The Effects of High Repetition Rate Stimuli on Electrocochleography performed on Normal Hearing Subjects

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DECLARATION

I declare that this research is my own work and that it has not been submitted to any other university

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25 - 06 - 1999

Date

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ABSTRACT

High stimulus repetition rates have been proposed as a solution to the poor sensitivity and specificity of the standard electrocochleogram. The use of this approach has been confounded, however, by conflicting literature reports on the effects of high stimulus repetition rates on normal subjects. This study aimed to confirm the effects of high stimulus repetition rates on normal hearing subjects as a precursor to clinical high stimulus repetition rate electrocochleography trials. Electrocochleogram tracings were recorded binaurally from 51 normal hearing subjects at 7.1 cps, 51.1 cps, 101.1 cps and 151.1 cps and the summating potential and action potential latencies and amplitudes, summating potential/action potential amplitude ratios and waveform widths were recorded. Statistical analyses showed that increasing the stimulus repetition rate caused statistically ($p<0.05$) and clinically ($p<0.01$ for latency and $p<0.005$ for amplitude) significant changes to the action potential latency and amplitude, summating potential/action potential amplitude ratio and waveform width, but caused only limited statistical ($p<0.05$) and clinical ($p<0.01$ for latency and $p<0.005$ for amplitude) changes to the summating potential amplitude and latency. Subject age had no effect on the results and there was no interaction between age and stimulus repetition rates. These findings provide the most comprehensive data on the effects of fast stimulus repetition rates to date, and have provided the beginnings of a valid clinical normative database for high stimulus repetition rate tympanic electrode electrocochleography.

1. INTRODUCTION

1. Introduction

The electrocochleogram (ECochG) is an early auditory evoked potential used to assess the functional integrity of the cochlea and the eighth cranial nerve (Ferraro, 1988). On its clinical introduction in the 1970's, the ECochG was only used to identify hearing impairment in difficult to test children (Mourney, Cullen, Berlin & Hughes, 1978). However by the 1980's, the ECochG became better known as the auditory evoked potential test of choice in the identification of the presence of endolymphatic hydrops and Ménière's disease (Coats, 1981; Gibson, Prasher & Kilkenny, 1983; Kanzaki, Ouchi, Yokobori & Ino, 1982). It was during these two decades that the bulk of the currently available ECochG literature was completed. The 1990's have seen the ECochG remain stable in its role as a diagnostic tool for endolymphatic hydrops and Ménière's disease (Hall, 1992; Mori, Asai, Shugyo & Sakagami, 1994) and recent ECochG esearch remains scarce.

The longstanding support for the ECochG as a test of choice in the identification of the presence of endolymphatic hydrops (ELH) and Ménière's disease does not imply that the ECochG is without significant problems. Of primary concern is the poor sensitivity and specificity of the current ECochG test, using standard clinical protocols, to ELH itself particularly during ELH's nonactive phases.

This concern has led to an increased interest in ways of improving the ECochG's sensitivity

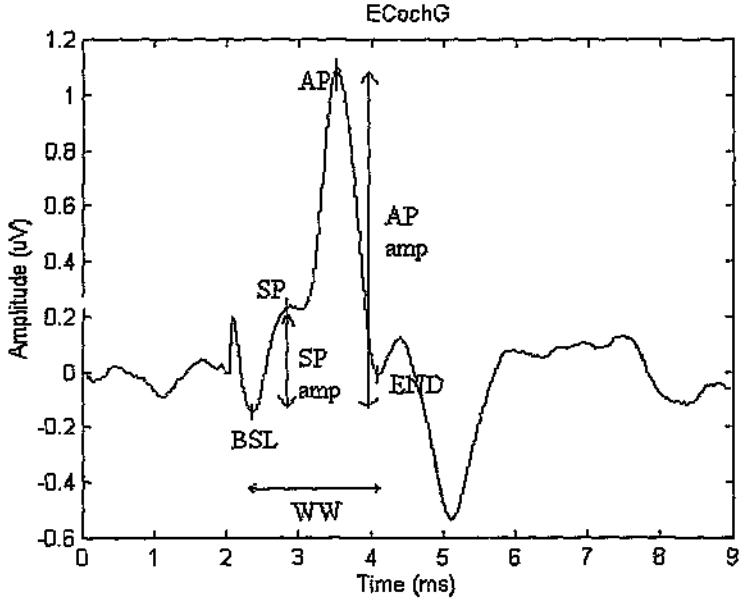
and specificity. However, before such methods can be investigated a summary of ECochG measurement, its various components and current difficulties in recording and analysis must be considered.

2. The Normal ECochG

The ECochG is typically recorded by placing electrodes in the external ear canal, on the tympanic membrane, or on the cochlear prominence. Other electrode sites typically include the forehead and the mastoid. The electrodes record gross electrical potentials derived from the activity of numerous individual receptors and nerve cells in the cochlea during the physiological processes of sensory transduction (Honrubia, Strelioff & Sitko 1976; Pickles, 1988).

A diagram of the ECochG is depicted in Figure 1, note a prestimulus interval of 2 msec was used in all ECochG recordings. The ECochG itself consists of three main potentials: the cochlea microphonic (CM), summating potential (SP) and the action potential (AP) (Hall, 1992). The CM is an alternating current potential that originates from the outer hair cells of the Organ of Corti (Dallos, 1976; Ferraro, 1988; Pickles, 1988) and provides a rough measure of cochlear function (Hall, 1992). It is uncertain as to whether the CM plays a role in the mechano-electrical transduction at the hair cell level or if it is merely an epiphenomenon of the process itself (Dallos, 1976; Ferraro, 1988). Despite the uncertainty of the role of the CM there is general agreement that diagnostic reliance on the CM is impossible as it is too general for drawing conclusive inferences (Aran & Charlet de

Figure 1: A typical ECochG recording showing the baseline (BSL), summating potential (SP), action potential (AP), the end of the ECochG waveform (END), waveform width (WW), and SP and AP amplitudes (amp).



Sauvage, 1976) and it often obliterates the electrocochleogram tracing (Hall, 1992).

The second potential, the SP, is a direct current potential which follows the envelope of the stimulus (Ferraro, 1988). It is a complex, multicomponent potential that reflects the sum of the cochlear distortion products (Sass, 1998) and various nonlinearities associated with cochlear processes (Ruth, 1994). These nonlinear mechanisms are thought to be generated predominantly by the inner and outer hair cells, but also from other cochlea sources particularly within the Organ of Corti (Pickles, 1988). The size of the SP component is dependent on the presence of hair cells capable of producing an electric output (Sass, 1998) and the amount of basilar membrane displacement (Gibson, 1978). The literature remains uncertain of the properties and role of the SP component (Ferraro, 1988; Hall, 1992), but maintains that it represents a measure of the functional status of the cochlea (Dallos, 1976; Hall, 1992).

The third and final component of the ECochG, the AP, is the most well studied component (Ferraro, 1988; Ruth, 1994). The AP represents the summed response of synchronous nerve fibre activity of numerous individual nerve fibers located in the distal portions of the auditory nerve, namely the high frequency region of the cochlea (Ferraro, 1988; Ruth, 1994). It is Wave I of the auditory brainstem response (Ferraro, 1988; Hall, 1992).

The clinical analysis of the ECochG is based on the following features (See Figure 1):

1. SP latency: the time interval, in milliseconds, between the onset of the stimulus and the

peak of positive shift of the SP wave from the baseline.

2. AP latency: the time interval, in milliseconds, between the onset of the stimulus to the peak of positive shift of the SP wave from the baseline
3. SP amplitude: the absolute voltage, in microvolts, between the peak of positive shift of the AP potential and the predetermined baseline.
4. AP amplitude: the absolute voltage, in microvolts, between the peak of positive shift of the AP potential and the predetermined baseline.
5. SP/AP amplitude ratio: the SP amplitude divided by the AP amplitude
6. Waveform width: the time interval, in milliseconds, between the beginning of the first positive shift from baseline of the SP component and the end of the positive shift from baseline of the AP component. Whilst some authors measure the SP and AP widths separately, many authors combine the two to give a 'full ECochG waveform width" (Aran & LeBert, 1968; Booth, 1980; Gibson, Moffat & Ramsden, 1977; Podoshin, Ben-David, Pratt, Fradis & Feiglin, 1986). Support for the measure of a 'full ECochG waveform width' comes mostly from the difficulties encountered when trying to separate the SP component from the AP component as there is often no clear distinction between the end of the SP component and the beginning of the AP component (Hall, 1992).

The use of these ECochG measures for diagnostic applications requires normative data. Normative data provides ranges and values from numerous healthy ears for the ECochG components to provide a basis from which abnormal responses from unhealthy ears can be

identified. Non-pathological subjects characteristics (age, hearing status, level of arousal and usage of drugs), stimulus (stimulus frequency, duration, intensity rate and polarity) and recording parameters (filter bandwidth, the electrode type and electrode placement) all significantly influence the final ranges of normative data. Examples of a few normative data ranges as limited in the literature are shown in Table 1.

Considering the impact that stimulus and recording parameters, age and hearing loss have on the ECochG, examples of some normative data ranges listed in the literature are shown in Table1.

Table 1: Normative ranges of ECochG data cited in the literature

ECochG components		Sass, Densen & Arlinger (1998)	Ferraro (1988)	Coats (1986)
Electrode type		Transtympanic	Extratympanic	Extratympanic
SP latency (msec)	Mean Range		0.36 0.30 – 0.50	
SP amplitude(μV)	Mean Range	1.3	0.37 0.10 – 1.00	0.49 0.16 – 1.07
AP latency (msec)	Mean Range	1.92	1.04 0.8 – 1.25	
AP amplitude (μV)	Mean Range	18.4	1.35 0.60 – 3.10	2.68 0.78-7.09
SP/AP amplitude ratio	Mean Range	0.26	0.28 0.11 – 0.47	0.20 0.8 – 0.44

To ensure that valid normative data is used in diagnostic work, the same stimulus and recording parameters used by the investigators must be implemented (Hall, 1992). Reliance on published normative data for further clinical work is prob[illegible]tic due to inflexibility in

test protocols as adjustment of any parameter renders the normative data invalid (Hall, 1992).

Normative studies conducted for ECochG are scarce (Hall, 1992) and many have only considered the amplitude of the components, with most latency components having been derived from auditory brainstem response studies, and few normative studies have considered normative data for the waveform width as it is shows great clinical variability.

3.The abnormal ECochG

Two abnormal ECochG morphology types have been recognised (Hall, 1992). The first abnormality shows absent or reduced amplitudes and delayed latencies of the various components. This pattern is commonly recorded in patients with severe sensori-neural hearing losses above 1000Hz (Hall, 1992) but has proven to be too variable to be clinically useful. The second ECochG abnormality consists of clear SP and AP components, but the SP amplitude is enlarged (Ferraro, 1988, Hall, 1992). This pattern has been successfully associated with Ménière's disease and is thought to indicate the clinical presence of endolymphatic hydrops (Hall, 1992; Mori, Koshimune & Asai, 1990).

One of the major difficulties in the diagnosis and assessment of Ménière's disease has been to match the clinical symptoms of the disorder to an objective correlation (Sass, 1998). Subsequently the matching of morphological abnormalities to endolymphatic hydrops has resulted in various ECochG analyses approaches (Hall, 1992). Patient's suffering from

endolymphatic hydrops disease were initially identified based on an enlarged SP amplitude (Coats, 1981; Daumann, Aran, Sauvage & Portmann, 1988; Gibson et al., 1983; Goin, Staller, Asher & Mischke, 1982; Mori et al., 1994). The clinical usefulness of this information was doubted, however, as the absolute SP amplitude was found to be highly variable between subjects (Eggermont, 1974; Goin et al., 1982). The SP/AP amplitude ratio measure was subsequently introduced to strengthen the validity of the endolymphatic hydrops diagnosis (Goin et al., 1982; Hall, 1992) as it controlled for some inter-subject variability. An abnormal SP/AP ratio is still considered to be one of the best indicators of endolymphatic hydrops and Ménière's disease (Mori, Asai & Sukagami, 1988). The duration or waveform width of the SP/AP complex has also been analysed in endolymphatic hydrops, and has been recorded in 60% of patients (Gibson, Moffat & Ramsden, 1977) but due to the extreme variability of the measure it has not gained widespread acceptance or use (Coats, 1981; Goin et al., 1982).

The abnormal ECochG morphology observed in patients with endolymphatic hydrops is attributed to the pathological changes in the cochlea (Gibson et al., 1977), however the exact nature of the disease process is unknown. The most commonly reported anatomical structure that leads to endolymphatic hydrops and Ménière's disease is a dysfunctional stria vascularis within the endolymphatic sac. The stria vascularis' primary function is to absorb components from the blood (the stria vascularis, as its name suggests is well vascularised) and to produce endolymphatic fluid (Pickles, 1988). Malabsorption of the fluid by the stria vascularis or the obstruction of the flow of endolymph through the endolymphatic duct

causes an over-accumulation of endolymph in the endolymphatic sac (Bretlau, Thomsen, Tos, Johnsen, 1983; Friedman & Arnold, 1993). This increase in endolymph fluid, increases the pressure of the endolymph and can result in distention, herniation and rupture of the endolymphatic system (Bretlau, et al., 1983). The increased endolymphatic pressure places the hair cells of the Organ of Corti under constant pressure and distends both the basilar membrane and Reissner's membrane (Ferraro, Arrenberg & Hassanein, 1985). The increased pressure in the cochlea alters the hydromechanical characteristics of the cochlea (Ferraro, et al.,1985; Ferraro, 1988) and generates vibrational asymmetry.

The asymmetrical vibration of the basilar membrane and the distorted pattern of hair cell stimulation, due to the endolymphatic hydrops, causes a nonlinear response of the CM and generates an enlarged SP amplitude (Ferraro et al., 1985; Goin et al., 1982; Sass, 1998). However some investigators maintain that the enlarged SP amplitude is due to the nonlinearities of the equipment and the use of high stimulus intensity levels (Eggermont, 1979; Gibson, 1978). Despite the unknown origin of the enlarged SP amplitude, substantial experimental and cl.. ical evidence suggests that an enlarged SP amplitude, which leads to an abnormal SP/AP amplitude ratio, is consistently recorded in Ménière's disease patients.

4.Problems with the current ECochG recording and analysis methods

In spite of the widespread availability of qualitative definitions of ECochG abnormalities, such as an enlarged SP amplitude and abnormal SP/AP ratio, the exact quantification of these abnormalities has proven to be more difficult. There is a general lack of agreement in

test results (Sass, 1998) which has resulted in substantial reports of poor sensitivity and specificity as highlighted by the following research findings:

1. An enlarged SP amplitude has only a moderate incidence in patients with endolymphatic hydrops (Goin et al., 1982) as only approximately 65% (Coats, 1981; Ferraro et al., 1985; Hall, 1992; Mori, et al., 1988) of endolymphatic hydrops cases are successfully identified. This suggests that a third of patients with the endolymphatic hydrops remain undiagnosed following ECochG assessment (Goin et al., 1982).
2. There is a high degree of overlap between the SP/AP ratio results seen in normal subjects and those seen in patients with endolymphatic hydrops and other cochlear dysfunction (Gibson, et al., 1983). Normative data sampled by Gibson (1990) shows SP/AP amplitude ratios of 3-41 % in normal subjects; 2-46 % in subjects with a sensori-neural hearing loss and 7-100 % for patients suffering from Ménière's disease. The SP/AP amplitude ratio overlap limits accurate differentiation of Ménière's disease from various other cochlear aetiologies and disorders.
3. An abnormal SP/AP amplitude ratio is only moderately sensitive to Ménière's disease patients, as it is not recorded exclusively from patients suffering from Méniere's disease. Goin, Staller, Asher & Mischke (1982) recorded an abnormal SP/AP ratio in 62% of patients with Ménière's disease, 4% in normal patients and 17% in patients with other cochlear pathologies.
4. The SP/AP waveform is broadened in only 65% of patients with endolymphatic hydrops due to the moderate incidence of an enlarged SP amplitude in these patients

(Gibson et al., 1977).

5. Coats (1981) considered the SP/AP waveform duration too variable to be clinically feasible.

These research findings highlight that the ECochG is only moderately sensitive to changes in the status of the cochlea (Goin et al., 1982; Kumagami, Nishida & Baba, 1982). It is evident that a positive ECochG result is a reliable indication of the presence of endolymphatic hydrops (Sass, 1998), but a negative finding needs to be interpreted with caution, as measurements show approximately 30% false findings. This severely limits the ECochG as a clinical tool in the assessment of Ménière's disease. Therefore it is imperative that the sensitivity and specificity of this diagnostic be addressed.

5. Possible reasons for poor ECochG sensitivity and specificity

The moderate incidence of abnormal ECochG tracings in patients suffering from endolymphatic hydrops and Ménière's disease can most likely be attributed to the episodic nature of these disorders. Normal ECochG tracings in confirmed Ménière's disease patients are most likely to be recorded from patients not suffering actively from typical symptoms of the disease (which include vertigo, aural fullness and fluctuating hearing) on the day of ECochG testing (Ferraro et al., 1985; Goin et al, 1982). This suggests that the ECochG is only sensitive to the active stages of the disease (Goin et al, 1982; Kumagami, et al., 1982). The poor ability of the electrocochleogram to detect the presence of endolymphatic hydrops during the inactive stages of Ménière's disease (Kumagami, et al., 1982) is one of the major limiting factors in the clinical usefulness and sensitivity of this technique.

6. Possible solutions poor ECochG sensitivity and specificity

In view of the problems faced by the ECochG, methods to improve its sensitivity and specificity must be sought. One successful approach has been to manipulate the stimulus recording parameters to optimise ECochG diagnostic sensitivity. The manipulation of various stimulus and recording parameters that influence the ECochG recording, are discussed below.

The CM obliterates the SP and AP component as it mimics the frequency waveform and the polarity of the stimulus (Hall, 1992). Manipulation of the polarity of the stimulus to an alternating polarity has eliminated the interference of the CM component (Yoshie, 1971) which has assisted in waveform identification.

The SP component is recorded for the duration of the stimulus, as it mimics the stimulus envelope. Increase in the duration of the stimulus is helpful in separating the SP and AP component (Hall, 1992). The SP is only recorded at high intensity levels (Hall, 1992), thus forcing protocols to implement high intensity levels. Manipulation of the filter settings has shown that the SP component is best recorded with little or no high pass filter, usually 3-10 Hz (Hall, 1992) which often results in substantial patient artifact. The need for little or no high pass filter is due to the fact that the SP is a direct current potential and therefore has an effective frequency nearing 0 Hz.

Manipulation of the placement of the electrode has shown differences in the amplitude and

clarity of the ECochG waveform. Three electrode types are commonly used to record the ECochG, but differ in their placement. The trans-tympanic electrode is placed directly on the cochlear prominence, the tympanic electrode rests on the tympanic membrane and the extra-tympanic electrode is in the external auditory earcanal (Ruth, 1994). Clear waveform morphology and robust amplitude recordings are obtained from direct placement of the electrode in the cochlea, however as the electrode is placed further away from the cochlea the amplitude decreases and the waveform becomes distorted (Ferraro, 1988; Ruth, 1994).

Whilst these stimulus and recording manipulations have led to some improvement in ECochG sensitivity, further manipulations that will improve the ECochG sensitivity and specificity levels need to be explored.

7. Successful manipulation of stimulus and recording parameters to improve sensitivity and specificity of other auditory evoked potentials - Manipulation of stimulus repetition rate

One method that has proven successful in improving the sensitivity and specificity of other auditory evoked potentials is the use of increased stimulus repetition rates. In particular, increased stimulus repetition rates in auditory brainstem response (ABR) have been successfully used to improve the diagnosis of neurological abnormalities, such as auditory neuropathy, tumours and demyelination in Multiple Sclerosis (Pratt, BenDavid, Peled, Podoshin & Scharf, 1981).

The improved diagnostic ability of the high stimulus repetition rate ABR to subtle

neuropathologies at high stimulus repetition rates is based on the premise that the nervous system is stressed beyond its functional capacity (Hall, 1992). It is believed that high repetition rates stress the auditory system and strain VIIIth cranial nerve and brainstem transmission to a higher degree than slow stimulus repetition rates (Musiek & Gollegy, 1985; Pratt, et al., 1981). The physiological basis for detecting subtle neuropathologies at high stimulus repetition rates has been attributed to neural fatigue and adaptation (Hall, 1992).

The success of using high repetition rate stimuli to improve test sensitivity of the auditory brainstem response is based on the exploitation of the physiological responses of the auditory system to rapid stimuli. When over-stimulated, a normal auditory system will fatigue, adapt quickly to the stimulus, reduce subsequent firing rates (Eggermont, 1974; Moore, 1997; Soucek & Mason, 1992), and require a longer refractory or resting period to recover (Don, Allen & Starr, 1977; Musiek & Gollegy, 1985; Pratt & Sohmer, 1976). In a diseased auditory system however, excessive stimulation causes rapid and pathological adaptation (Moore, 1997), and the system breaks down resulting in grossly degraded waveforms, prolonged latencies and reductions in amplitude (Eggermont & Odenthal, 1974; Freeman, Sohmer & Silver, 1991; Paludetti, Maurizi & Ottavini, 1983; Suzuki, Kobayashi & Tagaki, 1985; Yagi & Kaga, 1979; Zollner, Karnahl & Stange, 1976;). The elicitation of pathological adaptation from a diseased auditory system provides valuable site of lesion information within the clinical setting (Fowler & Noffsinger, 1982; Moore, 1997).

However, not all literature reports support the use of high repetition rate stimulation (Campbell & Abbas, 1987). Researchers who oppose the use of high stimulus repetition rates maintain that it merely results in degraded responses that prevent accurate wave identification (Campbell & Abbas, 1987; Chiappa, Gladstone, Young, 1979) and nullifies any diagnostic advantages present in the procedure.

Although there are conflicting opinions regarding the role of using increasing stimulus repetition rates to detect subtle pathologies, neurological success has been well documented (Don, Allen & Starr, 1977; Pratt et al., 1981).

8. Manipulation of stimulus repetition rate as a method of improving ECochG sensitivity and specificity

Despite the success of using high stimulus repetition rates to improve the sensitivity and specificity of the ABR, and the close association of the ABR to the ECochG, the application of high stimulus repetition rates remains relatively unexplored in assessment by ECochG. In a manner similar to the diseased VIIIth cranial nerve and auditory brainstem, the diseased cochlea could elicit abnormalities at high repetition rates due to the limited reserve of a damaged cochlear system. The high stimulus repetition rates could therefore have the potential to stress a diseased cochlea and elicit abnormal responses even during the non-active endolymphatic episodes, thereby improving the ECochG's sensitivity and specificity to Ménière's disease.

Research studies exploring the effects of increasing stimulus repetition rates in ECochG remain few in number. Studies that have been completed suffer from significant differences in protocols and procedures in terms of the electrode montage, aetiologies, subject populations and stimulus and recording parameters (Coats, 1981; Harrison, 1981; Mourney et al., 1978; Rolland & Walsh, 1994; Soucek & Mason, 1992; Stephens, Charlet de Sauvage & Aran, 1974), and have been predominantly performed on normal subjects only.

Mourney, Berlin, Cullen & Hughes (1978) have provided the most cited study on the effect of increasing repetition rates on ECochG in which they assessed changes in the ECochG AP component as a function of stimulus repetition rates to determine which rate yielded the maximum amplitude response. On close inspection, however, it can be seen that their study suffers from a poorly defined sample of only 12 normal subjects. Despite its repeated citing, Mourney, et al's., (1978) study hardly provides a framework for the application of high stimulus repetition rate ECochG to the clinical setting.

Despite the various methodologies used, research has suggested that high stimulus repetition rates have different effects on ' and AP components of the normal subject electroco 'eogram. Difficult wave ication at increased stimulus repetition rates (Yagi & Kaga, 1979) resulted in ea orts that the AP component was nchanged at fast rates (Pratt & Sohmer, 1976). However it is now widely accepted that the AP component is prolonged in latency and decreased in amplitude at fast stimulus repetition rates (Eggermont, 1974; Harrison, 1981; Mourney et al., 1978; Soucek & Mason, 1992;

Stephens, et al., 1974; Van Olphen, Rodenburg & Verwey, 1979) due to the process of adaptation (Soucek & Mason, 1992).

It is generally accepted that the SP latency and amplitude remains unaltered in the normal subject at fast stimulus repetition rates (Mourney et al., 1978; Coats, 1981; Soucek & Mason, 1992). The limited change in the SP component is attributed to the lack of adaptation in the cochlea (Charlet de Sauvage & Aran, 1976). This is based on the premise that the SP component originates peripheral to the hair cell-neuron junction, namely from the sensory hair cell itself. However the stability of the SP component in the damaged cochlea is disputed by Rolland & Walsh (1994) who detected changes in SP amplitude at increasing stimulus repetition rates in the identification of a perilymph fistula.

9. Long term aim of using high stimulus repetition rate ECochG in Ménière's disease

The clinical usefulness of ECochG in the assessment of Ménière's disease and other cochlear pathologies is currently limited due to the technique's poor test sensitivity. The theoretical promise of improving test sensitivity and specificity of the ECochG at increased stimulus repetition rates warrants further study. In the long term, full clinical trials on subjects with cochlear pathologies, during both symptomatic and asymptomatic periods are needed before the true diagnostic value of high stimulus repetition rate ECochG can be confirmed.

10. Problem statement preventing immediate research of high stimulus repetition rate ECochG in patients with cochlear disorders

Current normative data bases for high stimulus repetition rate ECochG on normal subjects cannot be used for immediate clinical trials as they suffer from insufficient subject numbers, poor subject selection, and limited use of different electrode types. Before full clinical trials on subjects with Ménière's disease and other cochlear disorders can be investigated, a more comprehensive normative database for high repetition rate stimuli CochG on normal hearing subjects needs to be completed. Such a database is the required prerequisite for obtaining measurements valid for future clinical and diagnostic work (Sass, Densert & Arlinger, 1998).

2. METHODS

2.1 Aims

The aims of this study were:

1. To measure the SP latency and amplitude, the AP latency and amplitude, the SP/AP amplitude ratio and the waveform width in three groups of subjects, grouped according to test ear and age categories, in response to a standard stimulus repetition rate of 7.1 clicks per second, and the faster stimulus repetition rates of 51.1, 101.1 and 151.1 clicks per second.
2. To compare the SP latency and amplitude, the AP latency and amplitude, the SP/AP amplitude ratio and the waveform width between all four stimulus repetition rates to assess the effects of stimulus repetition rate on the measured ECochG variables.
3. To evaluate the effect of age on the measured ECochG variables at all four stimulus repetition rates.
4. To assess for interaction between subject age and stimulus repetition rate for all measured ECochG variables.
5. To create a normative database to allow research of high stimulus repetition rate ECochG in endolymphatic subjects

Based on the known physiological mechanisms in the cochlea and the eighth cranial nerve

it is reasonable to predict that the morphology, latencies and amplitudes of the ECochG components would change as the repetition rate increases, as follows:

1. Wave components can become indistinct, less identifiable or can even disappear (Don, Allen & Starr, 1977; Fowler & Noffsinger, 1983).

2. The SP absolute wave latencies of the ECochG (the SP being a direct current potential) would remain stable at increased stimulus repetition rates, but the AP absolute wave latencies would increase (Mourney, et al., 1978; Soucek & Mason, 1998).

3. The SP amplitude component would remain stable, but the AP amplitude would decrease with increasing stimulus repetition rate (Coats, 1981; Mourney, et al., (1978)).

4. The stability of the SP amplitude and the reduction in the AP amplitude at increased stimulus repetition rates would result in increased SP/AP ratios.

5. The stability of the SP latency and the increase in the AP latency at increased repetition rates would result in an increased waveform width.

2.2 Research design

A non-experimental, repeated measures design was used throughout the study. The non-experimental design was chosen as this study had no random allocation of subjects to conditions (subject age, gender and hearing status was predetermined prior to the study) and only limited tester control over all independent variables. The repeated measures design component (all subjects were tested at all stimulus repetition rates) was chosen to reduce intersubject variability.

The dependent variables were defined as the individual ECochG measures of SP latency and amplitude, AP latency and amplitude, SP/AP amplitude ratio and ECochG waveform width. The independent variables were defined as the stimulus repetition rate and subject age.

2.3 Population

Subjects were sampled from the general, adult population of Gauteng, South Africa.

2.4 Sampling method

Subjects were sampled using a convenience sampling technique.

2.5 Subject selection criteria

The following subject criterion were specified:

1. Subjects should be between 18-60 years of age. This age range was selected as the onset of Ménière's disease varies according to specific demographic regions (Watanabe, 1983). No specific figures are available for South Africa at the present time.
2. Subjects should have no obvious tympanic membrane abnormalities and unoccluded external auditory canals to ensure that the tympanic membrane electrode used could be easily inserted. This was confirmed on otoscopic examination by the researcher.
3. Subjects should have hearing thresholds within normal limits in both ears. Normal

hearing sensitivity is defined as hearing thresholds of 20 dBHL or better at 250 Hz, 500 Hz, 1000 Hz, 2000Hz, 4000 Hz and 8000 Hz (Hall, 1992). This ensured that subjects with any hearing impairment were excluded, as ECochG is degraded by co-existing hearing losses (Hall, 1992).

4. Subjects should have acoustic immittance measurements within normal limits. Normal immittance measurements were based on Northern s (1980) recommendations:

Middle ear static compliance: 0.28 ml to 2.5 ml

Middle ear pressure: -150 daPa to 50 daPa and

External ear canal volume: 1.0 cc to 1.5 cc.

This ensured that subjects with outer and/or middle ear disorders detectable by audiometric testing were eliminated as ECochG can be degraded by middle ear disorders (Hall, 1992). Subjects with perforated eardrums, as identified on acoustic immittance or otoscopy, were excluded from the sample as the tympanic electrode could be inserted through the eardrum and damage the middle ear.

5. Subjects should have no history of ear disease. This criteria was selected to exclude subjects with a history of ear disease that could possibly affect the ECochG.

2.6 Subjects

Fifty-one subjects were accepted for the ECochG testing. Subjects were divided into three groups, according to their age. The three groups were 18-30, 31-45 and 46-60 years of age. The subject's age in years at the time of testing determined group membership. As a

repeated measures design was used throughout the study, each subject acted as their own control.

The subjects' age and gender distribution is depicted in Table 2.

Table 2: Age and gender distribution of the sample

GROUP (years)	GENDER	NUMBER	MEAN (years)	STANDARD DEVIATION	RANGE (years)
18-30	Male	10	24.3	3.2	20-30
	Female	10	22.3	2.1	20-27
31-45	Male	6	40.0	4.9	31-43
	Female	8	36.0	5.2	32-45
46-60	Male	7	50.0	2.6	48-53
	Female	10	57.0	3.9	47-60

2.7 Instrumentation and materials

The following equipment was used during the test procedure:

- A Grason-Stadler Incorporated GSI 33© diagnostic acoustic immittance machine was used for acoustic immittance measurements.
- A Grason-Stadler Incorporated GSI 10© diagnostic audiometer with TDH-49 earphones and MXAR-41 cushions was used for pure tone hearing testing.
- A Biologic Systems© Incorporated, Navigator Evoked Potential unit© running Evoked Potential Software©, version 4.31 for DOS was used for all ECochG testing.
- Cotton wool, alcohol, Nuprep© abrasive agent and Nuprep© conductive gel were used to clean and abrade the subjects' skin.

- Electropyres© AR-15 disposable surface electrodes were used for the active and ground electrodes, and a TMECochGtrode tympanic electrode, Part number 101125, manufactured by Biologic Systems© Incorporated was used as the reference electrode.
- Lectron II© Conductivity gel was placed on the tympanic electrode to facilitate its insertion.
- Micropore tape was used to secure the tympanic electrode in place.

All audiometric equipment met ANSI S3.6 (1969) requirements in that it was manually administered and calibrated. Daily listening checks were performed to ensure accurate calibration and functioning.

The recording and stimulus parameters used on the Biologic Systems Incorporated are illustrated in Table 3.

The stimulus and recording parameters used were those recommended by the American Biologic Systems Corporation, which was included with the equipment and electrodes. It closely parallels the protocol offered by Hall (1992).

Table 3: The stimulus and recording parameters

GENERAL SET UP	
Recording channels	1
Time windows	a) 9.58 msec used for 7.1 cps, 51.1 cps and 101.1 cps b) 5.2 msec used for 151.1 cps
Pre Stimulus delay	-2 msec
Analogue to Digital Conversion	256
AMPLIFIER SET UP	
Gain	75 000
High cut filter	1500 Hz
Low cut filter	3 Hz
50 Hz Mains Power Notch Filter	Out
Artefact rejection	32.7 μV
Electrode Montage	*Active:* Non test mastoid (M1 or M2) *Reference:* Tympanic membrane electrode *Ground:* Forehead (Fz)
STIMULUS SET UP	
Stimulator	TDH49 headphones with MXAR41 cushions
Type of stimulus	Alternating click (100 μs duration)
Intensity	90 dBnHL
Rate	7.1 cps 51.1 cps 101.1 cps 151.1 cps
Masking	None

2. 8 Reasons for Choice of Stimulus Repetition Rates

The click rate of 7.1 cps was selected as it is a standard repetition rate used in ECochG testing (Hall, 1992). The other repetition rates were selected as they represented evenly spaced higher repetition rates and have been used by other authors. Paludetti, Maurizi & Ottaviani, (1983) and Zollner, Karnahl & Stange (1976) used repetition rates of 50 cps and

100 cps and Coats (1981) and (1986) used repetition rates of 150 cps.

2.9 Reasons for using a combined SP and AP component waveform width

The waveform width represented the duration of the SP and AP component. Some authors measure the SP and AP widths separately, however other authors combine the two to give a combined 'full ECochG waveform width' (Aran & LeBert, 1968; Booth, 1980; Gibson, Moffat & Ramsden, 1977; Podoshin, Ben-David, Pratt Fradis & Feiglin, 1986). Support for the 'full ECochG waveform width' is derived from the difficulties encountered trying to separate the SP and AP component, as there is often no clear distinction between the end of the SP component and the beginning of the AP component.

2.10 Test procedures

All subjects were tested at the University of the Witwatersrand Speech and Hearing Clinic. Each subject completed a case history form that included details of fluctuating hearing, dizziness, nausea and fullness in the ear.

An otoscopic examination was performed followed by immittance audiometry and pure tone audiometry, in a sound proof booth. Once all the selection criteria were fulfilled, the subjects were positioned for ECochG testing.

Each subject was placed in a sitting position on a chair in the sound proof room. The

ECochG test procedure was discussed. The subject's forehead (Fz), and the left and right mastoid areas (M1 and M2) were cleaned with alcohol and an abrasive agent. Disposable electrodes were attached to the cleaned sites with conductive paste. The tip of a flexible tympanic electrode, was coated with conductive gel to facilitate its insertion. The tympanic electrode was then inserted into the ear canal of the test ear until it touched the tympanic membrane. Following insertion the electrode wire was secured to the subject's cheek with micropore tape and attached to a connecting cable.

The impedance of the electrodes was checked. Impedance readings were accepted for the surface electrodes if they were below 5 kohms, and for the tympanic electrode if below 40 kohms as recommended by Hall (1992).

TDH-49 headphones with MXAR41 cushions were carefully positioned over the subject's ears and the subject was instructed to relax throughout the testing.

2.11 Data collection

Two ECochG tracings were performed at each respective click rate for the left and the right ears of each subject, to facilitate accurate identification of the various components of ECochG and to ensure waveform repeatability. When repeatable waveforms could not be obtained in two recordings, a third recording was conducted. The best two recordings were then used in the data analysis. All recordings were stored on disk for offline reanalysis after the recording session.

The stimulus repetition rates were presented in ascending order (7.1 cps to 151.1 cps), in an attempt to parallel protocols used in clinical settings.

The SP and AP absolute wave latencies and amplitudes, SP/AP amplitude ratio, and waveform width were identified from the ECochG recordings of each ear of each subject, at each respective repetition rate by two independent raters.

2.12 Statistical treatment of the data

The individual ECochG measures of the two repeat ECochG tracings for each ear, at each respective repetition rate, were assessed for statistical repeatability using a two-tailed paired Student t-tests ($p<0.05$) (Howell, 1995). If the two tracings for the same ear, at the specified repetition rate were statistically repeatable, they were averaged to give single SP, AP latencies and amplitudes, SP/AP amplitude ratio and waveform width values. These averaged values were used for all further statistical analyses. Descriptive statistics for each ECochG component were then calculated. Correlations between ears for each of the SP and AP amplitudes, latencies, SP/AP amplitude ratio and waveform widths were analysed separately using Pearson's Product Moment Correlation Co-efficient analysis ($p<0.05$) (Howell, 1995). Differences between each respective ECochG component between the four stimulus repetition rates, and differences between each respective ECochG component between age groups were assessed using one way between groups repeated measure ANOVAs ($p<0.05$). Tukeys Honest Significance Difference Analysis ($p<0.05$) was used to

identify specific differences [chosen because it is one of the more conservative post-hoc difference tests (Huck, Cormiser & Brunds, 1974)]. Nonparametric Friedman ANOVA ($p<0.05$), Kruskal Wallis ($p<0.05$) and Wilcoxon Matched Pairs ($p<0.05$) tests were used when parametric assumptions were breached, where appropriate (Lindman, 1974).

Whilst statistically significant differences were emphasized, their relation to the clinical application of ECochG was also considered. Due to the high variability of ECochG recordings, statistical differences between ECochG components were only considered to be clinically significant if their p values were less than 0.01 for latency components (which are more stable (Hall, 1992)), and 0.005 for amplitude components and the SP/AP amplitude ratio and waveform width (which are less stable (Hall, 1992)) respectively. These reduced p values were used to minimise the chance of type I error when classifying the ECochG results as clinically normal or abnormal.

2.13 Reliability and validity considerations

Gibson (1978) reported that the AP latency recorded at intervals of several weeks is consistent and reliable, but the amplitude of the components is more variable due to the placement of the electrode. Roland, Rosenbloom, Yellin & Meyerhoff (1993) reported large variations in the SP/AP amplitude ratio among normal hearing subjects on repeated testing, however the SP/AP amplitude ratio remained within normal limits. A more recent study by Margolis, Rieks, Fournier & Levine (1995) reported good test-retest reliability for both latency measurements ($p<0.05$, $r=0.99$) and amplitude measurements (SP latency ($p<0.05$,

r=0.88) and AP latency ($p<0.05$, r=0.99)) at high stimulus intensity levels. However, the SP/AP ratio showed the poorest repeatability ($p<0.05$, r=0.57) despite the high reliability of the SP and AP measures, confirming Rolland et al's., (1993) findings. Margolis et al., (1995) attributed this to the fact that the combination of SP and AP measures in a ratio compromises its reliability.

The sensitivity and validity of the ECochG as a clinical tool to patients with Ménière's disease shows sensitivity figures between 60% - 90% (Sass, 1998). The differences in the results have been attributed to various recording parameters and different normative and pathological ranges used (Sass, 1998). It is logical to assume that the validity of the ECochG is enhanced when recording parameters and norms are used consistently.

With the above points in mind, repeatability and validity aspects of the ECochG measures in the current study were considered. The reports of acceptable validity and reliability of the ECochG were accepted from the literature. To further establish ECochG reliability in this study (i.e. agreement between the individual ECochG variables of SP and AP latency and amplitude, SP/AP amplitude ratio, and waveform width, between repeat waveforms) two-tailed, paired Students t-tests were conducted to compare the individual ECochG measures between pairs of repeat ECochG recordings. This measure assessed whether the two individual measures were in agreement and was chosen over a correlation coefficient as the correlation coefficient has been shown to be misleading and inappropriate as a measure of agreement and reliability (Altman and Bland, 1983; Bland and Altman, 1986).

2.14 Ethical considerations

Ethics clearance was obtained from the Committee for Research on Human Subjects (Reference Number R14/49 and Protocol Number: M980408).

3. RESULTS

The results will be discussed according to the aims specified.

3.1 The measurement of the ECochG components at the different stimulus repetition rates, in three groups of subjects, grouped according to test ear and age.

3.1.1 ECochG SP and AP amplitude and latency, SP/AP amplitude ratio, and waveform width measures

ECochG measurements obtained from one subject at 7.1; 51.1; 101.1, and 151.1 cps are depicted in Figure 2 (note a prestimulus interval of 2 msec was used in all ECochG recordings).

The ECochG components measurements at 7.1, 51.1, 101.1 and 151.1 cps are shown in Table 4. The mean values of each ECochG component in left and right ears are plotted in Figures 3 to 8.

3.1.2 Waveform reliability

All individual ECochG components were statistically repeatable between repeat waveforms ($p<0.05$) in all subjects, for each ear, at each stimulus repetition rate. As all the ECochG components were reliable, the values for each component were averaged to give single values for the individual ECochG components. These averaged results were used in all

subsequent descriptive and statistical analyses.

Figure 2: The ECochG components recorded at 7.1,51.1,101.1 and 151.1 cps from one subject

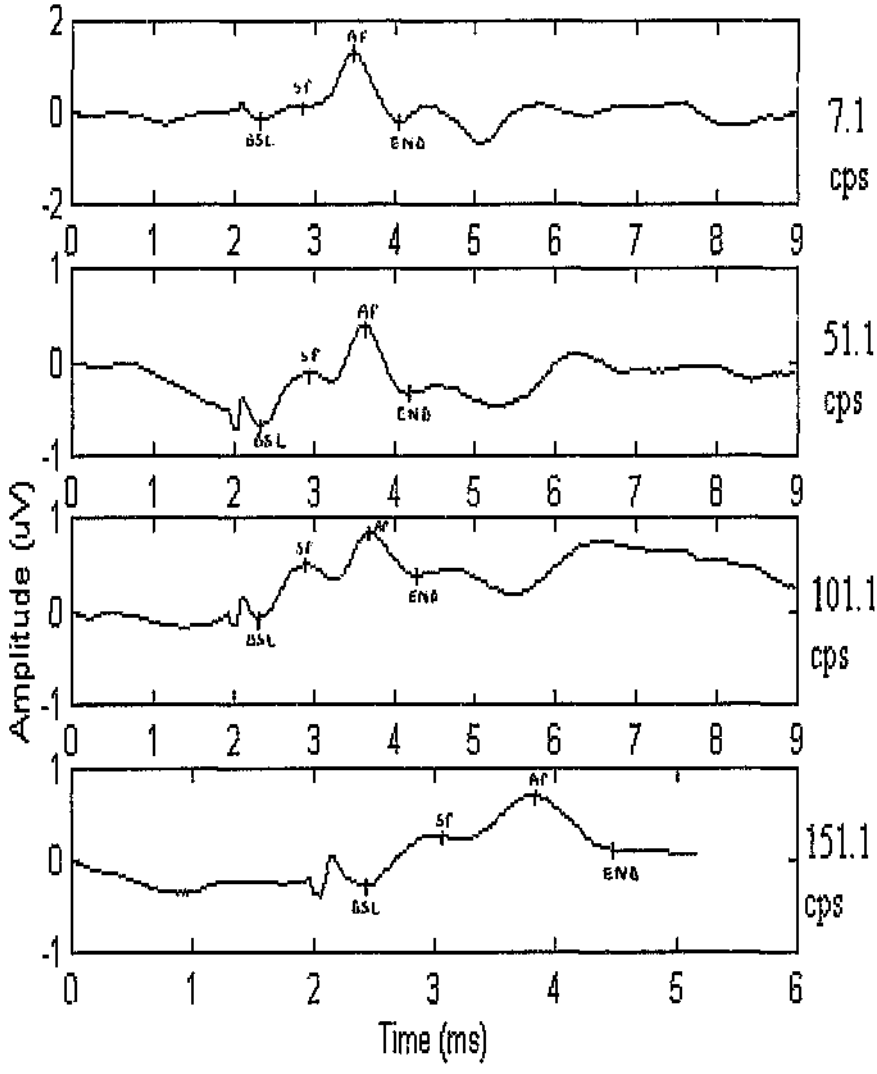


Table 4: The mean and standard deviations of all the ECochG components across the repetition rates for all subject groups

ECochG component	Age	Ear	n	7.1 cps	n	51.1 cps	n	101.1 cps	n	151.1 cps
SP latency (ms)	18-30	Left	20	0.87 ± 0.13	19	0.90 ± 0.13	19	0.95 ± 0.10	17	1.02 ± 0.24
		Right	20	0.88 ± 0.12	20	0.95 ± 0.09	17	0.94 ± 0.10	17	1.03 ± 0.22
SP latency (ms)	31-45	Left	14	0.88 ± 0.05	14	0.90 ± 0.10	13	0.88 ± 0.08	14	0.97 ± 0.12
		Right	14	0.86 ± 0.18	14	0.99 ± 0.13	12	0.99 ± 0.17	14	1.02 ± 0.10
SP latency (ms)	46-60	Left	17	0.90 ± 0.10	17	0.99 ± 0.09	17	0.95 ± 0.10	17	1.02 ± 0.24
		Right	17	0.85 ± 0.09	17	0.94 ± 0.09	17	0.94 ± 0.10	17	1.03 ± 0.22
AP latency (ms)	18-30	Left	20	1.54 ± 0.12	19	1.69 ± 0.12	17	1.73 ± 0.17	17	1.95 ± 0.23
		Right	20	1.56 ± 0.13	20	1.67 ± 0.11	17	1.77 ± 0.19	17	1.88 ± 0.23
AP latency (ms)	31-45	Left	14	1.53 ± 0.13	14	1.66 ± 0.15	13	1.71 ± 0.15	13	1.86 ± 0.11
		Right	14	1.57 ± 0.13	14	1.71 ± 0.14	12	1.8[illegible] 0.14	14	1.83 ± 0.25
AP latency (ms)	45-60	Left	17	1.57 ± 0.13	17	1.67 ± 0.16	17	1.73 ± 0.17	17	1.95 ± 0.23
		Right	17	1.53 ± 0.13	17	1.65 ± 0.12	17	1.77 ± 0.19	17	1.88 ± 0.23
SP amplitude (μV)	18-30	Left	20	0.08 ± 0.08	19	0.16 ± 0.09	17	0.19 ± 0.13	20	0.30 ± 0.20
		Right	20	0.08 ± 0.08	20	0.10 ± 0.07	18	0.15 ± 0.13	19	0.25 ± 0.40
SP amplitude (μV)	31-45	Left	14	0.13 ± 0.12	14	0.23 ± 0.19	13	0.27 ± 0.17	13	0.26 ± 0.23
		Right	14	0.04 ± 0.09	14	0.10 ± 0.27	12	0.13 ± 0.09	14	0.25 ± 0.45
SP amplitude (μV)	46-60	Left	17	0.13 ± 0.19	17	0.24 ± 0.23	17	0.19 ± 0.14	17	0.22 ± 0.23
		Right	17	0.10 ± 0.14	17	0.18 ± 0.23	17	0.16 ± 0.14	17	0.23 ± 0.17
AP amplitude (μV)	18-30	Left	20	0.59 ± 0.18	19	0.33 ± 0.18	16	0.29 ± 0.17	20	0.47 ± 0.23
		Right	20	0.54 ± 0.21	20	0.33 ± 0.16	17	0.31 ± 0.15	19	0.47 ± 0.53
AP amplitude (μV)	31-45	Left	14	0.66 ± 0.31	14	0.45 ± 0.32	13	0.32 ± 0.20	13	0.41 ± 0.26
		Right	14	0.51 ± 0.28	14	0.27 ± 0.24	12	0.22 ± 0.15	14	0.39 ± 0.59
AP amplitude (μV)	46-60	Left	17	0.47 ± 0.19	17	0.36 ± 0.20	17	0.26 ± 0.18	17	0.45 ± 0.42
		Right	17	0.42 ± 0.24	17	0.28 ± 0.19	17	0.20 ± 0.11	17	0.38 ± 0.31
SP/AP amp ratio (μV)	18-30	Left	20	0.31 ± 0.12	19	0.61 ± 0.34	16	0.80 ± 0.46	20	0.97 ± 0.81
		Right	20	0.29 ± 0.08	20	0.56 ± 0.18	17	0.73 ± 0.33	19	0.65 ± 0.23
SP/AP amp ratio (μV)	31-45	Left	14	0.31 ± 0.13	14	0.67 ± 0.55	13	0.96 ± 0.64	13	0.61 ± 0.23
		Right	14	0.29 ± 0.18	14	0.59 ± 0.25	12	0.77 ± 0.54	14	0.79 ± 0.38
SP/AP amp ratio (μV)	46-60	Left	17	0.33 ± 0.12	17	0.74 ± 0.50	17	0.90 ± 0.60	17	0.82 ± 0.31
		Right	17	0.32 ± 0.17	17	0.92 ± 0.85	17	0.95 ± 0.43	17	1.09 ± 1.20
Width (msec)	18-30	Left	20	1.67 ± 0.21	19	1.84 ± 0.26	16	2.00 ± 0.41	20	2.06 ± 0.41
		Right	20	1.63 ± 0.14	20	1.77 ± 0.26	17	1.93 ± 0.24	19	1.96 ± 0.17
Width (msec)	31-45	Left	14	1.71 ± 0.15	14	1.91 ± 0.20	13	1.98 ± 0.17	13	2.04 ± 0.16
		Right	14	1.64 ± 0.13	14	1.80 ± 0.26	12	1.89 ± 0.15	14	1.91 ± 0.22
Width (msec)	46-60	Left	17	1.68 ± 1.63	17	1.83 ± 0.19	17	1.87 ± 0.18	17	1.97 ± 0.14
		Right	17	1.69 ± 0.14	17	1.79 ± 0.18	17	1.90 ± 0.17	17	1.92 ± 0.36

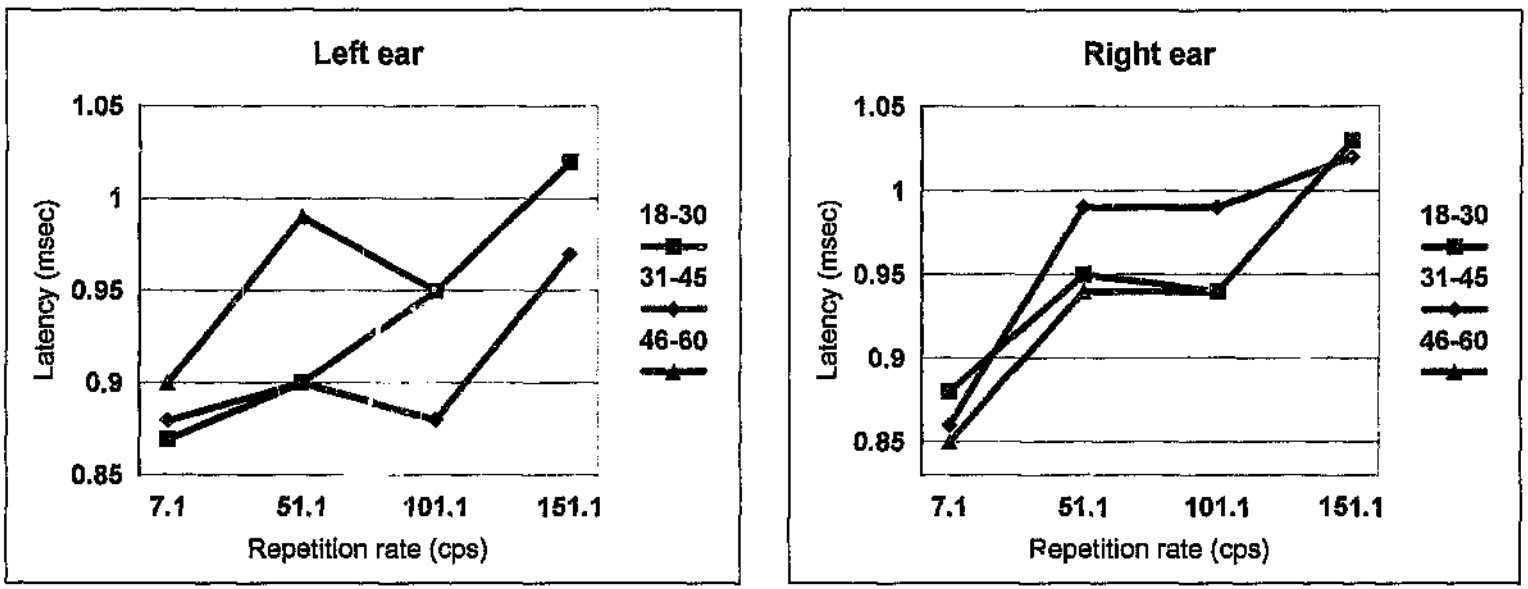


FIGURE 3: The SF I tactics for the left and the right ear across the repetition rates for all groups

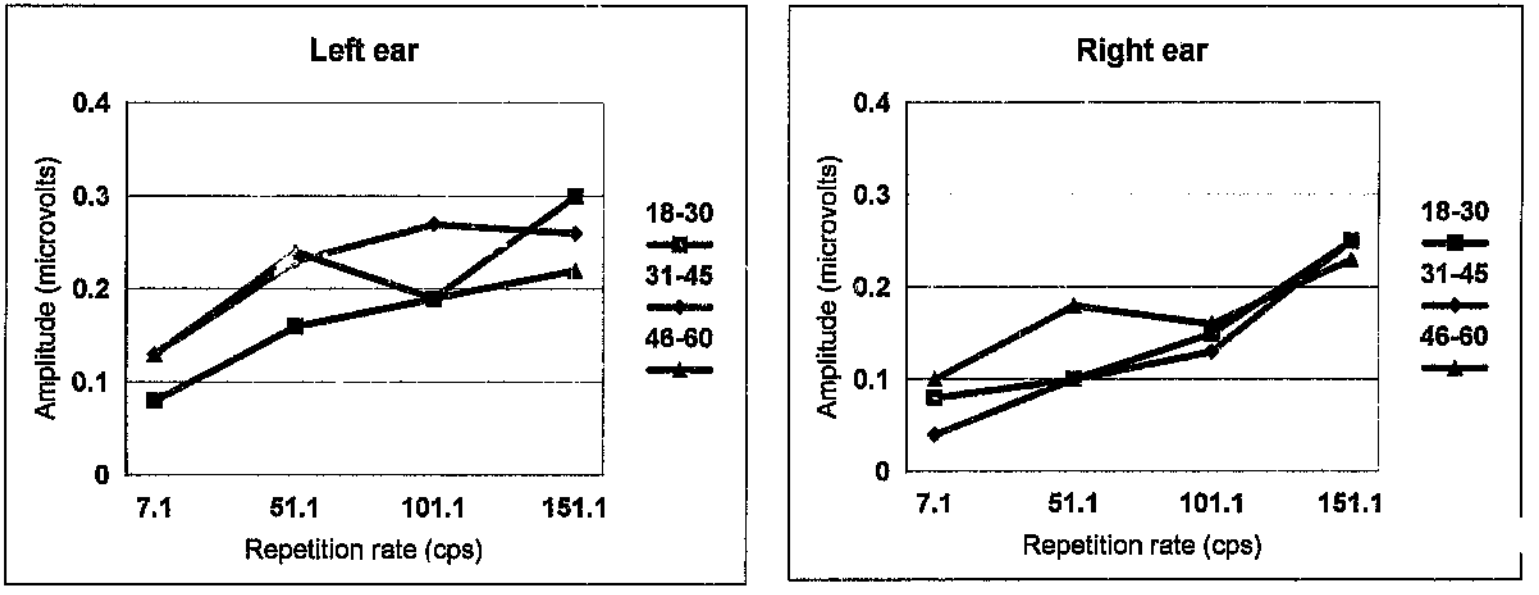


FIGURE 4: The SP amplitudes for the left and the right ear across repetition rates for all groups

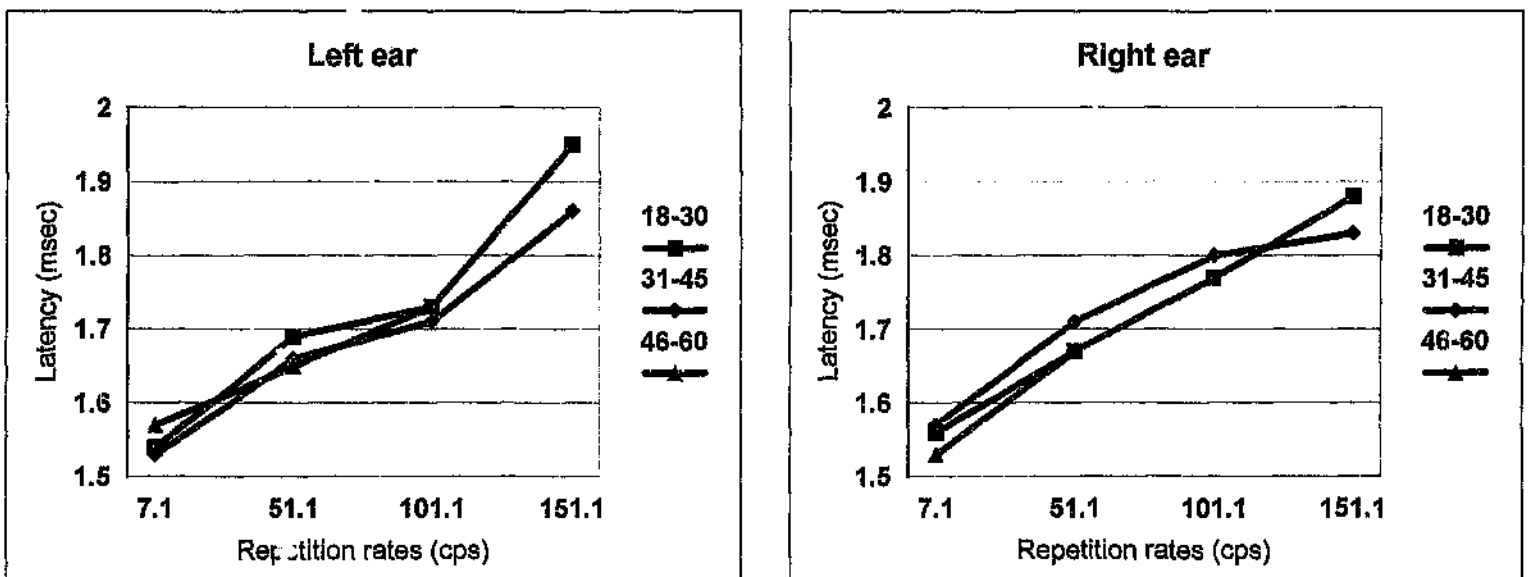
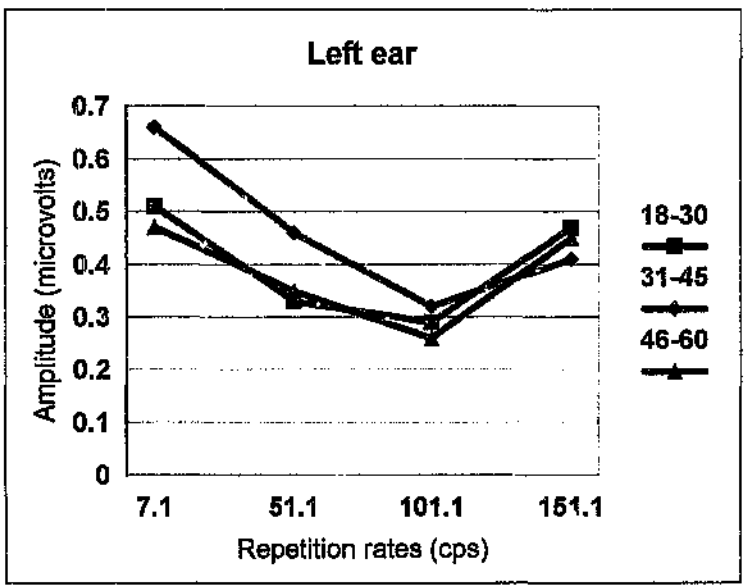


FIGURE 5: The AP latencies for the left and right ears across the repetition rates for all groups



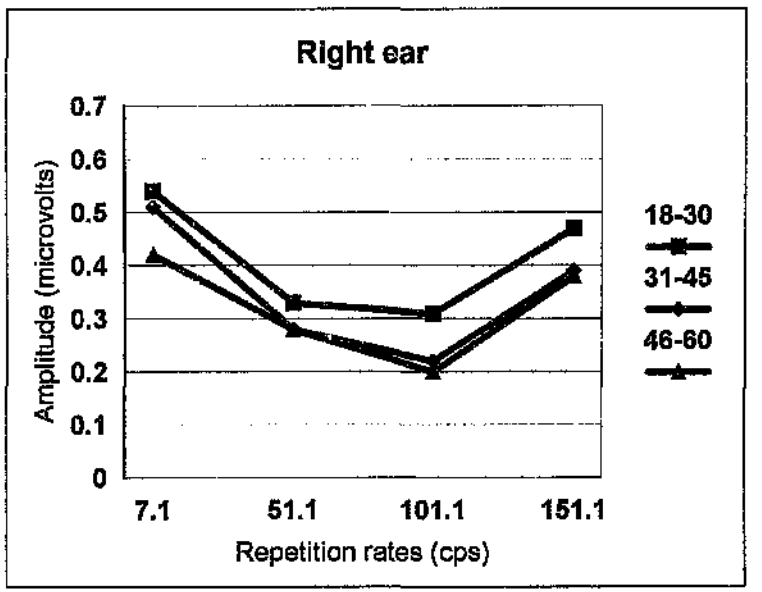


FIGURE 6: The AP amplitudes for the left and the right ear across the repetition rates for all groups

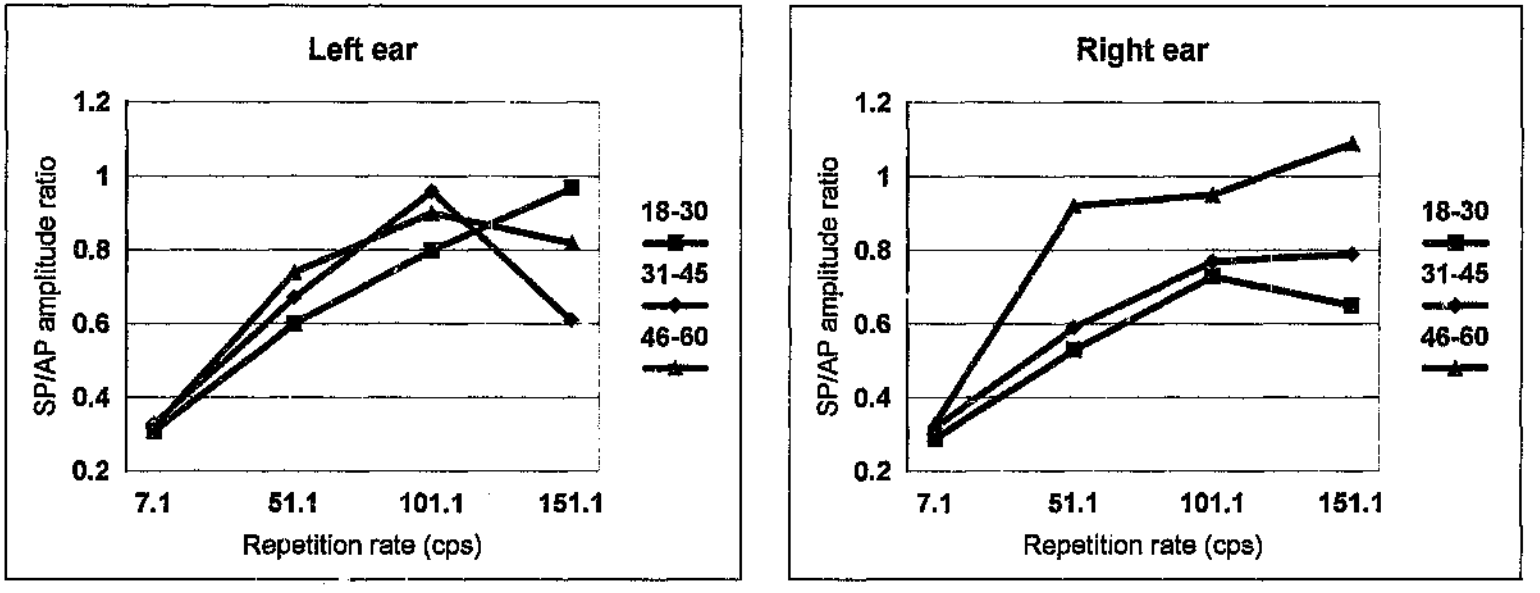


FIGURE 7: The SP/AP ratio for the left and the right ear across the repetition rates for all groups

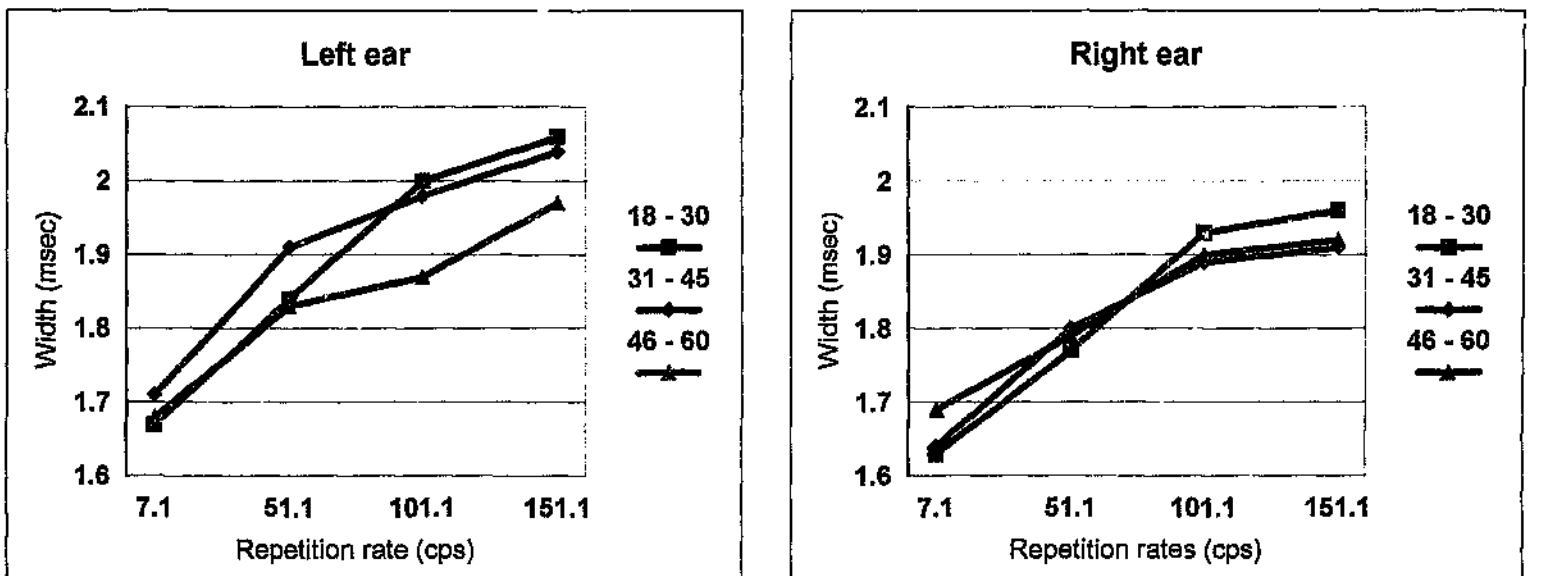


FIGURE 8: The waveform widths for the left and the right ears across the repetition rates for all groups

3.1.3 General waveform morphology

ECochG waveform morphology recorded at the standard stimulus repetition rate of 7.1 cps was similar to that described as being within normal limits in the literature, i.e. clear and easily definable waves with little evidence of interference or artefact (Ferraro, 1988).

The waveform morphology at higher stimulus repetition rates was not as clear and defined as at slow repetition rates, making waveform identification difficult. The waveform morphology showed increases in absolute wave latencies with increasing stimulus repetition rates, particularly of the AP component, and the amplitude of all components was reduced.

The SP and AP components were absent at stimulus repetition rates of 101.1 cps and 151.1 cps in 3 subjects in both ears. Absent ECochG components were predominantly recorded in 18-30 year old males.

3.1.4 Differences and correlations in ECochG components between ears, within each subject

Thirty-four percent of the measured correlations in individual ECochG components between ears were significant ($p<0.05$, $r>0.4$), whereas only 1% of difference comparisons were significant ($p<0.05$). The most frequent correlations were recorded for the SP and AP

latencies, whereas the most frequent differences were recorded for the SP amplitude and latency at 51.1 cps.

3.2 The comparison of the ECochG components between all four stimulus repetition rates.

Table 5 illustrates the repeated measures ANOVA results for each of the ECochG components in each ear, and each subject group. The differences between the four stimulus repetition rates at each respective measure are ranked and the clinical significance of these differences is denoted.

3.3 The effects of the age of the subjects on the ECochG components

Differences between the ECochG components between age groups are depicted in Table 6

The left ear's SP latency at 51.1 cps was the only variable that yielded statistical significance ($p<0.05$). However, it was not clinically significant. No specific differences were identified by Tukeys Honest Significance Difference Analysis Test.

3.4 The interaction effects of age and rate on the ECochG components

No interaction effects between the age of the subjects and the stimulus repetition rates for the ECochG components were recorded, using a three by four between groups repeated measures ANOVA ($p<0.05$).

Table 5: The repeated measures ANOVA and Friedman's ANOVA*, Tukeys HSD and Wilcoxon Matched Pairs* test results for the differences between each of the ECochG components at four stimulus repetition rates

ECochG Components	Age	Ear	ANOVA	Tukeys HSD	Clinical Significance
SP latency	18-30	Left (n=73)	p=0.06	-	NO
		Right (n=74)	p<0.05	1<4	NO
SP latency	31-45	Left (n=55)	p<0.05	1<4	NO
		Right (n=54)	p=0.09	-	NO
SP latency	46-60	Left (n=68)	p<0.05	1<4	NO
		Right (n=68)	p<0.005	1<4	YES
AP latency	18-30	Left (n=73)	p<0.000001	1<(3,4) (2,3)<4	YES
		Right (n=74)	p<0.000005	1<(3,4); 2<4	YES
AP latency	31-45	Left (n=54)	p<0.000001	1<(2,3)<4	YES
		Right (n=54)	p<0.000001	1<2<(3,4)	YES
AP latency	45-60	Left (n=68)	p<0.000005	1<(2,3)<4	YES
		Right (n=68)	p<0.000001	1<(3,4); 2<4	YES
SP amplitude	18-30	Left (n=73)	p<0.00001*	1<(2,3,4) * 2<4*	YES
		Right (n=74)	p<0.005*	(1,2)<4*	YES
SP amplitude	31-45	Left (n=55)	p=0.08	-	NO
		Right (n=54)	p<0.005*	1<(3,4)* 2<4*	YES
SP amplitude	46-60	Left (n=68)	p=0.14	-	NO
		Right (n=68)	p=0.42	-	NO
AP amplitude	18-30	Left (n=73)	p<0.0005	(2,3)<1 (2,3)<4	YES
		Right (n=74)	p<0.005	(2,3)<1	YES
AP amplitude	31-45	Left (n=54)	p<0.005	(2,3)<4 1<4	YES
		Right (n=54)	p<0.005	(2,3)<1	YES
AP amplitude	46-60	Left (n=68)	p=0.14	-	NO
		Right (n=68)	p<0.05	3<1	NO
SP/AP amp ratio	18-30	Left (n=76)	p<0.005*	1<(2,3,4)*	YES
		Right (n=75)	p<0.000001*	1<(2,3,4)*	YES
SP/AP amp ratio	31-45	Left (n=54)	p<0.0003*	1<(2,3,4)*	YES
		Right (n=54)	p<0.0005*	1<(2,3,4)*	YES
SP/AP amp ratio	46-60	Left (n=68)	p<0.005*	1<(2,3,4)*	YES
		Right (n=68)	p<0.05*	1<(2,3,4)*	NO
Width	18-30	Left (n=75)	p<0.00001	1<(2,3,4)	YES
		Right (n=76)	p<0.00001	1<(2,3,4)	YES
Width	31-45	Left (n=54)	p<0.0005	1<(2,3,4)	YES
		Right (n=54)	p<0.00005	1<(2,3,4)	YES
Width	46-60	Left (n=68)	p<0.00005	1<(2,3,4)	YES
		Right (n=68)	p<0.00001	1<(2,3,4)	YES

Key: 1 = 7.1 cps; 2 = 51.1 cps; 3 = 101.1 cps and 4 = 151.1 cps

n = the sum total of all the subjects across all four stimulus repetition rates

Table 6: The repeated measures ANOVA and Kruskal Wallis ANOVA* test results for differences between the three age groups and the ECochG components across the repetition rates for the left and right ears

ECochG Components	Ear	7.1 cps	51.1 cps	101.1 cps	151.1 cps
SP latency	Left	p=0.72	p<0.05	p=0.32	p=0.30
	Right	p=0.78	p=0.34	p=0.44	p=0.60
AP latency	Left	p=0.87	p=0.80	p=0.84	p=0.30
	Right	p=0.73	p=0.97	p=0.76	p=0.60
SP amplitude	Left	p=0.43	p=0.23*	p=0.28	p=0.43*
	Right	p=0.64	p=0.80*	p=0.81	p=0.81*
AP amplitude	Left	p=0.07	p=0.14	p=0.82	p=0.80*
	Right	p=0.35	p=0.91	p=0.10	p=0.36*
SP/AP amp ratio	Left	p=0.31	p=0.43*	p=0.31*	p=0.22*
	Right	p=0.18	p=0.67*	p=0.15*	p=0.53*
Waveform Width	Left	p=0.48	p=0.35	p=0.36	p=0.84
	Right	p=0.59	p=0.73	p=0.72	p=0.43

4. DISCUSSION

This study assessed fifty-one normal hearing subjects between the ages of 18-60, in three subject age groups of 18-30; 31-45 and 46-60 years. Subjects underwent ECochG testing, at four stimulus repetition rates of 7.1 cps; 51.1 cps; 101.1 cps and 151.1 cps. The ECochG components of SP and AP latencies and amplitudes, SP/AP amplitude ratio and waveform width, were analysed for statistical differences between ears, ages and stimulus repetition rates. Clinical differences were defined based on the effects the statistical differences would have on comparisons with clinical normative databases.

Results showed that all ECochG components were statistically repeatable ($p<0.05$) between repeat tracings. One third (34%) of the individual ECochG components correlated significantly ($p<0.05$, $r>0.4$), but only 1% of ECochG components differed significantly ($p<0.05$) between ears. The subjects' age had no affect on the ECochG values, but all ECochG components were affected by the faster stimulus repetition rates. Many of the ECochG components showed statistically significant changes on increasing stimulus repetition rates, but not all differences reached clinical significance. There were no significant interactions between the age and rate for any of the ECochG components.

The results will now be discussed in the order of the study's stated aims.

4.1 The measurement of the ECochG components at the different stimulus repetition rates, in three groups of subjects, grouped according to test ear and age

4.1.1 ECochG SP and AP latency and amplitude, SP/AP amplitude ratio, and waveform width measures

The specific values recorded for all the individual ECochG components for this study are recorded in Table 4. At slow stimulus repetition rates, the SP and AP latency, SP and AP amplitude and SP/AP waveform width measurements were within clinical ranges specified in the literature (Coats, 1981; Ferraro, 1988; Sass, Densert & Arlinger, 1998).

As the stimulus repetition rate was increased, the SP and AP absolute wave latencies increased, however these values still remained within the normal ranges specified in the literature (Coats, 1981; Ferraro, 1988; Sass, Densert & Arlinger, 1998). The SP amplitude showed fluctuation at faster stimulus repetition rates, but remained within the normal ranges, however the AP amplitude did not remain within normal clinical ranges at faster stimulus repetition rates.

The SP/AP amplitude ratio increased with faster stimulus repetition rates. However, SP/AP amplitude ratio measurements were abnormally enlarged in relation to normal clinical ranges at faster stimulus repetition rates (51.1 cps, 101.1 cps and 151.1 cps)

4.1.2 Waveform repeatability

All ECochG components were statistically repeatable, regardless of the stimulus repetition rate. The repeatability of all the ECochG components at slow stimulus repetition rates confirms findings by Margolis et al., (1995) and Rolland et al., (1993) who reported good test repeatability for both SP and AP latency and amplitude measurements. The repeatability of the ECochG components at higher stimulus repetition rates has not been previously investigated, and requires confirmation by other investigations.

4.1.2 General waveform morphology

Standard stimulus repetition rate of 7.1 cps recorded clear and easily identifiable waveform morphology with no evidence of degradation or artefact and could therefore be considered to be within normal limits (Ferraro, 1988). This finding supports the normal status of the test subjects at the time of testing. It also confirms other researchers findings of testing normal hearing subjects with no history of ear disease (Rolland et al., 1993; Sass, Densert & Arlinger, 1998).

The increases in absolute wave latencies, reduced amplitude and indistinct or absent components of the waveform morphology at high stimulus repetition rates is consistent with reports by Campbell & Abbas (1987) and Don, Allen & Starr (1977).

The absence of individual ECochG components at the higher stimulus repetition rates of

101.1 cps and 151.1 cps could be attributed to the loss of temporal synchrony and gross degradation of various ECochG components as suggested by Moore (1997).

4.1.3 Differences and correlations of the ECochG components between ears

The relatively low number of significant ($p<0.05$, $r>0.4$) correlations (34% of all possible correlations) recorded between individual ECochG components, between the ears, suggest that the ears' responses were only partially related to one another. The fact that the majority of correlations were between the SP latency between ears and the AP latency between ears is consistent with literature reports that ECochG latencies are more related between ears than amplitudes (Hall, 1992). Some degree of correlation between individual ECochG components within the same normal hearing subjects was expected, however factors such as the variability of the placement of the tympanic electrode on the eardrum (Eggermont, 1974; Coats, 1986) and some inherent random asymmetry between the left and right cochlea was also expected to contribute. As the ears' responses were not completely independent of each other, they were not treated as independent samples in this study.

Difference comparisons between individual ECochG components, between ears, showed only 1% of comparisons were significantly ($p<0.05$) different. Of the differences that were recorded, none occurred at the slowest repetition rate. This suggests that the ears' ECochG responses were of similar size between ears within individual subjects and opposes Coats (1981) and Chatrian, Walsh, Edwards, Lettich & Snyder (1985) who reported discrepancies between the right and left ECochG components at slow stimulus repetition rates. The

contradictory results between studies could be attributed to methodological differences however, in particular the use of extratympanic electrodes versus tympanic electrodes used in the current study.

4.2 The comparison of the ECochG components between all four stimulus repetition rates

4.2.1 SP latency

Only statistical differences ($p<0.05$) in the SP latency between the extreme stimulus repetition rates of 7.1 cps and 151.1 cps were recorded, but the poor clinical significance of these results suggests that the SP latency shows limited variation with changes in stimulus repetition rates. This finding partly supports Mourney, et al (1978), Coats (1981) and Soucek & Mason (1992), who found the SP latency remained stable at stimulus repetition rates as fast as 200 cps.

4.2.2 SP amplitude

The statistical and clinical significance of the increase in the SP amplitude in both ears for the 18-30 year old group, and in the right ear of the 31-45 year old group, at faster stimulus repetition rates suggests that the SP amplitude was only partially influenced by stimulus repetition rates. It partially agrees with literature reports of SP amplitude remaining stable at faster repetition rates (Mourney et al., 1978; Coats, 1981; Soucek & Mason, 1992).

Physiologically the increase in the SP amplitude seen in this study could be attributable to

additional energy generated by the SP generators, due to the active mechanical amplification of the travelling wave or the greater depolarisation of the sensory hair cells caused by increasing stimulus repetition rates (Pickles, 1988).

This study's findings of some changes in the SP amplitude with increasing stimulus repetition rates casts doubt on the conclusions of Rolland & Walsh (1994) who reported an overall increase in the SP amplitude of subjects with a confirmed perilymph fistula at increasing repetition rates, namely 11cps, 22cps, 45cps using transtympanic electrodes. However, their study did not report or refer to the effects of high stimulus repetition rates of the SP amplitude in normal subjects. The possibility that there could be some inherent change in the SP amplitude with increasing stimulus repetition rates limits Rolland & Walsh's (1994) technique of using the SP amplitude as a diagnostic tool.

Overall, the lack of consistent statistically and clinically significant changes in the SP latency and amplitude with increasing stimulus repetition rates for all groups, seen in this study and in literature reports, suggests that these variables remain mostly stable at fast stimulus repetition rates, but that minor fluctuations should not be ruled out.

4.2.3 AP latency

The statistically and clinically significant increase in the AP latency with faster stimulus

repetition rates confirmed previous investigators' findings (Terkildsen, Osterhammel & Huis in't Veld, 1975; Zollner et al, 1976; Mourney et al., 1978; Soucek & Mason, 1992). The repeated confirmation of the prolongation of the AP latency at increased stimulus repetition rates continues to strengthen the theory that the auditory nerve adapts to the increased stimulus repetition rate, as suggested by previous researchers (Moore, 1997; Soucek & Mason, 1992).

4.2.4 AP amplitude

The statistically and clinically significant decreases in AP amplitude between slow stimulus repetition rates and the initial faster repetition rates (51.1cps and 101.1cps) suggests that the eighth nerve has adapted to the stimulus due to excessive stimulation. This supports Mourney et al. (1978) and Coats (1981) who reported a decrease in AP amplitude as the stimulus repetition rate was increased and, again, supports the physiological phenomenon of adaptation to excessive stimulation (Moore, 1997; Soucek & Mason, 1992).

However, the significant increase in AP amplitude from stimulus repetition rates of 101.1 cps to 151.1 cps suggests that the auditory nerve may not always fatigue in a linear fashion to fast stimulus repetition rates, which has implications regarding the physiological understanding of the eighth nerve action potential. The following suggestions are speculative theories in the light of this study's results and the current physiological literature. The sudden increase in AP amplitude could indicate variations in the discharge

and firing rates of various neurons (Moore, 1997), as neurons have different discharge patterns and different critical parameters for discharge due to stimulus parameters, such as repetition rate and duration of stimulus (Moore, 1997). Alternatively, the increase in the AP amplitude could be a centrally mediated response to complex stimuli (Pickles, 1988; Moore, 1997), or the emergence of a ceiling effect at continually increasing stimulus repetition rates. However, this is uncertain due to the fact that stimulus repetition rates above 151.1 cps were not tested.

The increase in AP amplitude at fast stimulus repetition rates and the domination of the AP component at fast stimulus repetition rates observed in this sample remains largely unreported, however Coats (1981) reported that waveforms at very fast stimulus repetition rates consist primarily of the AP component, rather than the SP component. The domination of the AP component at very fast stimulus repetition rates could be attributed to the loss of synchrony during neural firing (Moore, 1997) or smearing of the waveform in time as a result of the broadening of the AP components, which is a compound action potential (Guyton, 1986; Sherwood, 1993). It is logical to conclude that at slow repetition rates the temporal synchrony of neural firing is enhanced resulting in a shortened waveform width, however at fast stimulus repetition rates, the neurons fire at separate times resulting in a broadened AP component that obliterates the SP component.

4.2.5 SP/AP amplitude ratio

The statistical and clinical differences in the SP/AP amplitude ratio with an initial increase in repetition rate, followed by stabilisation of the ratio at further faster repetition rates, suggests that the relative amplitudes of the SP and AP alters most dramatically with an initial increase in repetition rate. The stabilisation of the SP/AP amplitude ratio could possibly be attributed to different generator sites of the cochlea or separate responses of the same generator at high stimulus repetition rates as suggested by Moore (1997).

4.2.6 Waveform width

The findings of statistically and clinically significant increases in the waveform width were expected based on the prolongation of the AP latency at high stimulus repetition rates reported by Mouney et al. (1978). An increase in the waveform width is attributed to the general stability of the SP latency and the prolongation of the AP latency, which was observed statistically. The stability of the SP latency suggests that the cochlea shows limited adaptation, however the clinical changes in the AP latency suggest that the eighth nerve adapts rapidly to excessive stimulation. This supports a similar explanation provided by Soucek & Mason (1992).

4.3 Effect of age on the ECochG compone ts at the four stimulus repetition rates

No statistical differences between individual ECochG components, between the three age groups were recorded at any of the stimulus repetition rates. This shows that the ECochG components were stable between ages for subjects in this sample. These results only partially support Chatrian, et al (1985), who reported inconsistent age related differences for the ECochG components for normal hearing subjects.

Despite the lack of changes in the ECochG components with age, statistical analyses for the effect of stimulus repetition rates on the ECochG component were completed on each subject age group separately. This provided clinical applicability and paralleled the methods used by previous investigators (Coats, 1981, Chatrian et al., 1985).

4.4 Interaction effects of age and stimulus repetition rate on the ECochG components

The lack of interaction between age and stimulus repetition rate on the ECochG components suggests that the ECochG components are influenced exclusively by stimulus repetition rates in subjects between the ages of 18-60.

4.5 The creation of a normative database to allow research of high stimulus repetition rate ECochG in endolymphatic hydrops patients

This study has aimed to provide a larger and more controlled normative data base on the

effects high stimulus repetition rates on tympanic membrane electrocochleography among normal hearing subjects, than has been provided by the scientific literature to date. The repeatability of the EcochG components and the confirmation of the effects of high stimulus repetition rates will allow for clinical trials to be implemented.

5. CONCLUSION

This study has supplemented the paucity of studies regarding high stimulus repetition rate ECochG in normal hearing subjects. The study confirmed that the use of increasing stimulus repetition rates had significant statistical and clinical effects on the ECochG, in particular ECochG morphology, the AP latency and amplitude, SP/AP amplitude ratio and the waveform width. The SP amplitude and latency was the most resilient and stable ECochG component at increasing stimulus repetition rates, however, minor fluctuations were recorded. The ECochG morphology components remained stable across subjects between 18-60 years of age, despite the increased stimulus repetition rates.

These findings have confirmed existing viewpoints reported by Mourney, et al., (1978), Yagi & Kaga, (1979) and Coats, (1981), that the AP latency is prolonged, the SP latency remains largely unchanged, and waveform identification is difficult at fast stimulus repetition rates. The study, however, has conflicted with other viewpoints. It has highlighted that the SP amplitude does show minor fluctuations and the AP amplitude does not decrease in a linear fashion as previously reported (Coats, 1981). Subsequently current insight regarding the physiological functioning of the normal cochlea and auditory nerve has been reiterated.

6. CLINICAL IMPLICATIONS AND IMPLICATIONS FOR FURTHER RESEARCH

There are several important implications for this study. First, this study has provided the initial comprehensive documentation of tympanic ECochG on normal hearing subjects. This database will improve clinical implementation, as old normative data obtained by extra-tympanic and trans-tympanic electrode recordings will be replaced by new data using tympanic electrodes. This is particularly important in light of the increased popularity of tympanic electrodes in clinical practice.

Secondly, this study has provided a clinical database on normal hearing subjects that could be utilised for clinical trials of high stimulus repetition rate on diseased patients. These trials should include the comparison of both ECochG variables and the changes in general ECochG morphology. The degradation of waveform morphology recorded in normal subjects in this study, must be considered in patients with endolymphatic hydrops or Ménière's disease, as they may yield different responses.

The provision of a normative database for high stimulus repetition rates now provides the opportunity for further clinical trials in patients suffering from Ménière's disease, but present with normal ECochG results on the day of testing. The use of high stimulus repetition rates to elicit abnormal and/or degraded ECochG waveforms to improve the sensitivity and specificity needs to be ascertained. This technique would assist Audiologists

and Ear, Nose and Throat specialists to identify those patients suffering from endolymphatic hydrops or Ménière's disease who present with normal ECochG results on the day of testing. This could assist Ear, Nose and Throat surgeons in early diagnosis and treatment of the disease. In addition, the positive benefit of this technique could assist in monitoring the effectiveness of medication and the progression or improvement in disease status.

In addition, further research on a larger sample size, particularly in the smaller 31-45 year old group would be valuable, as it would assist in establishing conclusive profiles on the effects of increasing stimulus repetition rates for each component and normative data on all three subject groups.

Additional investigations with different subject, stimulus and recording parameters is needed, as the applicability and generalisation of these findings, is specific to the current protocol implemented in this study.

The finding in this study that the auditory nerve does not fatigue in a linear fashion indicates that this is still an area that requires ongoing research.

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