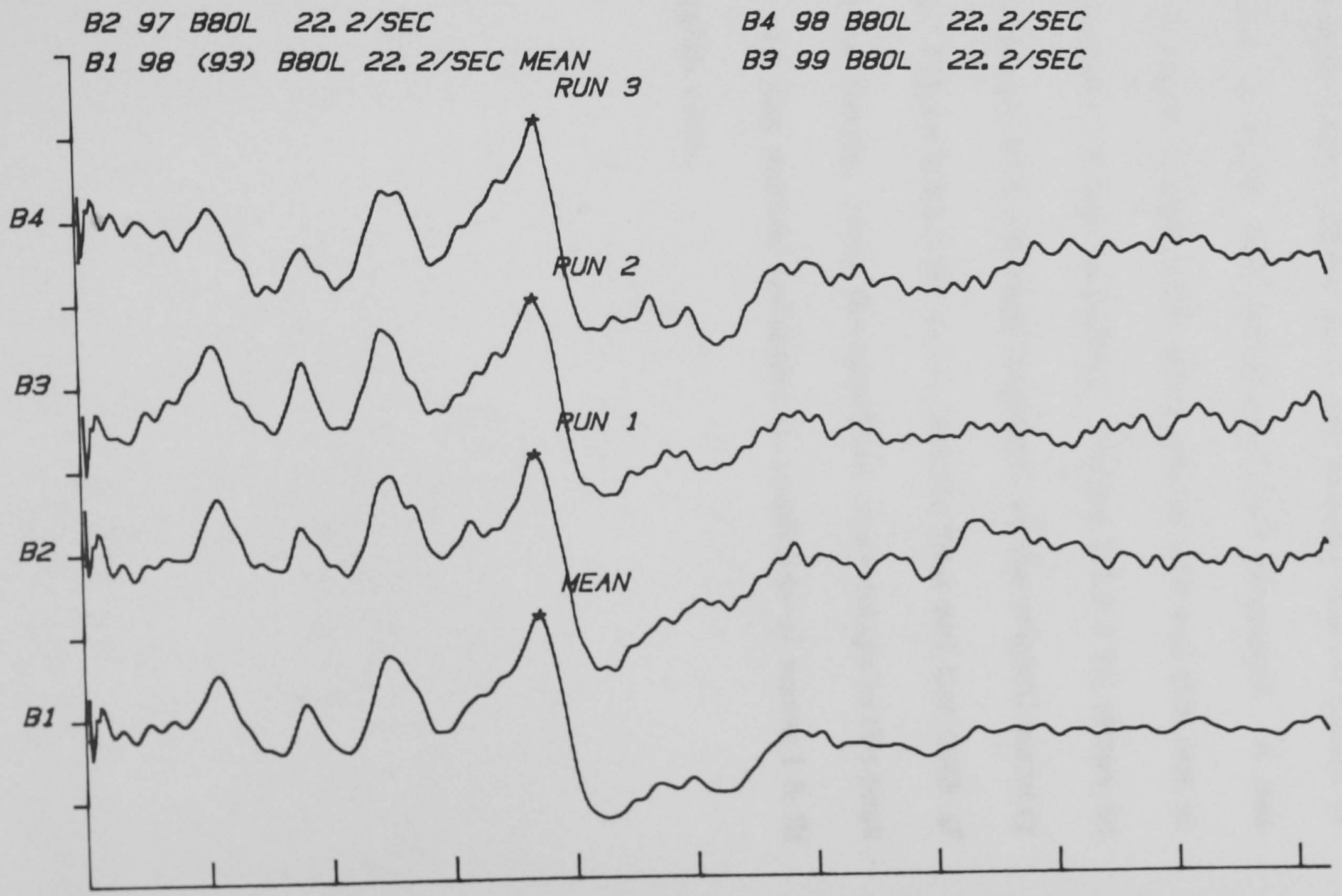


FIGURE 2.4.3.1 (b)

Example of a typical Test Ear higher rate ABR

2.4.3.2 *Click train analysis*

For analysis purposes a train analysis programme, ATRAIN.CMD, was written in which the 4096 point 93ms waveform was segmented into eight consecutive 512 memory blocks, each holding the ABR waveform evoked by a given click within the eight-click stimulus paradigm. All eight waveforms were subject to 2kHz low pass digital filtering and the eight waveforms were superimposed for the purposes of analysis. Group A subjects had click train test results at both TRRs and for each, the latency and amplitude of waves I, III and V for all eight ABR waveforms were measured. A less detailed analysis was made in subjects in other groups who had this test at only one TRR. Only wave V was measured. Figure 2.4.3.2 (a) shows an example of a typical result with the eight segments of the original memory block superimposed. Figure 2.4.3.2 (b) shows just the first and last click of the previous figure for clarity. Note the small but clear delays in the peak latencies together with the marked reduction in amplitude of waves I & III arising from the eighth click.

FIGURE 2.4.3.2 (a)

Example of a typical Test Ear click train ABR

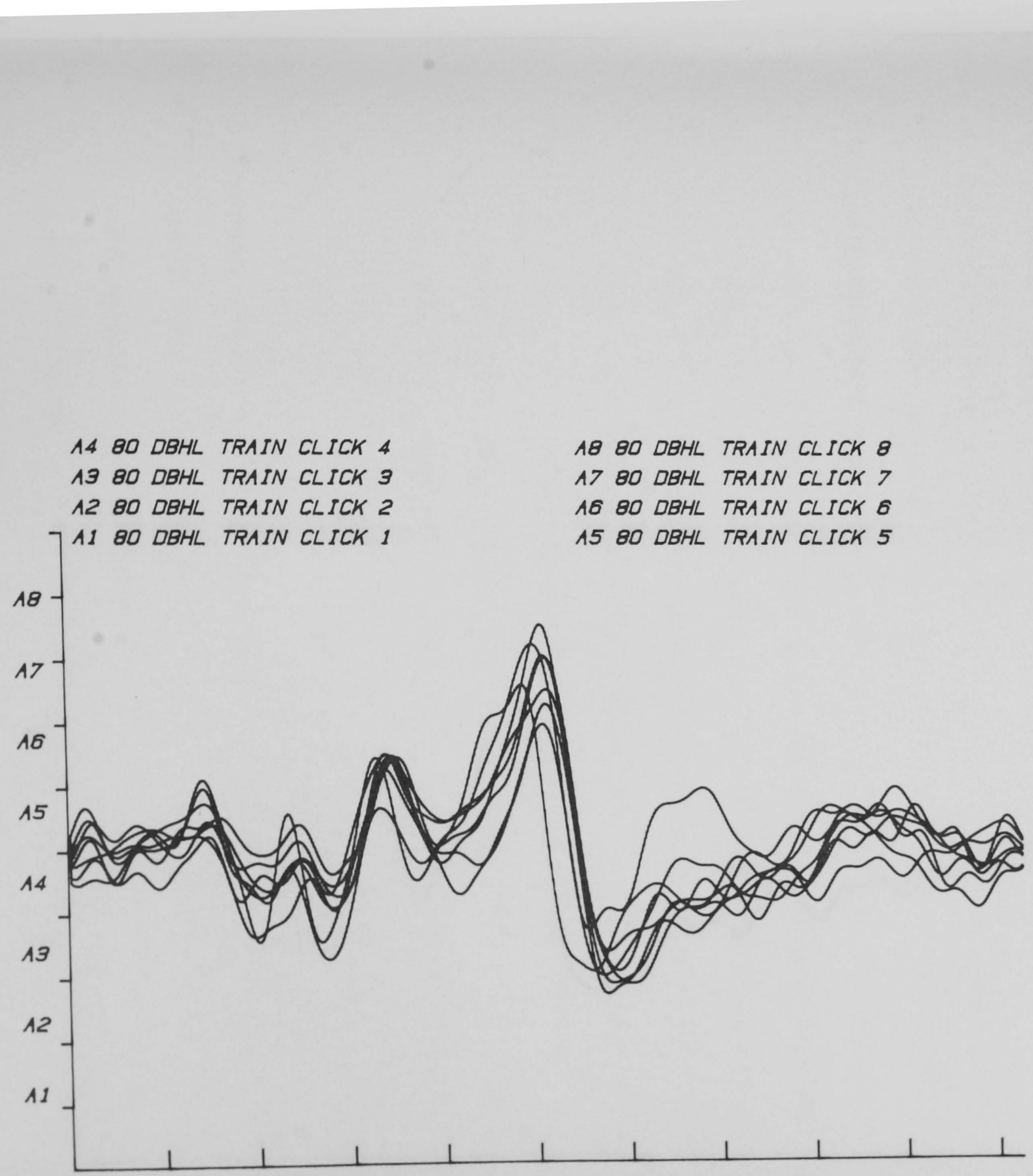
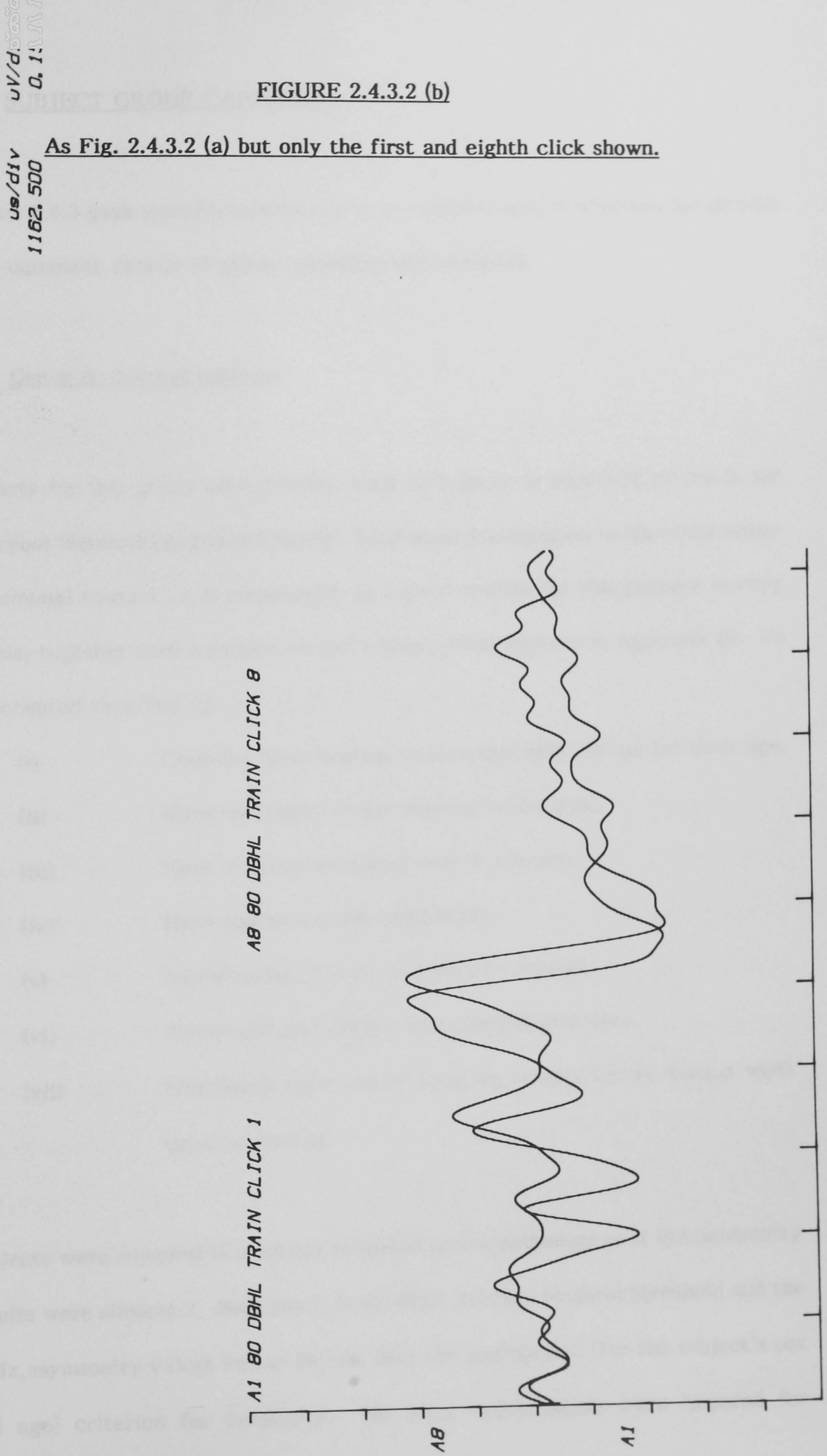


FIGURE 2.4.3.2 (b)

As Fig. 2.4.3.2 (a) but only the first and eighth click shown.



2.5 SUBJECT GROUP CANDIDACY

Section 1.4.3 gave introductory details of the subject groups whereas this section gives complete details of group candidacy requirements.

2.5.1 Group A: Normal subjects

Subjects for this group were friends, work colleagues or members of the Royal Liverpool Hospital League of Friends. They were attracted on to the study either by personal contact or in response to an appeal written for this purpose (a copy of this, together with information and consent form appears in Appendix B). To be accepted they had to:

(i) Consider their hearing to be reasonably normal for their age.

(ii) Have no history of ear disease in the past.

(iii) Have no tinnitus lasting over 5 minutes.

(iv) Have had no serious head injury.

(v) Never suffered from dizziness or vertigo.

(vi) Never suffered from a neurological disorder.

(vii) Not taken sedatives or sleeping tablets for at least a week prior to testing.

Subjects were rejected if otoscopy revealed active pathology or if tympanometry results were abnormal. Both the 1, 2 and 4kHz average binaural threshold and the 4kHz asymmetry values had to be less than the appropriate (for the subject's sex and age) criterion for candidacy. No other requirements were imposed for

candidacy purposes and subjects were irreversibly accepted prior to ABR testing if they satisfied the above conditions, ie they could not be rejected for any reason associated with their ABR results.

2.5.2 Group B: Subjects with normal hearing but with tinnitus and/or vertigo

Subjects in this category had to satisfy the same audiometric requirements as group A subjects. The results of all the investigations (except ABR rate effects) had to contraindicate a retrocochlear disorder in a similar way to group C subjects (see below).

2.5.3 Group C: Subjects with cochlear dysfunction

In this group there had to be evidence of cochlear pathology in at least one ear, either because the 1, 2 and 4kHz average binaural threshold or their 4kHz asymmetry (or both) were beyond the appropriate criteria. Given the range of differential diagnostic indices which can be applied to the tests given to such subjects, there are inevitably instances where test results conflict in a given subject. In order to apply some form of consensus and to avoid unrealistically categorising many subjects in the "suspected retrocochlear" group, the following scheme was devised following consultation with a small number of highly experienced and respected British audiologists.

Up to one "retrocochlear" finding was allowable with all other results within normal limits in the following list:

(i) ABR I-V IPL >4.4ms but <4.6ms

(ii) ABR I-III IPL >2.6ms

(iii) ABR III-IV IPL >2.2ms

(iv) ABLB "incomplete neural" or worse[1]

(v) ARD abnormal

(vi) IAM imaging showing significant asymmetry.

Notes on the Above

The ABR IPL results from the test ear refer to the "mean" (not the "start" and "end") waveform. In imaging results, Magnetic Resonance Imaging (MRI) overrules Computerised Tomography (CT) and CT overrules IAM tomography.

[1]After Priede & Coles (1974)

2.5.4 Group D: Subjects with suspected but unconfirmed retrocochlear dysfunction

These subjects could have any audiometric status and were suspected of having a retrocochlear disorder because either:

(i) they had two or more retrocochlear findings in the above list, or

(ii) their ABR I-V IPL was >4.6ms.

By definition, these subjects' diagnoses were incomplete and the group inevitably represents a variety of pathologies, probably ranging from pure cochlear dysfunction to acoustic neuromata. Sadly, not all referring clinicians could be persuaded to proceed to MRI or even enhanced CT to resolve whether a space-occupying tumour existed. Group D subjects who had normal MRI or CT results stayed in this group since there are retrocochlear pathologies which cannot be imaged even with the most modern techniques.

2.5.5 Groups E & F: Subjects with confirmed acoustic neuromata

The presence of an acoustic neuroma was the only requirement here, the vast majority of the diagnoses being confirmed at subsequent surgery. A small number of patients declined surgery with their diagnosis made by a consultant neurosurgeon following thorough investigations, including MRI. They were included in one of these groups only if there was no serious doubt concerning their clinical status.

Group E subjects were those who received "test ear" tests on their tumour ear whereas Group F subjects received "reference ear" tests on the side of the tumour. The pure tone audiogram obtained from an ear on the side of such a tumour can range from normal limits to a profound or total (immeasurable) loss. In cases of substantial hearing loss there frequently may be secondary cochlear damage and so it is not surprising that in these cases the ABR is absent or recordable only at a slow SRR. If either of these findings were apparent From ABR tests on the side of the tumour, the subject was entered into Group F and the more exhaustive "test ear" investigations were on the side contralateral to the tumour in an attempt to observe any effects of brainstem displacement or compression. Where ABR results on the tumour ear were repeatable (though abnormal) the tumour ear was designated the test ear and received the more detailed investigations and the subject was entered into Group E.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 ANALYSIS OF GROUP A: NORMAL SUBJECTS

The primary aim of this section is to characterise the more important ABR diagnostic indices, including potentially useful rate effect measurements for later comparison with other subject groups. A secondary aim is to undertake a more detailed analysis of SRR and click train adaptation effects in an attempt to understand their nature in normal subjects.

3.1.1 ABR Diagnostic Indices

3.1.1.1 *Variables being studied*

The following variables were considered with a view to their inclusion in studies between normal and other groups:

MI-III	the I-III IPL of the "test ear" mean (ie combined "start" & "end") 11.1/s waveform
MIII-V	as above for the III-V IPL
MI-V	as above for the I-V IPL
MI/V	as above for the I/V amplitude ratio
QI-III	the MI-III IPL above minus the I-III IPL recorded from the reference ear

QIII-V	the MIII-V IPL above minus the III-V IPL recorded from the reference ear
QI-V	the MI-V IPL above minus the I-V IPL recorded from the reference ear
ILDV	the test ear wave V latency (mean waveform) minus the reference ear wave V latency, both at 11.1/s. This variable is often referred to as IT[5].
ILDV44	the test ear wave V latency at 44.4/s minus the reference ear wave V latency at 44.4/s
V22-11	the latency of the test ear wave V at 22.2/s minus that at 11.1/s
V44-11	the latency of the test ear wave V at 44.4/s minus that at 11.1/s
V66-11	the latency of the test ear wave V at 66.6/s minus that at 11.1/s
V88-11	the latency of the test ear wave V at 88.8/s minus that at 11.1/s
V22/11	the amplitude of the test ear wave V at 22.2/s divided by that at 11.1/s
V44/11	the amplitude of the test ear wave V at 44.4/s divided by that at 11.1/s
V66/11	the amplitude of the test ear wave V at 66.6/s divided by that at 11.1/s
V88/11	the amplitude of the test ear wave V at 88.8/s divided by that at 11.1/s

QV44-11	V44-11 above minus the corresponding rate-induced latency shift recorded from the reference ear
QV88-11	V88-11 above minus the corresponding rate-induced latency shift recorded from the reference ear
JIT22	the test ear 22.2/s wave V latency of the 400-600 click sub average minus that of the 0-200 click sub average
JIT44	as JIT22 but at 44.4/s
JIT66	as JIT22 but at 66.6/s
JIT88	as JIT22 but at 88.8/s
AVJIT	the average of JIT22, JIT44, JIT66 & JIT88
COEF22	the average of the three correlation coefficients between the three sub averages in the test ear 22.2/s rate series
COEF44	as COEF22 but at 44.4/s
COEF66	as COEF22 but at 66.6/s
COEF88	as COEF22 but at 88.8/s
AVCOEF	the average of COEF22, COEF44, COEF66 & COEF88

A note on level of statistical significance

In most instances, the p value attached to the significance of results of statistical tests will be quoted, and p=.05 was adopted.

3.1.1.2 *Tests of normality*

One of the prerequisites of parametric statistical tests is that the variables have distributions which are approximately normal or at least, not grossly non-normal. To ensure validity in the following application of such tests, a non-parametric test, the Kolmogorov-Smirnov (K-S) one sample test was applied to the above variables for the normal distribution. The chosen test criterion was the 2-tailed p =.1.

All variables had p >.1 and so were not excluded from parametric tests on the basis of their distribution. This does not mean that the variables are normally distributed but rather that the risk of significant errors arising because of distribution anomalies is acceptably low.

3.1.1.3 *The effects of age and gender*

The application of diagnostic indices in the clinic must reflect any effects due to the patient's age and gender. Clearly those for which there is no effect require no correction and are easiest to implement. To search for such effects, each variable was subject to a 2-way analysis of variance (ANOVA) for gender and age. For this purpose, the subjects were grouped into three age bands: 1 = up to 40 yrs, 2 = 41 to 60 yrs, 3 = over 61 yrs. This allowed the main effects of age and gender to be evaluated together with age / gender interaction. The significance level chosen for all three was p =.05.

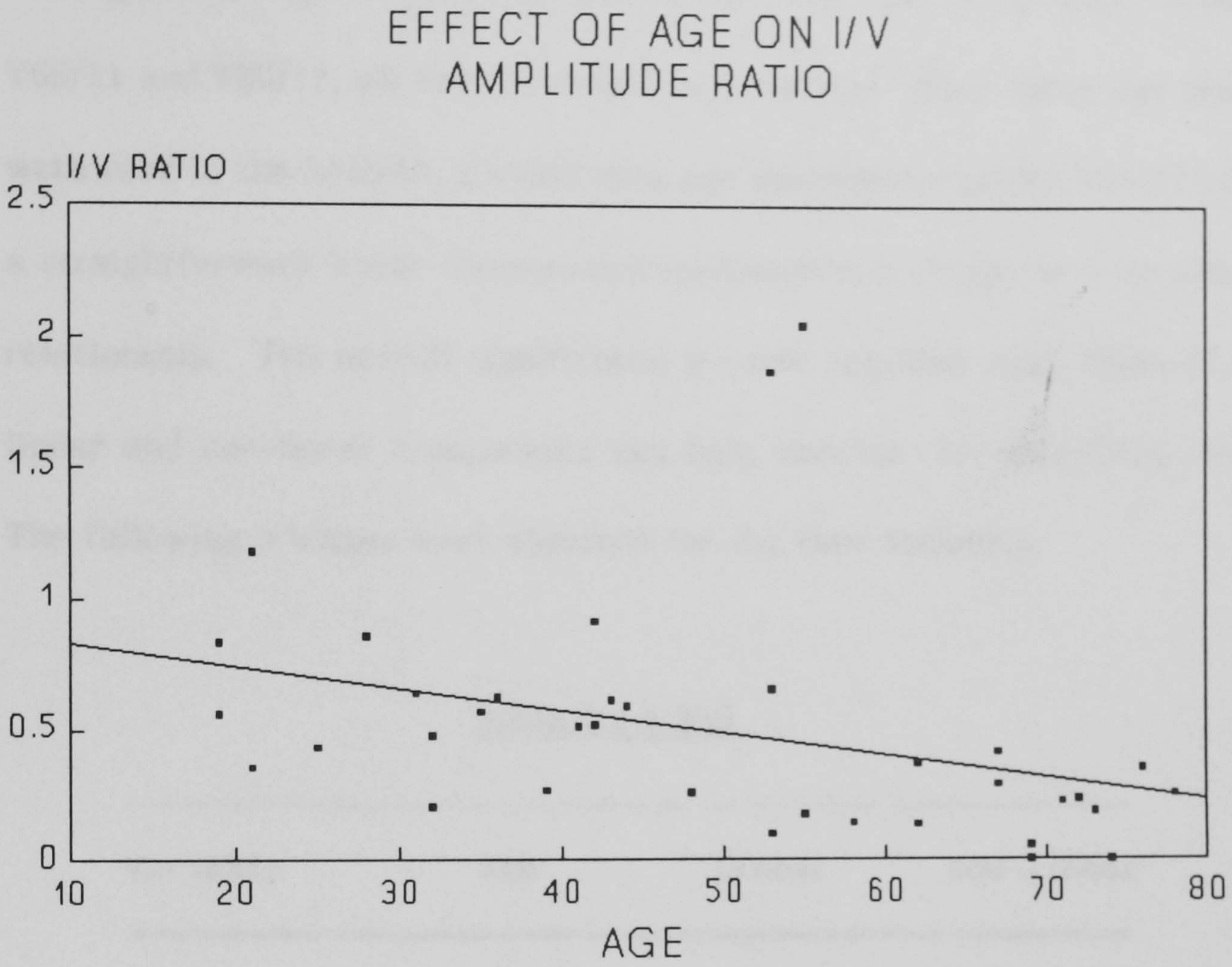
With the exception of those variables discussed below, there were no significant interactions with age, gender or age / gender combination.

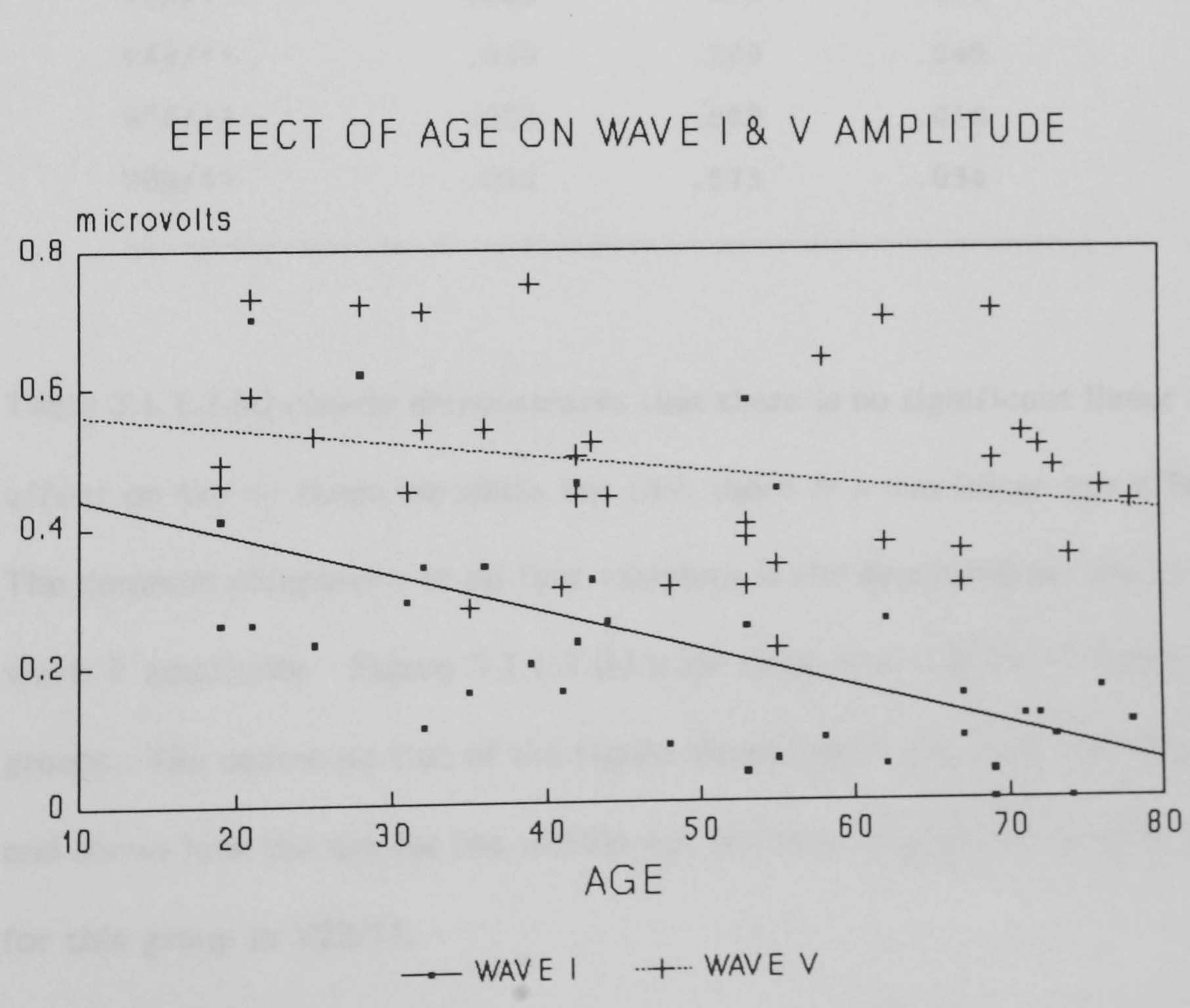
Age effects

Variable MI/V had a borderline age effect (p=.06). To explore this further, an ANOVA of MI/V with age (continuous rather than three groups) was repeated which yielded p=.038, suggesting a highly probable age effect upon MI/V. Figure 3.1.1.3(a) illustrates this and the lower portion of the figure shows that it is the wave I amplitude which is dominating this effect. To achieve optimum precision when employing this variable as a diagnostic measure, age related criteria should be established and applied. Before doing so however, the likely benefits should be evaluated. Simple linear regression was performed between MI/V and age. The results produced an R Square of 0.1199, suggesting that only 12% of the variability of MI/V is explicable by its dependency with age. Adopting age related MI/V criteria would lead to a reduction of the standard deviation of MI/V from 0.45 to 0.43 or less than 5%.

These results therefore demonstrate that whilst there appears to be a genuine effect of age upon MI/V, the likely advantage of accounting for it is low in relation to the effort required to do so. For this reason, subsequent use of this variable will ignore any relationship with age.

Figure 3.1.1.3.(a)





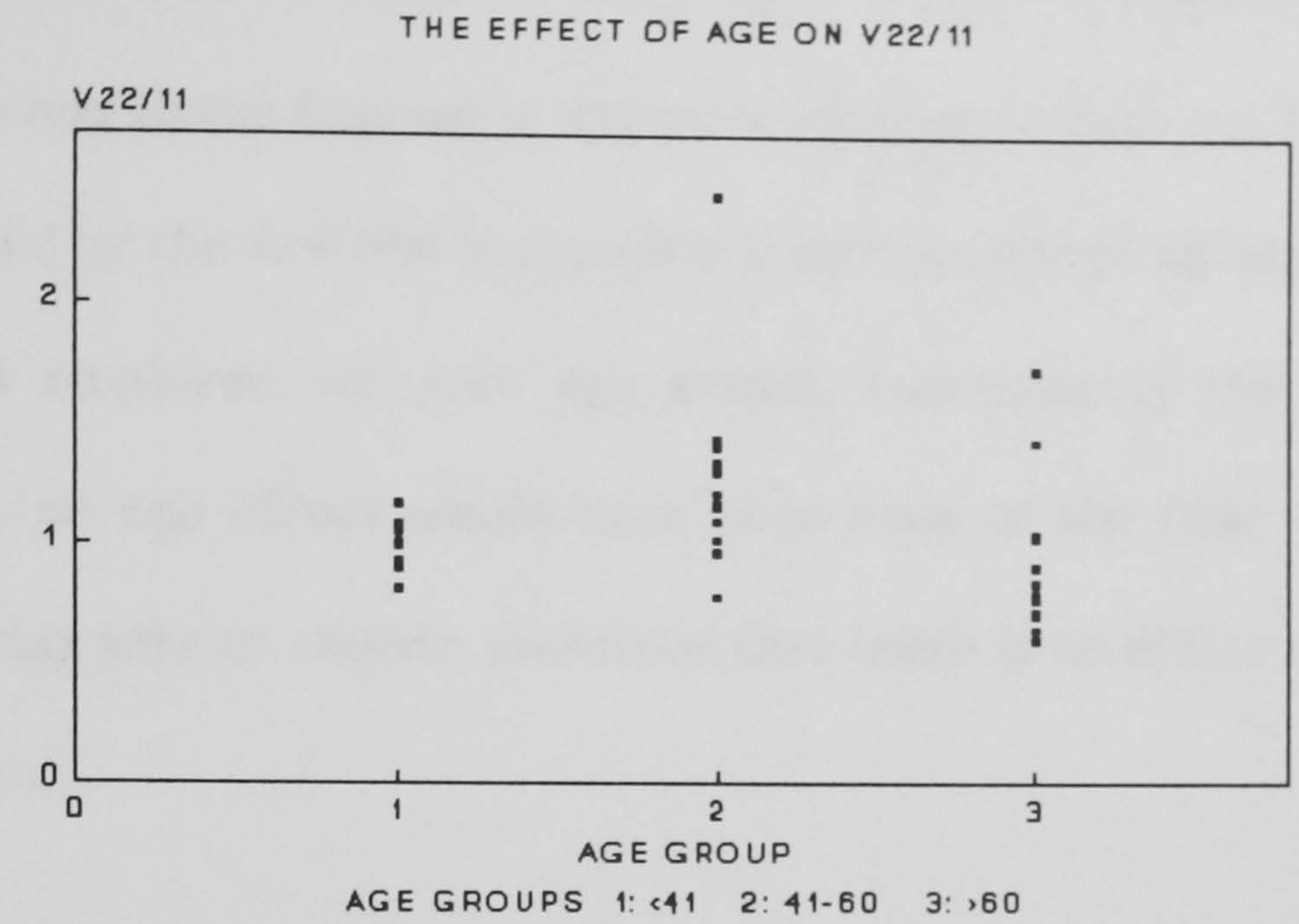
The wave V rate-induced amplitude decrement variables V22/11 and V44/11 had significant age effects. Because of the close similarity with variables V66/11 and V88/11, all four were analysed further. Since three age groups were used in the ANOVA, a significant age dependency can be identified by a straightforward linear (monotonic) relationship with age or a non-linear relationship. The overall significance p value together with those of the linear and non-linear components can help uncover the underlying trend. The following p values were obtained for the four variables.

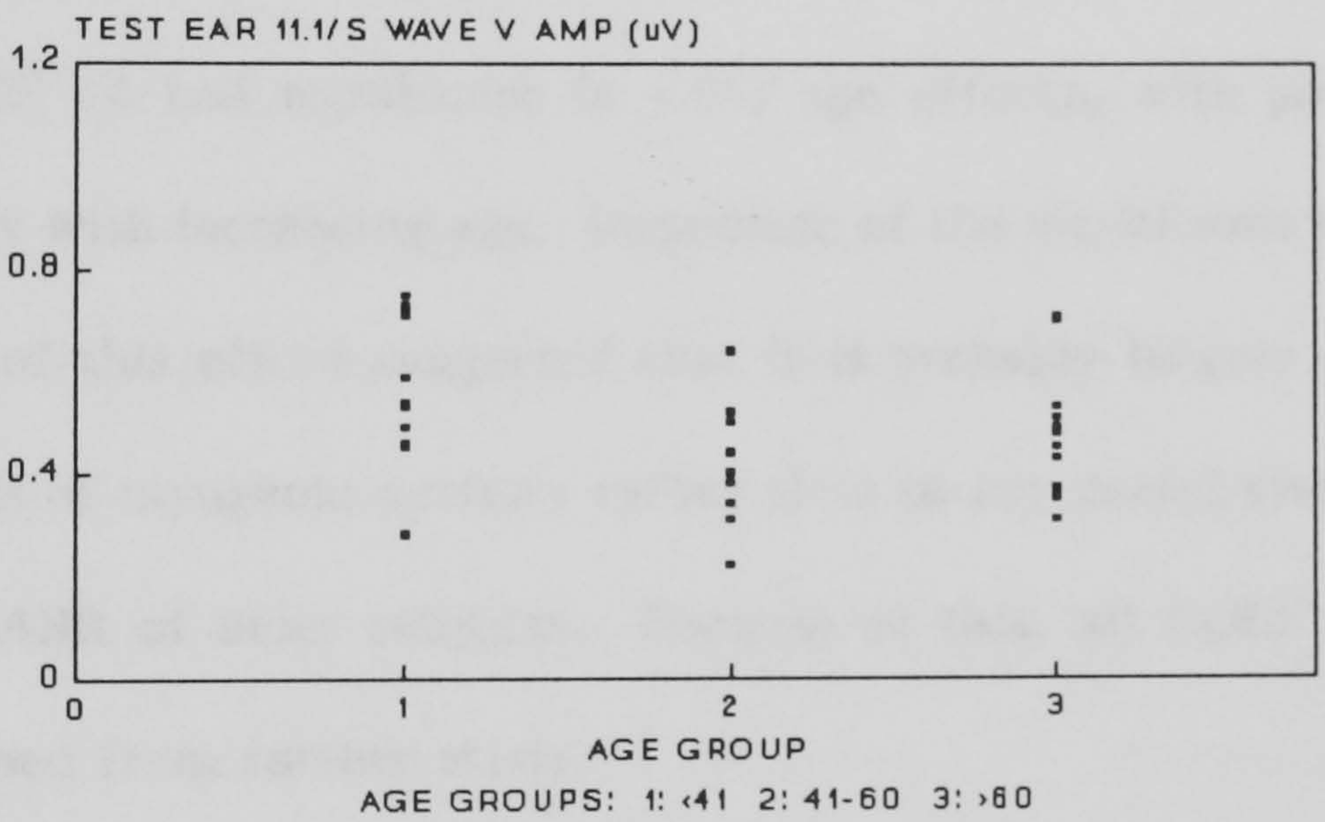
Table 3.1.1.3(a)

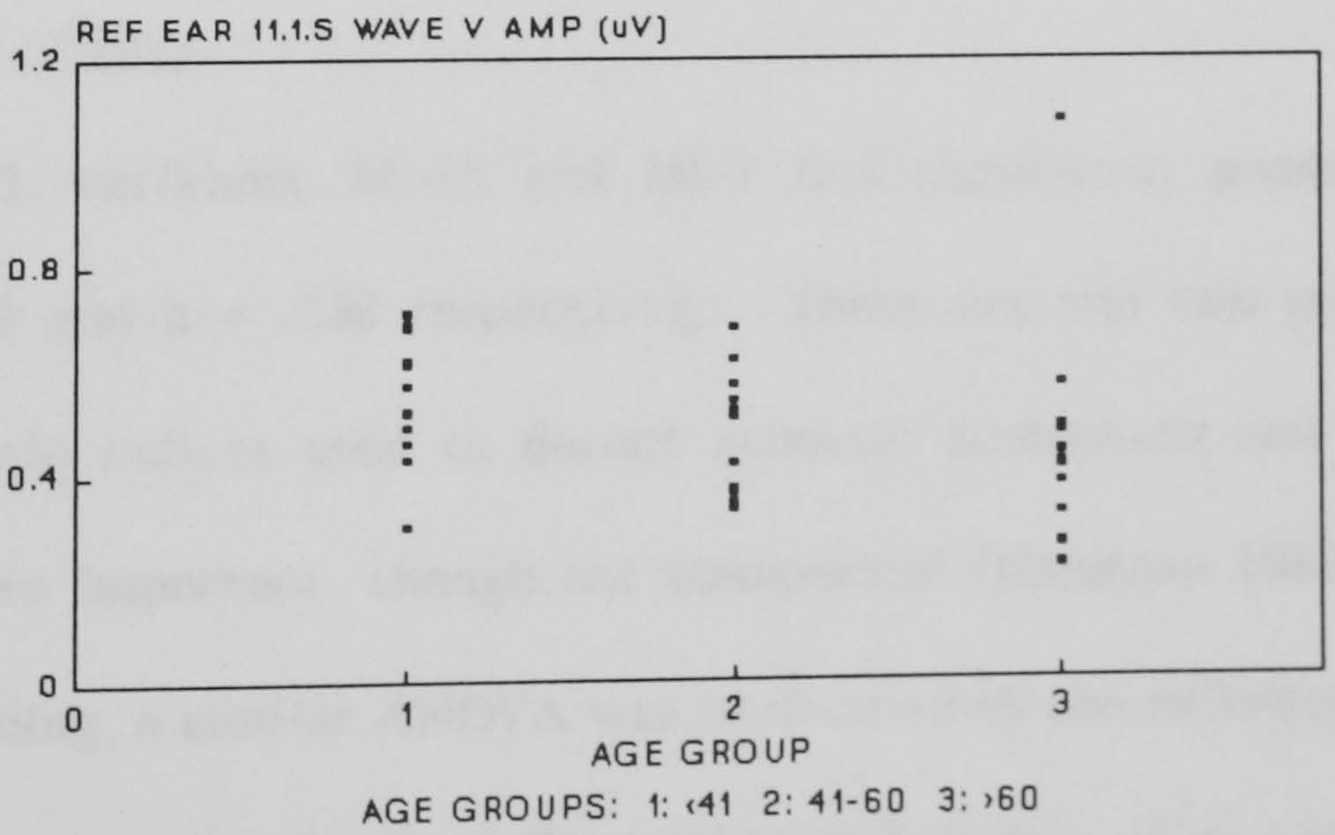
Variable	Age	Linear	Non-linear
V22/11	.033	.514	.011
V44/11	.039	.209	.045
V66/11	.053	.589	.018
V88/11	.092	.573	.034

Table 3.1.1.3 (a) clearly demonstrates that there is no significant linear age effect on any of these variables but that there *is* a non-linear age effect. The common component in all four variables is the denominator: the 11.1/s wave V amplitude. Figure 3.1.1.3 (b) (top) illustrates V22/11 in three age groups. The centre portion of the figure shows the 11.1/s wave V amplitude and shows how the dip for the middle age group is responsible for the peak for this group in V22/11.

Figure 3.1.1.3(b)







Is this finding repeatable? To test this, the 11.1/s wave V amplitude from the reference ear is shown in the bottom portion of Figure 3.1.1.3 (b), and no such non-linear feature is apparent suggesting that the age dependency identified by the ANOVA is probably a spurious sampling anomaly. Had the ANOVA employed only two age groups, representing the young and the elderly, no age effect would have been seen in the first instance. It is reasonably safe to assume therefore that there is no effect of age on these variables.

The waveform cross correlation variables COEF44, COEF66 COEF88 and AVCOEF all had significant ($p < .05$) age effects, with poorer waveform stability with increasing age. Inspection of the waveforms for clues to the source of this effect suggested that it is probably largely due to variable amounts of myogenic activity rather than to any useful systematic change in the ABR of older subjects. Because of this, all COEF variables were abandoned from further study.

Gender effects

Two IPL variables, MI-III and MI-V had significant gender differences: $p = .019$ and $p = .038$ respectively. These are the two most established diagnostic indices used to detect acoustic neuromata and this finding is therefore important, though not unexpected (Thornton 1987). To confirm this finding, a similar ANOVA was performed on the *reference* ear IPLs and again gender was clearly influential upon I-III ($p = .004$) and I-V ($p = .002$). Separate male and female norms are therefore required.

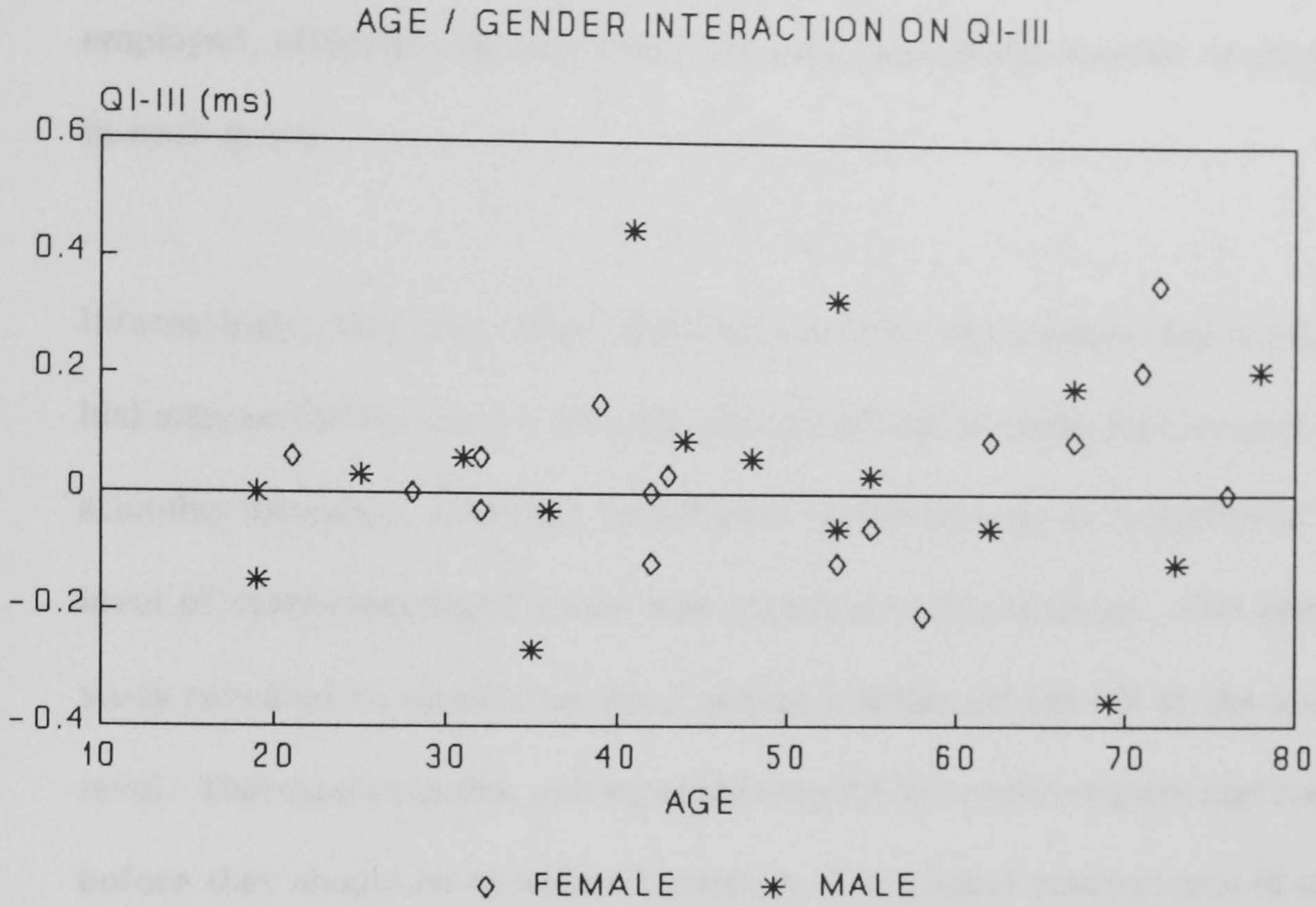
The per-stimulatory wave V latency jitter variables JIT44 and AVJIT had gender effects (p = .002 and p = .027). Separate gender norms are therefore required for these.

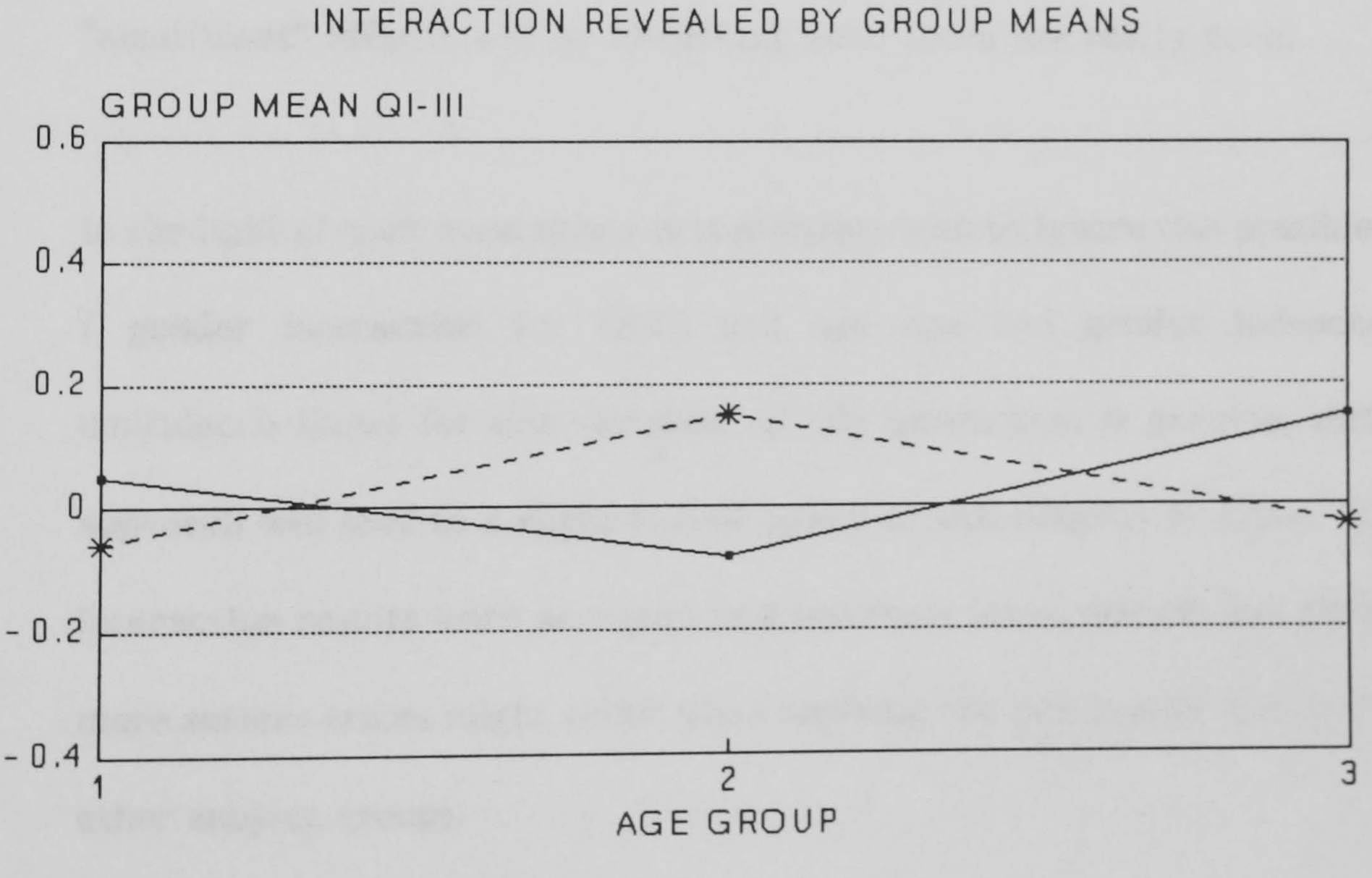
Gender was not found to have a significant effect on the other variables at the p = .05 level.

Age / gender interaction

The 2-way ANOVA allowed this interaction to be evaluated and in only one variable was there a significant effect at the p = .05 level. The QI-III variable (ie the difference in the I-III IPLs of a subject's two ears) had an age / gender interaction p = .006. Figure 3.1.1.3(c) illustrates this using a scatterplot of the data although careful examination is required to observe the interaction. The lower portion of the figure is clearer. Here, the mean value of QI-III is plotted for each gender in each of the three age groups in the ANOVA. Such a polytonic effect is bizarre and difficult to accept as representative of the normal population, especially since this variable is an inter-aural difference with the subject's test and reference ears being chosen randomly.

Figure 3.1.1.3 (c)





Such findings *can* occur erroneously by chance. The significance of the interaction becomes less ($p = .117$) if six, rather than three age groups are employed, although this procedure of course halves the number of subjects in each group.

Interestingly, Thornton (1987) reported a similar and unusual (my word, not his) interaction for the I-V IPL, the pattern of which markedly changed with stimulus intensity. Although he referred to the effects as "significant", no level of statistical significance was attached to his findings. The present study revealed no significant age / gender interaction for I-V at the $p = .05$ level. Thornton's results, and especially my QI-III results require replication before they should be considered genuine. The logical consequence of using a significance level of .05 is that the chances are one in twenty that "significant" effects will be identified when there are really none.

In the light of such uncertainty it is probably wise to ignore this possible age / gender interaction for QI-III and use age and gender independent confidence limits for this variable. If the interaction *is* genuine, such an approach will lead to a slight loss of power of this diagnostic index. If the interaction results were accepted and accommodated when it was illusory, more serious errors might occur when applying the criteria for this index to other subject groups.

3.1.1.4 *Determination of 95% confidence limits*

Having examined the variables for any dependency on age and gender it is now possible to calculate their appropriate 95% confidence limits to permit comparison of patient groups to normal subjects. Before doing so however, two issues need to be considered.

The first is whether the confidence limits should be calculated from a single or 2-tailed distribution. This depends on whether we have a priori expectation of the directionality of an abnormal finding (Sklare 1990). Diagnostic indices such as the I-V IPL are used in the knowledge that a neurologically abnormal result has a value greater than normal and so we are interested in only one tail of the distribution. A single tail 95% confidence limit is at 1.645 times the standard deviation (σ) above the mean. For some indices though, we may have no such prior knowledge and an abnormal result may lie in either tail of the distribution of the reference data. An example is the ILDV and indeed most other measures of inter-aural asymmetry (actually, for many patients we *do* have a "suspect" ear and it is debatable whether in such cases a 1-tailed derivation for the confidence limit is more valid). For the purposes of this study, such variables will be considered as having 2-tailed 95% confidence limits leading to lower and upper criteria at 2.5% and 97.5% of the distribution. These values are calculated as the mean $\pm 1.96\sigma$.

The second issue concerns the mean of the inter-aural variables. These were calculated and as expected, were all very close to zero. The question is: are their means significantly differently from zero or can we accept that their non-zero means are within the limits of sampling error and that the population this sample represents has a genuine zero mean. The appropriate variables were subject to a one sample T-test against the value 0. None was rejected ($p > .2$ in all cases) so they may be assumed to have zero means. The confidence limits for these variables are therefore symmetrical about zero. Although Table 3.1.1.4 shows the actual sample means for these variables, which are indicated "(*)", their 95% confidence limits are calculated from $\pm 1.96\sigma$ (ie 2-tailed) and assume a *zero* mean.

The 1-tailed confidence limits are prefixed by ">" or "<" to illustrate the directionality implicit in use of a 1-tailed limit. Note that to use these confidence limits as diagnostic indices, the sign needs to be reversed! At this point it is prudent to spell out the perhaps obvious assumptions that for the latency measures, an abnormal result will be one in which the latency is extended beyond normal limits and for amplitude/rate measures, an abnormal result will be one in which there is an abnormally great reduction with increasing rate.

The table also shows the "applicability" of each variable. This is the proportion of cases in which the variable was able to be measured. As one would hope when testing a normal group, applicability was high.

TABLE 3.1.1.4

MEANS AND 95% CONFIDENCE LIMITS FOR GROUP A VARIABLES

VARIABLE	MEAN	STD.DEV.	95% C.L.	%APPLIC	TAILS
MI-III (F)	2.1159	0.1056	<2.2896	94	1
MI-III (M)	2.2465	0.1894	<2.5581	94	1
MIII-V	1.9017	0.1578	<2.1613	100	1
MI-V (F)	4.0006	0.2119	<4.3492	94	1
MI-V (M)	4.1541	0.2140	<4.5061	94	1
MI/V	0.4994	0.4502	<1.2400	100	1
QI-III (*)	0.0282	0.1676	±0.3285	94	2
QIII-V (*)	0.0347	0.2098	±0.4112	100	2
QI-V (*)	0.0059	0.2190	±0.4292	94	2
ILDV (*)	0.0294	0.1835	±0.3600	100	2
ILDV44 (*)	0.0089	0.1507	±0.2954	100	2
V22-11	0.0567	0.0731	<0.1770	100	1
V44-11	0.1961	0.1159	<0.3868	100	1
V66-11	0.3686	0.1383	<0.5961	100	1
V88-11	0.4958	0.1502	<0.7429	100	1
V22/11	1.0810	0.3376	>0.5257	100	1
V44/11	1.0981	0.4796	>0.3092	100	1
V66/11	0.9912	0.3396	>0.4326	100	1
V88/11	1.0144	0.4451	>0.2822	100	1
QV44-11 (*)	0.0317	0.1490	±0.2920	100	2
QV88-11 (*)	0.0022	0.2202	±0.4316	100	2
JIT22	0.0154	0.1027	<0.1843	97	1
JIT44 (F)	0.0750	0.0939	<0.2295	100	1
JIT44 (M)	-.0183	0.1201	<0.2159	100	1
JIT66	0.0641	0.1308	<0.2793	94	1
JIT88	0.0326	0.1033	<0.2025	97	1
AVJIT (F)	0.0563	0.0359	<0.1154	89	1
AVJIT (M)	0.0194	0.0535	<0.1074	100	1

(*) Although the recorded means are quoted for these variables, their confidence limits assume a zero mean and are therefore symmetrical about zero (since K-S test results show that their distributions are not significantly non-normal, and therefore not asymmetrical).

3.1.2 The effects of test protocol

In this study, there are differences in the way in which the tests were performed on each ear and the way in which the data were manipulated. Since comparisons will be made of the results obtained from each ear and between different variables for the same ear, the possible effects of test protocol need to be considered and evaluated.

3.1.2.1 *The effects of digital filtering*

One of the claimed advantages of digital filtering over analogue filtering is that it does not introduce any time or phase shift in the filtered waveform. In this study, the full rate series data of the test ear was subject to a low pass 2kHz digital filter whereas the start, end and mean waveforms and all reference ear waveforms were not.

To test for any effect of digital filtering, paired T-tests were conducted between test ear 11.1/s wave I, III & V latencies and amplitudes and I-III, III-V & I-V IPLs in both filtered and unfiltered form. No significant differences were identified at the $p = .05$ level, demonstrating that digital filtering indeed does not perturb the data.

3.1.2.2 *Effects of interruption of the stimulus in the rate series*

In the reference ear, the waveforms generated with SRRs of 44.4/s and 88.8/s were obtained with conventional continual stimulation in a similar fashion to all 11.1/s waveforms. In the test ear, SRRs of 22.2/s and above had stimuli which were periodically interrupted by a 10 second stimulus-free period. For the results of test ear rate effects to be validly compared to those obtained from the reference ear and to results derived from other studies, any effect of stimulus interruption on the grand average waveform for each SRR needs to be insignificantly small. Paired T-tests were conducted between test ear variables V44-11 & V88-11 and their reference ear counterparts. No significant differences were apparent at the $p = .05$ level.

It should be noted that the waveforms from which these variables were derived were digitally filtered in the case of the test ear but were not in the case of the reference ear. However, the effects of digital filtering have been shown to be insignificant and the chance of very slight and opposite effects resulting in this finding are acceptably remote. It therefore appears that the periodic interruption of a higher rate stimulus every 600 or 1200 clicks does not materially modify the wave V latency of the grand average and the results obtained in this way can be considered equivalent to those from continuous stimulation.

3.1.3 Stimulus repetition rate effects

Section 3.1.1 (ABR Diagnostic Indices) included several variables based upon SRR effects. This section examines SRR effects in more detail.

3.1.3.1 *The linearity of latency shift with increasing rate*

In section 1.3.2 reference was made to the observation by several investigators that the latency of wave V increased in a seemingly linear fashion with SRR and hence the term "μs/decade" was used. In order to investigate the validity of this conclusion in normal subjects a 2-way ANOVA was performed on wave V latency with subjects (36) and rate (5 levels) as factors. Orthogonal polynomial contrasts for the rate factor with the ratios 1:2:4:6:8 were used to account for the rates used in the study. This allows the linear, quadratic, cubic and quartic components to be evaluated in the relationship between latency and rate.

The wave V latency (VLAT) was analysed using the SPSS command:

```
MANOVA VLAT BY RATE (1,5) SUBJ (1,36)
/PRINT PARAMETERS (ESTIMATES) SIGNIF (SINGLEDF)
/OMEANS TABLES (RATE)
/CONTRAST (RATE) POLYNOMIAL (1,2,4,6,8)
/ERROR RESIDUAL
/DESIGN RATE SUBJ
```

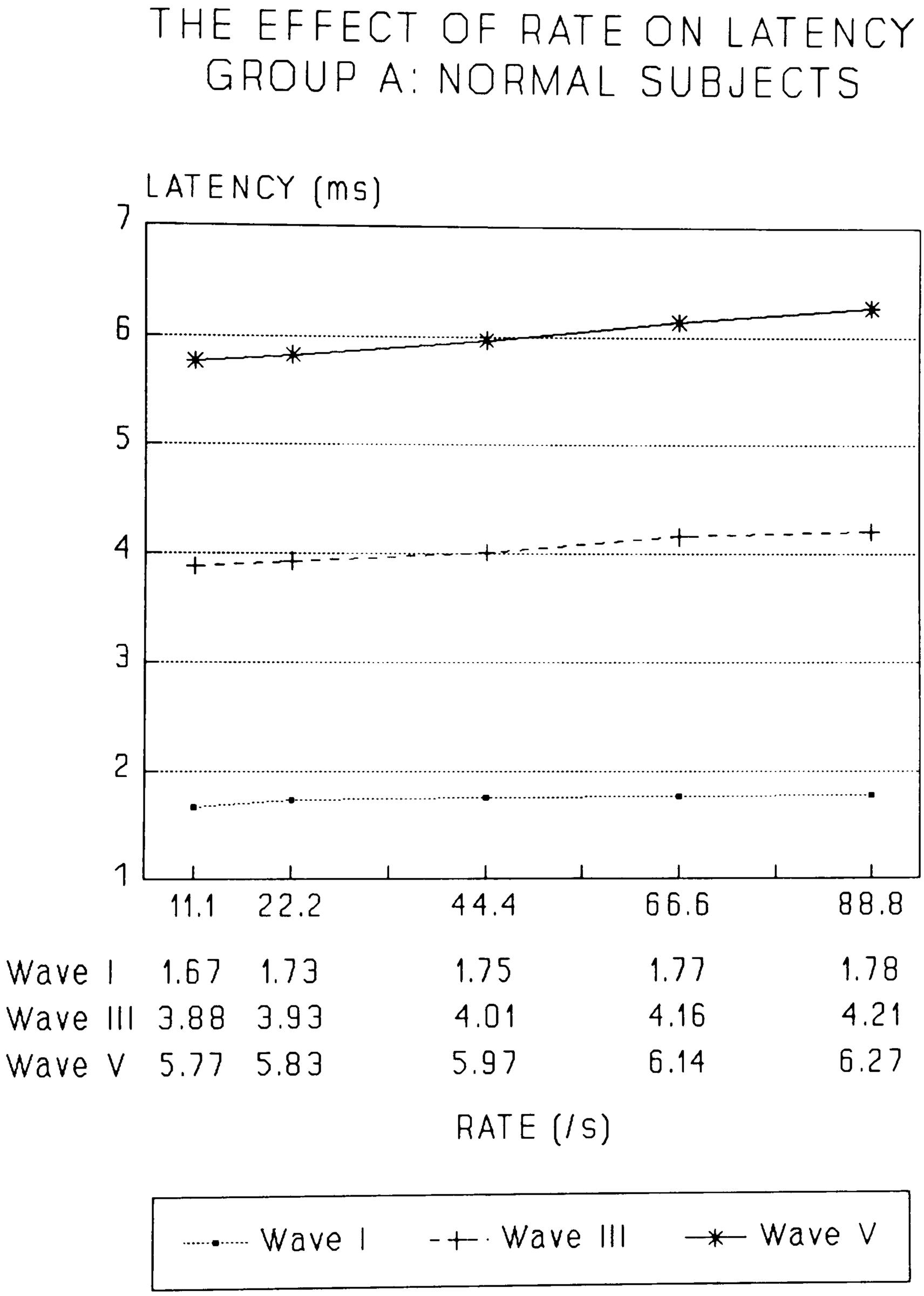
Similar analyses were performed for waves I & III. For all three waves, the linear component of the latency / rate function was significant at the p=.001 level and none of the non-linear components was significant at the p=.05

level. This suggests that a straightforward linear model adequately describes the latency / rate relationship for all three waves and that the term "μs/decade" is a valid descriptor of the slope of these functions. Figure 3.1.3.1 (a) depicts the mean latency across subjects of waves I, III & V at each rate and demonstrates the linearity of the functions.

The results of the above statistical analyses provide some useful data. First, the sums of squares for the linear component of the rate effect can be divided by the sums of squares of the overall rate effect to give the proportion of the variability between rates that is explained by the linear component. In Table 3.1.3.1 (a), this figure, expressed as a percentage, is denoted by "%Lin". Second, the slopes of the latency / rate functions may be derived and expressed in terms of μs/decade (for details see Appendix C). In addition to the mean (or best fit) slope, The ANOVA output provides the 95% confidence limits for the slope. This is obviously valuable in establishing the confidence of the slope estimate but also aids comparison with the range of slopes published in previous studies reviewed in Section 1.3.2.1. These figures also appear in Table 3.1.3.1 (a). The results show that the present study is in good agreement with previous studies. Note, however, the very wide range of values quoted across studies.

As far as can be determined from reading the research literature, no other study has used this level of sophistication in the analysis of SRR effects. Latency / rate slopes have instead been calculated by simple methods which do not provide details of slope linearity or confidence limits.

Figure 3.1.3.1 (a)



	11.1	22.2	44.4	66.6	88.8
Wave I	1.67	1.73	1.75	1.77	1.78
Wave III	3.88	3.93	4.01	4.16	4.21
Wave V	5.77	5.83	5.97	6.14	6.27

Data rounded to 3 significant figures

Table 3.1.3.1 (a)

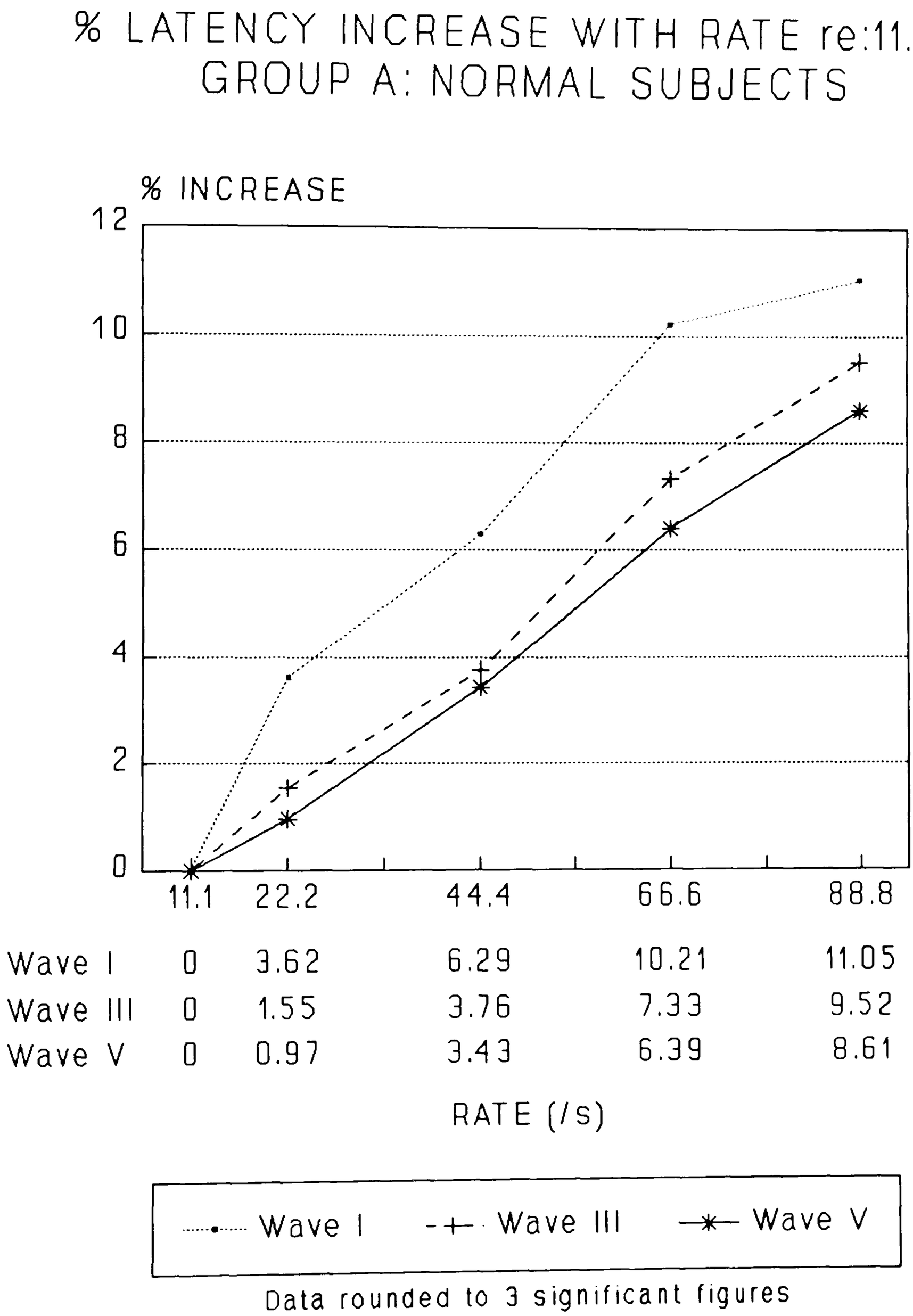
The linearity and slope (in μs/decade) of the latency / rate functions of waves I, III & V in Group A subjects

ABR Wave	%Lin	Mean Slope	95% Conf. Limits Lower	Upper	Previous Studies
I	95.4	23.94	18.18	29.70	13 - 71
III	99.4	47.37	43.63	51.11	33 - 61
V	99.7	65.47	61.12	69.83	35 -100

How do the slopes of the latency / rate functions for the three waves compare when expressed as a percentage shift of the wave's latency at 11.1/s? Recall that from the literature, the greatest percentage shift was recorded for wave I and that the shifts for waves III & V were less, and approximately equal. Figure 3.1.3.1 (b) shows these data obtained from the present study and illustrates exactly that trend described above.

Consider, for a moment, that contained within all recorded latencies will be a static time delay due to the propagation of the stimulus from the transducer through the ear canal, middle ear system to the basal turn of the cochlea. If this component were to be subtracted from all latencies in order to examine the "neurological" element of the latencies, the three curves in Figure 3.1.3.1 (b) would fan out and reveal a steeper slope for wave I over wave III, with wave III in turn being steeper than wave V.

Figure 3.1.3.1 (b)



Wave I	0	3.62	6.29	10.21	11.05
Wave III	0	1.55	3.76	7.33	9.52
Wave V	0	0.97	3.43	6.39	8.61

Data rounded to 3 significant figures

Although all ABR waves have no significant non-linear component, wave I exhibits the most non-linear variability, albeit less than 5%. Inspection of Figures 3.1.3.1 (a) & (b) reveals a disproportionate latency shift in wave I between 11.1/s and 22.2/s. The mean difference in latency here is only 0.06ms, representing only two data points on the ABR waveform (cursor resolution = 0.03ms). There may be some element of "quantisation error" causing this finding.

This finding may be real, however. Comparison of these results with those reviewed from the literature shows that for rates up to about 40/s, a greater latency shift has been observed than one described by a linear regression (least squares) model covering all available rates. In Figure 1.3.2.1, all data points up to 40/s are on or above the regression line, suggesting that others have observed the same trend as in this study, that at modest increases in SRR, wave I exhibits a somewhat greater percentage rate shift than that seen at higher rates, not only in wave I but also in waves III & V.

Figure 3.1.3.1 (b) also shows that ABR waves III & V exhibit broadly similar *percentage* latency changes with rate. This has an important implication with regard to the way in which rate-induced latency shift measurements are used clinically since one might reason that a greater rate-induced shift will accompany a long latency wave. It is therefore vital that the effects of absolute latency are considered when analyzing latency shift data in clinical populations where longer absolute latencies might be encountered.

In other words, there may be more merit in considering *percentage* rate-induced latency shifts in clinical populations if this helps offset a systematic interaction between absolute latency and latency shift. To this end, additional variables need to join those considered in Section 3.1.1. Table 3.1.3.1 (b) is therefore an addendum to Table 3.1.1.4 and provides summary statistics of the following:

PV22-11 the percentage increase in latency of wave V as the rate is increased from 11.1/s to 22.2/s

PV44-11 the percentage increase in latency of wave V as the rate is increased from 11.1/s to 44.4/s

PV66-11 the percentage increase in latency of wave V as the rate is increased from 11.1/s to 66.6/s

PV88-11 the percentage increase in latency of wave V as the rate is increased from 11.1/s to 88.8/s

These four variables were subject to the same K-S and 2-way ANOVA tests as the other variables and the results indicated that none of their distributions was significantly non-normal ($p>.1$ in all cases) and that there were no significant age or sex effects at the $p=.05$ level.

TABLE 3.1.3.1 (b) (Addendum to Table 3.1.1.4)

MEANS AND 95% CONFIDENCE LIMITS FOR ADDITIONAL GROUP A VARIABLES

VARIABLE	MEAN	STD.DEV.	95% C.L.	%APPLIC	TAILS
PV22-11	0.9733	1.2512	<3.032	100	1
PV44-11	3.4248	2.0051	<6.723	100	1
PV66-11	6.3911	2.3771	<10.301	100	1
PV88-11	8.6051	2.6162	<12.909	100	1

3.1.3.2 *The effect of rate on IPLs*

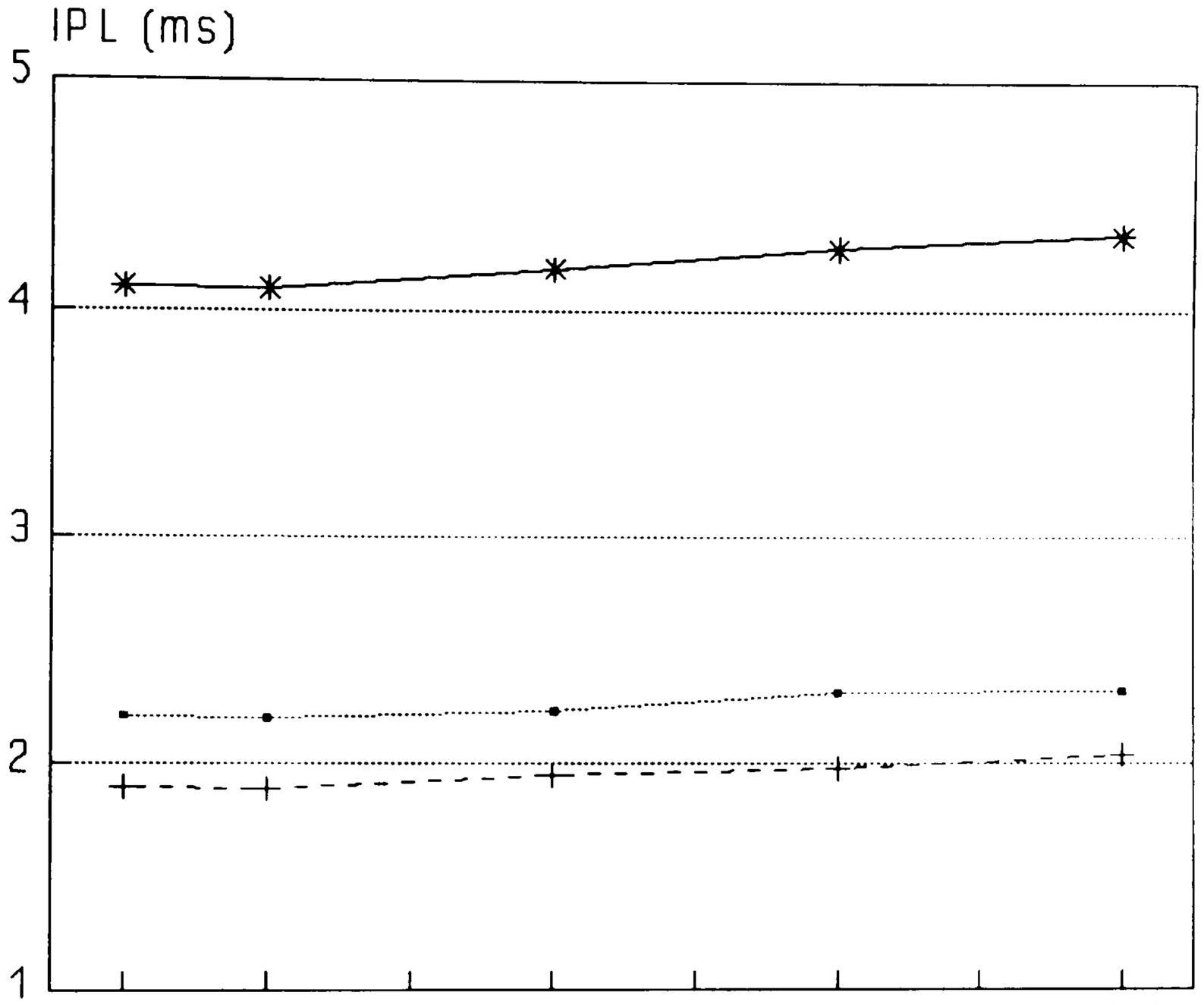
If the latency / rate functions of ABR waves I, III & V are genuinely linear, the I-III, III-V and I-V IPLs will be also linear. The preceding section alluded to a slight non-linearity in the wave I function although it failed to achieve any meaningful level of statistical significance. To examine the effects of SRR on the IPLs, the three IPLs were derived for each subject at each rate and these data were analysed in a similar fashion to that used for the absolute latencies.

For each IPL, the linear component was significant at the p=.001 level and none of the non-linear components was significant at the p=.05 level. Like the absolute latencies, this suggests that a linear model adequately describes the SRR / IPL relationship and that again, the term "μs/decade" is appropriate. Statistical purists may balk at this analysis however. Unlike the analysis for absolute latencies, IPLs are a derived measure and contain two sources of potential error rather than one, which affects the degrees of freedom used in the calculations. To overcome this objection a more elaborate ANOVA was performed on latency, including WAVE (3 levels) as a factor. The rate by wave linear component was still significant at the p=.001 level and none of the non-linear components was significant at the p=.05 level, suggesting that all three IPLs change linearly with rate.

Figure 3.1.3.2 (a) shows the mean IPLs of all subjects at each rate.

Figure 3.1.3.2 (a)

THE EFFECT OF RATE ON IPL
GROUP A: NORMAL SUBJECTS



	11.1	22.2	44.4	66.6	88.8
I-III	2.21	2.2	2.23	2.31	2.32
III-V	1.9	1.89	1.95	1.98	2.04
I-V	4.1	4.09	4.18	4.27	4.33

Data rounded to 3 significant figures

Table 3.1.3.2

The linearity and slope (in μs/decade) of the IPL / rate functions in Group A subjects

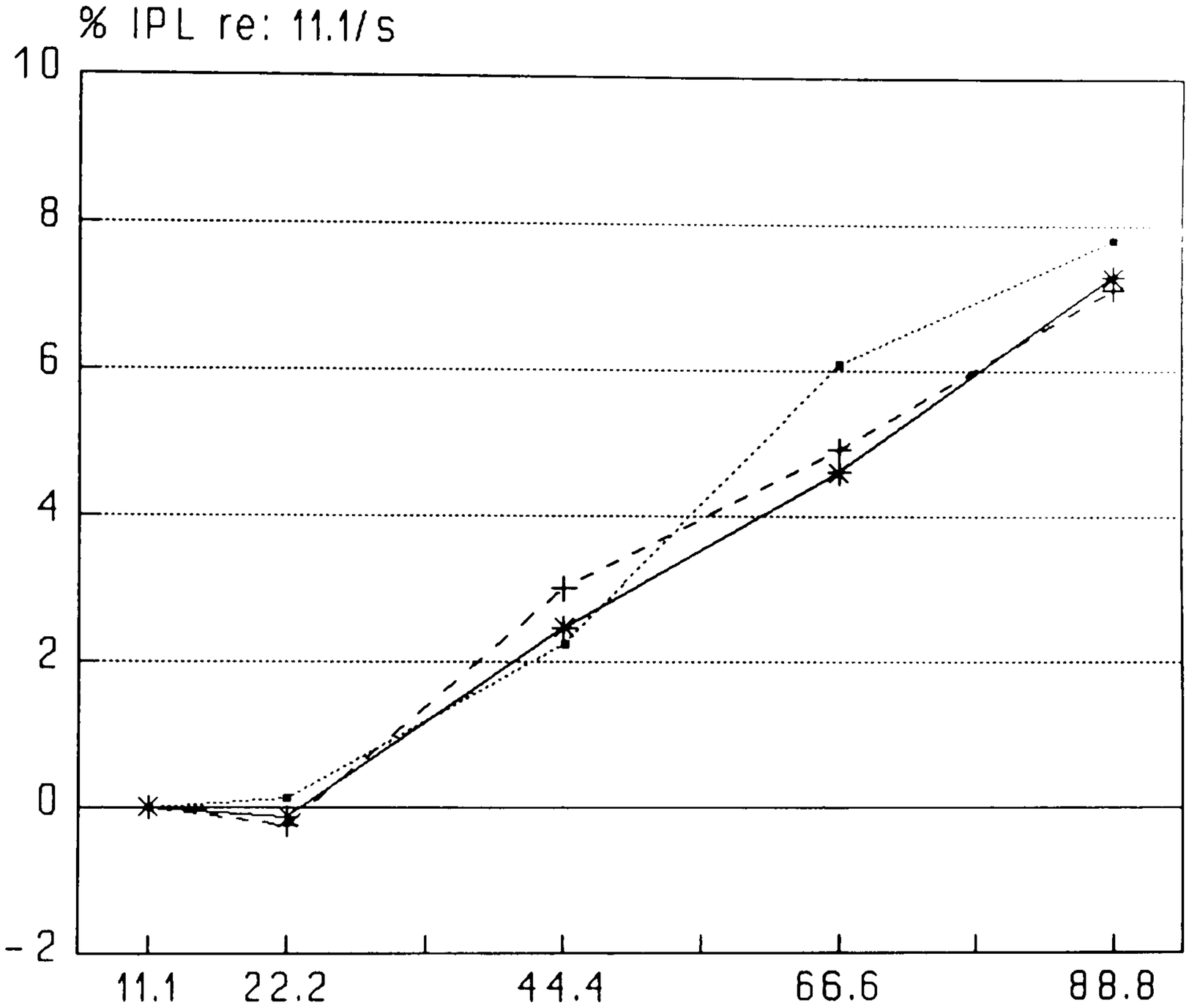
IPL	%Lin	Mean Slope	95% Conf. Limits Lower	Upper	Previous Studies
I-III	92.9	22.80	15.87	29.74	17 - 33
III-V	95.8	18.25	12.63	23.88	9 - 17
I-V	96.7	38.37	31.83	44.90	29 - 64

Table 3.1.3.2 summarises the results of the IPL analysis in the same format and nomenclature as Table 3.1.3.1 (a). It is reassuring that the slopes of these IPL / rate functions are almost exactly that which is obtained by appropriate subtraction of the slopes of the individual ABR wave latency / rate functions.

Like absolute latencies, IPL rate effects can be expressed as a percentage shift relative to 11.1/s and this is illustrated in Figure 3.1.3.2 (b). Here we see an unexpected and fascinating finding: all three IPL / rate functions, which should be a straight line, actually appear to kink, with zero slope (no effect of rate upon IPL) between rates of 11.1/s and 22.2/s, followed at higher rates by the expected linear trend. Also worthy of note is that in percentage terms, all three IPLs appear to exhibit very similar rate effects.

Figure 3.1.3.2 (b)

% IPL INCREASE WITH RATE re:11.1/s
GROUP A: NORMAL SUBJECTS



I-III	0	0.12	2.23	6.08	7.8
III-V	0	-0.24	3	4.91	7.13
I-V	0	-0.14	2.46	4.6	7.29

Data rounded to 3 significant figures

The fact that this kink in the IPL / rate functions was not revealed in the statistical analyses may be a consequence of the loss of precision of the first analysis due to the IPLs being a derived measure. Incidentally, if the IPLs are accepted as a derived measure, then so of course are amplitude measurements (peak to trough), as are interaural measures such as ILDV. In the second, more elaborate ANOVA, a full factorial design was prohibited by SPSS memory limitations. The subject factor had to be excluded, resulting in a residual sums of squares which was much greater than the linear rate by wave sums of squares. Under these conditions, it is not surprising that a linear, and only a linear component was significant.

Taken at face value, Figure 3.1.3.2 (b) suggests that rate might have no effect on IPL between 11.1/s and 22.2/s. To test this, each IPL was subject to a paired T-test to see if their values at the two rates were different. None was at the p=.05 level (indeed, all three had p>.75).

This means that although waves I, III & V undergo a latency prolongation between 11.1/s and 22.2/s, the IPLs do not change. Further, the standard deviations of the IPLs are almost identical at the two rates suggesting that the 95% confidence limits derived at 11.1/s may be used with validity at 22.2/s.

3.1.3.3 *The effect of rate on amplitude*

Although previous studies have suggested that ABR *latency* changes in a linear fashion with SRR, no such claims have been made of amplitude. Nevertheless, the ANOVA analysis technique with orthogonal polynomial contrasts for rate would seem to be a good starting point. The amplitudes of waves I, III & V were therefore examined in this way.

The results are in accord with the literature in that for waves I & III, there is a diminution of amplitude with increasing SRR. Indeed, the ANOVA reveals that there is a highly significant ($p<.001$) linear component. Non-linear components are insignificant (ie $p>.05$) for wave I amplitude and only the quartic component is just significant ($p=.048$) in wave III.

Figure 3.1.3.3 (a) shows the mean amplitudes of I, III & V versus SRR in normals. Unlike waves I & III, wave V does not show a monotonic change with rate and the ANOVA failed to identify any significant ($p<.05$) linear, quadratic, cubic or quartic elements in the relationship. Figure 3.1.3.3 (a) shows the increase in amplitude at around 40/s that has been reported widely and exploited in the "40Hz response". To test whether the wave V amplitudes at 11.1/s and 44.4/s are significantly different, a paired T-test was used. Although correlated ($r=.50$, $p=.002$), there was no significant difference in the two amplitudes ($p=.421$). In fact, similar T-tests between the wave V amplitude at 11.1/s and all other rates yielded the same conclusion - rate does not affect wave V amplitude.

The ANOVA again permits the calculation of the percentage of the variability which is explained by the linear component of the amplitude / rate function, together with the mean and 95% confidence limits for the slope, this time expressed in terms of nV/decade. Table 3.1.3.3 (a) documents these results but excludes data for wave V (for which rate had no significant effect) and excludes reference data from previous studies, since no other work has quoted amplitude slopes.

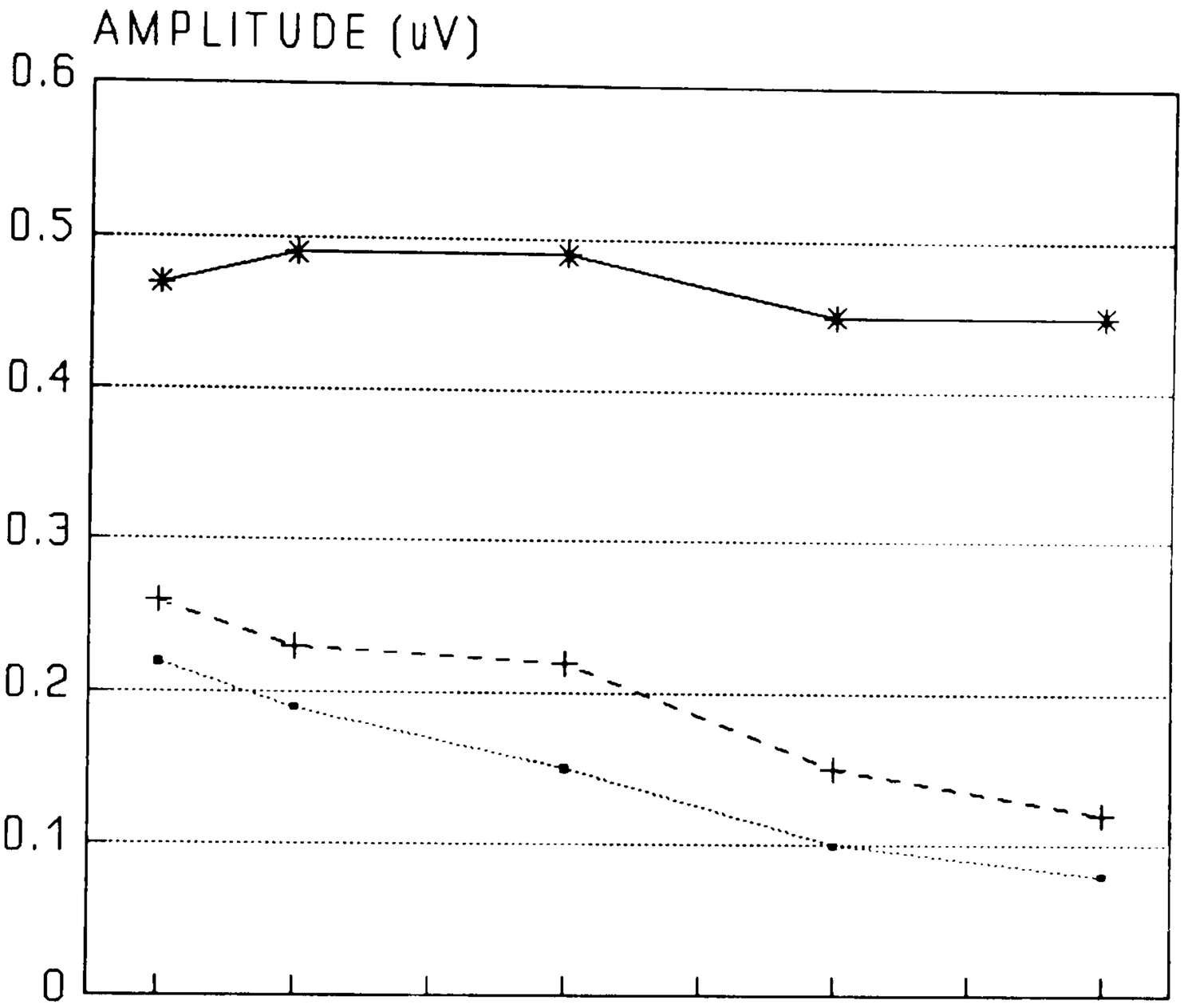
Table 3.1.3.3 (a)

The linearity and slope (in nV/decade) of the amplitude / rate functions of waves I & III in Group A subjects

ABR Wave	%Lin	Mean Slope	95% Conf. Limits Lower	Upper
I	98.0	-18.1	-21.3	-14.9
III	93.9	-17.9	-21.8	-13.9

Figure 3.1.3.3 (a)

THE EFFECT OF RATE ON AMPLITUDE
GROUP A: NORMAL SUBJECTS



	11.1	22.2	44.4	66.6	88.8
Wave I	0.22	0.19	0.15	0.1	0.08
Wave III	0.26	0.23	0.22	0.15	0.12
Wave V	0.47	0.49	0.49	0.45	0.45

RATE (/s)

Wave I Wave III Wave V

Data rounded to 3 significant figures

Unlike ABR latency, amplitude has a large inter-subject variability and consequently, instead of using an absolute measure such as nV/decade, intra-subject percentage changes are more often used. The amplitude of waves I, III & V at the rates 22.2/s to 88.8/s were therefore expressed as a fraction of the 11.1/s value in each subject. The mean results are shown in Figure 3.1.3.3 (b), illustrating a similar pattern to that seen in Figure 3.1.3.3 (a) except that the 11.1/s figures of all three ABR waves are of course unity.

These data were used in a MANOVA analysis, allowing the *relative* amplitude changes to be expressed as a percentage change (re: 11.1/s) per decade, and so aid comparison with other studies. The results appear in Table 3.1.3.3 (b). As with absolute amplitude, waves I & III had a very significant ($p<.001$) linear rate component and no significant ($p>.05$) non-linear components. Again, wave V amplitude appears to be immune to SRR, the p-level of the combined rate components being $p=.265$.

Table 3.1.3.3 (b)

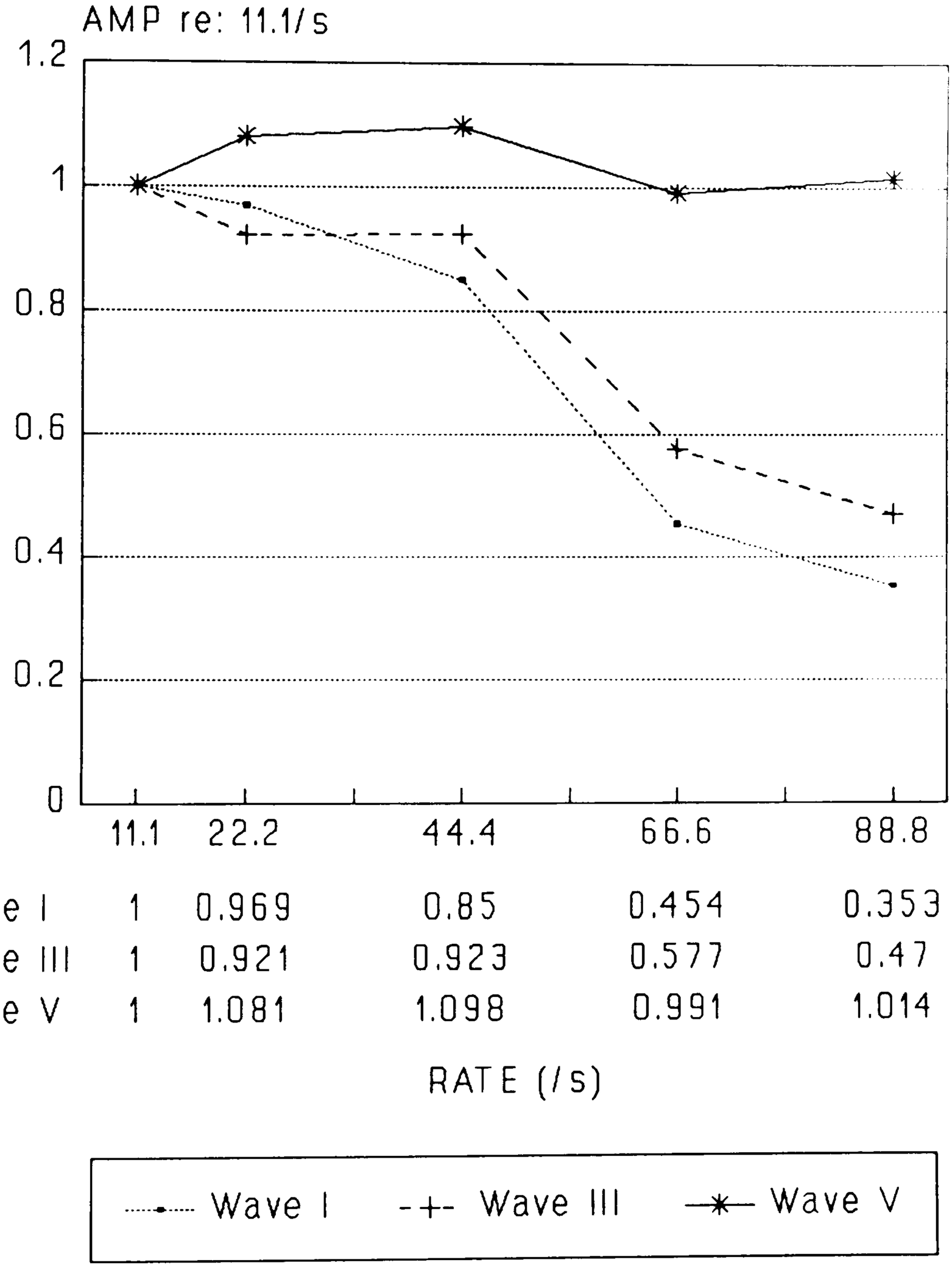
The linearity and slope (in %/decade re: 11.1/s) of the amplitude / rate functions of waves I & III in Group A subjects

ABR Wave	%Lin	Mean Slope	95% Conf. Limits Lower	Upper	Other Studies
I	93.3	-9.52	-12.22	-6.82	-10 to -38
III	90.3	-7.10	-9.17	-5.04	-6.2 to -9.5

Figure 3.1.3.3 (b)

RELATIVE AMPLITUDE BY RATE re:11.1/s

GROUP A: NORMAL SUBJECTS

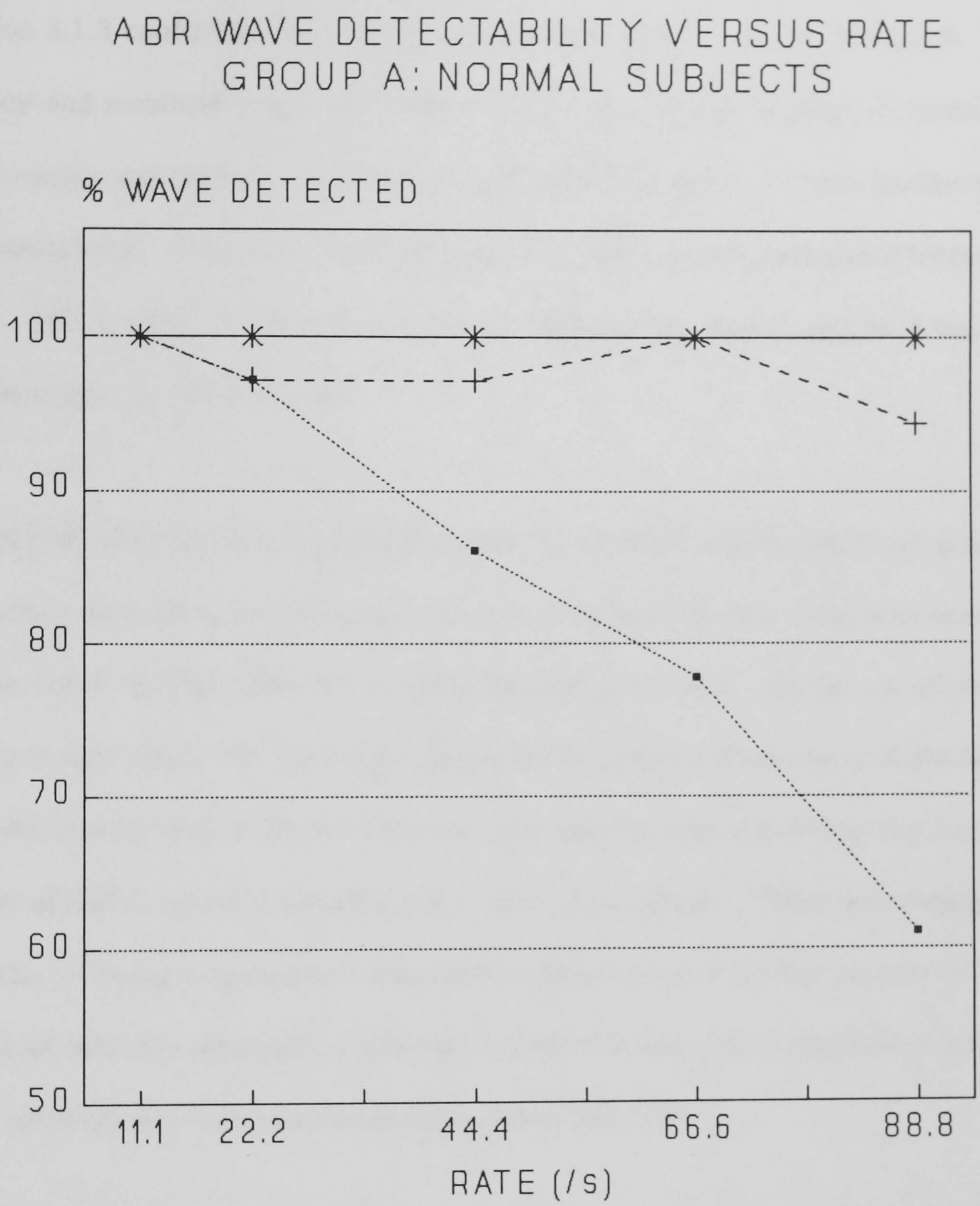


Wave I	1	0.969	0.85	0.454	0.353
Wave III	1	0.921	0.923	0.577	0.47
Wave V	1	1.081	1.098	0.991	1.014

3.1.3.4 *The effect of rate on ABR wave detectability*

Performing ABR tests at higher SRRs may or may not provide diagnostically useful information, but one clinically important characteristic needs to be established early on: does increasing SRR reduce our ability to recognise or detect ABR waves? Clearly, this has a close link to amplitude and in pathological populations there is likely to be an additional link with hearing loss. Figure 3.1.3.4 shows the percentage of the three ABR waves which were observed at the five SRRs. As expected, because of its low amplitude and susceptibility to rate-induced diminution, wave I is the most vulnerable. Any problems with wave I identification at slow SRRs are therefore likely to be exacerbated by the use of fast SRRs. The applicability of measures such as the I-III and I-V IPL at high stimulus rates would therefore be expected to be problematic and it is for this reason that this study concentrates upon the use of wave V at high stimulus rates.

Figure 3.1.3.4


ABR WAVE DETECTABILITY VERSUS RATE
GROUP A: NORMAL SUBJECTS
% WAVE DETECTED
100
90
80
70
60
50
11.1
22.2
44.4
66.6
88.8
RATE (/s)
Wave I
Wave III
Wave V

3.1.4 The time course of adaptation & recovery - click train tests

Section 3.1.3 confirmed the findings of previous studies on SRR effects on ABR latency and amplitude: that the latency of all three waves undergo a systematic prolongation and that the amplitudes of waves I & III systematically decline with increasing rate. Only wave V amplitude is the odd man out, being unaffected by rate. This section deals with the time course of the onset, and to a limited extent offset, of these effects.

Recall that from the three papers reviewed in Section 1.3.2.10, there was general agreement that for wave V latency, the steady-state high rate value was reached by the third to fifth click of an adapting stimulus train. As far as offset or recovery was concerned, Tietze & Gobsch (1980), using a 200ms inter-train silent interval, showed that a longer recovery time was necessary whereas the work of Don *et al* (1977) showed that 500ms was more than enough. Whilst acknowledging that the differing stimulation parameters in the studies will have influenced the extent of auditory adaptation, it would appear that the time required to achieve total recovery lies somewhere between 200ms and 500ms.

The inter-click interval of 11.3ms within the click trains used in this study allows direct comparison with the steady-state 88.8/s rate used in the rate study. The train repetition rates (TRR) of 3.1/s and 5.9/s were chosen to permit study of the effect of silent inter-train recovery period. Since both procedures employed eight clicks per train, these recovery periods were 243.5ms and 90.4ms respectively, the former being slightly more than Tietze & Gobsch's inadequate 200ms, and the

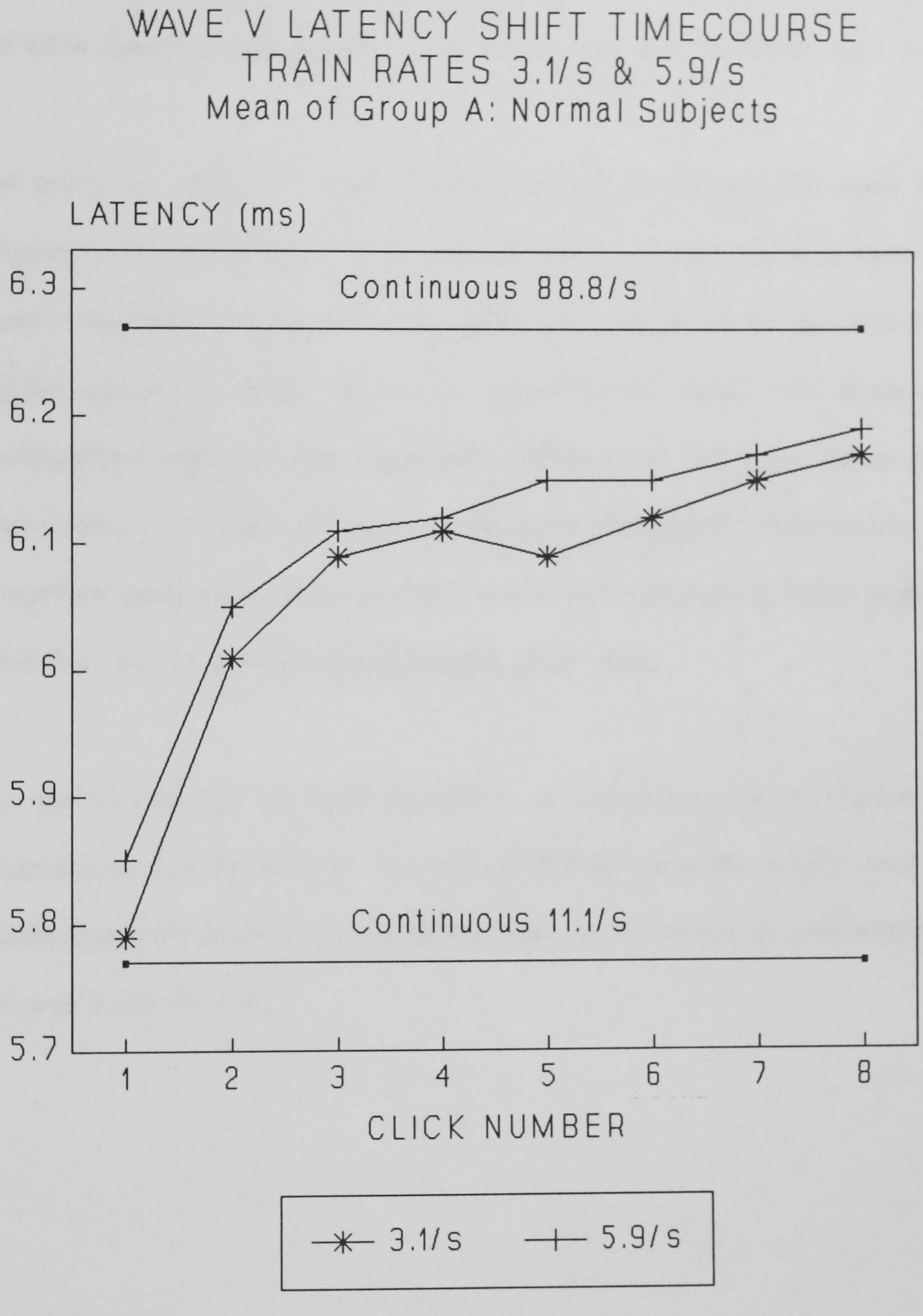
latter being equivalent to a standard 11.1/s as well as being the same period as that used by Thornton & Coleman (1975).

3.1.4.1 *Latency adaptation onset and recovery*

Figure 3.1.4.1 (a) shows how ***wave V*** latency changes during the eight click train at the two TRRs. The lower and upper horizontal lines indicate the steady-state latencies at 11.1/s and 88.8/s. It is clear that neither curve reaches the 88.8/s value and paired T-tests between the 88.8/s latency and each of the two TRR eighth click latencies showed that the differences were highly significant (p=.001). This finding is contrary to previous work since it suggests that more than eight clicks (at 88.8/s) are required for the wave V latency to become insignificantly different from the asymptotic 88.8/s value. A similar T-test between the two TRR eighth click latencies failed to reveal a significant difference (p=.454).

Turning to the recovery time course, how does the silent recovery period influence wave V latency? If both intervals (243.5ms & 90.4ms) are sufficiently long to provide complete recovery, then the first click latencies at the two TRRs should be similar, and both should equal the steady-state low rate (11.1/s) value. Figure 3.1.4.1 (a) shows, as expected, that this is not so with the 90.4ms period leaving some residual adaptation, shown by a longer latency wave V at the first click in the 5.9/s train. A T-test between this latency and the 11.1/s value confirmed that this difference was significant (p=.007) whereas the difference between the slower TRR

Figure 3.1.4.1 (a)



Standard Deviations

Click	1	2	3	4	5	6	7	8
3.1/s	.23	.30	.29	.27	.26	.27	.27	.29
5.9/s	.26	.27	.30	.25	.27	.26	.26	.27

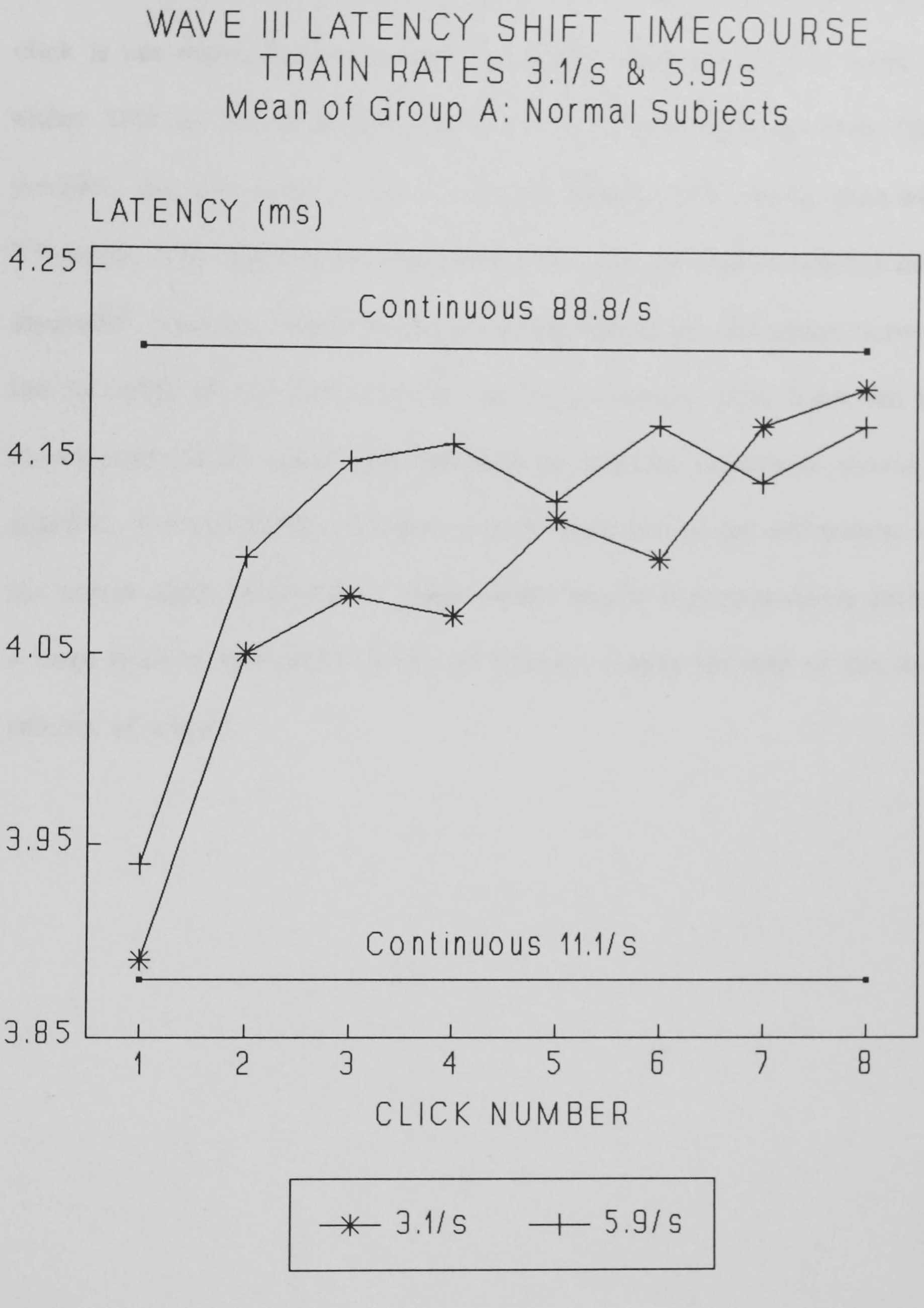
Continuous 11.1/s: .24 Continuous 88.8/s: .28

(243.5ms recovery period) wave V first click and the 11.1/s value was not significant (p=.288). This suggests that 243.5ms is probably sufficiently long to allow complete recovery and that 90.4ms is almost certainly not.

So much for wave V. Similar analyses were performed for ***wave III.*** Figure 3.1.4.1 (b) illustrates that wave III follows a similar trend to wave V, except that the latencies due to the eighth click are somewhat closer to the 88.8/s asymptote. Here, the T-tests comparing the eighth click latencies to the 88.8/s value were not significantly different (p=.332 & p=.391) for the two TRRs. The onset of the wave III latency adaptation time course is therefore more rapid than that for wave V, with adaptation being largely complete by the seventh or eighth click after onset.

As far as recovery of wave III latency is concerned, the conclusion is identical to that for wave V. A period of 243.5ms is probably sufficient to allow complete recovery (significance of latency difference: p=.266) whereas 90.4ms is not (p=.016).

Figure 3.1.4.1 (b)



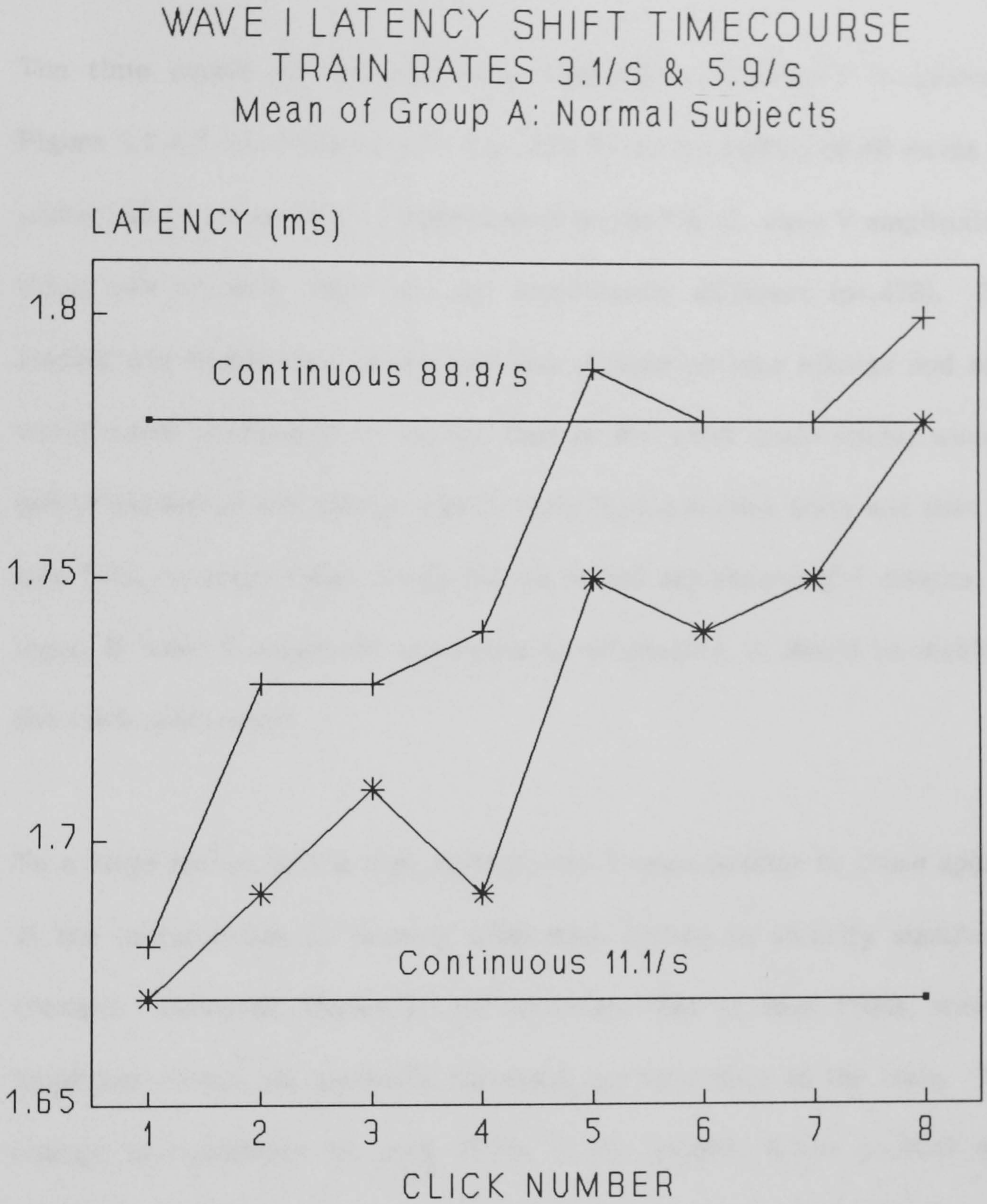
Standard Deviations

Click	1	2	3	4	5	6	7	8
3.1/s	.25	.28	.25	.25	.29	.28	.35	.32
5.9/s	.25	.29	.32	.28	.30	.27	.27	.31

Continuous 11.1/s: .25 Continuous 88.8/s: .26

Applying the same treatment to ***wave I*** latency, depicted in Figure 3.1.4.1 (c), like wave III and unlike wave V, the latency for the eighth click is not convincingly different from the 88.8/s asymptotic value for either TRR (p=.382 & p=.430) and there is no difference between TRRs (p=.906). So, like wave III, wave I latency adapts more rapidly than wave V latency. The significance results for the recovery time course are more equivocal, however. There is not a convincingly large difference between the latencies of the first click at the long recovery time train and the steady-state 11.1/s value although with p=.176, the conclusion should be guarded. For the 90.4ms recovery period there is a larger difference, but not convincingly so (p=.099). These rather woolly results probably reflect a large relative variability in wave I latency, maybe because of the short latency of wave I.

Figure 3.1.4.1 (c)



Standard Deviations

Click	1	2	3	4	5	6	7	8
3.1/s	.22	.23	.19	.17	.23	.22	.22	.21
5.9/s	.20	.20	.25	.21	.23	.23	.20	.23

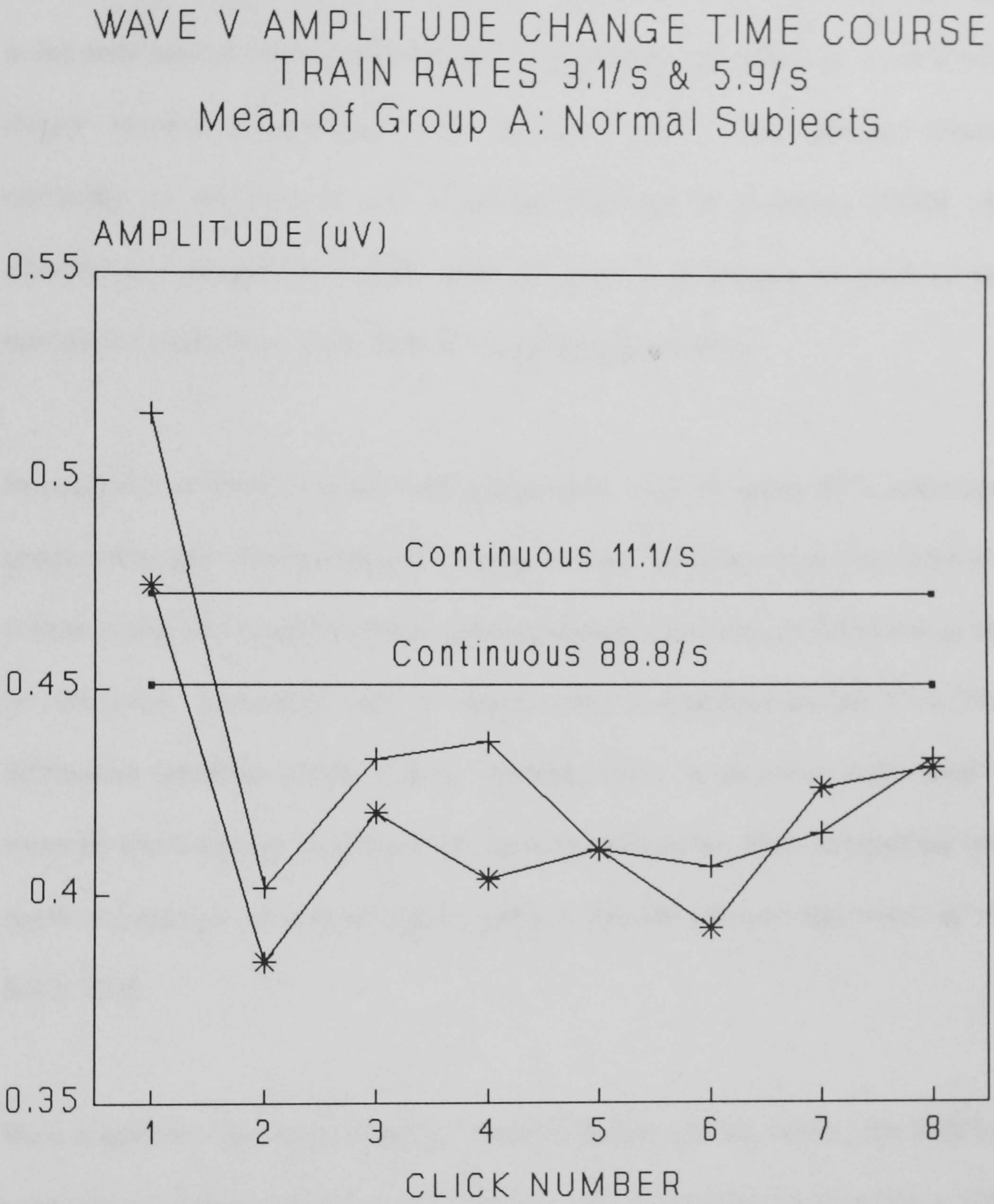
Continuous 11.1/s: .20 Continuous 88.8/s: .25

3.1.4.2 *Amplitude adaptation onset and recovery*

The time course of the amplitude adaptation of ***wave V*** is shown in Figure 3.1.4.2 (a). Unlike the 11.1/s to 88.8/s latency shifts of all waves and unlike the 11.1/s to 88.8/s amplitudes of waves I & III, wave V amplitude at these two extreme rates are not significantly different (p=.478). This finding was highlighted in the previous section on rate effects and so it would seem reasonable to expect that in the click train study, wave V amplitude should not change significantly during a click train and that the two TRR recovery times would fail to reveal any meaningful effects. In short, if wave V amplitude undergoes no adaptation, it should be stable in the click train study.

To a large extent this is true, with paired T-tests similar to those applied in the investigation of latency adaptation failing to identify significant changes. However, Figure 3.1.4.2 (a) shows that at both TRRs, wave V amplitude diminishes markedly following the first click in the train. This change is significant at both TRRs (3.1/s: p=.007, 5.9/s: p=.001) with amplitude starting to recover by the third click. Comparing the first and eighth clicks, there is no significant difference at the slower TRR (p=.108) yet surprisingly, there *is* a difference at the faster TRR (p=.016). This is inexplicable since, if there were to be any subtle adaptation taking place, one would expect to see it with the longer, not shorter, recovery time paradigm.

Figure 3.1.4.2 (a)



Standard Deviations

Click	1	2	3	4	5	6	7	8
3.1/s	.13	.17	.17	.15	.18	.18	.15	.17
5.9/s	.17	.15	.17	.18	.15	.17	.13	.17

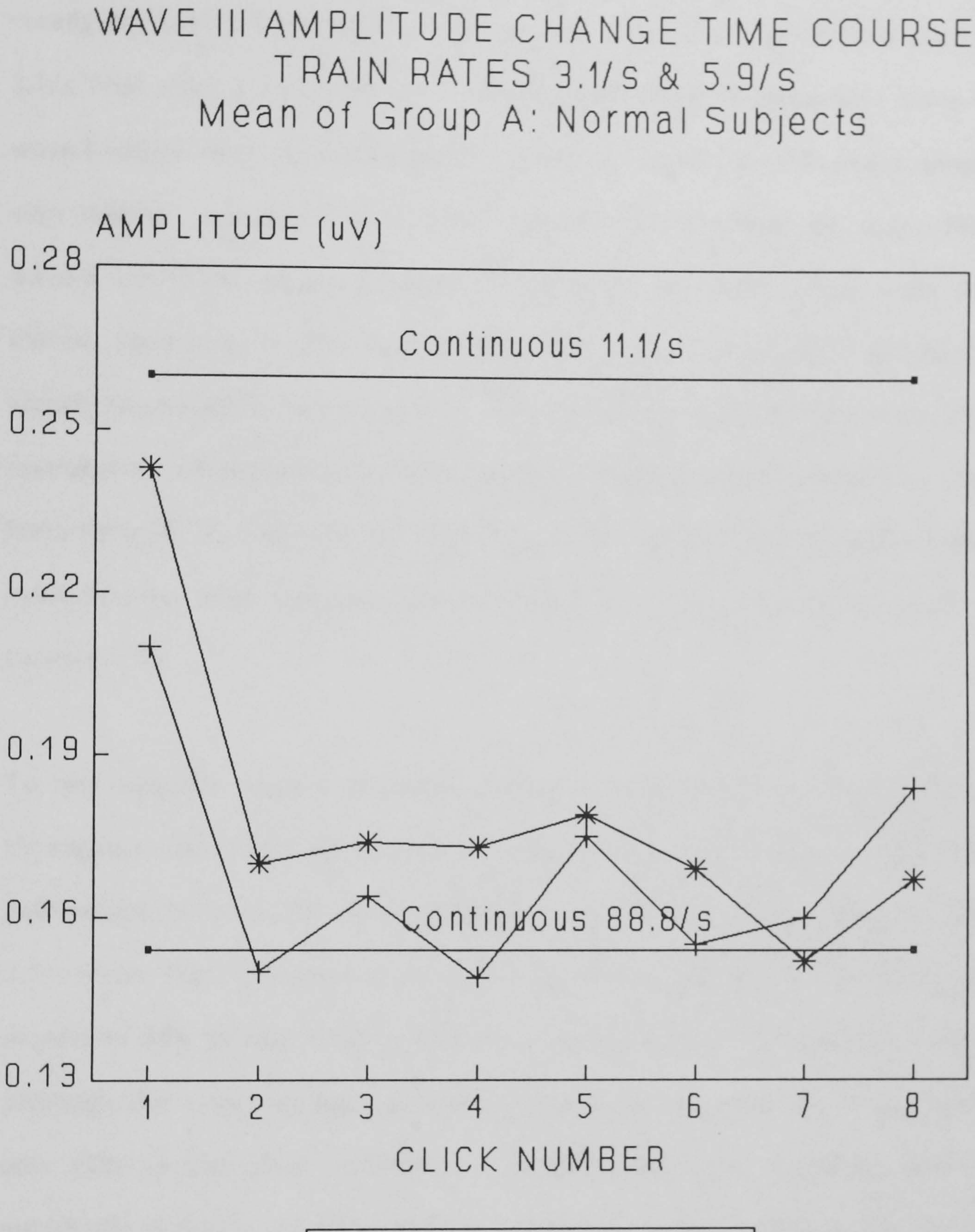
Continuous 11.1/s: .14 Continuous 88.8/s: .18

The response of wave V amplitude to changes in rate is an enigma with its apparent lack of adaptation, or even slight enhancement at 40Hz, often being ascribed to some mechanism involving superimposition of wave V with longer latency components from earlier stimuli. The present results certainly do not square with those of Thornton & Coleman (1975) who illustrated a progressive diminution of wave V amplitude to each of the successive stimuli in their four-click train experiment.

In contrast to wave V amplitude adaptation, that of ***wave III*** is relatively predictable and well mannered. Figure 3.1.4.2 (b) illustrates this, with the steady-state 11.1/s and 88.8/s amplitudes being significantly different at the p=.001 level. The same level of significance is attached to the 3.1/s TRR difference between clicks 1 & 8. Indeed, there is no clear difference in wave III amplitude at 88.8/s and at the second click (p=.145), suggesting very rapid amplitude adaptation onset, with a similar pattern apparent at the 5.9/s TRR.

With regard to the time course of wave III amplitude recovery, the 243.5ms recovery period allows complete recovery (11.1/s steady-state and first click amplitude difference p=.257). For the 90.4ms period, adaptation is *in*complete (p=.010), implying that some intermediate period is required for wave III amplitude adaptation recovery.

Figure 3.1.4.2 (b)



Standard Deviations

Click	1	2	3	4	5	6	7	8
3.1/s	.13	.11	.11	.11	.12	.11	.11	.10
5.9/s	.14	.09	.11	.09	.12	.11	.12	.14

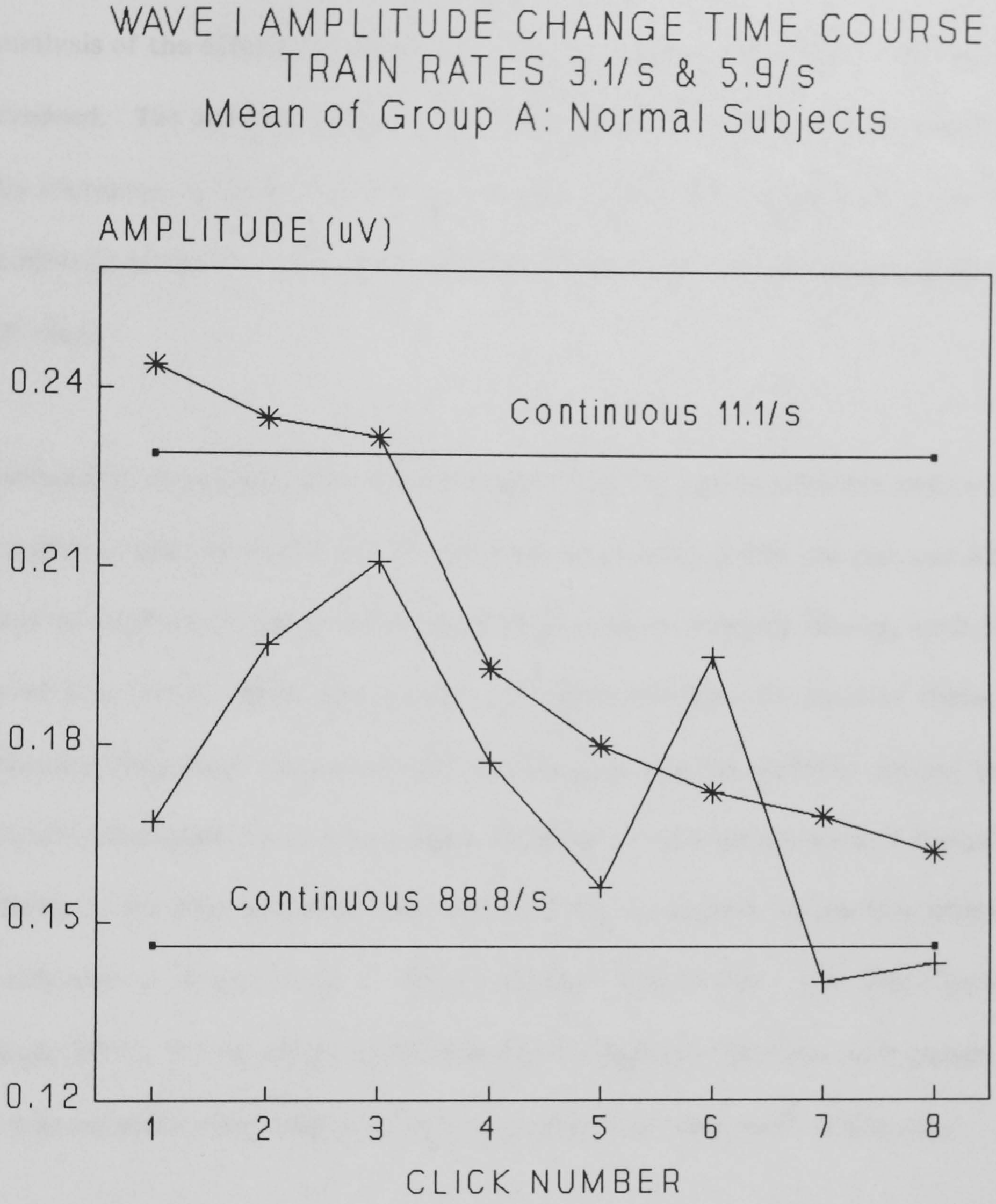
Continuous 11.1/s: .14 Continuous 88.8/s: .10

The conclusions which can be drawn from the ***wave I*** amplitude adaptation onset and recovery are similar in some respects to those of wave III. The steady-state 11.1/s and 88.8/s amplitudes are different ($p<.001$) as are the 3.1/s TRR click 1 and click 8 amplitudes; like wave III and *un*like wave V, wave I adapts with rapid stimulation. However, unlike wave III which adapts very rapidly, it can be seen from Figure 3.1.4.2 (c) that the 3.1/s TRR wave I amplitude adapts gradually throughout the eight click train and indeed, adaptation is still incomplete at the eighth click (click 8 and 88.8/s amplitudes being different, $p=.021$). The general pattern of this adaptation conforms to established models of auditory adaptation (see Eggermont, 1985 for a review). In contrast, the 5.9/s TRR adaptation pattern does not, being most bizarre, with the mean wave I amplitude *increasing* during the first three clicks.

To test whether wave I amplitude changes significantly and progressively throughout the click train for either train rate, an ANOVA with orthogonal polynomial contrasts for click number was performed. As expected, for the 3.1/s train, the click number sequence was highly significant ($p<.001$), and explained 34% of the total variability in amplitude. With the 5.9/s train, although the click number sequence was significant ($p=.019$), it explained only 11% of the total variability. At this train rate therefore, wave I amplitude is highly variable and any conclusion made regarding adaptation onset should be guarded.

The recovery of wave I amplitude over the two periods is similar to wave III: 243.5ms is sufficient (11.1/s and first click difference $p=.918$) and 90.4ms is not ($p<.001$).

Figure 3.1.4.2 (c)



Standard Deviations

Click	1	2	3	4	5	6	7	8
3.1/s	.16	.13	.13	.10	.12	.10	.10	.11
5.9/s	.10	.15	.13	.12	.10	.09	.09	.08

Continuous 11.1/s: .17 Continuous 88.8/s: .08

3.1.5 Long time course changes

The analysis of the effects of rate illustrated that wave V latency extends as rate is increased. The analysis of the click train experiments revealed that wave V rapidly increases in latency after the onset of a high rate stimulus although full adaptation (ie the steady state high rate latency asymptote) is not achieved by the eighth click.

The remaining adaptation clearly takes place after the eighth click but over what time course or number of clicks? Recall from section 2.1.5 that the test ear ABR at rates of 22.2/s and above were acquired into three memory blocks, each the result of 200 clicks. Prior to the start of acquisition into the first of these, a 10s stimulus-free silent period ensured that the run started with the subject in a completely unadapted state. The latency difference between the wave V from the waveforms in the first and third memory block was measured. A positive latency here indicates a longer wave V latency in the third block. The four "jitter" variables, JIT22, JIT44, JIT66 & JIT88 would be expected to have zero means if there was no observable long time course adaptation, measured in this way.

To put the latency change being sought into some form of context, the click train experiments, which employed trains of eight clicks at 88.8/s, showed that (for the slower of the two train repetition rates) the wave V latency at the eighth click was on average 0.12ms less than the steady state 88.8/s value. It is highly likely that most if not all of this residual adaptation is completed before the 200th click, ie well within the first memory block. It is reasonable, therefore, to

predict that the wave V latency recorded from the first 200 click block will be a value close to, but marginally less than that recorded from the third block which should be equal to the steady state value. The magnitude of the actual latency difference, when compared to this initial residual value, will be a rough guide to the time course over which the adaptation becomes complete. A significant and large mean JIT88 (of, say, a third to a half of the 0.12ms quoted above) will suggest an adaptation process which extends well into the first 200 click waveform. An insignificant JIT88 mean suggests that adaptation is effectively complete after several tens of clicks.

The JIT88 mean value is 0.0326ms (or about one data point on a waveform). Is this significantly different from zero? The four jitter variables were subject to a paired T-test against the value 0 and the significance, together with the variable mean is shown in Table 3.1.5.

Table 3.1.5

VARIABLE	MEAN (ms)	P	TIME (s)
JIT22	0.0154	.381	9
JIT44	0.0283	.153	4.5
JIT66	0.0641	.007	6
JIT88	0.0326	.071	4.5

Using the usual p=.05 criterion, JIT88 is not significant, though nearly so. JIT66 does demonstrate an effect, however. The *time* column in Table 3.1.5 is the time in seconds taken to acquire 200 clicks. The times between the mid-points in the acquisition of the first and third waveforms are twice these values. The reason why the 66.6/s and 88.8/s times are double the expected times is because only every other click was accepted into the average, using an epoch of 15ms. These times assume no delay due to artifact rejection, so should be taken as illustrative.

Is it possible to explain this combination of findings? At the relatively slow rate of 22.2/s, there is little adaptation taking place and with a duration of 9s for the acquisition of 200 clicks, it is not surprising that there is no observed effect. Comparing the JIT66 and JIT88 results, the greater degree of adaptation at the faster rate, together with the shorter acquisition time, would be expected to lead to a more marked effect at 88.8/s over 66.6/s (assuming a rate-independent long time course adaptation model). The opposite was found, alluding to a mechanism whereby the time constant of a slow adaptation process is reduced (ie adaptation speeds up) in a non-linear fashion as stimulus rate is increased.

3.1.6 Very long time course changes

The test ear 11.1/s measurements were conducted twice, both before and after the rate series and click train tests. In Group A subjects, who all received click train tests at both train rates, the time between the "start" and "end" 11.1/s tests was just over 27 minutes during which time at least 44,000 clicks were delivered.

The purpose of repeating the 11.1/s test was twofold. Firstly, any significant difference in the latencies or amplitudes of the ABRs could be taken as evidence of very long time course adaptation of the ABR. If such evidence was apparent, an important secondary purpose was to be aware of order effects in the rate series and click train data, since the order of these tests was fixed rather than randomized.

To investigate these possible very long time course changes, six paired T-tests were conducted: on the start and end latencies and amplitudes of waves I, III & V. In none of these comparisons were any significant differences observed ($p>.05$ in all cases). From this it may be concluded that there are no such changes in the ABR and that the results of rate series and click train tests do not contain distortion due to order effects.

3.2 THE EFFECTS OF TINNITUS AND VERTIGO ON THE ABR

3.2.1 The effect of presence or absence of tinnitus and vertigo

This section attempts to answer the question of whether tinnitus, vertigo or combined tinnitus and vertigo has an effect on the ABR in subjects having normal hearing for their age and gender. Group A subjects (n=36) had normal hearing and had neither tinnitus nor vertigo. Group B subjects (n=50) satisfied the same audiometric criteria as Group A subjects but had either tinnitus, vertigo or both. Groups A and B were combined and a grouping variable, TVGROUP, was assigned to each of the 86 subjects thus:

TVGROUP	Category	n
0	neither T nor V	36
1	V but no T	17
2	T but no V	9
3	both V and T	24

Variables categorizing the duration of tinnitus or vertigo or the ear in which the tinnitus occurred were not considered at this stage. To see whether this broad grouping of subjects was capable of yielding characteristically different ABR data, a discriminant analysis was performed. This is a multivariate technique whereby a maximally efficient combination of discriminating variables is sought for the purpose of discriminating between the various groups. One means of measuring the success of the resulting function is to see how well it can predict the group of each subject from their data. It is tempting to include all possible ABR variables in such an analysis but in doing so, the power of the analysis is reduced. A more sensitive analysis results from a smaller number of key (and preferably independent or only weakly correlated) variables.

The variables used were the latencies and amplitudes of waves I, III & V - the six basic measures of the ABR waveform - and a selection of the major diagnostic variables of interest - the I-V IPL, ILDV and the 88.8/s - 11.1/s wave V latency shift.

The following SPSS PC+ command was employed:

```
DSCRIMINANT /GROUPS TVGROUP (0,3) /VARIABLES MIL MIIIL MVL MIA MIIIA
MVA MI_V ILDV V88_11 /METHOD WILKS /PRIORS SIZE /STATISTICS 1 2 13.
```

The analysis failed to reveal a significant (p=.14) means of discriminating between the four groups as the following small extract of SPSS output illustrates:

Step	Action Entered	Removed	Vars In	Wilks' Lambda	Sig.	Label
1	MVL		1	.92094	.0878	
2	MIIIA		2	.87765	.1122	
3	MIA		3	.84180	.1406	

Canonical Discriminant Functions

Fcn	Eigenvalue	Pct of Variance	Cum Pct	Canonical Corr		After Fcn	Wilks' Lambda	Chisquare	DF	Sig
					:	0	.8418	13.519	9	.1405
1*	.1514	82.69	82.69	.3626	:	1	.9692	2.452	4	.6533
2*	.0307	16.76	99.45	.1726	:	2	.9990	.079	1	.7784
3*	.0010	.55	100.00	.0318	:					

3.2.2 A closer look at the effects of tinnitus

The analysis in the preceding section was a rather blunt instrument. In the case of tinnitus, details are available concerning the duration and location (variables TINDUR and TINEAR), and further discriminant analyses were performed utilising this information with the same discriminating variables as before.

When tinnitus duration (TINDUR with seven levels ranging from 0: no tinnitus, to 6: continual tinnitus) was used as the grouping variable, wave I amplitude and wave III latency together formed the basis of a significant (p=.0228) discriminant function. This function correctly classified 60% of the subjects although on closer inspection, only one group (0: no tinnitus, n=52) had any subjects correctly predicted. Indeed, the function assigned all but three subjects to this group.

This finding requires further investigation. Table 3.2.2 gives the details of the grouping variable TINDUR and the group means (and standard deviations) for the two variables identified as significant by the analysis: wave I amplitude (MIA, p=.039) and wave III latency (MIIIL, p=.023).

Table 3.2.2

TINDUR GROUP	n	MIA (SD)	MIIIL (SD)
0: no tinnitus	52	.237 (.15)	3.81 (.20)
1: T < 1 min	3	.427 (.23)	3.75 (.17)
2: T 1-5 min	3	.353 (.06)	3.51 (.21)
3: T 5-60 min	2	.420 (.14)	3.65 (.11)
4: T 1-24 hr	2	.420 (.33)	3.84 (.34)
5: T 1-7 days	4	.173 (.13)	4.05 (.36)
6: T continuous	17	.208 (.11)	3.82 (.18)
ALL GROUPS	83	.247 (.15)	3.81(.22)

One might reasonably expect that any genuine link between tinnitus and an ABR variable would show a progressive monotonic relationship between the variable and a measure such as tinnitus duration. Table 3.2.2 clearly shows that this is not the case and that the source of the significance attached to the analysis lies in the intermediate TINDUR groups which had only two or three subjects. Comparison of the variable group means for the 0: no tinnitus and 6: continuous tinnitus groups show little difference.

This line of reasoning was pursued by another discriminant analysis considering only TINDUR groups 0 and 6 and further restricted group 6 subjects to those who had tinnitus in their test ear (TINEAR = 1, n=13). This provides the most favourable conditions for revealing any real effect of tinnitus on the ABR. No significant (at the p=.05 level) ABR variable or discriminant function was identified by this analysis.

The conclusion of these analyses is that tinnitus probably has no effect on the ABR variables being considered and that the "significant" variables identified in one of the analyses is probably an abberation within the sample. A definitive answer requires the analysis of a larger group. Interestingly, none of the "diagnostic" ABR variables (eg the I-V IPL) showed any hint of correlation with tinnitus so from the clinical viewpoint, it is fairly safe to ignore tinnitus when using ABR techniques on subjects having normal hearing.

3.2.3 A closer look at the effects of vertigo

Just as the duration of tinnitus was available for analysis, the duration of vertigo (variable VERTDUR) may be harnessed for a more detailed inspection of any effect on the ABR. The seven levels of VERTDUR (from 0: no vertigo, to 6: continual vertigo) was used in a discriminant analysis with same ABR variables as before. The best combination of ABR variables produced by the analysis was insignificant (p=.85).

A further variable, ROT, groups the nature of any vertigo into two categories, non-rotatory and rotatory. To see whether these two categories could be discriminated using ABR variables a further analysis was performed on the 43 Group B subjects with vertigo. Again, the discriminant function was not significant (p=.145). As a final attempt to seek any effect of vertigo on the ABR, the preceding analysis was repeated with *three* levels of the grouping variable: 0: no vertigo, 1: non-rotatory vertigo, 2: rotatory vertigo. This resulted also resulted in an insignificant function (p=.335).

Like tinnitus therefore, vertigo does not appear to modify the ABR results of normally hearing subjects.

3.3 THE EFFECTS OF COCHLEAR HEARING LOSS ON THE ABR

3.3.1 Dealing with out of range audiometric data

Since one of the purposes of section 3.3 will be to identify the effects of hearing loss on the ABR, it is important to have complete records of the subjects' pure tone thresholds. At most frequencies of interest, the maximum available output of the audiometer being used was 120dBHL. However, the maximum at 8kHz was only 100dBHL and since the general trend in many severe sensorineural hearing losses is for a progressively greater loss with frequency, it is not surprising that in a small number of cases the 8kHz threshold will be beyond the limits of measurement. Ten such cases appear in the data of Group C. Groups E & F also contain thresholds beyond the audiometer limit, but unlike Group C, where only 8kHz was involved, the pure tone thresholds were beyond the limit of measurement at other frequencies.

For the purposes of analysis, a solution is to predict a likely value for the missing variable in a way that causes minimal perturbation of the relationship between it and related variables. One common approach is to simply assume that the true value is one increment beyond the measuring limit, in this case, 105dBHL. Another, more statistically valid method, is to employ multiple regression analysis of a complete data set having a similar distribution to predict a value for the missing variable. This second approach was applied to the Group C 8kHz variable.

Multiple regression was undertaken using all five available frequencies with 8kHz

as the dependent variable. The data of 126 of the 136 subjects in Group C were employed since they were complete. Table 3.3.1 (a) shows the correlations between the five frequencies in this data set.

TABLE 3.3.1 (a)

Correlation between the five pure tone thresholds

	PTA500	PTA1	PTA2	PTA4	PTA8
PTA500	1.000	.861	.647	.357	.369
PTA1	.861	1.000	.829	.462	.408
PTA2	.647	.829	1.000	.690	.524
PTA4	.357	.462	.690	1.000	.732
PTA8	.369	.408	.524	.732	1.000

As expected, the above results suggest greatest correlation between adjacent frequencies and any predictor of 8kHz will therefore rely most heavily on the 4kHz datum of a given subject. The best linear equation for predicting the 8kHz threshold from the other four frequencies was calculated as:

$$T_{8k} = 11.44 + 0.85 \times T_{4k} + 0.18 \times T_{500} - 0.10 \times T_{2k} + 0.004 \times T_{1k}$$

Using this equation allows actual and predicted values to be compared, and as Figure 3.3.1 (a) shows, the model fits the data quite well.

FIGURE 3.3.1 (a)

Normal Probability Plot - observed -v- predicted 8kHz

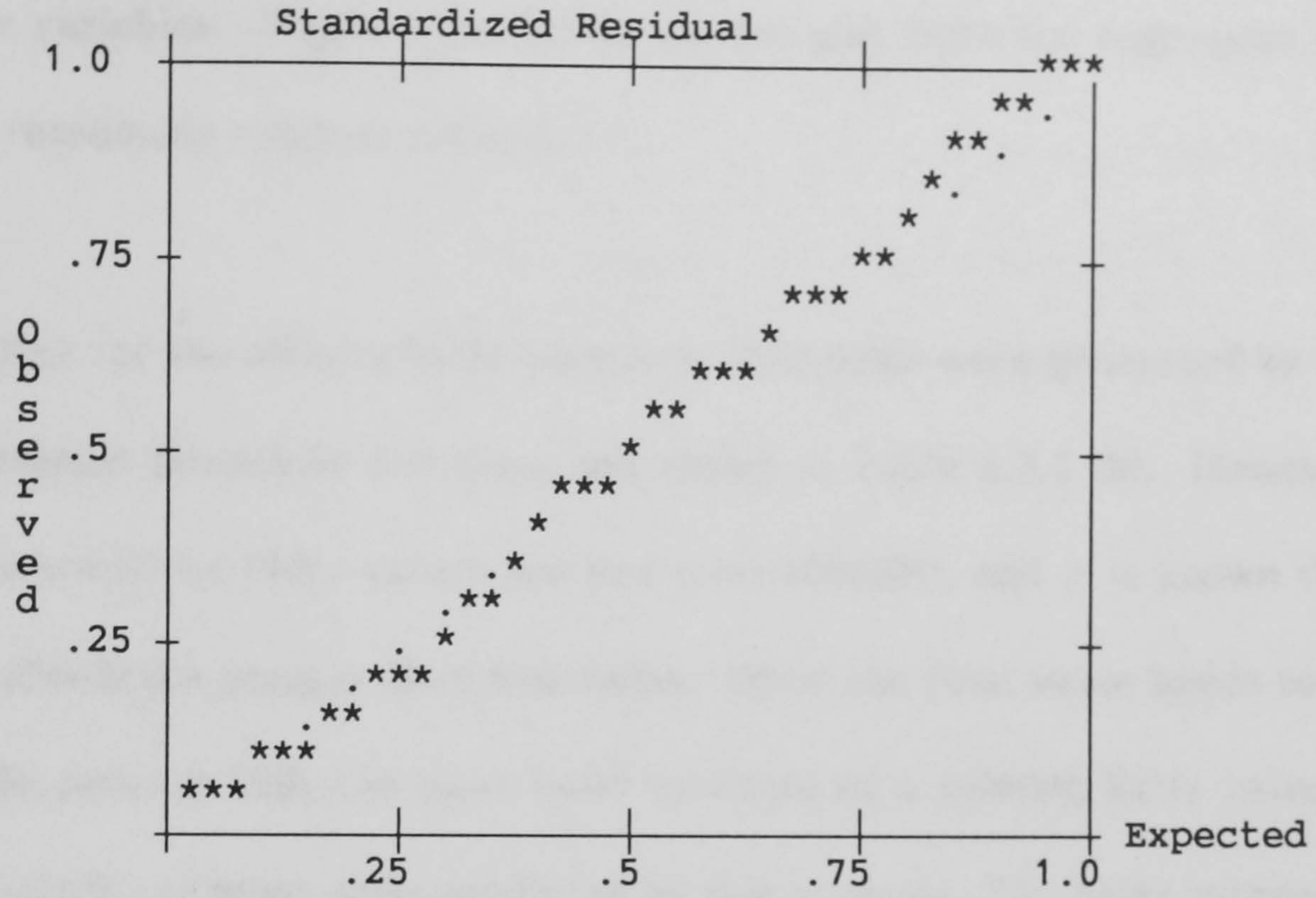
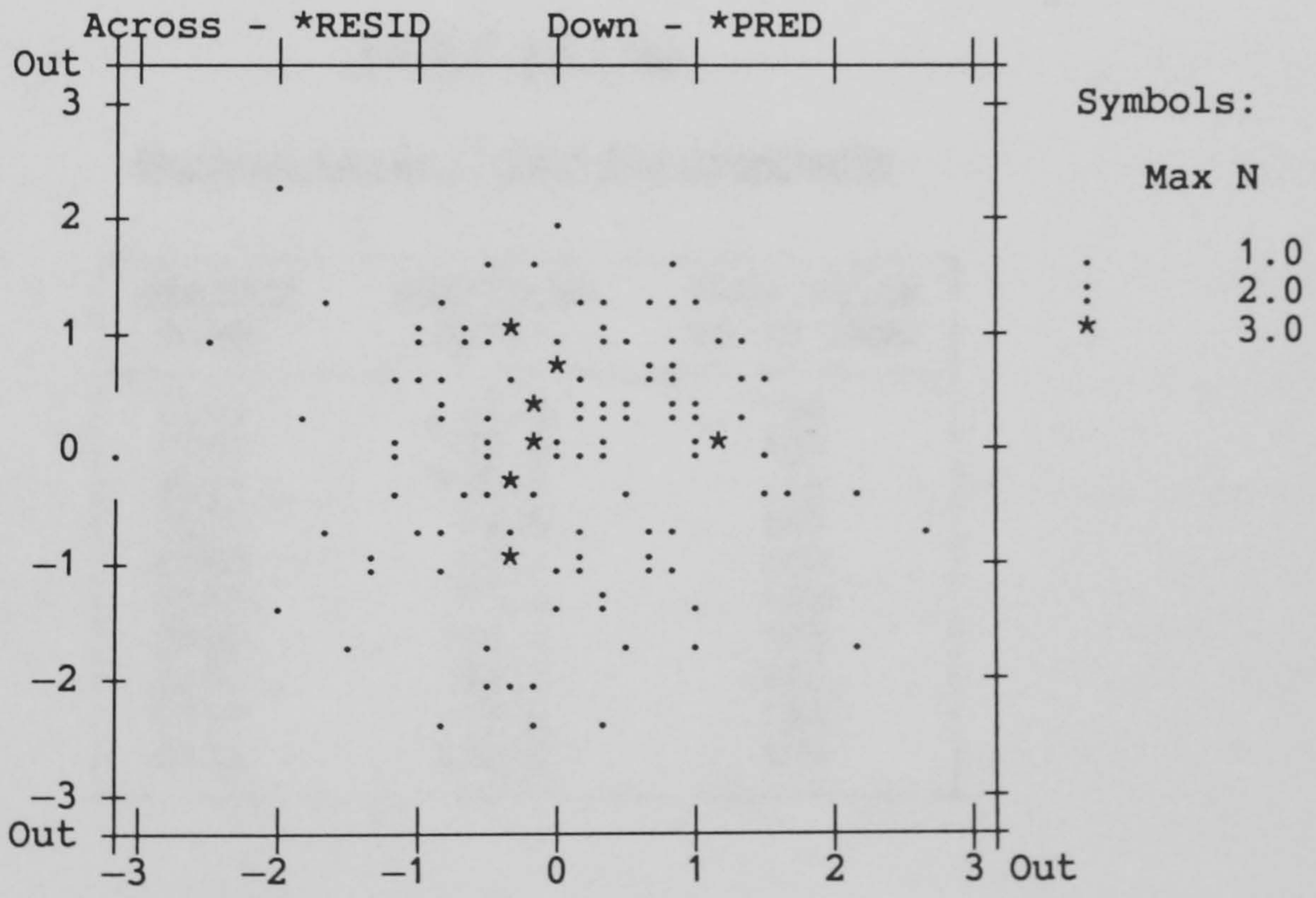


FIGURE 3.3.1 (b)

Standardized scatterplot of residuals -v- predicted 8kHz



There are a number of ways of measuring the validity or success of this technique.

Plotting the residuals against the predicted values gives a visual clue of any

systematic error. Ideally, the plotted points should form a featureless cloud and any distinct pattern warns of non-linearity in the relation between the predicted and predictor variables. Figure 3.3.1 (b) shows this plot from the regression and illustrates a reasonably random pattern.

Predicted values for the missing 8kHz pure tone thresholds were generated by the multiple regression procedure and these are shown in Table 3.3.1 (b). However, six of the ten predicted 8kHz values are less than 100dBHL and it is known that the true thresholds are greater than this value. Since the final value needs to be rounded to the nearest 5dB, the most valid estimate of a missing 8kHz value is therefore 100dBHL, or more when predicted by this analysis. The 8kHz estimates to be used are shown in the rightmost column of Table 3.3.1 (b).

TABLE 3.3.1 (b)

Results: Group C Test Ear thresholds

SUBJECT CODE	PREDICTED 8kHz	8kHz VALUE TO BE USED
C016	96.0	100
C025	77.5	100
C031	108.2	110
C035	94.6	100
C060	87.4	100
C068	103.5	105
C089	103.7	105
C102	92.5	100
C111	77.0	100
C124	100.5	100

3.3.2. Characterising the group and the variables

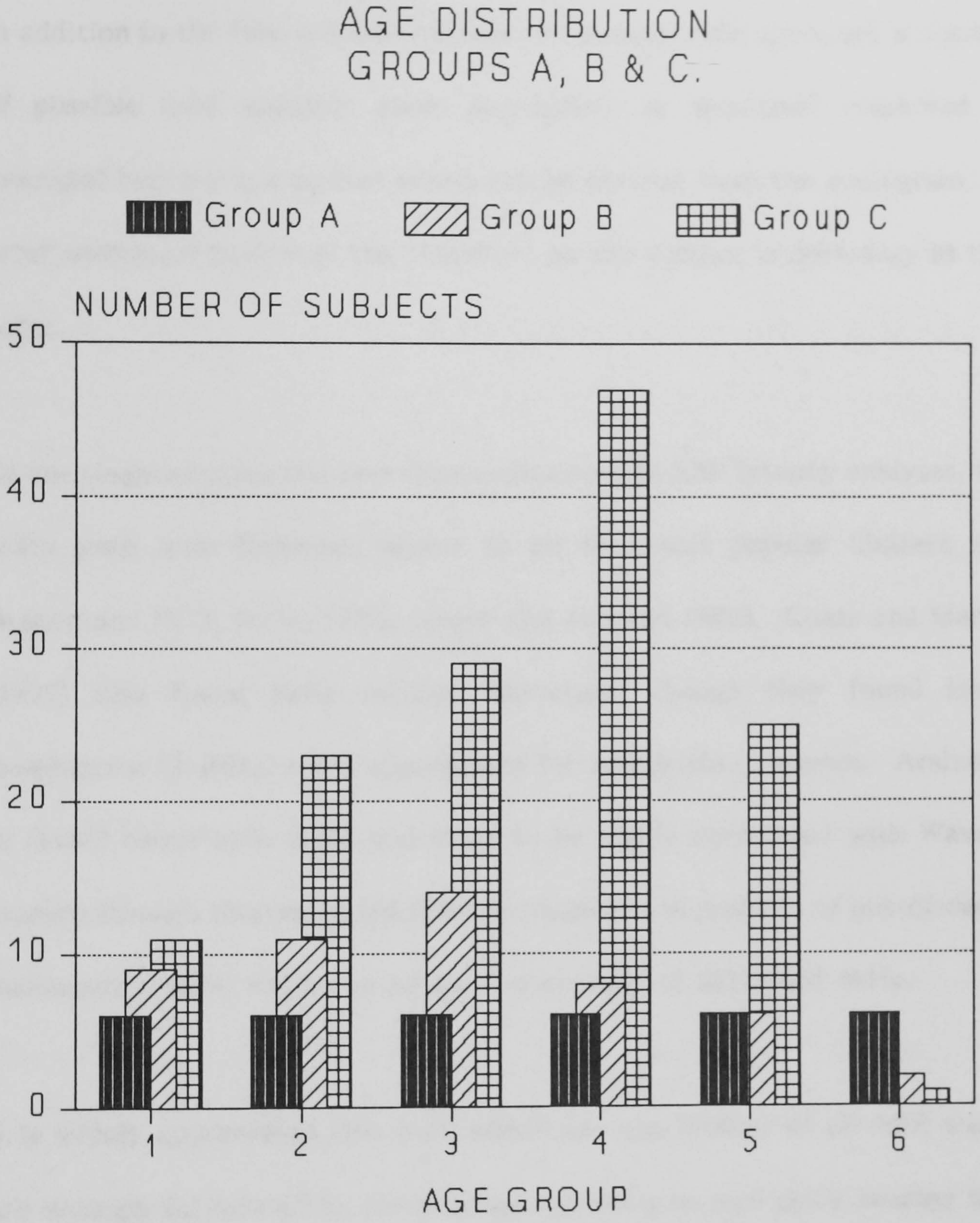
The subjects entering Group C had abnormal hearing in their test ear under either or both of the criteria outlined in section 2.3.1. In order to examine any effects of hearing loss on ABR variables, the full spectrum of hearing loss configurations should be included and to this end, Groups A,B and C were combined for analyses in the remainder of Section 3.3.

The next three subsections deal with this combined group: its age and gender distributions, the variables available for representing hearing loss and the distributions of the ABR variables themselves.

3.3.2.1 *Age and gender distributions for group ABC*

Figure 3.3.2.1. shows the numbers of subjects in each of 6 age bands in Groups A,B and C. Whilst the age and gender distribution of Group A was controlled, those of Groups B and C reflect the numbers of patients meeting the group candidacy criteria for the data collection phase of this study. The combined Group ABC totals 221 subjects with (conveniently) almost exactly equal numbers of each gender (111 males, 110 females).

Figure 3.3.2.1



AGE GROUPS:
1: ‹31 2: 31-40 3: 41-50
4: 51-60 5: 61-70 6: ›70

3.3.2.2. *Variables available for representing hearing loss*

In addition to the five audiometric pure tone thresholds, there are a number of possible (and arguably more appropriate or sensitive) combined or averaged hearing loss indices which can be derived from the audiogram. A brief additional review of the literature on this subject is necessary at this point.

Of the single audiometric test frequencies used in ABR latency analyses, the 4kHz pure tone threshold seems to be the most popular (Selters and Brackmann 1977, Hyde, 1985, Jerger and Johnson 1988). Coats and Martin (1977) also found 8kHz equally important, though they found lower frequencies (2-4kHz) more appropriate for amplitude measures. Arslan *et al* (1988) found both 2kHz and 4kHz to be highly correlated with Wave V latency (though they excluded 8kHz because of the problem of out-of-range audiometric data) and so opted for the average of 2kHz and 4kHz.

It is widely appreciated that both amplitude and latency of all ABR waves are strongly influenced by the stimulus intensity as well as by hearing loss. As in the present study, Jerger and Johnson (1988) employed a single stimulus intensity in each subject, but *that* intensity varied according to the ease with which the ABR was recorded and this in turn is, of course, dependent upon the subject's hearing loss. In such cases one can either analyze hearing loss effects upon the ABR in subgroups in which only one intensity is employed, or else analyze the effects not of hearing loss *per se*

but rather of sensation level of the stimulus (i.e. the intensity of the click minus the hearing loss of the subject at a given frequency or average of frequencies).

The effect of audiogram slope is another possible consideration and although those authors who have attempted to look for any effect have found none, all have commented on the difficulty of adequately controlling for the effects of absolute loss, the two measures being inextricably linked.

With all of the above in mind, the following approach was used to look for any effects of hearing loss on the ABR: two audiometric measures were applied in each of two ways. The first audiometric measure is simply the 4kHz pure tone threshold. The second measure is the best two average (BTA). This the average of the best two (i.e. least loss) thresholds at frequencies of 2, 4, and 8kHz. This approach is not new to audiology, being common in speech audiometry but adapted here to hopefully best reflect the extent to which audiometric loss and contour affects the ABR. The first way in which these measures were applied was to consider those subjects in whom 80dBnHL was used, thus avoiding any confounding problems of stimulus level, but necessarily restricting the analysis to those subjects who did not have a very severe loss requiring a higher stimulus intensity. The second way in which the two measures were applied was to adopt a sensation level approach, allowing all subjects to be considered.

The four treatments used in the analysis of hearing loss were therefore:

treatment (a): the absolute 4kHz pure tone threshold (restricted to subjects receiving a stimulus at 80dBnHL)

treatment (b): the 2, 4, 8kHz BTA (restricted to subjects receiving a stimulus at 80dBnHL)

treatment (c): the 4kHz sensation level (all subjects)

treatment (d): the 2,4, 8kHz BTA sensation level (all subjects).

The four variables used for these treatments were named: PTA4, BTA248, SL4 and SLBTA respectively.

3.3.2.3. *The distributions of the ABR variables being examined for any effects of age, gender and hearing loss*

Although those variables analyzed in Group A were not sufficiently non-normal to risk serious errors in parametric tests such as ANOVA, the same findings cannot be assumed in a group containing subjects with hearing loss. As a preliminary measure, therefore, a K-S test was performed on variables from combined Group ABC, including the absolute wave V latency (MVL - not considered earlier because of it's well known susceptibility to the effects of hearing loss). Note that the inter-aural variables (eg ILDV) will not be considered at this stage. Since a patient's ears have the same age and gender, only the effects of hearing loss will be evaluated and this will

be considered in Section 3.3.4. Table 3.3.2.3. shows the p value of the K-S test. As before, a reasonable criterion is p = .1, and it is of no great surprise that ratio variables such as the I/V amplitude ratio are clearly not normal.

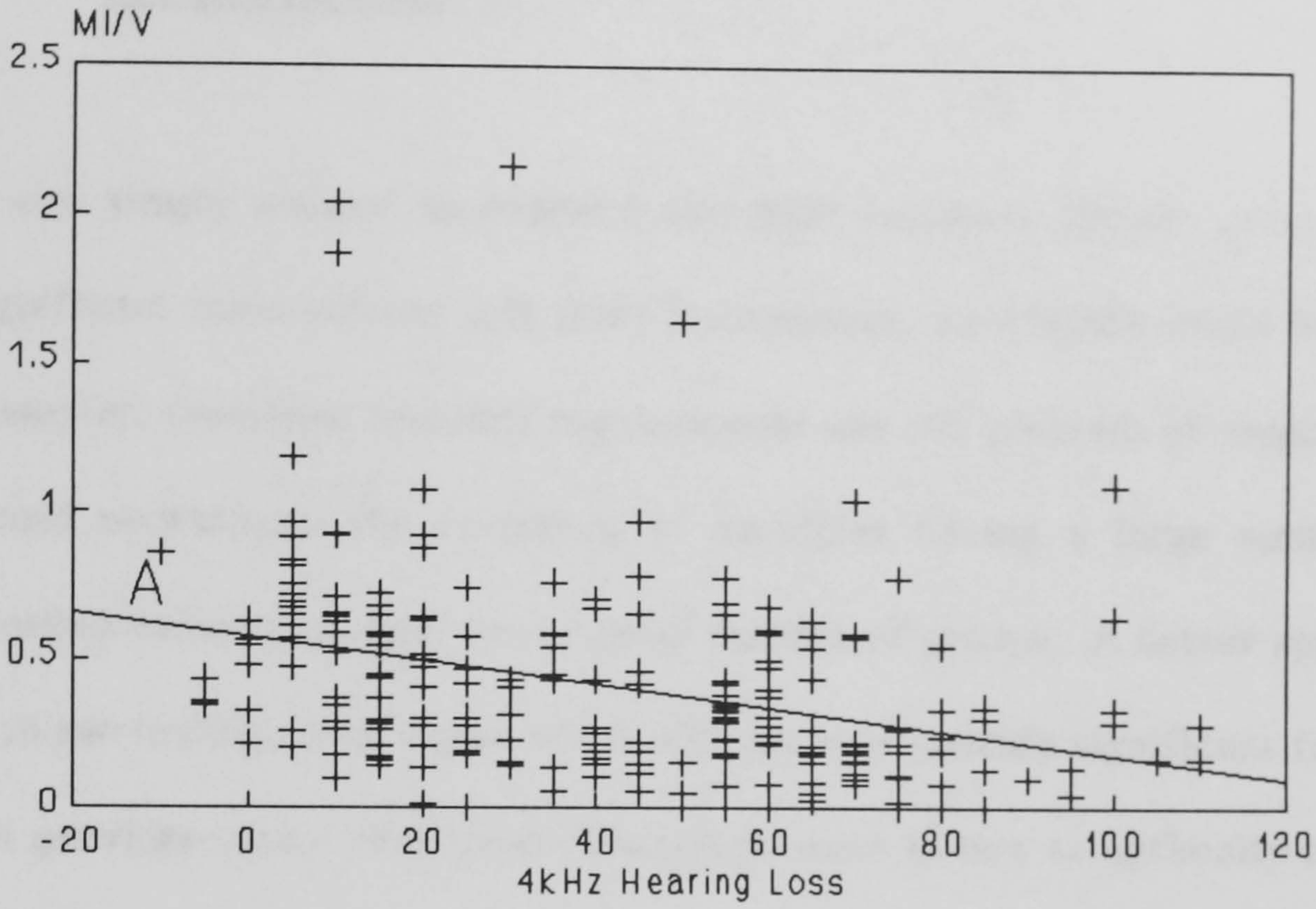
Table 3.3.2.3

K-S p value of variables under scrutiny for effects of age, gender & hearing loss

VARIABLE	K-S p	VARIABLE	K-S p
MVL	.401		
MI-III	.253	V22/11	.147
MIII-V	.532	V44/11	.005
MI-V	.584	V66/11	.106
MI/V	.009	V88/11	.383
V22-11	.008	PV22-11	.098
V44-11	.032	PV44-11	.263
V66-11	.015	PV66-11	.454
V88-11	.126	PV88-11	.635

Figure 3.3.2.3. illustrates why this is so. The majority of measures yield a value of less than unity but there is a small number of data with values over 1.5 - ie there is a long tail in the distribution so it is skewed. It is often possible to overcome this by transforming the data (taking logs would be worth a try in this case) before statistical treatment.

Figure 3.3.2.3



A: Least squares regression line

The important question in such cases is this: are parametric tests of variables with these characteristics invalid? The answer is 'not necessarily', provided that the distributions can be explained adequately by the independent variables. What really matters in such analyses is whether the *residual* is normally distributed, and this can be determined in two ways: a K-S test can be performed on the residual and the model (in procedures such as multiple regression) can be tested by observing the pattern of residual with respect to the dependent variable or its predicted value. Rather than excluding variables such as MI/V from parametric analysis therefore, the distributions of the residual of such an analysis will show whether the procedure is invalid and an appropriate transformation necessary.

3.3.3. The effects of age, gender and hearing loss on the ABR

3.3.3.1. *Analysis methods*

If one simply wanted to examine the ABR variables for the presence of significant main effects and their interactions, an ANOVA could be used. However, computer memory requirements and the problem of empty cells would necessitate the re-coding of variables having a large number of possible values (e.g. age) into a small number of groups. A better approach is to use multiple regression which will not only identify significant factors, but provides useful additional information such as how to optimally correct for these effects.

Unlike an ANOVA, in which the interaction terms of the individual variables are automatically included (i.e. in a full factorial design), in the SPSS regression procedure only those variables which are specified are evaluated. In order to permit evaluation of any significant interactions (for example an age/gender interaction) the interaction variables need to be generated for use in the regression. If age, gender and hearing loss are to be used as independent variables, a full factorial design requires three two-way interaction variables and one three-way interaction variable. However, there are to be four treatments of hearing loss and so the new interaction variables were generated as follows:

Two way interaction variables:

AGE * GENDER	(AGESEX)
AGE * PTA4	(AGEPTA4)
AGE * BTA248	(AGEBTA)
AGE * SL4	(AGESL4)
AGE * SLBTA	(AGESLBTA)
GENDER * PTA4	(SEXPTA4)
GENDER * BTA248	(SEXBTA)
GENDER * SL4	(SEXSL4)
GENDER * SLBTA	(SEXSLBTA)

Three way interaction variables

AGE * GENDER * PTA4	(ASPTA4)
AGE * GENDER * BTA248	(ASBTA)
AGE * GENDER * SL4	(ASSL4)
AGE * GENDER * SLBTA	(ASSLBTA)

Rather than including age, gender, the four hearing loss treatments and all of the above variables in a single regression for each dependent variable, four separate regressions were performed for each dependent, one for each of the four hearing loss treatments. This restricts the number of independent variables in each regression to seven instead of sixteen.

Stepwise regression is a popular method whereby only those independent variables demonstrating a significant effect are allowed into the regression equation. This is fine for "main effect" variables but cannot be used with validity when interaction terms are involved. This is because it is possible to have significant interaction terms in the equation without the main effects, resulting in rather strange and unintended effects. Because of this, a forced entry method was employed in the multiple regression analysis.

3.3.3.2 *Results of multiple linear regression*

The seventeen ABR variables shown in Table 3.3.2.3 were the subject of four analyses (one for each of the hearing loss treatments) each followed by a K-S test of normality of the residual. An example of one of the 64 such procedures, here investigating wave V latency (MVL) for the effects of age (AGE), gender (SEX) and 4kHz hearing threshold (PTA4) is shown below.

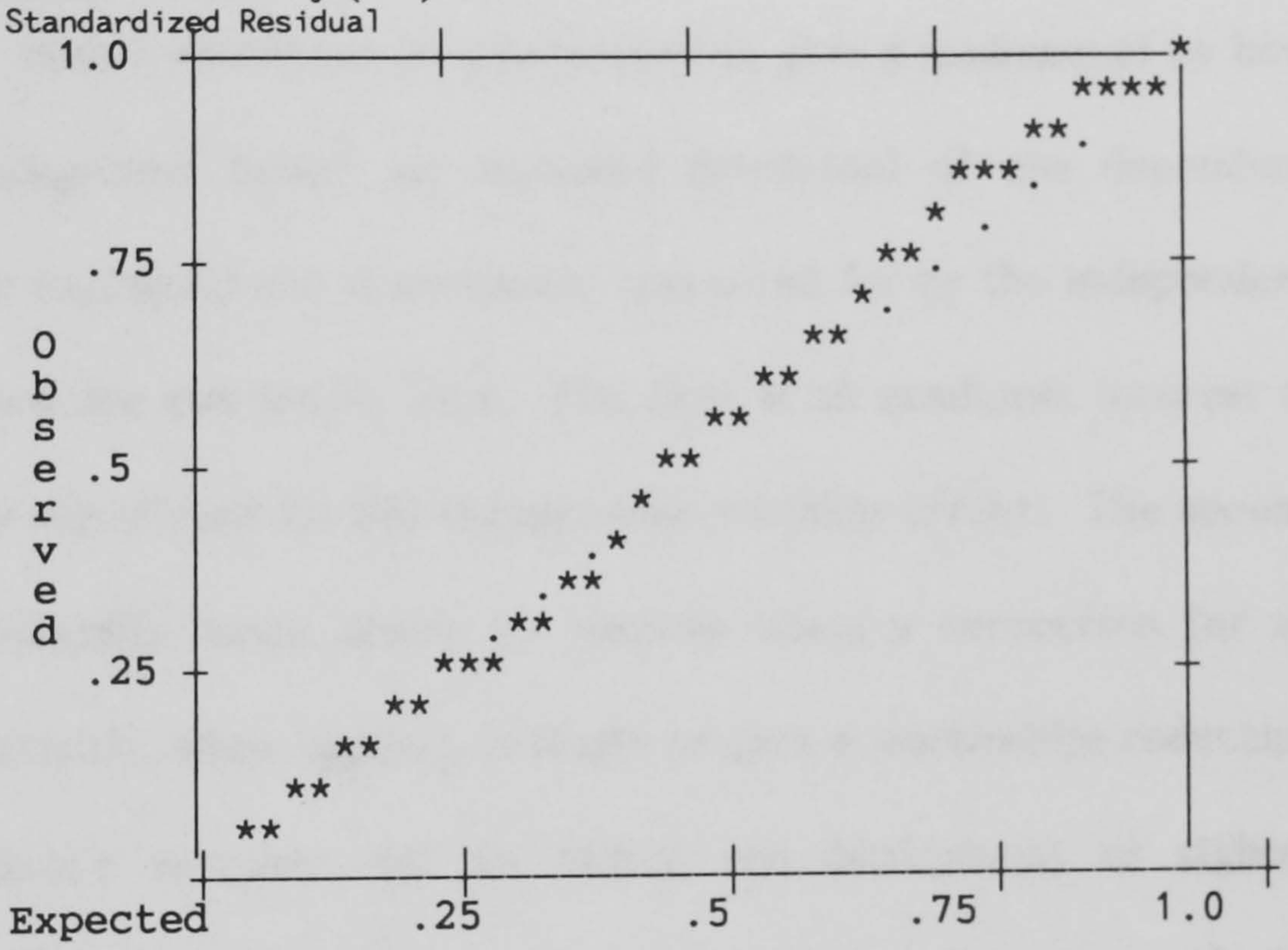
```
PROCESS IF (ABRDB EQ 80).
REGRESSION /VARIABLES MVL AGE SEX PTA4 AGESEX AGEPTA4 SEXPTA4 ASPTA4
/DESCRIPTIVES DEFAULT
/STATISTICS DEFAULTS CI
/DEPENDENT MVL
/METHOD ENTER
/RESIDUALS HISTOGRAM NORMPROB
/SCATTERPLOT (*RESID *PRED)
/SAVE RESID (R1).

* *   M U L T I P L E   R E G R E S S I O N   * *

Listwise Deletion of Missing Data

                Mean    Std Dev

MVL            5.749       .274
AGE           46.936     14.536
SEX             .494       .501
PTA4          32.355     22.739
AGESEX        24.110     26.288
AGEPTA4     1664.826   1360.736
SEXPTA4       19.041     25.092
ASPTA4      1006.017   1420.277

N of Cases =    172

Correlation:

              MVL       AGE       SEX      PTA4    AGESEX   AGEPTA4   SEXPTA4

MVL         1.000      .379      .414      .338      .461      .410      .407
AGE          .379     1.000      .126      .445      .360      .697      .310
SEX          .414      .126     1.000      .269      .931      .270      .770
PTA4         .338      .445      .269     1.000      .380      .919      .657
AGESEX       .461      .360      .931      .380     1.000      .446      .834
AGEPTA4      .410      .697      .270      .919      .446     1.000      .637
SEXPTA4      .407      .310      .770      .657      .834      .637     1.000
ASPTA4       .426      .428      .719      .647      .856      .699      .965

              ASPTA4

MVL           .426
AGE           .428
SEX           .719
PTA4          .647
AGESEX        .856
AGEPTA4       .699
SEXPTA4       .965
ASPTA4       1.000
```

```
--------------------------------------------------------------------
        * * * *  M U L T I P L E   R E G R E S S I O N  * * * *

Equation Number 1    Dependent Variable..   MVL

Beginning Block Number  1.  Method:  Enter


Variable(s) Entered on Step Number
   1..     ASPTA4
   2..     AGE
   3..     PTA4
   4..     SEX
   5..     AGEPTA4
   6..     AGESEX
   7..     SEXPTA4


Multiple R              .54486
R Square                .29687
Adjusted R Square       .26686
Standard Error          .23457

Analysis of Variance
                     DF        Sum of Squares        Mean Square
Regression            7               3.80983             .54426
Residual            164               9.02360             .05502

F =        9.89172       Signif F =  .0000


---------------------- Variables in the Equation -----------------------
Variable                B         SE B     95% Confdnce Intrvl B       Beta

ASPTA4      -1.15748E-05 1.17598E-04 -2.43776E-04 2.206266E-04    -.06001
AGE          3.741805E-03 3.08926E-03 -2.35806E-03 9.841665E-03     .19854
PTA4        -1.65848E-04 3.71942E-03 -7.50998E-03 7.178279E-03    -.01377
SEX              .23889       .20650      -.16884       .64662     .43725
AGEPTA4      5.397254E-05 8.04160E-05 -1.04812E-04 2.127567E-04     .26809
AGESEX      -2.56191E-05 4.91085E-03 -9.72226E-03 9.671026E-03 -2.458E-03
SEXPTA4     -1.01615E-03 5.58129E-03      -.01204       .01000    -.09307
(Constant)       5.40280       .12829       5.14948      5.65612


---------- in -----------

Variable            T  Sig T

ASPTA4           -.098  .9217
AGE             1.211  .2276
PTA4            -.045  .9645
SEX             1.157  .2490
AGEPTA4          .671  .5031
AGESEX           -.005  .9958
SEXPTA4          -.182  .8558
(Constant)     42.113  .0000
--------------------------------------------------------------------
Residuals Statistics:

                    Min          Max       Mean  Std Dev     N

*PRED            5.4675       6.0666     5.7494    .1493   172
*RESID           -.5768       1.0424      .0000    .2297   172
*ZPRED          -1.8882       2.1252     -.0000   1.0000   172
*ZRESID         -2.4589       4.4440      .0000    .9793   172

Total Cases =       172

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
```

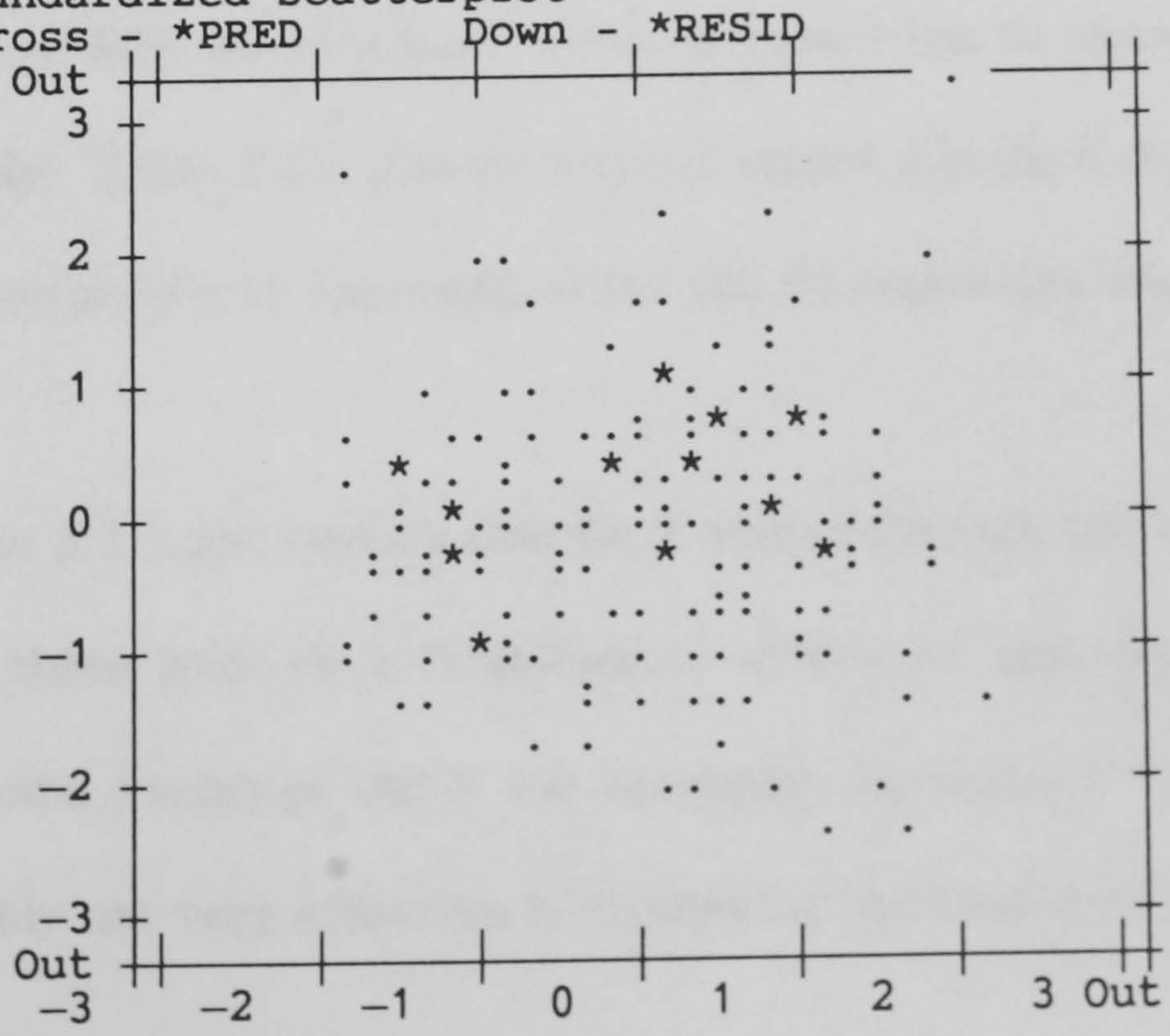
Histogram - Standardized Residual

```
NExp N      (* = 1 Cases,    . : = Normal Curve)
1  .13   Out *
0  .26  3.00
1  .67  2.67 :
2 1.53  2.33 *:
3 3.14  2.00 **:
4 5.75  1.67 **** .
4 9.44  1.33 ****    .
9 13.9  1.00 *********     .
* 18.3   .67 ******************:****
* 21.5   .33 ***********************:*****
* 22.8   .00 ************************:**
* 21.5  -.33 ***********************:****
* 18.3  -.67 ************     .
* 13.9 -1.00 ************:**
* 9.44 -1.33 ********:*
3 5.75 -1.67 ***  .
4 3.14 -2.00 **:*
2 1.53 -2.33 *:
0  .67 -2.67 .
0  .13   Out
```

Normal Probability (P-P) Plot
Standardized Residual



Standardized Scatterplot
Across - *PRED Down - *RESID



NPAR TESTS /K-S (NORMAL) R1.

- - - - - Kolmogorov - Smirnov Goodness of Fit Test

R1 Residual

Test Distribution - Normal Mean: .0000000
Standard Deviation: .2297163

Cases: 172

Most Extreme Differences

Absolute	Positive	Negative	K-S Z	2-tailed P
.06723	.06723	-.03683	.882	.419

The above results provide a wealth of information. Perhaps the most useful figure is the R square which can be interpreted to give a measure of by how much the "background noise" (or standard deviation) of the dependent variable can be explained and if necessary corrected for by the independent variables. There are two issues here. The first is an academic interest in identifying any significant ($p<.05$) independent variable effect. The second is a more practically based desire to identify when a correction for an independent variable, when applied, is likely to give a worthwhile reduction in the dependent's variance and so permit the deployment of tighter confidence limits. In order to reduce the standard deviation of the dependent to 90% or 80% of its overall value, R square has to exceed 0.19 or 0.36 respectively. Table 3.3.3.2(a) gives the R square and the K-S p value from the test of normality on the residual for the 64 regression analyses.

Inspection of Table 3.3.3.2(a) reveals that no R square exceeds the value of 0.36 and, whilst there may be a "significant" effect of age, gender or hearing loss in some variables (MI-V for example), correction for these effects are probably not very effective in tightening the confidence limits.

Table 3.3.3.2(a)

R square from the regression analyses for age, gender and hearing loss treatments (HLT) together with the residual K-S p

VARIABLE	HLT (a)		HLT (b)		HLT (c)		HLT (d)	
	R^2	K-S p	R^2	K-S p	R^2	K-S p	R^2	K-S p
MVL	.297	.42	.303	.45	.312	.48	.317	.36
MI-III	.160	.39	.155	.49	.079	.24	.081	.38
MIII-V	.053	.86	.061	.80	.059	.91	.057	.95
MI-V	.208	.60	.208	.83	.160	.62	.160	.94
MI/V	.192	**.02**	.194	**.03**	.210	**.01**	.210	**.02**
V22-11	.071	.81	.053	.43	.060	.72	.051	.58
V44-11	.060	**.08**	.070	.27	.058	.28	.066	.26
V66-11	.038	.55	.045	.62	.064	.63	.069	.72
V88-11	.100	.77	.097	.82	.083	.54	.085	.61
V22/11	.052	**.08**	.051	.12	.059	.20	.058	.22
V44/11	.094	**.01**	.093	**.01**	.044	**.00**	.038	**.00**
V66/11	.058	**.02**	.061	**.02**	.054	**.03**	.047	**.05**
V88/11	.021	.26	.017	.28	.015	.31	.012	.36
PV22-11	.066	.74	.047	.55	.053	.82	.043	.63
PV44-11	.050	.15	.056	.20	.043	.27	.049	.37
PV66-11	.026	.50	.028	.64	.036	.77	.040	.82
PV88-11	.090	.85	.080	.94	.066	.75	.063	.78
LOG(MI/V)	.243	.69	.245	.77	.234	.22	.235	.45
LOG(V44/11)	.120	.20	.119	.11	.055	.10	.049	**.08**
LOG(V66/11)	.083	.10	.083	**.09**	.068	**.06**	.059	**.07**

The validity of the linear regression is in serious doubt for variables MI/V, V44/11 and V66/11 since the K-S p<<.1 for all four hearing loss treatment regressions. Since these are ratio variables it makes sense to perform a logarithmic transformation of the variables and the lower portion of Table 3.3.3.2(a) shows the results of the regression procedures following transformation. The K-S significance p value is here much greater than in the untransformed case although a question mark still hangs over V66/11.

It is worth examining the results of those analyses where R square exceeds 0.19 to see which factors can be harnessed for possible (though modest) improvement of the diagnostic criteria through tighter confidence limits.

For MVL, the absolute wave V latency, both age and gender show significant ($p<.05$) effects in hearing loss treatments (c) and (d) (but not in (a) and (b)). For MI-V, gender is significant in analyses (a) and (b). For LOG(MI/V), the transformed I/V amplitude ratio, only the age / gender interaction factor is significant, in analyses (a) and (b). In no other analyses with an R square >0.19 are there any significant factors.

The important conclusion from this analysis of the effects of hearing loss on the ABR is therefore, surprisingly, that there is none for which a correction for *hearing loss* would be particularly fruitful.

Backward stepwise multiple regression with main effects only

The inclusion of seven independent variables in a forced entry regression analysis tends to "water down" the significance levels obtained and it is quite possible that significance would be greater if, say, only the main effects of age, gender and hearing loss were considered using a stepwise method. To this end, and with a practically applicable means of obtaining a reasonable improvement in confidence limits in mind, a further series of regression analyses were performed on the key variables MVL, MI-III, MIII-

V, MI-V, LOG(MI/V) and V88-11. Hearing loss treatment (c) was used, ie SL4, the sensation level with respect to the 4kHz hearing threshold, since in the former analyses, there was little to chose between the four treatments and SL4 has the advantages of being applicable to all patients and ease of calculation. A backward stepwise regression method was used in which all three independents were initially included, then excluded sequentially until only significant factors remained. The exclusion criterion was p>.1.

Table 3.3.3.2(b) summarises the results of these analyses.

Table 3.3.3.2(b)

Summary of backward stepwise multiple regression with main effects

VARIABLE	SIGNIFICANT EFFECTS (p<.05)	R^2	K-S p
MVL	age, gender, sensation level	.304	.27
MI-III	gender	.043	.17
MIII-V	age, gender, sensation level	.054	.80
MI-V	gender, sensation level	.128	.85
LOG(MI/V)	age, gender, sensation level	.209	.30
V88-11	age	.040	.90

With the exception of MVL and LOG(MI/V), the R square results are all low, indicating little reward in applying a correction for "significant" factors.

MVL

The problem with MVL is that all three factors need to be considered to achieve the 16% tightening of confidence limits that the .304 R square

suggests. The prediction equation for MVL is:

MVL = 5.624 + (AGE * 0.0042) + (SEX * 0.18) - (SL4 * 0.00313) ms

where AGE is in years, SEX = 0 for females and 1 for males and where SL4 is in dB. This gives a prediction of the most likely value of MVL for a given subject. To this must be added a further quantity to obtain the appropriate 95% confidence interval. This is 1.645 (ie 1-tailed) times the square root of the sum of the square of the new standard deviation (84% of the original) plus the square of the standard error of the predicted value. This second component was evaluated for 32 typical predicted values of MVL covering both genders, ages from 20 to 80 years and SL4 values from 20 to 80dB. When appropriately converted to ms, this component changed the confidence limit by 0.01 to 0.003ms or alternatively by 0.16% to 0.05% - an amount so small as to be safely ignored. Taking just 1.645 times 84% of the original standard deviation (0.29ms) gives 0.4ms and so the prediction equation for the 95% confidence limit for MVL is therefore:

5.624 + (AGE * 0.0042) + (SEX * 0.18) - (SL4 * 0.00313) + 0.4 ms

This equation will be used in the calculation of the MVL confidence limit when applied as a diagnostic index in the tumour groups.

The IPLs

In the regression results of all three IPLs, the gender factor was the most significant and because of the ease of correction (ie simply having separate limits for each gender) it would be churlish not to account for gender, despite the low R square.

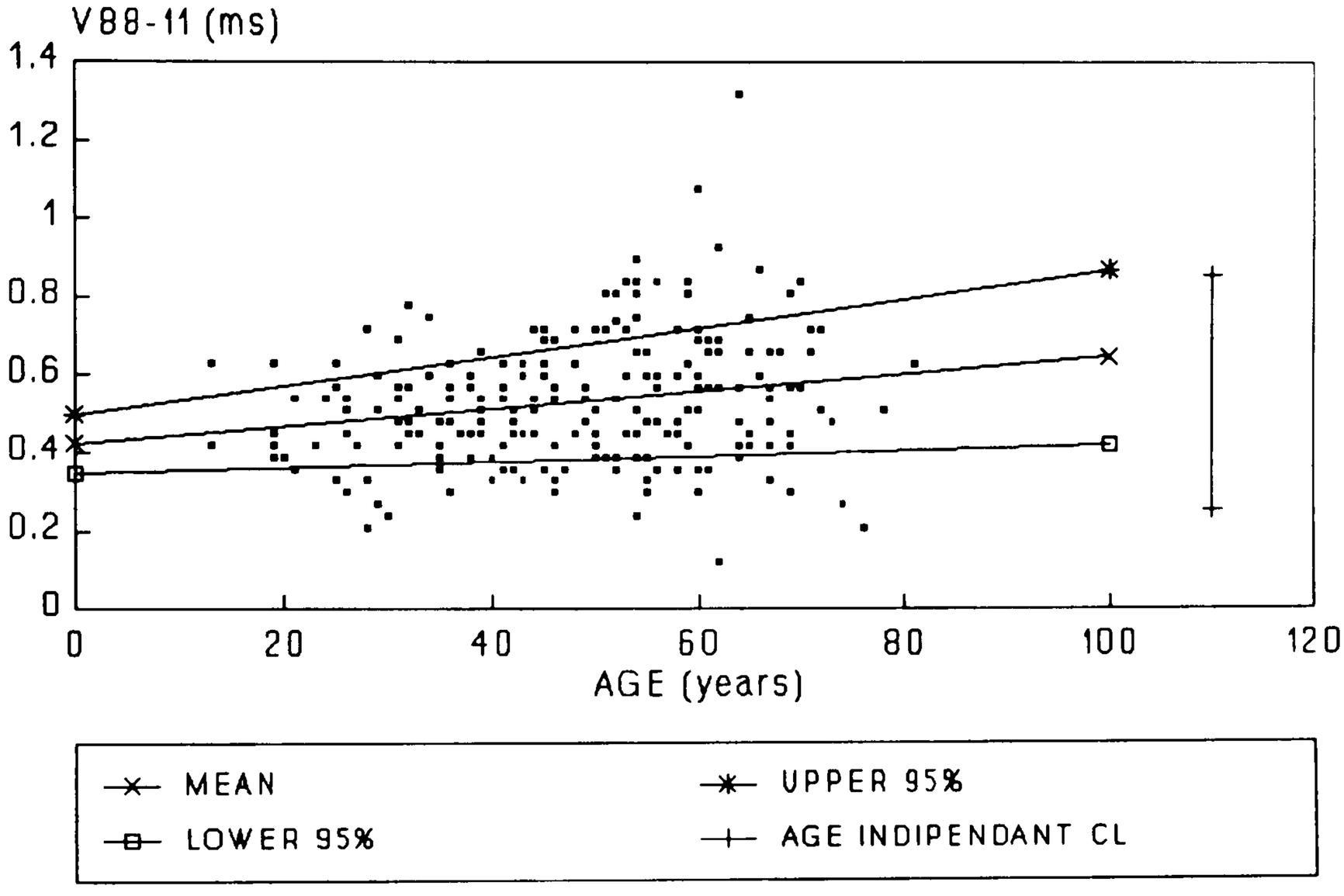
LOG(MI/V)

In order to obtain the 11% reduction in variance (R square = .209), not only is a three factor regression equation necessary, but also a logarithmic transformation. Whilst the regression is probably worth undertaking for MVL, MI/V with its lower R square and need of transformation is probably best left as it is. Unlike other variables, I/V is a bit of a blunt instrument. From the literature, in tumour cases where I/V is abnormally large (and in most tumour cases with an identifiable ABR, wave I is absent so I/V is zero), I/V is quite clearly abnormal and great precision is not required.

V88-11

What of the age factor in V88-11? The R square of .04 is not very exciting. To see how age influences V88-11, Figure 3.3.3.2 depicts the data plus the mean and lower and upper 95% confidence limit lines derived from the regression analysis. Also shown is the age-independent limits calculated in the normal manner.

Figure 3.3.3.2



It can be seen that many false positives would occur if the age-related upper 95% limit was deployed compared to the static limit. Unless sensitivity is a problem when using the static limit with this variable, its greater specificity (not to mention its ease of application) makes it the limit of choice and correction for age is not warranted.

To summarise this section therefore, it does not appear worthwhile to correct for any effects of hearing loss except in MVL, the absolute wave V latency.

3.3.4 The effect of hearing loss on inter-aural ABR variables

The IDLV and similar inter-aural ABR variables offer the advantage of immunity from the effects of age and gender. This section will therefore examine these variables for the possible effects of hearing loss alone.

3.3.4.1. Analysis Methods

The four hearing loss treatments described earlier are available for use in a stepwise regression analysis. Gone are the factors of age and gender, but we now have not only treatments (a) to (d) for each ear but additionally inter-aural difference variables. Variables SL4DIFF and SLBTADIFF were generated where they represent the test ear minus non-test ear difference in the 4kHz and best two average (2,4,8kHz) stimulus sensation levels respectively. These two new variables are most likely to illuminate any dependency of inter-aural ABR measures on asymmetries in the hearing status of subjects.

3.3.4.2. Results of multiple linear regression

Table 3.3.4.2. shows the results of this analysis. In QI-III, QV44-11 and QV88-11, no hearing loss treatment was significant at the $p<.05$ level. In QIII-V and QI-V the 4kHz sensation level of the test ear (SL4) was just significant, but the R square was very low and clearly unworthy of further

investigation. ILDV (at 11.1/s) and ILDV44 (at 44.4/s) were, as one would reasonably expect, very sensitive to the asymmetry of the sensation level of the stimuli, SLBTADIFF being the important factor. The R square values are not insignificant and testify to the need for some form of correction for the effects of hearing loss as first suggested by Selters & Brackmann (1977). The K-S p value of the regression residual is on the low side, however. Inspection of the residuals' distribution revealed that the non-normality is not the result of skewness, but rather of a symmetrical but rather peaked distribution (Kurtosis = 3.8 for ILDV). This finding does *not* invalidate the regression or the resulting regression equation.

Table 3.3.4.2

R square from the regression analysis for hearing loss on inter-aural ABR variables together with the residual K-S p.

VARIABLE	SIGNIFICANT EFFECT (p<.05)	R^2	K-S p
QI-III	none	-	-
QIII-V	SL4	.038	.68
QI-V	SL4	.054	.60
ILDV	SLBTADIFF	.134	.07
ILDV44	SLBTADIFF	.156	.07
QV44-11	none	-	-
QV88-11	none	-	-

3.3.4.3. IDLV correction methods

Unlike the IPLs, ILDV requires only a recordable Wave V from each ear and therefore promises a greater coverage in patients with a considerable high frequency hearing loss. However, it is in exactly these cases where the weakness of ILDV is exposed - its susceptibility to the effects of hearing loss. Appropriate ILDV correction methods have been suggested, based on the extent of the loss (usually at 4kHz) but these require equal stimulus intensities in both ears.

Two alternative correction techniques were examined and compared to the now accepted method of Selters & Brackmann. Both allow differing stimulus intensities to be employed in the two ears. This is not a minor technical or academic point since, in the case of a patient with one normal and one severely hearing-impaired ear, a stimulus capable of eliciting a clear Wave V in the poorer ear may be intolerably loud in the better ear.

Since this thesis is primarily concerned with stimulus repetition rate effects, full details of the computation and assessment of the two novel ILDV correction techniques are given in Appendix D.

Briefly, the concept of the first technique is *not* to adjust the measured ILDV, but rather to choose a pair of stimulus intensities (one for each ear) that take account of an individual's hearing loss status. This is achieved by conducting an alternate binaural loudness balance (ABLB) test at 4kHz prior

to ABR testing, and then performing the non-test or reference ear ABR at 80dBnHL. This is followed by the test ear ABR at whatever intensity the ABLB shows as equal in loudness (at 4kHz) to 80dBHL in the non-test ear. This technique will be called the "Loudness Balanced ILDV".

The concept of the second technique is to apply a latency correction to ILDV. Unlike existing correction methods, this technique applies a *sensation level* correction, permitting unequal stimulus intensities to be employed in the two ears. This technique will be referred to as the "SL corrected ILDV".

Appendix D shows that the Selters & Brackmann correction and the loudness balanced ILDV perform reasonably well, but that the SL correction technique is superior to either, with a mean which is closer to zero and with a smaller variance, especially in subjects with a large inter-aural hearing asymmetry.

The strategy behind the use of ILDV44, the ILDV conducted at 44.4/s, is that it takes less time to perform (important only if the trials are conducted for ILDV measurement alone) and that it encompasses the potential benefits of both the ILDV and the rate-induced latency shift. In other words, if the Wave V latency on one side is delayed because of neurological dysfunction, a further delay may be expected on this side because of an abnormally great rate effect, resulting in a more abnormal ILDV at 44.4/s than would be observed at 11.1/s.

In Group ABC, ILDV and ILDV44 are quite well correlated ($r = 0.66$, $p < .001$)

and a paired T-test failed to distinguish the two variables (p = .816). Since the 11.1/s - 44.4/s wave V latency shift (variable V44-11) is not significantly influenced by hearing loss, it is reasonable to conclude that the SL correction may be applied with validity to both ILDV *and* ILDV44.

3.3.5 Basic diagnostic ABR data from non-tumour subjects

Subjects in Groups A, B & C all have one thing in common: we are as sure as one can be that none have a retrocochlear disorder. These three groups have been combined and various measures of their ABR have been analysed for any dependency on age, gender and hearing loss. Taking account of these factors where appropriate (ie when it is useful and reasonably convenient to do so), it is now possible to calculate 95% confidence limits from this non-tumour group. Such data can be used as diagnostic criteria in the evaluation of future clinical subjects with hearing loss of unknown aetiology.

Table 3.3.5 summarises these confidence limits and also gives the percentage applicability - the percentage of cases (in Group ABC) for which each variable could be calculated. The reason for missing data usually relates to the ability to identify the requisite ABR peak(s). The exception to this is SLILDV (and SLILDV44) where, because of the sensation level correction, the variable is employed only when sensation levels of over 10dB were used on both sides.

Note that the highest applicability is for variables which rely on only wave V. The wave V rate-induced latency shift variables all have an applicability of at least 99%. An additional and very simple diagnostic criterion can be derived from this observation: if a repeatable wave V can be identified at 11.1/s, the disappearance of the wave at higher SRRs is itself abnormal and could be taken as suggestive of retrocochlear dysfunction.

TABLE 3.3.5

MEANS AND 95% CONFIDENCE LIMITS FROM GROUP ABC

VARIABLE	MEAN	STD.DEV.	95% C.L.	%APPLIC	TAILS
MVL (use regression equation - section 3.3.3.2)				100	1
MI-III (F)	2.1337	0.1796	<2.429	95	1
MI-III (M)	2.2188	0.2210	<2.582	92	1
MIII-V (F)	1.8446	0.1595	<2.106	97	1
MIII-V (M)	1.9032	0.1796	<2.199	96	1
MI-V (F)	3.9783	0.2220	<4.344	98	1
MI-V (M)	4.1221	0.2037	<4.457	95	1
MI/V	see text		<0.942	96	1
QI-III (*)	0.0147	0.2063	±0.404	90	2
QIII-V (*)	0.0271	0.1864	±0.365	94	2
QI-V (*)	0.0124	0.2158	±0.423	93	2
SLILDV (*)	0.0034	0.1788	±0.351	96 #	2
SLILDV44 (*)	0.0065	0.1987	±0.389	96 #	2
V22-11	0.0649	0.0803	<0.197	100	1
V44-11	0.2394	0.1205	<0.438	100	1
V66-11	0.4069	0.1452	<0.646	99	1
V88-11	0.5366	0.1631	<0.805	99	1
V88/11	0.9673	0.3701	>0.359	99	1
QV44-11 (*)	0.0025	0.1692	±0.332	94	2
QV88-11 (*)	0.0163	0.2094	±0.410	95	2
PV22-11	1.1228	1.3897	<3.409	100	1
PV44-11	4.1644	2.0672	<7.565	100	1
PV66-11	7.0742	2.4624	<11.125	99	1
PV88-11	9.3330	2.7723	<13.893	99	1

(*) Confidence limits assume a zero mean.

\# 4% of cases excluded because sensation level ≤10dB in one or both ears.

All inter-aural variables have 2-tailed distributions and means very close to zero. As in the analysis of Group A, these variables were subject to a paired T-test against the value zero. None was significantly different from zero and so when calculating the confidence limits, a zero mean is assumed.

Variable MI/V is not normally distributed although logarithmic transformation can be used to overcome this. In fact, the SPSS PC+ "HAVERAGE" procedure was used, which uses the distribution of the experimental data.

The relationships between the diagnostic variables

Exactly how useful each of the variables shown in Table 3.3.5 are in terms of their ability to detect acoustic neuromata will be addressed in section 3.5. However, it would be pointless to use any two or more variables as diagnostic indices if they are basically measuring the same thing. A more powerful combination of diagnostic indices is likely to be one in which the variables are relatively unrelated and can be seen as measures of different aspects of neurological function. To this end, the correlation of the major variables of interest is given in Table 3.3.5(b).

Table 3.3.5(b)

Correlation of major diagnostic variables

Correlations:	MVL	MI-III	MIII-V	MI-V	SLILDV	V88-11
MVL	1.0000	.2484**	.3539**	.4898**	.3715**	.1893*
MI-III	.2484**	1.0000	-.2766**	.6889**	.0082	.1172
MIII-V	.3539**	-.2766**	1.0000	.5060**	.1803*	-.2068*
MI-V	.4898**	.6889**	.5060**	1.0000	.1434	-.0508
SLILDV	.3715**	.0082	.1803*	.1434	1.0000	-.0451
V88-11	.1893*	.1172	-.2068*	-.0508	-.0451	1.0000

1-tailed Signif: * - .01 ** - .001

As one would have guessed, MVL is significantly related to all other variables which include the wave V latency although less so with V88-11. All the IPLs are related - again reasonable since they are all measures of neural propagation velocity. Since the IPLs are probably the most popular diagnostic indices for the detection of retrocochlear dysfunction, it is interesting and maybe encouraging that both SLILDV and V88-11 do not appear to be strongly related to them in this neurologically normal population. Moreover, SLILDV and V88-11 seem to be independent of each another.

A logical but tentative conclusion to be drawn from this is that it may unhelpful to employ all three IPLs when only one will do. A combination of the best of the IPLs with both SLILDV and V88-11 may be more rewarding if these variables reflect multiple aspects of neurological function.

An obvious but important point to make clear is that the correlation between the variables may be totally different in a neurologically abnormal population. Indeed, we would like it to be so.

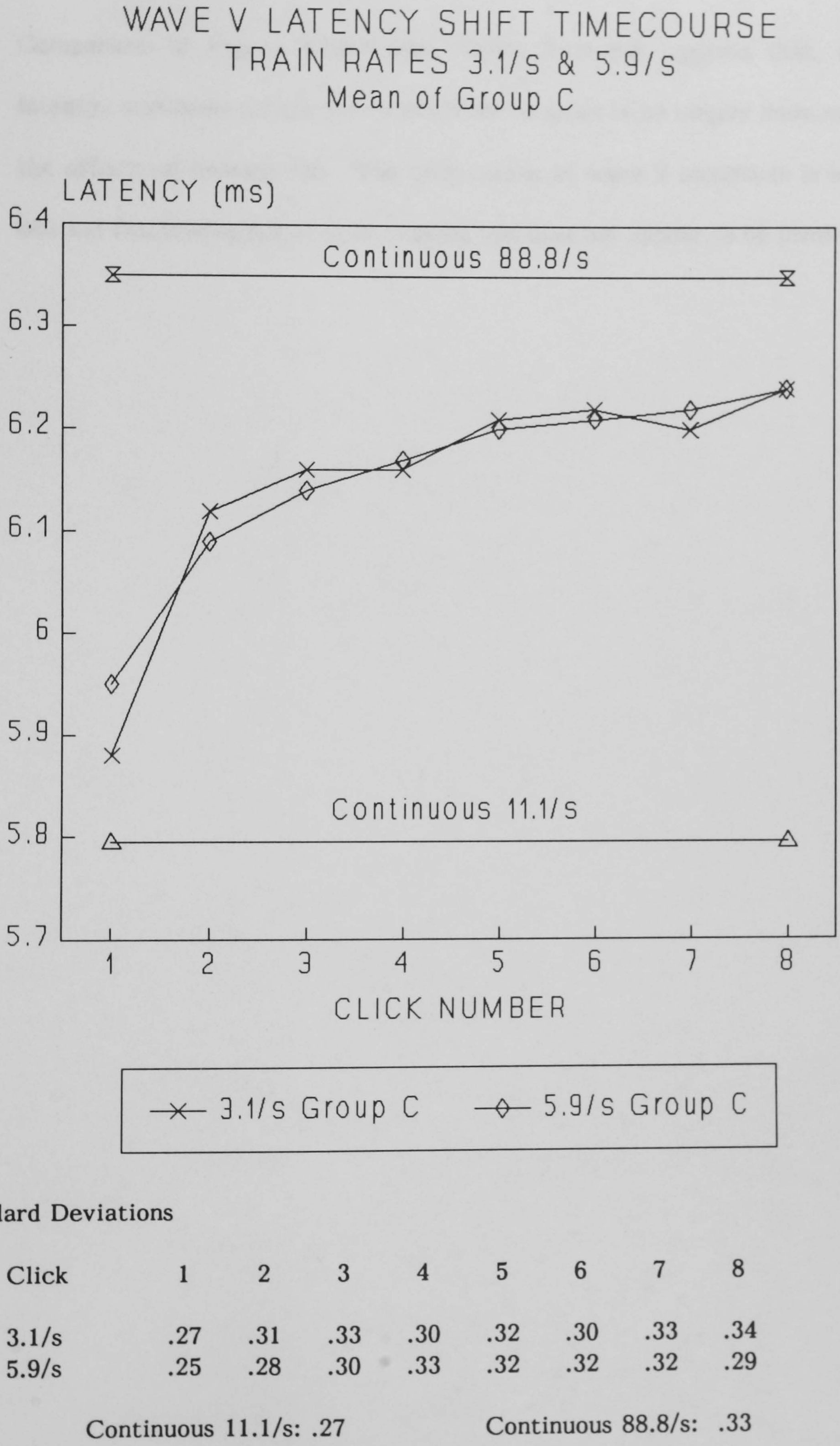
3.3.6 The effect of hearing loss on the time course of adaptation & recovery

We saw in section that there was no important effect of hearing loss on the rate effect variables, though there was an age effect demonstrated in V88-11. Even though there may be little effect of hearing loss on the *steady-state* rate-induced latency shift or amplitude diminution variables, it is worth examining the click train results of Group C subjects to see whether there is any obvious departure from the temporal characteristics revealed in the analysis of normal subjects. In other words, does hearing loss influence the time course of adaptation and recovery? To answer this basic question in a fairly simplistic but valid way, the wave V 8-click train data of Group C subjects are presented in the same format as used in section 3.1.4.1 to allow direct comparison.

3.3.6.1 *The effect of hearing loss on latency adaptation onset & recovery*

Figure 3.3.6.1 bears a striking resemblance to Figure 3.1.4.1(a), its normal subject counterpart and the conclusions made for Group A hold true for Group C. There *is* a difference in these two figures however. Figure 3.3.6.1 shows longer latencies but this is a consequence of the hearing loss (mean BTA248 = 42.6 dBHL) in Group C compared to Group A (mean BTA248 = 13.4dBHL). It is nothing to do with rate-induced latency shift or the time course of its adaptation.

Figure 3.3.6.1



Standard Deviations

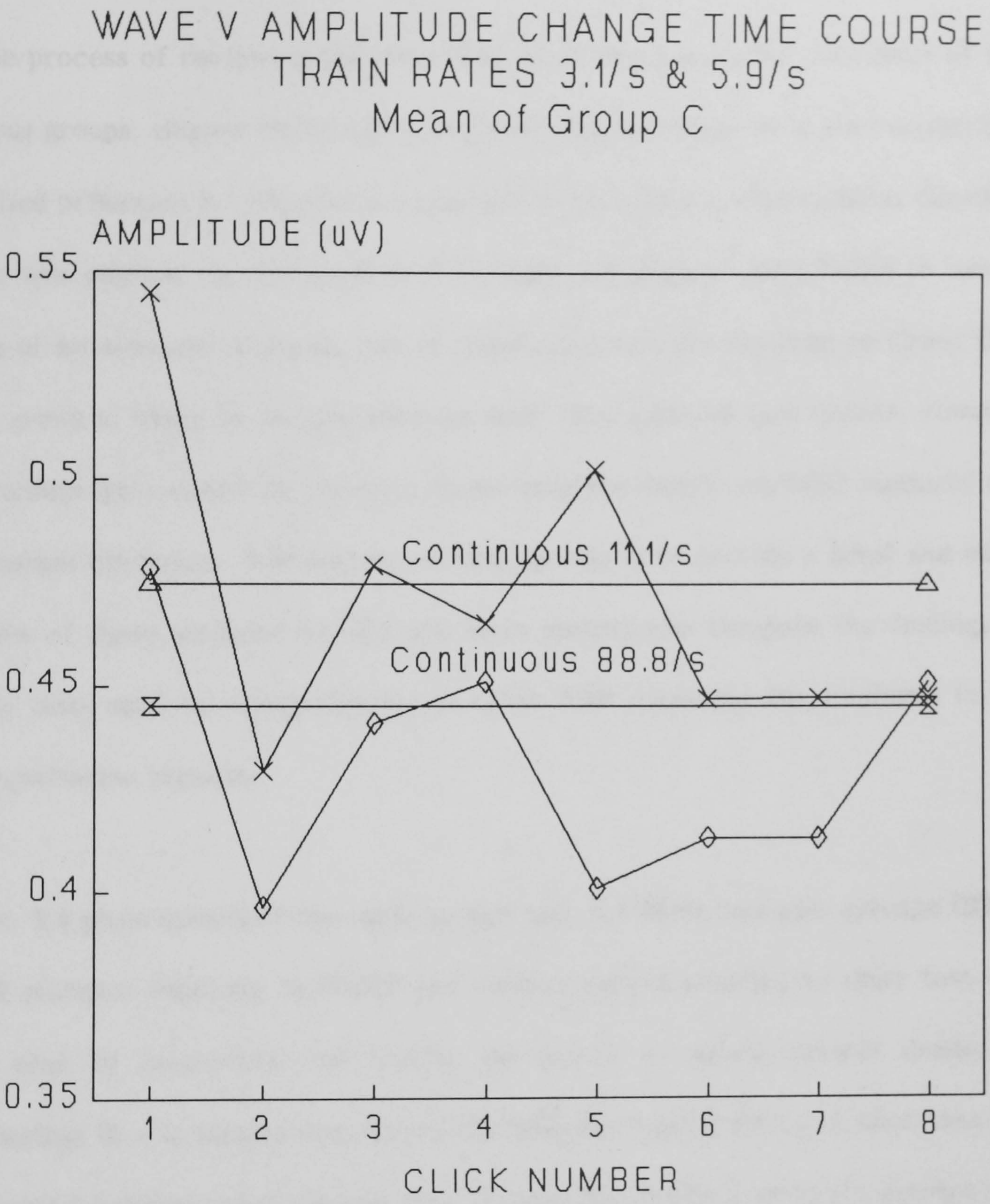
Click	1	2	3	4	5	6	7	8
3.1/s	.27	.31	.33	.30	.32	.30	.33	.34
5.9/s	.25	.28	.30	.33	.32	.32	.32	.29

Continuous 11.1/s: .27 Continuous 88.8/s: .33

3.3.6.2 *The effect of hearing loss on amplitude adaptation onset & recovery*

Comparison of Figure 3.3.6.2 with Figure 3.1.4.2(a) suggests that, like latency, amplitude adaptation characteristics seem to be largely immune to the effects of hearing loss. The time course of wave V amplitude is both odd and fascinating but at least hearing loss does not appear to be involved!

Figure 3.3.6.2



Standard Deviations

Click	1	2	3	4	5	6	7	8
3.1/s	.14	.25	.22	.22	.19	.19	.17	.18
5.9/s	.16	.17	.14	.19	.18	.18	.15	.19

Continuous 11.1/s: .16 Continuous 88.8/s: .13

3.4 A BRIEF LOOK AT GROUP D

In the process of reviewing the results of tests on patients for candidacy of the various groups, sixteen failed entry to groups B and C because of the restrictions detailed in Section 2.5 and thus were suspected of having a retrocochlear disorder. None was eligible for Groups E or F because radiological tests failed to reveal signs of an acoustic neuroma, and so these subjects were assigned to Group D. This group is likely to include subjects with false positive test results, acoustic neuromata (presumably too small to image using the locally available methods) and brainstem disorders. The purpose of this section is to provide a brief and basic review of these subjects' results and more specifically compare the findings of those tests used for categorisation to other ABR measures not employed in the categorisation process.

Table 3.4 gives details of the subjects age, sex, 2,4,8kHz best two average (BTA), ABR stimulus intensity (ABRDB) and various results relating to their test ear. For ease of inspection, the results are shown as within normal limits (n), borderline (B - ie almost exactly on the 95% confidence limit) or abnormal (A). A dash (-) indicates that the test was not performed and a query (?) denotes that the test was not possible (eg in the case of absent reflexes for ARD). For this purpose, the criteria against which the ABR results are compared are *not* those used for categorisation but rather those shown in Table 3.3.5. Note that ILDV is the sensation level corrected ILDV and that the criterion for MVL is that given by the regression equation.

Table 3.4

Summary of important results from Group D subjects

CODE	AGE	SEX	BTA	ABRDB	IAM	CT	ABLB	ARD	I-III	III-V	I-V	ILDV	MVL	V88-11	PV88-11
D01	56	F	70	105	n	n	A	?	n	A	A	A	A	A	A
D02	50	M	60	90	n	-	n	?	B	n	A	n	n	n	n
D03	34	M	50	80	-	n	A	A	n	n	n	n	n	n	n
D04	40	F	70	90	-	n	?	?	n	A	A	A	A	n	n
D05	44	F	45	80	n	-	n	n	n	A	A	n	n	n	n
D06	53	M	57	100	n	n	A	?	?	A	?	A	A	A	n
D07	59	M	62	80	-	n	A	A	n	n	n	n	n	n	n
D08	56	M	42	80	-	n	n	n	A	B	A	A	A	n	n
D09	60	F	17	80	-	n	?	?	A	n	A	n	A	A	A
D10	51	M	70	95	-	n	n	?	A	n	A	A	A	A	n
D11	59	M	52	80	n	DNA	n	?	n	n	A	n	n	n	n
D12	40	M	17	80	A	n	n	n	A	n	A	n	n	n	n
D13	46	F	30	80	-	n	n	?	A	n	A	A	n	A	n
D14	51	F	60	100	n	n	A	A	?	n	?	n	n	n	n
D15	66	F	55	80	n	n	A	A	n	n	n	n	n	n	n
D16	50	M	17	80	-	n	?	?	n	A	A	n	n	A	n

Inspection of Table 3.4 permits comparison of the IPL results with ILDV, MVL and rate effect results of subjects in sub-groups which have common features and for whom the most likely disorder can be guessed. It is important to stress that the following should not be taken too seriously but this simple analysis is provided in the hope that it gives an interesting albeit not rigorous glimpse of how the various ABR findings compare. The following sub-groups are grouped the basis of the results which put the subjects into Group D.

ABLB and ARD abnormalities alone

Subjects D03, D07, D14 & D15 all had normal IPLs and normal ILDV, MVL, V88-11 and PV88-11. From the work of Turner *et al* (1984) and others it is

tempting to conclude that these subjects actually have no neurological dysfunction and that the abnormal results are false positives.

Extended I-III and I-V

It is possible and indeed probable that at least some of these subjects have small acoustic neuromata despite negative CT findings. Of subjects D08, D09, D10, D12 & D12, three had an abnormal ILDV, three had an abnormal MVL and three had an abnormal V88-11 rate shift. One had an abnormal PV88-11. ABLB and ARD results were either normal or unobtainable in all five subjects.

Extended III-V and I-V

Subjects D01, D04, D05 & D16 had results suggestive of brainstem dysfunction. Of these four, two had an abnormal ILDV (the other two had abnormal III-V IPLs on the other side suggesting a bilateral problem so an abnormal ILDV might not be expected), two had an abnormal MVL and two had an abnormal V88-11 (of which one had an abnormal PV88-11).

Others

Subjects D02 & D11 both had a I-V IPL of 4.62ms but no other abnormality. D11 failed to attend for CT on two occasions. It is possible that these are false positive results or else represent very small acoustic neuromata. Subject D06 showed ABLB derecruitment and an extended III-V IPL. I-III and I-V could not be assessed because wave I was not observed. ILDV, MVL and V88-11 were also abnormal. The subject has subsequently developed an

audiologically dead ear and must therefore be considered at a high risk of having an acoustic neuroma.

Of the twelve subjects with abnormal IPLs, six had an abnormal ILDV, six an abnormal MVL and six an abnormal V88-11. Only two had an abnormal PV88-11. ILDV and MVL agreed in ten of the twelve subjects. V88-11 disagreed with both ILDV and MVL in only two of the twelve subjects (both in the brainstem sub-group). When V88-11 was abnormal there was always at least one other ABR abnormal finding and when V88-11 was normal there was always at least one other normal finding.

On the basis of this crude analysis, the outlook for wave V rate effect measurements look very promising in that it appears to be in substantial agreement with other ABR results. The percentage shift version of V88-11 (PV88-11) appears less hopeful however, being abnormal only when very substantial degrees of rate-induced latency shift are recorded.

3.5 THE ABR IN SUBJECTS WITH ACOUSTIC NEUROMATA: GROUPS E & F

Having examined various ABR measures and determined their 95% confidence limits it is possible to apply these limits to the 31 subjects with acoustic neuroma. This will allow the sensitivity and applicability of each measure to be evaluated.

3.5.1 Theoretical objections to the use of multiple ABR criteria

The traditional approach in the use of the ABR to investigate patients with a suspected acoustic neuroma is to use a number of ABR measures as diagnostic criteria. The IPLs and the ILDV are the undoubted favourites. However, if more than a single ABR measure is employed (using the appropriate 95% confidence limit derived from a non-tumour population), the overall specificity falls below 95%. The more ABR measures that are used, the more the specificity will drop, increasing the risk of at least one false positive error.

To pursue this line of reasoning for a moment, if we can assume that the measures are mutually independent (most are not of course, but more of that later), it is possible to calculate the overall specificity as follows:

Assume that we have a neurologically normal subject. With one test, the chance of saying so is .95. With *n* independent tests, the chance of saying so is $(.95)^n$. Consequently the chance of making a type 1 (false positive) error is 1-.95 = .05 for one test and $1 - (.95)^n$ for *n* tests. As an example, if 6 independent tests are applied (n=6) the chance of one of the six producing an abnormal result is .265, ie typically one in every four patients

will produce one abnormal result.

One obvious way of dealing with this problem is to require that more than one of the *n* results needs to be abnormal before the patient is categorized as being abnormal. If we require *x* abnormal results of *n* applied independent tests, the chance of a false positive outcome is:

$$\frac{n!}{x!\,(n-x)!}\,(.05)^{x}\,(.95)^{n-x}$$

For example, if *n=6* and *x=2*, the probability of making a type 1 error is about .03, ie the specificity is 97%.

Whilst this appears to overcome the objections to the use of multiple ABR measures by allowing the overall specificity of a combination of tests to be calculated, it is inappropriate here since many of the ABR measures are correlated (eg I-III, I-V and ILDV) and therefore not independent. Unfortunately, knowledge of the correlation and covariance matrices of the ABR measures does not allow an appropriate modification to the above probability derivation so we are rather stuck! However, *because* many of the ABR measures are correlated, the reduction in specificity imposed by the use of more than a single criterion is less than it would have been had the measures been independent.

The lesson here is to use a small number of highly efficient criteria rather than a multitude of marginally useful tests which would serve only to increase the number of diagnostic errors.

3.5.2 Evaluating sensitivity and applicability

The act of splitting subjects with acoustic neuromata into groups was an acknowledgement of the fact that many such patients had no useful (from the point of view of ABR testing) hearing in their tumour ear. Rather than wasting time performing the extended "test ear" rate tests on the tumour side of such subjects, the opposite ear was treated as the test ear in the hope of revealing more rate-related information about the effects of possible brainstem compression or displacement. In retrospect, it would have been wise to perform the extended "test ear" rate tests on the non-tumour side of all tumour subjects. For the purpose of the following analysis, groups E & F were combined with the data of group F being transposed such that the data of all tumour ears were aligned as were those of all non-tumour ears. The range of ABR measures on the tumour ear was therefore restricted to mirror those available from the opposite side with variables involving the rates of 22.2/s and 66.6/s being dropped. For convenience the "M" in some of the test ear (now tumour ear) variables was maintained (eg MI-III) and the prefix "Z" employed for the opposite, non-tumour ear. The prefix "Q" was retained for the inter-aural IPL and rate effect variables.

Notes on determining applicability and abnormal results

In general, the 95% confidence limits shown in Table 3.3.5 were used for both tumour ear and non-tumour ear ABR variables. The absolute wave V latency, MVL or ZVL, was considered applicable providing that the SLBTA for that ear was >10dB even if wave V was absent (when the result was considered as abnormal) since in non-tumour subjects, wave V was *always*

present when SLBTA > 10dB. Similarly, the rate-induced latency shift variables (eg V44-11) were considered applicable *and abnormal* even if wave V was absent at the higher rate, providing that it was present at 11.1/s. Wave V was *always* present in non-tumour subjects at 44.4/s and present in 99% of non-tumour subjects at 88.8/s.

MI/V and ZI/V were considered applicable and normal even if the result was 0, ie wave I was absent and wave V present. If the opposite was true, the result (∞) was again applicable but abnormal (actually, this never occurred). The measures were considered not applicable only when neither wave was available.

Table 3.5.2 gives the results of applying the criteria of Table 3.3.5 to all 31 tumour subjects. The % sensitivity (applicable) is the percentage of abnormal findings in the subset of subjects for whom the measure was considered applicable. The % sensitivity (total) refers to the percentage of abnormal findings in all 31 tumour subjects.

Much of the contents of Table 3.5.2 confirm what is already known, MI-III and MI-V are ideal in those subjects for whom the measures are possible yet these measures are unavailable in the majority of tumour ears (% applicability <50%). MI/V is almost useless, despite its higher applicability. Of the tumour ear measures, the findings of MVL and V88-11 are most encouraging, performing better than all others because of their relatively high applicability.

Table 3.5.2

Applicability & sensitivity of ABR variables: all tumour subjects

VARIABLE	n APPLIC	n ABNORM	% APPLIC	% SENSITIVITY applic	% SENSITIVITY total
Tumour ear					
MVL	19	19	61	100	61
MI-III	12	12	39	100	39
MIII-V	12	6	39	50	19
MI-V	13	13	42	100	42
MI/V	19	3	61	16	10
V44-11	19	12	61	63	39
V88-11	19	16	61	84	52
PV44-11	19	10	61	53	32
PV88-11	19	12	61	63	39
Non-Tumour ear					
ZVL	30	3	97	10	10
ZI-III	30	0	97	0	0
ZIII-V	30	12	97	40	39
ZI-V	30	8	97	27	26
ZI/V	30	2	97	7	6
ZV44-11	30	8	97	27	26
ZV88-11	30	10	97	33	32
Inter-aural measures					
QI-III	12	11	39	92	35
QIII-V	12	6	39	50	19
QI-V	13	13	42	100	42
QV44-11	18	9	58	50	29
QV88-11	18	14	58	78	45
SLILDV	17	17	55	100	55
SLILDV44	17	17	55	100	55

The performance of tests on the ear opposite to the tumour again confirms the conventional wisdom. All the tests are highly applicable, with ZIII-V doing the best (n=12/30) presumably identifying those subjects in whom the tumour is compromising the brainstem by some means. The runner up is again V88-11 (n=10/30). Interestingly, these two variables do not appear to be measuring the

same thing since only 5 subjects had abnormal findings on both accounts. If one accepts an abnormal finding from either measure, 55% of all subjects will be found to be abnormal (n=17/31), a very respectable overall sensitivity when compared to the tumour ear overall sensitivity.

Of the inter-aural variables, the IPLs are simply identifying those subjects already found to be abnormal by the individual ear IPLs. The same is true of the rate-induced latency shift variables. The sensation level corrected ILDV and its 44.4/s counterpart performed well but again, simply reinforced the findings already made, this time by MVL. The logical interpretation of this is that the separate sensation level corrections of MVL (or rather its 95% confidence limit) and SLILDV are equivalent and satisfactory and that in MVL, the correction for age and gender effects (inherently unnecessary in ILDV) is effective.

Taking all the ABR measures and accepting any one abnormal result as a positive outcome (a very silly thing to do, admittedly), on the tumour side they combine to provide an overall sensitivity of 65% (not a great deal more than the 61% from MVL alone). The non-tumour ear measurements together provide an overall sensitivity of 58% as do the combined interaural measures. Taking all 23 measures yields a global sensitivity of 87%. The cost of taking any one abnormal finding would be huge in terms of a very poor specificity so this is not suggested. An efficient diagnostic strategy in the application of these variables should optimise both sensitivity and specificity whilst maximising applicability.

3.5.3 The effects of hearing loss on sensitivity and applicability

The literature on the overall sensitivity of the ABR in detecting acoustic neuromata is usually consistent in giving values of over 90%. Less frequently mentioned is the number of separate ABR measures being deployed or the usual stipulation that these high sensitivities relate to a sub-group of subjects in whom an ABR could be elicited from the tumour ear. If SLBTA is used as a realistic index of our ability to adequately stimulate the tumour ear, 39% (n=12/31) had SLBTA < 10dB on the tumour side even when the maximum stimulus intensity was 105dBnHL. The majority of these cases had audiologically dead ears.

The number of abnormal results found in the 3 groups of measures are shown in a casewise manner in Table 3.5.3(a). The absence of positive findings clearly correlates with these very deaf tumour ear subjects. If we simply group the subjects according to whether SLBTA >10dB in both ears or not, a clear division of findings occur as depicted at the bottom of Table 3.5.3(a). Tables 3.5.3(b) and (c) follow the format of Table 3.5.2 for these two sub-groups.

Table 3.5.3(a)

The number of abnormal ABR results in each tumour subject

SUBJECT CODE	NUMBER OF ABNORMAL RESULTS M	Z	Q	TOTAL	SLBTA >10dB
E001	5	1	4	10	Y
E002	7	0	6	13	Y
E003	1	3	4	8	Y
E004	6	2	6	14	Y
E005	7	2	6	15	Y
E006	2	0#	0#	2	Y#
E007	7	4	6	17	Y
E008	5	2	4	11	Y
E009	5	1	4	10	Y
E010	8	0	7	15	Y
E011	6	2	5	13	Y
E012	0	1	0	1	No
E013	6	0	5	11	Y
E014	5	0	4	9	No
E015	4	0	2	6	Y
E016	7	0	7	14	Y
E017	8	0	7	15	Y
E018	2	0	2	4	Y
F001	6	1	5	12	Y
F002	0	0	0	0	No
F003	0	1	0	1	No
F004	0	5	0	5	No
F005	0	0	0	0	No
F006	5	2	4	11	Y
F007	0	1	0	1	No
F008	0	5	0	5	No
F009	0	0	0	0	No
F010	0	2	0	2	No
F011	0	5	0	5	No
F012	0	0	0	0	No
F013	1	3	0	4	Y
% With ≥1 Abnormal Result:				Any 1	
Overall	65	58	58	87	
SLBTA > 10dB	100	61	94	100	
SLBTA < 10dB	15	54	8	69	

This subject had an audiologically dead non-tumour ear.

Table 3.5.3(b)

Applicability & sensitivity of ABR variables:

18 Tumour subjects with SLBTA > 10dB in both ears

VARIABLE	n APPLIC	n ABNORM	% APPLIC	% SENSITIVITY	
				applic	total
Tumour ear					
MVL	18	18	100	100	100
MI-III	11	11	61	100	61
MIII-V	11	5	61	45	28
MI-V	12	12	67	100	67
MI/V	17	3	94	18	17
V44-11	17	12	94	71	67
V88-11	17	14	94	82	78
PV44-11	17	10	94	59	56
PV88-11	17	11	94	65	61
Non-Tumour ear					
ZVL	18	1	100	6	6
ZI-III	18	0	100	0	0
ZIII-V	18	6	100	33	33
ZI-V	18	4	100	22	22
ZI/V	18	0	100	0	0
ZV44-11	18	5	100	28	28
ZV88-11	18	7	100	39	39
Inter-aural measures					
QI-III	11	10	61	91	56
QIII-V	11	5	61	45	28
QI-V	12	12	67	100	67
QV44-11	17	9	94	53	50
QV88-11	17	13	94	76	72
SLILDV	17	17	94	100	94
SLILDV44	17	17	94	100	94

Briefly, Table 3.5.3 (b) shows that when SLBTA > 10dB in the suspect ear, only test ear measures are necessary, with MVL and V88-11 out-performing the IPLs, because of their superior applicability. When available, MI-III and MI-V were always abnormal but their application was limited since wave I was absent in over one third of cases. These two measures appear equivalent, identifying the same tumour subjects.

Table 3.5.3(c)

Applicability & sensitivity of ABR variables:

13 Tumour subjects with SLBTA < 10dB in at least one ear

VARIABLE	n APPLIC	n ABNORM	% APPLIC	% SENSITIVITY applic	% SENSITIVITY total
Tumour ear					
MVL	2	1	15	50	8
MI-III	1	1	8	100	8
MIII-V	1	1	8	100	8
MI-V	1	1	8	100	8
MI/V	2	0	15	0	0
V44-11	2	0	15	0	0
V88-11	2	1	15	50	8
PV44-11	2	0	15	0	0
PV88-11	2	1	15	50	8
Non-Tumour ear					
ZVL	13	2	100	15	15
ZI-III	12	0	92	0	0
ZIII-V	12	6	92	50	46
ZI-V	12	4	92	33	31
ZI/V	12	2	92	17	15
ZV44-11	12	3	92	25	23
ZV88-11	12	3	92	25	23
Inter-aural measures					
QI-III	1	1	8	100	8
QIII-V	1	1	8	100	8
QI-V	1	1	8	100	8
QV44-11	1	0	8	0	0
QV88-11	1	1	8	100	8
SLILDV	0	-	0	-	-
SLILDV44	0	-	0	-	-

Table 3.5.3 (c), as expected, illustrates that when SLBTA < 10dB, only the non-tumour ear measures provide any reasonable sensitivity, with ZIII-V being the test of choice.

3.5.4 A suggested strategy when applying 95% confidence limit tests.

Knowledge of the above findings allow an optimally efficient diagnostic strategy to be developed concerning the ABR measures that would best applied. In this section, suggestions are made for an efficient strategy in the application of these measures. Because of the problems outlined in section 3.5.1, specificity for combinations of measures was derived empirically from the data of non-tumour subjects.

If SLBTA > 10dB in the suspect ear

Providing that the audiometric status of the suspect ear allows that ear to receive an effective stimulus (ie SLBTA >10dB with a click intensity of 80dBnHL or more) we expect to be able to record a wave V. If wave V is absent under these conditions a tumour should be suspected.

Table 3.5.3(b) suggests several candidates worthy of being the single ABR measure used to detect an acoustic neuroma, with MVL and its 95% corrected confidence limit at the top of the list. Do we drop MI-III and MI-V in favour of MVL? Such a suggestion is unlikely to find favour with the rest of the world and for good reason: this study is based on only 31 tumour cases and relatively large changes in sensitivity would be seen if one or two further cases gave different results.

To use the IPLs when they are measurable *does* appear to provide excellent sensitivity and if both MI-III *and* MI-V are required to be abnormal, a

specificity of 99% is afforded. The problem with the IPLs in subjects with acoustic neuromata is that waveform morphology is quite often poor and the confidence with which the tester places the cursor on wave I is frequently low. Wave V is usually less affected and its identity confirmed if required by performing an intensity series - wave V is the last wave to disappear as the threshold is approached.

Variables MI-V, MVL and SLILDV are basically measuring the same phenomenon: prolongation of wave V latency (MI-III is really just a special adaptation of MI-V in this regard). The only essential difference here is the way in which the effects of age, gender, hearing loss and stimulus intensity are accommodated. The use of the four variables: MI-III, MI-V, MVL & SLILDV and accepting *any two* abnormal findings as an abnormal result restricts the specificity to an acceptable 97.1%. Every one of these measures, when available, was abnormal in the subset of tumour ears with SLBTA > 10dB so the sensitivity of this combination should be as close to 100% as we could get. This combination also allows MI-III and MI-V to be unavailable in the event of an absent wave I.

The use of V88-11 in addition to any of the above combinations lowers the specificity considerably since it is independent of all 4 other measures, and adds 6% more false positives. Despite having good sensitivity and applicability therefore, its inclusion in a combination of measures to test an ear suspected of having an acoustic neuroma cannot be recommended.

Recommendation

(i) Employ MI-III, MI-V, MVL & SLILDV and accept any two abnormal findings as an abnormal outcome. If wave I is absent, both IPLs should be considered normal.

(ii) If wave V is absent accept this as an abnormal outcome.

(iv) Do not include any contralateral ear results.

This strategy should yield a very high sensitivity (as close to 100% as can be determined with the current sample size), with a specificity of 97%.

If SLBTA < 10dB in the suspect ear

Under this condition all test-ear and interaural measures are probably going to be unavailable. ABR tests on the suspect ear should *not* be discounted however. There are two good reasons for this. The first is that the audiometric data may be in error. Malingering patients often present with a total deafness and malingering does not protect the patient from developing an acoustic neuroma! The second reason is that a neuroma may, in theory, completely block all auditory nerve function and thus fail to produce waves III and V. If the function of the cochlea is sufficiently unimpaired to give a wave I, the only ABR measure available is the I/V amplitude ratio, which will be abnormal. This finding did not occur in the 31 tumour cases in this study but it has been reported elsewhere.

If tests on the suspect ear fails to produce a measurable ABR, as was the

case in 11 of the 12 tumour cases (with SLBTA < 10dB) ZIII-V should be used since it was found to be abnormal 50% of the time and has a specificity of 96%. In second place for sensitivity was ZI-V but this failed to identify any case not already identified by ZIII-V. The 3 cases found abnormal under ZV88-11 had also been identified by ZIII-V. However, the relative independence of IPLs and rate effect measures has already been inferred and the small numbers in this group may be masking an otherwise useful combination of measures. Employing both ZIII-V and ZV88-11 has a specificity of only 89% if one accepts an abnormality from either.

Recommendation

(i) Perform ABR tests on the suspect ear despite the magnitude of the hearing loss and apply the strategy recommended above. If wave I is present and V is absent, this is an abnormal finding.

(ii) Deploy both ZIII-V and ZV88-11 from the non-suspect ear. Since these measures are largely independent, a specificity of about 89% is presumed if one accepts a positive finding from either measure. A negative finding from both does not rule out a tumour in the opposite ear - it simply makes one about half as likely as if we had not performed the tests. In these circumstances the ABR test has failed to reveal a tumour, it does not exclude one, and further appropriate diagnostic imaging would be appropriate.

3.5.5 An alternative approach: Discriminant Analysis

The use of this statistical technique does not require the calculation of confidence limits but rather the ABR results of known tumour and non-tumour subjects. From these data an optimally efficient discriminant function is identified and this can be applied to an unclassified subject. Not only will this subject be classified (ie tumour or non-tumour) but the probability of the outcome is available as a measure of confidence.

Two discriminant analyses were performed, one based on MVL and SLILDV for subjects where the test ear SLBTA was >10dB and another based on ZIII-V and ZV88-11 for subjects where the test ear SLBTA was < 10dB.

3.5.5.1 *Discriminant Analysis for subjects with SLBTA > 10dB*

The analysis used MVL, SLILDV and the age, gender and SL4 variables to account for these effects in MVL. The resulting discriminant function correctly categorized all non-tumour subjects (ie 100% specificity) but only 68% of tumour subjects (68% sensitivity). To see whether a better sensitivity could be obtained, rather than using MVL with the accompanying 3 related factors, a simple dichotomous variable was used which simply indicated whether or not the MVL was within its corrected 95% confidence limit. This yielded a 98% specificity and 100% sensitivity, regardless of whether SLILDV was included. This is a rather ridiculous use of discriminant analysis but demonstrates the power of the MVL variable (in

the present sample, at least).

3.5.5.2 *Discriminant Analysis for subjects with SLBTA < 10dB*

This analysis used ZIII-V and ZV88-11 on all non-tumour cases, not just those where SLBTA < 10dB. Tumour cases were restricted to those where SLBTA < 10dB. The reason for this is that the number for which SLBTA < 10dB was very small in the non-tumour group. This analysis yielded a specificity of 100% and a sensitivity of 33%. The analysis was repeated with ZV88-11 excluded (ie ZIII-V alone). Specificity was retained at 100% but the sensitivity dropped to 25%.

The results of the discriminant analyses in this and the previous section are poor, almost certainly because an assumption regarding the data distributions has been violated, ie the requirement that the variables are from multivariate normal distributions. The variance of the ABR predictor variables is far greater in the tumour group. Box's M test is available as part of the SPSS discriminant analysis and in these analyses the results showed that the probability of inequality of the tumour and non-tumour groups' covariance matrices was very high ($p<.0000$). The analyses performed badly because optimum conditions were not in place.

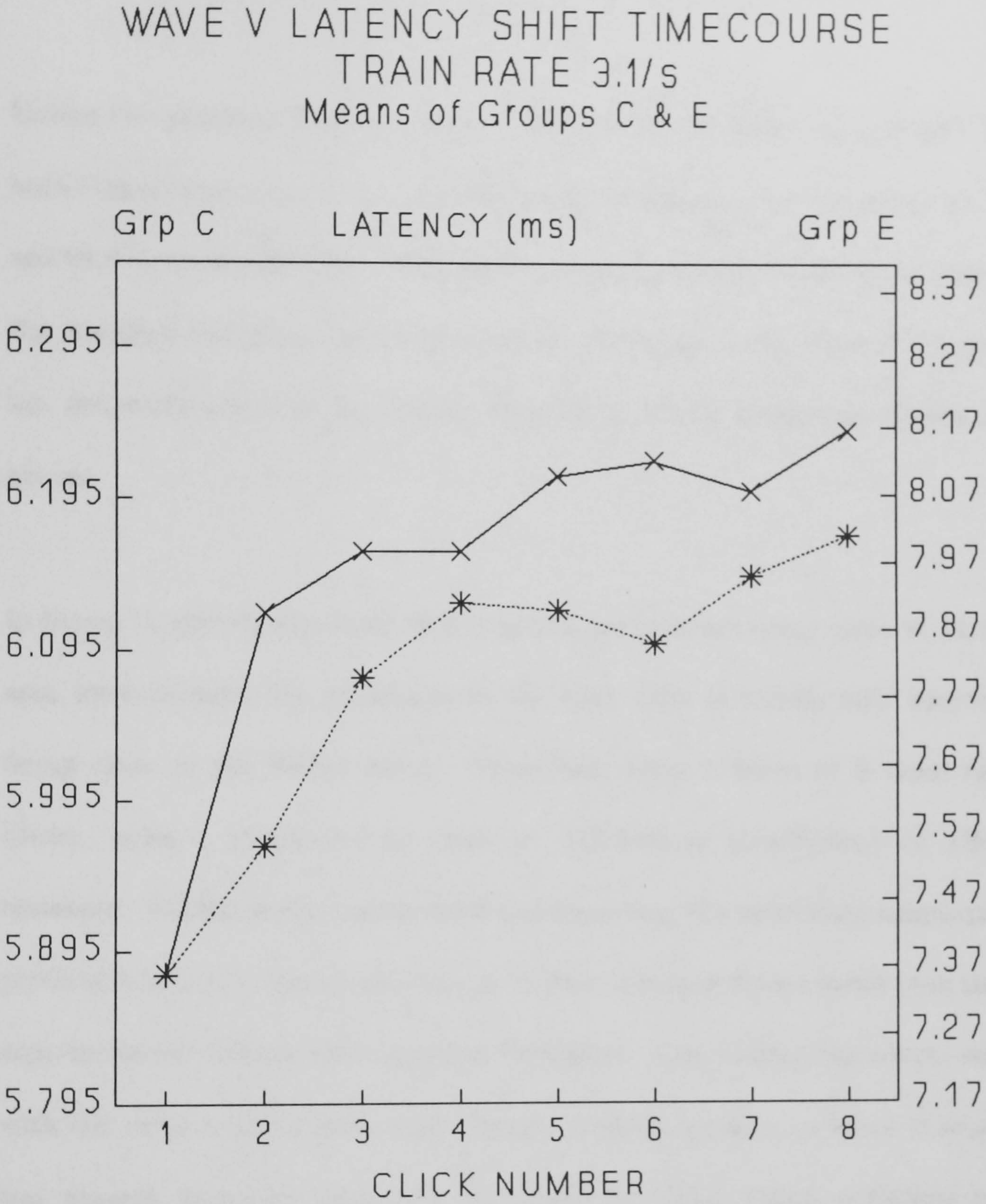
3.5.6 The effect of acoustic neuromata on the time course of adaptation & recovery

Because of the very poor general waveform morphology of the ABR of most subjects with an acoustic neuroma at higher SRRs, only four underwent the click train tests, all at a TRR of 3.1/s. Any conclusions resulting from an analysis of the click train tests should therefore be regarded with the utmost caution. Further, these four are unrepresentative of their group *because* their waveform morphology was reasonable. The following is therefore included as an insight rather than a definitive description of the effects of tumour on the temporal aspects of latency and amplitude adaptation and recovery.

3.5.6.1 *The effect of acoustic neuromata on latency adaptation onset & recovery*

Figure 3.5.6.1 compares the data of Group C (from Fig 3.3.6.1) and Group E at 3.1/s. Note here that the top and bottom borders of the figure represent the continuous 88.8/s and 11.1/s latencies of the two Groups which have different vertical axes to accommodate the much longer latencies of Group E. This was done to facilitate comparison of the two curves within the context of their appropriate adaptation extremes. The standard deviations shown at the bottom of Figure 3.5.6.1 show that, as one might expect with only four subjects representing a pathology of variable nature, the means of Group E latencies should be viewed with a large latitude and that in general, the pattern is not especially dissimilar to that of Group C.

Figure 3.5.6.1



Standard Deviations

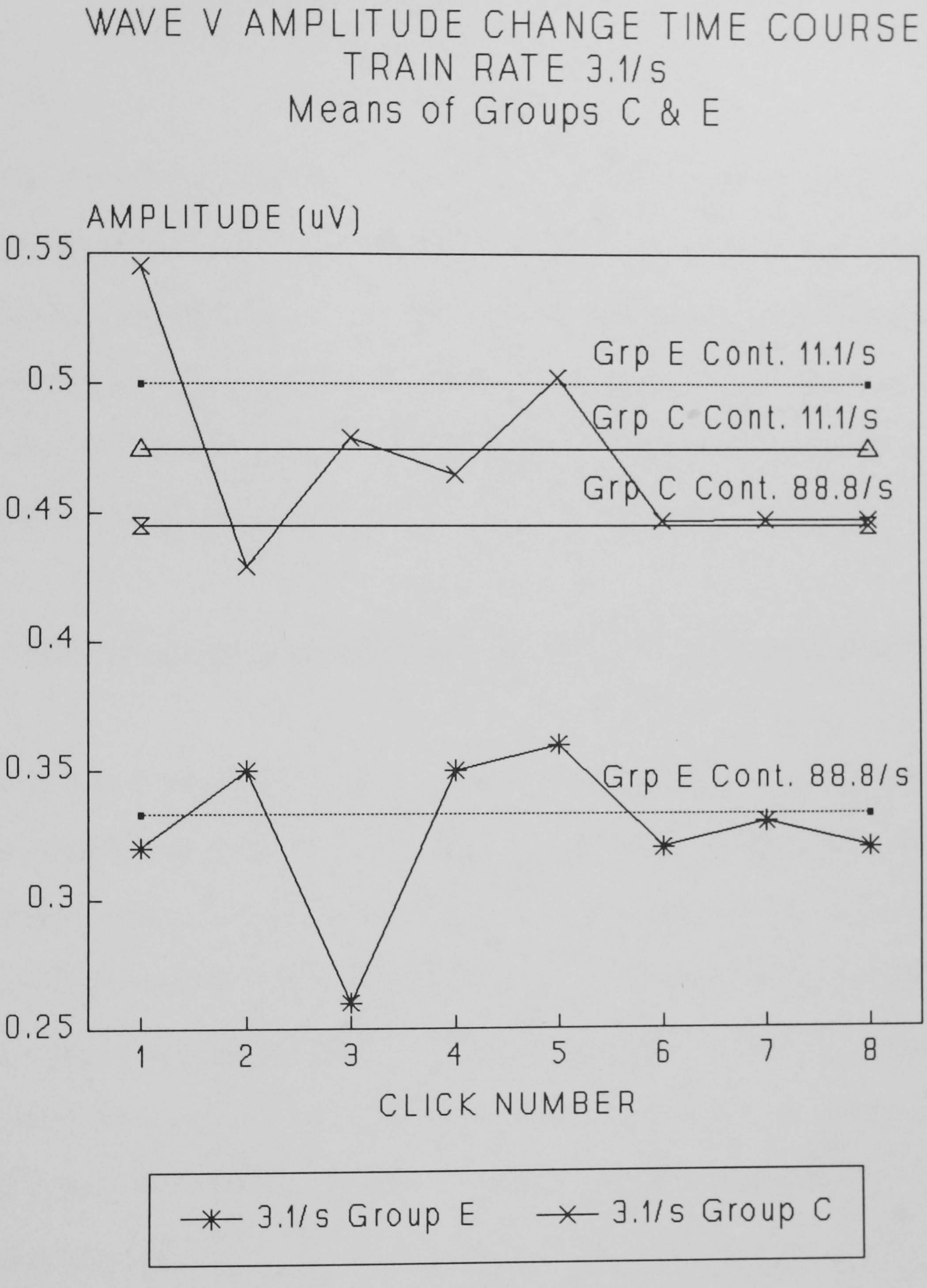
Click	1	2	3	4	5	6	7	8	Continuous 11.1	Continuous 88.8
Group C	.27	.31	.33	.30	.32	.30	.33	.34	.27	.33
Group E	.65	.92	.71	.80	.77	.72	.78	1.02	.91	1.34

3.5.6.2 *The effect of acoustic neuromata on amplitude adaptation onset & recovery*

Unlike the previous Figure, Figure 3.5.6.2 uses the same vertical axis for both Group mean data since the data extends beyond the continuous 11.1/s and 88.8/s horizontal lines which here are shown dashed for Group E. Again, the standard deviations for Group E means are larger than those of Group C but not sufficiently so to explain difference in the amplitude adaptation curves.

In Group E, the steady-state 88.8/s amplitude is much lower than at 11.1/s and, interestingly, the amplitude at the first click is clearly still adapted, being close to the 88.8/s value. Therefore, after a burst of 8 rapid rate clicks, even a stimulus-free time of 243.5ms is insufficient to allow recovery. Unlike latency adaptation and recovery, the amplitude adaptation process in acoustic neuromata seems to have a longer time course than that seen in normal and cochlear-impaired subjects. This finding correlates well with the point made earlier that in some tumour subjects, a wave V which was present at lower rates may be absent at higher rates: a finding not generally seen in non-tumour subjects.

Figure 3.5.6.2



Standard Deviations

Click	1	2	3	4	5	6	7	8	Continuous 11.1	Continuous 88.8
Group C	.14	.25	.22	.22	.19	.19	.17	.18	.16	.13
Group E	.22	.29	.17	.23	.29	.26	.26	.27	.21	.20

CHAPTER 4

SUMMARY AND CONCLUSIONS

Because of the breadth and complexity of the analysis contained in the results chapter, an initial interpretive discussion was included following each major finding, where appropriate. A separate Discussion chapter is avoided, and the primary purpose of this final chapter is to distil and restate the important results and their meaning in a more digestible and concise form. A secondary aim is to contrast the results with those of other studies.

4.1 CONVENTIONAL (NON-RATE EFFECT) ABR DIAGNOSTIC MEASURES

Although this research study focused upon the effects of stimulus repetition rate on the ABR, the more conventional and accepted ABR measures were also subject to analysis, principally to look for any effects of age, gender, or hearing loss/stimulus sensation level. In such analyses an important distinction must be made between the identification of statistically *significant* effects and whether such effects are sufficiently *important* to warrant correction. The latter is a rather subjective assessment since it combines a measure of how much is to be gained in terms of added precision with the ease with which a correction can be made in a clinical setting.

Gender is a significant factor in the inter-peak latencies (IPLs) and although gender differences account for only a small percentage of the inherent variability

of these measures, the ease with which separate gender norms can be applied justifies their use. The practice of establishing separate gender norms for the IPLs is gaining wide international acceptance although it is important for each laboratory to obtain their own normative data (Thornton, 1986).

The I/V amplitude ratio is a very interesting example of a variable in which age, gender and stimulus sensation level have clear statistically significant effects yet accounting for these effects, together with the necessary transformation of the variable (because of its non-normal distribution) is of sufficient complexity to deter one from making the correction. Another important consideration is that this variable has a poor track record as a diagnostic index of retrocochlear dysfunction.

4.2 NEW SUGGESTIONS FOR NON-RATE EFFECT ABR DIAGNOSTIC MEASURES

The Wave V inter-aural latency difference (ILDV or IT[5]) is known to be a powerful diagnostic index. It has the advantage of relying upon only Wave V but has two disadvantages: it requires results from both ears (at the same intensity) and its known susceptibility to the effects of hearing loss necessitates a correction such as that suggested by Selters and Brackmann (1977). The two-ear requirement can be made more palatable by allowing different intensities to be employed in the two ears and a more effective correction for hearing loss applied by the use of an inter-aural sensation level difference correction. This performs slightly better than the Selters and Brackmann correction and makes the test applicable to a wider range of subjects by the avoidance of loudness tolerance problems sometimes encountered when equal stimulus intensities are used.

The sensation level corrected ILDV is really just a measure of Wave V latency of the suspect ear with gender and age effects being accommodated by the use of an opposite ear reference latency. If age, gender and sensation level corrections are applied to the absolute Wave V latency, it is possible to use this in place of or in addition to ILDV. This has particular attraction when ILDV is inappropriate.

The result of applying these two measures to the acoustic neuroma group suggests that they offer a performance superior to any other ABR measure when used to identify these tumours.

4.3 RATE EFFECT ABR MEASURES

Waves I, III and V were analysed in some detail in the normal group and the degree of latency shift of these waves was found to be in very close agreement with previously published data. A small number of authors have, presumably by visual inspection of graphical data, suggested that the latency shift is linear with increasing stimulus rate. By applying an appropriate and powerful statistical technique, the present study has shown that the rate effect is indeed genuinely linear in Waves III & V and that it is probably so in Wave I as well. Since the three waves have differing degrees of rate effect, the IPLs also have an associated rate effect which is approximately similar for all three IPLs when expressed in percentage terms. However, the data suggests that there is little change in IPLs between 11.1/s and 22.2/s and the variance of the IPLs is similar at these two rates. The implication here is that the IPL measurements can be undertaken at about 20/s using the same confidence limits as derived from about 10/s. Although test time is halved by doing this, in some patients, presumably those with a high frequency hearing loss, the ability to identify Wave I may be reduced at the slightly higher rate.

The present study offers the wave V rate-induced latency shift measure V88-11 as a means of detecting acoustic neuromata. It is pertinent to compare its performance to that of similar measures as assessed in the work of Campbell & Abbas (1987). Their paper describes the only other similar study and was published after the start of the present study. The differences between the two studies are minor but need stating. Campbell & Abbas used 28 subjects, 20 with

cochlear hearing loss and 8 with acoustic neuromata and they required all to have a present ABR wave V at their slowest rate of 9.7/s. Four rates were used, the highest being 59.7/s. They used multiple two-sample T-tests for analysis.

As in this study, Campbell & Abbas reported a greater degree of wave V rate-induced latency shift in tumour patents than in cochlear patients. However, they observed a substantial overlap in the results of the two groups and concluded that the use of such rate effect measures in this application may be limited. They obtained a sensitivity of 86% using a mean plus *one* standard deviation criterion which gave an expectedly poor (79%) specificity. Nonetheless, they speculated that a higher rate may improve performance and the results of the present study confirm that this is the case.

The question of what value of criterion to apply to a test result is an interesting one and perusal of the literature on normative wave V rate effects reveals a range of values. The diagnostic criterion for V88-11 is the product of two things: the degree of latency shift as found in a study and the point on the normal distribution (frequently arbitrary) which is taken as the limit of normality. Table 4.3(a) shows the range of V88-11 criteria from various studies. The mean and standard deviation from the present study were used in the case of those studies that did not quote their own. This is valid in so far as we now know that the slope of the rate function is linear. Again, the value derived from the present study of about 0.8ms is near the middle of the range of values available from other sources.

Table 4.3(a)

CONFIDENCE LIMITS FOR THE 11.1/s - 88.8/s WAVE V LATENCY SHIFT

STUDY	ORIGIN	VALUE (ms)
CAMPBELL & ABBAS (1987)	mean + 1 SD	0.7
GERLING & FINITZO-HIEBER (1983)	mean + 3 SD	1.026
HECOX (1980)	60µs/decade + 0.4ms	0.866
MUSIEK & GOLLEGLY (1985)	100µs/decade + 0.2ms	0.977
PRATT *et al* (1981)	mean + 2 SD	0.863
PRESENT STUDY	upper 95% conf. limit (mean + 1.645 SD)	0.805

Turner & Nielsen (1984) introduced the parameter d' to the audiological community and it is now widely accepted as a figure of merit for the purposes of comparison between diagnostic tests. In their review of audiological, vestibular and radiological test performance, Turner *et al* (1984) calculated d'= 2.9 for ABR tests although this was for ABR testing as a whole rather than individual ABR measures. The claimed advantage of d' is that it is independent of the criterion being used but this is so only when the two populations being discriminated are both normally distributed and have equal variance. Tumour and non-tumour groups do not meet this requirement for ILDV (Turner & Nielsen, 1984) or for any useful ABR measure (this study) so d' will vary with criterion applied. The V88-11 criterion was varied in 0.1ms steps from 0.6ms to 1.1 ms and the corresponding d' determined from tables (Swets, 1964) using the hit rate and the false alarm rate derived from the data of the present study. As Table 4.3(b) shows, the highest d' (just below 2.5) corresponds to a criterion of 0.8ms to 0.9ms - by good fortune very close to the 95% single tailed confidence limit being used in this study.

Table 4.3(b)

THE EFFECT OF V88-11 CRITERION ON d'

CRITERION (ms)	HIT RATE %	FALSE ALARM RATE %	d'
0.6	89.5	30.0	1.78
0.7	89.5	15.2	2.30
0.8	84.2	7.4	2.44
0.9	68.4	2.3	2.48
1.0	57.9	1.4	2.35
1.1	47.4	0.9	1.27

Interestingly, as in the present study, Campbell & Abbas found that the false positive results of wave V rate effect measures in their cochlear group occurred in different subjects from those which gave false positive ILDV results, suggesting a different underlying mechanism for the two types of measure. Campbell & Abbas suggested that small wave V latency shifts could be potentially useful in reducing the false positive rate associated with low-rate ABR measures. The answer to this lies in the sensitivity of the rate effect measure. Since the sensitivity of V88-11 is only 84% (this study), a positive I-V or ILDV in the presence of a negative V88-11 does not definitely exclude a tumour, though admittedly, it casts some doubt onto the status of the patient.

4.4 DEVELOPING AN OPTIMUM ABR PROTOCOL FOR ACOUSTIC NEUROMA DETECTION

The rate-induced Wave V latency shift V88-11 has a better overall performance than the IPLs, principally because of its greater applicability since it is reliant only on Wave V. The promise of rate effects alluded to in Chapter 1 has therefore been positively confirmed. Nevertheless, it does not figure amongst the ABR measures being proposed as an optimum combination of ABR measures for the detection of acoustic neuromata. This is because of the superior performance of the appropriately corrected absolute Wave V latency measure and the sensation level corrected ILDV. Both appear to offer d'≈3.5 or better.[1]

These corrections clearly provide an excellent alternative to wave I in its role as a means of accommodating the effects of peripheral hearing loss. The high performance of these measures are both a tribute to the sensitivity of low rate wave V latency to retro-cochlear dysfunction and to the success of the correction methods.

Most of the conventional ABR measures are designed to identify a slowing of propagation velocity throughout the brainstem tracts and are naturally enough quite highly correlated. Because rate effect measures show a low correlation with propagation velocity measures, one is tempted to speculate that in the neurologically normal population, rate effects reveal a different aspect of

---

[1] d'=3.5 if the next subject to be tested had an acoustic neuroma and gave a normal result, ie was missed. d' cannot be calculated with a sensitivity of 100%.

neurological function. By studying only one pathological population it is impossible to explore this further. However, further work on different clinical populations may identify diseases in which only the rate effect measures are abnormal and in this event it may be possible to identify the pathophysiological mechanism responsible for the abnormal rate effect in patients with acoustic neuromata.

4.5 THE TIME COURSE OF ADAPTATION

The literature reviewed in Chapter 1 suggested that the latency adaptation of Wave V is largely complete by the fourth of fifth click in a train of such stimuli although inspection of the data of those studies suggest that in some instances, the authors did not adequately substantiate their conclusions. The present study shows that Wave V latency adaptation is *not* complete by the eighth click, though it is nearly so. The recovery time for Wave V latency adaptation appears to lie somewhere between about 90 and 243ms. Cochlear hearing loss or acoustic neuromata do not seem to substantially modify the pattern identified in normal subjects.

Wave V amplitude behaves in a rather odd way with a rapid decrease in amplitude appearing after the first click in the stimulus train, despite the lack of any significant amplitude difference in Wave V at the high and low rates. This amplitude adaptation behaviour is different to that identified by Thornton and Coleman (1975) yet the results of both studies may be explicable. The result of the present study may be a reflection of some form of under-damped oscillation in the metabolic processes upon which Wave V amplitude is based and of which it is a reflection. The precise inter-click intervals used in the two studies were different and this may be the source of the differing results - the second and subsequent stimuli from a click train occurring at different points on an under-damped oscillatory Wave V amplitude temporal function. There is another difference between the two studies. Thornton and Coleman used trains of 4 stimuli compared to the 8 used in the present study. The greater degree of

adaptation achieved by the use of 8 clicks may well have influenced the results.

The Wave V amplitude adaptation time course in patients with acoustic neuromata is very interesting and appears to be distinct from that seen in neurologically normal subjects. If one accepts the pattern illustrated in Figure 3.5.6.2 as being representative of this group despite the low numbers from which the figure was derived, it shows that not only is the Wave V amplitude more susceptible to the effects of high stimulus rates in showing a lower amplitude, but that even 243ms is insufficient to allow satisfactory recovery. In contrast to the *latency* adaptation time course in tumour subjects (which shows a similar prolongation of latency with click number as seen in other groups), the behaviour of Wave V *amplitude* has a different adaptation and recovery time course. The logical conclusion from these data is that in neither neurologically normal or abnormal groups different mechanisms, revealed by differing temporal patterns, are responsible for the latency and amplitude of Wave V adaptation. Further, whilst the mechanism responsible for coding Wave V latency adaptation is largely unaffected by a tumour (when latency shift is expressed in the context of the latencies at the two stimulus rate extremes), whatever mechanism is responsible for coding Wave V amplitude adaptation is modified by a tumour.

4.6 ANSWERS TO SPECIFIC QUESTIONS - A BRIEF SUMMARY

Section 1.4.2 posed five specific questions for the study to address.

1. *Do SRR tests provide additional or complementary diagnostic information to other ABR tests in the detection of retrocochlear pathology?*

The Wave V latency shift produced by increasing stimulus rate from about 10/s to about 90/s provides equivalent but not complementary diagnostic information to existing ABR tests. Whether it provides *additional* information cannot be adequately addressed by the present study however. The lack of correlation between such measures and other ABR measures would seem to suggest a different underlying mechanism in neurologically normal subjects. Whether additional information can be obtained will be known only after using the technique on other neurologically abnormal populations.

2. *What is the performance of SRR tests in terms of sensitivity and specificity and in what circumstances are they applicable?*

The Wave V rate-induced latency shift was applicable in 61% of all tumour subjects, a higher applicability than that of the IPLs. In the population of tumour subjects in which it could be applied, it had a sensitivity of 84%, (worse than the IPLs) but in all tumour subjects the sensitivity was 52% (better than the IPLs). These figures relate to a specificity of 94%.

3. *Do any corrections need to be made to account for factors such as age, sex, hearing loss etc.?*

Only age is a significant factor at the p=.05 level. However, the effect is very slight and a correction for age does not appear to be warranted.

4. *Can the magnitude of an abnormal SRR test result be related to the type or severity of retrocochlear disorder?*

Since only one neurologically abnormal group was available for study (no MS subjects were referred) the first part of this question cannot be addressed. With regard to the severity of the disorder, an attempt was made to obtain information concerning the size of the tumours from both radiological and surgical sources but unfortunately this was unsuccessful in many cases. When data was available, there was often considerable discrepancy between the size of the tumour as assessed by the Radiologist and by the Surgeon at operation.

5. *Can more be learnt about the temporal characteristics of SRR effects in order to identify the mechanism which produces them, and if so, are there different mechanisms at work in normal and abnormal populations?*

No, no more can be learnt of the mechanism responsible for rate effects but there are reasons to believe that there are different mechanisms in cochlear/normal and retrocochlear populations. However, it is clear from the previous section that there are still many unanswered questions, indeed probably more now than before.

4.7 SUGGESTIONS FOR FURTHER WORK

There seems to be no doubt that the rate-induced Wave V latency shift measure provides useful diagnostic information although it may not be included in an *optimum* combination of ABR diagnostic indices for identifying patients with acoustic neuromata. The application of rate effects to other pathological populations needs urgent investigation not only because this may be useful diagnostically but also in order to shed light upon the mechanism responsible for rate effects.

Further work is also suggested using click train adaptation tests in order to pursue the differences between the findings of the present study and those of Thornton and Coleman (1975) and the possibility of an oscillatory amplitude adaptation time course.

Finally, there is a possible use for rate effects which has not been hinted at thus far. The work of Lasky (1984) clearly identified a link between rate effect results and neurological maturation in neonates. The ABR is finding increasing popularity as a tool for screening for sensorineural hearing loss in neonates, especially pre-term neonates for whom the risk of hearing loss is heightened. Unfortunately, in very pre-term neonates the evidence to date suggests that more false positive results of such screening tests will occur unless the screening level is increased. It is reasonable to assume that there is a link between the hearing threshold (as measured by the ABR) and neurological maturation . If very young pre-term neonates are to be tested, then the level at which a screening test should be

applied could be chosen after performing suprathreshold Wave V latency rate effect tests. A neonate with a particularly long rate-induced latency shift could be regarded as neurologically immature and therefore expected to have a raised hearing threshold even without any cochlear hearing loss. The level at which an ABR screening test was to be applied could then be chosen to accommodate the child's neurological immaturity and so enhance test specificity.

APPENDIX A

LISTINGS OF PROGRAMS WRITTEN FOR THE STUDY

A (i): BASIC Program "AUD.BAS"

Nicolet Pathfinder data acquisition and analysis programs:

A (ii): MECOL Program "ERA.CMD"

A (iii): MECOL Program "RABRO.CMD"

A (iv): MECOL Program "RABR4R.CMD"

A (v): MECOL Program "ANAL.CMD"

A (vi): MECOL Program "ATRAIN.CMD"

A (i): BASIC Program "AUD.BAS"

A program to classify subjects on the basis of their pure tone thresholds with reference to appropriate age and sex related normitive data.

```
10 REM PROGRAM USED TO COMPARE THE RESULTS FROM
20 REM INPUT PATIENT'S DATA,TO REFERENCE DATA AND DETERMINE WHETHER
30 REM THEY ARE NORMAL OR ABNORMAL
40 CLS
50 REM KEYBOARD INPUT SECTION-----------------------------------
60 PRINT
70 PRINT
80 PRINT
90 PRINT
100 PRINT
110 PRINT TAB(25) ;"INPUT THE PATIENT DATA "
120 PRINT
130 PRINT
140 PRINT
150 PRINT TAB(35);"AGE          ";
160 INPUT A
170 IF A < 1 OR A > 80 THEN 1220:REM CHECK FOR INVALID AGE--------
180 PRINT TAB(35);"SEX          ";
190 INPUT S$
200 IF S$="f" THEN LET S$="F"
210 IF S$="m" THEN LET S$="M"
220 IF S$ <> "M" AND S$ <> "F" THEN 1300:REM CHECK FOR INVALID SEX
230 PRINT
240 PRINT TAB(15);"THRESHOLDS FOR THE BETTER EAR"
250 PRINT TAB(35);"1 kHz        ";
260 INPUT BEO
270 PRINT TAB(35);"2 kHz        ";
280 INPUT BET
290 PRINT TAB(35);"4 kHz        ";
300 INPUT BEF
310 PRINT TAB(15);"THRESHOLDS FOR THE WORSE EAR"
320 PRINT TAB(35);"1 kHz        ";
330 INPUT WEO
340 PRINT TAB(35);"2 kHz        ";
350 INPUT WET
360 PRINT TAB(35);"4 kHz        ";
370 INPUT WEF
380 REM CALCULATE PATIENT'S VARIABLES----------------------------
390 LET CHL =(BEO+BET+BEF+WEO+WET+WEF)/6
400 LET DIF = ABS(WEF-BEF)
410 LET BHL=(BEO+BET+BEF)/3
420 LET WHL=(WEO+WET+WEF)/3
430 REM ASSIGN REFERENCE VALUES ACCORDING TO AGE & SEX-----------
440 IF A>30 GOTO 480
450 IF S$="M" THEN LET HLREF=11:LET DIFREF=15
460 IF S$="F" THEN LET HLREF=10:LET DIFREF=11
470 GOTO 870
480 IF A>35 GOTO 520
490 IF S$="M" THEN LET HLREF=13.5:LET DIFREF=16
500 IF S$="F" THEN LET HLREF=12:LET DIFREF=11
510 GOTO 870
520 IF A>40 GOTO 560
530 IF S$="M" THEN LET HLREF=16:LET DIFREF=18
```

```
540 IF S$="F" THEN LET HLREF=14:LET DIFREF=12
550 GOTO 870
560 IF A>45 GOTO 600
570 IF S$="M" THEN LET HLREF=20:LET DIFREF=20
580 IF S$="F" THEN LET HLREF=16.5:LET DIFREF=14
590 GOTO 870
600 IF A>50 GOTO 640
610 IF S$="M" THEN LET HLREF=24:LET DIFREF=21
620 IF S$="F" THEN LET HLREF=19:LET DIFREF=15
630 GOTO 870
640 IF A>55 GOTO 680
650 IF S$="M" THEN LET HLREF=28:LET DIFREF=22
660 IF S$="F" THEN LET HLREF=22.5:LET DIFREF=16
670 GOTO 870
680 IF A>60 GOTO 720
690 IF S$="M" THEN LET HLREF=34:LET DIFREF=23
700 IF S$="F" THEN LET HLREF=26:LET DIFREF=16
710 GOTO 870
720 IF A>65 GOTO 760
730 IF S$="M" THEN LET HLREF=40.5:LET DIFREF=24
740 IF S$="F" THEN LET HLREF=31:LET DIFREF=16
750 GOTO 870
760 IF A>70 GOTO 800
770 IF S$="M" THEN LET HLREF=48:LET DIFREF=25
780 IF S$="F" THEN LET HLREF=36:LET DIFREF=16
790 GOTO 870
800 IF A>75 GOTO 840
810 IF S$="M" THEN LET HLREF=58.5:LET DIFREF=25
820 IF S$="F" THEN LET HLREF=43:LET DIFREF=17
830 GOTO 870
840 IF S$="M" THEN LET HLREF=68:LET DIFREF=25
850 IF S$="F" THEN LET HLREF=50:LET DIFREF=18
860 REM ASSIGN DEFAULT RESULTS-----------------------------------
870 LET CHLRES$="NORMAL"
880 LET BHLRES$="NORMAL"
890 LET WHLRES$="NORMAL"
900 LET DIFRES$="NORMAL"
910 REM ASSIGN ABNORMAL RESULTS----------------------------------
920 IF CHL>HLREF THEN LET CHLRES$="ABNORMAL    *"
930 IF BHL>HLREF THEN LET BHLRES$="ABNORMAL    *"
940 IF WHL>HLREF THEN LET WHLRES$="ABNORMAL    *"
950 IF DIF>DIFREF THEN LET DIFRES$="ABNORMAL    *"
960 REM RESULT SCREEN--------------------------------------------
970 CLS
980 PRINT
990 PRINT
1000 PRINT
1010 REM PART OF TABULATED OUTPUT
1020 PRINT TAB(20);"PATIENT'S AGE | ";A;"YEARS";TAB(50);"PATIENT'S SEX
| ";S$
1       0       3       0                       P       R       I       N       T
TAB(20);"-------------------------";TAB(50);"----------------"
1040 PRINT
1050 PRINT "YOUR PATIENT INPUTS WERE | ";TAB(28);"BETTER EAR 1kHz = ";BEO
1060 PRINT TAB(28);"                  2kHz = ";BET
1070 PRINT TAB(28);"                  4kHz = ";BEF
1080 PRINT TAB(28);" WORSE EAR 1kHz = ";WEO
1090 PRINT TAB(28);"                  2kHz = ";WET
1100 PRINT TAB(28);"                  4kHz = ";WEF
1110 REM TABULATION OF OUTPUT
1120 PRINT
1130 PRINT
1140 PRINT
1150    PRINT    TAB(20);"PATIENT'S    VALUE";TAB(40)"REFERENCE
VALUE";TAB(65)"ANALYSIS"
1       1       6       0                       P       R       I       N       T
TAB(20);"===============";TAB(40)"===============";TAB(65)"========"
1170 PRINT"COMBINED EARS  |"TAB(25);CHL;TAB(45);HLREF;TAB(65);CHLRES$
1180 PRINT"BETTER EAR     |"TAB(25);BHL;TAB(45);HLREF;TAB(65);BHLRES$
1190 PRINT"WORSE EAR      |"TAB(25);WHL;TAB(45);HLREF;TAB(65);WHLRES$
```

```
1200 PRINT"4K DIFFERENCE   |"TAB(25);DIF;TAB(45);DIFREF;TAB(65);DIFRES$
1210
GOTO 1390
1220 REM ERROR MESSAGE FOR AGE INPUT
1230 CLS
1240 PRINT TAB(15);"THE AGE YOU HAVE INPUT IS UNACCEPTABLE"
1250 PRINT TAB(15);"    IT MUST BE LESS THAN 80 YEARS     "
1260 PRINT
1270 PRINT TAB(15);"        PRESS RETURN TO RETRY         "
1280 INPUT R
1290 GOTO 40
1300 REM ERROR MESSAGE FOR SEX INPUT
1310 CLS
1320 PRINT TAB(15);"YOUR INPUT FOR THE SEX IS UNACCEPTABLE"
1330 PRINT TAB(15);"      IT SHOULD BE EITHER M OR F      "
1340 PRINT
1350 PRINT TAB(15);"        PRESS RETURN TO RETRY         "
1360 INPUT E
1370 GOTO 180
1380 RETURN
1390 REM RETRY OR QUIT AT PROGRAM'S END
1400 PRINT
1410 PRINT"::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::"
1420 PRINT TAB(25);"R TO RERUN"
1430 PRINT TAB(25);"Q TO QUIT"
1440 INPUT "",D$
1450 IF D$="r" THEN LET D$="R"
1460 IF D$="q" THEN LET D$="Q"
1470 IF D$ = "R" THEN 40
1480 IF D$="Q" THEN REM QUIT
1490 CLS
1500 SYSTEM
```

A (ii): MECOL Program "ERA.CMD"

The main ERA program from which specific overlays are called.

```
WAIT IDN
WAIT PLT
DSP:C
ECHO=OFF
WRITE:3\SCROLL=1
MABORT=OFF
ASSIGN "D0" TO LOGDSK END!****************** DELETED FROM ERARPT
ASSIGN "UNDEFINED !!" TO PATDIR END!******** DELETED FROM ERARPT
ASSIGN "UNDEFINED !!" TO PATNAM END!******** DELETED FROM ERARPT
SIZ B1 B2=512!****************************** DELETED FROM ERARPT
SET MSA"0":MOD=0
SET MSA:NMOD=0
!=============================================================
!========================== MAIN MENU ========================
!=============================================================
REPEAT
REPEAT
DSP:C
SCROLL=1
CURCOL=YELLOW
NICGL:SELCT RAST\NICGL:SETWW 0,0,1000,1000 \NICGL:SETVP 0,0,1000,1000
WAVCOL=WHITE
!============ MAIN BOX WITH HEADER INSERT ====================
NICGL:MOVE 100,1000\NICGL:DRAW 900,1000,900,0,100,0,100,1000
NICGL:MOVE 110,983\NICGL:DRAW 300,983,300,900,700,900,700,983
NICGL:DRAW 890,983,890,17,110,17,110,983
!=============================================================
NICGL:DTEXT 350,935,"ERA MAIN MENU"
!============ PATNAM BOX =====================================
NICGL:MOVE 300,850\NICGL:DRAW 700,850,700,750,300,750,300,850
IF PATNAM="UNDEFINED !!" THEN
   WRITXY"23,29,CURRENT PATIENT: <UNDEFINED>"
ELSE
   WRITXY"23,29,CURRENT PATIENT: ^PATNAM"
ENDIF!FOR PATNAM

!============ MENU BOX =======================================
NICGL:MOVE 200,700\NICGL:DRAW 800,700,800,100,200,100,200,700,200,700
!=============================================================
NICGL:CLOSE
SCROLL=1
CURCOL=RED
WRITXY"25,22,<U>   =  UTILITIES"
WRITXY"25,19,<C>   =  CORTICAL TESTS"
WRITXY"25,16,<B>   =  BRAINSTEM TESTS"
WRITXY"25,13,<S>   =  SUBJECTIVE TESTS"
WRITXY"25,10,<E>   =  EXIT ERA"
REPEAT
INKEY"                        <SELECT> ==@>":1
WRITE:3
ASSIGN SYSTEM TO MMENU END
UNTIL (MMENU="U") OR (MMENU="C") OR (MMENU="B") OR (MMENU="S") OR
   (MMENU="E") END
!=============================================================
!==================== UTILITIES MENU =========================
!=============================================================
IF MMENU="U" THEN
REPEAT
PRINT" "END
DSP:C
```

```
SCROLL=1
NICGL:SELCT RAST\NICGL:SETWW 0,0,1000,1000 \NICGL:SETVP 0,0,1000,1000
WAVCOL=GREEN
CURCOL=RED
!============ MAIN BOX WITH HEADER INSERT ====================
NICGL:MOVE 100,1000\NICGL:DRAW 900,1000,900,0,100,0,100,1000
NICGL:MOVE 110,983\NICGL:DRAW 300,983,300,900,700,900,700,983
NICGL:DRAW 890,983,890,17,110,17,110,983
!============ PATNAM BOX ================================
NICGL:MOVE 300,850\NICGL:DRAW 700,850,700,750,300,750,300,850
IF PATNAM="UNDEFINED !!" THEN
   WRITXY"23,29,CURRENT PATIENT: <UNDEFINED>"
ELSE
   WRITXY"23,29,CURRENT PATIENT: ^PATNAM"
ENDIF!FOR PATNAM
!============ MENU BOX ==================================
NICGL:MOVE 200,700\NICGL:DRAW 800,700,800,100,200,100,200,700
!=======================================================


NICGL:DTEXT 340,935,"UTILITIES MENU"
NICGL:CLOSE
SCROLL=1
WRITXY"25,22,<N>   =  NEW PATIENT"
WRITXY"25,20,<O>   =  OLD PATIENT"
WRITXY"25,18,<T>   =  TRANSFER DATA D0-@> D1"
WRITXY"25,16,<I>   =  INITIALISE DISK IN D1"
WRITXY"25,14,<L>   =  CHANGE LOG DISK (<^LOGDSK>)"
WRITXY"25,12,<P>   =  <p2> LOCAL MODE"
WRITXY"25,10,<E>   =  EXIT THIS MENU"


REPEAT
INKEY"                    <SELECT> ==@>":1
WRITE:3
ASSIGN SYSTEM TO UMENU END
UNTIL (UMENU="I") OR (UMENU="L") OR (UMENU="N") OR (UMENU="O")
     OR (UMENU="T") OR (UMENU="P") OR (UMENU="E") END
!==================== UTIL OPTION (I) ======================
   IF UMENU="I" THEN
      PRINT" "END
      DSP:C\SCROLL=2
      INPUT"     Eusure a blank disk is in drive D1 "TO DUMMY END
      INIT D1:N&
      PRINT"     Waiting for initialisation to complete "END
      WAIT INIT
      VERIFY D1:N
      WAIT VERIFY
      SCROLL=3
      PRINT" "END
      INPUT"INIT & VERIFY COMPLETE. <RETURN> TO CONTINUE "TO DUMMY END

   ENDIF
!==================== UTIL OPTION (L) ======================
   IF UMENU="L" THEN
     DSP:C\SCROLL=2
     REPEAT
     PRINT" "END
     INPUT"     Enter new log disk ( D0, D1 OR D2 ) "TO LOGDSK END
     UNTIL (LOGDSK="D0") OR (LOGDSK="D1") OR (LOGDSK="D2") END
     PRINT" "END
     SCROLL:C
   ENDIF
!==================== UTIL OPTION (P) ======================
   IF UMENU="P" THEN
     SCROLL:C
     PRINT" "END
     REPEAT
     INPUT" p2> "TO CMD END
```

```
      ^CMD
      UNTIL CMD="" END
      SCROLL:C
   ENDIF
!==================== UTIL OPTION (N) ========================
   IF UMENU="N" THEN
      SCROLL:C
      INPUT"     Enter new patient's surname: "TO PATDIR END
      ASSIGN PATDIR TO PATNAM END
      IF LOGDSK="D0" THEN
         ASSIGN "SCRATC" TO PATDIR END
         DEL -D0-SCRATC.ERA-*.*:N
         ADM -D0-SCRATC.ERA-INFO
      ELSE
         MKDIR -^LOGDSK-^PATDIR.ERA
         ADM -^LOGDSK-^PATDIR.ERA-INFO
      ENDIF
   ENDIF
!====================== UTIL OPTION (O) ======================
   IF UMENU="O" THEN
      DSP:C\SCROLL=1
      INPUT"     Enter old patient's surname : ( Default: ",PATNAM,
" ) : "TO OPS END
      IF OPS<>"" THEN
         ASSIGN OPS TO PATDIR END
         ASSIGN OPS TO PATNAM END
      ENDIF
      SCROLL:C
      IF LOGDSK="D0" THEN
         DIR -D0-SCRATC.ERA-*.*:F
      ELSE
         DIRECT D1 D1
         DIR -^LOGDSK-^PATDIR.ERA-*.*:F
      ENDIF
      WRITE:5
      PRINT"     Data currently on log disk "END
      REPEAT!FOR VALID ADM RESPONSE
      PRINT" "END
      INKEY"     <ADM routine ? ( >Y</>N< )> ":1
      WRITE:3
      ASSIGN SYSTEM TO ADMIN END
      UNTIL (ADMIN="Y") OR (ADMIN="N") END
      IF ADMIN="Y" THEN
      SCROLL:C
      IF LOGDSK="D0" THEN
         ASSIGN "SCRATC" TO PATDIR END
         ADM -D0-SCRATC.ERA-INFO
      ELSE
         MKDIR -^LOGDSK-^PATDIR.ERA
         ADM -^LOGDSK-^PATDIR.ERA-INFO
      ENDIF
      ENDIF!ADMIN="Y"
      SCROLL:C
   ENDIF
!====================== UTIL OPTION (T) ======================
   IF UMENU="T" THEN
DSP:C
IF PATNAM="UNDEFINED !!" THEN
  PRINT"     The patient's name is currently undefined"END
  PRINT" "END
  INPUT"     Enter the patient's surname: "TO PATDIR END
  ASSIGN PATDIR TO PATNAM END
ENDIF
REPEAT
SCROLL:C
INKEY"     <Modify ADM file before transferring? (> Y</>N< )> ":1

WRITE:3
ASSIGN SYSTEM TO MODADM END
UNTIL (MODADM="Y") OR (MODADM="N") END
```

```
SCROLL:C
IF MODADM="Y" THEN
   ADM -D0-SCRATC.ERA-INFO
ENDIF
ASSIGN "P" TO CONT END
!-- See if PATNAM already exists in D1
TXTCOL=BLACK
DIRECT D1 D1
MKDIR -D1-^PATNAM.ERA
IF ERROR THEN
  ASSIGN "OLDDIR" TO D1DIR END
ELSE
  ASSIGN "NEWDIR" TO D1DIR END
ENDIF!MKDIR Error trap
SCROLL:C
TXTCOL=YELLOW
IF D1DIR="OLDDIR" THEN
  DIR -D1:D
  WRITE:3
  WRITE"      <WARNING      WARNING      WARNING      WARNING>"
  PRINT" "END! THIS LINE CONTAINS CTRL-G (BELL)
  PRINT"      Directory for ",PATNAM," already exists on D1"END
  PRINT" "END
  REPEAT
  INKEY"      A<bort or >P<roceed with transfer ?> ":1
  ASSIGN SYSTEM TO CONT END
  UNTIL (CONT="A") OR (CONT="P") END
ENDIF!For OLDDIR
IF (D1DIR="NEWDIR") OR ((D1DIR="OLDDIR") AND (CONT="P")) THEN
  !See if there is enough room on D1
SCROLL:C
DIR -D0-SCRATC.ERA-*.*:F
WRITE"<              NOTE THE NUMBER OF BLOCKS USED>"
DIR -D1:D
WRITE"<                              NOTE THE NUMBER OF BLOCKS EMPTY>"
        WRITE:1
        PRINT"      Check for sufficient space on D1"END
        PRINT" "END
        REPEAT
        INKEY"      A<bort or >P<roceed with transfer ?> ":1
        ASSIGN SYSTEM TO CONT END
        UNTIL (CONT="A") OR (CONT="P") END
        ENDIF!For NEWDIR or OLDDIR + Proceed
        PRINT" "END
        SCROLL:C
        IF CONT="A" THEN
          WRITE"      Transfer of files <ABORTED>"
        ELSE
          PRINT"      ",PATNAM," files being transfered to D1"END
          COPY -D0-SCRATC.ERA-*.* -D1-^PATNAM.ERA-*.*:N
          PRINT" "END
          SCROLL:C
        ENDIF!CONT=A or P
   ENDIF
!================ UTIL OPTION (E) - EXIT UTIL ==========
   UNTIL UMENU="E" END
ENDIF
IF LOGDSK="D0" THEN
  ASSIGN "SCRATC" TO PATDIR END
ENDIF
!================ CHECK THAT PATNAM IS DEFINED ==============
IF (PATNAM="UNDEFINED !!") AND (MMENU<>"E") THEN
  SCROLL:C
  WRITE" The patient name is <NOT DEFINED> - define before proceeding"

  PRINT" "END
  INPUT" Press <RETURN> and use utility menu "TO DUMMY END
  SCROLL:C
ENDIF
```

```
UNTIL (PATNAM<>"UNDEFINED !!") OR (MMENU="E") END
!============================================================
!====================== CORTICAL MENU ========================
!============================================================
IF MMENU="C" THEN
DSP:C
SCROLL=1
NICGL:SELCT RAST\NICGL:SETWW 0,0,1000,1000 \NICGL:SETVP 0,0,1000,1000
WAVCOL=BLUE

!============ MAIN BOX WITH HEADER INSERT ===================
NICGL:MOVE 100,1000\NICGL:DRAW 900,1000,900,0,100,0,100,1000
NICGL:MOVE 110,983\NICGL:DRAW 300,983,300,900,700,900,700,983
NICGL:DRAW 890,983,890,17,110,17,110,983
!============================================================
NICGL:DTEXT 350,935,"CORTICAL MENU"
!============ PATNAM BOX ====================================
NICGL:MOVE 300,850\NICGL:DRAW 700,850,700,750,300,750,300,850
   WRITXY"23,29,CURRENT PATIENT: ^PATNAM"

!============ MENU BOX ======================================
NICGL:MOVE 200,700\NICGL:DRAW 800,700,800,100,200,100,200,700,200,700
!============================================================
NICGL:CLOSE
SCROLL=1
CURCOL=RED
WRITXY"25,22,<C>   =  COMBINED RIGHT/LEFT A-C"
WRITXY"25,19,<R>   =  RIGHT A-C"
WRITXY"25,16,<L>   =  LEFT  A-C"
WRITXY"25,13,<B>   =  BONE CONDUCTION"
WRITXY"25,10,<E>   =  EXIT TO MAIN MENU"
REPEAT
INKEY"                    <SELECT> ==@>":1
WRITE:3
ASSIGN SYSTEM TO CMENU END
!================= TONE TEST ================================
IF CMENU="T" THEN
SET SYS:REM
SCROLL=3
PRINT"  WARNING !!!!! HIGH LEVEL TONE TEST"END
PRINT" "END
INPUT"  ENSURE NO ONE IS WEARING EARPHONES       <Return> to cont."TO D
END
SET MSA"0":FRE=4000;TRA=0;LEV=0
SET STIM:RAT=3;MOD=1;GAT=0
SET MSA"0":ENV=1;MOD=6;RAM=10;PLA=20
PRINT"Testing synthesiser 1"END
PRINT"Testing LEFT earphone..."END
ASSIGN 3000 TO DF END
REPEAT
ASSIGN DF+200 TO DF END
SET MSA"1":TRA=1;LEV=130;FRE=^DF
UNTIL DF=4000 END
PRINT"Testing synthesiser 1"END
PRINT"Testing RIGHT earphone..."END
ASSIGN 3000 TO DF END
REPEAT
ASSIGN DF+200 TO DF END
SET MSA"1":TRA=2;LEV=130;FRE=^DF
UNTIL DF=4000 END
SET MSA"1":MOD=0;LEV=0;TRA=0
PRINT"Testing synthesiser 2"END
PRINT"Testing LEFT earphone..."END
ASSIGN 3000 TO DF END
REPEAT
ASSIGN DF+200 TO DF END
SET MSA"2":TRA=1;LEV=130;FRE=^DF
UNTIL DF=4000 END
PRINT"Testing synthesiser 2"END
PRINT"Testing RIGHT  earphone..."END
```

```
ASSIGN 3000 TO DF END
REPEAT
ASSIGN DF+200 TO DF END
SET MSA"2":TRA=2;LEV=130;FRE=^DF
UNTIL DF=4000 END
SET MSA"0":LEV=0;TRA=0;MOD=1
SET SYS:LOC
RSW
PRINT"TTEST COMPLETE"END
PRINT" "END
PRINT" "END
ENDIF !OPTION T - TONE TEST
UNTIL (CMENU="C") OR (CMENU="R") OR (CMENU="L") OR (CMENU="B") OR
   (CMENU="E") OR (CMENU="N") END

!================ CALL CORTICAL OVERLAY ================
IF (CMENU="C") OR (CMENU="R") OR (CMENU="L") OR (CMENU="B")
   OR (CMENU="N")  THEN
DSP:C
WAVCOL=RED
ERACOL=RED
CURCOL=YELLOW
AXSCOL=TURQUOISE
HLTCOL=RED
TXTCOL=YELLOW


IF CMENU="C" THEN
   AUTO ERA.OVR-LRSVRO.CMD\!CALL LRSVR OVERLAY
ENDIF
IF CMENU="R" THEN
   AUTO ERA.OVR-RSVRO.CMD\!CALL RSVR OVERLAY
ENDIF
IF CMENU="L" THEN
   AUTO ERA.OVR-LSVRO.CMD\!CALL LSVR OVERLAY
ENDIF
IF CMENU="B" THEN
   AUTO ERA.OVR-BCSVRO.CMD\!CALL BCSVR OVERLAY
ENDIF
IF CMENU="N" THEN
   AUTO ERA.OVR-LRNORM.CMD\!CALL NORM RESEARCH LRSVRO OVERLAY
ENDIF
ENDIF!CMENU=C,R,L,B or N
ENDIF!MMENU="C"

!=============================================================
!================= BRAINSTEM MENU ============================
!=============================================================

IF MMENU="B" THEN
DSP:C
SCROLL=1
NICGL:SELCT RAST\NICGL:SETWW 0,0,1000,1000 \NICGL:SETVP 0,0,1000,1000
WAVCOL=YELLOW

!============ MAIN BOX WITH HEADER INSERT ===================
NICGL:MOVE 100,1000\NICGL:DRAW 900,1000,900,0,100,0,100,1000
NICGL:MOVE 110,983\NICGL:DRAW 300,983,300,900,700,900,700,983
NICGL:DRAW 890,983,890,17,110,17,110,983
!============================================================
NICGL:DTEXT 335,935,"BRAINSTEM MENU"
!============ PATNAM BOX ====================================
NICGL:MOVE 300,850\NICGL:DRAW 700,850,700,750,300,750,300,850
   WRITXY"23,29,CURRENT PATIENT: ^PATNAM"

!============ MENU BOX ======================================
NICGL:MOVE 200,700\NICGL:DRAW 800,700,800,100,200,100,200,700,200,700
!============================================================
NICGL:CLOSE
```

```
SCROLL=1

CURCOL=RED

WRITXY"22,23,<RS>   =  RIGHT STANDARD ABR"
WRITXY"22,21,<LS>   =  LEFT  STANDARD ABR"
WRITXY"22,19,<RR>   =  RIGHT RATE ABR"
WRITXY"22,17,<LR>   =  LEFT  RATE ABR"
WRITXY"22,15,<RT>   =  RIGHT THRESHOLD ABR"
WRITXY"22,13,<LT>   =  LEFT  THRESHOLD ABR"
WRITXY"22,11,<BC>   =  BONE CONDUCTION ABR"
WRITXY"22,9,<EE>   =  EXIT TO MAIN MENU"
REPEAT
INKEY"                    <SELECT> ==@>":2
WRITE:3
ASSIGN SYSTEM TO BMENU END
UNTIL (BMENU="RS") OR (BMENU="LS") OR (BMENU="RR") OR (BMENU="LR")
 OR (BMENU="RT") OR (BMENU="LT") OR (BMENU="BC") OR (BMENU="EE") END

!================= CALL BRAINSTEM OVERLAY ===============

IF (BMENU="RS") OR (BMENU="LS") OR (BMENU="RR") OR (BMENU="LR")
 OR (BMENU="RT") OR (BMENU="LT") OR (BMENU="BC") THEN
DSP:C
WAVCOL=RED
ERACOL=RED
CURCOL=YELLOW
AXSCOL=TURQUOISE
HLTCOL=RED
TXTCOL=YELLOW


IF BMENU="RS" THEN
   AUTO ERA.OVR-RABRO.CMD\!CALL RABR OVERLAY
ENDIF
IF BMENU="RT" THEN
   AUTO ERA.OVR-RTABRO.CMD\!CALL RTABR OVERLAY
ENDIF
IF BMENU="RR" THEN
   AUTO ERA.OVR-RABR4R.CMD\!CALL RABR4R OVERLAY
ENDIF
IF BMENU="LS" THEN
   AUTO ERA.OVR-LABRO.CMD\!CALL LABR OVERLAY
ENDIF
IF BMENU="LT" THEN
   AUTO ERA.OVR-LTABRO.CMD\!CALL LTABR OVERLAY
ENDIF
IF BMENU="LR" THEN
   AUTO ERA.OVR-LABR4R.CMD\!CALL LABR4R OVERLAY
ENDIF
IF BMENU="BC" THEN
   AUTO ERA.OVR-BCABRO.CMD\!CALL BCABR OVERLAY
ENDIF
ENDIF!BMENU=RS,LS,RR,LR,RT,LT,BC
ENDIF!MMENU="B"
!=============================================================

IF MMENU="S" THEN
   AUTO ERA.OVR-THRO.CMD\!CALL THR OVERLAY
ENDIF
!================== EXIT ERA.CMD ==================
UNTIL MMENU="E" END
GAIN=SWITCH
DSP A1 A2
ECHO=ON
MABORT=ON
WAVCOL=RED\ERACOL=RED\CURCOL=YELLOW
AXSCOL=TURQUOISE\HLTCOL=RED\TXTCOL=YELLOW
SET SYS:LOC\RSW
!=============================================================
```

A (iii): MECOL Program "RABRO.CMD"

An overlay to ERA.CMD to perform standard ABR tests

on test or reference ears.

This relates to right ear tests - LABRO.CMD is essentially similar

```
!PROGRAM RABRO.CMD:- AN OVERLAY TO ERA.CMD
!ERA.CMD HANDS DOWN: LOGDSK, PATDIR, PATNAM
!=============================================
ECHO=OFF
MABORT=OFF
GAIN=SWITCH
WAVCOL
ASSIGN SYSTEM TO WAVHUE END
ERACOL
ASSIGN SYSTEM TO ERAHUE END
WAVCOL=RED
ERACOL=RED
STACK
DSP A1 B1
ZAP X1-X8
PRINT" "END
PRINT" "END
INPUT"     Right ear ABR on Ch #1 - ",
"check montage & electrodes  "TO DUMMY END
PRINT" "END
BIND MSA
SET SYS:REM\CHN=1\TME=15\SWP=2000
SET STIM:RAT=11.1;DUR=100;GAT=1;TRG=0
SET AMP"1":LBP=100;HBP=3000;SNS=50;NCH=0;CAL=0
ASSIGN 1 TO MEMNUM END
ASSIGN "Q" TO FNAME END
ASSIGN 50 TO GAIN END
ASSIGN 50 TO SNS END
ASSIGN "R" TO EAR END
REPEAT
!============== MAIN PROGRAM LOOP ================
SET MSA"0":MOD=0;LEV=0
SET MSA:NMOD=0;NOI=0
!================ SELECT BLOCKS ================
PRINT" "END
PRINT" "END
INPUT"     Use blocks A",MEMNUM," & B",MEMNUM," ( Default )",
" or state block number : "TO %NEWMEM END
PRINT" "END
IF NEWMEM<=8 THEN
     ASSIGN NEWMEM TO MEMNUM END
  ENDIF
!============== SELECT SENSITIVITY ============
PAUSE=ON
ASSIGN SNS TO GAIN END
VIEW=INPUT
DSP A^MEMNUM B^MEMNUM\ZAP
AVE A^MEMNUM&
REPEAT
PRINT" "END
PRINT" "END
INPUT"     Amp sensitivity ( currently ",GAIN," ) : "TO %GAIN END
```

```
  IF GAIN<>MAXINT THEN
     ASSIGN GAIN TO SNS END
     SET AMP"1":SNS=^GAIN
  ENDIF
UNTIL GAIN=MAXINT END
CLR AVE
PAUSE=OFF
VIEW=AVERAGE
!====================== SELECT RATE ======================
PRINT" "END
PRINT" "END
INPUT"     Repetition rate ( Default 11.1 ) : "TO RAT END
IF RAT="" THEN
   ASSIGN "11.1" TO RAT END
   ASSIGN "" TO RATE END
ENDIF
   SET STIM:RAT=^RAT
IF RAT="22.2" THEN
   ASSIGN 2 TO RATE END
ENDIF
IF RAT="44.4" THEN
   ASSIGN 4 TO RATE END
ENDIF
IF RAT="66.6" THEN
   ASSIGN 6 TO RATE END
ENDIF
IF RAT="88.8" THEN
   ASSIGN 8 TO RATE END
ENDIF
!============== SELECT NOISE ==================
REPEAT
PRINT" "END
PRINT" "END
INPUT"     Do you want ipsilateral filtered noise ",
"( Default NO ) : "TO INOISE END
IF INOISE="" THEN
   ASSIGN "N" TO INOISE END
ENDIF
UNTIL (INOISE="Y") OR (INOISE="N") END
IF INOISE="Y" THEN
  PRINT"     Set freqencies on noise filters"END
  PRINT" "END
  INPUT"     Set noise level re: stim ( Default -15 ) : "TO %RNL END
  IF RNL=MAXINT THEN
    ASSIGN -15 TO RNL END
  ENDIF
ELSE
  ASSIGN "OFF" TO RNL END
ENDIF
     REPEAT
     PRINT" "END
     INPUT"     Enter non-test ear air-bone gap ",
"( Default=0, max=30 ) : "TO %ABG END
     IF ABG=MAXINT THEN
       ASSIGN 0 TO ABG END
     ENDIF
     UNTIL ABG<=30 END
!============== SELECT INTENSITIES ============
REPEAT
PRINT" "END
INPUT"     Stimulus intensity ( 105 dB max ) : "TO %DB END
UNTIL (DB<=105) AND (DB>=-35) END
ASSIGN DB+35 TO LEV END
     ASSIGN LEV-40+ABG TO NDB END
     IF (NDB<0) THEN
       ASSIGN 0 TO NDB END
     ENDIF
TAG=^DB
!================= INITIALISE MSA CHANNELS =========
SET MSA"1":MOD=1;TRA=2;LEV=0
```

```
SET MSA:NMOD=1;NTR=1;NOI=0
IF INOISE="Y" THEN
  SET MSA"2":MOD=7;TRA=2;LEV=0
ELSE
  SET MSA"2":MOD=0;TRA=0;LEV=0
ENDIF
SET STIM:GAT=0
ASSIGN 0 TO X,Y,Z END
!================== TURN ON CONTRA NOISE ==========
PRINT" "END
PRINT"     Introducing contralateral noise.... "END
REPEAT
ASSIGN X+5 TO X END
SET MSA:NOI=^X
UNTIL X>=NDB END
!================== TURN ON IPSI NOISE IF REQD =====
IF INOISE="Y" THEN
PRINT" "END
PRINT"     Introducing ipsilateral noise.... "END
ASSIGN (LEV+RNL) TO INLEV END
REPEAT
ASSIGN Z+5 TO Z END
SET MSA"2":LEV=^Z
UNTIL Z>=INLEV END
ENDIF
!================== TURN ON STIMULUS ==============
PRINT" "END
PRINT"     Introducing stimulus..... "END
REPEAT
ASSIGN Y+5 TO Y END
SET MSA"1":LEV=^Y
UNTIL Y>=LEV END
!================== FINAL MSA SETTINGS ============
SET MSA"1":MOD=1;LEV=^LEV
SET MSA:NOI=^NDB
IF INOISE="Y" THEN
  SET MSA"2":LEV=^INLEV
ENDIF
!================== AVERAGING SECTION ==============
PRINT"     Stimulus ----- Rate ----- Ipsi noise --- Contra noise"END
PRINT"     ",DB," dBHL        ",RAT,"/s          ",RNL,
"           ",NDB-35," dBEM"END
ERACOL=RED
SWP=1000
!DSP A^MEMNUM B^MEMNUM\ZAP\OVR
AVE A^MEMNUM&
WAIT IDN
WAIT PLT
ERACOL=RED
WAIT AVE
ERACOL=RED
BLC
SET MSA"1":MOD=2
AVE B^MEMNUM
BLC
SET MSA:NMOD=0
SET MSA"0":MOD=0
SET STIM:GAT=1
DSP A^MEMNUM B^MEMNUM
!================ LOCAL COMMAND SECTION ============
ZAP X^MEMNUM
MOVE B^MEMNUM X^MEMNUM
ADD A^MEMNUM X^MEMNUM
DSP A^MEMNUM B^MEMNUM X^MEMNUM
OVR A^MEMNUM B^MEMNUM
SMO
    RMK A^MEMNUM=RIGHT EAR, RAR, ^DB DBHL
    RMK B^MEMNUM=RIGHT EAR, CON, ^DB DBHL
    RMK X^MEMNUM=RIGHT EAR, RAR+CON, ^DB DBHL
REPEAT
```

```
PRINT" "END
INPUT"P2› "TO CMD END
^CMD
UNTIL CMD="" END
!================= IDN SECTION ====================
DIFF=OFF
VERT=OFF
IDN ABR:N
PRINT" "END
PRINT" "END
INPUT"     Do you want to plot this IDN'd waveform ",
"( Default NO ) : "TO IDNPLT END
IF IDNPLT="Y" THEN
  IDN ABR:P&
ENDIF
!=================== DISK SECTION =================
PRINT"     Default filename: B",DB,"R",RATE,""END
PRINT" "END
INPUT"     Enter filename ( or Q to skip ) : "TO FNAME END
  IF FNAME<>"Q" THEN
    IF FNAME="" THEN
      LOG A^MEMNUM B^MEMNUM -^LOGDSK-^PATDIR.ERA-B^DB^EAR^RATE&
    ELSE
      LOG A^MEMNUM B^MEMNUM -^LOGDSK-^PATDIR.ERA-^FNAME&
    ENDIF
  ENDIF
ASSIGN (MEMNUM+1) TO MEMNUM END
IF MEMNUM›8 THEN
  ASSIGN 1 TO MEMNUM END
ENDIF
!================= CONTINUE OR STOP ==============
    PRINT" "END
    PRINT" "END
    INPUT"     Another run ( Default YES ) : "TO MORE END
UNTIL MORE="N" END
REPEAT
PRINT"     Local command - about to exit program"END
PRINT" "END
INPUT"P2› "TO CMD END
^CMD
UNTIL CMD="" END
SET MSA"0":MOD=0;TRA=0;LEV=0
SET MSA:NMOD=0;NTR=0;NOI=0
WAVCOL=^WAVHUE
ERACOL=^ERAHUE
SET SYS:LOC\RSW
ERARPT
```

A (iv): MECOL Program "RABR4R.CMD"

An overlay to ERA.CMD to conduct the test ear rate series test.

This reates to right ear tests - LABR4R.CMD is essentially similar.

```
!PROGRAM RABR4R.CMD:- AN OVERLAY TO ERA.CMD
!ERA.CMD HANDS DOWN: LOGDSK, PATDIR, PATNAM
!!================================================
ECHO=OFF
WAVCOL
ASSIGN SYSTEM TO WAVHUE END
WAVCOL=RED
ERACOL
ASSIGN SYSTEM TO ERAHUE END
ERACOL=RED
STACK
DSP A1 A2\ZAP
PRINT" "END
INPUT"RIGHT EAR ABR ON CH #1 - CHECK MONTAGE & ELECTRODES "TO DUMMY END
BIND MSA
SET SYS:REM\CHN=1\TME=15\SWP=200
SET STIM:DUR=100;GAT=1;TRG=0;RAT=11.1
SET AMP"1":LBP=100;HBP=3000;SNS=50;NCH=0;CAL=0
SET MSA"0":MOD=0
ASSIGN "Q" TO FNAME END
ASSIGN 50 TO GAIN END
ASSIGN 50 TO SNS END
REPEAT
!============== MAIN PROGRAM LOOP ================
!
!=============== SELECT SENSITIVITY ============
ASSIGN SNS TO GAIN END
PAUSE=ON
VIEW=INPUT
AVE A1&
REPEAT
PRINT" "END
PRINT" "END
INPUT" AMP SENSITIVITY ( CURRENTLY ",GAIN," ) ? "TO %GAIN END
  IF GAIN<>MAXINT THEN
     ASSIGN GAIN TO SNS END
     SET AMP"1":SNS=^GAIN
  ENDIF
UNTIL GAIN=MAXINT END
CLR AVE
PAUSE=OFF
VIEW=AVERAGE
!============== SELECT INTENSITIES ============
REPEAT
PRINT" "END
PRINT" "END
INPUT"CLICK INTENSITY ? ( MAX 105 dBnHL ) "TO %DB END
UNTIL (DB<=105) END
ASSIGN DB+35 TO LEV END
REPEAT
PRINT" "END
INPUT"ENTER NON-TEST EAR AIR-BONE GAP ( DEFAULT 0, MAX=30 ) "TO %ABG END

IF ABG=MAXINT THEN
  ASSIGN 0 TO ABG END
ENDIF
UNTIL ABG<=30 END
```

```
ASSIGN LEV-40+ABG TO NDB END
IF (NDB<0) THEN
  ASSIGN 0 TO NDB END
ENDIF
TAG=^DB
!================= AVERAGING SECTION ==============
REPEAT!FOR VALID RESPONSE
PRINT"5 X 3 X 200 SWEEPS AT 22.2, 44.4, 66.6 & 88.8/SEC "END
PRINT" "END
INPUT"      Do you want to run the 4 rate section? (Y/N) "TO R4R END
UNTIL (R4R="Y") OR (R4R="N") END
IF R4R="Y" THEN
SECNDS
ASSIGN SYSTEM TO SEC END
GAIN=SWITCH
ASSIGN 0 TO N END
REPEAT !FOR N=1 TO 4 - RATES OF 22.2,44.4,66.6,88.8
ASSIGN (N+1) TO N END! INCREMENTS N
IF N=1 THEN
   ASSIGN "22.2" TO RATE END
   ASSIGN "A" TO MB END
   ASSIGN 1 TO X END
ENDIF
IF N=2 THEN
   ASSIGN "44.4" TO RATE END
   ASSIGN "A" TO MB END
   ASSIGN 4 TO X END
ENDIF
IF N=3 THEN
   ASSIGN "66.6" TO RATE END
   ASSIGN "B" TO MB END
   ASSIGN 1 TO X END
ENDIF
IF N=4 THEN
   ASSIGN "88.8" TO RATE END
   ASSIGN "B" TO MB END
   ASSIGN 4 TO X END
ENDIF
ASSIGN X+1 TO Y END
ASSIGN X+2 TO Z END
DSP ^MB^X ^MB^Y ^MB^Z\ZAP
SET MSA"1":MOD=3;TRA=2;LEV=0
SET MSA:NMOD=1;NOI=^NDB;NTR=1
SET STIM:RAT=^RATE
SET STIM:AVE=1
AVE ^MB^X:A
AVE ^MB^Y:A
AVE ^MB^Z:A
SET STIM:AVE=0
SET MSA"1":LEV=^LEV
RMK ^MB^X=RIGHT EAR, ^DB DBHL, ^RATE, 0-200 SWPS
RMK ^MB^Y=RIGHT EAR, ^DB DBHL, ^RATE, 200-400 SWPS
RMK ^MB^Z=RIGHT EAR, ^DB DBHL, ^RATE, 400-600 SWPS
ASSIGN 0 TO RUN END
REPEAT !FOR 5 RUNS
ASSIGN (RUN+1) TO RUN END
REPEAT !FOR 10 SEC DELAY
SECNDS
UNTIL (SYSTEM=(SEC+10)) END
PRINT" "END
PRINT"CLICKS AT ",DB," dBnHL, RATE=",RATE,", RUN ",RUN," "END
SET STIM:AVE=1
AVE ^MB^X:BC
AVE ^MB^Y:BC
AVE ^MB^Z:BC
SET STIM:AVE=0
SECNDS
ASSIGN SYSTEM TO SEC END
UNTIL RUN=5 END
BLC
```

```
SMO
UNTIL N=4 END
ENDIF!R4R="Y" END
!=================== CLICK TRAIN SECTION ===========
REPEAT
PRINT" "END
INPUT"Do you want to run the click train test ( Y/N ) :"TO TRAIN END
UNTIL (TRAIN="Y") OR (TRAIN="N") END
IF TRAIN="Y" THEN
REPEAT
PRINT"     SELECT RATE (I.T.I.):  3.1 (250)    4.4 (150)   5.9 (90)"END

PRINT" "END
INKEY"                            3.1          4.4          5.9":3
ASSIGN SYSTEM TO RAT END
UNTIL (RAT="3.1") OR (RAT="4.4") OR (RAT="5.9") END
SET STIM:MOD=2;RAT=^RAT;CNT=8;ISI=11.3
SET MSA"1":MOD=1;LEV=^LEV;TRA=2
SET MSA:NMOD=1;NOI=^NDB;NTR=1
SECNDS
ASSIGN SYSTEM TO SEC END
REPEAT !FOR 10 SEC DELAY
SECNDS
UNTIL (SYSTEM=(SEC+10)) END
DSP A7 B7\ZAP
SIZ A7 B7=4096
TME=93
SWP=1000
AVE A7&
ZOOM=8
ROLL=ON
PRINT" "END
INPUT"     Roll waveforms to desired position, then <RETURN> "TO D END

PRINT" "END
PRINT"     Click trains at ",DB," dBnHL  Rate = ",RAT,"/sec "END
ROLL=OFF
WAIT AVE
BLC
SET MSA"1":MOD=2
AVE B7
BLC
RMK A7=^DB DBHL, RATE=^RAT
RMK B7=^DB DBHL, RATE=^RAT
ENDIF
!=================== DISK SECTION ==================
SET MSA"0":MOD=0;TRA=0;LEV=0
SET MSA:NMOD=0;NTR=0;NOI=0
PRINT" "END
PRINT"     Logging data....."END
ASSIGN "R22" TO R22 END
ASSIGN "R44" TO R44 END
ASSIGN "R66" TO R66 END
ASSIGN "R88" TO R88 END
ASSIGN "R" TO R END
IF R4R="Y" THEN
  LOG A1 A2 A3 -^LOGDSK-^PATDIR.ERA-B^DB^R22
  LOG A4 A5 A6 -^LOGDSK-^PATDIR.ERA-B^DB^R44
  LOG B1 B2 B3 -^LOGDSK-^PATDIR.ERA-B^DB^R66
  LOG B4 B5 B6 -^LOGDSK-^PATDIR.ERA-B^DB^R88
ENDIF!R4R="Y"
IF TRAIN="Y" THEN
  IF RAT="3.1" THEN
    ASSIGN "31" TO RATE END
  ENDIF
  IF RAT="4.4" THEN
    ASSIGN "44" TO RATE END
  ENDIF
  IF RAT="5.9" THEN
    ASSIGN "59" TO RATE END
```

```
  ENDIF
  LOG A7 B7 -^LOGDSK-^PATDIR.ERA-T^DB^R^RATE
ENDIF
!==================== CONTINUE OR STOP =============
SET STIM:MOD=0;RAT=11.1
SET MSA"0":MOD=0;LEV=0
    PRINT" "END
    PRINT" "END
    INPUT" ANOTHER RUN ( DEFAULT YES ) : "TO MORE END
UNTIL MORE="N" END
SIZ A7 B7=512
WAVCOL=^WAVHUE
ERACOL=^ERAHUE
SET SYS:LOC\RSW
ERARPT
```

A (v): MECOL Program "ANAL.CMD"

A program to analyse the rate series results.

```
ECHO=OFF
MABORT=OFF
STACK
GAIN=SWITCH
LOAD -D0-CORREL.LOD&

SCROLL:C
PRINT"ABR RATE & ADAPTATION ANALYSIS PROGRAM"END
PRINT" "END

INPUT"SPECIFY DISK ON WHICH FILES RESIDE ( DEFAULT D0 ): "TO DSK END
PRINT" "END
IF DSK="" THEN
  ASSIGN "D0" TO DSK END
  ASSIGN "SCRATC.ERA" TO SUBDIR END
ELSE
DIR ^DSK
PRINT" "END
INPUT"SPECIFY SUBDIRECTORY.EXT : "TO SUBDIR END
ENDIF
SCROLL:C
DIR -^DSK-^SUBDIR-*.*
PRINT" "END
PRINT" "END
INPUT"SPECIFY ROOT FILENAME (e.g. B60L) : "TO ROOT END
PRINT" "END
ADM -^DSK-^SUBDIR-INFO:P
ZAP A1-B4
!PLOT 11.1/22.2/44.4/66.6/88.8 MEANS ================================

DSP A1-A5
RTV ^SUBDIR-^ROOT-^DSK A1 A2 A3 A4
ZAP A1-A4
RTV ^SUBDIR-^ROOT-^DSK A1 A2 A3 A4
BLC\ADD A2 A1\ADD A3 A1\ADD A4 A1\ZAP A2-A4
RMK A1=^ROOT  11.1/SEC MEAN
ASSIGN "22" TO RATE END
RTV ^SUBDIR-^ROOT^RATE-^DSK A2 A3 A4
ADD A3 A2\ADD A4 A2\ZAP A3 A4
RMK A2=^ROOT^RATE 22.2/SEC MEAN
ASSIGN "44" TO RATE END
RTV ^SUBDIR-^ROOT^RATE-^DSK A3 A4 A5
ADD A4 A3\ADD A5 A3\ZAP A4 A5
RMK A3=^ROOT^RATE 44.4/SEC MEAN
ASSIGN "66" TO RATE END
RTV ^SUBDIR-^ROOT^RATE-^DSK A4 A5 A6
ADD A5 A4\ADD A6 A4\ZAP A5 A6
RMK A4=^ROOT^RATE 66.6/SEC MEAN
ASSIGN "88" TO RATE END
RTV ^SUBDIR-^ROOT^RATE-^DSK A5 A6 A7
ADD A6 A5\ADD A7 A5\ZAP A6 A7
RMK A5=^ROOT^RATE 88.8/SEC MEAN
BLC
EXC FILTER A1 B1:LP2000
EXC FILTER A2 B2:LP2000
EXC FILTER A3 B3:LP2000
EXC FILTER A4 B4:LP2000
EXC FILTER A5 B5:LP2000
```

```
DSP B1-B5
REPEAT
PRINT" "END
PRINT" "END
INPUT"P2> "TO CMD END
^CMD
UNTIL CMD="" END
REPEAT!UNTIL MOREIDN=N
IDN ABRR
PRINT" "END
INPUT"     ANOTHER IDN OF THIS SCREEN? (Y/N) : "TO MOREIDN END
UNTIL MOREIDN="N" END
DSP A1-A3\ZAP
!ANALYSE & PLOT 11.1/SEC ==========================================
ZAP A1-A5
DSP A1-A5
RTV ^SUBDIR-^ROOT-^DSK A2 A3 A4 A5
AVEPAR A5[9]
BLC\MOVE A2 A1\ADD A3 A1\ADD A4 A1\ADD A5 A1
RMK A1=^ROOT  11.1/SEC MEAN
ASSIGN SYSTEM TO A5SWP END
IF A5SWP=1000 THEN
DSP A1 A2 A3 A4 A5\OVR A2 A3 A4 A5
ELSE
DSP A1 A2 A3\OVR A2 A3
ENDIF
REPEAT
PRINT" "END
PRINT" "END
INPUT"P2> "TO CMD END
  ^CMD
UNTIL CMD=""END
IDN ABR
!ANALYSE & PLOT 22.2/SEC ==========================================
DSP B1-B4\ZAP
ASSIGN "22" TO RATE END
RTV ^SUBDIR-^ROOT^RATE-^DSK B2 B3 B4
BLC
ADD B2 B1\ADD B3 B1\ADD B4 B1
EXC CORREL B2 B1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR1 END
EXC CORREL B3 B1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR2 END
EXC CORREL B4 B1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR3 END
ASSIGN (COR1+COR2+COR3)/3 TO AVCOR END
!::::::::: 3-Way cross correllation ::::::::::::
REPEAT
EXC CORREL B2 B3 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR4 END
EXC CORREL B3 B4 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR5 END
EXC CORREL B2 B4 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR6 END
UNTIL (COR4<101) AND (COR5<101) AND (COR6<101) END
ASSIGN (COR4+COR5+COR6)/3 TO AVCOR2 END
RMK B2=^COR1 ^ROOT  22.2/SEC
RMK B3=^COR2 ^ROOT  22.2/SEC
RMK B4=^COR3 ^ROOT  22.2/SEC
RMK B1=^AVCOR (^AVCOR2) ^ROOT 22.2/SEC MEAN
MOVE B1 A6
DSP B1-B4
REPEAT
PRINT" "END
PRINT" "END
INPUT"P2> "TO CMD END
  ^CMD
UNTIL CMD=""END
IDN ABRA
!ANALYSE & PLOT 44.4/SEC ==========================================
```

```
DSP A1-A4\ZAP
ASSIGN "44" TO RATE END
RTV ^SUBDIR-^ROOT^RATE-^DSK A2 A3 A4
BLC
ADD A2 A1\ADD A3 A1\ADD A4 A1
EXC CORREL A2 A1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR1 END
EXC CORREL A3 A1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR2 END
EXC CORREL A4 A1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR3 END
ASSIGN (COR1+COR2+COR3)/3 TO AVCOR END
!:::::::::: 3-Way cross correllation ::::::::
REPEAT
EXC CORREL A2 A3 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR4 END
EXC CORREL A3 A4 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR5 END
EXC CORREL A2 A4 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR6 END
UNTIL (COR4<101) AND (COR5<101) AND (COR6<101) END
ASSIGN (COR4+COR5+COR6)/3 TO AVCOR2 END
RMK A2=^COR1 ^ROOT  44.4/SEC
RMK A3=^COR2 ^ROOT  44.4/SEC
RMK A4=^COR3 ^ROOT  44.4/SEC
RMK A1=^AVCOR (^AVCOR2) ^ROOT 44.4/SEC MEAN
MOVE A1 A7
DSP A1-A4
REPEAT
PRINT" "END
PRINT" "END
INPUT"P2> "TO CMD END
  ^CMD
UNTIL CMD=""END
IDN ABRA
!ANALYSE & PLOT 66.6/SEC ==========================================
DSP B1-B4\ZAP
ASSIGN "66" TO RATE END
RTV ^SUBDIR-^ROOT^RATE-^DSK B2 B3 B4
BLC
ADD B2 B1\ADD B3 B1\ADD B4 B1
EXC CORREL B2 B1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR1 END
EXC CORREL B3 B1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR2 END
EXC CORREL B4 B1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR3 END
ASSIGN (COR1+COR2+COR3)/3 TO AVCOR END
!:::::::::: 3-Way cross correllation ::::::::
REPEAT
EXC CORREL B2 B3 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR4 END
EXC CORREL B3 B4 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR5 END
EXC CORREL B2 B4 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR6 END
UNTIL (COR4<101) AND (COR5<101) AND (COR6<101) END
ASSIGN (COR4+COR5+COR6)/3 TO AVCOR2 END
RMK B2=^COR1 ^ROOT  66.6/SEC
RMK B3=^COR2 ^ROOT  66.6/SEC
RMK B4=^COR3 ^ROOT  66.6/SEC
RMK B1=^AVCOR (^AVCOR2) ^ROOT 66.6/SEC MEAN
MOVE B1 A8
DSP B1-B4
REPEAT
PRINT" "END
PRINT" "END
INPUT"P2> "TO CMD END
  ^CMD
UNTIL CMD=""END
```

```
IDN ABRA
!ANALYSE & PLOT 88.8/SEC ========================================
DSP A1-A4\ZAP
ASSIGN "88" TO RATE END
RTV ^SUBDIR-^ROOT^RATE-^DSK A2 A3 A4
BLC
ADD A2 A1\ADD A3 A1\ADD A4 A1
EXC CORREL A2 A1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR1 END
EXC CORREL A3 A1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR2 END
EXC CORREL A4 A1 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR3 END
ASSIGN (COR1+COR2+COR3)/3 TO AVCOR END
!::::::::: 3-Way cros correllation :::::::::
REPEAT
EXC CORREL A2 A3 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR4 END
EXC CORREL A3 A4 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR5 END
EXC CORREL A2 A4 B7:X4-9Y4-9L1I0N
ASSIGN SYSTEM TO COR6 END
UNTIL (COR4<101) AND (COR5<101) AND (COR6<101) END
ASSIGN (COR4+COR5+COR6)/3 TO AVCOR2 END
RMK A2=^COR1 ^ROOT  88.8/SEC
RMK A3=^COR2 ^ROOT  88.8/SEC
RMK A4=^COR3 ^ROOT  88.8/SEC
RMK A1=^AVCOR (^AVCOR2) ^ROOT 88.8/SEC MEAN
DSP A1-A4
REPEAT
PRINT" "END
PRINT" "END
INPUT"P2> "TO CMD END
  ^CMD
UNTIL CMD=""END
IDN ABRA
FORMFD
PRINT"ANALYSIS DONE"END
MABORT=ON
ECHO=ON
```

A (vi): MECOL Program "ATRAIN.CMD"

A program to analyse the click train ABR results

```
ECHO=OFF
MABORT=OFF
!Program to analize click train waveforms
!Assumes train waveforms are already in B1&B2
!ADD B2 B1
LOAD SEGMNT.LOD
NICGL:INITB
NICGL:SELCT PRINT
NICGL:SETWW 0,0,1000,1000
NICGL:SETVP 0,0,1000,1000
STACK
ZAP A1-A8
DSP A1-A8
SMO B1
EXC SEGMNT B1 A1:512
EXC SEGMNT B1 A2:492,512
EXC SEGMNT B1 A3:983,512
EXC SEGMNT B1 A4:1474,512
EXC SEGMNT B1 A5:1965,512
EXC SEGMNT B1 A6:2456,512
EXC SEGMNT B1 A7:2947,512
EXC SEGMNT B1 A8:3438,512
PRINT" "END
INPUT"     Do you want the waveforms filtered? ( Y/N )  "TO FILT END
IF FILT="Y" THEN
EXC FILTER A1 A1:LP2
EXC FILTER A2 A2:LP2
EXC FILTER A3 A3:LP2
EXC FILTER A4 A4:LP2
EXC FILTER A5 A5:LP2
EXC FILTER A6 A6:LP2
EXC FILTER A7 A7:LP2
EXC FILTER A8 A8:LP2
ENDIF
DSP A1-A8\OVR
AVEPAR B1[10]
ASSIGN SYSTEM TO SENSIT END
PRINT"SENSIT=",SENSIT END
AVEPAR B1[11]
ASSIGN SYSTEM TO SWEEPS END
PRINT"SWEEPS=",SWEEPS END
RMK B1
ASSIGN SYSTEM TO REMARK END
NICGL:TEXT 800,900,"^REMARK"
NICGL:DTEXT 300,900,"TRAIN ABR ANALYSIS"
NICGL:TEXT 10,800,"WAVE #"
NICGL:TEXT 250,800,"LATENCY (US)"
NICGL:TEXT 700,800,"AMPLITUDE (NV)"
NICGL:TEXT 150,700,"JI"
NICGL:TEXT 300,700,"JIII"
NICGL:TEXT 450,700,"JV"
NICGL:TEXT 600,700,"JI"
NICGL:TEXT 750,700,"JIII"
NICGL:TEXT 900,700,"JV"
!=========================
INPUT"     STOP AT THIS POINT OR CONTINUE ( S/C ) : "TO STOP END
IF STOP<>"S" THEN
REPEAT!UNTIL WAVE="Q"
```

```
DSP
REPEAT!UNTIL CORRECT WAVE INPUT
PRINT"IDN ROUTINE FOR WAVE I, III, V"END
PRINT" "END
INPUT"                SELECT 1,  3,  5,  ( 'Q' TO QUIT ) : "TO WAVE END
UNTIL (WAVE="1") OR (WAVE="3") OR (WAVE="5") OR (WAVE="Q") END
IF WAVE <>"Q" THEN
IF WAVE="1" THEN
ASSIGN 150 TO Y END
ENDIF
IF WAVE="3" THEN
ASSIGN 300 TO Y END
ENDIF
IF WAVE="5" THEN
ASSIGN 450 TO Y END
ENDIF
ASSIGN (Y+450) TO Z END
ASSIGN 600 TO X END
ASSIGN "*" TO LN1,LN3,LN5,AN1,AN3,AN5 END
IDN TRAIN:N
PRINT"     WAIT...."END
ASSIGN 0 TO N END
REPEAT! FOR N=1 TO 8
ASSIGN (X-70) TO X END
ASSIGN (N+1) TO N END
ASSIGN (N-1) TO M END
!Obtain data points of peak in Nth block
ASSIGN (33+(2*N)) TO A END
AVEPAR A1[^A]
ASSIGN (SYSTEM-(M*32768)) TO PN END
!Obtain data points of trough in Nth block
ASSIGN (50+(2*N)) TO B END
AVEPAR A1[^B]
ASSIGN (SYSTEM-(M*32768)) TO TN END
!Obtain normalized amplitudes
ASSIGN (PN+(M*491)) TO C END
AVESUM B1[^C]
ASSIGN SYSTEM TO PAN END
ASSIGN (TN+(M*491)) TO D END
AVESUM B1[^D]
ASSIGN SYSTEM TO TAN END
ASSIGN (PAN-TAN) TO AN END
!Convert into absolute latency and amplitude
IF WAVE="1" THEN
ASSIGN (PN*23) TO LN1 END!In us
ASSIGN (AN*SENSIT)/512 TO AN1 END!In nV
ASSIGN AN1*(2000/SWEEPS) TO AN1 END!Correct for SWPS<>2000
  IF LN1<100 THEN
    ASSIGN "?" TO LN1,AN1 END
  ENDIF
NICGL:TEXT ^Y,^X,"^LN1"
NICGL:TEXT ^Z,^X,"^AN1"
ENDIF!WAVE="1"
IF WAVE="3" THEN
ASSIGN (PN*23) TO LN3 END!In us
ASSIGN (AN*SENSIT)/512 TO AN3 END!In nV
ASSIGN AN3*(2000/SWEEPS) TO AN3 END!Correct for SWPS<>2000
  IF LN3<100 THEN
    ASSIGN "?" TO LN3,AN3 END
  ENDIF
NICGL:TEXT ^Y,^X,"^LN3"
NICGL:TEXT ^Z,^X,"^AN3"
ENDIF!WAVE="3"
IF WAVE="5" THEN
ASSIGN (PN*23) TO LN5 END!In us
ASSIGN (AN*SENSIT)/512 TO AN5 END!In nV
ASSIGN AN5*(2000/SWEEPS) TO AN5 END!Correct for SWPS<>2000
  IF LN5<100 THEN
    ASSIGN "?" TO LN5,AN5 END
  ENDIF
```

```
NICGL:TEXT ^Y,^X,"^LN5"
NICGL:TEXT ^Z,^X,"^AN5"
ENDIF!WAVE="5"
NICGL:TEXT 30,^X,"^N"
ASSIGN "*" TO LN1,LN3,LN5,AN1,AN3,AN5 END
UNTIL N=8 END
ENDIF!FOR WAVE <>"Q"
UNTIL WAVE="Q" END
PRINT"PRINTING DATA...."END
NICGL:CLOSE
MABORT=ON
PRINT" "END
PRINT"TRAIN ANALYSIS DONE"END
ECHO=ON
ELSE
NICGL:DSELC PRINT
ENDIF
```

APPENDIX B

MATERIAL GENERATED FOR THE RECRUITMENT OF GROUP A SUBJECTS

B (i) Appeal Form, posted on Hospital notice boards

B (ii) Information sheet supplied prior to consent

B (iii) Consent form

HELP!

NORMAL VOLUNTEERS NEEDED FOR HEARING TEST RESEARCH

Would you be willing to assist in this research study by having your hearing tested?

First the good news:

- the tests are a one-off, there is no need for repeat tests later
- over half the testing is done with you relaxing in a reclining chair, asleep if you like!
- any travelling expenses will be reimbursed
- the study has the approval of the R.L.H. Ethical Committee
- strict confidentiality is assured
- you would be making a valuable contribution to medical research, since without normal 'control' subjects such research is of little value.

and now the bad news:

- the tests can only be conducted at the Royal Liverpool Hospital
- the tests take up to $1^{1}/_{2}$ hours to complete
- you have to have reasonably normal hearing for your age and be free from dizziness and tinnitus (ear or head noises) lasting over five minutes at a time.

For further information or to help by enrolling onto the study please contact:

Guy Lightfoot
Audiological Scientist
Work telephone (051) 709 0141 ext 2718
Home telephone (051) 625 9002 (after 8.00 pm)

HEARING TEST RESEARCH - DETAILS FOR INFORMED CONSENT

This form is designed to outline the research being conducted to help detect people who have a problem with the nerves which carry information about their hearing.

Before any test can be used to diagnose an abnormality, the range of results to be expected from normal people needs to be established. It is for this reason that you have been asked to consider having these tests. It is important to point out that the tests will be of no direct benefit to you but neither will they do you any harm whatsoever. If, after reading this you are willing to have these special hearing tests, please complete and sign the attached form and the tests will be arranged at a mutually convenient time.

The reason for the research

Most people with hearing problems have something wrong with a part of their ear, which can often be corrected medically, surgically or by the use of a hearing aid. However, there are a few rarer problems which affect the nerves of hearing rather than the ear itself and these are usually more difficult to treat. The aim of the research programme is to develop a new test to distinguish between nerve damage and ear disease.

A description of the tests

In total, the procedure takes about $1^{1}/_{2}$ hours and involves having three types of hearing test. The first two are basic and quite straight-forward. The third is completely automatic and involves measuring the electrical responses from the hearing nerves. This is done by sticking four small EEG electrodes onto the scalp using double sided sticky tape. You will be asked to lie down in a comfortable reclining chair and wear earphones. The test is most successful when the subject is relaxed or even asleep. A medium-to-loud volume clicking or buzzing noise is presented through the earphones intermittently for about 40 minutes, but since the test is automatic you do not have to respond or even listen to these sounds. At the end of the test the electrodes are removed. No part of the procedure is hazardous, painful or unpleasant and the worst feature of the test is that it is rather boring. Strict confidentiality will be observed at all times. Thank you very much for your help.

Mr G. R. Lightfoot
Audiological Scientist
Royal Liverpool Hospital

Consent Agreement for ABR hearing test research

Please tick the boxes below if the following apply to you

I have:

- ☐ reasonably normal hearing for my age
- ☐ no history of ear disease in the past
- ☐ no ear or head noises lasting over 5 minutes at a time
- ☐ never had any serious head injury
- ☐ never suffered from dizziness/vertigo
- ☐ never suffered from a neurological (nerve) problem or disease
- ☐ Not taken/will not take any sedatives or sleeping tablets for at least a week before the tests

I have read the attached details and consent to have the ABR hearing test conducted.

Signature ..... Date .....

Name ..... Age .....

Home Tel No .....

Home Address .....

.....

.....

.....

This form should be returned to:

Mr G. R. Lightfoot
Audiological Scientist
Institute of Medical & Dental Bioengineering
Royal Liverpool Hospital
Prescot Street
Liverpool
L7 8XP

APPENDIX C

CALCULATION OF THE SLOPE OF THE LATENCY / RATE FUNCTION OF ABR WAVE V IN NORMAL SUBJECTS

Section 3.1.3.1 deals with the linearity of the latency / rate relationship of the ABR waves in Group A (normal) subjects. This appendix describes how the slope of the linear component can be derived, using wave V as an example.

The mean latency of wave V at each rate was:

RATE	R_1 (11.1)	R_2 (22.2)	R_3 (44.4)	R_4 (66.6)	R_5 (88.8)
V_{lat}	5.77167	5.82833	5.96778	6.14028	6.2675 (ms)

From the mean latency at each rate, a linear contrast "L" is derived which, had the five rates been equally spaced would be:

$$L = -2R_1 - 1R_2 - 0R_3 + 1R_4 + 2R_5$$

since the mean latency at each of the rates 1,2,3,4,5 is multiplied by its rate minus the mean of the rates, eg 1 - (1+2+3+4+5)/5, 2 - (1+2+3+4+5)/5 etc.

When the five rates are in the ratio 1:2:4:6:8 the derivation becomes:

$$L = -3.2R_1 - 2.2R_2 - 0.2R_3 + 1.8R_4 + 3.8R_5$$

since $1 - (1+2+4+6+8)/5 = -3.2$

and $2 - (1+2+4+6+8)/5 = -2.2$ etc.

Using the mean latencies in this case gives:

$$L = -18.4704 - 12.8216 - 1.1936 + 11.0520 + 23.8184$$

$$\underline{L = 2.3848}$$

The slope of the contrast is $L^{slope} = \frac{L}{q}$

where $q = 3.2^2 + 2.2^2 + 0.2^2 + 1.8^2 + 3.8^2 = 32.8$

thus $L^{slope} = \frac{2.3848}{32.8}$

$\underline{L^{slope} = 0.0727073}$ (in ms per unit rate)

The following is an extract from the SPSS output:

Estimates for VLAT

CONSTANT

Parameter	Coeff.	Std. Err.	t-Value	Sig. t	Lower -95% CL-	Upper
1	5.99511111	.00626	957.97189	.000	5.98274	6.00748

RATE

Parameter	Coeff.	Std. Err.	t-Value	Sig. t	Lower -95% CL-	Upper
2	**.416225662**	**.01399**	**29.74400**	**.000**	**.38856**	**.44389**
3	.004636155	.01399	.33131	.741	-.02303	.03230
4	-.02115055	.01399	-1.51144	.133	-.04882	.00652
5	-.00676686	.01399	-.48357	.629	-.03443	.02090

Parameter 2 is the linear component for the rate factor and the estimated coefficient, 0.416225662, should be equal to L^{slope}. However, this is a normalized figure and to convert it, it must be divided by $\sqrt{q}$. This gives $L^{slope} = 0.072676$, almost exactly the same value as calculated manually. Note that the SPSS output also gives lower and upper (ie 2-tailed) 95% confidence limits for the linear coefficient.

To convert L^{slope} into μs/decade, we must account for the actual rates used: rather than using decades we have integer multiples of 11.1, thus

$L^{slope} = \frac{0.072676}{1.11}$ (ms per decade)

$L^{slope} = \underline{65.474\ \mu s/decade}$

APPENDIX D

HEARING LOSS CORRECTION METHODS FOR ILDV (IT_5)

In section 3.3.4.2. multiple linear regression showed that the ILDV of subjects in Group ABC was influenced by variable SLBTADIFF, the inter-aural difference between subjects' 2,4,8 kHz best-two average sensation levels. SLBTADIFF is one measure of the asymmetry in effective 'loudness' of the ABR stimuli. This finding is hardly surprising, since Wave V latency is known to be sensitive to the effective loudness of a stimulus. Figure D1 illustrates the effect in a scatter plot of ILDV data versus SLBTADIFF. The slope of the least squares regression line is a measure of the strength of the effect.

Figure D1

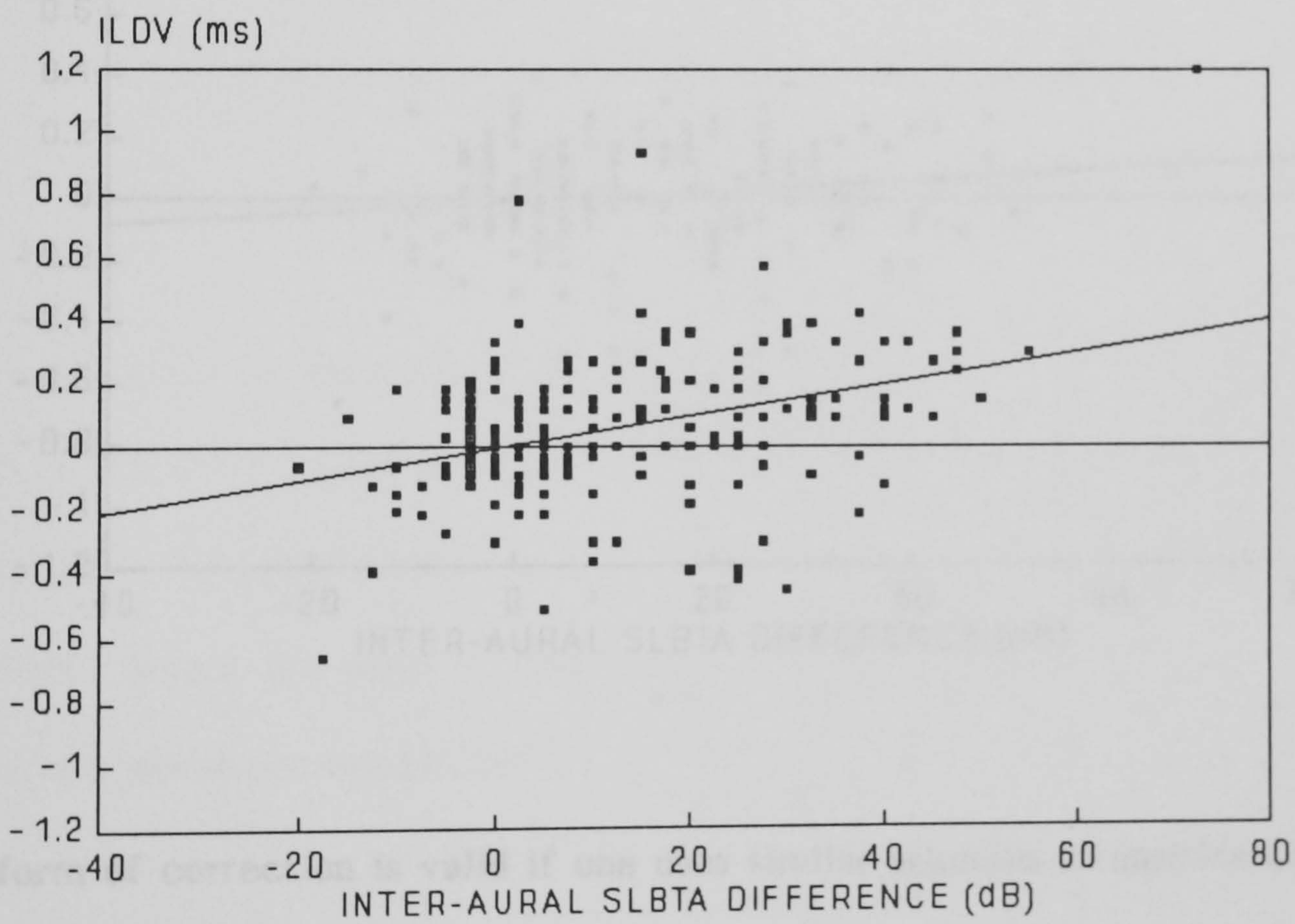


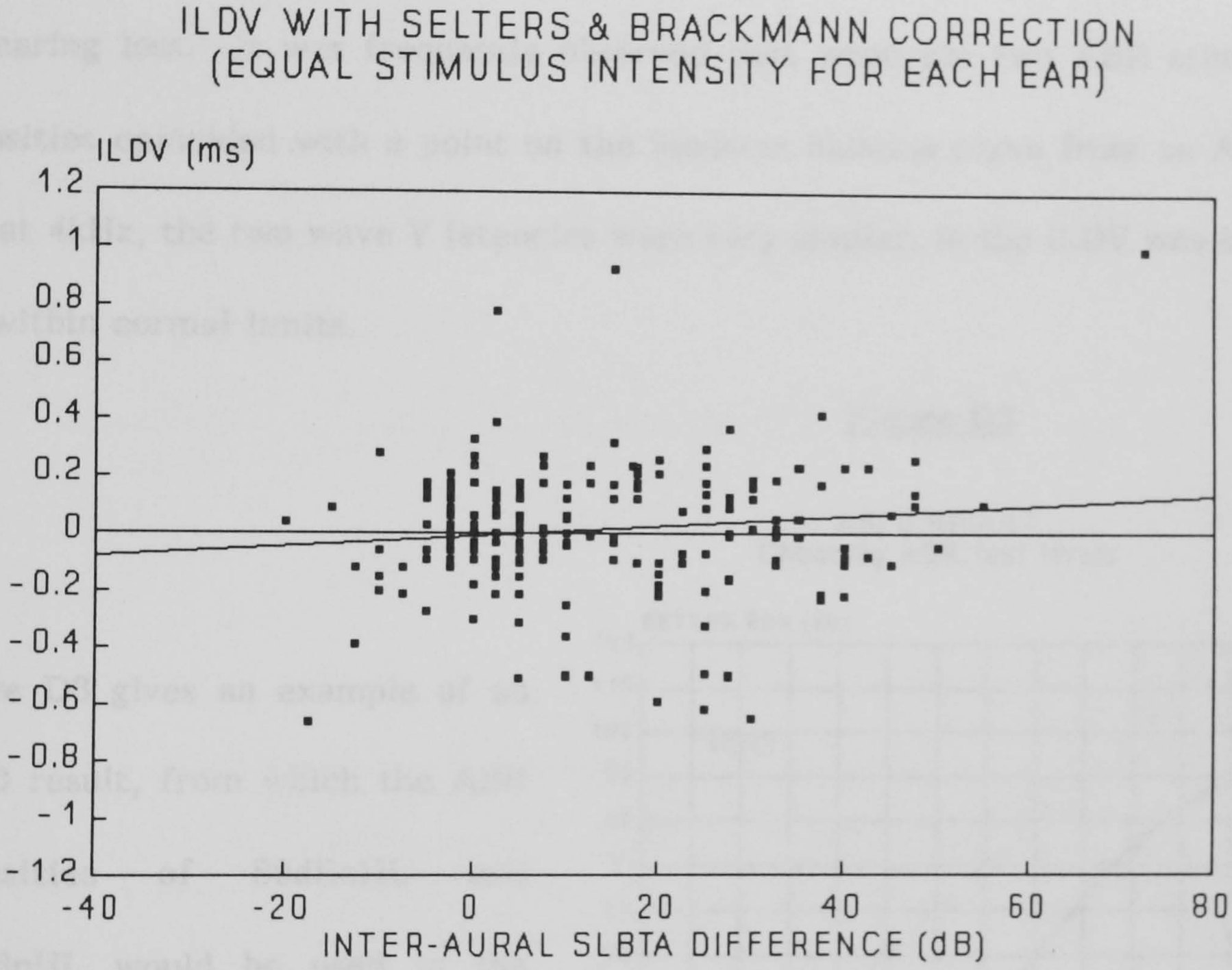
Figure D2 shows the data after being adjusted in a manner similar to that suggested by Selters & Brackmann (1977). In fact, they suggested a widening of the confidence limit with increasing loss. Instead of this, Figure D2 depicts an ILDV derived from the subjects' two Wave V latencies after each has been

corrected according to the following criteria:

(a) no correction for 4kHz thresholds up to 50 dBHL

(b) 0.01 ms deducted from the Wave V latency for every decibel that the 4kHz threshold exceeds 50dBHL.

Figure D2



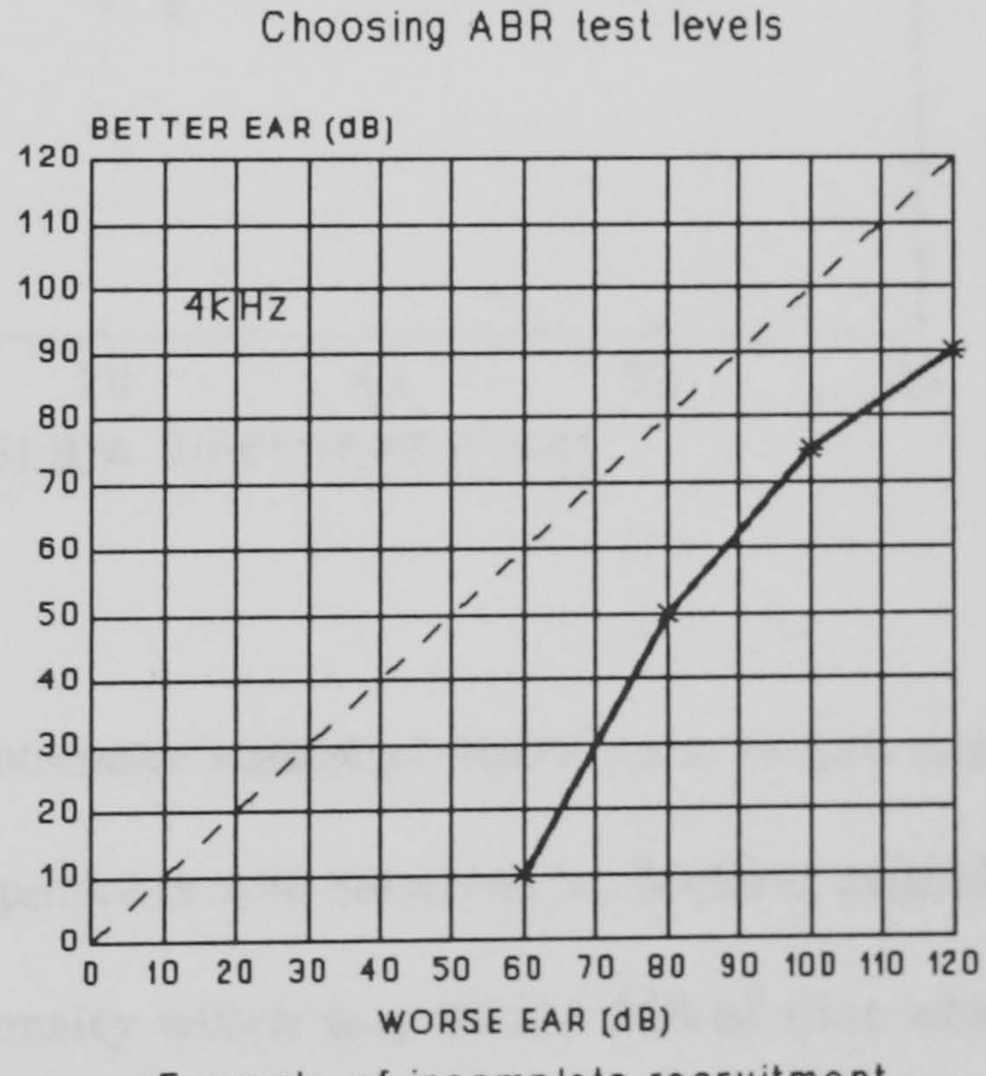
This form of correction is valid if one uses similar stimulus intensities on both sides. Thus, Figure D2 depicts a sub-group of Group ABC in which both ears received the same intensity. Comparison of Figures D1 and D2 show that the slope of the regression line is shallower, though not zero following correction.

The loudness balanced ILDV

About half way through the data collection phase of this study, the test ear intensity selection criterion was formalised. The previous procedure was common to that used in most ABR labs: a standard (in this case 80dBnHL) intensity was employed, but if the ABR waveform was unsatisfactory, with absent early peaks and/or a delayed Wave V, higher intensities were employed to offset the effects of hearing loss. It was frequently observed that when the two ABR stimulus intensities coincided with a point on the loudness balance curve from an ABLB test at 4kHz, the two wave V latencies were very similar, ie the ILDV was small and within normal limits.

Figure D3

Figure D3 gives an example of an ABLB result, from which the ABR intensities of 80dBnHL and 105dBnHL would be used in the better and worse ear respectively.



The latter part of the study used this method as a means of predicting the required test ear stimulus intensity. If such a prediction method is successful, it

should result in offsetting the combined effects of asymmetrical high frequency hearing loss and accompanying recruitment that plagues the ILDV. The attraction is that, unlike other corrections, the loudness balance technique is sensitive to the degree of recruitment in the *individual* patient.

Figure D4

ILDV USING STIMULUS LOUDNESS BALANCE TECHNIQUE AT 4kHz

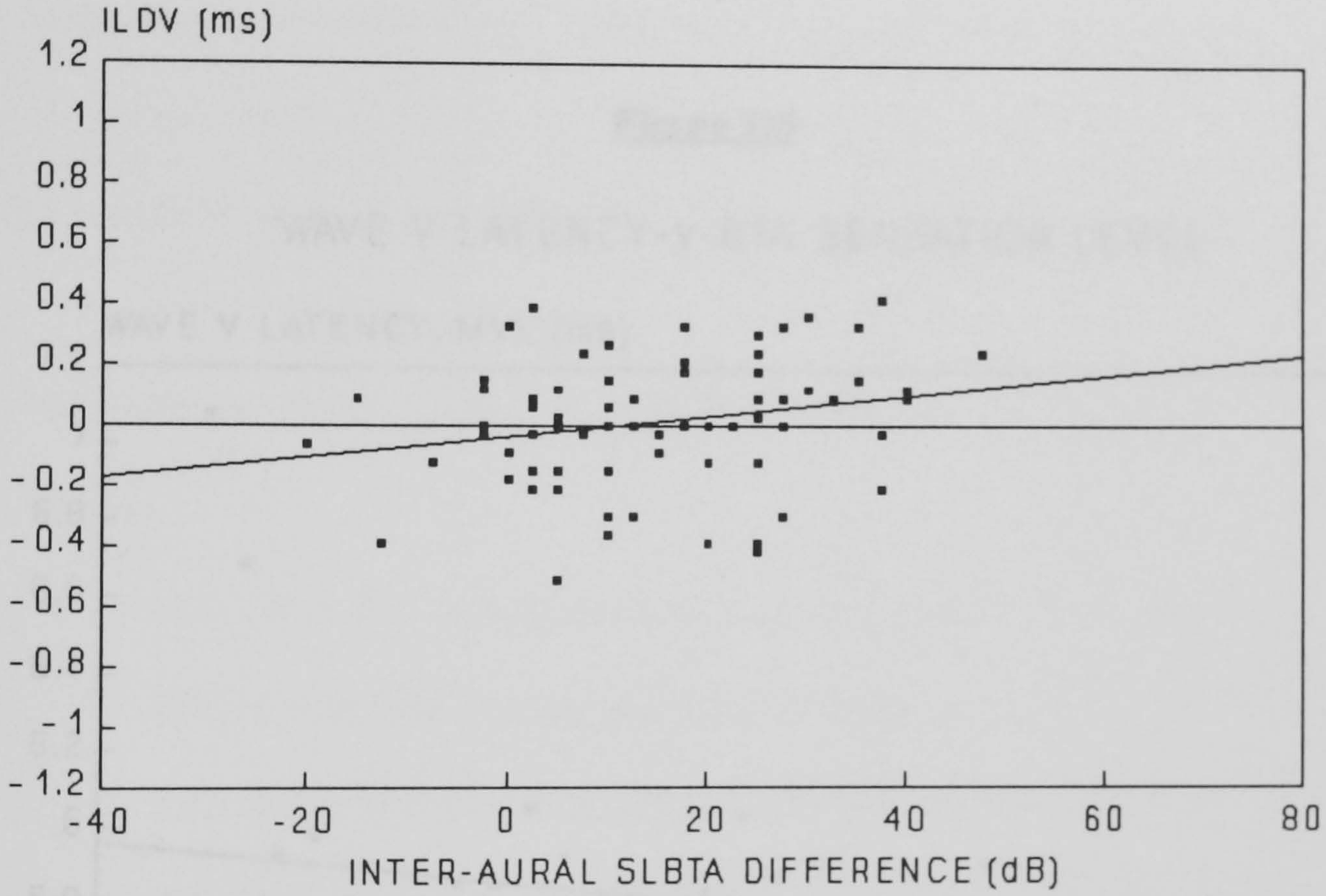


Figure D4 shows the results of the loudness balanced ILDV test in the same format as before. These subjects were patients who received an 80dBHL stimulus in their non-test ear and a stimulus intensity which was within 5dB of that which the 4kHz ABLB showed as being equally loud. Whilst an improvement on the simple uncorrected ILDV, this technique is slightly poorer than the Selters & Brackmann measure in so far as the slope of the regression line is concerned. Perhaps the technique would be more successful if ABLB results at other

frequencies were considered.

The sensation level corrected ILDV

In section 3.3.3.2 all four hearing loss/sensation level treatments were identified as significant factors influencing the Wave V latency. Since SLBTADIFF was similarly identified by the regression on ILDV, SLBTA was plotted against MVL, the Wave V latency.

Figure D5

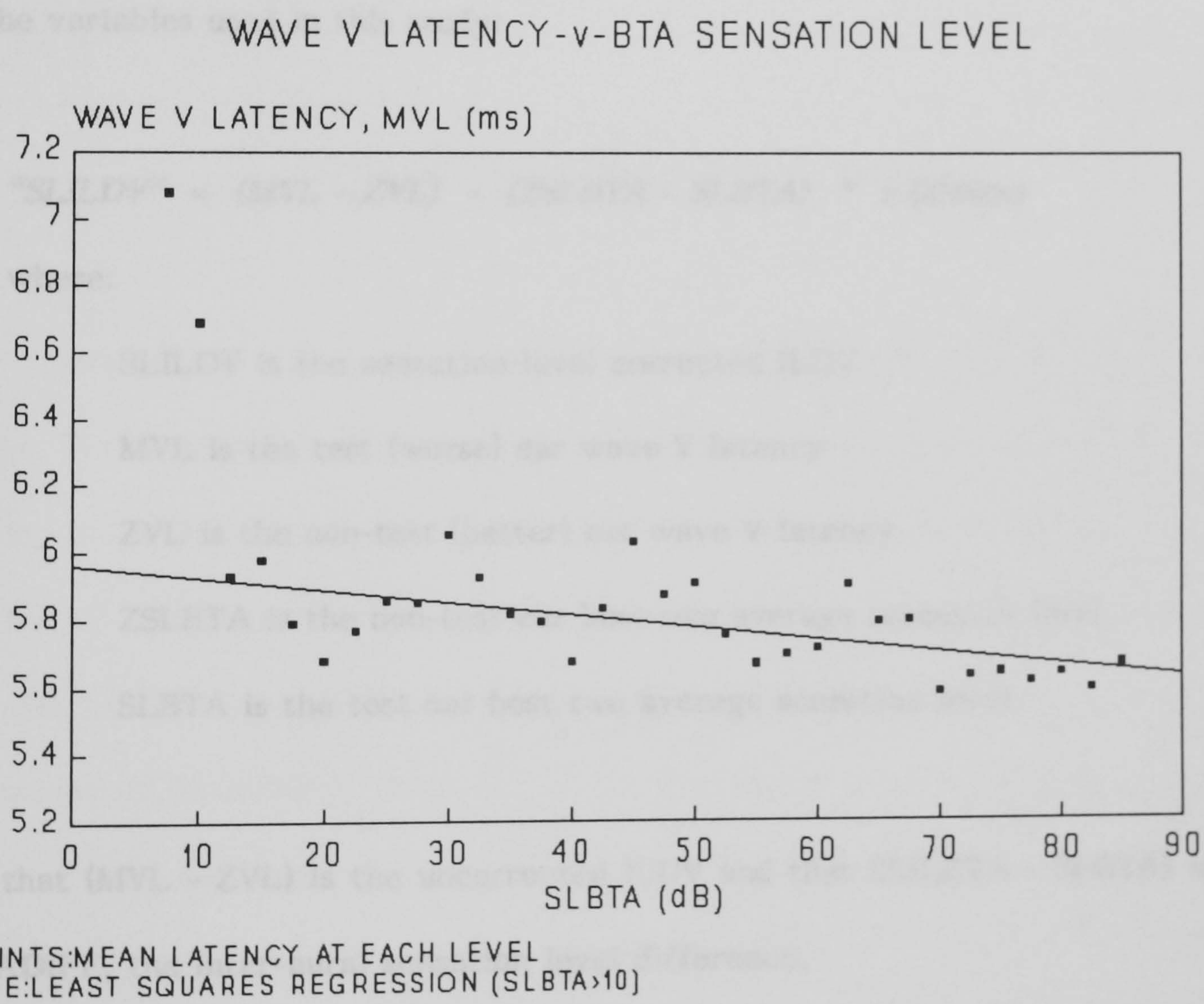


Figure D5 shows the mean of the MVL values at each value of SLBTA. At low values of SLBTA (i.e. <10dB), where the effective sensation level of the stimulus is very low, Wave V latency is, as expected, extended. At higher levels MVL

appears to show a reasonably linear function with SLBTA. The regression (least squares) line was computed for values of SLBTA greater than 10dB. The slope of this line is -0.0046ms/dB.

Can these results be used to advantage in a sensation level correction method for ILDV? The appropriate adjustment in ILDV is to deduct from ILDV:

*(better ear sensation level - worse ear sensation level) * 0.0046ms*

For the variables used in this study:

*"SLILDV" = (MVL - ZVL) - (ZSLBTA - SLBTA) * 0.0046ms*

where:

SLILDV is the sensation level corrected ILDV

MVL is the test (worse) ear wave V latency

ZVL is the non-test (better) ear wave V latency

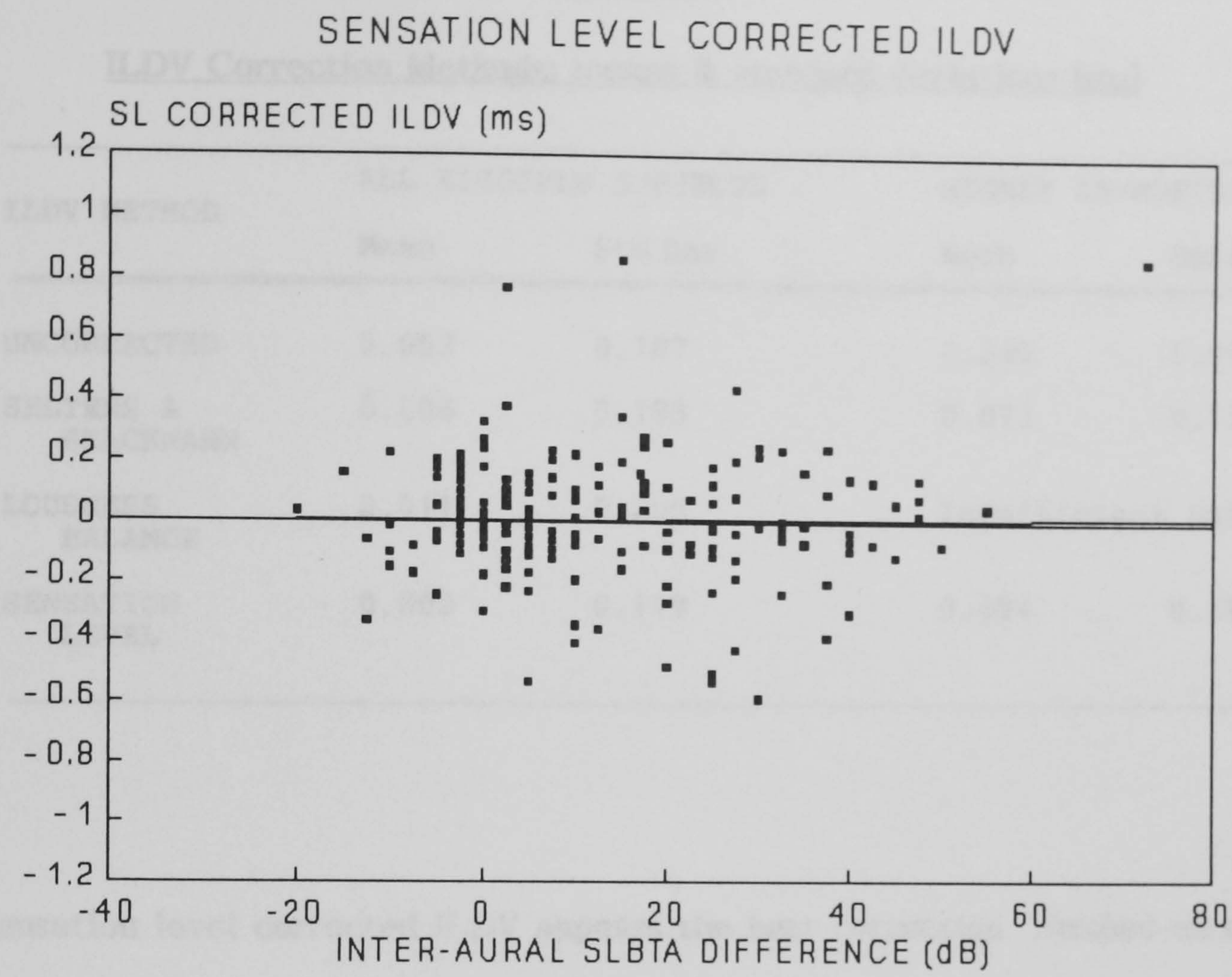
ZSLBTA is the non-test ear best two average sensation level

SLBTA is the test ear best two average sensation level

Note that (MVL - ZVL) is the uncorrected ILDV and that (ZSLBTA - SLBTA) is SLBTADIFF, the inter-aural sensation level difference.

This ILDV correction was applied to Group ABC subjects, providing they received adequate sensation levels (SLBTA and ZSLBTA both greater than 10dB) and Figure D6 shows the individual data points plus the least squares regression line, which this time is almost perfectly horizontal.

Figure D6



These figures show how well or poorly the correction methods account, on average, for inter-aural differences in hearing loss. A further useful way of assessing the relative merits of the methods is to look at the mean and standard deviation of the corrected data. Table D1 does this, both for all subjects for whom the methods are appropriate and for a sub-set of especially difficult cases: those where SLBTADIFF > 40dB, i.e. those who had a large inequality in the hearing of their two ears.

Table D1

ILDV Correction Methods: means & standard deviations (ms)

ILDV METHOD	ALL ELIGIBLE SUBJECTS		HIGHLY ASYMMETRIC	
	Mean	Std Dev	Mean	Std Dev
UNCORRECTED	0.052	0.187	0.240	0.097
SELTERS & BRACKMANN	0.006	0.193	0.073	0.131
LOUDNESS BALANCE	0.011	0.205	Insufficient Data	
SENSATION LEVEL	0.003	0.179	0.024	0.095

The sensation level corrected ILDV appears the best correction method on the basis of smaller mean and standard deviation, especially in the difficult cases of highly asymmetric sensation levels (which represent highly asymmetric hearing thresholds). It is preferable to hearing loss correction methods in that it does not demand equal stimulus intensities, nor does it require an additional test, as in the loudness balance method.

BIBLIOGRAPHY

Anderson, H., Barr, B. & Wedenberg, E. 1970.
Early diagnosis of eighth nerve tumors by acoustic reflex tests.
Acta Otolaryngologica, Supp. 263: 232-237.

Antonelli, A.R., Bellotto, R., Bertazzoli, G.P., NunezCastro, M., Felisati, G. & Romagnoli, M. 1986.
Auditory Brain stem response test battery for Multiple Sclerosis patients: Evaluation of test findings and assessment of diagnostic criteria.
Audiology; 25: 227-238.

Arslan, E., Prosser, S. & Rosignoli, M. 1988.
The behaviour of wave V latency in cochlear hearing loss.
Acta Otolaryngol (Stockh); 105: 467-472.

Bauch, C.D., Rose, D.E. & Harner, S.G. 1982.
Auditory brain stem response results from 255 patients with suspected retrocochlear involvement.
Ear Hear.; 3(2): 83-86.

Bauch, C.D. & Olsen, W.O. 1989.
Wave V interaural latency differences as a function of asymmetry in 2,000 - 4,000Hz hearing sensitivity.
Am. J. Otol.; 10(5): 389-392.

British Society of Audiology, 1981.
Recommended Procedures for Pure-Tone Audiometry Using a Manually Operated Instrument.
Brit. J. Audiol.; 15: 213-216.

British Society of Audiology, 1986.
Recommendations for masking in pure tone threshold audiometry.
Brit. J. Audiol.; 20: 307-314.

BS2497 (Part 5), 1988.
Standard reference zero for the calibration of pure tone air conduction audiometers.
British Standards Institution.

BS6950, 1988.
A Standard reference zero for the calibration of pure tone bone conduction audiometers.
British Standards Institution.

BS6951, 1988.
Threshold of hearing by air conduction as a function of age and sex for otologically normal persons.
British Standards Institution.

Campbell, K.C.M. & Abbas, P.J. 1987.
The effect of stimulus repetition rate on the auditory brainstem response in tumor and nontumor patients.
J.Speech Hear. Res.; 30: 494-502.

Cashman, M.Z. & Rossman, R.N. 1983.
Diagnostic features of the auditory brainstem response in identifying cerebellopontine angle tumours.
Scand. Audiol.; 12: 35-41.

Chiappa, K.H., Gladston, K.J. & Young, R.R. 1979.
Brainstem auditory evoked responses. Studies of waveform variation in 50 normal human subjects.
Arch. Neurol. (Chic); 36: 81-87.

Chiappa, K.H. 1980.
Pattern shift visual, brainstem auditory and short latency somatosensory evoked potentials in Multiple Sclerosis.
Neurology; 30: 110-123.

Clemis, J.D. & McGee, T. 1979.
Brain Stem electric response audiometry in the differential diagnosis of acoustic tumors.
Laryngoscope; 89: 31-42.

Coats, A.C. & Martin, J.L. 1977.
Human auditory nerve action potentials and brain stem evoked responses. Effects of audiogram shape and lesion location.
Arch. Otolaryngol.; 103, 605-622.

Coats, A.C. 1978.
Human auditory nerve action potentials and brain stem evoked responses: Latency-intensity functions in detection of cochlear and retrocochlear abnormality.
Arch. Otolaryngol.;104: 709-717.

Davis, A. 1988.
Normal reference data on hearing threshold asymmetry at 4kHz. From the MRC Institute of Hearing Research National Study of Hearing.
Personal communication.

Despland, P.A. & Galambos, R. 1980.
The auditory brainstem response (ABR) is a useful diagnostic tool in the intensive care nursery.
Pediatr. Res.; 14: 154-158.

Don, M., Allen, A.R., & Starr, A. 1977.
Effect of click rate on the latency of auditory brain stem responses in humans.
Ann. Otol. Rhinol. Laryngol.; 86(2): 186-195.

Eggermont, J.J. 1985.
Peripheral auditory adaptation and fatigue: A model oriented review.
Hear. Res.; 18: 57-71.

Eggermont, J., Don, M., & Brackmann, D. 1980.
Electrocochleography and auditory brainstem electric responses in patients with pontine angle tumors.
Ann. Otol. Rhinol. Laryngol.; 89: Supp 75.

Elidan, J., Sohmer, H., Gafni, M., & Kahana, E. 1982.
Contribution of changes in click rate and intensity on diagnosis of Multiple Sclerosis by brainstem auditory evoked potentials.
Acta Neurol. Scand.; 65: 570-585.

Fowler, C.G., & Noffsinger, D. 1983.
Effects of stimulus repetition rate and frequency on the auditory brainstem response in normal, cochlear-impaired and VIII nerve / brainstem-impaired subjects.
J. Speech Hear. Res.; 26(4): 560-567.

Fujikawa, S.M., & Weber, B.A. 1977.
Effects of increased stimulus rate on brainstem electric response (BER) audiometry as a function of age.
J. Am. Audiology Soc.; 3: 147-150.

Galambos, R., Makeig, S., & Talmachoff, P.J. 1981.
A 40Hz auditory potential recorded from the human scalp.
Proc. Natl. Acad. Sci. USA; 78(4): 2643-2647.

Gerling, I.J., & Finitzo-Hieber, T. 1983.
Auditory brainstem response with high stimulus rates in normal and patient populations.
Ann. Otol. Rhinol. Laryngol.; 92: 119-123.

Harkins, S.W., McEvoy, T.M., & Scott, M.L. 1979.
Effects of interstimulus interval on latency of the brainstem auditory potentials.
Intern. J. Neuroscience; 10: 7-14.

Hayes, D. 1980
Effect of degree of hearing loss on diagnostic audiometric tests.
Am. J. Otol.; 2(2): 91-96.

Hecox, K.E. 1980.
ABR and brainstem involvement.
Presented at a symposium on Auditory Evoked Response in Otology and Audiology. Cambridge, MA. August 1980.

Hecox, K.E., Cone, B. & Blaw, M.E. 1981.
Application of the brainstem auditory evoked responses to the diagnosis of paediatric neurological diseases.
Neurology; 31: 832-840.

House, J, & Brackmann, D.E. 1979.
Brainstem audiometry in neurologic diagnosis.
Arch. Otolaryngol.; 105: 305-309.

Hyde, M.L., Stephens, S.D.G., & Thornton, A.R.D. 1976.
Stimulus repetition rate and the early brainstem responses.
Brit. J. Audiol.; 10: 41-50.

Hyde, M.L. 1985.
The effect of cochlear lesions on the ABR.
In: The Auditory Brainstem Response. Ed. J.T.Jacobson. Taylor & Fransis. London.

Jacobson, J.T. 1983.
Auditory and electrophysiological effects in Multiple Sclerosis.
Presented at the 17th Colorado Otology-Audiology workshop, Aspen, Colorado.

Jerger, J. & Johnson, K. 1988.
Interactions of age, gender, and sensorineural hearing loss on ABR latency.
Ear Hearing; 9(4): 168-176.

Jewett, D.L., & Williston, J.S. 1971.
Auditory evoked far fields averaged from the scalp of humans.
Brain; 94: 681-696.

Josey, A.F. 1985.
Auditory brainstem response in site of lesion testing. In: Handbook of clinical audiology (3rd ed.) Ed. J Katz.

Keith, R.W., & Jacobson, J.T. 1985.
Physiological responses in Multiple Sclerosis and other demyelinating diseases.
In: The auditory brainstem response. Ed. J.T.Jacobson.

Klein, A.J., & Teas, D.C. 1978.
Acoustically dependent latency shifts of BSER (wave V) in man.
J. Acoust. Soc. Am.; 63: 1887-1895.

Lasky, R.E. 1984.
A developmental study on the effect of stimulus rate on the auditory evoked brainstem response.
Electroenceph. Clin. Neurophysiol.; 59: 411-419.

Mason, S.M. 1984.
Effects of high-pass filtering on the detection of the auditory brainstem response.
Brit. J. Audiol.; 18: 155-161.

Moffat, D.A., Baguley, D.M., Hardy, D.G. & Tsui, Y.N. 1989.
Contralateral auditory brainstem response abnormalities in acoustic neuroma.
J. Laryngol.Otol.; 103(9): 835-838.

Mogensen, F. & Kristensen, O. 1979.
Auditory double click evoked potentials in Multiple Sclerosis.
Acta Neurol. Scandinav.; 59: 96-107.

Moller, A.R. & Jannetta, P.J. 1985.
Neural generators of the auditory brainstem response.
In: The Auditory Brainstem Response. Ed. J.T.Jacobson. Fransis & Taylor. London.

Mouney, D.F., Berlin, C.I., Cullen, J.K., & Hughes, L.F. 1978.
Changes in human eighth nerve action potential as a function of stimulation rate.
Arch. Otolaryngol.; 104: 551-554.

Musiek, F.E., & Gollegly, K.M. 1985.
ABR in eighth nerve and low brainstem lesions.
In: The Auditory Brainstem Response. Ed. J.T.Jacobson. Taylor & Fransis. London.

Nodar, R.H. 1980.
Brainstem auditory evoked potentials on individuals with multiple sclerosis.
In: Evoked Potentials. Ed. C.Barber. University Park Press.

Paludetti, G., Maurizi, M., & Ottaviani, F. 1983.
Effects of stimulus repetition rate on the auditory brain stem responses (ABR).
Am. J. Otology; 4 226-234.

Picton, T.W., Stapells, D.R., & Campbell, K.B. 1981.
Auditory evoked potentials from the human cochlea and brainstem.
J. Otolaryngol.; 10 (Supp 9): 1-41.

Portmann, M., Cazals, Y. Negrevergne, M. & Aran J.M. 1980.
Transtympanic and surface recordings in the diagnosis of retrocochlea disorders.
Acta Oto-laryng.; 89: 362-369.

Pratt, H., & Sohmer, H. 1976.
Intensity and rate functions of cochlea and brainstem evoked responses to click stimuli in man.
Arch. Oto. Rhino. Laryng.; 212: 85-92.

Pratt, H., Ben-David, Y., Podoshin, L., & Scharf, B. 1981.
Auditory brain stem evoked potentials: Clinical promise of increasing stimulus rate.
Electroenceph. Clin. Neurophysiol.; 51: 80-90.

Priede, V.M. & Coles, R.R.A. 1974.
Interpretation of loudness recruitment tests - some new concepts and criteria.
J. Laryngol. Otol.; 88: 641-662.

Robinson, D. 1988.
Statistical properties of normal reference data on hearing thresholds.
Personal communication.

Robinson, K., & Rudge, P. 1977.
Abnormalities of the auditory evoked potentials in patients with Multiple Sclerosis.
Brain; 100: 19-40.

Sand, T., & Sulg, I. 1984.
The influence of click phase and rate upon latencies and latency distributions of the normal brain-stem auditory evoked potentials.
Electroenceph. Clin. Neurophysiol.; 57: 561-570.

Schaefer, S.D., Gerling, I.J., Finitzo-Hieber, T., & Freeman, F. J. 1983.
Brainstem conduction abnormalities in Spasmodic Dysphonia.
Ann. Otol. Rhinol. Laryngol.; 92: 59-64.

Scott, M.L., & Harkins, S.W. 1978.
Amplitude of the brainstem auditory evoked response: the effect of interstimulus interval.
Int. J. Neurosci.; 8: 146-152.

Selters, W.A. & Brackmann, D.E. 1977.
Acoustic tumor detection with brain stem electric response audiometry.
Arch. Otolaryngol.; 103: 181-187.

Shanon, E., Gold, S., & Himelfarb, M.Z. 1981.
Assessment of functional integrity of brain stem auditory pathways by stimulus stress.
Audiology; 20: 65-71.

Sklare, D.A. 1990.
Directionality in the interpretation of clinical auditory brain stem response measures.
Ear Hearing; 11(1): 29-30.

Sorensen, H. 1959.
Auditory adaptation in nerve action potentials recorded from the cochlea in guinea pigs.
Acta Oto-laryng. (Stockh.); 50: 438-450.

Stockard, J.J., & Rossiter, V.S. 1977.
Clinical and pathological correlates of brainstem auditory response abnormalities.
Neurology (Minneap.); 27: 316-325.

Stockard, J.J., Stockard, J.E., & Sharbrough, F.W. 1978.
Nonpathologic factors influencing brainstem auditory potentials.
Am. J. EEG Technol.; 18: 177-209.

Stockard, J.E., Stockard, J.J., Westmoreland, B.F., & Corfits, J.L. 1979.
Brainstem auditory-evoked responses. Normal variation as a function ofç stimulus and subject characteristics.
Arch. Neurol.; 36: 823-831.

Swets, J.A. ed. 1964.
Signal detection and recognition by human observers.
John Wiley & Sons, Inc.

Terkildsen, K., Osterhammel, P., & Huis In't Veld, F. 1975.
Far-field electrocochleography. Adaptation.
Scand. Audiol.; 4: 215-220.

Thinkett, H.O., Threw, H.O. & Larf, H.O. 1952.
The hazardous application of statistical tests in lieu of common sense.
Personal communication.

Thomsen, J., Terkildsen, K., & Osterhammel, P. 1978.
Auditory brain stem responses in patients with acoustic neuromas.
Scand. Audiol.; 7: 179-183.

Thornton, A.R.D., & Coleman, M.J. 1975.
The adaptation of cochlea and brainstem auditory evoked potentials in humans.
Electroenceph. Clin. Neurophysiol.; 39: 399-406.

Thornton, A.R.D. 1983.
Standardisation in Evoked Response Measurements.
Brit.J.Audiol.;17: 115-116.

Thornton, A.R.D. 1987.
Stimulus, recording and subject factors influencing ABR diagnostic criteria.
Brit.J.Audiol.;21: 183-189.

Tietze, G., & Gobsch, H. 1980.
Measurements of adaptation of brainstem responses.
Scand. Audiol.; Supp 11: 91-96.

Turner, R.G. & Nielsen, D.W. 1984.
Application of clinical decision analysis to audiological tests.
Ear Hear.; 5(3): 125-133.

Turner, R.G., Shepard, N.T. & Frazer, G.J. 1984.
Clinical performance of audiological and related diagnostic tests.
Ear Hear.; 5(4): 187-194.

Yagi, T., & Kaga, K. 1979.
The effect of the click repetition rate on the latency of the auditory evoked brain stem response and its clinical use for a neurological diagnosis.
Arch. Otorhinolaryngol.; 222: 91-97.

Zollner, C., Karnahl, T., & Strange, G. 1976.
Input-output function and adaptation behaviour of the five early potentials registered with the earlobe-vertex pick-up.
Arch. Oto. Rhino. Laryngol.; 212: 23-33.