THE CLINICAL UTILITY OF THE MIDDLE LATENCY AND 40HZ AUDITORY EVOKED POTENTIALS IN AUDIOLOGICAL ELECTRODIAGNOSIS.

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SUMMARY.

The two electrophysiological tests currently favoured in the clinical measurement of hearing threshold are the brainstem evoked potential (BAEP) and the slow vertex response (SVR). However, both tests possess disadvantages. The BAEP is the test of choice in younger patients as it is stable at all levels of arousal, but little information has been obtained to date at a range of frequencies. The SVR is frequency specific but is unreliable in certain adult subjects and is unstable during sleep or in young children. These deficiencies have prompted research into a third group of potentials, the middle latency response (MLR) and the 40Hz responses.

This research has compared the SVR and 40Hz response in waking adults and reports that the 40Hz test can provide a viable alternative to the SVR provided that a high degree of subject relaxation is ensured.

A second study examined the morphology of the MLR and 40Hz during sleep. This work suggested that these potentials are markedly different during sleep and that methodological factors have been responsible for masking these changes in previous studies.

The clinical possibilities of tone pip BAEPs were then examined as these components were proved to be the only stable responses present in sleep. It was found that threshold estimates to 500Hz, 1000Hz and 4000Hz stimuli could be made to within 15dBSL in most cases.

A final study looked more closely at methods of obtaining frequency specific information in sleeping subjects. Threshold estimates were made using established BAEP parameters and this was compared to a 40Hz procedure which recorded a series of BAEPs over a 100msec. time sweep. Results indicated that the 40Hz procedure was superior to existing techniques in estimating threshold to low frequency stimuli.

This research has confirmed a role for the MLR and 40Hz response as alternative measures of hearing capability in waking subjects and proposes that the 40Hz technique is useful in measuring frequency specific thresholds although the responses recorded derive primarily from the brainstem.

Keywords: Middle latency response - 40Hz response - sleep - tone pip BAEPs - slow vertex response - audiometric threshold assessment.

To Mum and Dad.

ACKNOWLEDGEMENTS.

I would first like to thank my supervisor, Dr Lesley Jones for her guidance and support throughout this research project. Secondly, thanks to Professor Graham Harding, my associate superivisor for his expertise.

A big thank you to the entire technical staff of the Neurophysiology Unit at Aston especially to Paul Furlong for invaluable discussions and assistance.

I would also like to thank the students and staff of the Vision Sciences department who acted as subjects for me and in particular to those who took part in the all- night sleep studies for 'service beyond the call of duty'.

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CHAPTER 1

THE DEVELOPMENT OF EVOKED RESPONSE AUDIOMETRY (ERA).

1.1 HISTORICAL PERSPECTIVE.

The earliest observation of sensory stimuli altering the ongoing electro- encephalogram (EEG) dates back to Richard Caton (1875). In his pioneering paper, 'The electric currents of the brain', Caton described the way in which sensory imput altered the ongoing activity of the brain producing what we now call an evoked response. Caton further attempted to localise sensory areas in the brain of rabbits and monkeys, having some success in recording responses to light but poor results to auditory and olfactory stimuli.

Working at the University of Cracow in Poland, Adolf Beck (1890,1891) submitted his doctoral thesis on cortical responses to sensory stimulation. Beck successfully replicated the findings of Caton and was also able to demonstrate an auditory response to a shouted voice from electrodes placed over the temporal regions of the brain. At the turn of the century, a Russian named Larionov performed an ambitious series of experiments. Recording intracranially from dog brains, he found distinct auditory responses to tones of different frequency generated by three tuning forks. Larionov differentiated three distinct response areas on the temporal lobes thus being the first to demonstrate the existance of frequency selectivity within the auditory cortex. Since recording technology was not sufficiently advanced during the late nineteenth century and amplification of these tiny voltages produced by the brain in response to auditory stimulation was not possible at this time, the data produced by these pioneering researchers lacked convincing support. In addition, Caton, Beck and Larionov had no cameras with which to photograph their results (for a comprehensive review of the earliest literature refer to Brazier, 1984).

The twentieth century brought with it the necessary advances in recording technology and

therefore stronger support for the physiological basis for evoked potentials was provided (Berger, 1929). Pauline Davis (1939) and her husband Hallowell provided the first contribution of the english speaking world to the subject of evoked potentials. They described sound as evoking a triphasic wave (with a periodicity of around 70 msec.) which could be recorded from the scalp at around 100-200 msec. after the delivery of an auditory stimulus (Davis, 1939).

The evaluation of hearing through observing sound induced changes within the EEG (Gidoll, 1952; Perl et al., 1953) was greatly enhanced with the advent of averaging techniques. The first application of this principle was made by Dawson (1947). He developed a photographic superimposition method whereby corresponding (and concurrent) epochs of EEG after auditory stimulation were visually superimposed. With the development of increasingly more powerful analogue computer systems, it was soon possible to improve Dawson's photographic superimposition technique by using a mechanical rotator synchronised to the presentation of the stimulus to calculate the resultant average of successive samples (Dawson, 1950,1951,1954). Random activity, unrelated to the stimulus would attenuate over a sufficiently large number of averages and the 'time-locked' evoked response would be enhanced.

As digital computing systems emerged in the 1950s, dedicated electronic equipment was produced for the first time. The clinical applications of evoked potentials (the term 'evoked response' will be used interchangably in this thesis), have now become established over the ensuing decades as a powerful technique for objectively assessing the body's sensory systems. The audiological significance of this is the possibility of measuring auditory sensitivity in a manor that is independent of patient participation. Neurologically speaking, auditory evoked potentials have also allowed the possibility of non-invasively investigating the integrity of the brainstem and diagnosing retrocochlear pathology.

The possible clinical applications of evoked responses were very quickly realised, but still more powerful recording systems were required in order to reliably record these potentials. Up until the advent of EEG recording, investigations of auditory function and hearing deficit

had depended upon subjective inferences made by the patient. Whilst this was adequate in a large majority of clinical investigations, certain groups of patients were untestable by conventional means. These included young children, unable to actively participate in the experimental procedure because of their age or competence and mentally and physically handicapped patients of all ages. Evoked responses offered the possibility of objectively measuring the auditory integrity in these groups served poorly by existing techniques.

Averaging procedures have now been used extensively to categorise the brain's response to sound stimulation from the level of hair cells in the cochlea to the responses generated from the auditory cortex. In the remainder of this chapter, the auditory responses as they stand today will be catagorised and the areas in which these potentials have been used clinically, highlighted. The chapter will conclude with a summary of the instances in which existing responses are limited and the experimental aims of this thesis examining the ways in which techniques might be improved.

1.2 THE CLASSIFICATION OF AUDITORY EVOKED RESPONSES.

The most widely accepted classification of auditory evoked potentials currently in use has defined the auditory evoked responses on the basis of their latency (Picton et al., 1974). The importance of this work was that it served to give some structure to the emerging science of electro- physiological audiology and the framework laid down by Picton and collegues is now widely if not universally accepted. Picton et al. (1974) identified 15 components of the auditory evoked potential arise after auditory stimulation and classified these potentials into three successive groups. Early latency components (0-8 msec.), middle latency components (8-40 msec.) and long latency components (40-290 msec.). According to Picton and collegues, six early latency , five middle latency and four long latency components may be recorded from a vertex to ipsilateral mastoid scalp derivation.

Picton's classification system does not include later auditory potentials which have since been defined (occurring after 290 msec.). These responses reflect the psychological state of the

subject and may more properly described as event related potentials. The P300 response is a positive component arising at around 300 msec. in response to a stimulus which requires active (conscious) detection on behalf of the subject. For example the delivery of a novel stimulus amonst a train of uniform stimuli or alternatively the omission of a stimulus within such a series will elicit the P300 response (Picton and Hillyard, 1974). The contingent negative variation (CNV) is a negative d.c. shift which occurs between two stimuli if the second stimulus is dependant (contingent) upon the occurrence of the first and when the second requires a perceptual or motor decission. It is thus a reflection of expectancy on behalf of the subject (Jones, 1979). Both the P300 and the CNV responses give insight into the psychological correlates of auditory cognition but further discussion of these lies outside the scope of this thesis. Fig 1.1 shows the characteristic morphology of the early, middle and long latency groups of potentials recorded to a 60dBSL monaural click presented at 1/ sec. The filter bandpass is 10-3000Hz for the early and middle components and 1-500Hz for the long latency components. 1024 stimulus presentations have been summed for each trace and the electrode derivation is from vertex to ipsilateral mastoid (reproduced from Picton et al., 1974).

1.21 Early latency components (0-8 msec.).

1.21 a The cochlear microphonic potential.

Also occurring within the first 8 msec. after stimulus onset is a potential which directly replicates the waveform of the stimulus. This potential, the cochlear microphonic (CM), is a non-neural response thought to be the result of mechanical deformations of the hair cells upon the basilar membrane. It is of little interest in audiological electrodiagnosis as the response is purely a function of the stimulus characteristics and has no discernable threshold. The CM will only be recordable if the stimulus is delivered in one phase i.e. positive (compression) or negative (rarefaction). If an alternating stimulus is presented, the CM will be effectively cancelled out and consequently wil not be visualised. A further disadvantage of recording the CM is that, due to its origin, it may only be reliably recorded trans-tympanically requiring an invasive medical procedure.

Figure 1.1 Morphology of early, middle and late auditory evoked responses (Picton et al.,1974).

1.21 b The frequency following response.

As with the cochlear microphonic, the frequency following response (FFR) is a potential which mimics the frequency of the stimulus delivered. Unlike the CM, the FFR is considered to be a neural response to auditory stimulation rather than a purely acoustic phenomenon (Moushegian et al., 1973, 1978; Sohmer and Pratt, 1977; Sohmer et al., 1977) and therefore, if an alternating stimulus were presented, the FFR would be double the frequency of the stimulus and not cancelled out as with the CM. The localisation of the FFR is also different to that of the CM. The latter can only be recorded from around the ear whilst the FFR is recorded maximally at the vertex, again suggesting and supporting its neural origin. The latency of the FFR (around 6 msec.) has lead some authors to suggest that it originates from the inferior colliculus (Davis and Hirsch, 1976). Other workers however have suggested that the FFR has a more caudal origin (Gardi et al., 1979). In clinical audiometry the FFR has been shown to be of limited clinical utility. The reasons for this are twofold. Firstly, it is quite variable between subjects and secondly, it usually can only be seen clearly at high intensities and therefore is not appropriate in the assessment of audiological threshold. Its neurogenic origin means that if a FFR is identified, the clinician might conclude that the stimulus has been heard and elicited a response from a patient. However, the response's variability means that the converse is not the case.

1.21 c The brainstem auditory evoked potential (BAEP).

The series of positive and negative deflections occurring within the first 8 msec. after auditory stimulation is thought to represent an activation of the ascending auditory brainstem pathway (Sohmer and Feinmesser, 1967; Sohmer et al., 1974 ; Sohmer et al., 1977 ; Jewett, 1970; Jewett and Williston, 1971; Picton et al.,1974). These authors suggested that the first, vertex positive wave, wave I originated from the auditory nerve itself. This was deduced from the observation that wave I was recorded as negative at the mastoid ipsilateral to stimulation and positive at the vertex. Wave I attenuated rapidly and disappeared altogether as the recording derivation moved away from the ear. Depth recordings and lesion studies (Jewett, 1970;

Jewett and Williston, 1971; Starr and Hamilton, 1976; Buchwald and Huang, 1975) also confirmed this conclusion as to the origin of wave I. Waves II-VI of the early response are less easily defined but have been attributed to far field recording of the summation of multiple generators from the auditory brainstem pathway from the cochlear nucleus to the lateral lemnisci and inferior colliculus (Jewett and Williston, 1971; Picton et al., 1974). Since its characterisation during the late sixties and seventies, the BAEP has been proved to be a reliable and robust tool in the electrophysiological diagnosis of neurological and audiological deficit. It therefore currently represents the test of first choice in most modern, clinical environments. Figure 1.2 shows the relationship with stimulus intensity of the BAEP.

1.22 Middle latency responses (8-40 msec.).

To date the most problematic of the auditory evoked potentials, the middle auditory components (8-40 msec.) have been the source of debate since their initial discovery by Geisler et al. in 1958. Since the MLR and its properties are the central area under investigation in this thesis, this section is just intended to introduce the components and highlight the controversy that has surrounded them. Originally, the middle latency auditory evoked potentials were attributed to neurogenic activity deriving possibly from the thalamus and/or the primary auditory cortex (Geisler et al.,1958; Goldstein and Rodman, 1967; Ruhm et al., 1967; Goff et al., 1969; Mendel and Goldstein, 1969a). Audiologically, they were proposed as an effective, objective measurement of auditory threshold. However, despite some encouraging reports, the MLR has never gained full clinical acceptance. The reasons for this are that the response has not been found to be as reliable to record as the BAEP or other, longer latency potentials (described in section 1.23).

As shall be discussed now, the variability of the MLR has been attributed the interaction between neurogenic and myogenic elements lying within the 8-40 msec. latency range.

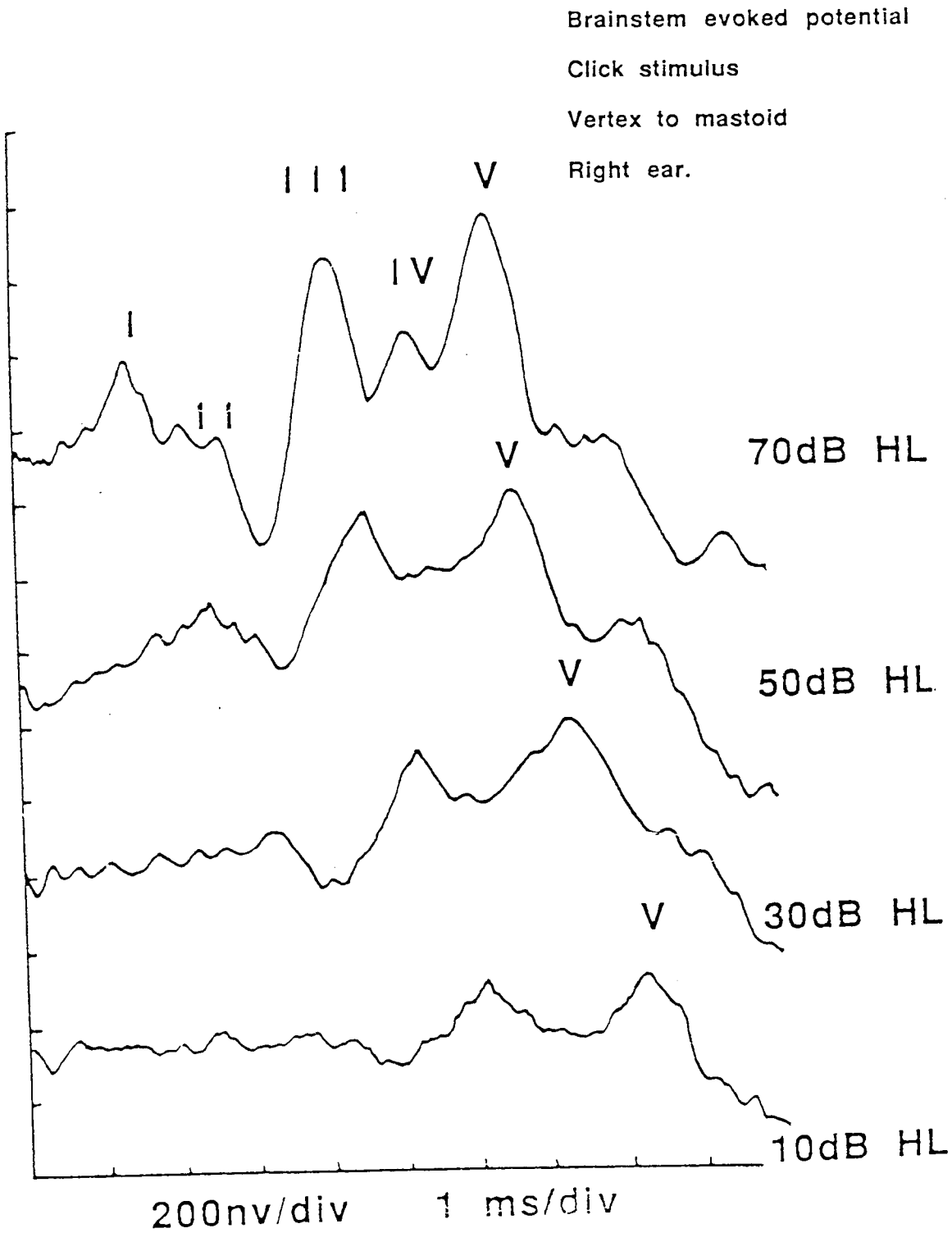

Figure 1.2 The effect of reducing stimulus intensity upon the BAEP.

1.22 a Myogenic components lying within the middle latency range.

It is not suggested that the MLR is uniquely suceptable to contamination from muscular artefact. If myogenic activity is too high, the signal (evoked response) to noise (non time-locked background activity) ratio is reduced and as a result all evoked responses are degraded in clarity and hence less easy to visualise. However, it was initially thought that time-locked responses, purportedly deriving from the vestibular system (and not the cochlea), were the sole source of components within the 8-40 msec. latency range (Bickford et al., 1964; Borsanyi and Blanchard, 1964).

In addition, a further more localised myogenic response has been reported within the 8- 40 msec. latency range after presentation of an auditory stimulus (Kiang et al., 1963). This post auricular muscle potential (PAMP) is thought to be mediated by the cochlea and ascending brainstem pathway to the level of the lateral lemnisci, but reflects subsequent activity of the facial (VIIth cranial) nerve serving the post-auricular muscle (Gibson, 1978). This response to auditory stimulation represents a mechanism by which the ear can physically orientate itself in the direction of a sound stimulus. This adaption is of great importance in the animal kingdom but is more vestigial in humans.

Fig. 1.3 examines more closely the myogenic influences effecting responses within the 8-40 msec. latency range (the MLR). Figure 1.3 a illustrates the apparent enhancement of the 8-40 msec. responses when the activity of scalp musculature is increased through traction (Bickford et al., 1964) in comparison to a much smaller response recorded after the administration of curare, a neuromuscular blocking drug. This finding suggested to some authors that the MLR was infact of myogenic origin and did not reflect auditory (cochlear) neural activity. Fig 1.3 b shows the specific effect upon the neurogenic MLR caused by increased activity of the post-auricular muscle (Yokoyama et al., 1987). This response is recorded from vertex to ipsilateral mastoid with a bandpass of 10Hz -1kHz with a click stimulus (0.1 msec. duration) delivered at 10/sec. The figure shows that a large positive - negative deflection occurs at around 15 msec. in the waking state and that this component is not present if the subject is more fully relaxed or asleep. Therefore, this so- called post-auricular

Figure 1.3 a The effect of enhanced myogenic acitivity upon the morphology of components in the 8-40 msec. latency range (Bickford et al., 1964).

Figure 1.3 b The post-auricular muscle potential (Yokoyama et al., 1987).

muscle response occurs over a similar latency range to the middle components of the neurogenic MLR. This means that, if subject relaxation is not adequately ensured, then the PAMP (in addition to a general increase in the 'noise' of the response) can be superimposed upon the MLR in certain subjects. The relative contributions of the auditory pathway and scalp musculature to the middle latency responses (originally known as the early responses), have been debated since their initial discovery by Geisler et al. (1958). The greater reliability of the brainstem evoked potential, occurring in the first 8 msec. after stimulus onset (Jewett and Williston, 1971) and the long latency potentials (see below), 40-300 msec. (Davis, 1939, Davis and Zerlin, 1966, Rapin et al., 1966), in certain populations left the MLR with no obvious clinical application. In addition to the controversy that surrounds the generators of the response, there has been slow acceptance of the MLR as a viable clinical tool due to methodological and subjective conflicts over correct recording procedures which have arisen in the literature. To date, the most enthusiastic support for the MLR has been forthcoming from Mendel, Goldstein and co-workers (Goldstein and Rodman, 1967; Mendel and Goldstein, 1969 a and b; Madell and Goldstein, 1972; Mendel and Kupperman, 1974; Mendel et al., 1975). Other workers have expressed doubts as to the clinical viability of the MLR. These doubts concern the most appropriate recording parameters (such as filter bandpass and stimulus characteristics) for recording the response (Scherg, 1982; Kavanagh et al., 1984), the equivocal effects of arousal level (Mendel et al., 1975; Davis et al., 1983; Erwin and Buchwald,1986a;Kavanagh and Domico, 1986) and the effects of age and maturation on the MLR (Suzuki et al. 1983b, Okitsu, 1984; Kraus et al., 1987 a, b and c). Chapter 3 deals with these specific effects and the consequences of their interaction upon the MLR in detail.

1.22b The 40Hz steady- state evoked potential.

Despite the reported difficulties with recording a reliable middle latency response highlighted above, interest in the response has increased in recent years with the development of the 40Hz response (Galambos et al., 1981). This is a steady-state potential which is produced by matching the repetition rate of the stimulus to the intrinsic frequency of the combined BAEP and MLR (i.e. 40Hz) waveform (Fig. 1.4). This causes a superimposition of successive MLR

Figure 1.4 The generation of the 40Hz steady state potential by the superimposition of successive BAEP and MLR transients to stimuli delivered at 40 times per second (Galambos et al., 1981).

transients thus producing a larger response which, it has been suggested, is easier to detect near audiometric threshold than the ordinary MLR (Galambos et al., 1981; Brown and Shallop, 1982; Osterhammel et al., 1983). Evaluation of the audiological applications of the 40Hz response has been central to the research carried out in this thesis.

1.23 Long latency auditory evoked potentials (40-290 msec.).

The long latency potentials were first recorded by Davis (1939). Although maximally recorded at the vertex, the exact generators of this response has been the source of some debate with some researchers claiming that they derive from the primary auditory cortex situated around the Sylvian fissure (Vaughan and Ritter, 1970; Peronnet et al. 1974; Cohen et al., 1982). Other workers have suggested that this response represents a more widespread cortical activation (Davis, 1939; Cody et al., 1964; Davis and Zerlin, 1966; Kooi et al. 1971; Picton et al., 1974; Streletz et al., 1977).

The clearest evidence to date indicates that the long latency potentials are in fact maximal at the vertex (Woods and Wolpaw, 1982 a and b; Scherg and von Cramon, 1986) and therefore, this response is also commonly known as the slow vertex response (SVR) or simply, the vertex potential. Figure 1.5 shows the effect of varying stimulus intensity upon the SVR. The good correlations reported between the vertex potential and audiometric threshold has meant that this response has been used extensively in the clinical environment. It is successfully recorded to click, tonal and even verbal stimuli and as such the vertex potential may give frequency specific information concerning cochlear integrity. However, since the SVR is believed to derive from multiple generators within the cortex (Zerlin and Naunton, 1974; Jones, 1979), its morphology and clarity depends upon considerable integration from within a large and varied population of cortical neurons which are affected by both subjective variables and stimulus characteristics. The most notable subjective variables which have been shown to detrimentally affect the detection of the vertex potential are, level of arousal (Weitzman and Kremen, 1965; Ornitz et al., 1967; Osterhammel et al., 1973) and age (Cody and Townsend, 1973; Goodwin et al., 1978). The variability of the SVR under certain

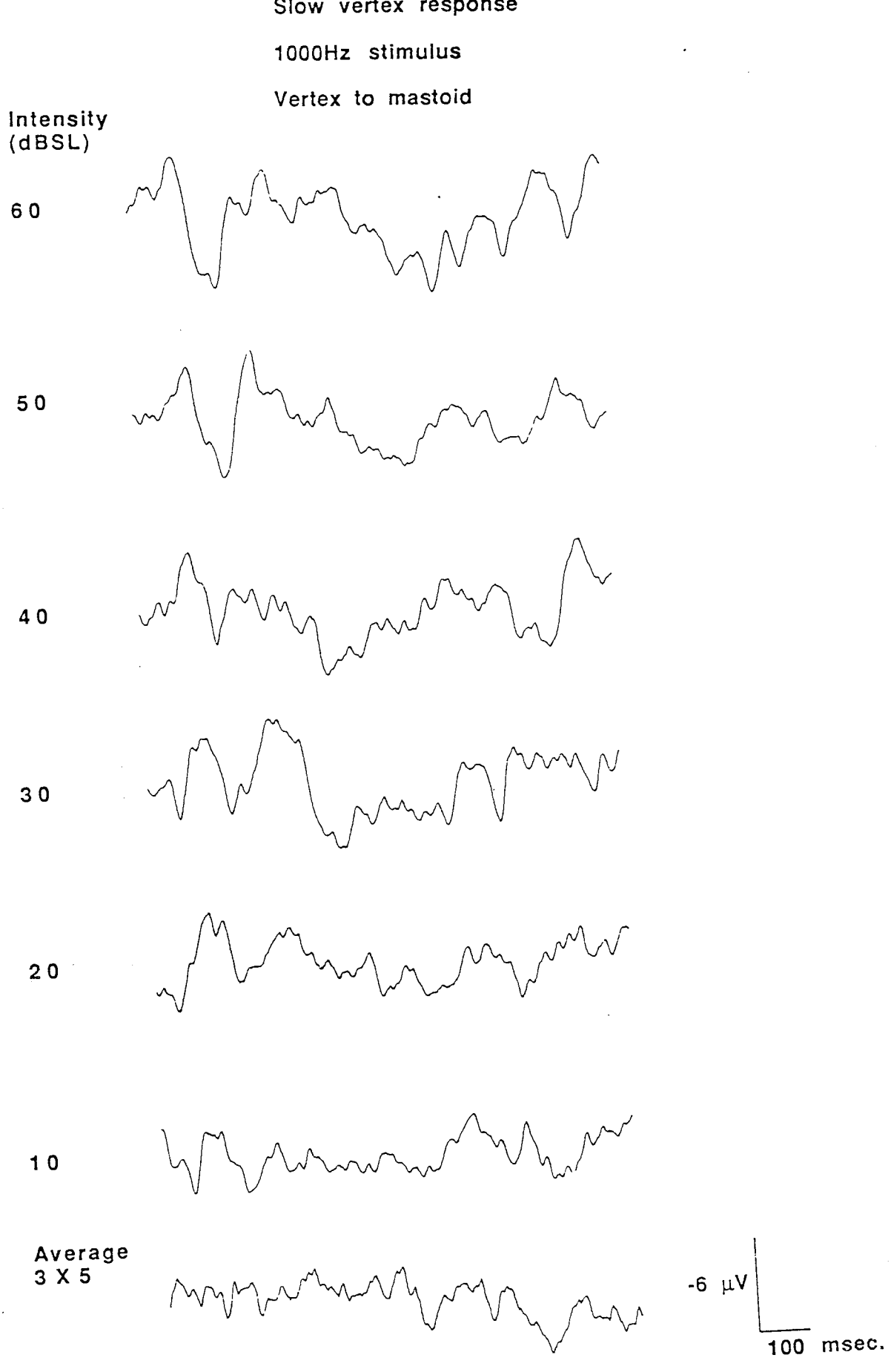

Figure 1.5 The effect of reducing stimulus intensity upon the vertex potential.

experimental conditions, has limited its clinical reliability for certain subject groups (Davis, 1968). Having now introduced the principal auditory evoked potentials, the following section shall to illustrate the areas in which evoked response audiometry can offer an aid to the clinican in the diagnosis of hearing losses in both adult and child populations.

1.3 THE ROLE OF EVOKED RESPONSE AUDIOMETRY (ERA) IN THE OBJECTIVE ASSESSMENT OF HEARING.

Firstly, it is important to define what is exactly meant by the 'objective assessment' of hearing. The electrophysiological procedures described, are objective in sense that the patient plays no active part in the production of the response. However, the interpretation of the value and reliability of the evoked potentials necessarily depends upon subjective judgements made by the clinician. Therefore, evoked responses audiometry (and indeed other modalities of evoked potential) effectively means the removal of subjectivity from the control of the patient placing it within the hands of the experienced clinician.

Jerger (1987), in a historical review of the impact made by evoked response audiometry (ERA), saw the following specific application of these techniques as being of paramount importance:

> *" I believe that for audiologists the most important influence that evoked potentials have had is simply the incredible leap forward it has given us in the early identification and early quantification of hearing loss in babies and small children."*

Currently this is the clinical population served least well by existing techniques of audiological measurement in terms of measuring frequency specific responses. The significance of prompt diagnosis at an early age is so that learning difficulties that can result from deafness might be rectified through specialised tuition as soon as possible. Goodman et al. (1964) defined this requirement in the following terms:

" If we are to teach (the deaf) normal speech, some method of hearing (assessment) must be discovered and instituted, if possible by 6 months of age when babbling normally begins in a child. If the deafness so identified is not absolutely complete, we can use, through amplification and education, any remaining cochlear responses. If the deafness is complete, we can aim at the establishment of some other method of extra-cochlear sound reception and transmission and exploit other sensory channels to help cope with impairment ".

A second major consideration is the use of auditory evoked potentials in the assessment of the mentally and physically handicapped. In these groups, lack of the appropriate behavioural responses might be the result of an auditory defect, an inability to respond or alternatively a central problem relating to the handicap. Differentiation between these two causes is of great importance in order that the correct management of the patient is initiated. Mis-diagnosis of deafness as apparent mental handicap can result in the inappropriate treatment of a patient who has full possession of his/her faculties but has a sensory hearing loss. Further important areas in which ERA is potentially useful is in the diagnosis of psychogenic deafness and in medico-legal cases in which subjective responses may be influenced by the prospect of compensation (financial reward).

Evoked potential audiometry (ERA) has developed in recent years as a powerful objective assessment of audiological and neurological function. Audiologically, ERA has given information about the integrity of the periphral auditory system (cochlea) and the nature of its response to sound delivered at different intensities and frequencies. ERA has provided a valuable addition to the tests of hearing function available to the clinician for both adult and infant populations.

1.31 The use of ERA in infant populations.

Firstly, for neonates and young children unable to actively participate in conventional test procedures, evoked responses are valuable in the prompt diagnosis of peripheral hearing loss (Davis, 1976; Schorn and Stecker, 1988). Speech and language development relies upon the auditory system functioning correctly from a very early age. If cochlear hearing losses are not compensated for very rapidly during this critical period of growth, perhaps

with the prescription of an appropriate hearing aid, a child's subsequent development might be significantly impaired. Since a young child is unable to report its perception of sound to the clinician, techniques such as startling the baby and distraction testing are used to provide an estimate of hearing function and indicate if the child has a crude orientation reaction to an auditory stimulus. Since even these rough procedures cannot be reliably used in children under six months of age, auditory evoked potentials have provided a much needed more refined objective assessment of hearing in the newborn. Secondly, ERA has been of considerable use in the detection of possible deafness in children who are mentally handicapped with the additional possibility of deafness compounding their difficulties. Thirdly, evoked responses have been used to investigate children with deafness of psychogenic origin and no obvious physiological basis. Lastly, children with behavioral disorders such as autism or behavioural difficultes (i.e. hyperactivity) who could not be relied upon to respond accurately to conventional techniques have been assessed using ERA.

In addition to the confirmation of a peripheral hearing losses (either conductive or sesori-neural) in young children, auditory evoked potentials may be used to assess deafness originating from a central, neurological impairment of the auditory system (perhaps due to a space occupying lesion present within the brain or brainstem or alternatively pressure upon auditory nerve fibers arising from an extrinsic tumour). For such children a hearing aid would provide no benefit and other procedures to either surgically correct the defect or improve the child's capacity for learning if this is not possible, must be implemented.

1.32 ERA and adult audiological diagnosis.

In adults, as in a much younger population, ERA is of considerable use in the diagnosis of psychogenic deafness and in the assessment of the hearing capabilities of patients with mental or behavioral difficulties if this has not been assessed in childhood. Objective auditory testing in adults has, in addition, proved a valuable asset in the area of

medico-legal audiometry. This branch of audiology is concerned with the accurate diagnosis of adult patients who claim that their hearing has been adversely effected by excessive exposure to noise at their work-place. A cochlea that has been damaged by excessive exposure to loud noise will exhibit high frequency loss with low frequencies remaining within normal limits. As the patient stands to gain financial reward from his responses if his case is proven, it is essential that the clinician is able to use a completely objective procedure over which the patient can exert no conscious control. Objective audiometry may be of considerable use in medico-legal work in corroborating or rejecting a diagnosis of noise induced hearing loss as distinct from simple maturational presbycusis. Often a patient will be referred for evoked response audiometry if the clinician finds inconsistant or contradictory results to other audiological investigations. ERA should not be considered as an alternative to existing audiometric testing. Conventional, subjective procedures are favoured in the majority of cases because their greater accuracy, relative low cost and shortness of test duration. ERA is an expensive and time consuming procedure to implement and is certainly no more accurate (perhaps less so) than existing techniques of audiological (as opposed to neurological assessment) in a cooperative and able subject. It is in the specific clinical populations described above which cannot be tested by conventional means that ERA has proved valuable. The following section will examine the areas in which each specific electrophysiological test of hearing might be appropriate and also indicate the limitations of the procedures currently used.

1.4 CHOOSING THE APPROPRIATE TEST FOR SPECIFIC CLINICAL REQUIREMENTS.

1.41 Young children and neonates.

There are three essential requirements of an objective clinical test of auditory function in an infant or neonatal population. Firstly, such a test should be sensitive to changes in intensity and give an easily defined response down to values approaching audiometric threshold (the lowest intensity of sound a patient can hear unaided). Secondly, in

evaluating the hearing of a young population, the persistance of the response during sleep and under sedation is of importance. This is because the very young (or the mentally/physically handicapped) cannot be directly instructed or expected to sit still for the duration of the test procedure. (often in excess of 60 min.). As a consequence, sedation is often important to ensure the removal of extraneous muscle activity which will serve to obscure the potentials being recorded. A further advantage of the response - and the one served least well in a neonatal population at the present time, would be that it could allow a comparison of different frequencies. This enables the clinician to differentiate between a broad cochlear deficit and a hearing loss which has spared some of the speech frequencies.

At the present time, neonatal audiological asessment has most commonly relied upon the brainstem auditory evoked potential (BAEP). This response which was discovered by Sohmer and Feinmesser (1967) and characterised clinically by Jewett and Williston (1971) occurs within the first 8 msec. after auditory stimulation and is generated most effectively by very brief auditory stimuli (acoustic clicks). The main advantage of the BAEP is that it is resistant to change with different levels of arousal (Hecox and Galambos, 1974). This is because the BAEP originates from the nuclei and tracts of the ascending auditory pathway within the brainstem and is therefore ever-present regardless of subjective state. In addition, the BAEP is stable in very young (full term) infants and remains detectable with the same degree of accuracy regardless of the age of the patient. The BAEP has thus been the test of choice for assessing young patients under sedation. A further advantage with the response is its fidelity to audiometric threshold. The BAEP provides a very accurate measurement of auditory acuity with responses visible in most patients to within 5-10dB of their hearing threshold. The principal disadvantage with the BAEP is that, because of the very small amplitude of the response (< 1μV), especially at low stimulus intensities, the response is most effectively generated to a brief acoustic stimulus which is able to activate a large portion of the cochlear partition simultaneously. Therefore, a wide range of frequencies, principally those in excess of 2kHz, are most commonly stimulated during BAEP recording to click stimulation and little accurate frequency specific information is obtained (Eggermont, 1982). To summarise, the BAEP has become a powerful clinical

tool in the diagnosis of peripheral hearing losses and central, neurological disorders in the newborn and young children. However, because of the restrictions placed upon the type of stimulation needed to effectively record the BAEP, little reliable clinical (audiological) information has yet been obtained to stimuli delivered at different frequencies.

1.42 Adult testing.

The second area in which auditory evoked potentials have been recognised of clinical importance is within the sphere of medico-legal audiometry. As stated previously, the characteristic feature of a noise-damaged audiogram is a selective high frequency hearing loss with lower frequencies remaining within normal limits for the age of the patient. Diagnosis of noise-induced hearing losses therefore requires an objective audiological test able to discriminate between responses to different frequencies of stimulation. The current test of choice in medico-legal cases tested in the clinical neurophysiological unit at Aston University, is the slow vertex response (SVR). This potential occurs at a longer latency than the BAEP (around 100 msec.) and is believed to reflect activity originating from within the auditory cortex (Vaughan and Ritter, 1970; Peronnet et al., 1974) and the auditory association areas (Kooi et al., 1971; Streletz et al., 1977; Woods and Wolpaw, 1982 a and b;). In the same way as the BAEP, the SVR provides a sensitive assessment of audiological threshold present in adult, waking subjects to within 10-20dB of audiometric threshold under conducive recording conditions (Hyde et al., 1986). The principle difference between the SVR and the BAEP is that due to a far larger number of neurons contributing to its composition, it is a far larger potential and is far more readily recorded to tonally specific stimuli. This means a frequency specific audiogram may be constructed and inferences made as to the nature, cause and extent of any abnormality discovered. Furthermore, a differential diagnosis can be made between a cochlea damaged by loud noise (primarily a high frequency loss) and a presbycustic ear. There are two main disadvantages with the SVR. Firstly, the response has been found to be only dependable in wakefulness and is unreliable in sleeping (or sedated) subjects (Weitzman and Kremen, 1965; Osterhammel et al., 1973). Secondly, the SVR is poorly defined in neonates and

young children due to insufficient development of higher levels of the auditory pathway from which the SVR originates (Cody and Townsend, 1973).

Although adult subjects mostly require no sedation in order to sit quietly for the duration of the experiment, the SVR test is often a lengthy procedure in which some patients may get bored and sleepy or restless. This can lead either to drowsiness and fatigue which results in an increase in contaminating alpha activity or frequently increased restlessness resulting in excessive muscular contamination. It is therefore important to constantly monitor the subjective state of the patient in order to ensure optimum recording conditions ie. alert, relaxed wakefulness.

The two most commonly used electrophysiological tests of audiometric function possess clear advantages but also significant drawbacks. The BAEP is resistant to sleep and is present in all ages but is poorly recorded to tonal stimuli. Conversely, the SVR is frequency specific but may only be reliably used in a waking adult population. These findings suggest that if the evoked response audiometry is to be more successfully utilised in the clinical setting, further research is justified in order to explore possible alternatives or modifications to the existing armamentarium.

1.5 THE AIMS OF THIS THESIS.

An investigation of the clinical utility of the auditory middle latency response (MLR) and the 40Hz response.

As has been stated previously, the neurogenic elements of the middle latency reponses (MLR) are thought to derive from neural structures lying between the brainstem (responsible for the generation of the BAEP) and the auditory cortex and association areas (considered to be responsible for the SVR). Although the MLR has been recognised for a number of years (Geisler et al., 1957; Ruhm et al., 1967; Goldstein and Rodman, 1967; Mendel and Goldstein, 1969 a and b), much debate has persisted as to the interplay of

neurogenic and myogenic elements within the response. In addition, many workers (with the exception of Mendel, Goldstein and collegues) have reported difficulty in successfully and reliably recording the MLR in the clinical setting. Therefore, the clinical utility of the MLR has been consistantly called into question as a viable alternative to the BAEP or the SVR. To date there has been major difficulties in recording the MLR with any great consistancy. Firstly, in waking subjects, the principal difficulty has been excessive contamination with the post-auricular muscle potential lying as it does within the same latency range. The second drawback reported with the MLR is the equivocal effects of sleep upon the morphology of the MLR. Some researchers have reported that the MLR is consistant at all levels of arousal (Mendel and Goldstein, 1969b; Mendel et al., 1975) whilst much of the more recent research has indicated that the MLR is significantly modified during sleep (Erwin and Buchwald, 1986). The reasons for the conflicting reports concerning the detection of the MLR during sleep has been attributed artificial distortions of the auditory evoked responses caused by using narrow bandpass filters with steep filter slopes (24dB/ Octave) in Mendel's work. (Scherg, 1982; Kavanagh and Domico, 1986; Kavanagh et al., 1988). A further issue that shall be addressed in this thesis is the feasibility of generating a clinically useful brainstem response to tonal stimuli. It has been stated that the BAEP is best generated to a broad stimulus containing a wide range of frequencies and poorly formed to frequency specific stimuli (especially low frequency stimuli). In the light of the conflicting reports regarding the clinical applications of the MLR and the generation of the BAEP to frequency specific stimuli, this research project has attempted to investigate how the MLR and 40Hz response might be of use in the frequency specific diagnosis of auditory threshold. The object of this is to strengthen and broaden the current clinical applications of ERA. The following questions have been examined with reference to both child and adult audiometry:

1. How do threshold assessments obtained using the 40Hz response compare to those obtained using the SVR in an adult population? In order to determine whether the 40Hz response may be used as a possible alternative clinical method of assessment to the SVR in adult electrophysiological diagnosis.

2. How resilient is the MLR and 40Hz response to changes in arousal level?

3. Can reliable information be deduced from brainstem evoked potentials to tonal stimuli?

The following chapters (2, 3 and 4) will examine the origins, characteristics and clinical applications of the MLR and 40Hz response. After this literature review, the experimental aims of this thesis will be expanded more fully.

CHAPTER 2

GENERATORS AND TOPOGRAPHY OF THE MIDDLE LATENCY RESPONSES.

2.1 INTRODUCTION.

Chapter one introduced the general aims and limitations involved in the audiological recording of the BAEP, MLR, 40Hz response and the vertex potential. This chapter will look more specifically at the MLR and examine fully the debate concerning the origins of these potentials. The arguments shall be laid out in a chronological manner and reference made to the parallel development of the BAEP and SVR throughout the sixties and seventies as clinical tests of audiological function and the subsequent depressing effect this had upon middle latency research.

2.11 Neurogenic generators in the middle latency range.

The responses now known as middle latency were the first auditory evoked potentials to be reported in the literature in a brief communication using the computer averaging techniques developed by Dawson (1950).

Geisler et al. (1958) generated an acoustic evoked response to a continuous train of click stimuli (400 averages, 1.5 monaural presentations / second) recorded between electrodes placed at the vertex and occiput (Fig. 2.1). By moving the electrodes to positions located symmetrically about the midline again referred to the occiput, Geisler found that the response was recordable bilaterally possessing similar morphology and amplitude at different locations on the head. The onset latency of the response was 20 msec. and the latency of the response peak recorded at around 30 msec. Geisler concluded:

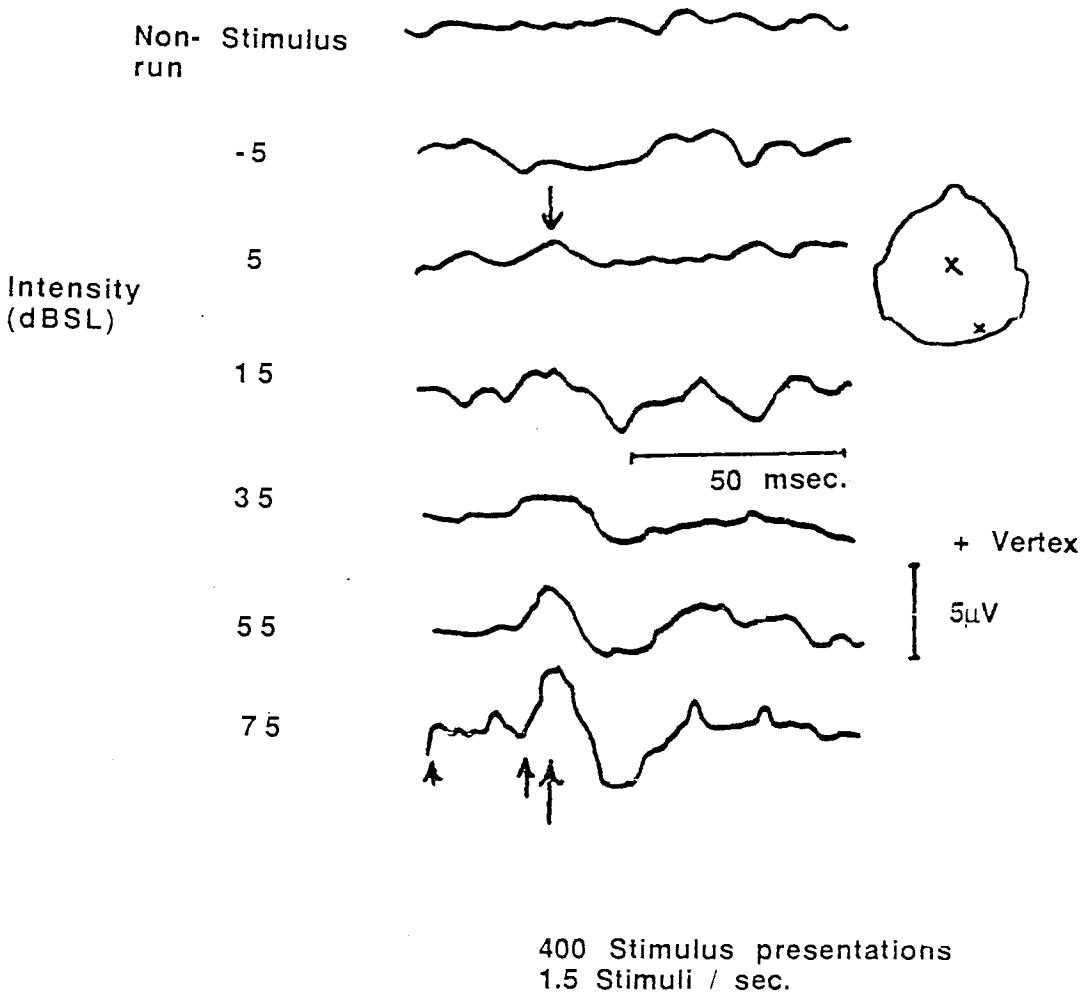

Figure 2.1 The first recording of the MLR (adapted from Geisler et al., 1958).

" These data, and the latency of the surface-negative component of evoked responses to clicks, in cats and monkeys, suggest that the responses which we obtain are cortical in origin. The fact that these responses can be obtained from many places on the scalp may reflect the deep location of the auditory cortex in man. "

In addition, Geisler observes the strong correlation between stimulus intensity and the MLR stating that the response was recordable to within 5dB of psychoacoustic threshold in the subject shown.

Geisler (1960) further examined the nature of these early potentials in the monkey and in man. By recording both upon the scalp and sub-durally in monkeys, Geisler was able to demonstrate that the 30 msec. surface negative potential recorded from the surface of the pia mater reflected faithfully that same potential recorded from the scalp. The fidelity of scalp recorded responses to the potentials recorded directly from the cortex itself gave two useful pieces of information. Firstly, it implied that the response was not significantly degraded or attenuated by transmission through the scalp. Secondly, normal (i.e. not excessive) activity of the scalp musculature did not significantly alter the response. In a topographic study of the early auditory potential in man, Geisler (1960) consistantly found that the 30 msec. negativity was maximal in amplitude over the occipital regions of the scalp. This location was somewhat surprising since the primary auditory projection centers of the brain are located around the Sylvian fissure (transverse gyrus of Heschl). Geisler therefore suggested that the response he had recorded was 'far field' and non-specific in origin as opposed to response originating directly from the primary auditory cortex. Büser and Borenstein (1956) defined three types of cortical response related to different sorts of sensory processing:

1. Primary or projection responses originating from cortical areas which are little affected by other, extraneous modes of sensory stimuli.

2. Secondary response areas of sensory "overlap" in which different stimuli could be evoked independently of eachother.

3. Areas of sensory "interaction" in which these secondary responses could integrate.

Using this definition, Geisler (1960) suggested that the response he had recorded at 30 msec. to auditory click stimulation was secondary in nature. In other words the occiput was a scalp location which reflected auditory activation but also other modalities of stimulus should they be present.

Whichever interpretation one places upon Geisler's data (1958; 1960), the main conclusion from this work is that the middle latency response is the reflection of neural events either directly or indirectly related to audition. However, Geisler himself highlights the possibility of myogenic activity contaminating the response but concludes:

> *" We have been unable to observe evidence of scalp displacements that are time-locked in a consistant manor to the delivery of click stimuli ..... We conclude that the musculature of the scalp does not contain the active sources that produce the 30msec. response components to clicks which we have recorded with scalp electrodes "*

2.12 The role of myogenic generators within the middle latency range.

The initial interpretation of the origins of the middle latency response as proposed by Geisler (1958; 1960) was not however universally accepted. Other researchers suggested anomalies within this auditory response recorded from the human scalp and the apparent enhancement of its amplitude with increased muscular activity. Bickford et al. (1964), Cody et al. (1964) and Borsanyi and Blanchard (1964) all contended that the musculature of the scalp was largely responsible for the potentials occuring in the 8-40 msec. latency range, maintaining that the MLR was the result of an activation occurring via the vestibular system and not the cochlea. This conclusion would appear to be at odds with Geisler's claim that the response he recorded varied with stimulus intensity and could be detected down at values approaching psychophysical threshold, a fact which was inconsistant which a purely vestibular origin for these potentials. Borsanyi and Blanchard (1964) did not wholly reject some sort of neurogenic element within the early auditory response but also emphasised a significant level of time-locked myogenic activity within this latency range. In reconsidering Geisler's (1958) initial findings, responses were reported as present down to within 5dB of threshold. The

myogenic potentials emphasised by Bickford et al. (1964) and others were only recordable to loud stimuli. This would suggest that the basic substrates of the MLR were infact neurogenic, with myogenic components overlaying these potentials at high stimulus intensities.

Bickford et al. (1964) studied 30 normal subjects and 4 patients with known lesions of the audio-vestibular system. Using an inion to ear derivation, Bickford presented binaural click stimuli (7.5/ sec.) presented at high intensity (120dB SPL). In the normals he found that the principal response components in relaxed subjects were two negative waves (with respect to the active inion electrode) with peaks at around 12 msec. (the A wave) and 26 msec. (the B wave). Bickford and collegues found that increases in muscle tonicity (through traction applied to the back of the head) greatly enhanced the amplitude of this response. Relaxation of the neck muscles (through forward traction) served to significantly attenuate the response such that it was no longer clearly detectable. This, Bickford suggested meant that the response was primarily a result of muscle activity. Further investigating the origins of the early auditory response, Bickford et al. (1964) examined patients with complete neurosensory deafness (both unilateral and bilateral) and one patient with a profound loss of labyrinthine function. In the patients with intact vestibular systems, he found a similar response to the normal population with traction enhancing the response. However, no responses were recordable In the patient without labyrinthine integrity. Bickford concluded, that this implied the auditory responses originally attributed to the cortex (Geisler et al., 1958; Geisler, 1960) were in fact due to time-locked activation of the scalp musculature deriving from the vestibular system and not the cochlea. The neural pathway for this mechanism was mediated by nerve fibers from the vestibular and not cochlear branch of the VIIIth nerve. Bickford et al. (1964) called the responses he had found, 'sonomotor' - indicating a myogenic, as opposed to neurogenic activation pathway.

It is not easy to directly relate Bickford's results with those obtained by Geisler et al. (1958). Firstly the electrode montages used by these two groups are not immediately comparable. Geisler recorded from the vertex (active electrode, positive upwards) to an occipital reference located at the inion. Bickford recorded from the inion (active, negative upwards) to a reference he describes as the 'ear' which could mean either the earlobe or the mastoid. This

would have a great influence over the degree of muscular activity that was recorded with the latter reference site being far more susceptable to myogenic activity. The morphology of the responses and the predominance of myogenic components in Bickford's study would imply that the mastoid process was infact the true location of the reference electrode. Secondly, Bickford often recorded under half the number of stimulus presentations in his experiment than did Geisler (150 c.f. 400). This is again not conducive to the recording of small neurogenic potentials from within larger amplitude myogenic activity. A third point to consider is the high stimulus intensity used by Bickford et al. (1964) of 120dB SPL. High intensities such as this are also liable to elicit a greater amount of muscular activity from the test subject. In short, it appears that whilst Geisler et al. (1958) had set out to record a neurogenic response, Bickford and co-workers did everything possible to record myogenic potentials and effectively mask neurogenic activity. In re-examining the data of Bickford and collegues, it is likely that the A wave (12 msec., inion negative) is infact the post-auricular muscle potential recorded first by Kiang et al. (1963). This response would not have been recorded by Geisler and collegues because the PAMP is localised to the mastoid region (Streletz et al., 1977) and Geisler recorded from a vertex to inion derivation. The relationship of the MLR with stimulus intensity reported by Geisler but rejected by Bickford could be explained by the fewer number of averages presented in the latter study. At low intensity, the amplitude of the neurogenic response to auditory stimulation will be reduced with respect to the ongoing (non time-locked) background activity. Therefore, the 150 stimulus presentations used by Bickford at the lower intensity of 98dB SPL may not have been sufficient to adequately visualise the emerging neurogenic MLR.

The hypothesis that the MLR was infact a time-locked myogenic response to auditory stimulation dominated research during the mid-nineteen sixties. Cody et al. (1964), members of Bickford's research group, saw a clear division between the potentials occurring between 8-40 msec and the later slow vertex responses (SVR). In a study of the shorter latency response (maximal at the inion) in normal subjects and patients with lesions of the cochlea, vestibular system and brainstem, Cody, using a similar inion to ear derivation to Bickford et al. (1964), found similar myogenic enhancement of the former response in agreement with Bickford et al. (1964) and Borsanyi and Blanchard (1964). In addition to this early component,

Cody and collegues also recorded a second, later response, maximal at the vertex (with respect to an ear reference). Binaural click stimuli, delivered at 1/second produced a diphasic wave with a negative component ranging in latency from 55 msec. to 95 msec. , followed by a positive peak at 125-195 msec. Cody observed several differences between this response and the earlier inion response. Firstly, the inion response could be recorded at high stimulus repetition rates (7.5 stimuli/ second) whereas the vertex response was recorded poorly at rates exceeding 1/ second. Secondly, unlike the inion response, the tonicity of the scalp musculature had a much smaller effect on the vertex response. From these findings, Cody defined two sets of auditory potentials with different characteristics distinguished on the basis of their latency. The fast group of responses were of short latency (< 40 msec.), were maximal in the region of the inion, were primarily myogenic in origin and mediated by the vestibular elements of the inner ear. The second (late) group of potentials were of longer latency (around 70 msec.) maximal at the vertex, and predominantly neurogenic in origin (i.e. mediated by the cochlea) reflecting activation of the cortex.

2.13 Restating the case for the MLR as a neurogenic response.

It was not until recordings were made direct from the surface of the exposed auditory cortex that the possibility of a neurogenic auditory response in the 8-40 msec. latency range was re-established. Ruhm et al. (1967) examined the origins of the auditory middle components in an attempt to clarify the relative contributions of neurogenic and myogenic potentials. Firstly, Ruhm and collegues compared scalp recorded responses at occipital and vertex electrodes. According to Bickford et al. (1964), the principal argument for a myogenic origin for these responses was the fact that they were maximally recorded over the occiput and were significantly enhanced by increased myogenic activity. Ruhm et al. (1967) presented 3000 click stimuli (7/ sec.) at 40 and 110 dBSL to both vertex and occiput refered to the nose. Fig. 2.2 a shows his results which demonstrate very similar responses between these locations at both intensities. This finding contradicted those of Bickford and collegues (who's work would have predicted a larger response to have been generated to the louder stimulus as recorded

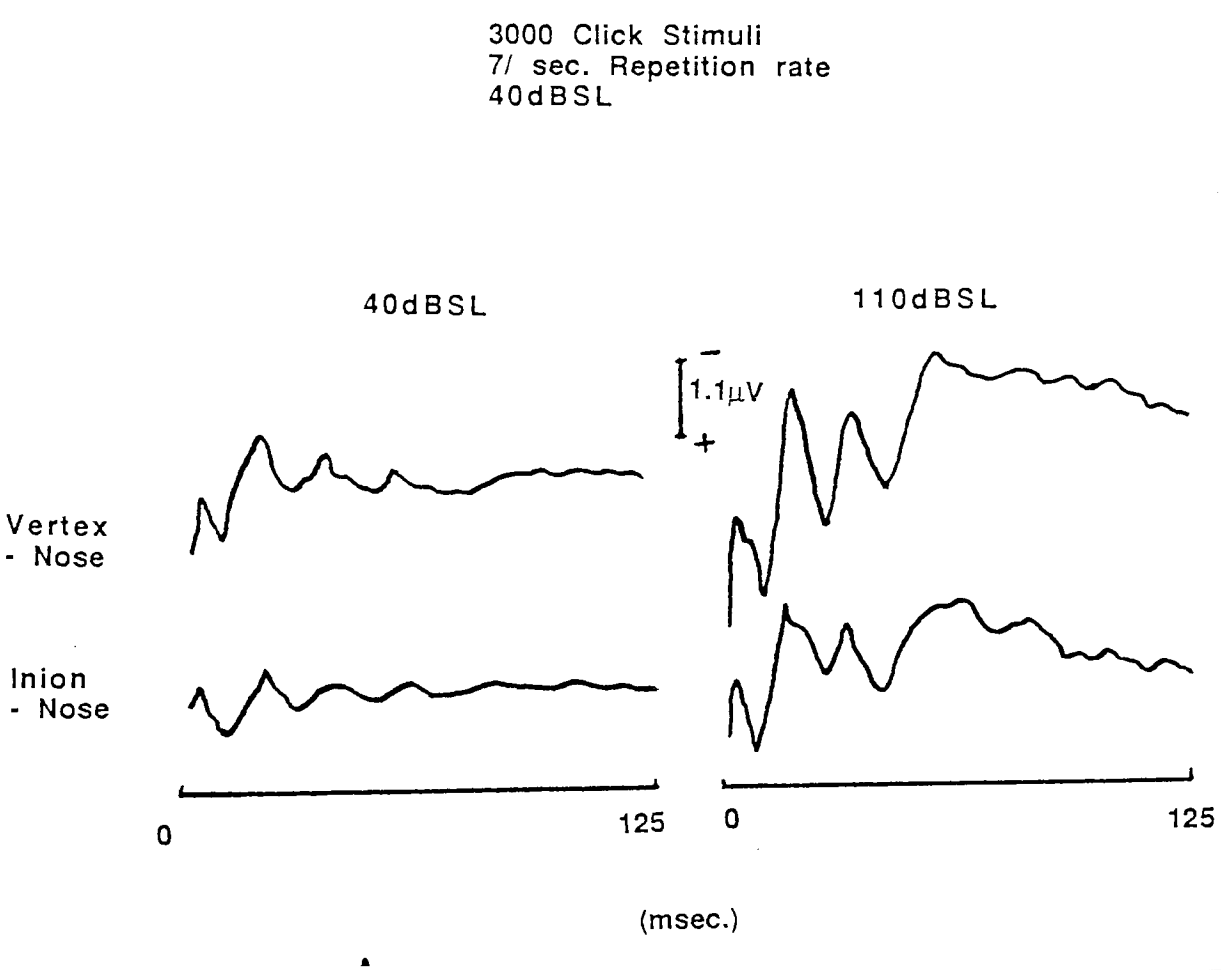

Figure 2.2 a A comparison of the morphology of the MLR using active vertex or occipital electrode sites referred to the nose.

Figure 2.2 b MLR morphology compared using either scalp or sub-dural electrodes (Ruhm et al., 1967).

with the occipital electrode) and suggested to Ruhm and co-workers that the auditory middle latency responses they had recorded derived primarily from neural activity with a minimal degree of muscular overlay as suggested by Geisler et al. (1958). Ruhm et al. (1967) further compared scalp recording of the middle responses with those obtained from direct recording from the exposed surface of the cerebral cortex of two patients undergoing surgery for seizures. The patients used were audiologically normal. Click stimuli were delivered at 40dBSL and recordings (both extra- and intra-cranial) were obtained from temporal electrodes (T3 and T4) and a point C2 located 10% of the distance between the vertex and auditory meatus. Fig 2.2 b shows the comparison between surface and cortical electrodes. Clearly the former responses are smaller due to the attenuation caused by intervening anatomical structures. However it can be seen that the response morphology is very similar whether recorded from the scalp or direct from the cortex. Therefore, this would suggest that muscle activity alone cannot account for the auditory middle components. Ruhm concludes:

> *" Under the conditions of (this) experiment, we must conclude that there was clear early response componentry at the vertex which was interpreted to be cochleoneurogenic. We suggest that this activity might be studied as part of the auditory response to acoustic stimulation."*
>
> (author's emphasis)

Harker et al. (1977) also reported a much smaller contribution of muscular contamination to the neurogenic MLR. Harker and collegues compared the morphology of the auditory middle components to a 1000Hz tone pip at 50dBSL, in resting wakefulness, mild sedation and complete succinylcholine muscle paralysis. Using a vertex to earlobe derivation (1600 presentations/average), he reported a consistant and similar MLR under all experimental conditions which suggested that muscular activity was not solely responsible for the middle components. Fig. 2.3 compares the data of Bickford et al. (1964) with that of Harker et al. (1977) showing clear differences in the MLR between these two groups. Harker et al. (1977) suggested that the large amplitude response observed by Bickford might have been due in part to the small number of averages recorded (200) and the high stimulus intensities used. In addition, with the choice of the earlobe reference site by Harker and collegues as opposed to the mastoid (Bickford et al., 1964), the possibility of recording a post-auricular muscle potential is greatly reduced. Since muscular activity is known to habituate or fatigue (Kiang et

Figure 2.3 A comparison between the data of Bickford et al. (1964) and Harker et al. (1977).

al., 1963), it could be suggested that if Bickford and collegues had recorded a greater number of averages, the influence of these potentials might have been far smaller.

The clinical status of the early components of the AER as a diagnostic test of hearing is dependent upon recording a reliable and replicable waveform. Therefore, the value of these components has been consistantly lessened because of the confounding variable of contamination with myogenic responses within the same latency range. One possible explanation for the heavy emphasis placed upon the predominance of myogenic elements in some of the early literature (Bickford et al.,1964; Borsanyi and Blanchard, 1964), might have been the result of an insufficient level of subject relaxation coupled with the small number of averages that were summed in these earlier experiments. The data was often based on the summation of 100 or 200 responses which was probably inadequate to adequately visualise the smaller neurogenic responses from within the larger amplitude myogenic contaminants.

Streletz et al. (1977) evaluated the topography and components of the auditory middle latency response and the possible role of myogenic responses occurring within the same latency range. The principal aim of this study was to assess the relative importance of neurogenic elements (as favoured by Geisler et al. 1958; Ruhm et al. 1967; Goldstein and Rodman, 1967; Mendel and Goldstein, 1969 a and b) and myogenic components (Bickford et al. 1964; Cody et al. 1964) to the morphology of the MLR. In order to ensure that their reference site was relatively inert with respect to the AEPs being measured, Streletz and collegues sometimes refered their active electrode to a balanced non-cephalic reference -BNCR (Stephenson and Gibbs, 1951; Lehtonen and Koivikko, 1971). The basic arrangement of the BNCR consists of two electrodes situated off the head. These two electrodes together comprise the reference for the active electrode(s) placed upon the scalp. One is located around the level of the seventh cervical vertebra and the other on the opposite side of the thoracic cavity at the supra-sternal notch. The resistance of both electrodes can be varied separately via potentiometers in order to prevent the electrical activity of the heart (ECG) from contaminating the electroencephalic activity being measured and hence the evoked response. Since no cephalic electrode reference site can be trully inert, the BNCR has been proposed by some researchers as offering a preferred alternative to a scalp

reference.

Using a 70dBSL click stimulus (delivered at 1/sec. or 10/sec.), Streletz et al. (1977) examined the topography of the MLR under relaxed conditions and with specific activation of frontalis, temporalis and occipitalis scalp muscle groups. In addition, the activity of the post-auricular muscle was recorded. Electrical activity was recorded between a bandpass of 1Hz-10kHz (-3dB down) and either 512 or 1024 responses were averaged for each trace. Fig. 2.4 shows the effects of varying muscle tension in the four groups indicated. Figure 2.5 demonstrates the localisation of the PAMP. The results demonstrated by Streletz and collegues suggest that the basic neurogenic MLR, seen clearly in the relaxed state, is present without any appreciable muscle activity. Activation of frontalis, temporalis and occipitalis muscle groups superimposes a myogenic (sonomotor) response upon the MLR mediated by the vestibular system and not the cochlea. The latency ranges of both myogenic and neurogenic components recorded by Streletz et al. (1977) are given in table 2.1 a and b.

Table 2.1 a Latency of the myogenic responses generated by the activation of certain scalp muscle groups.

	Latency (msec.)				
Muscle group activated.	*N*	*P*	*N*	*P*	*N*
Frontalis	*14-18*	*22-36*	—	—	—
Temporalis	*15-20*	—	—	—	—
Occipitalis	*14-18*	*18-20*	*28-32*	*36-42*	
Post-auricular muscle	*11-14*	*15-20*	—	—	—

Table 2.1 b Latency (msec.) of the neurogenic potentials of the MLR under conditions of relaxation. Recorded at maximally at Fz.

No	*8-12*
Po	*10-14*
Na	*16-22*
Pa	*26-36*
Nb	*32-42*

The post-auricular response (PAMR), first reported by Kiang et al. (1963) unlike the three vestibulo-myogenic responses shown above, is thought to originate from cochlear and not vestibular activity. Fig. 2.5 shows the localisation of this response around the region of the

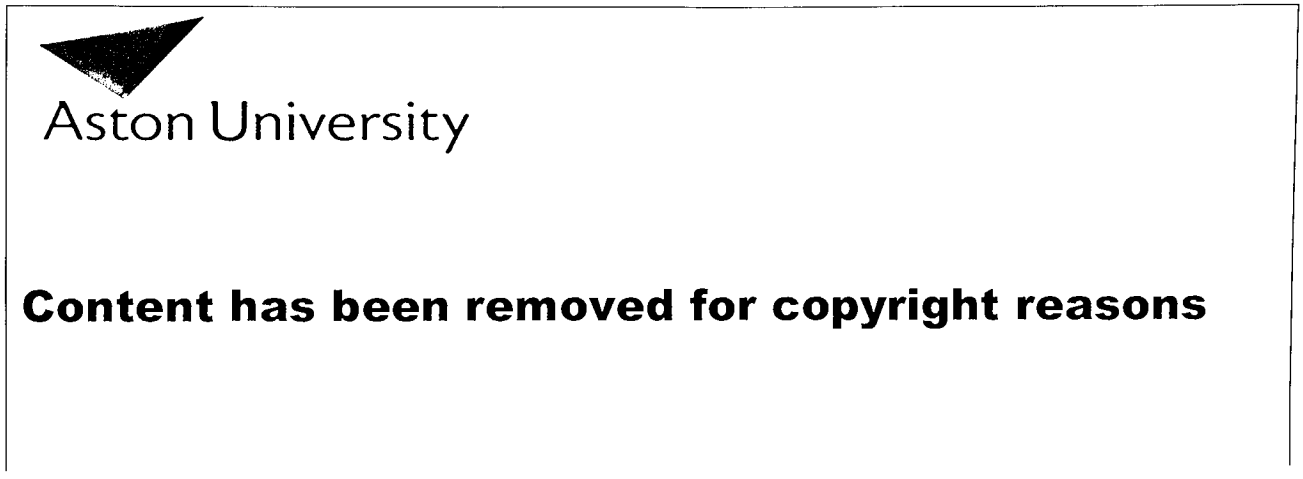

Figure 2.4 The effects of activating various muscle groups upon the morphology of the MLR (Streletz et al., 1977).

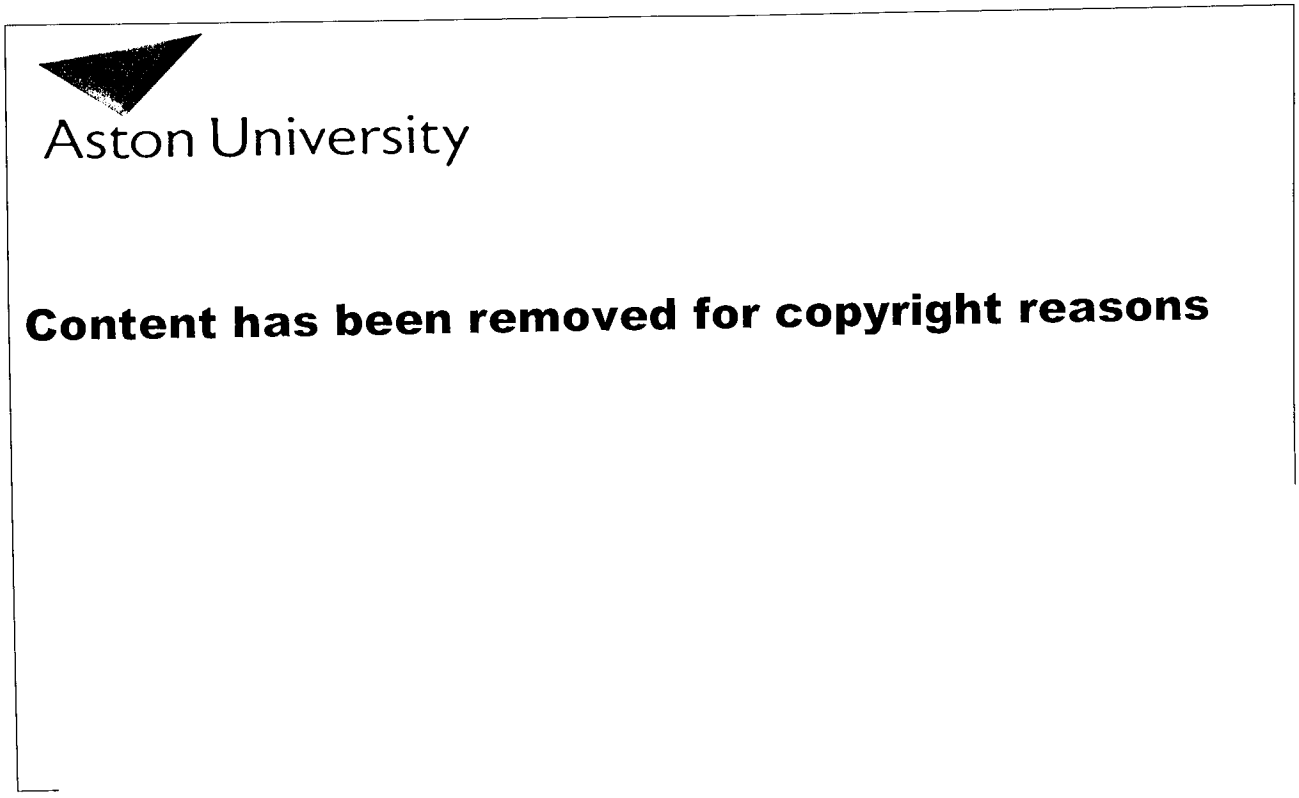

Figure 2.5 The localisation of the post-auricular muscle response (Streletz et al., 1977).

mastoid and post-auricular muscle. Despite its proximity, the earlobe electrode (A2) exhibits far less post-auricular activity than the mastoid and adnexa. This suggests that the ear lobe is a much more suitable site for recording a neurogenic MLR which is far less suceptable to contamination from muscular activity. It has been proposed that the PAMR reflects bilateral activation of the neck or ear muscles (Kiang et al. 1963; Jacobsen et al., 1964). The reasons for the proposed cochlear origins of the post-auricular muscle potential are that the response has been shown to present to low intensities of stimulation (a property uncharacteristic of a myogenic response) and is present regardless of the integrity of the vestibular system (Yoshie and Okudaira, 1969).

Gibson (1978) suggested that the PAMR was initiated by the cochlea and mediated by the brainstem auditory nuclei to the post-auricular division of the seventh (facial) cranial nerve. The suggested sequence of this activation may be summarised as follows:

i) Spiral ganglion of the cochlea.

ii) Ventral cochlear nucleus.

iii) Superior olive complex.

iv) Lateral lemniscii.

v) Reticular activating system (RAS) or inferior colliculus.

vi) Post- auricular branch of VIIth nerve.

The considerable variations in PAMP waveform reported in the literature have been attributed to methodological variations between experimenters; specifically in the type of electrode used (whether needle or wick electrodes), the location of electrodes upon the scalp and differences in stimulus and recording techniques (Jones, 1979).

Since the PAMR is believed to be of cochlear origin and its amplitude varies with intensity, some researchers have investigated the possibility of using this response as an objective assessment of auditory threshold. Both Jacobson (1964) and Yoshie et al. (1969) reported favourable detection of the response near audiometric threshold (within 20dB). However, the variability of the response and its lack of occurrence altogether in some subjects has meant

that the PAMP is not consistant enough to be relied upon clinically (Davis, 1973; 1976). If a post-auricular response were recorded from a patient then it could be concluded that the cochlea is functioning at that level of stimulation. However, the reverse cannot be assumed and therefore a cochlear deficit may not be diagnosed if the PAMP were absent. Furthermore, the potential usage of the PAMP in a child population is compromised by its attenuation of during sleep which is usually a prerequisite for electrophysiological recording.

Figure 2.6 (after Streletz et al., 1977) show a comparative study of the post-auricular response in sleep and wakefulness recorded from various locations around the ear. Sleep was found to diminish the amplitude of the response at all electrode sites. The post-auricular muscle potential is clinically very useful in difficult to test children or the handicapped who will not respond to sedation and remain too active to record other auditory evoked responses. In such cases, the only chance of recording meaningful data would be the occurrence of a PAMP which, if present, would suggest that the patient has neural integrity up to the level of the inferior colliculus (according to Gibson's hypothesis).

Thornton (1975) examined the post-auricular response in order to explore factors which might effect the morphology of the response. He attributed filter bandpass (especially the high-cut filter) as the most significant cause of waveform variations. Using a bandpass of 1- 4000 cycles/ sec., Thornton presented click stimuli (spectral peak around 2kHz) at a rate of 10/ sec. to reclining subjects (n=5) with their heads propped by a pillow. Responses were recorded from both mastoid processes referred to F4 (situated just above the hairline) and an Fz electrode served as a ground. Thornton recorded 5 clear components in the 8-40 msec. latency range.

Fig. 2.7 shows Thornton's waveform and the effect of altering the systems bandpass upon it. It may be seen from Fig. 2.7 that reducing the system bandwidth served to distort and attenuate some of the response waveform. Thornton (1975) then compared the morphology of the PAMR recorded by various research groups using different bandpass settings. Table 2.2 presents Thornton's summary of this body of data in which he implies that all the reported peaks given, are the result of post-auricular muscle activity.

Figure 2.6 Comparison of the topography and morphology of the PAMP recorded in sleep and wakefulness (Streletz et al., 1977).

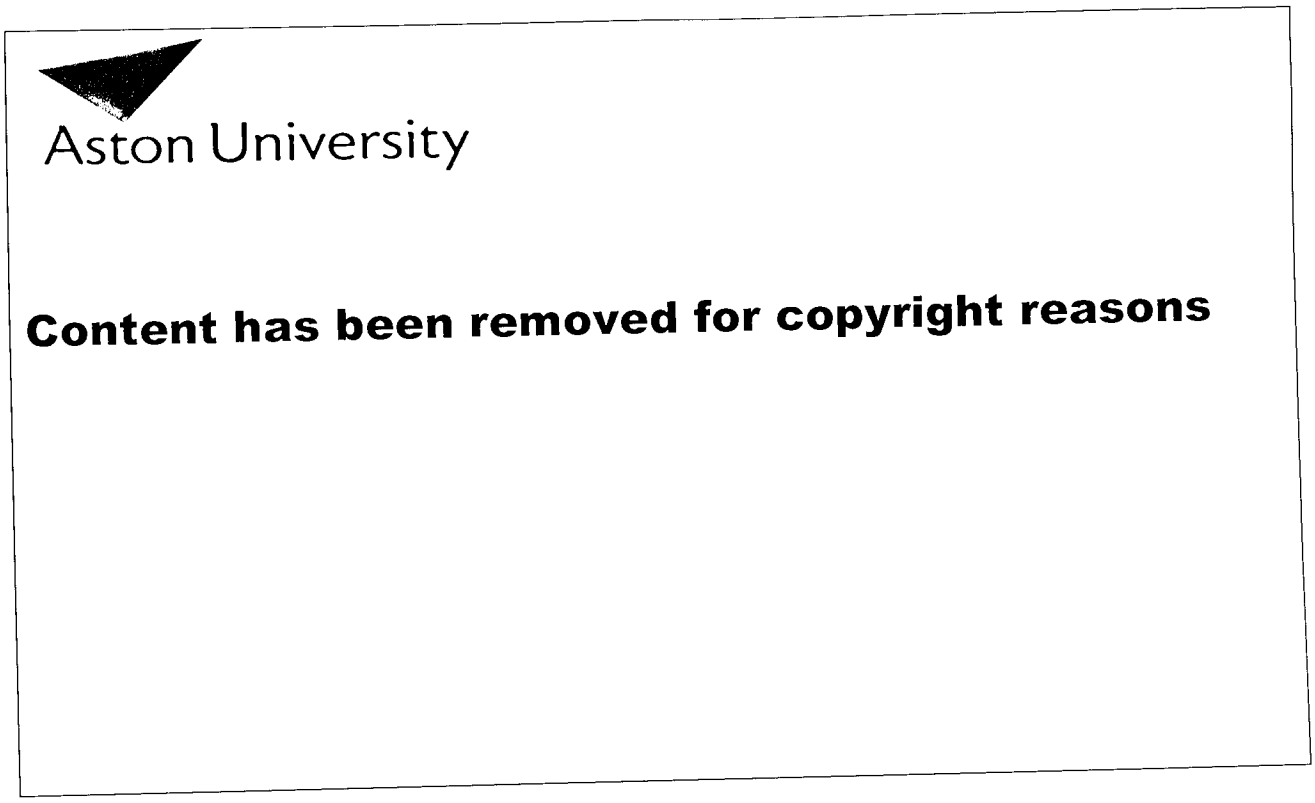

Figure 2.7 The effects of filter bandpass upon the detection of response components of the PAMP (Thornton, 1975).

Table2.2 After Thornton (1975).

Author	*Stimulus levels (dB)*	*High freq. limit (c/sec.)*	*Latency (msec.)*				
			P1	*N1*	*P2*	*N2*	*P3*
Mendel and Golstein (1969b)	*50*	*100*	_	*13*	_	_	*22*
Douek et al. (1973)	*70*	*200*	_	*14*	_	_	*25*
Yoshie and Okudaira (1969)	*80*	*500*	_	*12*	*16*	*25*	*36*
Picton et al. (1974)	*60*	*2500*	*9*	*12*	*16*	*25*	*36*
Thornton (1975)	*80*	*4000*	*10*	*12*	*15*	*19.5*	*24*

It is certainly true that Thornton demonstrates a reduction in the number of response components that may be seen with a narrow filter bandpass. However, there is some question as to whether muscular activity is wholly responsible for the components shown by Thornton (1975). As argued in the previous section, there also exists middle latency neurogenic potentials upon which myogenic responses can be superimposed if the recording conditions are unfavourable (Ruhm et al., 1967; Harker et al., 1977). In re-examining the data shown by Thornton (1975), the researchers quoted do not attribute their findings to exclusively muscle activity. Mendel and Goldstein (1969b) refer to their responses as cortical in origin and maximal at the vertex. Similarly, the data attributed to Picton et al. (1974) by Thornton is actually data given for the latencies of neurogenic components in the 8-40 msec. latency range and not muscular activity. For the composition of the post-auricular muscle response, Picton et al. (1974) actually quotes a large negativity with a latency of 11.8 msec. (± 0.8 msec.) and a positive component at 16.4 msec. (± 0.7 msec.). Jones (1979) suggested that as a result of this superimposition of both muscular and neuronal responses, the effects of filter bandpass are not being viewed in isolation. It might therefore be inappropriate to conclude that Thornton's (1975) 5 peaked response is exclusively derived from myogenic (post-auricular) activity. Although Thornton's (1975) inferences may not be fully accepted due to the superimposition of neurogenic and myogenic responses lying in the middle latency range, this experiment does illustrate something of great importance to the arguments that shall be proposed in this thesis. The influence of filter

bandpass upon the morphology of the MLR and the number of middle latency components that are visualised is of great significance in the detection of these responses. This is especially true in experiments that have studied these potentials at different levels of arousal. This argument is central to the controversy over the current clinical status of the MLR and is more fully examined in the experimental work that follows in later chapters.

Having now explored the possible generators of the potentials within the middle latency range, this discussion will now continue by examining the scalp topography of AEPs with special consideration for the MLR.

2.2 THE TOPOGRAPHY AND DISTRIBUTION OF AUDITORY EVOKED POTENTIALS WITH SPECIAL REFERENCE TO THE MLR.

Although this thesis is not directly concerned with the topography and generators of auditory evoked potentials, these subjects are perhaps of special relevance to our current understanding of the middle latency responses. This is true both in a historical sense, in order to refute the prevailing opinion in the mid-sixties that the MLR was a vestibulo-myogenic (as opposed to a cochleo-neurogenic) response. Secondly, the question of MLR generators is now of particular importance to the current debate concerning the reported changes in the MLR with different levels of arousal and with maturation. Furthermore, the experimental work performed in this thesis compares the MLR with both the BAEP and the SVR (as established clinical procedures) in the assessment of audiometric threshold. It is therefore useful to briefly set out the evidence concerning the anatomy and electrophysiological topography of these potentials. It lies outside the scope of this thesis to discuss in detail the sources of all of the auditory evoked potentials, but our current understanding on this topic is summarised below. Since the BAEP and SVR were established as neurogenic responses before the MLR, the topography and possible

generators of these potentials were investigated first. For a more comprehensive discussion of auditory anatomy the reader is referred to more specialised sources (Musiek and Baran, 1986; Musiek, 1986; Lippe, 1986).

2.21 The brainstem evoked potential.

Research has suggested that the individual components of the brainstem response derive from the nuclei and tracts of the auditory brainstem pathway. The surface manifestations of this activation are considered to be far-field, volume-conducted potentials originating from these generators (Jewett, 1970; Jewett and Williston, 1971; Picton et al., 1974; Streletz et al., 1977). The generators of the BAEP are generally considered to represent activity from the distal and proximal portions of the auditory (VIIIth cranial) nerve, the cochlear nucleus, the superior olivary body and the tracts and nuclei of the lateral Lemnisci (Møller and Janetta, 1981).

2.22 The slow vertex response.

Vaughan and Ritter (1970) were the first to examine the topography of the SVR. Recording from a coronal chain of electrodes referred to the nose, these workers reported that the response was maximal in amplitude at the vertex. Vaughan and Ritter reported a phase inversion of the vertex response at the level of the Sylvian fissure which, they concluded, meant that the origin of this response could be traced to this location. Since the primary auditory cortex is to be found at the Sylvian fissure Vaughan suggested that this was the generator of the SVR. Critisism was rapidly levelled at reference site used in this experiment, on the grounds that the nose could not be trully inactive with respect to the responses being measured (Kooi

et al., 1971). Secondly, Kooi suggested that the phase inversion reported by Vaughan and Ritter (1970) at the Sylvian fissure could be alternatively explained by the active and reference electrodes being equi- potential at this location and the nose effectively becoming more active than the vertex. Kooi et al. (1971) used a non-cephalic reference electrode (Stephenson and Gibbs, 1951) to demonstrate that the nose reference was not inert and it was also possible to record a vertex response at this location when referred to the NCR. As in Vaughan's experiment the maximal amplitude of the SVR was recorded at a fronto-central location. Because no phase inversion at the Sylvian fissure could be either corroborated or rejected, Kooi and collegues attributed the SVR to a secondary cortical activation in response to an auditory stimulus.

Peronnet et al. (1974) and collegues recorded the vertex response from a coronal chain of electrodes referred to the nose in an attempt to resolve the dispute concerning in activity/ inactivity of this location with respect to the recording of auditory evoked potentials. Twenty six normal adult subjects and three patients with definite lesions of the temporal lobe were tested (age range 20-45 years) using 1000Hz tonal stimuli (10 msec rise/fall time, 140 msec. plateau) delivered at a rate of 0.75 presentations/ second. A bandpass of 0.3Hz to 35Hz was employed and 100 presentations were summed for each averaged response. As in Vaughan and Ritter's (1970) experiment, Peronnet et al. (1974) reported a clear phase inversion of the response over the temporal regions which was absent in the patients tested. Peronnet et al. (1974) felt that the phase inversion exhibited in his normal subjects and absent in the pathological group was indicative of an auditory generator at the level of the Sylvian fissure unlike Kooi et al. (1971). Peronnet argued that the problem of the nose being active could be avoided by deriving the bipolar inferences from adjacent electrodes in his coronal chain. Using such a procedure, Peronnet reported that the phase inversion at the Sylvian fissure (as predicted by

Vaughan and Ritter's hypothesis) still occurred. This implied to Peronnet and collegues that the generators of the SVR lay at this location. However, the same critisism can be levelled at this experiment as at Vaughan and Ritter (1970). i.e. the active and reference electrodes (vertex and nose) may be reversed at the Sylvian fissure as the nose becomes more active than the vertex.

Other workers have re-examined the work of Vaughan and Ritter (1970) and Kooi et al. (1971) and the present position appears to corroborate the latter groups findings from both surface recordings (Picton et al., 1974; Streletz et al., 1977; Wolpaw and Wood, 1982) and intracranial procedures (Celesia and Puletti, 1971), that the generators of the SVR cannot be strictly localised to the primary auditory cortex.

2.23 The middle latency response.

Intuitively, If the BAEP is though to derive from the auditory tracts and nuclei of the brainstem and the SVR from summed neural activity at the cortical level, then, if one accepts the presence of neurogenic components within the MLR, occurring between BAEP and SVR, these should in theory be generated by structures intermediate to these locations. Specifically, this means the areas within the primary auditory cortex and / or the projections of the auditory system lying within the diencephalon. The first research investigating the generators of the MLR came from depth recordings carried out at operation (Ruhm et al., 1967). Ruhm's experiment (reviewed in the previous section), reported a promenent positive wave occurring around 25-30 msec. recordable from widespread areas (parietal, frontal and temporal lobes) of the exposed cerebral cortex.

The reported phase inversions of the SVR at the Sylvian fissure (Vaughan and Ritter, 1970; Peronnet et al., 1974) also have been claimed of the MLR (Picton et al., 1974; Streletz et al., 1977; Cohen, 1982). Picton et al. (1974) reported the MLR as being widely distributed over the scalp and maximal fronto-centrally. Owing to the wide-spread response distribution, Picton et al. (1974) concluded that the most likely sources of the MLR were the thalamus, primary auditory cortex, association cortex and (in certain circumstances) the scalp musculature. Streletz et al. (1977) similarly found the maximal amplitude of the MLR to be recorded slightly anterior to the vertex with respect to a non-cephalic reference. Streletz recorded responses to a click stimulus (0.05 msec. duration) delivered at a rate of 10/ sec. and an intensity of 70dB SL. The recording bandpass used in this experiment was 1-10000Hz. He reported a widely distributed negative wave (9 msec.) followed by a positive component of similar distribution (11 msec.). Streletz also found that the later negative component and the positive wave (17 and 33 msec. respectively), were more localised to fronto-central regions of the scalp. The generalised distribution of the N (9 msec.) and P (11 msec.) components was similar to that reported for the earlier latency (BAEP components). This suggested to Streletz that these waves were also the surface manifestations of volume conducted potentials deriving from subcortical structures, possibly the medial geniculate bodies, other thalamic nuclei or even from primary auditory cortical areas buried deep within the Sylvian fissure. The more localised fronto-central distribution of the later N (17 msec.) and P (33 msec.) potentials might suggest more rostral activity originating either from within the primary auditory cortex or deriving from the association cortex.

Cohen (1982) examined the MLR in seven subjects (age range 13-36 years) during natural sleep or wakefulness using 50dB SL click stimuli delivered at a rate of 11/ sec. The recording bandpass used was 30-250Hz. Figure 2.8 presents Cohen's data

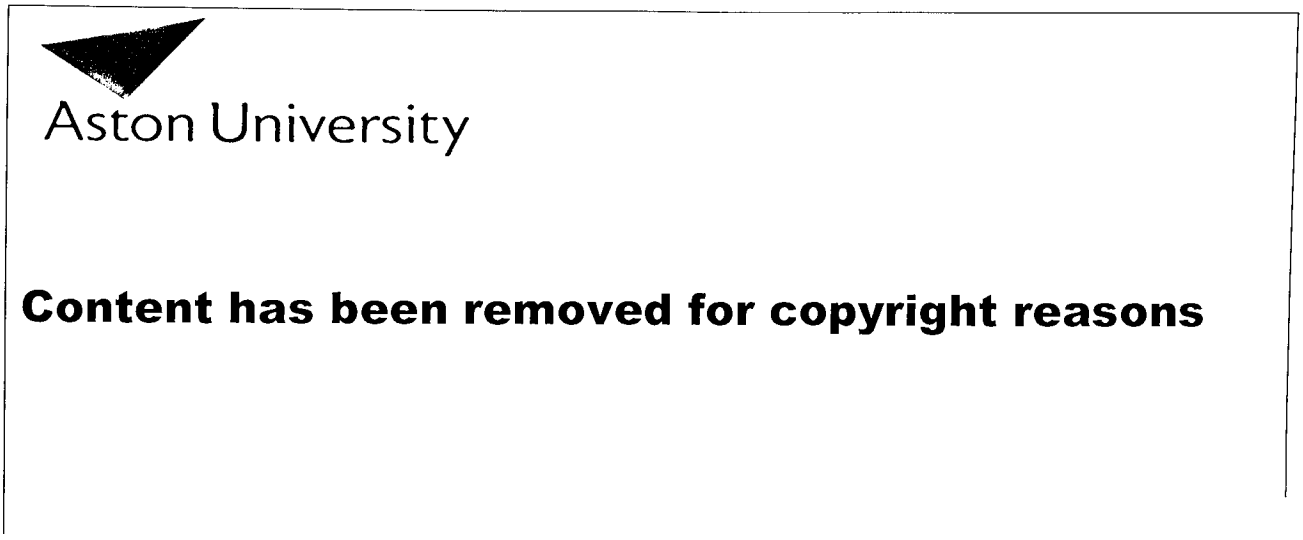

Figure 2.8 Scalp topography of the MLR (Cohen, 1982).

comparing a coronal chain of active electrodes to a nose reference. From this data, bipolar inferences are also calculated from adjacent electrode pairs in this chain. The results presented by Cohen bear a resemblence to the findings of Vaughan and Ritter (1970) for the inversion of the SVR at the Sylvian fissure. A similar phase inversion is reported this time of the Pa component (latency 28.1 msec.) of the MLR. Pa may be seen to reduce in amplitude from its maximum (fronto-centrally) to its minimum over the temporal regions. After phase inverting in this area, the amplitude of the component is seen to increase again on approaching the mastoid process. Cohen reported that Pa was the most consistantly recorded of the middle latency responses with other peaks being too variable in his small subject group to make topographical inferences. Cohen (a member of H. G. Vaughan's research group), argued that Pa was generated at the approximate level of the Sylvian fissure for three reasons. Firstly, bipolar derivations removed Kooi's critisism of Vaughan and Ritter (1970) concerning activity at the nose. Secondly, Kooi et al. (1971) own reference (the balanced non-cephalic reference electrode BNCR, Stephenson and Gibbs, 1951) may itself have been active with respect to components having axial orientation (Vaughan, 1974). However, Kooi's further critisism (concerning the nose being more active than the vertex) discussed above still cannot be ignored.

Özdamar and Kraus (1983) studied the amplitude of the Pa component of the MLR in seven normal subjects (age range 14-30 years) as recorded from the contralateral mastoid, temporal electrodes (T3 and T4) and the vertex (Cz) all referred to the ipsilateral mastoid. Responses were evoked to click stimuli delivered at a rate of 10/ sec. The bandpass of the recording system was 3-2000Hz (6dB/ oct.). Subjects were sedated with chloral hydrate (1000mg p.o.) and the authors state that subjects were in sleep or relaxed wakefulness throughout the experiment. Özdamar and Kraus reported that the consistantly largest amplitude of the Pa component was recorded from the vertex electrode. This difference was statistically significant ($P > 0.01$).

Although the amplitude of Pa was larger in all subjects at the contralateral temporal electrode than ipsilaterally, this difference was not significant ($P< 0.01$). Özdamar and Kraus (1983) concluded that both hemispheres contributed equally to the generation of the Pa component of the MLR and therefore this wave did not represent a neural process which was subserved preferentially by one or other hemisphere.

To summarise this review of MLR topography has suggested that the Pa component of the response originates from activity within the cortex. However, experiments which have attempted to localise this components to specific areas of the primary auditory cortex have not been conclusive (Cohen, 1982). The earlier Na component of the MLR has been attributed to a generator situated sub-cortically (within the thalamus) or located in the cortex, situated deep within the Sylvian fissure (Streletz et al., 1977). Regardless of the problems of response referencing, the most consistant finding to emerge from the studies cited thus far is that the SVR and MLR are of maximal amplitude at scalp locations slightly anterior to Cz (the vertex) using nose, NCR or mastoid reference electrodes.

A second method of analysis which has thrown light upon the possible generators of the MLR is information which has been obtained from patients with established lesions of the cortex and/or auditory pathway. If the responses of a patient with known and unequivocal aetiology can be investigated, the presence or absence of response components may be suggestive of the possible generators sites of such components. A number of clinical and pathological studies have been performed in man to investigate the possible subcortical generators of the brainstem evoked responses (Sohmer et al., 1974; Starr and Anchor, 1975; Stockard and Rossiter, 1977; Velasco et al., 1982). Patients with lesions of more rostral (cortical) structures have been used to investigate the possible generators of the MLR and SVR.

Özdamar et al. (1982) reported a case study of a patient (36 years old) with sub-arachnoid hemorrage as a result of a ruptured left middle cerebral artery. Computerised Tomography (CT) scanning revealed infarction of the left temporal and parietal lobes. The patient was behaviourally assessed on a number of occasions showing no response to acoustic stimuli at the first time of testing (also no startle reflex could be elicited). At this point in time, the patient was diagnosed as totally deaf (bilaterally). Auditory brainstem and middle latency responses were recorded simulataneously using a vertex to ipsilateral mastoid electrode derivation with click stimulation delivered at a rate of 10/ sec. The bandpass of the recording system was 3-2000Hz. Electrophysiological activity was recorded either in sleep or with the patient resting quietly. Özdamar and collegues reported normal BAEP results which indicated the integrity of the cochlea and auditory brainstem pathways. BAEP responses were recordable down to within 10dB HL bilaterally again indicating normal hearing sensitivity. In contrast, the authors report that no middle latency activity was recordable at any level of stimulation. Figure 2.9 shows the patient's MLR at the initial time of testing. A normal response (supplied by the authors) is placed at the top of the figure for comparison. It can be seen that stimulation of the left ear yields no MLR from the patient. Upon stimulating the right ear, a small Pa component is recorded on the first test but not at subsequent re- tests. The inconsistancy and small amplitude of this component would appear to call it's true physiological origin into question.

Özdamar et al. (1982) concluded from this experiment that Pa must be generated by the temporal lobes, owing to the component's absence as a result of pathology within this area of the cortex in the patient studied. Two points of contention arise from this study. Firstly, since Pa is believed to derive equally from both hemispheres independant of the ear of stimulation (Picton et al., 1974; Özdamar and Kraus, 1983), why is there no response recordable from the intact hemisphere? Secondly,

Figure 2.9 The topography of the MLR reported from a case study of a patient with a ruptured middle cerebral artery (Özdamar et al., 1982).

the subjective state of the patient (and that of the normal control) may not have been consistant between tests. Chapter Three of this thesis will examine in depth the effects of arousal level upon components of the MLR. At this point it is sufficient to say that the states of 'relaxed wakefulness' and 'sleep' used interchangeably in this experiment are not equivolent and therefore this alone could have accounted for the differences in waveform morphology reported by Özdamar et al. (1982) and attributed solely to a tempero-parietal infarct.

In a further study, the same team of workers (Kraus et al. 1982) looked at the scalp distribution of middle latency components in a group of twenty four patients with temporal lobe lesions in comparison to a group of normal subjects. Using an methodology the same as in the experiment described above (Özdamar et al., 1982) the patient population was divided into 16 patients with left hemisphere lesions, 6 with right hemiphere damage and 2 with bilateral pathology. Precise sites of damage were 6 temporal, 8 tempero-parietal, 5 fronto-temporal, 1 parietal and 4 lesions involving frontal, temporal and parietal lobes. BAEPs and MLRs were recorded at the vertex and at electrode sites placed just above the Sylvian fissure referred to the mastoid ipsilateral to stimulation. To summarise the results of this study, normal subjects exhibited the largest Pa component at the vertex (2.0 μV in a normal subject) and of similar morphology at both temporal electrodes. In patients possessing lesions with confirmed temporal lobe involvement, the amplitude of Pa was reduced over the damaged hemisphere with the response recorded at the vertex being reduced (1.0 μV $\pm$ 0.4) compared to normal. Kraus et al. (1982) concluded that the Pa component of the MLR is generated bilaterally in normal subjects from the temporal lobe. The maximal response amplitude is recorded at the vertex because this location represents the point at which the Pa generators originating from both temporal lobes are in greatest synergy (with respect to a mastoid reference).

Further evidence for a primary cortical generator responsible for the Pa component of the MLR was provided by Kileny et al. (1987). Kileny accepted the findings of the previous two experiments described (Özdamar et al., 1982; Kraus et al., 1982) as a starting point and sought to introduce two additional questions. Firstly, what effect, if any, did more generalised cortical lesions (i.e. those not directly involving the temporal lobes) have upon the Pa component and secondly, was there an interaction between the test ear and the site of the lesion. In other words, was the effect described by Kraus and collegues (1982) more noticable when stimulating the ear ipsilateral or contralateral to the lesion? This had been suggested from surface recordings (Woods and Clayworth, 1985) and from sub-dural recording from the temporal lobes (Lee et al., 1984) Sixteen patients were studied with an assortment of cortical lesions (principally cerebrovascular accidents). All patients were given extensive behavioural tests and the precise aetiology of their pathologies was well documented. Electrophysiological activity was measured from the vertex (Cz), C5 and C6 (situated approximately over the Sylvian fissure) and also in some cases, T3 and T4. All active electrodes were referred to a linked earlobe common reference. Kileny delivered click stimuli at 65dB SL at a rate of 9.12-9.7/ sec. and the filter bandpass was set at at 5-1500Hz (12dB/ oct. slope). A fundamental difference between this experiment and those performed by Özdamar et al. (1982) and Kraus et al. (1982) was that Kileny's subjects were all tested in relaxed wakefulness and not sleep. Kileny's data indicated that the amplitude of the Pa component of the MLR was reduced over the hemisphere possessing the temporal lesion. Pathology effecting more distant cortical regions had little or no effect upon Pa. Furthermore the intact Pa wave in patients with anterior temporal lesion narrows down the generator of this component to the posterior aspect of the temporal lobe. Another interesting finding was that the Na component (preceeding Pa) was unaffected in temporal lobe pathology, possibly indicating a separate generator for this earlier component.

The temporal lobe patients presented by Kileny et al. (1987) all showed responses of markedly reduced amplitude bilaterally, regardless whether the ear ipsilateral or contralateral to the lesion was stimulated. The most pronounced interhemispheric difference (asymmetry) was reported in the Na-Pa amplitude measurement when stimulating on the ipsilateral side to the lesion. Statistical tests showed that the Na-Pa amplitude was significantly reduced in the temporal lobe patients when compared to the patients with no such involvement ($P< 0.01$). The data offered by Kileny and collegues (1987) broadly agree with that presented by Özdamar, Kraus and collegues (1982). In some ways this experiment may be seen as potentially more meaningful than Özdamar et al. (1982) and Kraus et al. (1982) as the subjects used were all awake for the test period. This means that no confounding variables are introduced into the MLR morphology by the subjects being assessed at different levels of arousal.

Aside from strictly cortical generators of the MLR, other (sub-cortical) structures have been implicated. Woods et al. (1987) recently emphasised the importance of subcortical generators to the morphology of the MLR. These authors examined the MLR and SVR in 5 patients (age range 39-72 years)with cortical pathology either as the result of vascular damage (occlusive infarctions of the middle cerebral artery, n=3) or trauma. Four of these patients had bilateral lesions of the temporal lobe whilst the fifth possessed an extensive left hemisphere lesion of the temporal areas and also a right anterior hemispheric lesion involving the auditory association cortex. All the patients studied exhibited involvement of the primary auditory cortex. The initial clinical presentation of all the patients revealed total or near total hearing deficits. To insure the integrity of peripheral auditory pathways, brainstem evoked potentials were first recorded in all patients and showed no abnormalities. Middle latency responses were recorded to click stimuli delivered at a rate of 13/ sec. at intensities of around 50-60dB SL, active electrodes were placed

at the vertex and at two sites located over the superior temporal plane referred to the mastoid ipsilateral to stimulation. A filter bandpass of 3-300Hz was used. Woods et al. (1987) state that subjects were reclined in a semi-darkened room, but do not say whether they were asleep or awake during the investigations. The authors report that Na and Pa components could be recorded from all the subjects tested at all electrode sites regardless of pathology. Woods et al. (1987) concluded from this experiment that no simple relationship existed between primary cortical damage and the morphology of the Na and Pa components of the MLR. These authors go on to suggest that Pa cannot exclusively depend upon generators within the primary auditory cortex and probably also involves contributions from certain thalamic structures (medial geniculate bodies). Again the effects of patient arousal level might also be important in influencing the morphology of the MLR components. The presence of Pa in the experiment of Woods et al. (1987) would appear opposed to the findings of Kraus' group (Özdamar et al., 1982; Kraus et al., 1982) in similar patient populations. However, one possible explanation might be that Kraus's patients were tested asleep whilst Woods may have tested waking subjects.

To summarise the clinical significance of these studies, topographical information has been important for the clinical development of all of the auditory evoked potentials (BAEP, MLR and SVR), both audiologically and neurologically. Audiologically speaking, knowledge of morphological variations in responses as a result of using different recording locations is important in order to establish the optimum electrode positions which facillitate responses detection especially at low stimulus intensities (i.e. near audiometric threshold). The research summarised in this section has implied that the most favourable site at which to record middle latency responses is at the vertex (referred, for example to either mastoid). This provides a middle latency response of maximal amplitude, regardless of the specific generators of the individual response components.

Discussing briefly the wider significance of topography, neurologically the importance of generator sites has more far reaching implications. Kileny et al. (1987) suggested that the MLR might be able to provide the clinician with a valuable tool for assessing patients who have sustained temporal lobe lesions and to monitor the extent and long term effects of such damage if present. Secondly, the MLR could provide information concerning sub-clinical temporal lobe damage, if suspected as the result of other (more distant) pathology.

There are however dangers in the interpretation of lesion studies of the type described previously. As suitable patients for investigations of this type are rare and no two patients may be judged identical in terms of their pathology, it is necessary to remember that additional factors (trauma, drug regimes) specific to each patient might be responsible for abnormal waveform morphology. Secondly, it is also very difficult to make firm conclusions concerning response generators from case studies alone without the backing of firm statistical evidence.

2.3 SUMMARY.

This chapter has examined in detail the components of the auditory middle latency response. Originally it was thought that the MLR reflected a myogenic (sonomotor) response to sound not originating from auditory cortical structures but rather from the scalp musculature (Bickford et al., 1964; Cody et al., 1964). This initial conclusion prejudiced researchers from further examining the clinical possibilities of the MLR. A further myogenic potential can also be recorded within the middle latency range, the post-auricular response (Kiang et al., 1963). This potential is thought to derive from activity within the post-auricular muscle mediated by the

auditory brainstem pathway up to the level of the Superior Olives and then from the post-auricular division of the facial nerve (Gibson, 1978). The PAMP does have some diagnostic value in auditory assessment as it reflects activity cochlear functioning up to that level and is recordable in certain subjects down to intensities near audiometric threshold (Jones, 1979). Indeed, often the PAMP may be the only auditory response recordable in agitated patients who are unable to relax. The PAMP is however limited in its usefulness because of its inter-subject varaibility and also because it can fatigue quite rapidly (Kiang et al., 1963).

The acceptence of a neurogenic middle latency response occurring independant of muscular activation was slow in coming. In the first instance, the positive component of the MLR (Pa) was only detectable through recordings made directly from the auditory cortex at operation (Ruhm et al., 1967). This was nearly a decade after the middle latency response was originally reported by Geisler et al. (1958). It is now felt that the lack of success in recording the MLR reported by Bickford and others was due to inadequate subject relaxation and the recording of too few averages (i.e. not allowing myogenic activity and also muscular noise to attenuate).

Topographical studies of the neurogenic MLR have revealed that the response is maximally recorded slightly anterior to the vertex (Picton et al., 1974; Streletz et al., 1977; Wood and Wolpaw, 1982; Kileny, 1983; Özdamar and Kraus, 1983). The precise generators of individual components of the MLR have been investigated using surface and subdural electrodes in normal subjects and patients with fortuitous lesions (Picton et al., 1974; Lee et al., 1984; Kileny et al., 1987). This body of work has indicated that the most likely generators of the MLR are the thalamus, primary auditory cortex (situated around the posterior aspect of the temporal lobe) and also more generalised areas of the cortex. These findings have clinical implications for the neurological use of the MLR in the diagnosis of cortical

pathology.

This concludes the discussion of MLR origins and topography. The next chapter will explore factors (both methodological and subjective) which are relevant in the recording of middle latency and 40Hz responses.

CHAPTER 3

FACTORS AFFECTING THE MLR AND 40HZ RESPONSES.

3.1 INTRODUCTION.

Chapter 2 showed that the responses now known as middle latency (occurring in the 8-40 msec. latency range) derived primarily from neural activity in the appropriate (i.e. adequately relaxed) recording conditions. The effects of methodological and subjective influences upon the MLR now have to be discussed before the clinical viability of the response may be assessed. The the discussion of such factors is important before the application of any auditory evoked potential but have nowhere been more problematic than in MLR recording. Therefore, before the MLR can be used with confidence in the clinical environment, the clinician requires to know:

i) The response characteristics (morphology) of the MLR recorded to different stimuli (both click and tonal) in a normal population.

ii) The optimal recording conditions for recording the response (in terms of filter bandpass, analysis time and stimulus repetition rate).

iii) The effects of subjective variables upon the MLR (maturation and arousal level).

The reasons for the lack of acceptance of the MLR and 40Hz response in comparison with other AEPs (BAEP and SVR) were firstly the conflicting answers to these questions and secondly the establishment of a far more solid clinical base for the other potentials. A brief historical resume will illustrate this. After Geisler et al. (1958) initially recorded the MLR, the responses were at first rejected as myogenic in origin and subsequently reinstated as neurogenic (refer to the previous chapter). Following this, vigerous support for the MLR was

forthcoming from a small group of researchers (notably Mendel and collegues) who claimed that the response was able to provide frequency specfic audiometric threshold assessment at all levels of arousal. Methodological critisisms were then levelled at this work as it was claimed that the use of narrow bandpass filters had artificially distorted the MLR and that the response was infact markedly affected by subjective factors. Interest in the MLR was rekindled with the advent of the 40Hz steady-state response (Galambos et al., 1981) which was claimed to offer enhanced detectability over the MLR in audiological assessment. This discussion first examines the morphology of the MLR as it is recorded to non-frequency specific stimuli and under different experimental conditions. The 40Hz response will then be introduced and the chapter will conclude with an examination of the effects of subjective factors upon the MLR and 40Hz. Chapter four will subsequently examine the clinical applications of auditory evoked potentials in general (BAEP, MLR, 40Hz response and SVR) and particularly focus upon the less widely accepted use of frequency specific stimuli in BAEP recording.

3.2 RESPONSE CHARACTERISTICS OF THE MLR.

Although one of the principal aims of ERA is the frequency specific diagnosis of auditory integrity, most of the original research carried out on the MLR prior to 1971 used the acoustic click as the stimulus. This stimulus possesses a broad energy spectrum and encompasses a wide range of frequencies (i.e. is non- frequency specific). Therefore, the reason for using a click stems from the clarity of response it is able to generate through synchronising a large number of auditory neurons and thereby evoking a large response. This point is explained in greater detail in the sections which follows. As the reader progresses through this section, it will become apparent that the selection of filter bandpass is central to the recorded morphology of the MLR. This review therefore sets the scene for the detailed examination of filtering which follows.

Goldstein and Rodman (1967) recorded three principle peaks to a click stimulus delivered at 60dBSL recorded from the vertex (active) referred to the earlobe contralateral to stimulation. The latencies of these components are given in table 3.1. Stimuli were delivered at a rate of

10 per second to 20 normally hearing, relaxed subjects reclining in a dimly lit room. Two thousand responses were recorded within a filter bandpass of 1-50Hz (6dB/octave roll-off). Results showed a clear Na-Pa-Nb morphology which diminished in amplitude with decreasing intensity in most subjects. The effects of muscular contamination upon these responses have been minimised in this study through the use of an earlobe electrode, the high degree of subject relaxation and the large number of presentations averaged. Therefore, it may be assumed that the MLR shown by Goldstein and Rodman (1967) is primarily a neurogenic response. The encouraging correlation between the MLR and subjective threshold demonstrates the potential use of this response in clinical audiological assessment (as defined by the occurrence of the Na-Pa-Nb configuration). Care in the interpretation of these results should however be exercised because the morphology of the response components shown in this experiment might have been artificially accentuated through the use of such narrow bandpass filters (1-50Hz). A comparison of these data and that which was illustrated in chapter 1 (Fig. 1.1 after Picton et al., 1974), shows that far higher frequency activity is present in the first 40 msec. after auditory stimulation than would be detected by the narrow bandpass of 1-50Hz used by Goldstein and Rodman (1967). Only by the use of a broader filter bandpass i.e. 10-3000Hz (Picton et al., 1974), can such components be adequately visualised. More recent research has suggested that the brainstem and middle latency auditory components may be particularly suceptable artificial distortions through the use of narrow filter bandpass (Scherg, 1982; Suzuki et al., 1983a). The question of filter bandpass will become increasingly important as the arguments of this thesis develop.

Mendel and Goldstein (1969 a) presented click stimuli at 50dBSL at a rate of 9.6/second to 12 normal subjects under various test conditions. 1) Sitting in the dark with eyes closed 2) Sitting in light with eyes open 3) Reading (light condition). They defined a clear middle latency waveform, which they attributed to essentially neurogenic activity, which was found to be stable and consistant under all experimental conditions. In addition to the Na-Pa-Nb complex reported by Goldstein and Rodman (1967), two further earlier components were present. Recording from the vertex to the contralateral earlobe and using a filter bandpass of 3-100Hz, Mendel and Goldstein (1969 a) recorded a total of five components of the MLR in comparison to the 3 reported by Goldstein and Rodman (1967):

Table 3.1

	Latency (msec.)				
	No	*Po*	*Na*	*Pa*	*Nb*
Goldstein and Rodman (1967)	—	—	*20-24*	*31--45*	*46-50*
Mendel and Goldstein (1969a)	*7.6*	*16.5*	*26.9*	*40.6*	*54.0*

The first point which is apparent in comparing the data of Goldstein and Rodman (1967) and Mendel and Goldstein (1969 a), is the greater number of responses components visualised in the latter study. Mendel and Goldstein comment that the variability of these middle latency responses might not be physiological in origin, but rather might be due to differences in methodological procedures used in different experiments. Mendel suggested that the amount and type of filtering used to record evoked potentials was largely responsible for amplitude and phase discrepencies. Mendel comments:

> *" Preliminary study of the frequency spectrum of the early components indicates that they contain more high frequency activity than is found in later components. Extensive high frequency filtering which is often used to clean up noisy recordings .... can bring about a phase shift as well as an amplitude reduction of the early components"*

It is interesting to note that Mendel considered the bandpass of 3-100Hz as sufficiently wide to admit all the neurogenic elements of the early auditory response. This could possibly be rooted in the established traditions of EEG recording and the initial auditory evoked potential experiments which investigated the vertex potential (Weitzman and Kremen, 1965; Davis and Zerlin, 1966). With the realisation that higher frequency auditory responses components (such as the BAEP and MLR) could also be recorded, new and more specialised recording procedures were required in order to admit a far higher range of frequencies. Subsequently, much more information concerning the precise physiological morphology of the MLR has been deduced (Kavanagh and Domico, 1986). The development of our understanding of brainstem evoked potentials (Sohmer and Feinmesser, 1967; Jewett and Williston,1971) also relied upon the further realisation that filter bandpass was important in order to visualise these very small, high frequency auditory components. Jewett and Williston went further than Mendel and his co- workers and stated:

" We confirmed the suggestion of Mendel and Goldstein (1969) that the apparent latency of the early waves is markedly influenced by the high frequency cut-off filter. Since the first five waves occur in about 5 msec., the high frequency response should be greater that 1000Hz, at the very minimum."

With the benefit of hindsight, re- examination of the waveforms shown by Mendel and Goldstein (1969 a) appears to show a filtered remnant of the BAEP, unlabelled and at that time unclassified.

Mendel and Goldstein (1969 b) further examined the MLR at different subjective states. Response consistancy between arousal levels is of clinical importance if patients fluctuate between sleep and wakefulness during a lengthy experimental protocol. Mendel and Goldstein suggested that changes in response morphology over different arousal levels could lead to two principle difficulties in interpreting whether a stimulus had actually been 'heard'. Firstly, the stimulus was heard but the response mechanism was impaired in some way through somnolence such that no response was visible and secondly, the response might have altered its morphology as a result of an altered subjective state and therefore may not be recognised by the clinician. There is a difficulty here with the definition of what is precisely meant by 'to hear' a stimulus. Whilst asleep, a subject might have no conscious perception of a sound, yet lower neural centers (below the level of consciousness) may respond to the stimulus. To 'hear' in this sense, more properly means, 'to respond'. It is this property of evoked responses which means that they can be called 'objective', i.e. lying outside conscious control.

Using a similar protocol to their previous experiment (Mendel and Goldstein, 1969a), Mendel and Goldstein (1969b) examined the stability of the early auditory response (bandpass: 3Hz-100Hz) during a single, sleepless 24 hour period in 8 normal subjects to a click stimulus delivered at 50dB SL. EEG activity was monitored continuously throughout the experiment. This experiment was followed by an investigation into the subsequent effects of sleep on the responses in 3 of the subjects.

During prolonged wakefulness, the following components were consistantly recorded:

No	*8.3 msec.*
Po	*13.3 msec. (s.d.= 0.3)*
Na	*22.0 msec. (s.d.= 0.7)*
Pa	*32.3 msec. (s.d.= 1.3)*
Nb	*45.3 msec. (s.d.= 1.8)*

This data was calculated as the grand mean of 8 separate trials throughout the 24 hour period over which no circadian variations were reported. By similar calculation, the mean amplitudes of the waveforms were:

Po-Na	*0.86μV. (s.d.= 0.13)*
Na-Pa	*1.07μV. (s.d.= 0.19)*
Pa-Nb	*1.01μV. (s.d.= 0.15)*

The middle latency responses recorded during sleep were made whilst the subject was reclining in a chair over a test period of 1.0-1.5 hours. Mendel and Goldstein awknowledge that the experimental protocol employed was not specifically designed to accurately score subject's sleep stage. However, responses were reported as consistant and stable to 20dBSL during sleep of combined stages. The stability of the MLR over long periods and at different arousal levels led Mendel and Goldstein (1969b) to suggest that the response might be a viable alternative to the slow vertex response. The SVR had proved a valuable audiological test in an alert subject, but was very variable in subjects that were drowsy leading to an elevation in threshold estimation (Ornitz et al., 1967). The small subject sample size (n=3), the use of narrow filter bandpass (3-100Hz; -6dB down) and the lack of adequate sleep scoring in the experiment, would perhaps suggest a more cautious interpretation. Later research has shown that the MLR may also be affected by sleep but that these changes may not always be adequately visualised when narrow filter bandpasses are employed (Erwin and Buchwald, 1986 a and b; Suzuki et al., 1983a; Kavanagh and Domico, 1986). The current position concerning the effects of sleep on the MLR is discussed in detail later in this chapter.

Madell and Goldstein (1972) investigated the effect of changes in intensity on the middle latency components of the auditory evoked response. Using click stimulation (9.6

presentation / second), twenty four adult subjects were tested on two separate occasions. The filter bandpass used was 5-150Hz (6dB/oct.) Subjects were reclined and responses were recorded from the vertex to contralateral earlobe. 1536 averages were summed for each evoked response. The principal components of the response at 50dBSL were :

Po	*11.3 msec.*
Na	*20.8 msec.*
Pa	*32.4 msec.*
Nb	*46.5 msec.*

The effect of decreasing intensity was to reduced the amplitude and increase the latency of these components. Madell and Goldstein (1972) found good intra- subject agreement both in latency and amplitude between trials, but large variations in amplitude were observed between subjects. Evoked response amplitude of the Po-Na , Na-Pa and Pa-Nb peaks plotted against loudness estimates were found to be highly significant (0.94, 0.85 and 0.75 respectively). Madell and Goldstein (1972) found thet the earlier peaks (Po and Na) of the MLR tended to have the most linear input-output characteristics whereas later components (Pa and Nb) exhibited a decrease in slope at higher intensities.

Once again the influence of filter bandpass is relevant. Mendel and Goldstein (1969 b) quote the latency of the Po component as 13.3 msec. (filter bandpass 3-100Hz, 6dB/oct. slope). Madell and Goldstein (1972) report a Po latency of 11.3 msec. (5-150Hz, 6dB/oct.). Since stimulus intensity is the same in both these experiments (50dB SL) and all other recording parameters are essentially the same, it would seem correct to conclude that reducing the high cut filter serves to increase the latency of response components. In comparing these results with the reported latencies of the MLR given by Picton et al. (1974) using a bandpass of 10-3000Hz (no slope information provided, 60dB SL), it can be seen that there can exist a problem with nomenclature of components when different bandpasses are used. Comparing the peak latencies of wave V (BAEP) and Po (MLR), it can be seen that in Picton's experiment, the wave V component of the brainstem response (5.8 msec.) is clearly distinct from the Po component of the MLR (12 msec.). In the Mendel and Goldstein (1969 b) and

Madell and Goldstein (1972) papers, this distinction cannot be made with any confidence due to the high degree of waveform filtration. Therefore, it appears that the positivity, Po recorded in earlier experiments using narrow filter bandpasses, is really the peak of the low frequency positive wave upon which the individual (high frequency) waves of the brainstem response are added should the filtering be less severe. Picton's Po component, recorded with wider filter settings, would appear to reflect activity from higher centres along the auditory pathway and is clearly distinguishable from wave V.

To summarise, it has been consistantly demonstrated throughout this review of earlier literature that the nature of the recording system has significantly affected the morphology of the waveform. This phenomenon, although common to all branches and modalities of evoked potential, has nowhere been more significant than in the development of our current understanding of the MLR. This is because methodological parameters have been shown to be responsible for a large proportion of the variability of the MLR and also the conflicting reports concerning the response's presence or absence under different subjective conditions. The section which follows looks at the specific problems encountered in the repeatable recording of the MLR as a result of inconsistant filtering parameters.

3.3 THE EFFECT OF SYSTEMS BANDPASS UPON MLR RECORDING.

Analysis of the frequency spectrum of the MLR using the fast Fourier transform (FFT) has shown the principal frequency of the waveform to lie in the 30-50Hz range in the waking subject (Suzuki et al.,1983 a; Kavanagh and Domico, 1986). Historically, the observation that the frequency profile of the MLR is centered around 40Hz, has been the main reason for the extensive filtration used by some researchers to record the response (Mendel et al., 1969 a; Thornton et al., 1977; Vivion et al., 1980). McFarland et al. (1975) said:

> *" The exclusion of high-amplitude low-frequency activity (appears) to enhance visual recognition of the middle components "*

Indeed, the rationale behind the 40Hz steady state evoked potential is based upon the observation made by Galambos et al. (1981), that the potentials occurring 8-80 msec. after presentation of an auditory stimulus resembled the oscillations of a 40Hz sinusoid. In this section, the effects of filter settings upon MLR morphology shall first be discussed after which, the 40Hz response will then be introduced. It has been suggested in recent work that severe filtration of the MLR, as favoured in the original literature, was responsible for distorting its morphology and may have had the added effect of masking any changes in the frequency composition of the response which might occur as a result of changes in subjective state (i.e. arousal level).

Kavanagh et al. (1984) investigated the BAER and MLR recorded with different filter bandpasses. Click stimuli were delivered (0.1 msec. duration) at a rate of 9.7/ sec. and a vertex to mastoid electrode derivation was used in this study (Figure 3.1 a and b). Kavanagh and collegues defined a series of slow waves occurring in the first 36 msec. after stimulus onset. Examining first the bottom right hand trace of figure 3.1 a, (reproduced by Kavanagh from Mendel and Goldstein, 1969b) , a slow positive wave (Po) with a maximum corresponding to the latency of wave V may be seen. Secondly, a broad negativity (Na) with its nadir at around 25 msec. and finally a large positivity (Pa) peaking at approximately 36 msec. With increasing bandwidth (up to 15- 3000Hz), the high frequency individual waves I-V of the brainstem response emerge upon the Po wave, the peak of which had decreased in latency. Also now visible was a further complex between Po and Na comprising a negative component (SN) and a positive P wave (which is defined as the positive deflection occurring between the BAEP and the Pa component of the MLR; after Kavanagh et al., 1988). The latency of Na was also reduced and Kavanagh et al. re-labelled this component, Na_2 in order to differentiate it from SN. The SN negativity reported by Kavanagh et al. (1984) has been variously referred to as the SN10 (Davis et al. 1976) and No (Mendel and Goldstein, 1969b). With a bandpass of 15- 3000Hz , the latency of Pa had also reduced by around 10 msec. to around 26 msec. representing a complete polarity reversal between Na and Pa caused purely by changing the bandwidth.

Kavanagh et al. (1984) further examined the effect of stimulus intensity on the P wave

Figure 3.1 The effect of varying systems bandwidth upon the morphology of the BAEP and MLR (Kavanagh et al., 1984).

described above. It was found that as intensity was decreased, the latency of P increased at a faster rate than either Po (the filtered wave V) or Pa. At high intensities the P wave was seen upon the down slope of wave Po whilst at lower intensities , upon the up slope of Pa. This point is interesting because it means that at high stimulus intensities the latency of Na is measured to the trough of Na_2 whilst at low levels, it is measured to the trough of SN. Kavanagh suggested that this can result in an abrupt shortening of the latency of Na as intensity is decreased. Because of the disproportionate effects of intensity of the component, Kavanagh suggested that the neurogenic origin of the P wave might be called into question with its derivation from the post-auricular muscle response being indicated (Yokoyama et al., 1987). This work clearly illustrates the effect of lowpass filtration upon BAEP and MLR morphology. The effects of highpass filtering are shown in figure 3.1 b. With the 15- 3000Hz bandpass, waves I, III and V of the BAEP are recorded. Also visible are the SN, P, Na_2, Pa and Nb components of the MLR. As the highpass filter is raised to 30Hz and beyond, these response components are distorted. Between the 30- 3000Hz and 60- 3000Hz bandpasses there is a marked reduction in the amplitude of the Na_2- Pa- Nb configuration which would suggest that the predominant energy of this waveform lies below 60Hz. With filter bandpasses of 100- 3000Hz and above, the amplitude of the combined BAEP and MLR is reduced by approximately a factor of two (0.62μV) and only the wave V component of the BAEP may be readily identified.

Scherg (1982 a) examined the effect of analog and digital filtering on the waveform of the BAEP and MLR. Using 50dBSL click stimulation (4000 averages) and an initial wide recording bandpass of 1-2000Hz, Scherg first examined the effect of lowpass filtration on response morphology. An analog (Butterworth) filter with a slope of 24dB/oct. set at levels of 1000Hz, 500Hz, 200Hz and 100Hz was employed and responses were recorded from a vertex to earlobe derivation. Scherg (1982) found a progressive latency increase in the MLR as this filter was systematically decreased, amounting to 5 msec. difference between the latency of Na, Pa and Nb as measured with a 1kHz high frequency filter compared with 100Hz. Furthermore, the wave V component of the BAEP also became later and less well defined at filter levels less than 500Hz. Changing the level of the analog low frequency filter from

1-80Hz (24dB/oct slope) was found to introduce significant changes in both the latency and amplitude of the original response. Filter oscillations introduced by the earlier waveform components as the level of the highpass filter is increased, caused a progressive shortening of the later Nb-Pb complex and also a marked artificial increase in this component's amplitude. The latency shift induced by a 40Hz-2000Hz bandpass was sufficient to introduce a complete polarity inversion of Pa and Nb in comparison with the 1-2000Hz original waveform. The BAEP wave V component became reduced in amplitude at highpass filter levels in excess of 20Hz as the slower (lower frequency) components upon which it is situated were attenuated. Scherg (1982 a) also investigated the significance of filter slope upon the morphology of the brainstem and middle latency auditory responses. The slope of filters reflects the rapidity with which frequencies outside the desired bandpass are attenuated. So, for example, a filter with slope of 24 or 48 dB/octave will attenuate extraneous frequencies much more abruptly than will a shallower filter set at 6 or 12 dB/ octave. The steeper the filter, the greater the distortions brought to bear upon the waveform (caused by larger oscillations in the filter's response characteristic). Scherg found that the Pa component underwent a complete polarity inversion with a 48dB/ octave filter slope with respect to the original waveform. This illustrates that the more the original waveform is restricted through narrow filter bandpasses and steep filter slopes, the more the morphology of the waveform depends upon non-physiological phemomena.

A further point demonstrated by Scherg (1982 a) is the interaction between components in the brainstem and middle latency ranges. Both these sets of responses influence the morphology of the other and the extent to which this occurs is governed by the precise procedures involved in recording these responses. Other workers (Boston and Ainslie,1980; Doyle and Hyde, 1981) have also examined the effect of analog and digital filtering on the BAEP and have found similar latency and amplitude distortions with narrow analog filter bandpasses. Digital filtration or wide bandpass analog recording was recommended by both groups as being desirable if the true physiological morphology of the response is required. Elton et al. (1984) advised that zero-phase shift filters were recommended for recording the BAEP and if these were not available, highpass analog filters should be no greater than 100Hz with slopes not steeper than 6dB/oct.

An awareness of the distortions caused by filter bandwidth and slope on brainstem and middle latency responses is most important when comparing data obtained from different laboratories. As long ago as 1969, Mendel and Goldstein warned:

> *" It is not known to what extent the nature of the total recording system including filters affects the recorded characteristics of the early components of the AER.... differences between our observations of the AER and those of other investigators may possibly be accounted for by differences in the characteristics of the various recording systems. "*

This observation would appear to be justified as these differences have made a significant contribution to the reported variability of the MLR. It may be argued that the reported variability of the MLR in the literature is due to poor standardisation of optimal recording parameters and hence large inter-laboratory inconsistancies when recording these responses. This implies that if the true, physiological MLR is to be recorded, procedures must be implemented which do not filter the waveform too severely. Resulting from work investigating the frequency composition of the MLR the concept of the 40Hz staedy state potential emerged. As previously mentioned, the 40Hz response (Galambos et al., 1981) has generated renewed interest in the possible clincial applications of the MLR. The 1980s has seen the extensive investigation of this response. The following section shall therefore examine the rationale behind recording this steady state potential.

3.4 THE 40HZ RESPONSE.

The 40Hz response (defined in Chapter 1) has provided a new impetus for research into the possible clinical utility of the middle latency responses. The previous chapters of this thesis have illustrated the mixed fortunes of the MLR in comparison with the clinically better established BAEP and SVR. The reported controversies first concerning the response's origins and then its reliability under different recording conditions had meant that prior to the 40Hz era, confidence in the MLR was not high. It is important to remember that the 40Hz response does not only represent middle latency activity (i.e. components lying in the 8-40 msec. latency range). This response is the result of the superimposition (every 25 msec.) of

all activity occurring after the delivery of a stimulus and therefore combines brainstem and middle latency components. As such, the 40Hz response has been termed a steady-state evoked potential as distinct from a transient response (BAEP, MLR and SVR) in which no such 'overlapping' of consecutive responses takes place (Kavanagh and Domico, 1986).

Interest in the 40Hz response grew out of a clinical requirement for an objective frequency specific test of auditory threshold which could be recorded at all levels of arousal. Since both the constituents of the response (the BAEP and MLR) had been extensively characterised in the previous two decades, the clinical applications 40Hz response were quickly seized upon. The original description of the 40Hz response is credited to Galambos et al. (1981). Galambos suggested that the resonance of the MLR at 40Hz is also mirrored in the brain's response to other modalities of sensory stimulus. This concept of the convergence of sensory pathways within the brain is not however new and this section shall begin with a brief resumé of the literature which has examined the 40Hz activity of the brain.

3.41 The study of 40Hz brain activity.

There has been interest in the similarity of responses generated to different modalities of stimulus for a number of years. Adrian (1941) first noted such activity within the olfactory bulb upon the application of odourous substances. He termed this type of 40Hz activity an 'induced' response as distinguished from the bulb's intrinsic, ongoing activity centered at around 10Hz. Further research into other sensory pathways has suggested that 40Hz activity may be elicited to a wide range of sensory stimuli, including auditory stimulation (Galambos, 1982).

The most provocative feature of the 40Hz brain activity was that it appeared to be the result of changes in the attention state (arousal level) of a sensory region. This 'multi-modal' nature of 40Hz brain activity has led to the suggestion that the response may be originating from an area of the brain at which sensory pathways converge (Walter, 1964; Galambos, 1982; Suzuki et al., 1983 a). The postulated cortical (sub-cortical) location for this convergence of sensory pathways is thought to be within the reticular activating system (RAS) or the

diencephalon (thalamus, hypothalamus). The audiological applications of 40Hz brain activity are not only of clinical interest. Observing the similarity of the auditory middle latency response to a 40Hz sinusoid, Galambos et al. (1981) suggested that certain aspects of the middle latency response might be the manifestation of 40Hz brain activity within the auditory system. These theoretical considerations concerning the ongoing frequencies within the brain, also have some relevence to audiological investigation.

3.42 The auditory 40Hz response.

Galambos et al. (1981) suggested that using a stimulus repetition rate presented at the approximate fundamental frequency of this 'sinusoid' (i.e. 40Hz), would result in the superimposition of successive middle latency responses. This addition of concurrent waves (all in similar phase) would generate a larger response and could facillitate response detection at intensities near audiometric threshold. This type of response is classified as a steady state evoked potential (SSEP). An SSEP may be defined as a waveform generated to a stimulus presented at such a rate that responses from successive stimuli overlap (Kavanagh and Domico, 1986). Since the abbrieviation 'SSEP' can be be confused (with the Somato-sensory evoked potential), the term '40Hz response' shall simply be used to describe this steady state potential.

Galambos presented both click and tonal stimuli to subjects who were either awake or in light sleep. A filter bandpass of 10-100Hz was used. The results suggested that a super-imposition of consecutive brainstem and middle latency responses did occur at the 40Hz repetition rate and these responses yielded threshold estimates accurate to within 5dBSL with all stimuli. Figure 3.2 shows the influence of stimulus repetition rate upon the amplitude of the MLR.

Although the clinical applications of a MLR generated to a stimulus rate of around 40Hz may be accredited to Galambos et al. (1981), this observation was made originally by Geisler (1960). He found that varying stimulus repetition rate produced the largest response in the

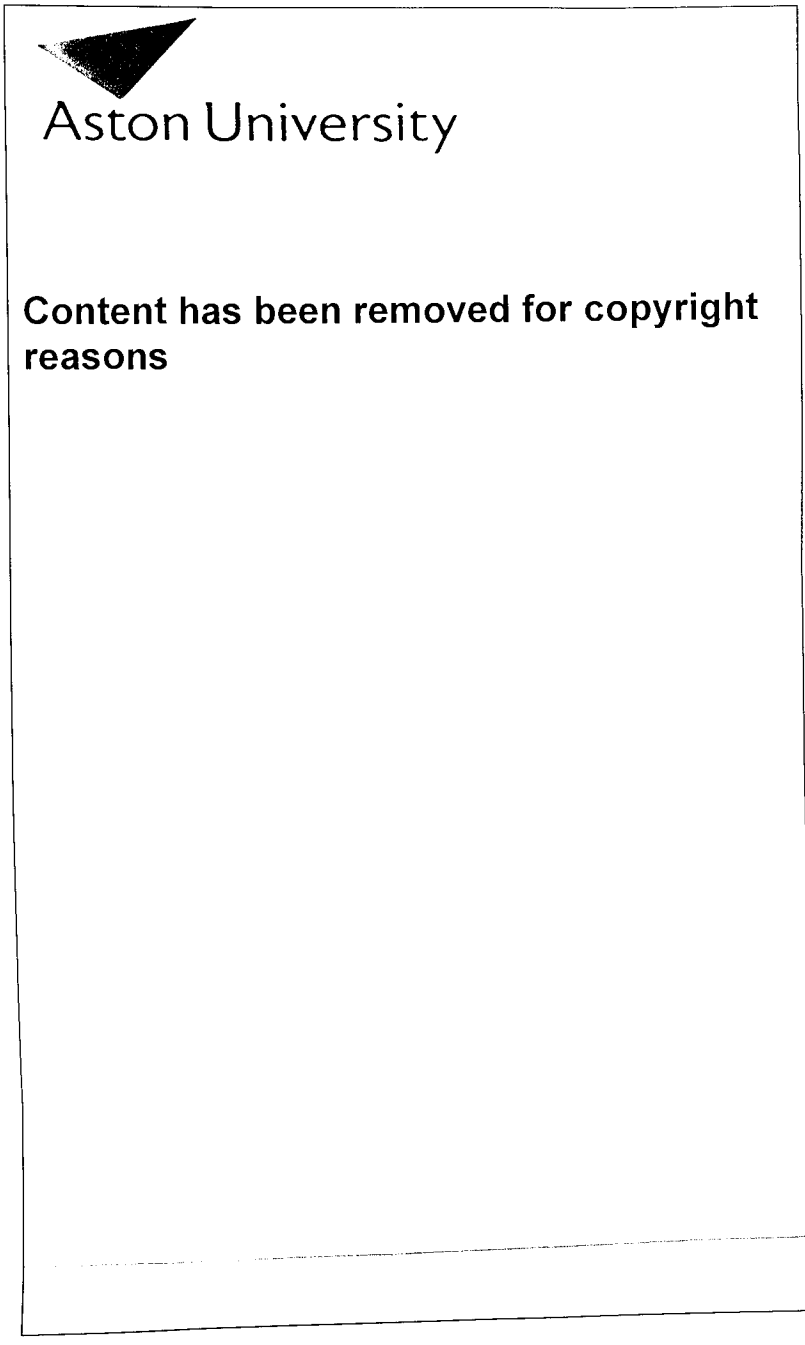

Figure 3.2 The effect of altering stimulus repetition rate on the morphology of the BAEP and MLR (Galambos et al., 1981).

30-40Hz range both in the subjects tested and also according to his theoretical model in which an idealised response was manipulated by a computer. Geisler (1960) commented:

> *" This type of average response (40Hz) can perhaps be explained by a 'skipping behaviour', a response is evoked by approximately every other click..... The increase in response amplitude in the 30-50/ sec range is probably caused by the overlap of response components ".*

In addition to the superimposition phenomenon noted at the 40Hz rate, Geisler (1960) found that the general effect of increasing stimulus repetition rate above the 40Hz rate, was to diminish the amplitude of the principal negative component of the response (Na, 30 msec) in the adult subjects tested. To summarise, the 40Hz response has developed from studies of the frequency composition of the MLR and has emerged in recent years as a possible tool in audiological electrodiagnosis. The clinical utility of this response is discussed fully in chapter 4 and the experimental work which follows.

The next section of this chapter continues the discussion of factors which can affect the MLR and 40Hz responses. Such factors might be called subjective variables (as opposed to methodological) and comprise, subject arousal level and maturation and how these might effect the morphology of the responses.

3.5 THE EFFECT OF SUBJECTIVE PARAMETERS UPON THE MLR AND 40HZ RESPONSES.

The concluding sections of chapter three will look at the literature which has examined the effects of arousal level (sleep and wakefulness) and age and maturation upon the MLR. Inevitably, there is a high degree of interplay between these factors and those methodological parameters already discussed and this point shall be emphasised as the discussion progresses.

3.51 The clinical significance of sleep in ERA.

Chapter one examined the aims of objective audiometry in the assessment of hearing. It was emphasised that successful electrophysiological testing in young children relied upon the patient being sedated or in natural sleep in order to attenuate movement artefacts and myogenic activity from the background EEG. It is well established that the clinical utility of the BAEP is not compromised by changes in level of arousal from relaxed wakefulness through to deep sleep (Jewett and Williston, 1971; Amedeo and Shagass, 1973; Picton et al., 1974; Starr and Anchor, 1975). Similarly, it is well known that the SVR is profoundly altered during sleep and hence offers no assistance in the clinical evaluation of patients who are not awake and alert (Osterhammel et al., 1973). Middle latency and 40Hz responses however occupy more uncertain ground. The discussion which follows sets out the evidence concerning the stability of these responses as arousal levels change.

3.51 a Classification of sleep stages.

Electrophysiologically, sleep is comprised of a number of distinct stages which are characterised by differences in EEG (electroencephalic), EOG (electro-oculographic) and EMG (electro-myographic) activity. The most widely established classification of sleep and sleep stages currently in use was developed by Rechscaffen and Kales (1968) and a brief description of their classification system is summarised below. The characteristic EEG, EOG and EMG waveforms seen in each stage of sleep are shown in figure 3.3.

Wakefulness (stage W or stage 0) corresponds to electro-cortical activity present during normal wakefulness. The ongoing EEG characteristic of this state will comprise primarily of **alpha** activity (8-13 cycles/ sec.). Stage W is also characterised by eye blinking and a relatively high level of muscular activity (see Fig. 3.3 a). Stage 1 sleep is the first stage of sleep and is characterised by a genereal decrease in muscular activity accompanied by slow, rolling eye movements. The EEG typical of this stage exhibits a reduction of alpha activity with an increase in lower frequency **theta** activity (4-7cycles/ sec.).

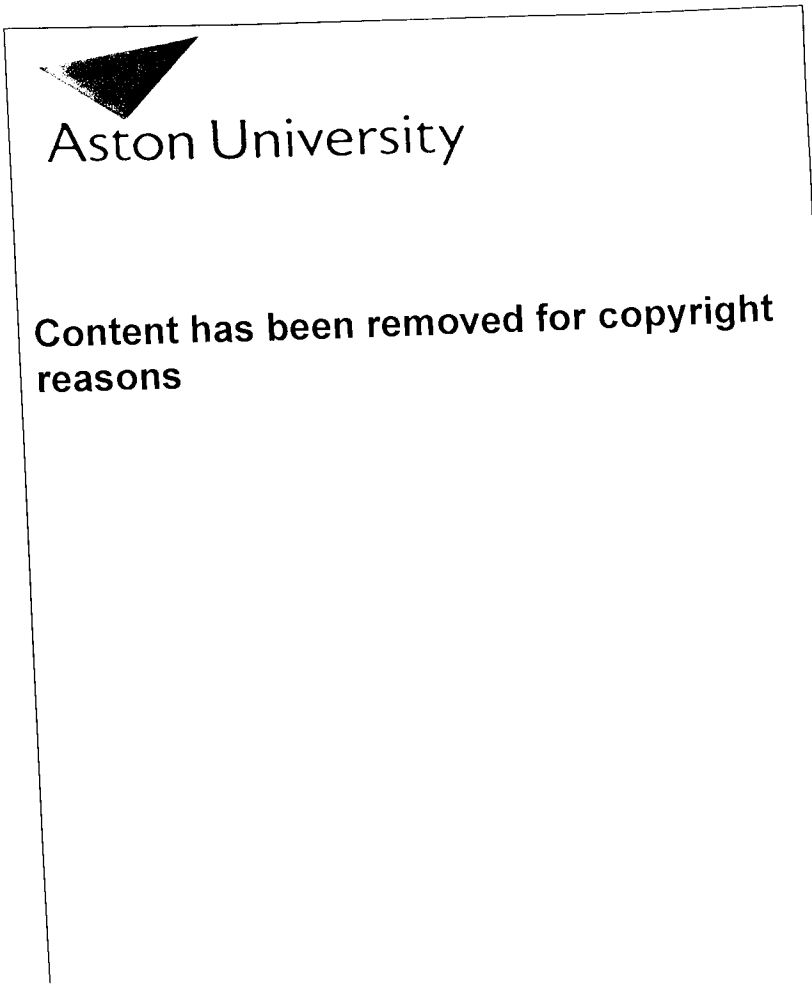

Figure 3.3 Electro-encephalic classification of relaxed wakefulness and sleep stages 2, 3, 4 and REM. (Rechschaffen and Kales,1968.)

Stage 2 sleep has a very distinctive EEG activity comprising of sleep spindles which are bursts of rhythmic fast activity (12-14 cycles/ sec.). Also present are K-complexes (Davis et al., 1938) and Vertex sharp waves (see fig. 3.3 b). Stage 3 and stage 4 sleep are collectively known as slow-wave sleep (SWS) and are characterised by a predominance of **delta** activity (0.5-3 cycles/ sec.). Delta waves are large in amplitude (75μV or more) and if present in 20-50% of the record, defines stage 3 sleep. Stage 4 sleep may only be scored if delta activity is present in excess of 50% of the sleep record (see fig. 3.3 c). Eye movements are unremarkable in stages 2, 3 and 4 sleep and muscle activity is seen generally to progressively attenuate. Sleep stages 1-4 are collectively known as Non-REM sleep (SWS). Rapid eye movement sleep (REM, also known as paradoxical sleep) comprises the majority of the remainder of sleep according to Rechschaffen and Kales (1968). The EEG characteristic of REM sleep may be described as 'activated' , low amplitude activity similar to that recorded during stage 1. For REM sleep to be scored, muscular activity must be at its lowest during the night's record. Eye movements are abrupt and periodic (see fig. 3.3 d).

3.52 The influence of subject arousal level the MLR and 40Hz response.

Much of the enthusiastic support for the MLR in ERA has been provided by Mendel and collegues in experiments carried out throughout the last twenty years (Mendel and Goldstein, 1969 a,1971b;Mendel and Hosick, 1975; Mendel et al., 1975; Mendel, 1980). Mendel et al. (1975) compared thresholds obtained with the MLR and SVR auditory components in adults in light (mixed stages 1, 2 and REM) and deep sleep (stages 3 and 4) and in wakefulness. 28 normal subjects were tested (mean age 25.5 years, 22- 39 range) and presented with click stimuli at a rate of 9/ sec. The montage employed was vertex to either mastoid (late potentials) or earlobe (MLR). Sleep was induced with secobarbital and depth was scored according to the criteria set down by Rechschaffen and Kales (1968). Table 3.2 a summarises the results from this experiment by showing the proportion of the twenty eight subjects who gave better, the same or worse estimates of audiometric threshold with either the MLR or SVR. The term 'both thresholds determined' means that estimates were lower than 30dBHL for each test. 'Indeterminate thresholds' means that no threshold could be reliably obtained below 30dBHL.

Table 3.2 a Relative sensitivity of the MLR and SVR in sleep and relaxed wakefulness (after Mendel et al., 1975).

State of consciousness	Awake	Asleep	
		Light	Deep
Both thresholds determinate			
Middle more sensitive	*14*	*23*	*8*
Middle = late	*4*	*0*	*3*
Late more sensitive	*5*	*1*	*2*
Indeterminate thresholds (i.e. above 30dBSL)			
Middle only	*2*	*1*	*4*
Both	*0*	*0*	*5*
Late only	*3*	*3*	*6*
Total subjects	*28*	*28*	*28*

Table 3.2b Audiometric threshold estimates (dBSL).

	Awake	Light	Deep
Middle components			
Range	*10-40*	*5-25*	*10-50*
Median	*17.5*	*15*	*20*
Mean	*18.5*	*15*	*21.5*
Number of determinate thresholds	*26*	*27*	*19*
Late components			
Range	*10-45*	*20-45*	*10-40*
Median	*30*	*30*	*30*
Mean	*27*	*30*	*27.5*
Number of determinate Thresholds	*25*	*25*	*17*

Mendel concluded that:

> *"... the middle components show more promise as a clinical audiological tool than do the late components. In each state of consciousness (they) yielded more sensitive estimates of auditory threshold and fewer indeterminate thresholds."*

In the light of the previous discussion, reservations might justifiably be raised due to the narrow filter bandwidth used to record middle responses in the study (10-100Hz). In addition, the mixing of sleep stages 1, 2 and REM in the light sleep category may have been not wholly justified as subsequent work has shown that these levels of arousal are not equivalent (Hinman and Buchwald, 1983; Erwin and Buchwald, 1986 a and b; Erwin and Buchwald,

1987). This body of work is discussed in detail shortly.

Since the initial work of Mendel and co-workers, strong evidence concerning morphological changes in the MLR during sleep has been suggested. The evidence for this conclusion has not only been gathered from specific studies examining sleep and the MLR but it shall also be argued that by re- evaluating work which set out to examine other features of the MLR effects of sleep can be observed.

Özdamar and Kraus (1983) examined the morphology of the BAER and MLR using wide bandpass filters (3Hz-2000Hz) and click stimulation. The authors reported that tree distinct types of MLR were exhibited in the subjects tested. These variants were classified as :

(A) Double peaked. Separate Pa and Pb components.

(B) Broad Pa only

(C) Absent Pb component. Pa only.

Figure 3.4 presents this data. Özdamar and Kraus proposed that these variations in MLR morphology represented natural variants or sub-types of the response displayed in different individuals. However, this conclusion may be challenged because the variable of sleep/ wakefulness was not controlled in this experiment. The researchers stated that responses were recorded either in sleep or relaxed wakefulness which means that these variations in morphology could be equally well attributed to changes in arousal level.

Partly in an attempt to replicate the results of Özdamar and Kraus (1983), Suzuki et al. (1983a), delivered click stimuli to sleeping subjects (though level of sleep was unspecified) using a wide recording bandpass of 0.8-4000Hz. Suzuki reported that three principal types of MLR could be recorded in accordance with Özdamar and Kraus (1983). Figure 3.5 a, b and c illustrates these variants and the effect of raising the highpass filter upon waveform morphology. Fourier analysis performed upon fig.3.5 a revealed its principal power to lie in the 30-50Hz range as is found in waking subjects (Kavanagh et al., 1984). Although the frequency content of figs. 3.5 b and c is not specified, it would appear that the principal

Figure 3.4 Naturally occurring variants of the MLR in normal, adult subjects (Özdamar and Kraus,1983).

Figure 3.5 a Variations in MLR morphology in sleeping subjects (Suzuki et al., 1983a).

Figure 3.5 b and c Variations in MLR morphology in sleeping subjects (Suzuki et al., 1983a).

energy of these waveforms is not centred around 40Hz but rather is lower than in Fig.3.5 a. Suzuki and collegues concluded that the reason for the variations in MLR morphology reported by Özdamar and Kraus (1983) might be due to using too wide a bandpass with low frequency components present in sleep masking the response. Suzuki and collegues proposed that a large degree of this inter-subject variability was eliminated with high pass filtering at 30Hz. However, there is danger in directly comparing the data of Özdamar and Kraus (1983) and Suzuki et al. (1983a). This is because the former study recorded responses in both sleep and wakefulness whilst the latter presents data soley from sleeping subjects. Suzuki does not comment on this lack of distinction between sleep or relaxed wakefulness present in the report of Özdamar and Kraus (1983). It could therefore be equally suggested, that the variations in morphology ascribed as three distinct types of MLR (Özdamar and Kraus, 1983), were in fact due to responses being recorded in different states of arousal. Similarly, an alternative explanation of Suzuki et al. (1983a) findings might be that the MLR waveform (as does the SVR), actually changes during some stages of sleep giving rise to a response with a larger amount of low frequency activity which would be subsequently filtered out by this filter setting.

Kavanagh and Domico (1986), in a similar study to that of Suzuki et al (1983 a), using wide bandpass filters (0.2Hz- 8000Hz) detected a second dominant frequency (in addition to 40Hz) in the MLR at around 10Hz during recordings in natural sleep. Unlike Suzuki et al. (1983a), Kavanagh and Domico (1986), attribute this low frequency activity to a biological response and not as a result of non-physiological noise due to a reduced systems bandwidth. The relatively small contribution of the 10Hz component in Suzuki et al. (1983a) in comparison to the 40Hz peak (estimated as 6 times larger than the 10Hz component) was due to an inaccuracy in calculation highlighted by Kavanagh and Domico (1986). The revised assessment of their data showed equal amounts of 10Hz and 40Hz activity within the MLR.

The low frequency (10Hz) energy present in the MLR has been frequently eliminated by researchers through response filtration as it exhibits a high degree of inter subject variability (Suzuki et al. 1983a) which it might be suggested is due to alterations in level of arousal. The data cited above would suggest that the characteristic morphology of the MLR as classically

described (Mendel and Goldstein, 1969 a and b) appears therefore not to hold true under all physiological conditions and may have been simply the product of procedural parameters imposing artificial effects upon the response components. The suggested modifications of the response during sleep have been reported as most noticable in the later components of the waveform (Pa, Nb, Pb), which it has been suggested, are generated in 'higher' (rostral) structures more sensitive to changes in arousal level (Osterhammel et al., 1985; Erwin and Buchwald, 1986 b; Imeri et al., 1988).

Osterhammel et al. (1985) examined the effect of changes in the BAEP and the MLR during stages 1, 2, 3, and 4 sleep using wide bandpass filters (BAEP: 125-2500Hz, MLR: 20-2500Hz). It was reported that the BAEP remained stable during all stages of sleep exhibiting no shifts in latency in the principal components of the response. The MLR however, showed a progressive decrease in amplitude through sleep stages 1-4. The Pa component latency remained stable, but the later components of the response (Nb, Pb) became later, less distinct and of decreased amplitude. Osterhammel comments:

> *" It is evident that the later part of the MLR is susceptable towards sleep, indicating that response generators from here on rise in the afferent auditory system to structures with more complex functions. "*

Osterhammel concluded that since there was a differential effect of sleep on the constituent components of the MLR, there would be no superimposition of successive responses at the 40Hz stimulus repetition rate in sleep as in the waking response. By this the author means that 40Hz may represent the 'intrinsic' frequency of the combined BAEP and MLR in waking subjects but if some of the later components of the response are lost during sleep, then the periodicity of the response is lost and superimposition does not occur. Chapter seven in the experimental work which follows, tests this hypothesis in great detail.

Linden et al. (1985) examined the amplitude of the MLR as a function of stimulus repetition rate during all stages of sleep. Using a filter bandpass of 5-1900Hz (6dB/ oct. slope) and varying the rate between 10 and 60Hz (2Hz increments), 500Hz tone bursts were presented to ten normal subjects (mean age 25 years, range 23-35 years). Linden found the

consistantly highest amplitude was in the 30-50Hz frequency range. A general reduction in amplitude of the MLR was reported during sleep but always with a consistant principal frequency maximum between 30 and 50Hz regardless of arousal state. Table 3.3 summarises these findings.

Table 3.3 The effect of arousal level upon the amplitude of the MLR.

Subjective state	*Repetition rate at Maximum response amplitude (/sec)*
Awake	*34± 12*
Stage 2 (early)	*35± 11*
Stage 2 (late)	*33± 7*
Slow wave	*28± 7*

Figure 3.6 shows the amplitude /rate functions for the MLR over all the subjective states measured. In addition to the peak seen at around 40Hz , there is another maxima observed at around 10Hz. The relative contribution of this lower frequency component increases during sleep accompanying a proportional decrease in 40Hz activity. Linden et al. (1985) reported that determination of threshold was not not significantly different in sleep (all stages) and wakefulness despite quite large variations being present in sleep (range: 20dB). These estimates of threshold were based on linear extrapolation of the amplitude/ intensity function at the high intensities measured. This result is of interest in the clinical application of the 40Hz response It suggests that although shifts in the frequency composition of the response do appear to occur during sleep, response detection is not compromised. However, in a subsequent experiment the same researchers revised their position on the effect of sleep claiming that threshold estimates were elevated by 11dB in sleep in comparison to wakefulness (Picton et al., 1987). They suggested that discrepency between the two experiments is due to firstly, the standard deviations tolerated in the original study (Linden et al., 1985) which could have been sufficient to mask a difference of up to 10dB. Secondly, according to Picton et al. (1987) the linear extrapolation of threshold used in the Linden et al. experiment may have been invalid.

Figure 3.6 Amplitude verses rate function of the MLR recorded at different levels of arousal (Linden et al, 1985).

Brown and Shallop (1982) examined the clinical possibilities of the 40Hz (referred to in chapter 4) and were also among the first to observe that sleep might exert an effect upon the 40Hz response. Figure 3.7 presents the data of these workers comparing the 40Hz response in wakefulness and sleep. Brown and Shallop suggested that the amplitude of the 40Hz response progressively decreases through stage 1 sleep, reaching a minimum of 40 - 50% of the waking value in stage 2. No further reductions are reported by these authors through stages 3 and 4 sleep and REM sleep is not mentioned. As to the detectability of the response near audiometric threshold, Brown and Shallop claim accuracy to within 20-25dB in all subjects and often to within 10-15dB in most cases to a 500Hz tone pip stimulus (methodology is fully detailed in chapter 4). Here again the issue of filter bandpass is important. Brown and Shallop used a bandpass of 30-100Hz and themselves comment that:

> *" When asleep both Pb and Pc are either greatly reduced in ampliude or absent.....The decrease (in amplitude of the 40Hz response) is probably due to the very small contribution of Pb and Pc to the combined response (in sleep).*

This suggests that the contribution of the MLR to the 40Hz response is variable and dependant upon subjective state. The 40Hz response has subsequently been analysed further by other workers using wider filter bandpasses (Kavanagh et al.,1984; Kavanagh and Domico, 1986) and is supportive to the arguments that shall be laid out in the experimental sections of this thesis.

3.53 Differential effects of sleep upon the individual components of the MLR.

This section examines the proposed physiological basis for the putative changes in MLR morphology which occur in sleep. In chapter 2, it was suggested that the MLR derived from neurogenic activity arising in the thalamus, primary auditory cortex and possibly more widely spread cortical projections (Streletz et al., 1977; Cohen, 1982; Kileny et al., 1987). It was also proposed that there is currently some controversy concerning the changes which might occur in the MLR accompanying changes arousal level. Current literature (cited in the previous

Figure 3.7 Comparison of the 40Hz response in wakefulness and sleep (Brown and Shallop, 1982).

section) has suggested that sleep stage and arousal level are able to influence the morphology of the MLR and hence the 40Hz response (Brown and Shallop, 1982; Kavanagh et al., 1984; Jerger et al., 1986; Picton et al., 1987). Evidence for this theory has been drawn from both single-cell recording techniques used in animal studies (Wolpaw, 1979; Kaga et al., 1980) and from multicellular, suface electrode recording. These findings have indicated that the components of the MLR might derive from different neural substrates and that the reticular activating system (RAS) and thalamic structures may be involved in the generation of the late positive (Pb) component of the human response (Erwin and Buchwald, 1986b; Erwin and Buchwald, 1987). Buchwald and co-workers, in experiments spanning the last decade, have characterised the middle latency response in the cat and from these data, drawn analogies as to the possible generators of components in the human waveform. The research which is summarised in this section briefly examines the postulated contributions of the thalamus and RAS to the morphology of the MLR in both animal and human studies. It is awknowledged at the outset that such intercomparisons between different species must be interpreted with caution.

It has long been established that electrical stimulation of certain thalamic nuclei induces sleep (Hess,1944) and the induction of changes in the electrocortical activity from these structures (Dempsey and Morrison, 1942). Similarly, changes in firing patterns have been noted in some thalamic neurons during sleep and wakefulness (Steriade and Deschenes, 1984; Steriade et al., 1986). Imeri et al. (1988) recorded from medialis dorsalis thalamic neurons in the cat during in slow wave sleep (SWS), desynchronised sleep (REM) and wakefulness. They found high levels of activity in these neurons in wakefulness but much reduced activity in SWS (significant differences, Wilcoxon test $p < 0.05$). The level of activity recorded in desynchronised sleep was larger than in SWS and was found to be not significantly different from the responses recorded in wakefulness. Lugaresi et al. (1986) illustrated a similar important role in the regulation of the sleep - wakefulness cycle for certain regions of the thalamus in a patient exhibiting fatal familial insomnia and dysautonomia (autonomic dysfunction including pyrexia, diaphoresis, miosis and sphincter disturbances). This condition was responsible for selective degeneration of thalamic nuclei a marked disturbance of the sleep -wakefulness cycle. Having postulated the involvement of the RAS and thalamus

in sleep, it is appropriate to ask how are these structures connected with the MLR. Original monocellular experimentation in the cat draws comparison between two specific components found in the middle latency responses of both species. Firstly, wave 7, an early cat wave recorded at a latency of 12-15 msec. (Buchwald et al., 1981) and also referred to as Pa (Kaga et al., 1980). This wave is thought to originate in the primary auditory cortex (Wolpaw, 1979; Karmos et al., 1982). The second component recorded in the cat is called wave A (latency 20-22 msec.). Depth recording techniques have suggested that this component derives from the RAS and certain nuclei of the thalamus (Hinman and Buchwald, 1983).

Hinman and Buchwald (1983) investigated the relationship of certain thalamic structures to the auditory evoked response in the awake cat. Responses were evoked to click stimuli and recorded using a filter bandpass of 0.1-3000Hz. Single cell responses of maximal amplitude were recorded from the centralis lateralis and centralis medialis nuclei and these correlated well with surface recorded potentials in the same latency range (17-25 msec.). The peak at this latency is labelled 'wave A' in the cat and is thought to be equivolent to the human Pb (PI). Responses recorded under chloralose anaesthesia saw a disappearance of the A wave which could imply a similar fate for the human Pb component.

Chen and Buchwald (1986) demonstrated differential effects of sleep and wakefulness on the MLR of the cat. In a study using implanted electrodes at the vertex and overlying the auditory cortex, they reported that the cat's wave A (present in wakefulness and equivolent to Pb in man; Kaga et al., 1980) disappeared during slow wave sleep to reappear again in REM. The earlier wave 7 (Pa in man), was unaffected by state of arousal and was found to derive from the primary auditory cortex. Figure 3.8 illustrates the changes in morphology of the MLR in the cat with sleep stage (Chen and Buchwald, 1986).

In a comparison of the effect of stimulus repetition rate on both the single cell and surface recorded MLR, the wave A complex was found to disappear at rates above 10/ sec. Earlier components of the responses remained stable at all repetition rates up to 20/ sec. Chen and Buchwald (1986) proposed that the A wave originated from thalamic nuclei mediated by the reticular system. The reduction in amplitude of wave A (Pb or P1 in man) under anaesthesia

Figure 3.8 Changes in the morphology of the MLR in the cat at different stages of sleep and in relaxed wakefulness (Chen and Buchwald, 1986).

led the researchers to also suggest the possibility of wave A being influenced by projections within the reticular activating system (RAS). The notion of an interconnection between the RAS and the thalamus had been demonstrated a number of years ago. Moruzzi and Magoun (1949) postulated from single cell recordings that there existed a rostrally oriented reticular substrate that gave rise to tonic activation of thalamocortical systems with high levels of activity occuring during wakefulness and REM sleep and low levels of activity occuring during slow wave sleep. Starzl et al. (1951 a) investigated conduction of impulses through the RAS in the cat and noted activity in wide ranging areas of the diencephalon (hypothalamus and thalamus) upon reticular stimulation. Starzl et al. (1951b) further linked these RAS- thalamic connections with audition by demonstrating the existence of afferent colaterals between both auditory and somato-sensory ascending pathways and the RAS in the cat. French et al. (1953) similarly reported 'extra leminiscal' pathways outside the classical ascending sensory systems. These processes he termed 'secondary' and commented:

> *" While no definite function was imputed to this 'secondary' sensory system, features concerning its course and distribution closely resembled those more recently shown to subserve the arousal responses to afferent stimulation."*

The significance of direct reticular correlates of certain components within the auditory MLR implies that there are possible differential effects of arousal upon the response. The evidence for this and its possible implications are discussed below.

Functional differentiation between the waves of the MLR has also been demonstrated in man. Using scalp electrodes (vertex to linked mastoid derivation), Erwin and Buchwald (1986 b) recorded middle latency responses to click stimulation (at 40dB HL, 1/ sec. rate) in 14 normal sbjects (age range 22-55 years) during all-night sleep. The systems bandwidth favoured in this study was 10-300Hz. They reported that whilst the amplitude of the earlier component Pa (30-40 msec.) was unaffected during wakefulness, slow wave sleep (SWS) or REM, the later P1 (Pb) peak (55-80 msec.) present in wakefulness, disappeared during SWS to reappear again in REM. Figure 3.9 shows the nature of these reported changes in the MLR with sleep stage. These findings, it was proposed, implied that P1 reflected a generator within the reticular activating system. A question arises here concerning whether a component

Figure 3.9 Changes in the human MLR at different levels of arousal (Erwin and Buchwald, 1986 b).

occuring at a latency of 55 msec. and later can properly be described as middle latency. Picton et al. (1974) proposes that the MLR is confined to the 8-40 msec. latency range whilst Kileny et al. (1983) extends the definition of the MLR to include components up to 100 msec. If the P1 (Pb) component described is really the initial wave of the SVR, then its disappearence during sleep need not imply an origin from with the RAS. This effect could simply be the result of diminished cortical activity during sleep. To further support this suggestion, Erwin and Buchwald (1986 a) found that increasing stimulus repetition rate differentially affected the different components of the MLR. This experiment was carried out on waking subjects , using click stimuli at repetition rates of 0.5/ sec., 1/ sec., 5/ sec., 8/ sec. and 10/ sec. Erwin and Buchwald found that the later component, P1 (Pb) was reduced or absent at the higher repetition rates, whilst the earlier Pa was unaffected. This finding is also consistant with the PI wave being part of the SVR which requires a longer recovery time than the MLR.

Erwin and Buchwald (1986 a) reasoned that P1 and Pa derived from different neural substrates. This conclusion appears reasonable. However, these workers ascribe the origin of the human Pb component to a generator lying within the RAS, a position is reached through references to an animal model. Since the two species cannot be directly compared and cortical generators may not be excluded in humans, a more cautious interpretation of these data might be suggested. A further consideration is the chioce of system bandpass (10-300Hz) for Erwin and Buchwald's (1986 b) experiment. It has been suggested that the components of the BAEP and MLR are considerably altered as a function of bandpass (Scherg, 1982). Therefore, it is possible that the reported stability of the Pa component throughout all stages of sleep could be the result of non-physiological methodological distortions. As has been mentioned before, Kavanagh and Domico (1986), using wide bandpass filters recorded a second dominant frequency within the MLR at around 10Hz. No such component is reported by Erwin and Buchwald within the first 50 msec. of stimulation which might suggest that systems bandwidth may be a contributing factor to the morphology of the responses they recorded.

To conclude this section, the possible effects of arousal level upon the MLR (and by

implication the 40Hz response) have been examined. As with the development of our understanding of the morphology of the MLR in the waking subject, the prevailing opinion concerning the effects of sleep has gradually changed over the years since the MLR's discovery. Initial experiments reported the stability of the response in sleep (Mendel, 1974; Mendel et al., 1975), whilst later research has added caution to this bold conclusion suggesting that the MLR (Hinman and Buchwald, 1983; Chen and Buchwald, 1986; Erwin and Buchwald, 1986 a and b) and 40Hz response (Brown and Shallop, 1982; Jerger et al., 1986) do change as a function of arousal level. These changes appear to result in a reduction on response amplitude during slow wave sleep with a postulated return in amplitude occuring in REM sleep by some workers. The postulated changes in the frequency composition of the MLR during sleep has consequences for the generation of the 40Hz response which has been reported to be of reduced amplitude in sleeping subjects (Brown and Shallop, 1982). As this steady-state potential depends upon the intrinsic periodicity of the MLR, it follows that if the predominant energy of the waveform alters in sleep, then a stimulus presented at 40 times a second will no longer be appropriate to cause a superimposition of successive averages.

Once again methodological factors have been shown to be important. The postulated physiological changes brought on as a result of alterations in subjective state have to be considered in the light of variations in recording parameters such as bandpass, which might alter the morphology of the MLR.

3.6 THE EFFECTS OF AGE AND MATURATION UPON THE MLR AND 40HZ RESPONSE.

The second subjective variable which now must be considered in examining the middle latency responses, is that of age and the aging process. In a similar way to the effects of arousal level (discussed in the previous section), it is critical to know the possible changes in waveform which might occur purely as a function of the degree of

maturity of the patient. Knowledge of such possible variations is important so that normative values for different age groups may be established. Again, much of the early literature concerning the effects of maturation upon the MLR reported little variability in the responses (see Mendel, 1980 review). As with the question of arousal level, the current view concerning maturation is that narrow filter bandpasses were probably responsible masking any changes in MLR morphology by filtering out slower components and for artificially generating middle latency response components in these earlier studies (Scherg, 1982; Kavanagh et al., 1984).

Since these same methodological criticisms apply to the original MLR data concerning maturational effects as to the more general literature on middle latency responses cited so far, it is not intended to review all the original papers in detail in order to simply level the same criticisms. Therefore, this section on maturation and the MLR will begin with a synopsis of the early work and then be followed by a more detailed discussion of more recent experiments in the field. The section will conclude with an examination of the interactions between both age and arousal level and illustrate how the current literature has not always adequately controlled for these factors.

Before the work of Scherg (1982) and others which highlighted the dangers in interpretation that can be caused by narrow bandpass filtration and steep filter slopes, the prevailing opinion concerning the stability of the MLR in neonates and infants using such protcols was favourable. Again a large proportion of the early data concerning the MLR and the maturation process was amassed by Mendel, Goldstein and co-workers. McRandle et al. (1974), Peters and Mendel (1974), Goldstein and McRandle (1976) and Mendel et al. (1977), all reported data which suggested that the MLR was recordable in the same way as the adult response down to intensities near audiometric threshold.

An illustration of this correlation between the MLR and audiometric threshold in babies of 1, 4 and 8 months old (six subjects/group) is given in figure 3.10 which shows the findings of Mendel et al. (1977). The stimuli used in this experiment were 1000Hz tone pips (rise/fall time =2.5 msec.) delivered at a rate of 6/ sec. Electroencephalic activity was measured between the vertex and ipsilateral mastoid and a bandpass of 25-175Hz (24 dB/ Octave filter slope) was used. In all cases, the babies were asleep when tested. The data of Mendel et al. (1977) clearly shows a good relationship between the presence of the MLR and intensity for all ages studied with similar responses being recorded regardless of age. No significant differences were found in component latency as a function of age.

Suzuki and collegues have examined the effects of maturation upon the middle latency responses in a number of experiments over recent years (Suzuki et al., 1983b; Suzuki and Kobayashi, 1984; Suzuki and Hirabayashi, 1987). The first of these papers examined the MLR in 26 normal children divided into two groups, 1-4 years (n=13) and 5-7 years (n=13). These responses were compared to those of an adult population (21-35 years, n=9). The stimuli used for this experiment were 1000Hz tone pips (2.5 sec. rise/fall time) delivered at a rate of 8/sec. Given the new awareness of the importance of filter bandpass which had occurred between this experiment and the previous paper cited (Mendel et al., 1977), the bandwidth chosen for this study permitted electroencephalic activity ranging from between 0.5Hz and 3000Hz (6dB/ oct. roll-off). The level of the high pass filter was systematically varied during this experiment in order to determine the optimum setting for recording the MLR in children. All the children used in this experiment were tested either in natural sleep or under sedation, whilst the adult population were reported to be either in relaxed wakefulness or natural sleep. Suzuki et al. (1983 b) concluded that the frequency composition of the MLR in children differed from that recorded in adults. Whilst in adults the principal frequency of the MLR

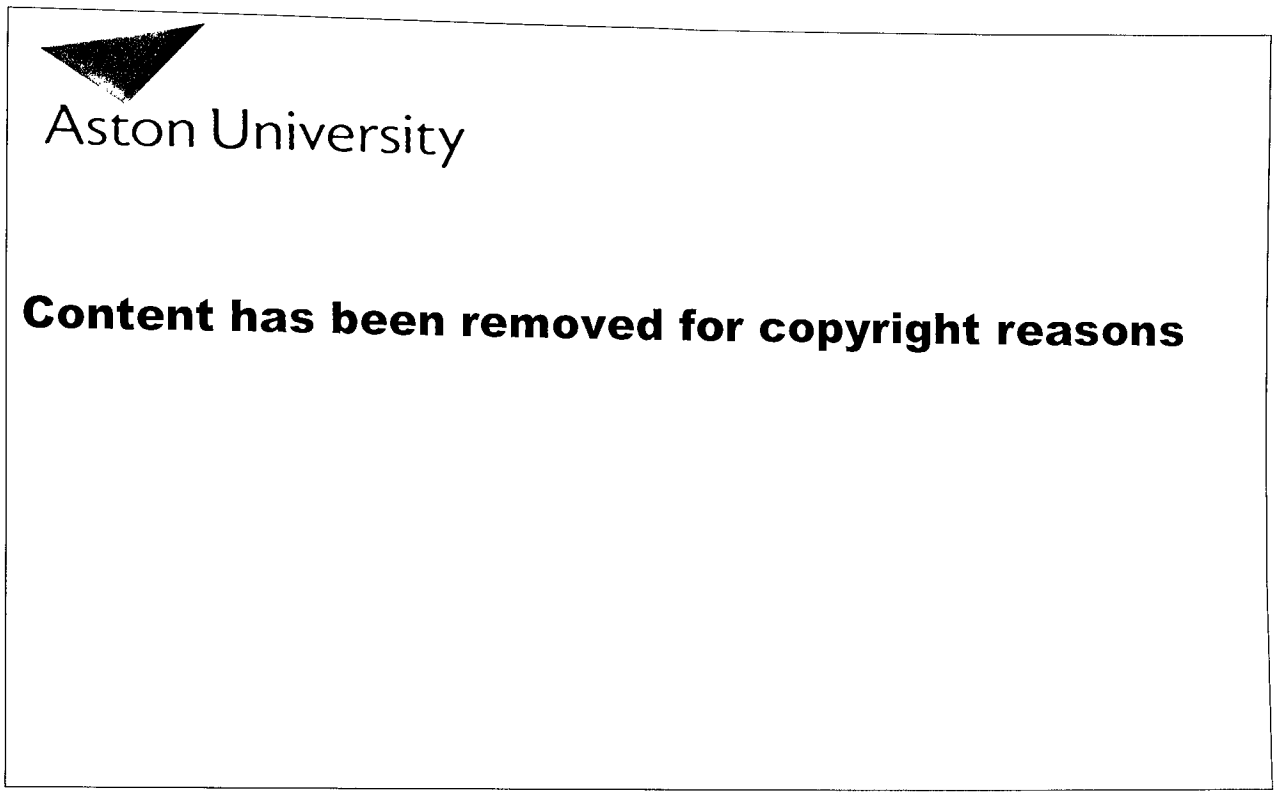

Figure 3.10 Audiometric threshold estimates in 1, 4 and 8 months old babies (Mendel et al., 1977).

waveform lay in the 30-50Hz range (Suzuki et al., 1983 a and b), in the children tested the main frequency was around 20Hz. This low frequency component was most prominant in the youngest children tested.

In a follow-up study, Suzuki and Kobayashi (1984) examined the effects of age upon the morphology of the 40Hz response. Click stimuli were delivered to 7 normal adult subjects (age range 23-36 years) and infants age from 3 months to 6 years. The children used in the experiment were judged to have normal hearing in the absence of any history of hearing disorders or disease. The passband of the recording system was set at 0.4 -4000Hz (6dB/ octave roll-off) and responses were recorded between the forehead and ipsilateral mastoid. Again, the maximum amplitude of the response was reported to be different for these two groups, with the adult response being largest in the 30-50Hz range whilst the children show the largest response at around 20Hz. These findings would suggest that the repetition rate which causes the greatest enhancement of the MLR waveform is 20Hz in children and around 40Hz in adults. In other words, the 40Hz paradigm proposed by Galambos et al. (1981) would appear to be appropriate for generating a response of enhanced amplitude in adult audiometry but not for a child population.

The three experiments discussed so far illustrate again the conflicting opinions regarding the effects of maturation on the MLR. Firstly, Mendel et al. (1977) reported stability of MLR across ages, but due to the use of narrow bandpass filters in this study (25-175Hz), later work has indicated that this finding might be the result of artificial filter distortions. The latter two papers writen by Suzuki and collegues (1983 b and 1984), did report a shift in the frequency composition of the MLR across ages with a lower frequency (20Hz) component being prevalent in younger subjects. If the consistancy of Mendel's data across ages may be explained by the removal of this slower component by filtration, is it then justified to accept

Suzuki's conclusions? It could be argued that since all the child subjects in Suzuki's work were sleeping throughout the experiment, it is impossible at this stage to tell whether this change in the dominant frequency of the MLR was the result of maturation, arousal level an interaction of the two. Furthermore, the adult controls used by Suzuki were reported as either sleeping or in relaxed wakefulness. As section 3.5 has suggested, these states have been shown to be not equivalent. Therefore, the data presented to this point must be reconsidered and (at best) qualified to allow for the possibility of arousal altering the MLR morphology independant of age. Finally, even the responses recorded from sleeping subjects cannot be directly compared because different levels of sleep have been shown to differentially effect the components of the MLR (Hinman and Buchwald, 1983; Chen and Buchwald, 1986; Erwin and Buchwald, 1986 a and b). These workers have reported the loss of the later (Pb) component of the MLR durng slow wave sleep with its reoccurrence again during REM sleep. The loss of the Pb wave in slow wave sleep would mean that the frequency composition of the MLR would be altered at this level of arousal with a progressive shift to lower frequencies being observed. Suzuki's reported changes in the frequency composition of the MLR with age could therefore be explained as an age effect, by changes in arousal level or both. Alternatively, other unknown factors may contribute to the morphology of the response.

Okitsu (1984), working independantly of Suzuki and collegues, was one of the first workers to recognise the points made above and to embrace both the effects of ageing and arousal in combination. He examined the MLR in sleep in 20 normal children with a mean age of 2.42 years (range 4 months to 3.25 years). These results were the compared to the waking responses of 9 further subjects (aged 3 years). A vertex to earlobe derivation was used and potentials were amplified between filter bandpass of 30Hz (18dB/ oct.) to 300Hz (6dB/ oct.). The stimuli used were monaural clicks presented at a rate of 8/ sec. Figure 3.11 shows the effects of falling asleep upon the

Figure 3.11 Changes in the MLR in relaxed wakefulness and in sleep in child and adult populations (Okitsu, 1984).

MLR in both child and adult subjects. In these two groups, a shift is seen in the frequency composition of the response as sleep progresses. In addition, the amplitude of the response (Na-Pa; Pa-Nb) decreases in sleep. Okitsu (1984) did not seek to accurately score level of sleep but simply to illustrate the transition from wakefulness and its effect upon the MLR which was independant of age. Table 3.4 shows the % detectability of the various components of the MLR in sleep and wakefulness for both adults and children.

	Po	Na	Pa	Nb	Pb
1. Asleep					
Children					
Intensity (dB)					
50	86	71	35	14	ND
40	96	88	36	25	ND
30	93	86	29	7	ND
MEAN	92	82	33	15	0

ND = Not detectable

2. Awake					
Children					
50	96	96	71	13	4
3. Awake					
Adults					
50	88	100	80	76	40

Okitsu (1984) stated that:

> *" In conclusion, from the present study, it is clear that the MLRs in sleep differ from those in the waking state, especially in children and it seems that the decrease in detectability of the response in sleep may relate to the depth of sleep. "*

Comparing the detectability of the Nb and Pb components in wakefulness in children compared with adults, it would appear to indicate that the adult response possesses a higher degree of complexity than that of the child as suggested by the presence of more later components. One point to consider is the 30Hz low frequency filter used by Okitsu which may be set too high to record all possible changes in the frequency composition of the MLR. It should also be remembered it is possible that myogenic contamination (often present in waking children) might have been responsible for masking later response components, although there is no reason to suppose that this should have only applied to the later parts of the MLR.

Suzuki and Hirabayashi (1987) examined age related changes in the MLR in 9 adults and 28 children aged between 4 and 14. In this investigation (unlike the previous work of these authors, discussed above), changes in arousal level were awknowledged as a possible cause of variability in the MLR. The children were divided into three groups, 4-7 (n=10), 8-11 (n=10) and 12-14 (n=8). All the subjects used in this study had no history of otologic disease or hearing disorder. Suzuki states that all subjects were tested during natural sleep or under sedation (2-5 mg p.o. Diazapam) and electroencephalic activity was recorded using a forehead to ipsilateral mastoid derivation. Alternating click stimuli (0.09 msec. duration) were delivered at a rate of 8/ sec. at an intensity of 60dB above the subjective threshold for the adult population. The bandpass of the recording system was 0.8-4000Hz (6dB/ oct. roll-off). As in the previous experiment (Suzuki et al., 1983 b), the level of the high pass filter was varied between 0.4Hz and 60Hz to examine the frequency composition of the responses in both child and adult populations. Figure 3.12 shows the effect of highpass filtration upon the MLR recorded in adults and the three child age groups. In all these traces the lowpass filter is set at 1500Hz. These results suggest that even in the oldest children studied (12-14 years), the adult MLR morphology has not been properly attained. The adult response shows a well defined

Figure 3.12 The effect of highpass filtration upon the morphology of the MLR in adults and children: 4-7 years, 8-11 years and 12-14 years (Suzuki and Hirabayashi, 1987).

Na-Pa-Nb-Pb complex with peak latencies of 17, 30, 45 and 63 msec. respectively. The MLRs recorded in children all show a markedly different morphology characterised by a broad positive Pa component which shortens in latency with increasing age.

Although Suzuki and Hirabayashi state that all subjects were sleeping during the experiment, the adult traces do appear to resemble more closely the MLR in relaxed wakefulness (current literature suggests the loss of the Pb components in sleep: Hinman and Buchwald, 1983; Chen and Buchwald, 1986; Erwin and Buchwald, 1986 a and b) and this component is clearly present in Suzuki's data. It is possible that sleep was only ensured in the child population in which case the criticism can still be levelled that the changes in MLR morphology exhibited in the children was the result of sleep and not the maturation process. Suzuki and Hirabayashi (1987) conclude that the major difference between child and adult MLR was the presence of the broad positive Pa component in children. Frequency analysis of the MLR in children again would indicate its predominant power to lie at around 20Hz and not in the 30-50Hz range as is the case in adults (Galambos et al., 1981; Suzuki et al., 1983a; Kavanagh et al., 1984; Kraus et al., 1985). In addition, the variability of the response was reported to be greater in children than in adults but that a large amount of this variability was due to low frequency activity and could be removed if the highpass filter was set at 20Hz.

Suzuki and Hirabayashi (1987) have suggested that there are maturational changes in the MLR which result in the adult response still not being fully attained by the age of 14 years. Even if all subjects were asleep during the experiment (adults as well as children), this conclusion is still hard to verify. This is because sleep cannot be viewed as a single level of arousal and no provision for sleep staging was made in this experiment. Therefore, there is no way of knowing whether the subjects used in this

study were at the same level of arousal and hence the effects of ageing are not being viewed in isolation (section 3.5). There is no way of knowing the precise state of arousal in Suzuki and Hirabayashi's study and therefore such effects as these cannot be eliminated.

The above criticism concerning the effects of sleep stage upon the MLR may be applied to a number of other recent papers which have looked at the ageing process with reference to this response. Kraus et al. (1985) looked at the effect of age on the MLR using wide bandpass filters 3 or 15Hz (6 or 12 dB/ oct. respectively) to 2000Hz and click stimulation (0.1 sec. duration, 11/ sec. repetition rate, 60dB HL). The subjects chosen for this experiment were normal volunteers (n=33), mentally retarded (n=56), language delayed (n=37) and post-meningitic (n=30). The age ranges used were: birth-6 months, 6 months-1 year, 1-2.5 years, 2.5-5 years; 5-10 years, 10-15 years and 15-20 years with approximately the same number of subject categories in each age group. All subjects were sedated with chloral hydrate (25-50mg/kg) and were asleep when tested. No significant differences from these normal responses were reported in any of the diagnostic categories studied. The waveforms shown demonstrate a wide variety of middle latency responses recorded at different ages, but no clear trend is discernable with increasing maturity. Whilst it is possible that Kraus et al. (1985) have shown clear differences between adult and child MLRs, it is impossible to rule out the effect of different sleep stages as being the cause of the observed variations.

More recent publications by the same authors (Kraus et al., 1987 a, b and c) using both animal and human models have suggested, in accordance with Suzuki et al. (1983 b), that the variability present in the MLR in young subjects can be removed by filtering out activity below 20Hz. Kraus et al. (1987 a), examined the detectability of the Na and Pa components of the MLR in a large range of ages (less

than 6 months up to adulthood) using highpass filter settings of 3Hz (6dB/ oct.) and 15Hz (12dB/ oct.) to a low pass filter set at 2000Hz. In this experiment, click stimuli were delivered at a rate of 11/ sec. Kraus et al. (1987a) state that their child subjects were sedated throughout the experiment (with chloral hydrate) but it is not clear whether the older subjects were asleep or awake. Kraus suggested that detectability was increased for both components when the 15Hz filter is used. This effect is most noticable for the Na component of the MLR. The over all % detectability of Pa was found to be much lower than for Na and this difference was greatest for the youngest subjects tested. The detectability of Na and Pa are similar in the adult subjects regardless of filter setting. Since it has not been made clear whether the adult subjects were asleep or what precise sleep stage any of the subjects were in, the reported changes in the detectability of the Na and Pa components of the MLR cannot be correctly ascribed to either age or arousal level. The poor detectability of Pa shown in all children of 10 and under has also been reported in sleeping, normal adults (see chapter 6 and supporting publications) and this would perhaps imply that the adults tested by Kraus et al. (1987 a) were in fact awake in order for the % detectability of Pa to be so high.

In the clincial setting, it is reasonable to assume that the large majority of younger patients will have to be asleep or sedated in order to be tested electrophysiologically. Therefore, the additive effects of sleep and age are important. If the detectability of the MLR is improved with the removal of lower frequency activity (Suzuki et al.,1983 a; Kraus et al., 1987 a), then it may be that the effects of arousal level are not relevant. Clinically speaking, sleep stage may be unimportant if the MLR can be enhanced by removing low frequencies in all sleep stages. Nevertheless, it is still true to say that very little can be confidently said about the development of the MLR to date whilst the confounding variable of sleep and sleep stage has not been adequately controlled. Reports on the effects of age and maturation and the MLR have

followed a similar course to the data concerning sleep. Initial favourable reports (Peters and Mendel, 1974; Wolf and Goldstein, 1977; Mendel et al., 1977) have been criticised on the grounds that narrow filter bandpasses were used (Scherg, 1982). Later research has suggested that the MLR recordable in neonates and children up to adolescence possesses fewer later components and is of lower frequency than the adult response (Suzuki et al., 1983 b; Suzuki and Kobayashi, 1984; Kraus et al., 1985; Kraus et al., 1987 a; Suzuki and Hirabayashi, 1987). However, this body of literature may be questioned on the grounds that arousal level of the subjects has not always been strictly controlled. This has meant that there is some ambiguity concerning whether the observed effects of aging are really due to changes from wakefulness to sleep and also from changes in sleep stage.

3.7 SUMMARY

This lengthy chapter has been necessary to set out all the methodological and subjective factors which have been shown to effect the MLR and 40Hz response. This has provided a theoretical basis from which the clinical usefulness of these responses may be discussed. The routine clinical use of any audiological test depends upon some consensus being reached about the most reliable way of recording the response. The next chapter will examine the clinical applications of auditory evoked potentials and demonstrate that whilst the BAEP and SVR have been long established, middle latency and 40Hz responses have been under-utilised clinically because of the reasons set out thus far.

CHAPTER 4

CLINICAL APPLICATIONS OF AUDITORY EVOKED POTENTIALS.

4.1 INTRODUCTION.

The initial part of this chapter will discuss the need for objective, frequency specific investigation of auditory function. This will be followed by a consideration of the appropriate techniques for assessing clinically recorded AEPs. The main body of this chapter shall be an evaluation of BAEPs, SVRs in brief and the MLR, 40Hz responses and tonal BAEPs in detail. The principal aim of this thesis is the re-evaluation of the MLR and 40Hz response as potential assessors of audiometric threshold in comparison to the more currently favoured BAEP and SVR potentials. Therefore, in order put the experimental work which follows into perspective, this section shall examine the principles of response waveform identification and the degree of correlation between objective (evoked potential) and subjective (behavioural) audiometry that we might reasonably expect from auditory evoked potentials. Since the MLR and 40Hz responses are under-utilised in the clinical setting, these responses will only gain recognition if they can be established as equally accurate and easy to use as existing clinical procedures. Therefore, it is intended to use the established BAEP and SVR responses and their relationships with audiometric threshold as the recognised norms against which the MLR can be judged.

The initially encouraging results claimed for the MLR illustrated earlier, led some authors to suggest these potentials could be considered a viable tool suitable for routine clinical use. However, up to this point, the experiments sited have all dealt with middle latency responses generated to click stimulation. The reason for this is because all the original investigations

carried out on the MLR by researchers such as Mendel and collegues (referred to above), favoured click stimuli as they gave the most clearly defined and largest evoked potentials due to a great degree of neural synchrony. The discussion which follows examines the nature of stimulus characteristics such as frequency, stimulus rise-time and duration upon the middle latency response. In order to properly understand the responses of the auditory system to sounds of different frequency, some references are inevitably made to the anatomy of the auditory system and in particular the characteristic responses of the cochlea to sound stimulation of different frequency. A more detailed treatment of of auditory anatomy lies outside the bounds of this thesis and where necessary, the reader is referred to other, more comprehensive and specialised sources.

The outer ear, the pinna and auditory canal are primarily concerned with the efficient reception of sound waves. The middle ear is essentially a transduction mechanism whereby the air-borne sound stimuli are converted (via the ossicle bones) to the fluid borne vibrations which are required for generating of nervous impulses within the inner ear. The inner ear or cochlea, is the first point at which different frequencies are differentiated and analysed (Dallos, 1973). Research has shown that the point of maximum displacement of the basilar membrane in response to a sound stimulus is directly influenced by stimulus frequency (von Békésy, 1941). With respect to auditory evoked potentials, it is of great significance to appreciate that sounds of different frequencies serve to excite selective regions of the basilar membrane and therefore maximally stimulate discrete populations of nerve cells (Beagley, 1979). Research has shown that in the mature cochlea, high frequencies correspond to the basal region of the basilar membrane (nearest the stapes), whereas lower frequencies elicit a maximal neuronal response in the apical cochlea where the membrane is at it's thinnest (Kiang and Moxon, 1974; Gorga and Worthington, 1983; Lippe, 1986). This frequency differentiation (tonotopicity) is preserved throughout the ascending auditory pathway up to the level of the cortex (Musiek and Baran, 1986; Musiek, 1986). The clinical relevance of this cochlear frequency correspondence is that deafness (of cochlear origin) might pertain to the majority of auditory neurons (i.e. a wide range of frequencies), or to only certain regions of the basilar membrane. Any effective measurement of hearing should therefore be able to investigate different frequencies in order to differentiate losses of different aetiology.

Relating this requirement to the use of auditory evoked potentials, it is clearly advantageous (in terms of response detection) to stimulate the auditory system in a way in which generates a response of large amplitude. In other words, the signal to noise ratio is favourable. Therefore, a stimulus which will synchronise the greatest number of individual auditory neurons (i.e. over a wide range of frequencies) will evoke a more easily detected response than a more localised (frequency specific) stimulus which is maximally stimulating neurons in one discrete location upon the basilar membrane. Thus response amplitude (detection) and frequency specificity are diammetrically opposed.

The small voltage BAEP relies heavily upon the synchronisation of neurons within the auditory nerve and brainstem (Davis, 1976; Galambos and Hecox, 1977). Therefore the click stimulus is favoured because of its rapid onset and short duration. The click evokes a broad area of nerve fibers originating primarily in the basal (high frequency) turn of the cochlea. In contrast, the SVR is a comparatively large potential originating from cortical activation in response to a sound stimulus (Vaughan and Ritter, 1970; Kooi et al., 1971; Peronnet et al., 1974). For this reason, a high degree of frequency specificity is possible. The use of the BAEP and the SVR in objective threshold assessment is now well established in clinical populations. Accompanying this extensive usage, the most appropriate recording parameters for measuring these potentials have evolved in order to maximise the experimenter's ability to detect these potentials at intensities near to audiometric threshold. Unfortunately, the same methodological and subjective consistancy does not apply to the MLR. The preceeding chapters have indicated why there is little consensus concerning the fidelity of the MLR and 40Hz response to audiometric threshold in both normal and patient groups and also the most appropriate conditions for recording these responses. However, there still exists a significant clinical requirement for an objective, frequency specific test of hearing which can be recorded consistantly at all levels of arousal in an infant and neonatal population. This chapter will illustrate that it is the inability of the BAEP to satisfy the first

criteria and SVR to satisfy the latter which has driven further research into more accurately categorising the MLR and 40Hz responses. Before the clinical effectiveness of the individual auditory evoked potentials are examined, it is necessary to explore the general rules which apply to the clinical detection of auditory evoked responses.

4.2 CLINICAL RESPONSE DETECTION CRITERIA.

There is a distinction to be drawn between evoked potential recording in an experimental (research) situation and the more practical procedures which must be often followed in the clinical environment. The research scenario is somewhat idealised and allows for the luxury of lengthy protocols and response replications in order to precisely define a subject's hearing profile (audiogram). The latter case demands easy-to-use practical guidelines which allow for speedy yet accurate diagnosis of hearing capabilities in circumstances which are often less than ideal. Therefore, clinical procedures must be as accurate as possible (in terms of assessing audiometric thresholds), whilst allowing the possibility of flexibility and expedience in less than ideal situations. Only in this way can difficult to test patients be served adequately using evoked response audiometry.

It is impossible to relate and interpret clinical findings without first establishing the characteristics of a given evoked potential in normal subjects. Therefore, the study of normal subjects necessarily preceeds clinical application and the principles which apply to the normative situation also relate to the subsequent use of responses in a patient population. The application of normative data to a clinical population can be achieved by first recording the differences between subjective and objective threshold in a normal population to get some indication of the fidelity of the evoked

response to an established (subjective) threshold. It is then assumed that in a patient population the relationship between the known objective response and the unknown subjective threshold is the same as in a normal group.

4.21 False negative and false positive results.

As has been stated, in order that clinical findings can be properly assessed and diagnosed, it is necessary to establish a strong normative database. This depends upon inter-laboratory agreement and a general consensus being reached as to what constitutes a positive detection of an evoked potential and what is a negative result. In the ideal situation, ERA would be able to exactly match the threshold of a patient's hearing at a given stimulus frequency. However, as threshold is approached the signal to noise ratio of the response decreases and thus it becomes more difficult for the response morphology to be distinguished from the random background activity. This problem is further increased if the subject or patient cannot be sufficiently relaxed and EMG activity further contributes to concealing a response.

Two potential dangers are apparent here. Firstly the scoring of an objective false negative - in which the patient is able to hear the stimulus, but the evoked potential procedure is unable to detect this response. A false negative result would have the effect of under-estimating a patient's hearing capabilities. A second area of inaccuracy is the detection of objective false positive responses. A false positive occurs when the evoked potential yields a lower threshold estimate than the patient can report subjectively. This may have the potentially serious consequence of over-estimating a patient's hearing capabilities and could result in not diagnosing a hearing loss in a patient where an abnormality did in fact exist.

4.22 Response detection near audiometric threshold.

Since response amplitude and morphology at low stimulus intensities is often reduced and unclear, it is necessary to observe experimental procedures which will give the maximum chance of detecting a response should it be present. Assuming the adequate degree of patient relaxation and cooperation which is required for any evoked response to be recorded, a number of further steps can be taken to maximise the chances of accurately modelling a patient's hearing profile. The following are widely used clinical procedures by which response detection may be enhanced.

1. The use of a template response. An evoked response recorded near threshold is compared to a clearer waveform recorded at high stimulus intensity used as a reference.

2. The use of averaging and superimposition procedures. If evoked responses to stimuli of decreasing intensity are superimposed, then it is easier to detect trends in latency increase and amplitude reduction. Such features can often be missed if responses are viewed in isolation.

3. The replication of a dubious response at low intensity and also the recording of an increased number of averages improves the chance of detecting a low amplitude evoked potential near audiometric threshold. Such procedures also are important in order to reduce the incorrect scoring of false positives.

4. Problems of false positive response identification can also often be avoided if a non-stimulus control run is added to the experimental protocol. In this way the clinician can assess the amplitude and features of background activity which may influence the detection of an evoked potential with low intensity stimuli.

Now having highlighted the general rules which apply to the clinical recording of auditory evoked responses, it is possible to apply these to the brainstem evoked potential and the slow vertex response. After this, the effectiveness of the MLR and 40Hz responses can be examined with reference to the more clinically favoured SVR and BAEP.

4.3 THE RELATIONSHIP OF THE SVR TO AUDIOMETRIC THRESHOLD.

The consistancy of the SVR in normally hearing adults is well recognised and has been established for a number of years (Cody and Bickford, 1965; Suzuki and Taguchi, 1965; Beagley and Knight, 1967; Beagley and Kellog, 1969; Picton et al., 1974; Jones, 1979). The SVR is less reliable in children and also in sleeping or drowsy subjects. One of the main advantages of the SVR is that it can be recorded to frequency specific stimuli which allows for the clinician to construct a detailed picture of a patient's hearing capabilities.

Cody and Bickford (1965) chose the detectability of the N1(50-100 msec.) and P2 (125-200 msec.) components as an index of the detectability of the SVR at different stimulus intensities. Testing twenty normal subjects at stimulus frequencies of 500Hz, 1000Hz and 2000Hz, they reported (combining the different frequencies), that 43% of subjects had identical subjective and objective thresholds; 83% were within 5dB, 93% within 10dB and 100% of subjects were within 15dB of subjective threshold. Cody and Bickford (1965) recorded a spread of data with objective - subjective threshold differences ranging from -15dB to +15dB. The negative sign denotes when the objective response was lower than the subjective threshold (i.e. a false positive condition). The positive sign indicates an objective result which exceeds subjective threshold.

Suzuki and Taguchi (1965) recorded slow vertex responses in nineteen normal adults at stimulus frequencies of 500Hz, 1000Hz, 2000Hz and 4000Hz. They found 25.4% of subjects showed no difference between subjective and objective threshold. 69.7% were within +10dB and 100% within +20dB of subjective threshold. Unlike Cody and Bickford (1965) Suzuki and Taguchi (1965) reported no false positive results. The possible reasons for this shall be discussed below.

In Suzuki and Taguchi's (1965) experiment, there is the posibility that the expectation of normality on behalf of the experimenter might have influenced his/her interpretation and subjective assessment concerning the presence or absence of the response near threshold. Experimenter bias can call into question the notion of true evoked response objectivity. Whilst the patient is still unable to influence the result of the procedure, assessment of the responses is compromised if the experimenter expects a certain outcome from the test. Thus in a normal subject, the clinician will be more willing to accept a dubious response at a low stimulus intensity than if that same response were recorded in a patient with a possible (or confirmed) hearing loss.

Therefore, there can be a difference in interpretation by the clinician between normative data and responses recorded in a clinical population resulting in a closer subjective - objective threshold difference (or greater number of false positives) in a normal population. Beagley and Kellog (1969) examined subjective/objective threshold differences using the SVR in 40 normal subjects (age range= 18-36 years). In order to evaluate the effects of experimenter bias, the authors also included 36 patients with known hearing losses (age range 18-52 years) in whom a normal threshold estimate could not be assumed. Three stimulus frequencies were tested, 500, 1000 and 2000Hz. Results showed that the number of false positives reported in the clinical group was far larger than in the normal subjects (21%

compared with 10%) across all frequencies tested. Since the experimenters were expecting a normal response from the clinical subjects, they were more willing to score a response as being present. The higher number of false positive in this group indicates the effects of experimenter bias.

Jones (1979) compared the detectability of the SVR at frequencies of 250Hz, 1000Hz and 4000Hz in normal adults and adults and children with known hearing losses. In the normal subjects (n=23), the same subjective and objective threshold was found in 81%, 70% and 68% of subjects (at the three frequencies respectively). In all the normal adults 100% of responses lay between 0 to +20 dB at 250Hz and -10 to +10 dB at 1000Hz and 4000Hz. In the adults with known auditory defects (n=22), the subjective/objective differences were greater for all three test frequencies with a far smaller number of subjects showing the same subjective and objective threshold, 19% (-50 to +20 range), 22% (-30 to +15 range) and 27% (-35 to +45dB range) respectively. The child population (n=20) was the most difficult to assess with the same subjective and objective thresholds only being recorded in 9% (-10 to +25) at 250Hz, 16% (-30 to +25) at 1000Hz and 26% (-15 to +20dB) at 4000Hz. What is more significant here than the precise threshold measurements, is the increase in the ranges of thresholds reported within the two clinical groups. Threshold measurements per se are not as important as knowing the level of confidence which can be placed upon recorded data and being able to explain the reasons why some subjects yield poor results. The data suggests that the poorest correlation between subjective and objective threshold was found in the child population. This finding could be attributed to a number of factors. Firstly, the inherent variability of the EP waveform in children promoted an increase in both false positives and negatives. Secondly, the amplitude of the background activity is larger in children than in adults which meant that the signal to noise ratio was decreased especially at low stimulus intensities. Thirdly, young

children are difficult to test in wakefulness because they are easily bored and distracted. Finally, the subjective audiograms may not be as reliable as those obtained in the adult groups a factor which would also increase the variability of the results. The main reason cited to account for the variability of the adult subjects with known auditory defects was the persistant presence of high levels of rhythmic activity within the subjects' background EEG. The presence of such activity is of great significance in the successful recording of slow vertex responses. Concerning the reliability of the SVR in the majority of individuals, Hyde et al. (1986) comments:

> *"Slow vertex audiometry is problematic in about 5% of our (clinical) cases, mainly because high levels of alpha activity (alpha rhythm, 8 to 13Hz) render the SVR very difficult to detect reliably ..... Cases of excessively rhythmic EEG are readily detectable after a few minutes of testing and for these ..... we use a variant of the MLR now most commonly known as the 40Hz.*

As emphasised by Hyde and collegues, one of the principal reasons for inaccuracy in SVR threshold assessment is high levels of alpha rhythm within the background EEG. Further inaccuracies are introduced by restlessness leading to excessive myogenic contamination (in common with all evoked potentials) and fluctuations in the subjective state of the subject.

Alpha rhythm is defined as electrical activity occurring between and including 8-13 cycles/sec., varying in amplitude from 1 to 100μV. Bartley (1940) defined alpha activity as the naturally occurring frequency of discharge of the cells of the visual cortex, alpha rhythm as the summation of this activity. Alpha waves originate from the posterior regions of the brain but are recordable from surface electrodes placed at many locations over the scalp. Alpha activity is attenuated by visual stimuli and also by arousal and attention. This led early workers to suggest that alpha was responsible for maintaining an alternative source of stimulation within the cortex in

the absence of such stimuli thereby preventing the onset of sleep (Adrian, 1943). It has been shown that the occurrence of alpha rhythm varies considerably between subjects (Harding, 1968).

The influence of environmental factors upon the occurrence of alpha rhythm is of relevence to the data collected clinically. Situations of novelty and constant visual stimulation cause a fall in alpha levels, whilst situations of fatigue, boredom and lack of novel sensory (visual) input, cause levels of alpha rhythm to increase. It is this latter situation which may directly apply to the successful recording of the SVR in the clinic. Some people (normally hearing or with hearing losses) possess persistant alpha rhythm within their ongoing EEG which cannot be attenuated and makes SVR audiometric threshold determinations impossible. At higher stimulus intensities, alpha is not usually a problem because of the high signal to noise ratio (amplitude of the SVR with respect to ongoing background activity). However, as intensity is lowered (and audiometric threshold approached) this ratio becomes poorer and alpha rhythm contamination becomes more obvious. Therefore, in order to gain consistant and reliable information from the SVR, it is necessary to continuously monitor the ongoing EEG activity. Only by such measures can the unwanted contributions of EMG and alpha rhythm be guarded against.

This review of threshold estimates made using the SVR suggests that in normal, adult subjects the response can be reliably recorded to within 10-20 dB SL in most cases. Factors affecting the detectability of the SVR near threshold include age and level of arousal which both increase the discrepency between subjective and objective threshold. Considerable changes occur to the SVR during all stages of sleep. These principally involve the generation of high amplitude later potentials not seen in the waking response (Weitzman and Kremen, 1965; Ornitz et al., 1967). Osterhammel et al. (1973) suggested that these later components reflected the summation of

K-complexes. The implications of the increased variability of the SVR during sleep are that inter-subject variability increases and little reliable audiological information can be drawn from this response in sleeping subjects. This reliability of the SVR is further compromised if subjects fluctuate between levels of arousal. The single most important factor which causes the greatest variability in the SVR in normal waking adults is the occurrence of high levels of rhythmic alpha activity within the ongoing EEG. It is this limitation which places a significant restriction upon the clinical application of the SVR in certain subjects who exhibit high levels of alpha rhythm. Hyde (1986) estimates that 5% of subjects fall into this category and although this figure may not seem large, the inability to assess five out of every one hundred patients tested (for this one reason alone) ammounts to an undesirably high figure when compensation claims are being considered.

4.4 THE RELATIONSHIP OF THE BAEP TO AUDIOMETRIC THRESHOLD.

As with the slow vertex response, the clinical applications and limitations of the BAEP are now well established. These applications can be broadly divided into two groups; audiological and neurological. Firstly, the brainstem evoked potential is able to give audiological information concerning hearing thresholds. The relationship between the principle components of the BAEP and stimulus intensity is similar to that of the SVR. This means that as intensity is lowered, the amplitude of the response decreases whilst the latencies of the components increase. In chapter one (figure 1.2), the effect of reducing stimulus intensity upon the morphology of the BAEP was presented. This demonstrated that the most easily detected component of the response at low stimulus intensities (near audiometric threshold) is wave V (according to the nomenclature of Jewett and Williston, 1971). The other waves (I, II, III and VI) are less easily defined at intensities less than 25dB SL.

The BAEP is also used to gain neurological information in order to evaluate pathological conditions of the brainstem. Neurologically, because the generators sites of the individual wave components of the response are now well established (refer to chapter 2), the BAEP provides an excellent non-invasive tool for examining the integrity of the brainstem. A fuller discussion of the neurological applications of the BAEP lies outside the scope of this thesis.

Audiologically, the BAEP is the first choice auditory evoked response for determining threshold estimates in neonatal or infant populations and in all patient groups which require sedation in order to be tested. The stability of the BAEP in infants is well established (Hecox and Galambos, 1974; Salamy and Mckean, 1976) as is the consistancy of the response with changes in arousal or mild sedation (Jewett and Williston , 1971; Amedeo and Shagass, 1973; Picton et al., 1974). As discussed in previous chapters, the main disadvantage of the BAEP is that to date, it has far more reliably been recorded to click stimuli than to frequency specific stimuli (this is especially true of low frequency stimuli). The click stimulus provides the greatest amount of neural synchronisation of cochlear nerve fibers due to it's rapid onset and short duration. Since the click is a high frequency stimulus (with its maximum power ≥2000Hz), the BAEP recorded to such a stimulus derives primarily from the basal turn of the cochlea (where high frequencies are maximally represented). The problem with delivering a low frequency stimulus is that firstly the longer ramp time necessary for frequency specificity means that neurons are not being stimulated synchronously. Secondly, it is impossible to effectively stimulate just the apical (low frequency) regions of the cochlea without also activating more distant (higher frequency) neurons. Since there is a time difference between the activation of the basal and apical regions of the basilar membrane (due to the time taken for the travelling wave to reach the apex), the responses generated at base and apex are not in synchrony and hence destructively interfere with eachother.

Since the accuracy of the BAEP in measuring auditory acuity to click stimuli is so well documented, these findings shall now be summarised briefly. However, the relationship of the brainstem response to tonal stimuli delivered at different intensities is less clear-cut and therefore this literature will be examined in greater depth.

Starr and Achor (1973) investigated the relationship to audiometric threshold of the BAEP to click stimulation in six normal adult subjects (age range 25-30 years). The wave V component was reported as present to within 5 dB of subjective threshold in all subjects whereas waves I, II and III were only recorded down to 25-30 dBSL. Similar correspondences were also reported by Davis (1976) and Thornton (1975). Jones (1979) examined the occurrence of the individual components of the BAEP in twenty eight normal subjects. Click stimuli (0.1 msec. duration) were presented to subjects (aged between 17 and 30 years) using a vertex to ipsilateral mastoid electrode derivation. The data from this experiment demonstrated consistantly that the wave V component was consistantly the easiest to detect at the widest range of intensities with in excess of 70% response recognition of this component at 10 dBSL. Further investigation (n=50 normal subjects) revealed that wave V showed a mean difference between subjective and objective threshold of +7.8 dB (the positive sign denoting that objective was higher than the subjective threshold), with a standard deviation of 6.9dB. . The range of subjective - objective differences varied from -10dB (indicating a false positive result) to +20dB with 84% of subjects showing a wave V to within 10dBSL.

To summarise this chapter so far, the SVR and the BAEP together represent the first choice auditory evoked responses currently used clinically. The SVR will provide frequency specific audiological information in the majority of suitably relaxed, (yet waking) adult subjects. The BAEP is able to obtain accurate threshold estimates in

subjects of all ages and at all arousal levels. The main drawback with the BAEP to date, is that it is most effectively recorded to a click stimulus (which is non-frequency specific). The inherent limitations of existing responses defined above has led researchers to wonder whether the MLR (and latterly the 40Hz) could provide frequency specific audiological information at all levels of arousal. Secondly, interest has also increased in the possibility of recording tonal BAEPs and the most appropriate recording parameters for doing so. The MLR and tonally derived brainstem evoked potentials are discussed now.

4.5 CLINICAL APPLICATIONS OF THE MLR.

As with the BAEP and the SVR, the clinical utility of the middle latency responses (and later the 40Hz response) has been extensively examined. Unfortunately, this examination has failed to yield the same consistant findings as with these other responses. Principally the work of Mendel and co-workers has been strongly supportive of the MLR in the clinical setting. Unfortunately, Mendel's faith in the MLR has not been echoed by other researchers in the field (Davis et al., 1976, 1985). Chapter 3 described the configuration of the MLR under various different methodological and subjective conditions and illustrated some of these reasons for the current clinical preference for the BAEP and SVR over the MLR. However, some encouraging results were reported in the early seventies concerning the correlation between the MLR and subjective threshold. The currently prevailing opinion is that the original middle latency recording was experimentally flawed through the use of narrow bandpass filters (chapter 3) leading to the creation of artificial response components (Scherg, 1982). Uncertainty over the precise effects of recording parameters has led to ambiguity concerning the stability of the MLR in children and with changes in arousal. However, some workers have suggested that the non-physiological distortions which appear to be brought about through narrow bandpass filtration might actually be desirable and assist in middle latency response detection near threshold (Musiek et al., 1984). The following review of the early clinical literature on the MLR awknowledges that methodological and subjective factors

might be influencing the potentials being measured. However, this data is still relevant to an appraisal of the current clinical standing of the middle latency responses.

It has been argued that the current test of choice for the frequency specific investigation of auditory function in waking adults is the slow vertex response (SVR). The increased variability of this response in both young subjects and as a result of drowsiness or sleep, precludes the universal use of the SVR. Much of the interest which has been directed towards the MLR is due to the desire to find an alternative test to the SVR which is resilient to such variability. As stated, the acoustic click is unable to provide frequency specific information about cochlear functioning. The spread of energy within the click means that it is only able to give information relating to general cochlear integrity (particularly at high frequencies).

As stated previously, the requirements of response clarity and frequency specificity are diametrically opposed. Since the former demands a high degree of neural synchrony, it is advantageous that the entire cochlear partition is activated by the stimulus. The frequency specific stimulus must elicit a response which originates from a discrete region of the basilar membrane to the exclusion of extraneous frequencies. Therefore, by definition a far smaller number of neurons must be activated if frequency localisation is to be acheived. Hence the evoked response generated to a tonal stimulus must be of reduced amplitude in comparison with that which is elicited to a broad spectrum (click) stimulus.

Davis et al. (1983) highlighted the difficulty of evoking a clear response to a low frequency stimulus. Brief acoustic stimuli such as clicks (duration in the order of 0.1 msec.) possess a wide range of frequencies. This is largely due to the rapidity of stimulus onset (i.e. the ramp-time) generating a wide spectrum of acoustic frequencies. It follows therefore, that a tonally specific stimulus requires a slower ramp-time and to be of longer duration in order to reduce these unwanted acoustic transients (extraneous frequencies). The frequency specific stimulus will therefore differ from the click in that it will longer and possess a greater number of cycles. Fig 4.1 a shows the profile of stimuli with frequencies of 500, 1000, 2000 and 4000Hz (after Davis et al., 1983) illustrating the increase in stimulus duration as frequency is lowered. Each of the stimuli shown possess a 2 cycle rise and fall time with a 1 cycle

The 2 cycles rise / fall, 1 cycle plateau tone pip (2-1-2).

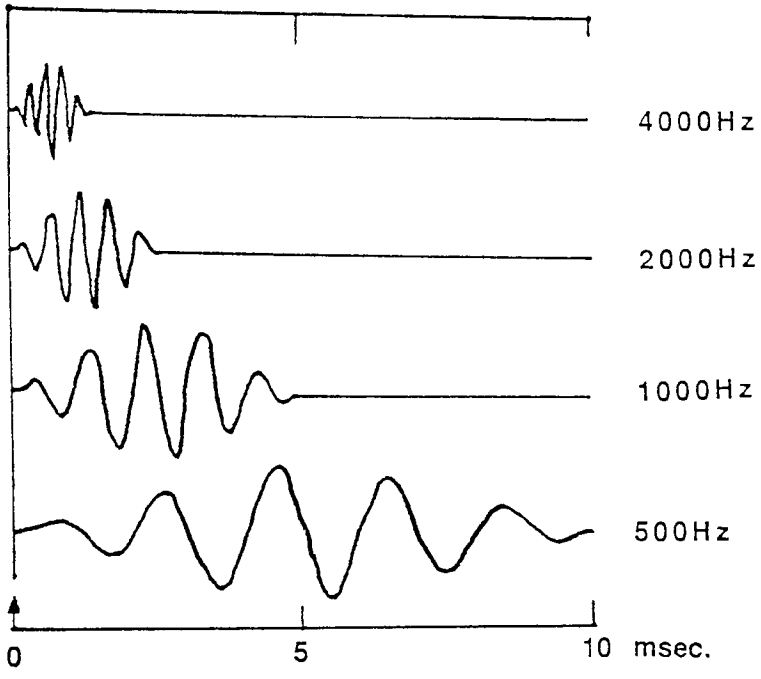

Figure 4.1 a Frequency specific stimulus characteristics for tone pips of 2 cycles rise/fall time and 1 cycle plateau.

4.1 b Frequency specificity of 500, 1000, 2000 and 4000Hz tone pips as calculated using the Fourier transform (Davis et al., 1983).

plateau. Fig. 4.1 b presents the power spectra as calculated by the Fourier transform for the four tones, demonstrating that stimuli which are equivolent in terms of cycles (in this case 2-1-2 cycles) possess the same degree of frequency specificity.

Zerlin and collegues, in a series of experiments performed in the early seventies, were among the first to report the effect of presenting tonally specific stimuli upon threshold determinations using the MLR (Zerlin et al., 1971, 1973; Zerlin and Naunton, 1974). Zerlin et al. (1973) presented click stimuli and tonal stimuli (5 msec. rise-time) with their principal frequencies centered at 500Hz and 2000Hz to six seated, waking subjects. A vertex to earlobe derivation was used and 750 responses were collected for each averaged evoked response (bandpass, 1-150Hz). Stimuli were presented at two intensities, 20 and 50dBSL. Zerlin and collegues reported that the amplitude of the Na-Pa component evoked to a click stimulus (at both intensities) was consistantly larger than tonal responses at either frequency (around 50% larger). Secondly, the responses definition to click stimuli was generally much clearer especially at low intensity (20dBSL). The reduction of amplitude with a tonal stimulus may be explained by the fact that this stimulus is not activating as large a portion of the cochlear partition compared with the click and therefore a smaller population of neurons are being excited. This illustrates the potential difficulty in recording tonal middle latency responses at low stimulus intensities.

Zerlin and Naunton (1974) further compared the detectability of the MLR and SVR to low intensity tonal stimuli. Using 1000Hz and 4000Hz tone pips presented to eight reading subjects, responses were delivered at 5/sec. (MLR) and 0.5/sec. (SVR) at intensities of 5, 10, 20 and 35dBSL. The active recording electrode was placed at the vertex and referred to the earlobe with responses collected using a bandpass of 1-150Hz in both procedures. Using the same stimuli to generate both late and middle potentials, Zerlin and Naunton found that although the amplitude of the Na-Pa component of the MLR was five to seven times smaller than that of the N1-P1 of the SVR in absolute terms, the variability of the MLR was far less than that of the SVR at low intensities. This smaller variability of the MLR was expressed both in terms of latency and amplitude. Zerlin and Naunton (1974) concluded that because of its low variability, the MLR offers a valuable addition to the tests used in clinical evoked response

audiometry despite its small amplitude. However, there are certain methodological factors which make a more cautious interpretation of the data necessary. Firstly, the filter bandpass employed was not ideally suited to SVR recording. This could have impaired the detection of this response near threshold thus giving a false impression of its variability. The SVR is commonly recorded with a narrower bandpass (often 1-50Hz) and therefore the higher frequencies admitted using 1-150Hz filters may have reduced the clarity of these potentials by increased contamination with higher frequency components and myogenic contamination. A further point to consider is that the SVR is easily affected by drowsiness, boredom and fatigue, whilst both the MLR and SVR are degraded by myogenic contamination caused by restlessness. It is therefore important to ensure that these variables are accounted for when recording these responses. Zerlin and Naunton do not specify whether they alternated MLR and SVR recording to eliminate any order effects that may have compromised response detection near threshold. In addition they do not mention whether they allowed breaks during the experiment in order to alleviate restlessness. These criticisms aside, this work would indicate a case for the use of the MLR in frequency specific audiological assessment as the authors report consistantly recordable Na -Pa components in the eight subjects tested.

Thornton et al. (1977) addressed the issue of frequency specificity of the MLR in adults recording responses from the vertex to earlobe with tones of 250Hz, 1000Hz and 4000Hz. The stimuli used had a linear rise/fall time of 2 msec. and a duration of 4.5 msec. Thornton used eleven normal, waking subjects and made measurements of middle latency Na, Pa, Nb, Pb and Nc components using a filter bandpass of 25-125Hz (roll-off 24dB/octave). Fig. 4.2 shows graphical representation of Thornton's findings. The data shows that the Pa and Nb components of the MLR show a linear relationship between amplitude and intensity whereas the later response components (Pb and Nc) demonstrate a far more variable relationship with intensity. Na, the ealiest MLR component measured, shows little change in amplitude as intensity is varied. No immediate differential effects of stimulus frequency are obvious. Thornton's results do not make a strong case for the recording of tonally specific MLRs. Very few components of the response show amplitudes significantly greater than the control (non-stimulus run) at intensities lower than 20dBSL. Therefore, in the waking adult population used in this experiment, it could be argued that closer tonal estimates of audiological

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Figure 4.2 Amplitude verses intensity functions for Na, Pa, Nb, Pb and Nc components of the MLR to frequency specific stimuli of 250, 1000 and 4000Hz (Thornton et al., 1977).

threshold might have been achieved using the SVR where consistant estimates of threshold under 20dBSL have been reported in normal subjects (see section 4.3).

In a similar study, McFarland et al. (1977) presented tones having rise/fall times of 3 msec. (no plateau) at frequencies of 500Hz, 1000Hz and 3000Hz to normal and hearing impaired subjects (with moderate bilateral sensorineural hypacusis). McFarland reported responses detectable at intensities ranging from 0-50dBSL using a filter bandpass of 25 -175Hz. Fig.4.3 shows the correlation with audiometric threshold found in a representative normal and hearing impaired subject. It may be seen that although the absolute amplitude of the responses are small (<1μV), clear middle latency components are visible down to within 10dB in both populations at all frequencies. The possible exception to this is the 500Hz response in the clinical population, where no clear waveform may be seen lower than 20dBSL. It is however possible that a higher degree of correlation between subjective and objective threshold would have been reported for all the frequencies tested if intensity had been reduced in 5dB decrements instead of the 10dB shown. The findings of McFarland et al. (1977) show promise for the MLR as a frequency specfic clinical tool.

Vivion et al. (1980) systematically investigated the effect of stimulus rise-time and duration upon the MLR in order to see if the stimulus duration could be lengthened giving greater frequency specificty with no loss in response amplitude. Using stimuli with frequencies of 500Hz, 1000Hz and 3000Hz, Vivion and collegues altered the rise-time (either 3, 5 or 10 msec.) and the duration of the stimuli (10 or 30 msec.). Vivion reported that the longer duration stimuli with the longest rise-times provided the most frequency specific tones with the smallest amount of energy spread away from the nominal frequency. Vivion et al. (1980) concluded that the latency of the middle latency components varied only slightly across the range of stimulus characteristics. However, they reported that the amplitude of the MLR was considerably reduced with the longer duration stimuli with the greatest rise/fall times. Since clinical response recognition depends upon an easily visualised waveform especially at intensities near psychometric threshold, Vivion concluded that a compromise must be reached between frequency specificity and amplitude. He comments:

Figure 4.3 The relationship of the MLR to audiometric threshold in normal and hearing impaired subjects using 500, 1000 and 3000Hz stimuli (McFarland et al., 1977).

" We conclude that combinations of rise/fall time and plateau duration which yield an equivalent duration of less than 10 msec., but which simutaneously result in narrow spectra stimuli, are optimal for clinical electroencephalic audiometry in which middle components are the response index. "

The effects of rise/fall time demonstrated by Vivion et al. (1980) are consistant with the results of other workers using similar methodology. Lane et al. (1971) and Skinner and Antonoro (1971) similarly reported only small changes in MLR latency with variations in rise/fall time but much larger reductions in amplitude as ramp-times were increased. Beiter and Hogan (1973) reported a reduction of amplitude of one half as rise/fall time was increased from 250 μsec. to 5 msec. Further increases from 5 msec. to 25 msec. yielded no further significant changes. The general conclusion reached by these workers was that a short rise/fall time around 5 msec. was optimal for generating clinically useful middle latency responses. Although this section has portrayed the MLR in a generally favourable light, it is important to consider the effects of the variables discussed in the preceeding chapters on MLR detectability. Lack of consensus of opinion has meant that the MLR has been less favoured clinically.

The 40Hz response was introduced in section 3.4. There it was stated that the response appeared to possess advantages over the MLR in terms of ease of detection near audiometric threshold. The next next section will examine the evidence supporting this claim.

4.6 THE CLINICAL APPLICATIONS OF THE 40HZ RESPONSE.

As discussed in the previous chapter, the 40Hz response renewed interest in the middle latency responses as a possible technique for producing a clinically useful, frequency specific audiogram. It is therefore difficult to separate experiments which have looked strictly at the 40Hz response in normal populations from those in which clinical inferences have been made by reference to patients with hearing losses. This section examines the development of the 40Hz response in normal populations and in clinical cases.

Brown and Shallop (1982) evaluated the clinical utility of the 40Hz response to 500Hz tone pip (4 msec. rise- fall time, 2 msec. plateau) in comparison with the conventional MLR as

generated to a 9.4/ sec. stimulus repetition rate. Using a bandpass of 30-100Hz they investigated threshold determinations in normal subjects and in patients with abrupt high and low frequency hearing losses. Brown and Shallop found response amplitude (and by implication, detectability near threshold) of the 40Hz SSEP to be improved in comparison with that obtained with the MLR transient response for the normal subjects. Fig. 4.4 examines the responses generated to a 500Hz stimulus. This shows that amplitude of the Na-Pa configuration in MLR transient response is approximately 75nV at 15dB HL. The 40Hz repetition rate by comparison has generated a response of 2-3 times this amplitude (around 225nV) at the same intensity. Fig. 4.5 a and b shows the audiograms for two hearing impaired patients and the evoked potentials (BAEP and 40Hz) obtained with click and 500Hz stimulation. The first case shows a severe high frequency hearing loss occuring very abruptly after 1000Hz. The 40Hz responses generated to a 500Hz tone are clearly visible down to 20dB HL (i.e. 10dB SL). The sensitivity of the click evoked brainstem response is such that no clear responses may be seen at intensities less than 85db HL. This result implied that the patient possessed a high frequency hearing loss (as is confirmed by the subjective audiogram) and therefore suggested that the BAEP was only effectively measuring cochlear functioning in the high frequency, basal cochlear region (Eggermont, 1982). Brown and Shallop concluded that the tonally derived 40Hz response was much better able to assess accurately the patient's low frequency (and considerably better) auditory acuity and therefore provided a valuable assessment of audiometric contour in this cases. Fig 4.5 b shows equally encouraging correlations between the 40Hz response to a 500Hz tone pip and audiometric threshold in a patient with a moderate mid-frequency hearing loss. The sensitivity of the BAEP shown in this figure, (with in this case wave V visible to 35dB HL) again would suggest that this response is measuring high frequency cochlear integrity.

In a similar study to that performed by Brown and Shallop (1982), Lynn et al. (1984) found a similar high level of agreement between subjective thresholds and objective recordings made with the 40Hz response at 500 and 1000Hz in a population of patients with selective cochlear hearing losses. Sixteen males and seven females were chosen (age range 17 to 76 years, mean 59) satisfying the selection criteria of: thresholds greater than 20dB for the two test frequencies and possession of a hearing loss of cochlear origin with no additional

Figure 4.4 A comparison of the amplitude of the Na-Pa configuration of the MLR using 9.4/ sec. and 40/ sec. stimulus repetition rates and a 500Hz stimulus (Brown and Shallop, 1982).

Figure 4.5 Audiometric threshold estimation using the 40Hz procedure in one hearing impaired subject with a severe high frequency hearing loss (Fig. 4.5 a) and another with a moderate mid- frequency hearing loss (4.5 b)(Brown and Shallop, 1982).

neurological pathology or conductive deficit. Stimuli (2 msec. rise/fall time and 6 msec. plateau) were presented at a rate of 39.1 / sec. and responses were recorded from waking (relaxed) subjects using a vertex to ipsilateral earlobe electrode derivation. The filter bandpass employed was 5-100Hz. Responses were independently assessed by experienced clinicians. Lynn and collegues reported high correlations between subjective and objective thresholds at both test frequencies (500Hz = 0.79; 1000Hz = 0.87). The range of objective threshold estimates were -30 to +10 (false positive condition) for the 500Hz stimulus and -20 to +20 for 1000Hz stimuli. 90% of 40Hz responses lay within 20dBSL for the 500Hz stimulus, whilst at 1000Hz the spread of data was slightly smaller with 90% of responses lying within 17dBSL. Within Lynn's patient group were a combination of flat and sloping hearing losses (i.e. patients with a similar deficit at all frequencies and those with selective low frequency loss with high frequency thresholds within normal limits). Lynn reported that patients with sloping audiograms produced a higher degree of false positive 40Hz responses (objective threshold lower than subjective) at both stimulus frequencies. This would seem to imply that the 500Hz and 1000Hz stimuli are evoking responses in more basal cochlear regions and are not totally specific to the apical cochlea. In the patients where there is no possibility of high frequency contributions to the 40Hz response, the objective responses are prone to being worse than subjective estimates. Lynn does not provide information concerning the statistical significance to this observation. Even given the possibility of high frequency contribution in some patients, the degree of correlation for the combination of both sub-groups (flat and sloping audiograms) still would suggest a clinical use for the 40Hz response in the diagnosis of hearing deficit in this case.

From the findings discussed above, the 40Hz response would appear to be a technique of considerable clinical potential. Its principal advantage over conventional middle latency recording is the greater ease with which it could be visualised at intensities near to audiometric threshold due to its larger amplitude. This could be of particular advantage in assessing low frequency auditory acuity, selectively diagnosing cases with such frequencies preserved as distinct from those with higher frequency hearing losses. Further work investigating the use of the 40Hz response in frequency specific audiological diagnosis was carried out by Lenarz et al. (1986).

Lenarz et al. (1986) presented stimuli (2-1-2 cycles) at frequencies of 500, 1000, 2000 and 4000Hz to thirty adults with normal hearing. Responses were recorded using a vertex to ipsilateral mastoid derivation and a filter bandpass of 30 to 100Hz (12dB/ oct. slope) was employed. Table 4.1 shows the correlation between behavioural and 40Hz threshold at all four test frequencies for normal subjects.

Table 4.1 Correlation between subjective and objective threshold using the 40Hz response in 30 normal adults (after Lenarz et al., 1986).

Objective threshold	*Pure-tone threshold*			
	500Hz	*1000Hz*	*2000Hz*	*4000Hz*
500Hz	***0.91***	*0.88*	*0.82*	*0.53*
1000Hz	*0.80*	***0.88***	*0.85*	*0.49*
2000Hz	*0.67*	*0.76*	***0.89***	*0.71*
4000Hz	*0.46*	*0.54*	*0.73*	***0.89***

The high degree of correlation seen between thresholds at equal frequency would suggest that the 40Hz response can provide accurate, frequency specific audiometric information. Since Lenarz compared objective responses (recorded to 2-1-2 cycle tone pips) to subjective thresholds obtained to pure tones, it is possible that subjective threshold presented above is actually lower than it would be if a pip had been used subjectively. Therefore the degree of correlation might actually be higher than Lenarz proposed. Lenarz reported that 87.8% of objective 40Hz threshold estimates were within 10dB of subjective threshold (combining all test frequencies). Lenarz and collegues found that amplitude of the 40Hz response was reduced if subjects were sleeping when tested and this had the effect of reducing responses detectability near audiometric threshold. In addition, enhanced myogenic activity also made response identification more difficult. Both these observations made by Lenarz are qualitative and are not corroborated by statistical proof.

Stürzebecher et al. (1985) compared the detectability of middle latency responses at audiometric threshold generated to stimulus repetition rates of 10/ sec, 20/ sec., 30/ sec. and

40/ sec. using wide (30-3000Hz) bandpass filters. Stürzebecher and collegues used normal subjects and also a patient population with sensorineural hearing loss. All those tested were sedated (10mg diazepam) and the authors state that as a rule, subjects slept for the duration of the experiment. To exclude any influence of test duration or sedation upon the results, the order of presentation of the four different repetition rates was varied. Stürzebecher found that the largest responses and therefore the most accurate assessment of threshold, were recorded to the 40/ sec. repetition rate with the 40Hz response detectable in 100% of subjects down to 10dBSL.

Sammeth and Barry (1985) presented tone pips at the 40Hz repetition rate at frequencies with their principal energy at 500Hz, 1000Hz, 2000Hz and 4000Hz to 16 normal awake subjects (filter bandpass: 10-100Hz). A forehead to ipsilateral earlobe electrode montage was used. Good agreement was found at all frequencies with small differences reported between subjective and objective thresholds. These are presented in table 4.2.

Table 4.2 Threshold estimation using the 40Hz response at four stimulus frequencies.

Stimulus frequency (Hz)	*40Hz threshold estimates (dB) and ranges.*	
500	*9.38*	*(0-20)*
1000	*10*	*(0-30)*
2000	*9.38*	*(0-15)*
4000	*15.63*	*(5-20)*

These data presented by Sammeth and Barry (1985) show a strong relationship between the 40Hz response and audiometric threshold for all frequencies tested. A point of particular interest is the close correlation of the 40Hz response with subjective threshold at a frequency of 500Hz. This result would suggest an obvious area in which the 40Hz response could provide a valuable service in frequency specific diagnostic audiology in a paediatric population where the SVR cannot be reliably recorded. However, Sammeth and Barry (1985) indicated that inspite of the encouraging correlations with behavioural threshold reported, their results also demonstrated some significant limitations with the 40Hz technique. Firstly, sleep or drowsiness caused a large reduction in the amplitude of the 40Hz response with a commensurate decrease in response detectability at or near threshold. A fact which would

limit the 40Hz response in infant or neonatal auditory assessment where sedation is often a prerequsite for successful testing. Secondly, Sammeth and Barry reported that responses were far easier to detect in experienced subjects, i.e. those who are accustomed to evoked potential recording. Subjects who were unused to sitting for such procedures produced poor threshold determinations and responses with a large amount of myogenic contamination. The authors commented that:

> *"..... initial attempts at obtaining reliable 40Hz (responses) at levels approaching behavioural threshold in inexperienced subjects were almost uniformly disappointing "*

This conclusion would imply a significant constraint to the application of the 40Hz response. Most audiological diagnoses performed using evoked potentials are recorded in patient population with little experience of the procedures involved. Indeed, the objectivity of the test procedures (with respect to the patient) demands that no conscious control can be exerted by the subject. Therefore, a test of auditory acuity which depends on a high degree of familarity on behalf of the patient, would be of only limited value as an accurate assessment of audiometric threshold. Sammeth and Barry (1985) also commented that the morphology of the 40Hz response recorded to a 500Hz stimulus differed markedly from that recorded to a 4000Hz stimulus. Figure 4.6 compares the morphology of the 40Hz response for six subjects using 500Hz and 4000Hz stimuli (Sammeth and Barry, 1985) The authors suggest that the latter response is less sinusoidal in appearance with the higher frequency stimulus eliciting a greater contribution from the individual waves of the BAEP to the shape of the waveform. It is also possible that the post-auricular muscle potential (refer to chapter 2) could be responsible for the less sinusoidal morphology of the 40Hz response to the 4000Hz stimulus. However, considering the earlobe was used as the location for the reference electrode and not the mastoid, then this possibility is less likely especially at low stimulus intensity. Considering the predominantly high frequencies (around 1000Hz) present in the BAEP (Suzuki et al., 1983 a and b) and the narrow filter bandpass used in this experiment (10-100Hz), it is hard to verify accurately the precise contribution of the individual brainstem components to the 40Hz response. Although it would be expected that the higher frequency stimulus would elicit a clearer BAEP, it would be desirable to examine the 40Hz response to different frequencies of

Figure 4.6 Comparison of 40Hz response morphology in six normal subjects using stimuli of 500 and 4000Hz (Sammeth and Barry, 1985).

stimulation using wider bandpass filters before such a conclusion could be properly verified.

Szyfter et al. (1984) examined objective threshold determinations in 31 normal subjects to low frequency tone pips centered at 250Hz, 500Hz and 1000Hz using the 40Hz procedure (bandpass = 16Hz-320Hz, 1000 averages). Szyfter and collegues found the 40Hz response present within an average of 15.1dB of threshold at the three frequencies tested in waking subjects. In addition to this being a fairly good estimate of threshold, the responses recorded by Szyfter and collegues were easy to detect near threshold and required only 15mins recording per frequency tested. A second study examined the effect of sleep on the 40Hz response and its effect upon threshold detection. Szyfter reported that somnolence reduced the 40Hz response amplitude to around half of that in the waking state. Threshold detection was also less accurate in sleep, increasing by a further 15dB from subjective threshold.

Since the 40Hz response bears close resemblence to a sinusoid, the frequency domain of the response is comparatively small (Stapells et al., 1987). This has lead some researchers to perform frequency analyses upon the response using techniques such as the fast Fourier transform (FFT) in addition to trying to assess the response by purely visual means. From this relatively new and complex type of procedure, valuable information regarding of the phase consistancy of the response also can be elucidated (Makeig and Galambos, 1983; Spydell et al., 1985; Stapells et al.,1987). Phase variability gives a measure of the degree of variation of phase angle at a given instant between subsequent averages and therefore gives information concerning the coincidence of peaks and troughs in successive samples. Since the 40Hz response is steady state, calculations of latency are not strictly applicable, phase measurements may be used as an alternative method of assessment to determine the presence of a steady state evoked response. These workers have reported consist relationships between the 40Hz response and stimulus intensity even at low intensity when response amplitude is too small to allow examination by visual inspection alone. Future work will show if measurements of phase offer valuable (and practical) clinical assistance in the analysis of the 40Hz response.

In summarising research on the 40Hz response, This steady-state potential has increased interest in the MLR and encouraging correlations between this response and audiometric threshold have been reported. However, it would be true to say that the 40Hz response has still not been shown to afford a significant advantage over the SVR (in frequency specific adult testing) or the BAEP (for testing children) and still remains under-used clinically.

4.7 RE-EVALUATING THE MLR AS A VIABLE CLINICAL TOOL.

At this point, the discussion of clinical applications of AEPs must move away from what is known and established and into areas which are not so clearly defined. The recording parameters and threshold relationships of the BAEP (generated to click stimuli) and the SVR (also to click but more commonly to frequency specific tone bursts) are not now the source of controversy. This however is not the case when considering the BAEP generated to tonal stimuli or the MLR as recorded with wider filter settings than previously described. The BAEP is effective in assessing general cochlear functioning but it is less often used for frequency specific audiometric measurement.

The classification system of auditory evoked potentials used most commonly (and up to now adheared to in this thesis) was set down by Picton et al. (1974) and described in chapter one. To summarise, Picton defined early and middle latency EPs as occurring between 0-8 msec. and 8-40 msec. respectively. Picton and collegues arrived at these latency ranges through studying the evoked potentials generated to click stimulation. Since frequency specific stimuli cause latency shifts in these responses away from these established norms (Kavanagh et al., 1988), it could be suggested that this classification system is not appropriate to encompass tonally derived brainstem responses. This implies that the boundaries of brainstem and middle latency responses are made much less well defined and it becomes necessary

to view these two sets of potentials (previously described separately) in combination. Recent experiments and review articles have broadened the latency ranges definitions of the BAEP and MLR (Musiek and Donnelly, 1983). Davis et al. (1985) commenting upon the latency of wave V to tonal stimuli defines a range of 5 to 15 msec. for the occurrence of this component depending on the frequency of the stimulus. Kileny (1983) has perhaps stretched the established boundaries the furthest by suggesting that middle latency activity occurs within a time frame of 100 msec. after stimulus onset. Kileny (1983, 1988) does draw a distinction between BAEP and MLR components but views both these sets of responses in their entirity when making clinical judgements. There does appear to be some need to clarify AEP response terminology concerning the components occurring within the first 100 msec. after stimulus onset. Picton et al. (1974) classification of 'brainstem' and 'middle latency' was based upon experimental evidence concerning the generators of these potentials. However, BAEP and MLR may be inappropriate terms when considering the clinical applications of these potentials to frequency specific stimuli. Before the evidence concerning the clinical applications of the MLR and tonally derived brainstem evoked potentials can be examined, it is therefore necessary to discuss response detection as a function of different experimental recording parameters. This essentially is a continuation of the discussion of recording parameters presented in chapter 3 but applied directly to the clinical situation.

4.71 Response detection as a function of filter bandpass.

Since the latencies of the individual brainstem and middle latency response components depend so heavily upon the choice of filter bandpass, it follows that threshold detection of the these responses will also be effected by such considerations. Kavanagh et al. (1984) compared the detection of the BAEP and MLR at intensities near audiological threshold to a

500Hz tone pip (2.5 msec. rise/fall time, no plateau) in 20 normal subjects (age range 19 - 29 years). Stimuli were presented at a rate of 9.7/ sec. and 1500 presentations were averaged at each trial with repeat runs performed if necessary. Tests were conducted under sedation (though Kavanagh does not specify whether this meant sleep or not) and responses were recorded using a vertex to ipsilateral mastoid derivation. Figure 4.7 presents the morphology of the MLR and BAEP using different filter bandpasses at stimulus intensities of 75 and 30dB nHL. The first conclusion which may be drawn from these data is that clear response waveforms can be seen at both intensities and with all permutations of filter bandpass. At 30dB nHL the wave V component of the brainstem response is hardest to detect when visualised using a 100Hz - 3000Hz filter bandpass. This is borne out in the following table (4.3) which shows the threshold estimates of wave V of the BAEP and MLR components obtained under the various filter conditions:

Wave form	*Bandpass of recording filters (Hz)*	*N*	*Threshold (dB nHL) mean*	*S.D.*
V	*15- 3000* *100 - 3000*	*10*	*26*	*8.43*
SN	*30 - 3000*	*10*	*18*	*7.84*
Pø	*15 - 3000*	*10*	*16*	*5.16*
Pø	*15 - 180* *15 - 100*	*10* *10*	*11* *11*	*5.27* *5.27*
Na	*15 - 3000* *15 - 180* *15 - 100*	*10* *10* *10*	*11* *11* *11*	*5.68* *5.68* *5.68*
Pa	*15 - 3000* *15 - 180* *15 - 100*	*10* *10* *10*	*10* *10* *10*	*4.71* *4.71* *4.71*
Nb	*15 - 3000* *15 - 180* *15 - 100*	*10* *10* *10*	*11* *11* *11*	*5.68* *5.68* *5.68*

The data presented by Kavanagh and collegues (1984) supports the use of the Na, Pa and Nb components as viable tools in the assessment of audiological threshold at 500Hz using the experimental parameters described by these authors. Table 4.2 shows these waves all have lower response thresholds to the 500Hz stimulus than did wave V of the BAEP or the

b)

Figure 4.7 Changes in the morphology of the BAEP and MLR using different filter bandpasses, relationship to audiometric thresholds (Kavanagh et al., 1984).

SN component (bandpass 30Hz -3000Hz). However, the detectability of wave V was elevated considerably (26dB nHL) with the high pass filter set at 100Hz unlike the Na, Pa and Nb waves where varying filter bandpass had little effect upon detection of response components near threshold. This would suggest that the 100-3000Hz bandpass is not optimally suited to recording wave V to lower frequency tones especially at low stimulus intensities. Kavanagh and collegues reported that the visualisation of wave V at low stimulus intensities was aided greatly by dropping the low-cut filter from 100Hz to 30 and even 15Hz. This phenomenon could be due to an augmentation of the wave V component with the latter filter setting or the increased contribution of the Pø component of the MLR upon which wave V is superimposed. Pø, recorded with narrow filter bandpasses, may be considered as the highly filtered remnant of the brainstem waves I - VI. The data presented by Kavanagh et al. (1984) suggests that detection of the Pø component is not greatly influenced by the presence or absence of high frequency activity. Whereas, for tonally derived responses, wave V is most successfully recorded with a low filter set at 15Hz at low stimulus intensities. With wide filter settings, the SN - P wave - Na_2 complex (preceeding Pa), was found to be clearly visible at 75 and 30dB nHL. Reduction in bandwidth resulted in the loss of the P wave and the formation of a broad negativity with its nadir at an intermediate latency to SN and Na_2. Kavanagh demonstrated that the threshold detection of SN (30-3000Hz bandpass) recorded over the 0-20 msec. timebase, was poorer than that of Na recorded over the wider sweep (0-60 msec.). This is due to the decrease in the slope of SN with the 0-20 msec. sweep and also the shorter analysis time cutting off a large proportion of the SN up-slope. Therefore, it would appear that the longer time-base has assisted in response detection near threshold (an effect which is largely independant of filter bandpass). The clinical requirement for frequency specific objective assessment recordable at all levels of arousal has fired research into the area of tonally derived BAEPs. This is the next area which will come under discussion.

4.8 FREQUENCY SPECIFIC BRAINSTEM EVOKED POTENTIALS.

Earlier in this chapter, a review was given of the BAEP (as generated to non-specific

stimuli) in audiological diagnosis. Commenting upon the value of this technique, Sohmer and Kinarti (1984) state:

> *" The auditory evoked potential whioh has made the greatest impact on auditory diagnosis is the auditory nerve-brainstem evoked response (ABR). Since the click stimulus is most effective in synchronously activating a maximal number of nerve fibers, it is the preferred stimulus in eliciting ABR. Many studies have shown that the objective electro-physiological audiometric threshold to the click corresponds best to the average subjective audiometric threshold in the 2-8kHz range"*

Given the two considerable advantages of the BAEP that it may be recorded without difficulty at all levels of arousal and also in infant and neonatal populations, many attempts have been made to extend the use of this response to providing more frequency specific information. The most significant problem here has been ensuring that responses actually originate from a discrete (frequency specific) region of the basilar membrane and not from generalised cochlear activity. A number of techniques have been used firstly to try and limit extraneous (high) frequencies from within the click stimulus (so called filtered clicks), but these have not been successful in localising activity to the apical regions of the basilar membrane (Kinarti and Sohmer, 1982). Another approach to the problem has been to deliver a click stimulus (thereby achieving maximal neural synchrony) in conjunction with white noise masking to limit the acoustic spread of the stimulus (Teas et al., 1962). Refinements of this procedure have attempted to selectively mask at different nominal frequencies and thereby derive (by subtraction of adjacent traces) the contributions of different frequencies to the overall BAEP (Don and Eggermont, 1978; Don et al., 1979; Parker and Throrton, 1978; Laukli and Mair, 1986; Mair and Laukli, 1987). The major drawback with complex masking procedures is the practicality of their implementation within the clinical situation. In the introduction to this chapter it was mentioned that the demands of clinical ERA are such that results need to be obtained quickly and accurately from often less than ideal (i.e. not relaxed or uncooperative) patients. Therefore procedures must be sufficiently robust and speedy to obtain the

maximum amount of information in the shortest possible time. Derived band masking paradigms require a considerable amount of data processing and calculation before a diagnosis can be reached. All this is very time consuming and might make such techniques not ideally suited to the clinical environment (Sohmer and Kinarti, 1984).

The simplest and most frequency specific method of stimulating the cochlea is by delivering a tonal stimulus with a slower ramp time which possesses far less spread of energy away from the nominal frequency. Such stimuli have been used successfully in MLR and SVR recording as neural synchronisation is not an essential requirement (Picton et al., 1974; Vivion et al., 1980). Given the less synchronous neural activity implicit with tonal stimuli, it follows that the frequency composition of tonal BAEPs is different to when clicks are used (Davis, 1976; Suzuki et al., 1977; Kodera et al., 1977; Davis et al., 1985). Therefore, in order to record tonal brainstem responses, modifications of the established techniques are necessary such as opening the filter settings to admit the lower frequencies that BAEP identification depends upon. This final section of literature presents some of the experimental work which has been conducted on tonal brainstem responses, the recording parameters which have been favoured and the degree of success which has been achieved in obtaining frequency specific information near audiometric threshold.

Kodera et al. (1977) examined the BAEP to tonal stimuli (500, 1000 and 2000Hz) in 10 normal subjects (age range 20-33 years). All subjects were tested during sleep using a vertex to ipsilateral mastoid electrode derivation using a filter bandpass of 16-1000Hz (3 and 6 dB/oct. slopes). Stimuli with 5 msec. rise/fall times (no plateau) were delivered at a rate of 10/ sec. and 2000 responses were collected in each average. Kodera and collegues reported good threshold correlation for all three stimuli with mean BAEP estimates of 15.5 ± 3.5 (500Hz), 16.5 ±3.9 (1000Hz) and 16.5±3.2 (2000Hz) respectively. Kodera also found that wave V response latency was inversely related to stimulus frequency (i.e. wave V was of

longer latency the lower the frequency of the stimulus). With the 500Hz stimulus, the latency of this component ranged from 10.0±0.5 msec. (at 50dB SL) to 13.8 ±1.3 msec. (at 20dB SL) in comparison with the 2000Hz stimulus where the corresponding latencies were 8.3±0.5msec. and 10.2±0.3 msec. respectively. The data presented by Kodera et al. (1977) shows encouraging approximations to behavioural threshold with tonally derived BAEPs in both normal subjects. The far longer latencies of the wave V component again illustrates the broader boundary definitions which are required when considering the BAEP to tonal stimulation and the apparent limitations of Picton et al. (1974) classification of BAEPs and the MLR when applied to the tonal brainstem response. The differences in wave V latency with 500, 1000 and 2000Hz stimulation might imply that these stimuli were selectively stimulating different populations of cochlear neurons and hence were frequency specific because of the extra time required for the low frequency stimulus to reach its locus of maximum excitation in the apical cochlear region. One possible critisism of this work is that objective threshold estimates may have been underestimated because Kodera and collegues compared 5 msec. tone pip objective responses with pure tone subjective thresholds. The pure tone stimuli used for subjective audiometry are of longer durations and ramp-times in order to ensure good frequency specificity. It is thererfore possible that subjective estimates would have been elevated with the shorter duration tone pips and thus subjective - objective threshold differences could have been smaller than those reported.

Hyde et al. (1987) examined threshold estimates made using tonal brainstem responses in a group of 4 month old children. A large number of 'normal' children (n=230) were screened during natural sleep using click stimuli (0.1 msec. duration) and tone pips (2 msec. rise/fall time and 1 msec. plateau) of frequencies of 500 and 4000Hz. The stimulus repetition rate chosen was 35 presentations/second. The criteria of normality applied was that the children had

been delivered without complication and were without any known risk factors. The recording bandwidth used for the click stimuli was 150-3000Hz and 30-3000Hz for the tone pips. Responses were recorded from a forehead to ipsilateral mastoid derivation. Hyde and collegues first determined the click evoked BAEP to give an indication of general cochlear function. If a clear response to the click stimulus was obtained below 30dBnHL (referred to a group of twenty normally hearing adults), then the child was deemed to be 'normal' by existing standards and was then tested using the tonal stimuli. Normality for 500 and 4000Hz tone pip responses was considered as a clear wave V component at or below 40dBnHL. Hyde and collegues reported that normal click responses (i.e. below 30dBnHL) were obtained bilaterally in 84% of cases. Failure to record successful responses in the remaining 16% was attributed to 'unsatisfactory' recording conditions (not sleeping or excessive myogenic artifacts). The detection of wave V to both tonal stimuli was worse than for the click. With the 500Hz tones, only 59% of babies exhibited a wave V component at the 40dBnHL level and even at 50dBnHL responses could only be obtained in 78% of cases. The situation was much improved using the 4000Hz tone pips with 83% and 92% detection of wave V at 40 and 50dBnHL respectively.

Figure 4.8 compares the morphology of the BAEP with the three different stimuli used in an infant with normal hearing (Hyde et al., 1987) This figure shows the progressive reduction in the frequency composition of the BAEP with decreasing stimulus frequency. The choice of filter bandpass for the tone pip stimuli (30-3000Hz) must be considered here. The poor definition of the 500Hz response at quite high stimulus intensities (40 and 50dBnHL) can also be seen as a function of the filtering parameters chosen. Kavanagh and Domico (1986) and Kavanagh et al. (1988) have suggested that the frequency composition of the brainstem and middle latency responses contains far greater amounts of low frequency activity centered around 10Hz to tonal stimuli delivered at low intensity. It is possible that Hyde et al.

Figure 4.8 Click and tonally evoked (500 and 4000Hz) BAEPs from a normally hearing infant (Hyde et al., 1987).

(1987) have failed to record an evoked response to lower stimulus intensities because they have effectively filtered out this slow component by using a 30Hz highpass filter. As mentioned previously, Kavanagh et al. (1984) have suggested that detectability of the wave V component of the BAEP is improved when the low filter is dropped to 15Hz. The latency differences reported by Hyde and collegues between wave V to the different frequency stimuli would suggest that different populations of cochlear neurons are being maximally stimulated (i.e. frequency specificity is being achieved). The sweep-time used for these recordings was 25 msec. again emphasising the need for a longer sweep to adequately visualise tonal brainstem responses. Hyde et al. (1987) reported a good success rate in detecting brainstem responses to click and 4000Hz tone pip stimuli in 4 month old children. Less success was obtained when using a 500Hz tone pip with only 59% of subjects exhibiting wave V at the 40dBnHL level. However, little more can be concluded from this experiment in the absence of follow-up data confirming or rejecting the diagnosis of normality in these babies. Riko et al. (1988) recently reported the current clinical status of their subject population. Whilst only 57% of these babies have been re-examined at this time, Riko and collegues report a higher detection rate for wave V for 500 and 4000Hz tone pips at the 40dBnHL level of 87% in children aged about 1 year.

Bauch et al. (1980) examined the detectability of waves I, III, IV and V of the BAEP to click stimuli and tone pips (2 msec. rise/fall time 1 msec. plateau) of 1000, 2000 and 4000Hz. Seventeen normal adult subjects (age range 22 to 31years) were tested in relaxed wakefulness using a vertex to ipsilateral mastoid derivation (filter bandpass 100-3000Hz). Bauch and collegues reported that wave V was consistantly recordable to between 10-15dBHL for all stimuli whereas all other components of the BAEP were far more variable and could only be consistantly recorded to intensities of greater than 30dBHL. This finding would appear to indicate

that wave V is the component most likely to be detected near audiometric threshold for both click and tonally generated brainstem responses. Concerning the relative detectability of wave V to the different stimuli used, all frequencies generated wave V components in 90-100% of cases at the 20dBHL level. Below 20dBHL, detectability of wave V dropped drammatically to around 70% at 15dBHL, 40% at 10dBHL and 10% at 5dBHL. No significant differences were reported between stimuli. As in the Hyde et al. (1987) experiment, the choice filter bandpass (100-3000Hz) in this study may have negatively influenced response detectability near audiometric threshold by removing physiological slow activity present within the BAEP.

The data reviewed so far has demonstrated that tonal brainstem responses have been quite successfully obtained in adults to within 20 dBSL (Kodera et al., 1977). In children (the 'target' group), success has been less evident with lower frequencies being found harder to measure than higher frequencies (Hyde et al., 1987; Riko et al., 1988). It has been sugested that response identification may have not always been assisted by the excessive filtering of low frequency response activity in some of these studies. It is also clear that the clinical strategies formulated using upon tonal BAEPs do not regard the brainstem response as a series of high frequency waves (I to VI) occurring within the first 8 msec. after stimulus onset (Picton et al., 1974). Whilst for higher frequency tone pips (i.e.4000Hz) other components of the BAEP may be recorded, for lower frequency tones, the frequency specific BAEP is interpreted as the slow (lower frequency) positivity (upon which the wave V component is superimposed), viewed over 20, 25 or 30 msec. sweep times.

Davis et al. (1985) presented a large body of clinical data obtained with tonally generated brainstem reponses. The clinical procedure favoured by Davis and collegues has been arrived at over many years experience and experimentation with all of the auditory evoked potentials. To summarise the methodology currently used

by Davis. 2-1-2 cycles/ sec. stimuli are presented at frequencies of 500, 1000, 2000 and 4000Hz. Click stimuli are also used to assess general cochlear integrity. A filter bandpass of 50-1700 (24dB/oct.) is used and 2000 stimulus presentations are averaged at each trial. The stimulus repetition rate used is 27 presentations/ sec. and a forehead to ipsilateral mastoid electrode derivation is employed. Figure 4.9 shows the relationship to hearing threshold of this Wave V-SN10 complex for 500, 1000, 2000 and 4000Hz stimuli in a six month old normal, sleeping child. This figure demonstrates that, in this case the wave V-SN10 complex is detectable down to 15dBnHL for all frequencies tested. At the 60dBnHL intensity, the 500Hz response is interesting as it illustrates the frequency-following response (FFR, see chapter 1) occurring with an onset latency of around 6 msec. The limited use of the FFR in the determination of audiometric threshold can be seen in this figure as it is only visible at the higher intensity levels. The sweep duration chosen by Davis et al. (1985) to adequately visualise the wave V-SN10 configuration ranges from 20 msec. (for the 4000Hz and 2000Hz stimuli) to 25 msec. (for the 1000Hz and 500Hz stimuli). Davis and collegues estimates the thresholds for all four frequencies to be 10dBnHL though does not present data at this intensity level. Close examination of these responses reveals that there is very little difference in morphology between the wave V components recorded to both 4000 and 2000Hz stimulation and similarly between the1000Hz and 500Hz frequencies. This could perhaps suggest that this method of testing is not sufficiently sensitive to distinguish these frequencies (i.e. between 4000 and 2000Hz and 1000 and 500Hz). Clinically this differentiation is not perhaps critical and it might be suggested that some indication of low frequency cochlear integrity (in the 500Hz to 1000Hz range) taken in conjunction with the established click protocol may be sufficient to establish a profile of a patient's hearing capabilities at different frequencies. As mentioned previously, the choice of bandpass (50-1700Hz) used by Davis and collegues also may be excluding low frequency brainstem activity present at low

Figure 4.9 Morphology of the Wave V - SNIO complex near audiometric threshold using 500, 1000, 2000 and 4000Hz stimuli in a six month old, normally hearing infant (Davis et al., 1985).

stimulus intensities and frequencies. This discussion of the clinical possibilities of the tonal brainstem response has focussed on experiments which have used tone pip stimuli of short duration in order to evoke responses. The recording of click evoked and tonally evoked BAEPs differs in three ways: in terms of stimulus characteristics, filter bandpass and the analysis times which are recorded. Most commonly, stimulus characteristics of 2 cycle rise and fall time (with often a 1 cycle plateau) are used to evoked tonal brainstem responses (Suzuki et al., 1977; Davis et al., 1985; Hyde et al., 1987; Riko et al., 1988). The favoured filter bandpasses used for tonal recording, admit greater amounts of low frequency activity than is the case when click BAEPs are recorded. Low filter settings ranging from 0.16Hz (Stapells and Picton, 1981) and 0.5Hz (Suzuki et al., 1977) up to 30 and 50Hz (Davis and Hirsh, 1979; Jerger and Hayes, 1982; Davis et al., 1985) are commonly employed. Also noticable when tonal BAEPs are recorded, is the necessity for viewing far longer sweep (analysis) times of EEG activity. Since tonal stimuli evoke responses of longer latency than do clicks, often 20, 25 and 30 msec. of activity are recorded as opposed to the 10 or 15 msec. required in the latter case.

4.9 SUMMARY.

This chapter has highlighted the clinical applications of the BAEP (to both click and tonal stimulation), the MLR, the 40Hz response and the SVR. This concludes the examination of relevant literature to the completion of this thesis. The following chapters present the experimental work carried out comparing the MLR and 40Hz responses to more established objective tests of auditory function. Chapter five sets the scene for the experiments which follow and re-states the precise aims of this thesis in the light of the literature cited.

CHAPTER 5

AN OVERVIEW OF THE EXPERIMENTAL WORK CARRIED OUT IN THIS THESIS.

5.1 INTRODUCTION - SUMMARY OF LITERATURE.

The literature review given in the previous chapters has given the reader some idea of why there is renewed interest in the auditory middle latency responses. Under the appropriate recording conditions, the BAEP, MLR, 40Hz response and SVR are all able to provide objective assessments of hearing threshold in the sense that the patient is not required to actively participate in the test procedure. This is desirable for both adult and child audiometry.

A further ideal requirement of audiological evoked response measurement is that of frequency specificity. Again this is of relevance to all patient age groups. In adult cases, frequency differentiation is important to establish hearing levels accurately if the clinician suspects that subjective findings are inconsistant. In child audiometry, frequency discrimination is useful to find out whether the patient has a broad spectrum deficit (encompassing a wide range a frequencies) or if there are regions of the basilar membrane (and hence a frequency range) which are still able to function normally. At present, the BAEP is routinely to click stimulation in the clinical environment. This procedure is very effective in giving information concerning cochlear integrity at higher frequencies (>2000Hz, Eggermont, 1982). However, to date less reliable information has been obtained concerning the patient's lower frequency hearing capabilities.

Subjective variables such as age and arousal level must also be considered. As stated above, sedation is required to record responses in children. It is therefore important that the evoked potentials measured are resistant to attenuation or modifications brought on by changes in arousal level and also stable in a neonatal and infant population.

The following is a summary of the relative merits and drawbacks of the BAEP and SVR, the two most commonly used electrophysiological measures of hearing:

The brainstem evoked potential (BAEP)

merits

1. Stable in neonatal patients in addition to adults.
2. Resisitant to modification at different levels of arousal (i.e. during sleep).
3. Consistantly recordable to within 5-10dB of audiometric threshold to click stimulation.

drawback

1. Most successfully recorded to non-frequency specific stimuli such as a click, which is only capable of giving information about high frequency hearing thresholds.

The slow vertex response (SVR)

merits

1. Consistantly recordable to with 10-20dB of audiometric threshold in adult subjects.
2. Responses may be recorded to frequency specific stimuli.

drawbacks

1. Variable and unreliable during sleep and drowsiness.

2. Variable and unreliable in neonates and infants.

The middle latency and 40Hz responses.

The drawbacks mentioned above have highlighted the need for further investigations into the third group of auditory evoked potentials, the MLR. These responses have been under-utilised clinically and remain controversial both in terms of their origins and applications (refer to previous chapters). The reasons for this controversy have been expanded on in the previous chapters and appear to be based largely upon widely differing experimental parameters being used by researchers. The 40Hz steady-state response (Galambos et al., 1981, see chapter 3) has generated new interest in the MLR and has been proposed as a frequency specific method of assessing auditory threshold at all levels of arousal and ages. This claim would appear to satisfy the shortcomings of both the BAEP and the SVR and provide the clinician with a frequency specific method of assessing auditory threshold in sleep or under sedation. Therefore further research appears to be justfied in order to test these hypotheses.

5.2 DESCRIPTION OF EXPERIMENTS.

EXPERIMENT 1 A comparison of the SVR and 40Hz response in the frequency specific objective measurement of audiometric threshold in normal, waking adults.

This experiment investigated whether the 40Hz response could be used as an alternative to the SVR in threshold determinations with equal reliability. This work was aimed at providing the clinician with a possible additional or alternative method of auditory

assessment for adult patients. This is of particular importance if the SVR is considered unreliable.

Although performed upon adult subjects, the next experiment was designed to investigate the possible applications of the MLR and 40Hz responses with special relevance to a child population due to the almost universal requirement for sedation in this patient group.

EXPERIMENT 2 The effects of sleep and sleep stage upon the middle latency and 40Hz responses to click and tone pip stimuli.

The first all-night sleep study was carried out in order to systematically investigate the precise effects of sleep stage upon the MLR and 40Hz response. An academic study with audiological applications, performed to examine changes in the morphology, latency, amplitude and frequency composition of these responses as arousal level changes to stimuli of different frequency.

The results of the sleep study suggested that the MLR was not a stable response at all levels of arousal with only BAEP components reliable. It was therefore felt that that it would be informative to study the characteristics and threshold determinations using brainstem responses to tone pip stimuli using firstly the established brainstem protocol and then comparing this with a 40Hz procedure in sleep developed from the sleep study. This provided the basis for the following two experiments which were combined into one experimental chapter due to the small subject size in the latter experiment.

EXPERIMENT 3 Brainstem auditory evoked potentials to click and frequency specific stimuli in normal relaxed adults.

i) **Normal response characteristics**

ii) **comparison of subjective and evoked response thresholds.**

This experiment was designed to describe the characteristics of the tone pip BAEP in terms of response morphology, latency and amplitude in comparison to the click BAEP used as a control. Following on from this objective threshold estimates were made using the tone pip BAEP recorded with conventional BAEP techniques. These conventional procedures were then compared to the thresholds obtained to tone pip stimuli in stage 2 and slow wave sleep using the BAEP generated to 10Hz and 40Hz stimulus repetition rates.

To summarise the aims of this thesis, the first goal was to compare the 40Hz response to the more established slow vertex response in the assessment of audiometric threshold. Therefore, experiment 1 (chapter 6) compares these two techniques in order to see whether the 40Hz response is able to measure thresholds with equal reliability to the SVR. The goal of chapter 7 (experiment 2) was to look at the nature of the MLR and 40Hz response recorded in sleeping subjects and compares them to those obtained in wakefulness. This work is necessary because sleep is a prerequisite for the clinical testing of infants and therefore before the clinical utility of the 40Hz response can be examined in sleep, the characteristics of these potentials must be clearly defined. Section 3.5 (chapter 3) of this thesis has illustrated the controversy which surrounds the recording of middle latency potentials at different levels of arousal and therefore, if the data in this thesis is not to be similarly criticised, experiment 2 defines the influence of sleep and sleep stage upon the MLR.

At the outset of this research, the goal of experiment 3 was to clinically extend the data from the preceding experiment (2) looking at the 40Hz response as a method of obtaining frequency specific threshold estimates in somnolent subjects. However, experiment 2 revealed that sleep had a profound, attenuating effect upon the MLR and consequently

the 40Hz response. This meant that experiment 3 was redesigned to firstly characterise the BAEP recorded to tone pips and then to investigate the brainstem evoked potential using frequency specific stimuli. Although this represents a change in the direction of this thesis away from the middle latency response, the demonstration of the marked influence of sleep upon the MLR is an important finding. The second part of experiment 3 is a pilot study which attempts to combine the theoretical experience of sleep recording gained in experiment 2 with the actual threshold estimates obtained using the BAEP in the earlier part of that chapter. Using a 40Hz protocol (viewing 100msec of post-stimulus time), frequency specific threshold estimates are compared to those obtained using established BAEP recording techniques in sleeping subjects with a view to improving existing techniques for assessing frequency specific brainstem responses. This summarises the aims of this thesis and the sequence in which the experimental research developed. The next section describes the subjects and recording equipment used.

5.21 The subject population.

This research project has been carried out upon audiologically normal, adult subjects drawn from the staff and student population of Aston University. It was decided to carry out this research upon normal subjects as it is necessary to establish a strong and reliable normative data-base for the MLR and 40Hz responses before it is possible to apply these potentials in the clinical arena. It is appreciated that caution is required when comparing results obtained from normal subjects with those obtained from patients with hearing losses. The limitations of such comparisons are discussed when appropriate within the experimental chapters of this thesis. At the Clinical Neurophysiology unit at Aston University (where this project was undertaken) the BAEP and SVR have been used routinely for many years. The middle latency and 40Hz responses have received little attention (for the reasons given above) and therefore, the need for standardisation of these responses in normative subjects was doubly important.

5.3 A DESCRIPTION OF THE RECORDING EQUIPMENT USED IN THIS THESIS INCORPORATING A DISCUSSION OF FOURIER ANALYSIS OF STEADY-STATE POTENTIALS.

Throughout this research, the recording equipment used has remained essentially the same. A Medelec Sensor ER94a four channel averager was used for all experiments in conjunction with an ST10 stimulator unit able to generate click and tonally specific stimuli. The filter characteristics for the ER94a are given below.

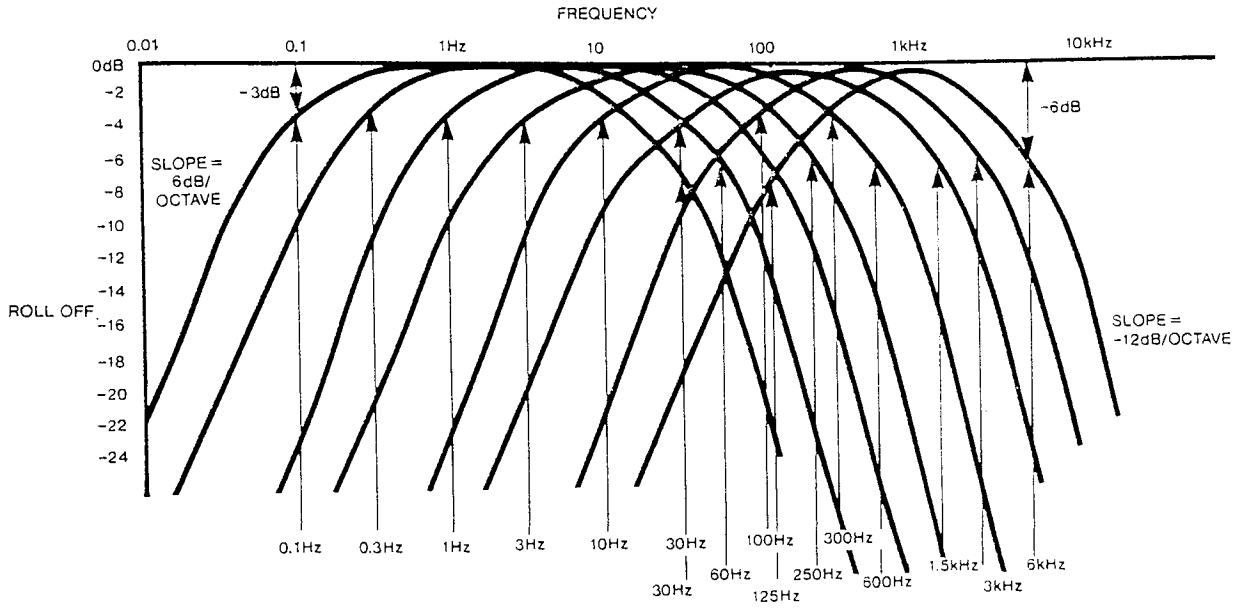

Figure 5.1 The filter characteristics for the Medelec Sensor ER94a

Data was stored on single density, double sided disks for analysis on an Apple IIe microcomputer and plotted on a Hewlett-Packard 7470A plotter. It was intended that frequency analyses would be performed on the 40Hz data presented in this thesis using a software package written by Medelec for the Apple IIe computer which offered a program for calculating fast Fourier Transforms (FFT) and appeared ideal for the off-line analysis of this data. Unfortunately, detailed examination of this program revealed serious difficulties with its implementation (namely its inability to remove trends from the raw data and its lack of a windowing facility). It was decided that data manipulations using this software were impossible without serious constraints being placed upon the validity of this data as the following discussion of the FFT and its role in electrophysiology will explain.

In order to use FFT analysis its is necessary to remove trends from the data, secondly to remove D.C. (itself a form of trend) and thirdly to apply a windowing function in order to remove spurious frequency components from each end of the observation window under analysis. Rigorous attempts to rectify these shortcomings in the Medelec software were unsuccessful despite repeated discussion with the manufacturer. A theoretical discussion of the importance of trend removal and windowing will make readers of this thesis aware of the need for controlling these factors before frequency analysis is embarked upon. Discussing trends first, acquired data (such as evoked potentials) is seldom representative solely of the parameter or parameters of interest. Consistent imperfections in response signals are called trends as distinct from random signal noise which are attenuated by the process of averaging. If such trends are not accounted for and removed from the waveform, they introduce spurious frequencies which FFT analysis will treat as deriving from physiological processes. Beauchamp (1973) demonstrated how trends may be removed mathematically from data through measuring the difference in amplitude between the beginning and end of the response epoch. From this information, it is possible to correct each data point within the trace by the appropriate fraction of this value as the following example will illustrate. If a response trace is generated in which the first and last data points are discrepent by XμV over an epoch of N msec., then the mean trend error X_m induced is calculated as X/N μV/msec. Therefore, the contribution of this trend to each data point can be corrected by adjusting the signal voltage by the appropriate fraction of this mean according to its position in the trace. Thus a point exactly half way along the waveform (N/2) will have a new value of $X - (X_m/2)$ where X is the uncorrected voltage and X_m is the mean trend voltage for the whole waveform. Similarly, the first data point (in a trace comprising 1024 data points) will have an adjusted value of $X - (X_m/1024)$. Thus the effect of trend removal is to ensure that non-physiological data distortion is accounted for and that the assumption of periodicity necessary for Fourier analysis is not violated.

The second problem of high values at either end of the data epoch is the introduction of

spurious components into the frequency analysis. In order to remove these edge effects, it is necessary to apply a window function and the principles and practical details of windowing are now discussed. It should be stressed that simply removing trends is not adequate as sharp transitions of frequency are not attenuated by merely setting the ends of the trace to zero. It is these transitions which windowing seeks to reduce. Firstly, it is necessary to illustrate the inadequacies of leaving data unmodified with respect to windowing. Figure 5.2 shows the phenomenon of data truncation which is central to the generation of distortions in quasi-periodic functions (Lynn, 1982). Figure 5.2a shows a periodic signal f(t) with a line spectrum $G(j\Omega)$. If the period of this waveform is given as T_0 sec., successive harmonic terms are spaced $2\pi/T_0$ radians/sec. apart. Thus the spectrum $G(j\Omega)$ represents the values of the various cosine harmonics. Truncation of the f(t) functio occurs if we assume that the waveform has zero values outside the limits $t = \pm T_0/2$. This assumption is valid given that only a small epoch of activity is being observed and we have no knowledge of the waveform's morphology outside the observation window. Figure 5.2b shows the truncated version of the original waveform f'(t) with its spectrum $G'(j\Omega)$. Since f'(t) is an aperiodic function, its corresponding spectrum $G'(j\Omega)$ *is now continuous. It* can be shown mathematically that the truncation process is equivalent to multiplying the original signal by a rectangular pulse (fig. 5.2c, left hand graph). The corresponding spectrum of the original waveform combined with the rectangular window is shown in the right hand graph of fig. 5.2c. In summary, viewing small epochs (observation windows) of periodic waveforms results in truncation of the spectral energy which is worsened as epoch size shortens. This leads to smearing of the relative magnitudes of closely related frequencies. Applying these theoretical considerations to evoked response recording, it can be seen that attempting FFT analysis on raw data acquired over short epochs is meaningless if the effects of truncation are not reduced. Having illustrated the shortcomings of rectangular windows (a problem which was insurmountable using the Medelec Sensor ER94a and Apple IIe software) the discussion will now turn to how truncation may be attenuated using windowing and superior computing facilities. From the arguments outlined above, it may be seen that a waveform of finite length X(t) can be

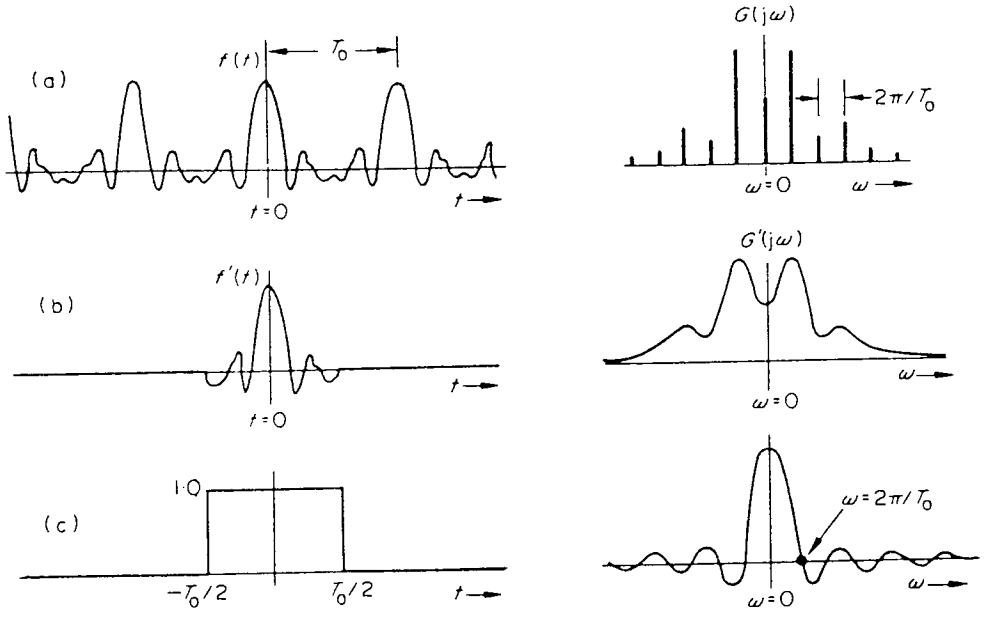

Figure 5.2 The effect of signal truncation upon a waveform within the time domain and its corresponding effect upon response frequency (after Lynn, 1982). See text for details.

considered as equivalent to the product of multiplying an infinite train of random data Y(t) with a finite rectangular window. Thus the Fourier transform of the modified time series X(t) which includes unwanted additional frequencies (side lobes) as a result of truncation is given by:

$$X(f) = \int_{\infty}^{T} X(t)\exp(-j\Omega t)dt = \int_{-\infty}^{\infty} Y(t)U_T.\exp(-j\Omega t)dt$$

Where U_T = 1.0 for 0<t<T and 0.0 for 0>t>T.

U_T is a measure of the magnitude of the effect of truncation in the time domain. Since distortions within the time domain will also effect the frequency domain U(f), the Fourier transform of U_T is given by:

$$U(f) = \int_{-\infty}^{\infty} U_T \exp(-j\Omega t).dt = 2T.\ \sin\Omega t/\Omega t$$

The form of this function is given by sinX/X and is shown in the right hand graph of figure 5.2c. This truncation is compensated for by introducing a second multiplying function which modifies the characteristics of the weighting function U_T. This second function is known as a lag window which has the effect of reducing the amplitude of the frequency side lobes and broadening the width of the main lobe. The precise mathematics of such windowing may be found in many specialised sources (eg Beauchamp, 1973) and many variants exist which seek to modify finite waveforms and attenuate unwanted side lobes. Probably the most widely used window function is the Hanning window (Blackman and Tukey, 1959). The Hanning window is also known as the raised cosine bell function, other window functions have been proposed by Bartlett (1950) and Parzen (1950) which use slightly different weighting functions to modify the rectangular window. Figure 5.3 illustrates the different attenuation characteristics of various window functions as they are applied to a waveform. The question next arises as to the percentage of the data within a trace which shold be windowed. Typically, 10% at either end is the agreed figure although some authors have suggested that a higher percentage is required in order to more fully compensate for the effects of truncation. In concluding this discussion of the

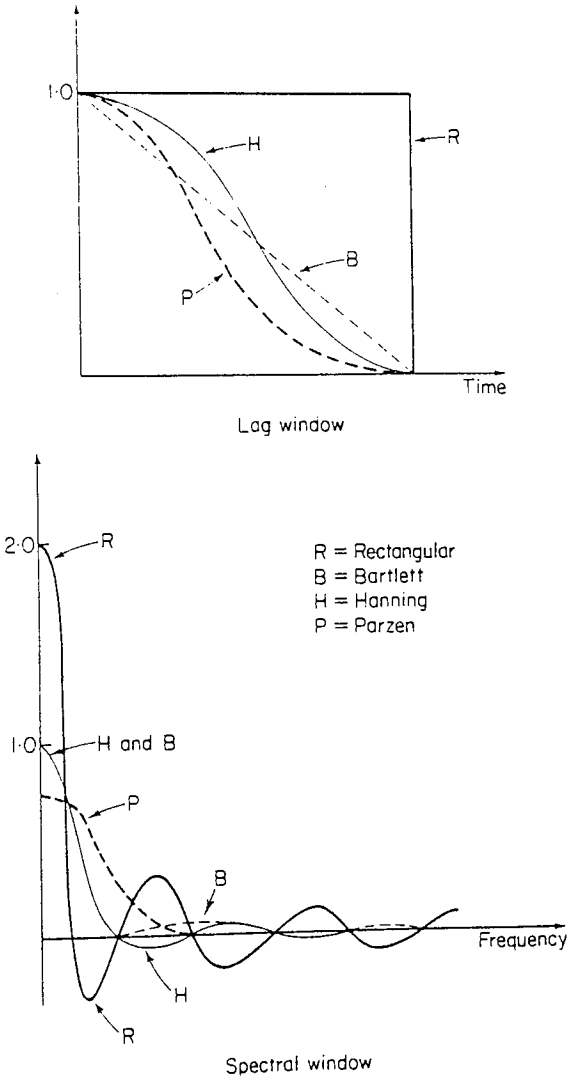

Figure 5.3 A comparison of different types of window functions and their effect upon the attenuation of extraneous frequencies (after Beauchamp, 1973). See text for details.

implementation of FFT procedures, it is clear that rigorous modifications of raw data are necessary if meaningful results are to be obtained from Fourier analysis. The research equipment used throughout this thesis was inadequate in this respect and therefore FFT data analysis could not be performed with confidence.

Returning to the details of the recording equipment used for this research, all experiments carried out on waking subjects used TDH-39 headphones manufactured by the Telephonics corporation, whilst for the sleep experiments, stimuli were delivered by an insert earpiece supplied by Medelec and compatible with the Sensor. According to the manufacturer's published literature, the frequency response for the TDH-39 headphone is essentially flat (± 5dB) over a 100Hz to 4000Hz frequency range. No published data could be obtained from Medelec for the insert earpiece.

In order to accurately score sleep stage during the all-night experiments, it was necessary to record ongoing EEG activity. This was done using a Nihon-Koden sixteen channel EEG machine linked to the Sensor via an analog to digital (A-D) converter. All experiments used standard silvered electrodes supplied by Nicolet Biomedical Instruments. In order to remove the influence of extraneous noise, all the experiments on waking subjects (performed during daytime) were carried out in a sound attenuated room designed especially for auditory investigations and regularly used for clinical audiometry within the neurophysiology unit. The all-night sleep studies were performed with the subject sleeping in an ordinary EEG laboratory because the sound-proof room was insufficiently ventilated for subjects to remain there for a 6 - 8 hour experimental protcol. Since this laboratory was quiet during the night, noise was not considered to be a confounding variable in these experiments.

As sleep studies played a major part in this thesis, the parameters decided upon for the analysis of sleep stage were reviewed in chapter 3 (section 3.5a).

5.4 SUMMARY.

This chapter has given a brief synopsis of the experimental aims of this thesis in the light of previous experiments and is intended to encapsulate the questions which this research project has set out to examine. A description of the recording system and subject population upon which this thesis was based is also important in order that the results of this project may be compared with other data. The precise procedural information relating to each individual experiment will be provided in the relevant chapters.

CHAPTER 6

A COMPARISON OF AUDITORY THRESHOLD DETERMINATIONS USING THE 40HZ RESPONSE AND THE SLOW VERTEX RESPONSE (SVR) IN NORMAL, WAKING ADULTS.

6.1 INTRODUCTION.

The aim of this experiment was to compare the relationship between subjective and objective threshold estimates using the Slow Vertex Response (SVR) and the 40Hz response in a normal adult population. At present, the SVR is favoured clinically in order to obtain a frequency specific audiogram in an adult population because of its clarity in the majority of cases. There are, however, difficult to test patients in whom the vertex potential cannot be taken as reliable (Hyde, 1985) and it is these cases for whom alternative methods of objective audiometry are sought. Reasons for a reduction in the reliability of the SVR are numerous: the result of high levels of alpha rhythm within the EEG, an inability to remain awake and alert for the duration of the test, the presence of excessive levels of myogenic artefacts or alternatively conscious attempts by the patient to confound the experimental procedure (e.g. a noise-induced hearing loss claimant keen to over-emphasize a hearing loss and so gain financial reward). With this in mind, alternative auditory evoked responses have been sought which might equally well measure threshold. Since the 40Hz response reflects summed BAEP and MLR activity in waking subjects, it is possible that the problems encountered with the more rostrally derived SVR such as its susceptibility to drowsiness and changes in arousal level could be avoided using this test.

However, to date little consensus has been reached as to the clinical applications of the MLR in the three decades which have passed since the initial discovery. The development of the 40Hz response has, however, regenerated interest in the MLR as a possible frequency specific test of auditory threshold.

The previous chapters have described the principles and mode of generation of the 40Hz response. The clinical applications of this still relatively new, steady-state response are still being established. This experiment, therefore, attempted to examine whether the 40Hz procedure could provide accurate estimates of audiometric threshold in a group of normally hearing adult subjects. Comparison of threshold estimates made using both the SVR and 40Hz procedures would then allow for the latter response to be judged against a well established baseline (the slow vertex response).

Cases in which either the SVR or 40Hz response gave superior estimations of audiometric threshold were of special interest. If the SVR and 40Hz response can be established to measure audiometric threshold with the same degree of accuracy then it is possible to use these potentials interchangeably. The causes and possible implications of differences in threshold estimation using these two procedures will be discussed.

6.2 METHODS.

Twenty-one normal subjects with no history of otological disease participated in both SVR and 40Hz experiments (age range 21 to 30 years). Subjects were seated in a sound attenuated room for the duration of the experiment and asked to stay awake by reading a magazine or a book. In an attempt to ensure that subjects had not become drowsy, the on-going electroencephalogram was constantly monitored and a short break was allowed (around 10 minutes) in the middle of the experiment. Subjects were also observed using a close-circuit television.

The technical specifications of the Medelec Sensor (ER94a) and ST10 stimulator have been described in Chapter 5. Electroencephalic activity was recorded using silvered cup-electrodes attached to the vertex and both earlobes. Electrode impedances were maintained below 2KΩ by using a saline gel and abraiding the scalp gently with a blunted syringe needle. An electrode placed on the forehead served as a ground. Both sets of responses (SVR and 40Hz) were recorded at the same experimental session. Subjects were told to sit quietly and still for the duration of the experiment. Optimal recording conditions for the SVR require that subjects maintain a consistent and alert state of arousal in order that responses are not confounded by alpha rhythm. The most appropriate recording conditions for the 40Hz response have yet to be established. However, since controversy exists over the stability of the MLR and 40Hz responses recorded during sleep (Brown and Shallop, 1982; Erwin and Buchwald, 1986), it was decided to record the 40Hz in the same manner as the SVR , i.e. relaxed wakefulness. As all the subjects were bilaterally otologically normal, it was decided to test one ear (right) in each case.

Subjective thresholds to both stimulus types were found prior to objective recording at all test frequencies. Subjects were asked to register their perception of the sounds at systematically reduced intensities by pressing a button which lit-up a bulb in the laboratory. Subjective responses were judged absent if the subject failed to register the stimulus at three consecutive presentations at a given intensity. In order to reduce (though not eliminate) the possible effects of experimenter bias, subjective audiometry was performed by an experienced technician and the results kept from the experimenter until objective responses had been recorded and objective threshold established.

In accordance with the established clinical procedures used within the Neurophysiology Unit at Aston University, the SVR was recorded to positive tone bursts of 10msec. rise and fall time with a 250msec. plateau at a repetition rate of 1 per second. The frequency bandpass was set between 1Hz (-6dB/oct) and 30Hz (-12dB/oct). Single channel responses were recorded from vertex to ipsilateral earlobe with 32 sweeps of 1000msec. averaged and stored on Apple

lle microcomputer discs for subsequent analysis. The four frequencies tested were 500, 1000, 2000 and 4000Hz with each of these frequencies being presented in random order between subjects. Monaural stimuli were delivered through standard TDH-39 headphones. The sensitivity of the recording system for slow vertex response recording was set at 20μV/division and an artefact rejection facility was used such that activity > 90% of the full scale deflection (4 divisions) set by the sensitivity (i.e. 90% of ± 80μV) was rejected.

The recording of the 40Hz objective responses required different experimental parameters. The stimuli used were tone pips with rise and fall characteristics of 2 cycles and a plateau of 1 cycle resulting in a stimulus duration of 10msec. at 500Hz, 5msec. at 1000Hz, 2.5msec. at 2000Hz and 1.25msec. at 4000Hz. The inter-stimulus time was 25msec. and 512 sweeps were averaged for each response. 100msec. of post-stimulus activity was viewed and filters were set at 10 to 125Hz (with -6dB/oct and -12dB/oct. slopes respectively). The sensitivity of the recording system for 40Hz recording was set at 10μV/division with artefact rejection set at > 90% of the full scale deflection (4 divisions) which meant that 90% of ± 40μV was rejected. Single channel responses were recorded from vertex to ipsilateral earlobe. The random sequence of frequency presentation was the same as with the SVR and responses were stored on computer in order to allow off-line analysis.

The criterion used to judge the accuracy of the cortical AER and the 40Hz steady-state response was the correlation between the evoked potential thresholds recorded at the four test frequencies (500, 1000, 2000 and 4000Hz) with the subjective thresholds obtained prior to testing. In both tests responses were recorded first at a high intensity (70dBnHL) to establish a clear positive result. Intensity was then systematically lowered in 5dB increments until the response could no longer be discerned. Threshold was then judged to be the lowest intensity at which a reproducible response was present on two out of three separate trials. Unlike the SVR, established detection criteria for the 40Hz response have not been universally agreed upon. If a response is being evoked within the subject, the 100msec. epoch of activity viewed in this experiment should be expected to show a rhythmic, sinusoidal

40Hz response possessing four clear peaks and four troughs. At the outset of the experiment the presence of all these components was considered necessary in order to score a positive 40Hz response to a given stimulus. In the discussion of this experiment, the possibilities of scoring a positive 40Hz result should all these components not be visible (as was often found to be the case at lower stimulus intensities) is examined. In order to improve the reliability of the experimental data, responses were scored by two independent observers at the end of the experiment (Dr L. A .Jones and R. J.Baxter).

As the total time taken for the experiment was approximately 2 hours and it is well established that the cortical AER is susceptible to fatigue and boredom effects, it was decided to perform all the cortical tests first and the 40Hz after a short break in the middle of the experiment. Table 6.1 summarises the recording parameters used for each procedure.

	SVR	*40Hz response*
Filters (Hz)	1-30	10-125
No. stimuli/sec.	1	40
Sweep (msec.)	1000	100
No. averages	32	512
Stimuli	Monophasic tonebursts	Alternating tone pips
	10msec. rise/fall	2 cycles/sec. rise/fall
	250 msec. plateau	1 cycle/sec. plateau
Gain	20μV/div.	10μV/div.

Table 6.1 Summary of SVR and 40Hz response recording techniques.

6.3 RESULTS.

The data from this experiment was analysed in the following ways:

i) Histograms plotted of Subjective / Objective threshold difference at the four different stimulus frequencies (500, 1000, 2000 and 4000Hz) using the SVR and 40Hz responses.

ii) Calculation of mean threshold differences between subjective and objective thresholds and ranges.

iii) Analyses of individual responses where either the 40Hz or slow vertex response was markedly better in objective threshold estimation than the other.

With special reference to point iii) above (though applying equally to all evoked response recording), the subjective state of subjects was carefully monitored during the period of testing. This was vital in order to predict and explain instances in which objective thresholds are poor because of obvious (and understandable) reasons (increased myogenic activity and/or the occurrence of alpha rhythm) and those subjects in whom recording was poor for no apparent reason.

6.31 Subjective-Objective threshold differences.

The accuracy of the SVR and the 40Hz responses was judged by the fidelity of the objective thresholds measured using these procedures compared with subjective threshold. Objective threshold was defined as the lowest intensity (within 5dBnHL) at which a clear SVR or 40Hz morphology could be determined at two out of three separate repetitions. The differences between subjective and objective threshold were then calculated and histograms plotted of these differences. If the objective threshold was higher (in terms of dBHL) than the subjective value, then the subjective minus objective calculation gave a negative number. If, however, the objective threshold estimate was lower than subjective threshold then the difference value was positive.

Table 6.2 shows the individual differences between subjective and objective thresholds for the SVR and 40Hz procedures at the four frequencies tested. The mean subjective-

500Hz

Mean difference = - 11.2dBSL.

Standard deviation = 8.4dBSL.

Range = -25 - +5dBSL.

1000Hz

Mean difference = - 11.9dBSL.

Standard deviation = 9.7dBSL.

Range = -40 - +5dBSL.

	SUBJECTIVE	OBJECTIVE	DIFFERENCE	SUBJECTIVE	OBJECTIVE	DIFFERENCE
DC	10	20	-10	15	20	-5
JG	5	30	-25	0	30	-30
KA	10	30	-20	0	20	-20
JM	5	20	-15	5	5	0
JR	10	10	0	5	15	-10
KW	10	20	-10	0	20	-20
SG	0	10	-10	0	10	-10
WS	15	10	5	5	10	-5
VV	15	20	-5	5	10	-5
DT	5	20	-15	5	0	5
AH	15	20	-5	5	15	-10
MB	10	20	-10	5	20	-15
AE	5	10	-5	0	5	-5
MD	0	10	-10	-5	5	-10
RD	5	25	-20	0	15	-15
LE	10	30	-20	5	20	-15
MR	20	40	-20	0	40	-40
RB	10	35	-25	5	25	-20
TP	10	20	-10	10	20	-10
RN	5	10	-5	5	15	-10
SA	20	20	0	20	20	0

2000Hz

Mean difference = -10.2dBSL.

Standard deviation = 8.4dBSL.

Range = -25 - +5dBSL.

4000Hz

Mean difference = -11.7dBSL.

Standard deviation = 11.0dBSL.

Range = -35 - +10dBSL

	SUBJECTIVE	OBJECTIVE	DIFFERENCE	SUBJECTIVE	OBJECTIVE	DIFFERENCE
DC	20	15	5	15	20	-5
JG	5	30	-25	5	30	-25
KA	0	10	-10	0	15	-15
JM	5	5	0	5	10	-5
JR	5	15	-10	0	20	-20
KW	5	20	-25	10	0	10
SG	15	30	-15	5	10	-5
WS	5	10	-5	0	10	-10
VV	5	10	-5	20	10	10
DT	0	20	-20	10	30	-20
AH	5	10	-5	0	15	-15
MB	5	20	-15	0	20	-20
AE	0	10	-10	0	5	-5
MD	0	5	-5	15	15	0
RD	0	10	-10	5	20	-15
LE	5	20	-15	10	20	-10
MR	5	10	-5	0	20	-20
RB	5	25	-20	-5	30	-35
TP	0	10	-10	10	30	-20
RN	5	20	-15	0	15	-15
SA	15	10	5	15	20	-5

Table 6.2a Subjective thresholds, objective thresholds and differences for the SVR at 500Hz, 1000Hz, 2000Hz and 4000Hz.

500Hz

Mean difference = -14.8dBSL.

Standard deviation = 9.8dBSL.

Range = -35 - +5dBSL

1000Hz

Mean difference = -11.2dBSL.

Standard deviation = 7.4dBSL.

Range = -25 - 0dBSL.

	SUBJECTIVE	OBJECTIVE	DIFFERENCE	SUBJECTIVE	OBJECTIVE	DIFFERENCE
DC	20	30	-10	25	30	-5
JG	15	40	-25	15	40	-25
KA	20	40	-20	15	30	-15
JM	15	40	-25	15	25	-10
JR	20	35	-15	20	25	-5
KW	20	35	-15	15	20	-5
SG	25	40	-15	25	40	-15
WS	20	20	0	15	20	-5
VV	15	50	-35	20	30	-10
DT	20	30	-10	15	20	-5
AH	15	30	-15	15	20	-5
MB	10	30	-20	10	30	-20
AE	20	25	-5	15	20	-5
MD	10	40	-30	10	35	-25
RO	10	40	-30	10	30	-20
LE	25	40	-15	20	30	-10
MR	25	40	-15	20	40	-20
RB	15	25	-10	15	20	-5
TP	20	25	-5	15	15	0
RN	15	10	5	10	20	-10
SA	25	35	-10	20	35	-15

2000Hz

Mean difference = -13.3dBSL.

Standard deviation = 7.2dBSL

Range = -25 - -5dBSL.

4000Hz

Mean difference = -13.1dBSL.

Standard deviation = 7.2dBSL.

Range = -25 - 0dBSL.

	SUBJECTIVE	OBJECTIVE	DIFFERENCE	SUBJECTIVE	OBJECTIVE	DIFFERENCE
DC	25	30	-5	25	50	-25
JG	15	40	-25	20	40	-20
KA	15	20	-5	20	30	-10
JM	15	25	-10	15	25	-10
JR	15	30	-15	20	25	-5
KW	15	25	-10	25	25	0
SG	35	40	-5	30	35	-5
WS	15	20	-5	15	20	-5
VV	20	40	-20	20	40	-20
DT	15	20	-5	20	40	-20
AH	15	30	-15	10	20	-10
MB	20	40	-20	15	30	-15
AE	15	30	-15	15	25	-10
MD	15	40	-25	25	30	-5
RO	15	30	-15	15	40	-25
LE	25	40	-15	20	40	-20
MR	20	35	-15	20	30	-10
RB	15	25	-10	5	25	-20
TP	15	30	-15	15	30	-15
RN	15	30	-15	15	30	-15
SA	20	35	-15	25	35	-10

Table 6.2b Subjective thresholds, objective thresholds and differences for the 40Hz response at 500Hz, 1000Hz, 2000Hz and 4000Hz.

objective threshold differences, the ranges of these differences and fidelity to audiometric threshold of the SVR and the 40Hz response are given in Table 6.3.

Table 6.3a The slow vertex response.

Frequency Hz	*Mean Dif. dBSL*	*S.D. dBSL*	*%Within 10dBSL*	*%Within 20dBSL*	*Range*
500	-11.2	8.4	62	90	-25 to +5
1000	-11.9	9.7	57	90	-40 to +5
2000	-10.2	8.4	62	90	-25 to +5
4000	-11.7	11.0	48	90	-35 to +10

Table 6.3b The 40Hz response.

Frequency Hz	*Mean dif. dBSL*	*S.D. dBSL*	*%Within 10dBSL*	*%Within 20dBSL*	*Range (Hz)*
500	-14.8	9.8	38	76	-35 to +5
1000	-11.2	7.4	62	90	-25 to 0
2000	-13.3	6.2	52	90	-25 to -5
4000	-13.1	7.2	53	90	-25 to 0

Table 6.3 a and b. Mean differences, standard deviations and ranges between subjective and objective threshold for the SVR and 40Hz response.

Histograms were plotted for the SVR and 40Hz response at each of these frequencies. Figures 6.1 and 6.2 present the differences between subjective and objective threshold for both procedures in histogram form.

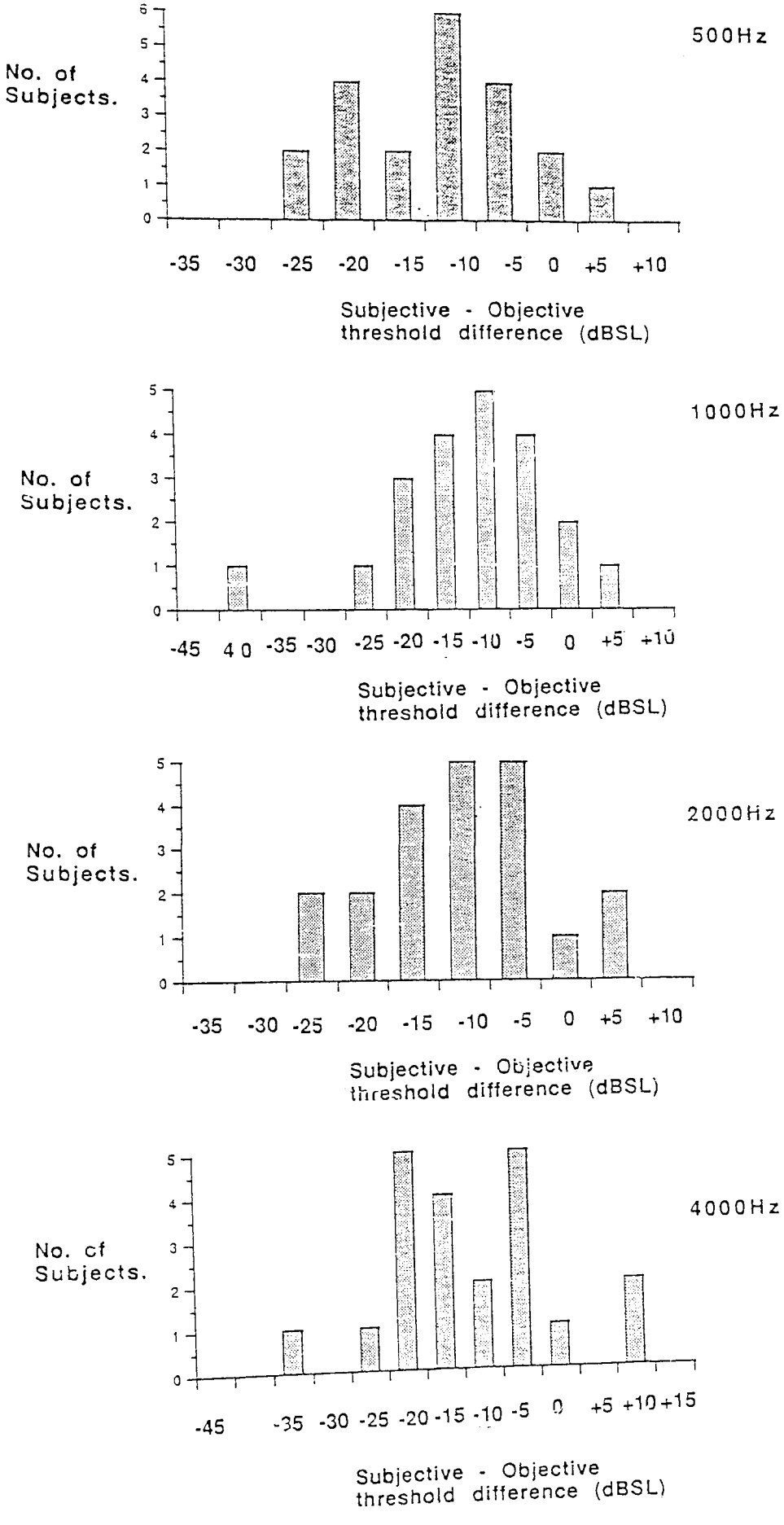

Figure 6.1 Subjective-objective threshold difference histograms for the SVR at frequencies of 500Hz, 1000Hz, 2000Hz and 4000Hz.

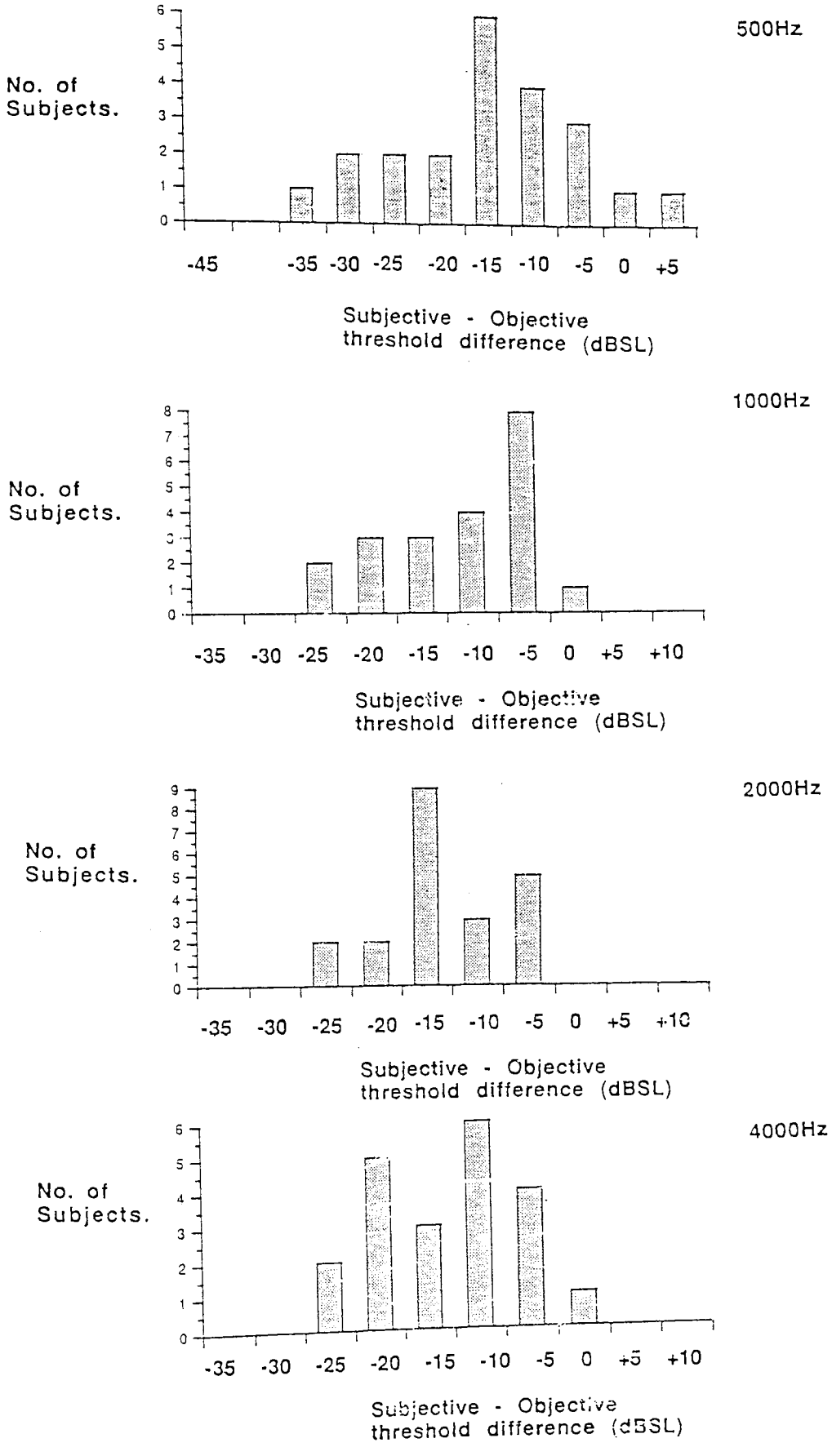

Figure 6.2 Subjective-objective threshold difference histograms for the 40Hz response at frequencies of 500Hz, 1000Hz, 2000Hz and 4000Hz.

An example of the relationship between stimulus intensity and response morphology of both potentials is given in Figure 6.3 a and b. This figure shows both sets of objective responses in one subject. The stimulus used was a 500Hz tone pip for both SVR and 40Hz procedures, the estimate of objective threshold is 10dBnHL which is equivalent to 5dBSL for both tests in this case. The response components are marked with arrows on the figure at the intensity of the objective threshold.

The similar mean threshold differences and ranges for the SVR and 40Hz response (Table 6.3 a and b) would imply that these two evoked responses are assessing audiometric hearing threshold with the same degree of accuracy in most cases. Using the Student t-test for related samples, no statistically significant difference between threshold estimates using SVR and 40Hz procedures could be established at any frequency. At 500Hz, t = 1.65; significance = 0.115: at 1000Hz, t = 0.344; significance = 0.775: at 2000Hz, t = 1.41; significance = 0.174: and at 4000Hz, t = 0.603; significance = 0.553. All these calculations are based on 20 degrees of freedom and demonstrate that no significant differences between the two procedures could be found for the 21 subjects used in this experiment (a significance of 0.05 or less would be required for 95% confidence in rejecting the null hypothesis).

6.32 Difference in threshold estimation using SVR and 40Hz response procedures.

Figures 6.4 and 6.5 shows threshold assessment in two subjects for whom either the SVR (6.4 a and b subject VV) or 40Hz response (6.5a and b subject MR) was more accurately reflecting audiometric threshold than the other response.

Figure 6.4 a shows the characteristic reduction in amplitude and increase in latency of the N1-P2 configuration of the SVR as intensity is decreased until no longer visible below 5dBSL. Figure 6.4 b shows the equivalent 40Hz responses obtained at the same relative intensities

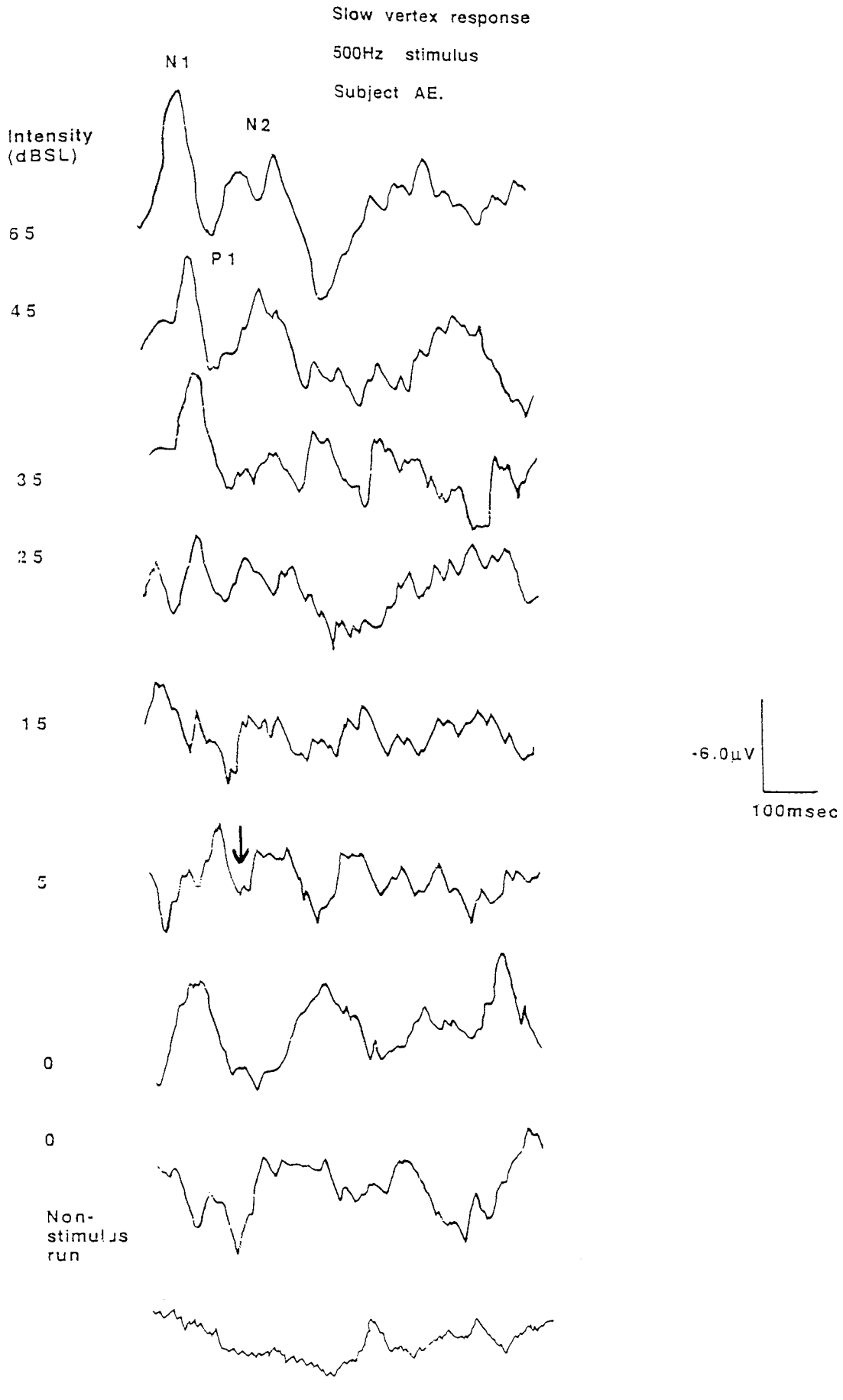

Figure 6.3a Morphology of the SVR at different stimulus intensities at a stimulus frequency of 500Hz (subject AE). Threshold is marked with an arrow.

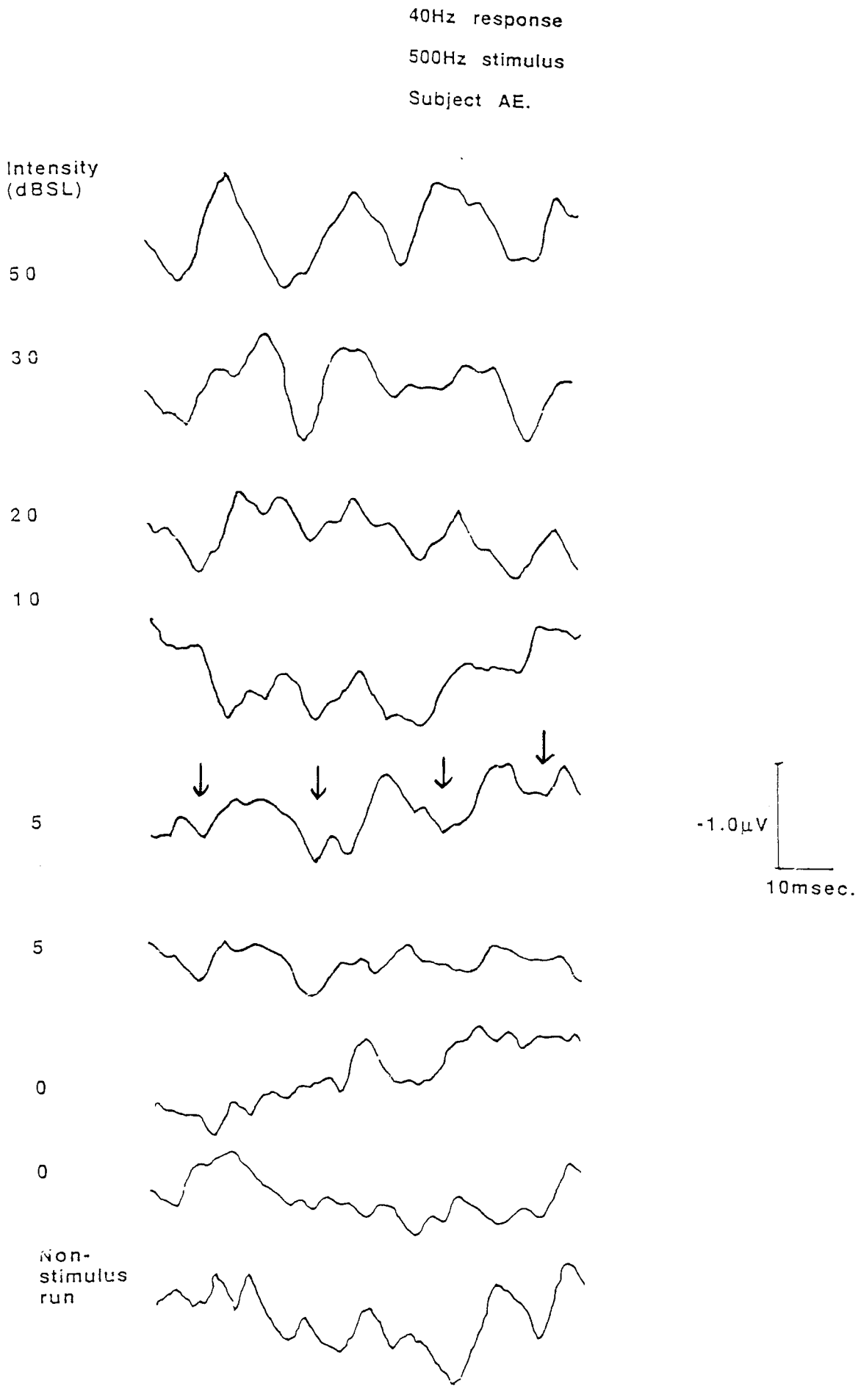

Figure 6.3b Morphology of the 40Hz response at stimulus frequencies of 500Hz, 1000Hz, 2000Hz and 4000Hz (subject AE). Threshold marked with arrows.

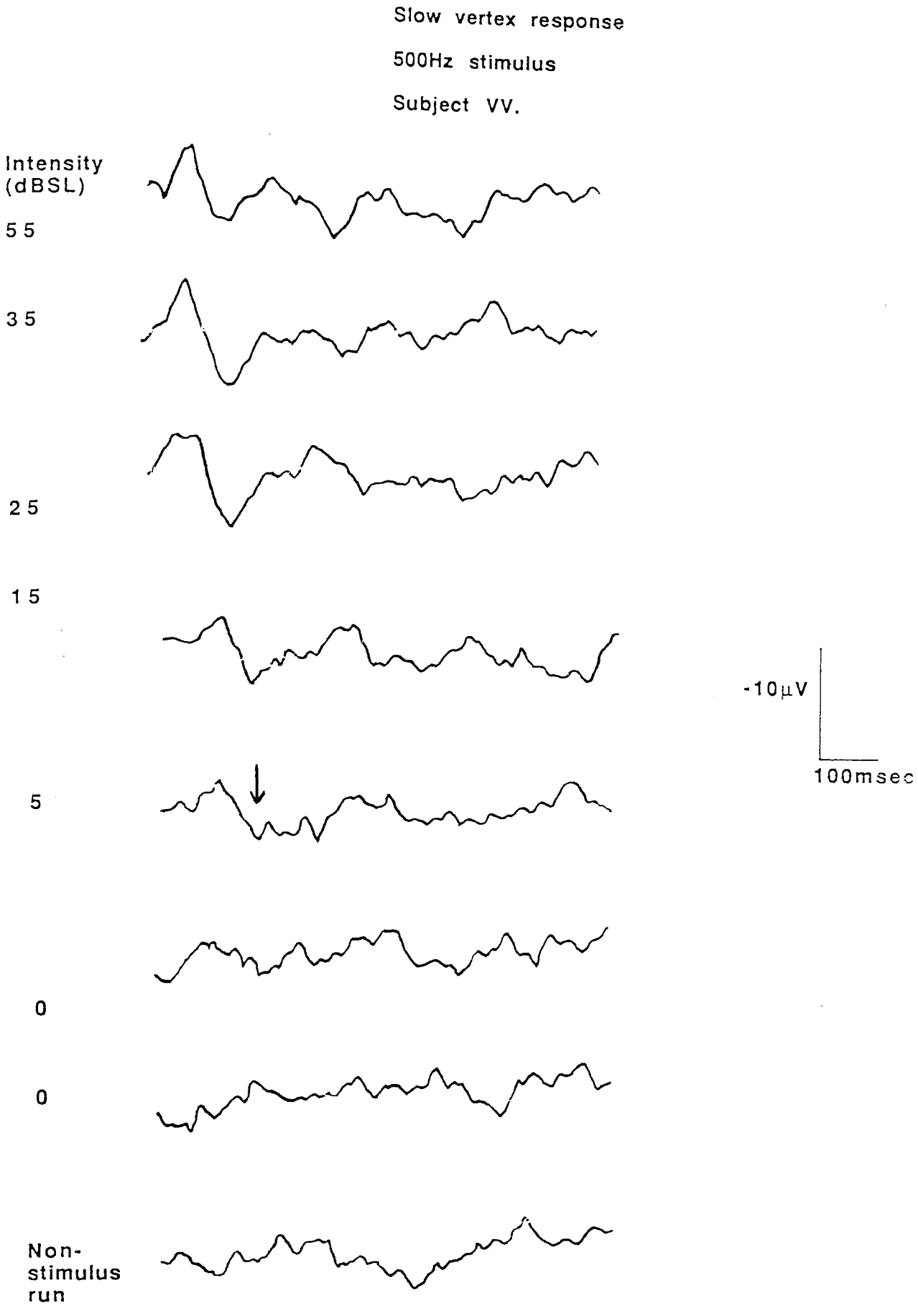

Figure 6.4a The SVR recorded in subject VV using a 500Hz stimulus. Threshold is marked with an arrow.

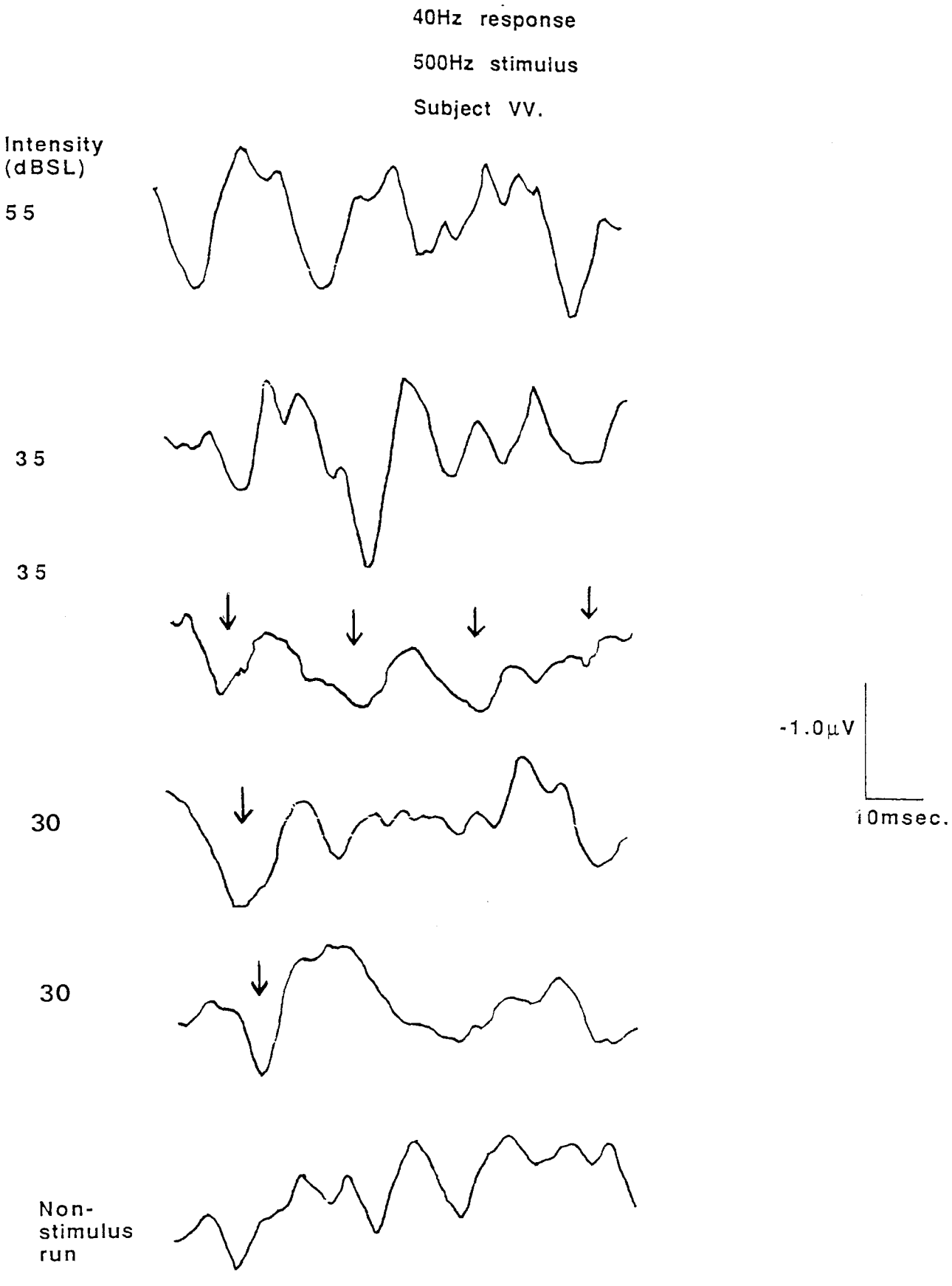

Figure 6.4b The 40Hz response recorded in subject VV using a 500Hz stimulus. Threshold is marked with arrows.

and stimulus frequency as Figure 6.4 a. At 55dBSL (top trace) a clear 40Hz response can be seen. At 35dBSL, the influence of enhanced myogenic activity upon the morphology of the response can be seen. The first recording at this intensity cannot be interpreted meaningfully because of increased myogenic activity. After recording was suspended in order to allow the subject to settle again, the second 35dBSL response was recorded and shows a clear response. At intensities of 30dBSL and lower, no recognisable 40Hz response could be determined even upon repeated testing in the absence of obvious muscular artefacts. The early positive deflection found in the first two repetitions at this intensity (arrowed), might suggest that some response is infact being evoked. But no clear sinusoidal morphology can be distinguished and therefore a negative finding has to be reported in this case. The reasons for this lack of success with the 40Hz response are not immediately apparent. If clear muscular contaminants were causing a distortion of the 40Hz rhythmicity, then it would be expected that these traces would resemble the first 35dBSL response discussed above. However, since recording conditions were favourable on this occasion, the variability of the 40Hz response in this subject (for no attributable reason) is not easily explained and is therefore a matter for discussion (see section 6.4).

The 40 Hz response shown in Figure 6.5a is relatively free of myogenic contamination and the characteristic sinusoidal morphology is present down to 20dBSL (and hence may be considered as a reasonable assessment of audiometric threshold). Conversely, Figure 6.5b shows the corresponding threshold estimates obtained using the SVR. No clear response may be seen at 35dBSL or below.

6.33 Reliability of results.

Since the overall accuracy of this experiment appeared acceptable, with by far the majority of estimates lying within 20dBSL, the number of threshold estimates occurring outside 20dBSL using both SVR and 40Hz procedures was small. Out of the twenty one subjects examined in

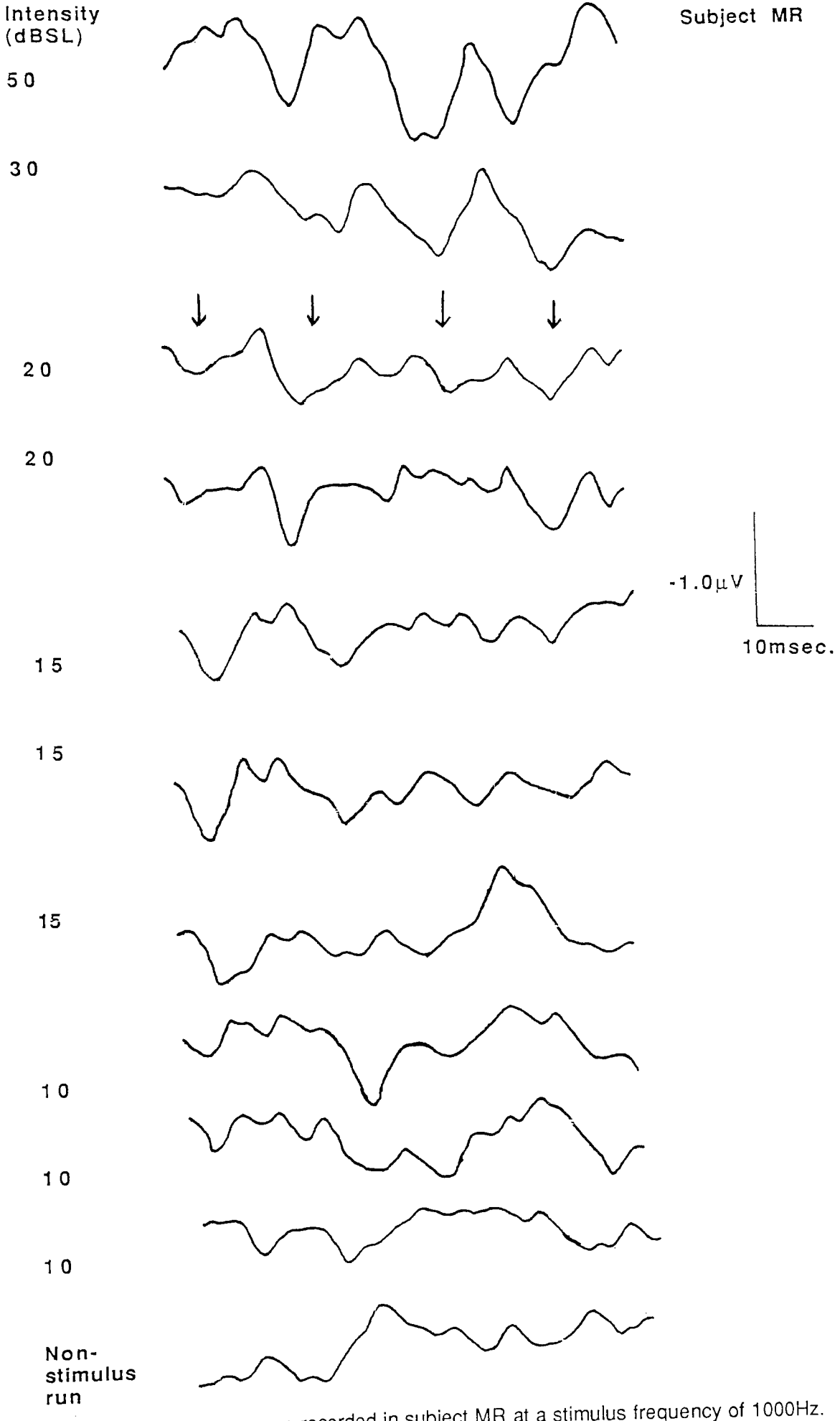

Figure 6.5a The 40Hz response recorded in subject MR at a stimulus frequency of 1000Hz. Threshold marked with arrows.

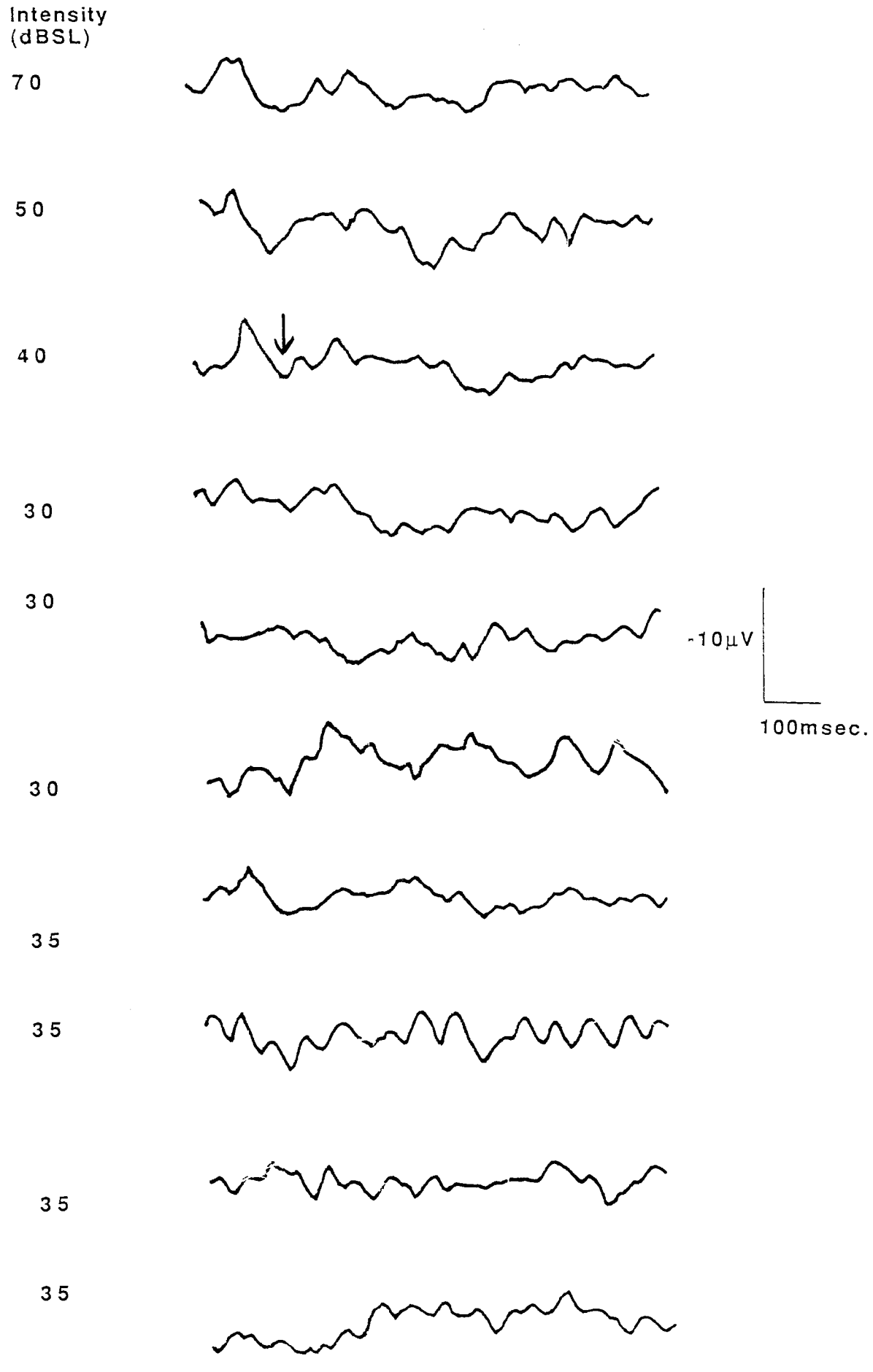

Figure 6.5b The SVR recorded in subject MR at a stimulus frequency of 1000Hz. Threshold marked with an arrow.

this experiment, the subjective - objective difference histograms (Figure 6.3) show that 3 (14.3%), 2 (9.5%), 1 (4.7%) and 3 (14.3%) of subjects gave threshold estimates of ≥ 20dBSL at 500, 1000, 2000 and 4000Hz respectively. This means that across all four frequencies tested, 3.6% of subjects gave audiometric threshold estimates of 25dBSL or worse using either SVR or 40Hz procedures.

On purely qualitative grounds, it must be said that in scoring the presence or absence of the SVR or 40Hz response at a given stimulus intensity, both independent judges found the 40Hz response more difficult to assess. This might have been due to a greater familiarity with the SVR as it is a far more commonly used evoked potential. In terms of recording time, each procedure required around 45 minutes for all responses to be recorded.

6.4 DISCUSSION.

6.41 The SVR and 40Hz response in the measurement of objective threshold.

The aim of this experiment was the comparison of the well established slow vertex response and the less clinically recognised 40Hz response in the measurement of audiometric threshold in normal subjects. The results of this experiment (presented in the histograms Figs. 6.1 and 6.2), indicated that both the SVR and the 40Hz response were able to assess objective audiological threshold to within 20dBSL in 90% of subjects at all stimulus frequencies (except for 500Hz tone pip, 40Hz response, where only 76% of subjects were within 20dBSL).

It is now necessary to relate the experimental findings presented here to existing literature concerning audiometric threshold determinations using SVR and 40Hz procedures. Owing to the far longer established clinical history of the former response and the relative newness

of the latter, much more data has been published investigating the SVR than the 40Hz response.

Many workers have reported a very high fidelity of this response threshold. Cody and Bickford (1965) found (across 500, 1000 and 2000Hz stimulus frequencies), 43% of subjects had identical subjective and objective thresholds, 83% were within 5dB, 93% within 10dB and all subjects gave threshold estimates within 15dBSL. Other researchers have all reported that SVR threshold estimates can be obtained to within 20dBSL in 100% of normal subjects at a wide range of frequencies (Suzuki and Taguchi, 1965; Beagley and Knight, 1967; Beagley and Kellog, 1969; Jones, 1979).

Unlike the SVR, the precise effects of variations in subjective and methodological parameters upon the 40Hz are recently being discovered. Therefore, any experimental inter-comparisons often have to be considered against a background of different recording conditions. In a study similar to the experiment described in this chapter, Sammeth and Barry (1985) reported good correlations between the 40Hz response and subjective threshold in normal subjects (n=16). Using identical test frequencies (500, 1000, 2000 and 4000Hz) and very similar recording procedures to the methods described in this experiment, Sammeth and Barry reported the following mean differences between 40Hz objective and subjective thresholds (ranges in brackets):-9.38 dB (0- -20), -10.00 dB(0- -30), -9.38 dB (0- -15) and -15.63dB (-5- -25). This data shows similar correlations to those reported in the experimental work presented in this study (mean threshold differences in this experiment were: 14.8, 11.2, 13.2 and 13.1dB at the same test frequencies) though it is interesting to note that in Sammeth and Barrys' experiment the best correlation between subjective and objective threshold was found at a stimulus frequency of 500Hz and the highest difference was reported at 4000Hz which is the reverse of what would be expected using the SVR (Antinoro et al., 1969; Jones, 1979) and also not borne out by the 40Hz data recorded in this study. Lenarz et al. (1986), also recording from waking, adult subjects reported high correlations

between subjective and 40Hz objective threshold with 80% of subjects giving estimates within 10dBSL at 500, 1000, 2000 and 4000Hz test frequencies.

6.42 Differences between SVR and 40Hz threshold estimation.

Although 90% of subjects gave slow vertex response threshold assessment within 20dBSL (57% with 10dBSL, across all test frequencies), these figures do not appear to suggest the same level of confidence in the SVR recorded in this particular normal subject population as has been demonstrated by other workers. The increase in the general variability of these data might be explained by the specific choice of subjects in this experiment. Students were used as subjects because of their high availability. However, it could be argued that such a population may not necessarily be viewed as representative of the public at large and it is possible that boredom effects were more manifest in such a group than would be encountered in other populations. Science students, used to repeated requests for participation in research projects, may not have regarded the experimental environment as 'novel' and therefore were more prone to restlessness (i.e. increased EMG activity) than would experimentally naïve subjects or clinical patients. The increased variability of the SVR data presented in this experiment may have been caused by a high number of subjects within the group falling into Hyde's 'problematic 5%' in whom the SVR is unreliable for the reasons given above. The causes of poor threshold estimation using the vertex potential and how these factors might apply to the data given here, will now be examined.

Figure 6.5b presents the SVR recorded from one subject used in this experiment. These traces were difficult to interpret and threshold estimation in this subject using the SVR was a very poor 40dBSL (this was the worst estimate of threshold recorded using the SVR in all twenty one subjects tested at any stimulus frequency). By examining these traces, the reasons for poor threshold estimation can be explained. The top three traces show clear N1-P2 response (70, 50 and 40dBSL). However, at 30dBSL the morphology of the response is

far more variable. Three repetitions of the 30dBSL stimulus failed to produce a consistent finding. The first 30dBSL trace possibly shows the presence of a response. This uncertain finding demanded repetition and the seond trace shows that there is little evidence of a response in this repeated presentation. A third repeat failed to resolve the ambiguity as it is not clear if a response is present or not due to the high amplitude of the background activity. Raising the stimulus intensity by 5dBSL revealed similar problems. The first trace would suggest the possible occurrence of a response at this intensity. Trace two shows a high level of alpha rhythm obscuring response detection. The bottom two 35dBSL repeats show no clear SVR components and therefore, no response is reported at this level of stimulation. The second 35dBSL trace illustrates the susceptibility of the SVR to alpha rhythm. Equal in amplitude to the N1-P2 components of the vertex response (around 5μV), alpha renders the SVR uninterpretable in this case. The first and the second 35dBSL responses were recorded consecutively, with only moments between the two trials. The markedly different response morphologies (as a result of the alpha rhythm in the second trace) illustrates the striking changes that occur should alpha be present when recording the SVR. Here we see an example of a case in which the SVR provided a poor estimate of audiometric threshold. However, it is possible to predict this inaccuracy due to the large amounts of high amplitude rhythmic activity present within the background EEG. If this series of responses had been recorded from a clinical case in whom a hearing loss was suspected, the clinician would not report the patient's hearing threshold to be 40dB with any confidence. This is because it is impossible to tell whether this disappearance of the SVR waveform at 40dB is a result of an auditory deficit or background contamination. Since this subject was known to have normal hearing, the former reason may be eliminated and the SVR regarded as an unreliable measurement of threshold in this case.

What can the 40Hz response tell us in this case? Figure 6.5a presents this data for the same subject. The subjective state of the subject at the time of testing was not visibly different from when recording the SVR. 40Hz responses are recordable down to 20dBSL (20dB better than the SVR) and in the absence of any known confounding artefacts, the 40Hz response

would appear to be assessing audiometric threshold with considerably more success than the SVR in this case.

The effects of sleep upon the SVR are well established (Ornitz et al., 1967; Osterhammel et al., 1973). The consistency of the SVR in audiometric threshold determination has been known for two decades. What matters more than arousal level *per se* is the detrimental effects of fluctuations in attention levels upon response morphology. Keating and Ruhm (1971) found the greatest variability in objective threshold estimates made using the SVR in conditions of quiet (with no attentional cues) and the least variability in the response in subjects who were quietly reading throughout the experiment (i.e. maintaining a consistent but attentive level of arousal). Despite the constant monitoring of subjects with a closed-circuit television in this experiment, making subjects read during the experiment and allowing subjects to rest durng the experimental period, many still reported experiencing drowsiness in an experimental protocol often lasting 1.5 hours and longer. Separating the combined effects of diminshed attention and restlessness is not, however, easy. Subjects were often observed to be becoming drowsy both by EEG monitoring and by direct observation with a close-circuit television and (presumably realising this), startling themselves into wakefulness again. Another example of poor threshold estimation using the SVR is given in Figure 6.6a. The traces do not exhibit a significant amount of alpha rhythm, yet the responses of this normally hearing subject are largely disappointing at all stimulus intensities. At 70, 50, 40 and 30dBSL, it is possible to score the SVR as being present. However, at 25dBSL and lower, repeated trials could not elicit a consistent response and therefore the 30dB level is as close to threshold as may be accurately predicted using the SVR in this case.

Considering now the 40Hz response, the effects of arousal level are less certain. Figure6.6b presents the equivalent 40Hz data for this subject. At 50 and 30dBSL a clear 40Hz sinusoidal morphology makes positive detection of the response relatively clear and easy. At 25dBSL a response is also visible. However, at lower stimulus intensities than 25dBSL, the 40Hz response ceases to be immediately distinguishable. The initial definitions of respons

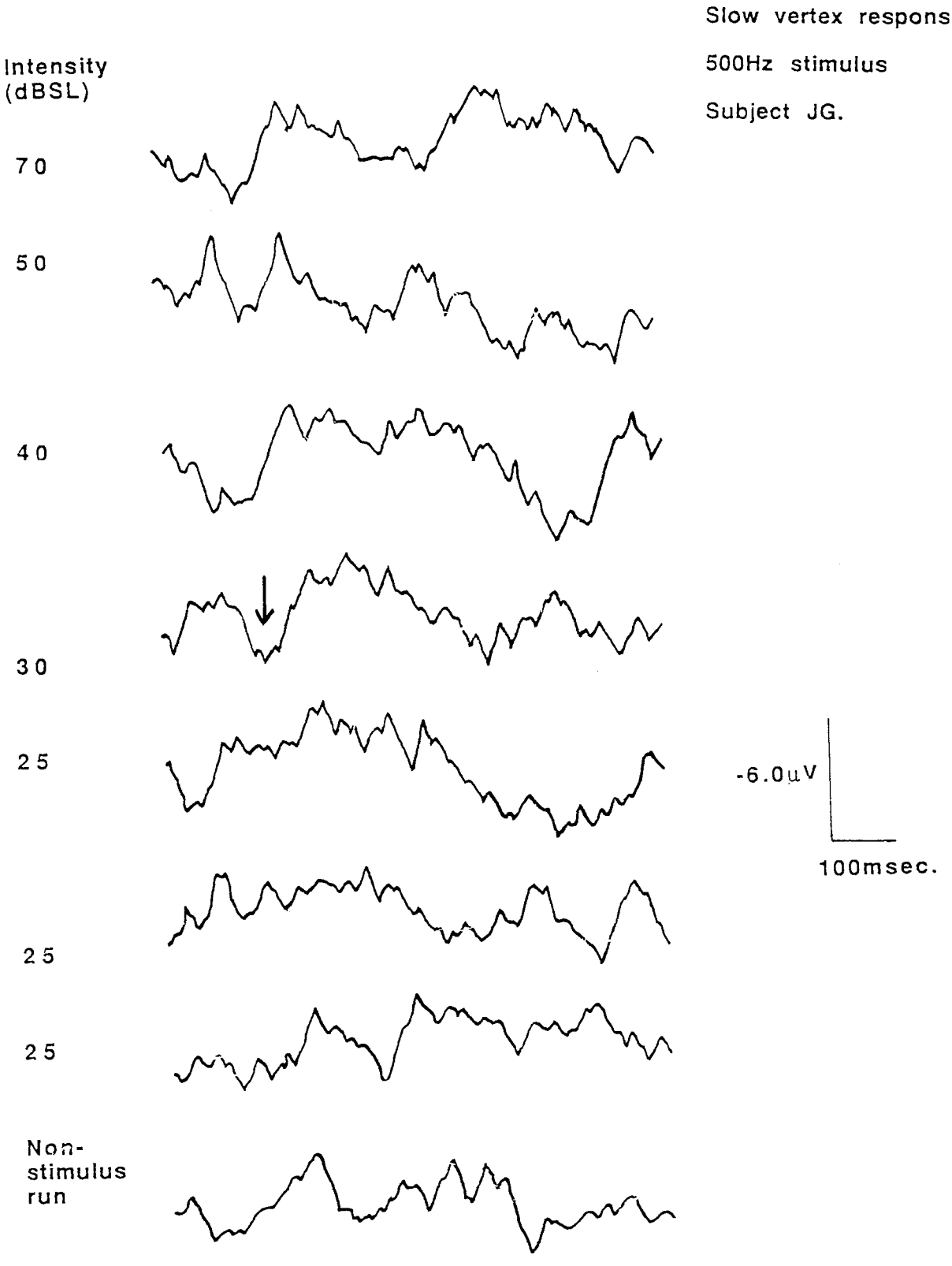

Figure 6.6a The slow vertex response to a 500Hz stimulus in subject JG. Threshold marked with an arrow.

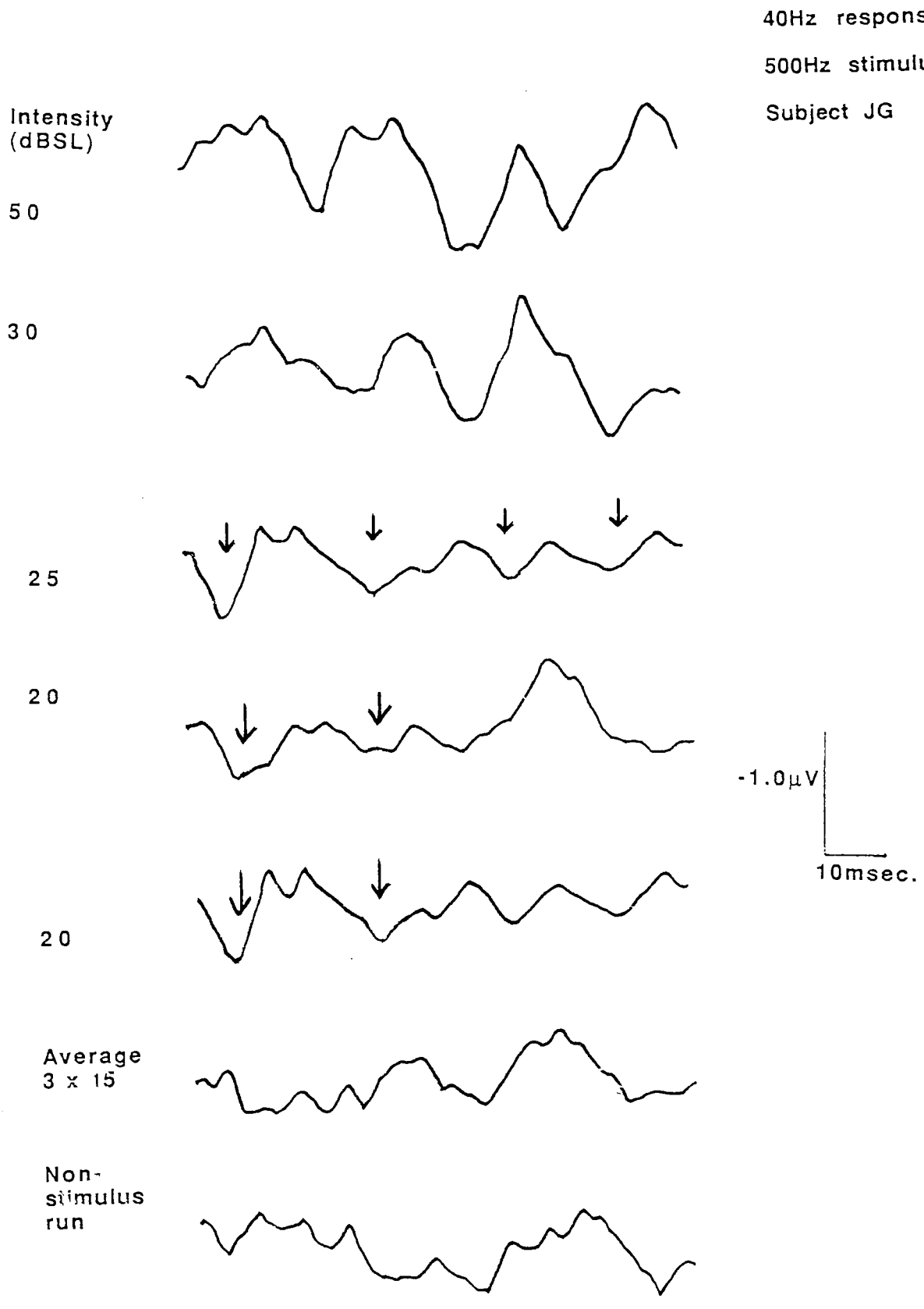

Figure 6.6b The 40Hz response to a 500Hz stimulus in subject JG. Threshold marked with arrows (25dBSL). Possible response conponents at 20dBSL also marked.

detection criteria (given in the experimental methods section) stated that a positive 40Hz would only be scored if all 4 peaks of the 40Hz response were present. In Figure 6.6b, at 20dBSL all the requisite components are not visible. However, repeated trials at this intensity revealed two consistent upward and downard deflections (marked on the figure) at latencies which would suggest that some response is in fact being evoked at this intensity.

The question now arises as to why the 40Hz response sometimes exhibits fewer components than expected particularly at low stimulus intensities? One possible explanation is that myogenic components are distorting the 40Hz response and disrupting its sinusoidal morphology. Alternatively, it could be suggested that there is an inherent variability in the middle latency response which renders it less useful in clinical diagnosis. In Figure 6.3b (see results section), it was commented that there was not always a uniform relationship between 40Hz amplitude and stimulus intensity. Chapter 2 discussed the role of myogenic components within the middle latency range and indeed one of the reasons for the limited use of the MLR clinically is the lack of reliability caused through enhanced muscular activity under certain conditions (Streletz et al., 1977). Even though an earlobe (as opposed to mastoid) reference electrode was used in this experiment in order to reduce the influence of myogenic artefact and reduce the influence of the post-auricular muscle potential, it is possible that the recording conditions used in this experiment (sitting and alert) were not conducive to optimal middle latency (and hence 40Hz response) recording.

At the completion of the main experiment, it was decided to re-test some of the subjects using an identical 40Hz procedure, except that rather than subjects sitting and reading for the duration of the test, they were asked to lie down and relax more fully (though not go to sleep). Eight subjects were selected in whom the 40Hz response had been considered poor in estimating objective threshold because of large myogenic artefacts. The 40Hz responses recorded from these subjects re-tested whilst sitting and reading and also whilst lying down (awake) are presented below.

All other experimental parameters were otherwise the same and as described in the experimental methods section (6.2).

Subject	*Objective-Subjective threshold differences (dBSL)*							
	500Hz		*1000Hz*		*2000Hz*		*4000Hz*	
	sitting	*lying*	*sitting*	*lying*	*sitting*	*lying*	*sitting*	*lying*
JR	15	20	5	5	15	15	15	15
RD	30	20	20	10	15	15	20	10
VV	35	5	10	5	20	5	20	10
JG	25	15	25	15	20	20	15	15
SG	15	15	15	5	5	5	5	0
AH	15	20	5	20	15	5	15	5
BA	15	10	10	10	5	5	10	10
MR	15	15	20	20	15	15	10	20
Mean	20.6	15	13.8	11.2	13.8	10.6	13.8	10.6
(s.d.)	8.2	5.3	7.4	6.4	5.8	6.2	5.2	6.2

Table 6.4 Threshold for the 40Hz response for selected subjects sitting and reading or lying down.

Figure 6.7a and b illustrates the 40Hz traces obtained from two of these subjects when lying down in relaxed wakefulness. Figure 6.7a was selected because it shows the subject VV who gave a poor 40Hz threshold estimation when sitting (shown in the results section fig. 6.4b). When re-tested lying down at the same test frequency (500Hz), the subjective-objective threshold difference was reduces by 30dBSL (fig 6.7a). Similarly subject RD (Figure 6.7b) gives a 10dB improvement. The most noticeable difference in threshold estimation was seen at 500Hz. However, looking more closely at Table 6.4, it is clear that the mean difference at

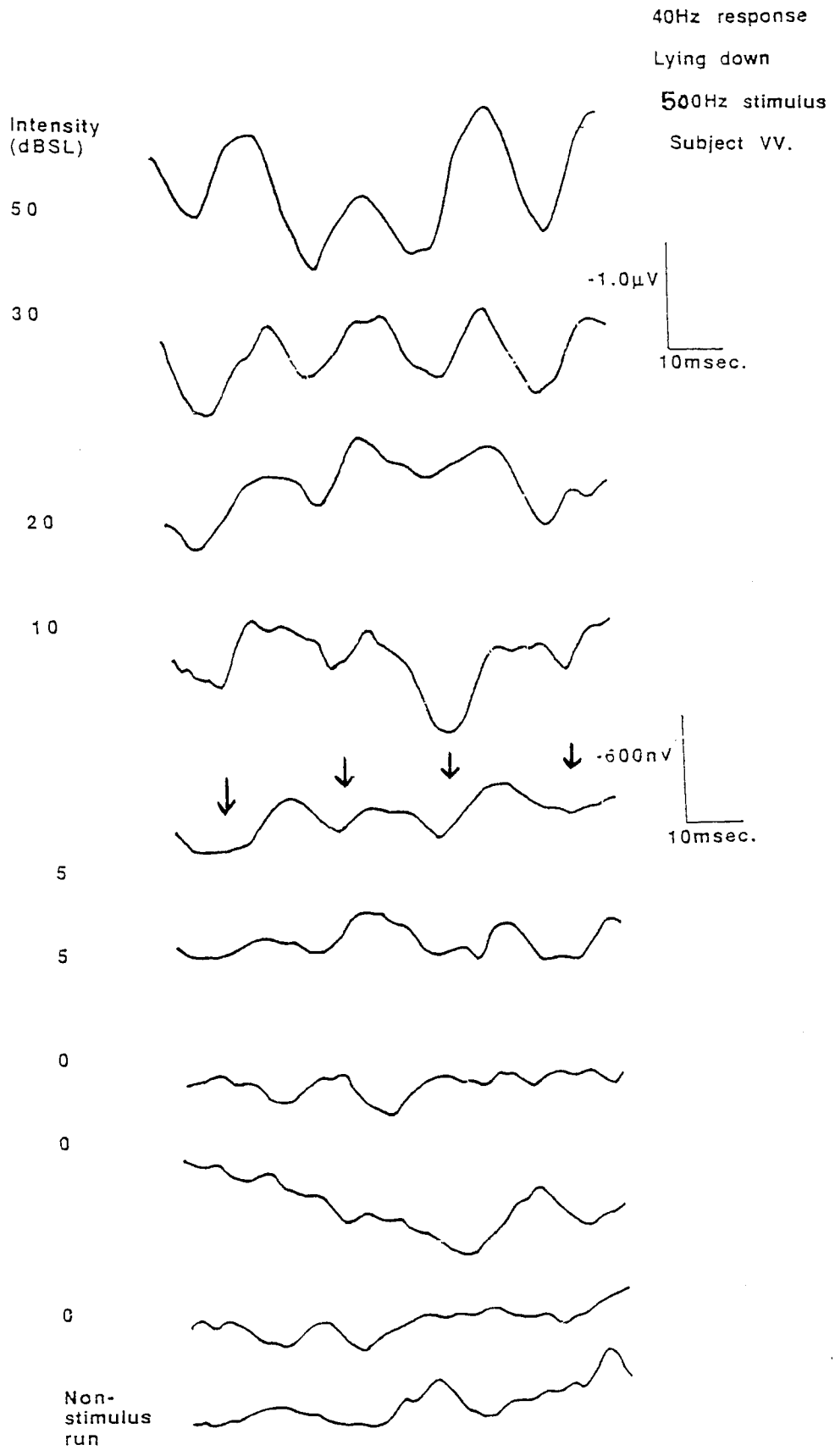

Figure 6.7a Repeated 40Hz response using a 500Hz stimulus in subject (VV), re-tested lying down as opposed to sitting (see figure 6.4b). Threshold marked with arrows.

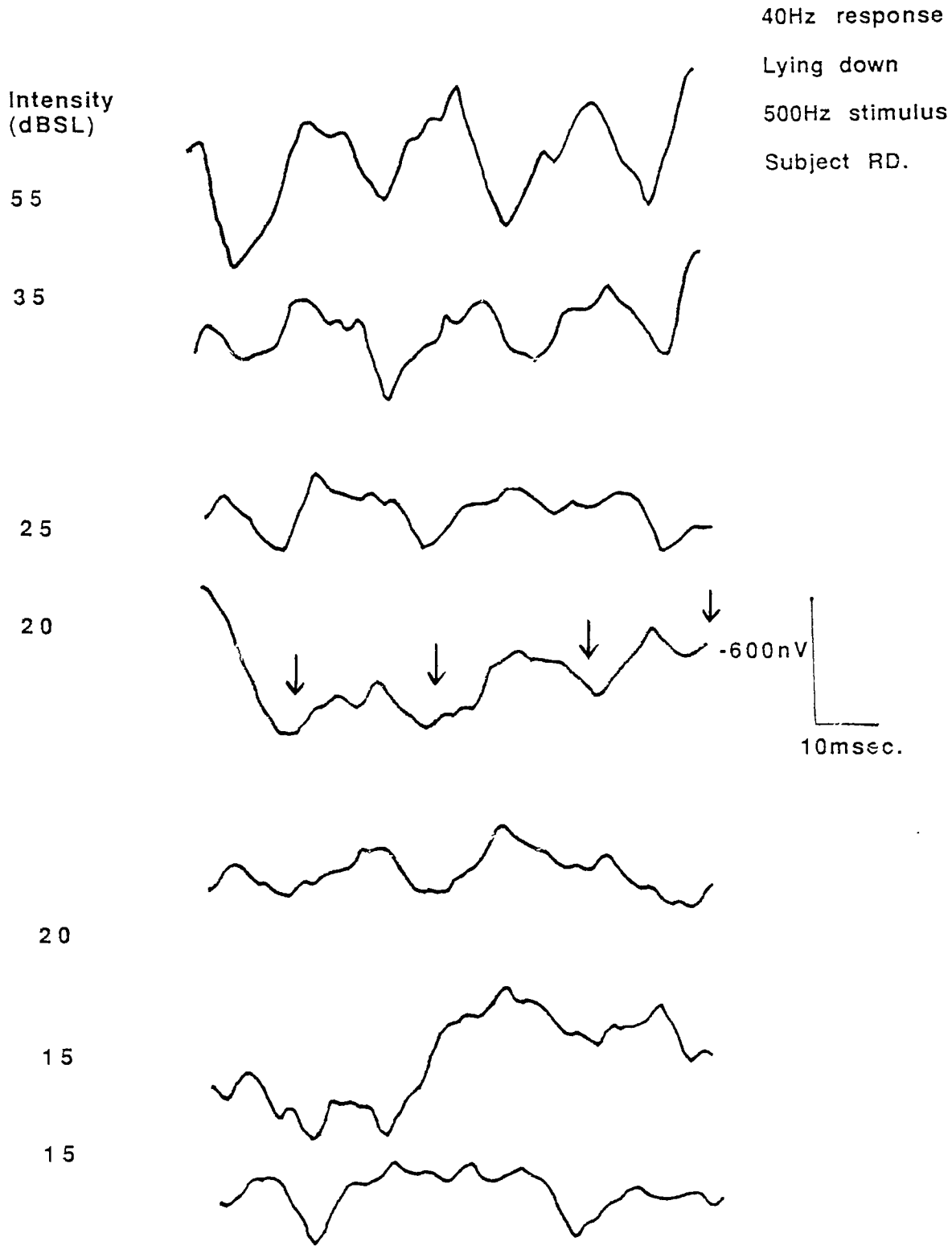

Figure 6.7b Reapeated 40Hz response in subject (RD) re-tested lying down as opposed to sitting. Threshold marked with arrows.

500Hz (20.6dBSL sitting compared with 15dBSL lying) is due primarily to only one subject (VV). Removing subject VV from the sample the new means at 500Hz are 18.5dBSL sitting (s.d. = 6.3) and 16.4dBSL lying (s.d. = 3.8). Performing statistical tests of significance on these data (Student's t-test), for all frequencies (with and without subject VV at 500Hz), no significant differences could be found between the sitting and lying protocols at the 95% level or higher. At 500Hz, t = 1.39; significance = 0.21: at 1000Hz, t= 0.837; signifiance = 0.43: at 2000Hz, t = 1.49; significance = 0.18: and at 4000Hz, t = 1.26; significance = 0.25.

It is now necessary to compare the 40Hz data (lying) with the SVR results for these eight subjects. Seven of these subjects took part in the main experiment (subject BA had left the department by the time of the retrospective study) and the following means and standard deviations were obtained for the SVR. 500Hz mean = 12.1 (s.d. = 9.5); 1000Hz mean = 17.1 (12.9); 2000Hz mean = 10.7 (7.3) and 4000 mean = 15.7 (6.7). Again statistical tests were performed comparing the threshold estimates using 40Hz procedures and the SVR for these subjects. Once more, no significant differences were found at the 95% level or better with the excepetion of the comparison between the 40Hz procedure lying down and the SVR at 4000Hz. At 500Hz, t = 0.658; significance = 0.35: at 1000Hz, t = 1.51; significance = 0.182: at 2000Hz, t = 0.354; significance = 0.736: and at 4000Hz, t = 4.3; significance = 0.004 (i.e. probability of rejecting the null hypothesis = 99.6%). Although this appears to be highly significant, some caution is required in interpreting this finding since the subjects were tested on separate occasions and therefore it is possible that the degree of relaxation was different between the two tests or that subject compliance was less favourable.

6.43 Other methods of assessing the 40Hz response.

The assessment of audiological threshold using evoked response audiometry usually relies upon the judgement of the clinician and his/her ability to define the lowest intensity at which response morphology can be discerned. The various strategies used to improve the

accuracy of this process were discussed in section 4.2 of this thesis. However, since the 40Hz response is a periodic 'steady-state' potential, recent research has investigated the possibility of analysing the waveform using frequency-based techniques such as Fourier analysis (Makeig and Galambos, 1983; Linden et al., 1985; Jerger et al., 1986). Stapells et al. (1987) have suggested that Fourier analysis offers a more objective method of determining audiometric threshold using the 40Hz response than can be achieved by the more traditional technqiues of latency, amplitude and response peak measurement. Central to the frequency analysis of the 40Hz response is the measurement of the phase of the waveform and the phase variability between successive response averages. Phase, refers to the fraction of a cycle through which a wave has passed at a given instant and phase variability measures the degree of concordance between different waveforms. Thus, in electrophysiological terms, the 40Hz waveform may be defined with respect to its phase and the constancy of successive 40Hz averages may be measured in terms of phase variability. In order to interpret the literature which has examined 40Hz phase and its relation to audiometric threshold, some mention of the mathematics behind phase calculations is necessary. Mardia (1972) defined phase variance as:

$$PV = 1 - [(1/n \sum_{i=1}^{n} \cos \phi_i)^2 + (1/n \sum_{i=1}^{n} \sin \phi_i)^2] \qquad 1.$$

When ϕ_i is the phase angle of the Fourier component of the ith sample and n is the number of samples. Fridman et al (1984) developed this into the component synchrony measure (CSM) which is calculated as:

$$CSM = 1 - PV \qquad 2.$$

Jerger et al. (1986) proposed the phase coherence (PC) measurement defined as:

$$PC = \sqrt{CSM}$$

$$= \sqrt{\quad} \left[(1/n \sum_{i=1}^{n} \cos \phi_i)^2 + (1/n \sum_{i=1}^{n} \sin \phi_i)^2 \right] \qquad 3.$$

Phase coherence varies between 0 and 1.0. When the variability of the response is small PC tends to 1.0 and similarly, when variability is high, PC tends to 0. Phase coherence has become increasingly popular in investigating the 40Hz response and its relationship to audiometric threshold. Spydell et al. (1985) examined the consistency of phase measurements of the 40Hz response near audiometric threshold to click stimulation reporting no significant change in phase to within 20dB of threshold. Stapells et al. (1987) examined the usefulness of phase coherence in the prediction of behavioural thresholds using the 40Hz response. Presenting 500Hz and 2000Hz tone pips at a rate of 39.1/sec. to waking adult subjects, the authors reported significant values of PC down to 6dB of threshold for both stimuli in comparison with the mean PC for non-stimulus contral run. Furthermore, no sigificant measurements of 40Hz response amplitude (in comparison with a non-stimulus run) could be determined at 25dBSL and therefore it would appear that phase coherence offered a more acute measurement of threshold in this case. The other major requirement of a clinically useful test of audiometric threshold is speed of data acquisition. Stapells and colleagues (1987) claim that threshold estimates to within 10dBSL could be obtained in 3.6 min. and estimates to within 25dBSL in 60 sec.

These results would suggest that this technique offers considerable benefits and extends the usefulness of the 40Hz response. However, at present little data exists applying phase measurements to hearing impaired populations, children or sleeping subjects and more work is required before this technique can be extensively exploited clinically.

6.5 CONCLUSIONS.

Frequency specific estimations of audiometric threshold were made using the SVR and 40Hz response procedures in twenty one normally hearing subjects. In the majority of cases, both sets of potentials gave similar estimates of threshold. As only a very small proportion of threshold assessments were worse than 20dBSL with either response, this might suggest that a combination of SVR and 40Hz testing would be ideal in order to more successfully estimate hearing thresholds and that the SVR and 40Hz response may be used interchangably in the majority of cases. However, considering the constraints of time and cost which apply to the clinical environment, this suggestion is untenable. Whilst the SVR is able to provide consistent and easier to assess waveforms in the majority of cases, it would appear unnecessary to routinely prefer 40Hz responses. However, where it would be useful to include the 40Hz responce within the clinical test battery is in patients (around 5% according to Hyde et al. 1986) who cannot be tested accurately using the SVR perhaps because of the occurrence of recurrent alpha activity. One interesting finding in this experiment was that the 40Hz response appeared subjectively to be more easily recognised (though was not statistically superior) in subjects who were lying down (awake) for the duration of the test as opposed to the responses recorded in subjects who were sitting down. This observation, reported by both independant observers, requires further corroboration and will be examined more fully in future work.

The aim of the experimental work described in this chapter was to examine the 40Hz response as a suitable alternative to the SVR in adult objective audiometry. In such a population, subjects may be tested in relaxed wakefulness (assuming an adequate degree of patient cooperation and compliance). A further problem is encountered when attempting to gain audiometric threshold in a child population namely, the SVR is too variable in younger subjects for reliable information to be obtained (Suzuki and Taguchi, 1965; Cody and Townsend, 1973).

Since sleep is an essential requirement in testing an infant or neonatal population (in order to record responses which are free from myogenic and movement artefacts), attention will now focus on the specific effects of changes in arousal level upon the middle latency and 40Hz responses.

CHAPTER 7

CHANGES IN THE AUDITORY MIDDLE LATENCY RESPONSE AND 40HZ RESPONSE DURING ALL-NIGHT SLEEP RECORDING.

7.1 INTRODUCTION.

The aim of this experiment was to examine one of the characteristics of the middle latency response (MLR) which still remains controversial, namely its sensitivity to state of arousal. This debate is perhaps of greatest relevance to the potential usage of the MLR in neonatal and infant populations where natural or sedated sleep is an essential prerequisite for successful testing in most cases.

As discussed in previous chapters, it has not always been easy to separate the variables of sleep and age in many recent experiments (Kraus et al., 1987a; Stapells et al., 1988). This has led to uncertainty over whether changes in morphology attributed to one of these two variables can be postulated with any certainty given the presence of the other, i.e. can a change in waveform morphology, latency or amplitude occurring in a sleeping infant be attributed to immaturity, somnolence or an interaction of the two?

Much of the original work reported that the MLR was stable and reproducible in subjects of all ages with no differences found in the responses of children compared with adults (McRandle et al., 1974; Mendel et al., 1977; Wolf and Goldstein, 1978, 1980; Mendelson and Salamy, 1981). Recent research however has failed to reproduce these earlier findings in the younger age group either reporting no convincing responses or MLRs which bear little resemblence to those recorded in adults (Sprague and Thornton, 1982; Kileny, 1983).

Similar controversy has been reported in the literature concerning the effects of sleep and sleep stage on the MLR. In the 1970's changes in the MLR with arousal were found to be negligible with only some reduction in amplitude in sleep but very little change in latency or morphology in comparison with the waking state (Mendel et al., 1975). Again, this earlier work has been questioned with marked changes currently reported in the morphology of the MLR and particularly the latency of the later components of the response (Brown, 1982; Osterhammel et al., 1985; Erwin and Buchwald, 1986).

Scherg (1982), Suzuki et al. (1983a and b) and Kraus et al. (1987) have all strongly suggested that the main theme underlying these inconsistencies has been the variations in recording procedures (specifically filter bandpass) used by different research groups. Therefore, in order to control for the effects of maturation and to examine solely the effects of sleep and sleep stage upon the MLR and 40Hz response, an adult population of subjects was used in this experiment. In order to exclude the possibility of narrow filter bandpasses generating non-physiological distortions into the responses being recorded, it was decided to use wide filter settings.

Even considering the controversies that surround the MLR, interest in these potentials has increased recently with the advent of steady-state recording techniques (namely the 40Hz response) by Galambos et al. (1981). This response (discussed in previous chapters) has been reported to offer a sensitive, frequency specific method of assessing auditory thresholds independent of subject age and level of consciousness (Shallop and Osterhammel, 1983; Musiek and Donnelly, 1983; Linden et al., 1985).

This experiment resulted from clinical observations of the morphology of the 40Hz response recorded in young children referred to the Clinical Neurophysiology Unit at Aston University for brainstem investigations. Figure 7.1 shows 40Hz responses recorded from an infant with a normal BAEP as recorded to click and tone pip stimulation in sedated sleep. It can be seen that with bandpass filters of 10-125Hz (commonly used for 40Hz response recording), the

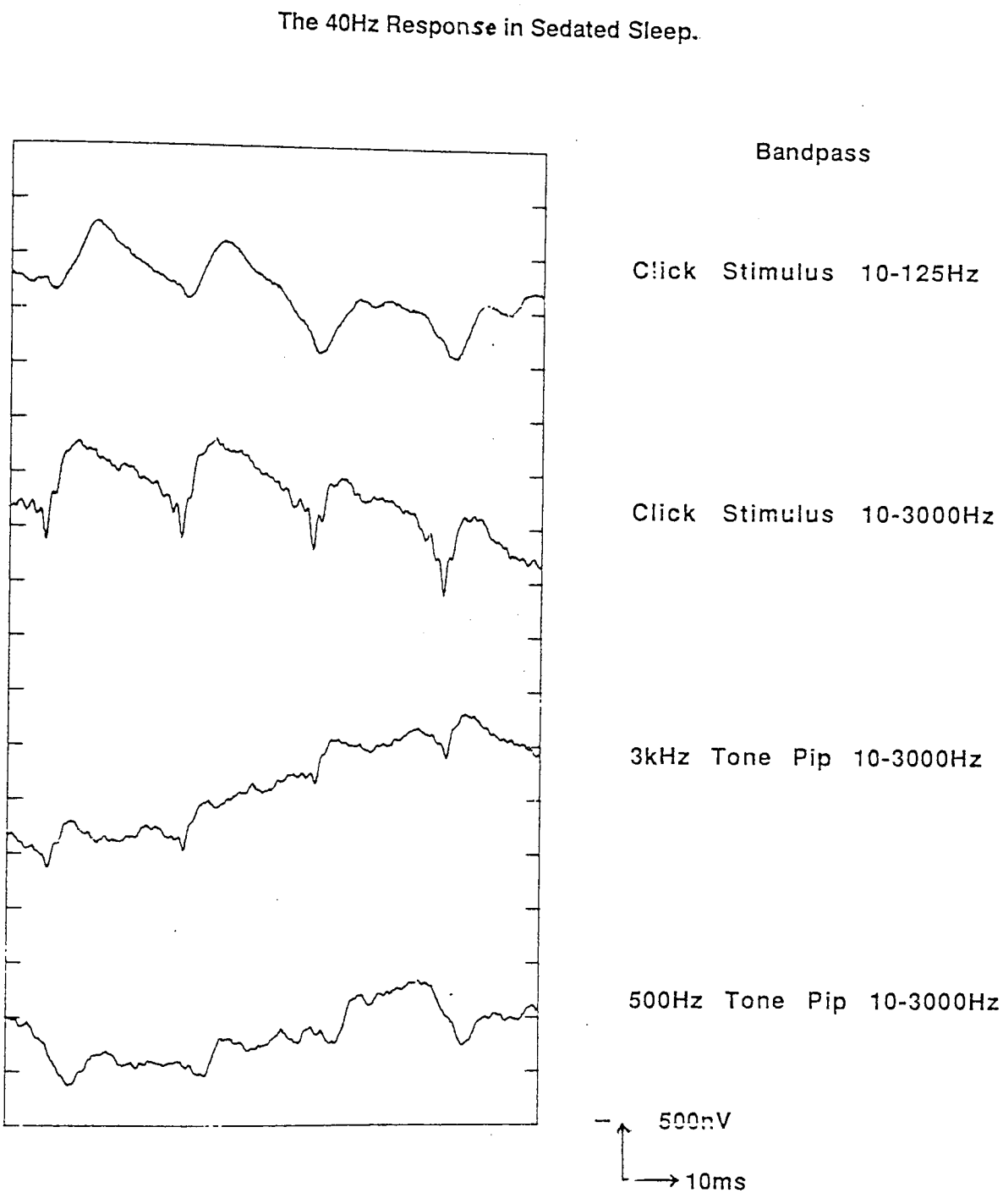

Figure 7.1 comparison of 40Hz responses recorded from a normally hearing infant. Click, 3000Hz and 500Hz stimulation with bandpass filters of 10-125Hz and 10-3000Hz.

response showed the predicted sinusoidal waveform in accordance with established literature. However, with a wider bandpass of 10-3000Hz, the morphology of the waveform changed and appeared to consist predominantly of four individual brainstem responses with a significant attenuation in middle latency activity.

7.2 METHODS.

This study was designed to investigate changes in the 5Hz MLR and 40Hz response during all night natural sleep.

Responses were recorded in 10 normally hearing adults aged between 23-30 years (mean age 26 years, 4 male and 6 female) using the Medelec Sensor ER94a averager and ST10 stimulator unit. Continuous stimulation throughout the night was provided using an insert earpiece supplied by Medelec and compatible with the Sensor. The choice of the insert earpiece was made in order to provide maximum comfort and convenience for subjects during an experimental protocol lasting between 6 and 8 hours. Similarly, owing to the long experimental procedure, whilst it would have been ideal to conduct the sleep study in the sound-proof room, poor ventilation meant that this was inadvisable. Extraneous noise was not considered a likely source of error as all experimentation was carried out during the night.

Responses were recorded in Stage 2, Stage 3/4 and Stage REM sleep to click stimuli (100µsec.duration) and tone pip stimuli (2 cycles rise/fall time and 1 cycle plateau) delivered at frequencies of 500 and 4000Hz. Two stimulus repetition rates were chosen, 5/sec. and 40/sec. The 5Hz stimulus repetition rate was chosen in order to observe any changes in the morphology of the transient MLR response which may occur at different stages of sleep. The 40Hz steady state response recorded at the corresponding levels of arousal could then be related to the composition of the transient MLR. All responses were stored on floppy disks on the Apple IIe microcomputer for detailed off-line analysis. Before commencing the

experiment, subjective auditory thresholds were measured for all stimuli at rates of 5 and 40Hz. Stimulation was maintained throughout the night at 45dB above these thresholds. This intensity was chosen as a compromise because it was considered sufficiently quiet as not to unnecessarily disturb the sleeping subjects whilst being loud enough to evoke an easily recognisable response. Sleep was continuously monitored on a Nihon-Koden EEG machine and accurate sleep scoring was performed using the criteria of Rechtschaffen and Kales (1968). When possible at least two responses were obtained in Stages 2, combined 3 and 4 and REM sleep for each stimulus condition in order to assess the reproducibility of the evoked potentials that were recorded.

The montage used for measuring EEG activity during sleep recorded from the vertex and referred to the mastoid ipsilateral to stimulation. This derivation was also used for evoked potential recording. In order to accurately score sleep stages, eye movements were monitored by electrodes at the outer canthi each referred to the same mastoid and myogenic activity was recorded between two electrodes on the chin. With the exception of the canthi electrodes (which were attached with Blenderm and Micropore tape for considerations of comfort), all other electrodes were glued to the head to ensure that they were secure for the duration of the experiment. After glueing, all electrodes were taped down with Blenderm and Micropore in such a way that they would not cause discomfort to the subject and were not likely to become dislodged. In order to prevent the earpiece delivering the stimulus from slipping out of the ear canal, this too was taped. All EEG, EOG and EMG activity was recorded throughout the experiment and written out on the Nihon-Koden EEG machine for rechecking at the end of the experiment. On-line sleep scoring was performed by Dr L.A. Jones.

Responses were recorded using wide bandpass filters of 0.3-3000Hz at 3dB down and slopes of -6dB and -12dB/octave respectively. The amplifier gain was set at a sensitivity of 50μV/division on the Sensor. The decision to use such a 'coarse' gain (thus potentially admitting EMG artefacts), was taken so that averaging was possible in slow wave sleep (SWS) where EEG amplitude can reach up to 200μV. The dangers of EMG contamination were

considered small, firstly because muscle levels tend to be lower in sleep than in wakefulness. Secondly, since all electrical activity was continuously monitored throughout the experiment, it was possible to suspend recording should myogenic contamination be suspected. The analysis time used for recording both 5 and 40Hz responses was 100 msec. and the number of sweeps recorded was 1024. After the sleep study was completed and on a separate occasion, responses were recorded during relaxed wakefulness using identical experimental conditions in order to compare the effects of sleep on the MLR with the normal waking response.

7.3 RESULTS.

At the end of the experiment, all the EEG activity recorded throughout the night was reanalysed by Dr Jones in order to ensure the accuracy of each sleep stage and to remove any responses which were recorded in mixed or uncertain sleep stages. All sleep staging was performed by Dr Jones.

7.31 Data analysis.

The nature of the recording equipment did present one difficulty with data handling in this experiment. Because of limitations to the software package provided for the Apple IIe by Medelec, the data recall and analysis facility did not allow for group averaged results to be calculated. Attempts were made to ask Medelec to rectify this shortcoming and program modifications were attempted within the Clinical Neurophysiology Unit with no success. However, since the subject sample size was small it was considered preferable to examine all data individually. All traces shown, however, are the average of two separate trials (where possible) as the addition of responses within subjects was possible with the recording system provided.

7.32 Latency changes in the MLR during sleep.

Despite its not being possible to group average response traces, numerical analyses of latency changes of response components were possible.

Graphical representations of the latency changes in wave V, Na and Pa in sleep using click and tone pip stimuli are shown in Figures 7.2, 7.3 and 7.4. Table 7.1a, b and c presents the mean latencies and amplitudes of all components recorded to the click, 500Hz and 4000Hz stimuli. The raw data relating to these values may be found in Appendix 1. These figures demonstrate that wave V remained stable throughout all stages. The Na component also appeared fairly stable in latency although its clarity and amplitude were reduced in sleep. Pa showed clear increases in latency from wakefulness through Stage 2 and Stage 3/4 sleep, returning to near waking levels in Stage REM. Analysis of these data using paired Student's t-tests, revealed that the differences in Pa latency between wakefulness and Stage 2 and wakefulness and Stages 3/4 were significant at the 5% level or better for click, 500Hz and 4000Hz stimuli. There were no significant differences in the latency of Pa between wakefulness and Stage REM. The Na component also showed significant changes in latency for the click stimulus between wakefulness and Stage 3/4 sleep ($p < 0.01$) and also between Stage 2 and Stage 3/4 sleep ($p < 0.02$). For the 500Hz stimulus, Na latency increases were also significant between wakefulness and Stage 2 ($p< 0.01$) and between wakefulness and Stage 3/4 sleep ($p < 0.03$). Significant changes in amplitude were also observed with variations in arousal level. Using click stimulation, the wave V-Na amplitude was found to be significantly reduced in Stage 3/4 sleep when compared with the waking state ($p < 0.02$). With the 500Hz stimulus, the wave V-Na reduction was also found when comparing wakefulness and Stage 2 ($p < 0.02$) and Stage 3/4 sleep ($p < 0.02$). In addition, the Na-Pa amplitude was also significantly reduced between wakefulness and Stage 2 sleep ($p < 0.03$). The exact t-test values can be found in Appendix 1. It is accepted that conclusions drawn from statistical tests on small subject sample sizes must be viewed with caution.

Click											
				Amplitude		Amplitude		Amplitude			Amplitude
		Wave V (ms)	Na (ms)	V- Na (nV)	Pa (ms)	Na- Pa (nV)	Nb (ms)	Pa- Nb (nV)	Pb (ms)	Nb- Pb (nV)
	Mean	7.24	19.6	755	31.4	950	43.2	481	56.1	714
Awake	S.D.	0.8	1.8	162	1.9	321	2.6	286	3.8	433
	N	10	10	10	10	10	10	10	10	10
	Mean	7.1	21.1	567	35.5	1159	48.4	682	57.2	700
Stage 2	S.D.	0.75	1.8	444	4.2	393	5.8	467	0	0
	N	9	9	9	8	8	4	4	1	1
	Mean	7.25	22.1	467	38	1066	42.8	28	62.8	
Stage 3/4	S.D.	1	2.4	157	3.3	533	0	0	0	
	N	8	8	8	8	8	1	1	1	
	Mean	7	20.1	684	34.3	982	46.9	400	62.4	829
REM	S.D.	0.7	1.4	408	3.8	608	5.6	270	6.1	388
	N	6	6	6	6	6	5	5	4	4

Table 7.1a The mean latencies and amplitudes of all components of the MLR and wave V of the BAEP using click stimuli during wakefulness, stage 2, stage 3/4 and stage REM sleep. Standard deviations and numbers within each mean also provided.

500Hz												
		Wave V (ms)	Na (ms)	Amplitude V- Na (nV)	Pa (ms)	Amplitude Na- Pa (nV)	Nb (ms)	Amplitude Pa- Nb (nV)	Pb (ms)	Amplitude Nb- Pb (nV)
Awake	Mean	10.9	24.2	609	34.5	683	45.9	310	60.2	766
	S.D.	0.9	1.4	168	1.4	325	2.5	281	3.7	279
	N	9	10	9	9	9	9	9	9	9
Stage 2	Mean	11	25.8	219	42.1	1242	50.7	607	57.6	378
	S.D.	1.3	2.3	183	4.7	618	3.5	844	1.6	28
	N	9	9	9	9	10	3	3	2	2
Stage 3/4	Mean	11.2	26.2	278	42.9	1304	—	980	—	—
	S.D.	1.3	1.8	271	4.8	669	—	0	—	—
	N	10	9	8	8	6	—	1	—	—
REM	Mean	11.2	26.2	678	36.4	635	44.6	304	58.8	490
	S.D.	1.6	2.4	379	3.7	479	1.9	135	0	0
	N	6	6	6	6	6	3	3	1	1

Table 7.1b The mean latencies and amplitudes of all components of the MLR and wave V of the BAEP using 500Hz tone pip stimuli during wakefulness, stage 2, stage 3/4 and stage REM sleep. Standard deviations and numbers within each mean also provided.

4000Hz		Wave V (ms)	Na (ms)	Amplitude V- Na (nV)	Pa (ms)	Amplitude Na- Pa (nV)	Nb (ms)	Amplitude Pa- Nb (nV)	Pb (ms)	Amplitude Nb- Pb (nV)
	Mean	7.5	20.3	628	29.9	745	41.3	523	53.9	524
Awake	S.D.	0.6	1.3	410	0.8	256	1.7	306	1.3	268
	N	9	9	9	9	9	9	9	9	9
	Mean	7.4	20.9	284	36.7	1160	48.4	1190	—	—
Stage 2	S.D.	0.6	1.3	231	3.2	665	0	0	—	—
	N	10	9	9	9	9	1	1	—	—
	Mean	8	21.8	360	35.3	759	46.9	224	59.6	840
Stage 3/4	S.D.	1.6	1.7	210	4.6	287	2.4	196	0	0
	N	8	7	7	7	7	2	2	1	1
	Mean	7.6	20.9	495	30.8	433	44.4	324	56.2	346
REM	S.D.	0.7	1.9	176	2.7	248	2	186	2.5	75
	N	8	8	8	8	8	7	7	3	3

Table 7.1c The mean latencies and amplitudes of all components of the MLR and wave V of the BAEP using 4000Hz stimuli during wakefulness, stage 2, stage 3/4 and stage REM sleep. Standard deviations and numbers within each mean also provided.

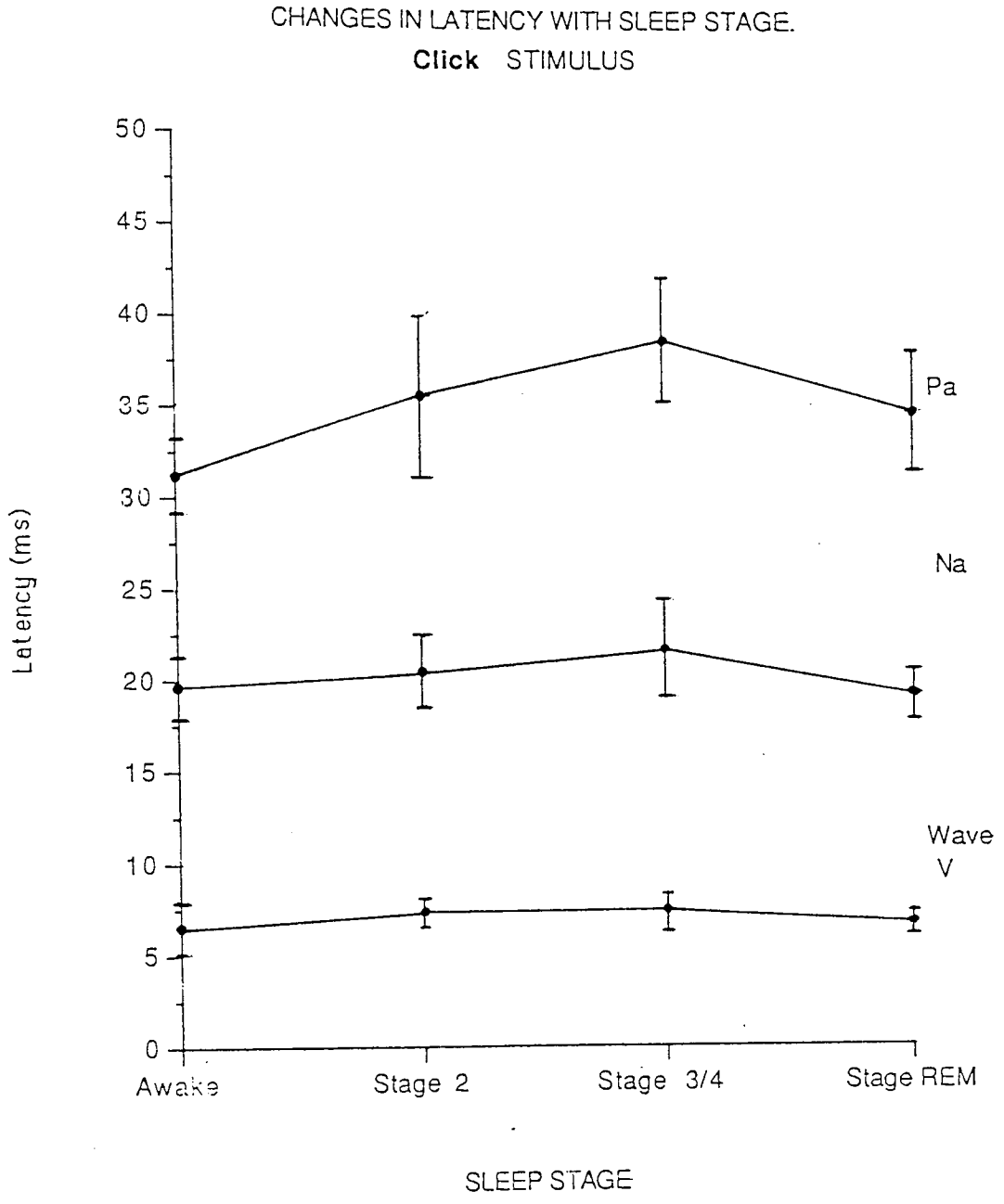

Figure 7.2 Changes in the mean latency of wave V, Na and Pa in wakefulness, stage 2, stage 3/4 and stage REM sleep using click stimuli.

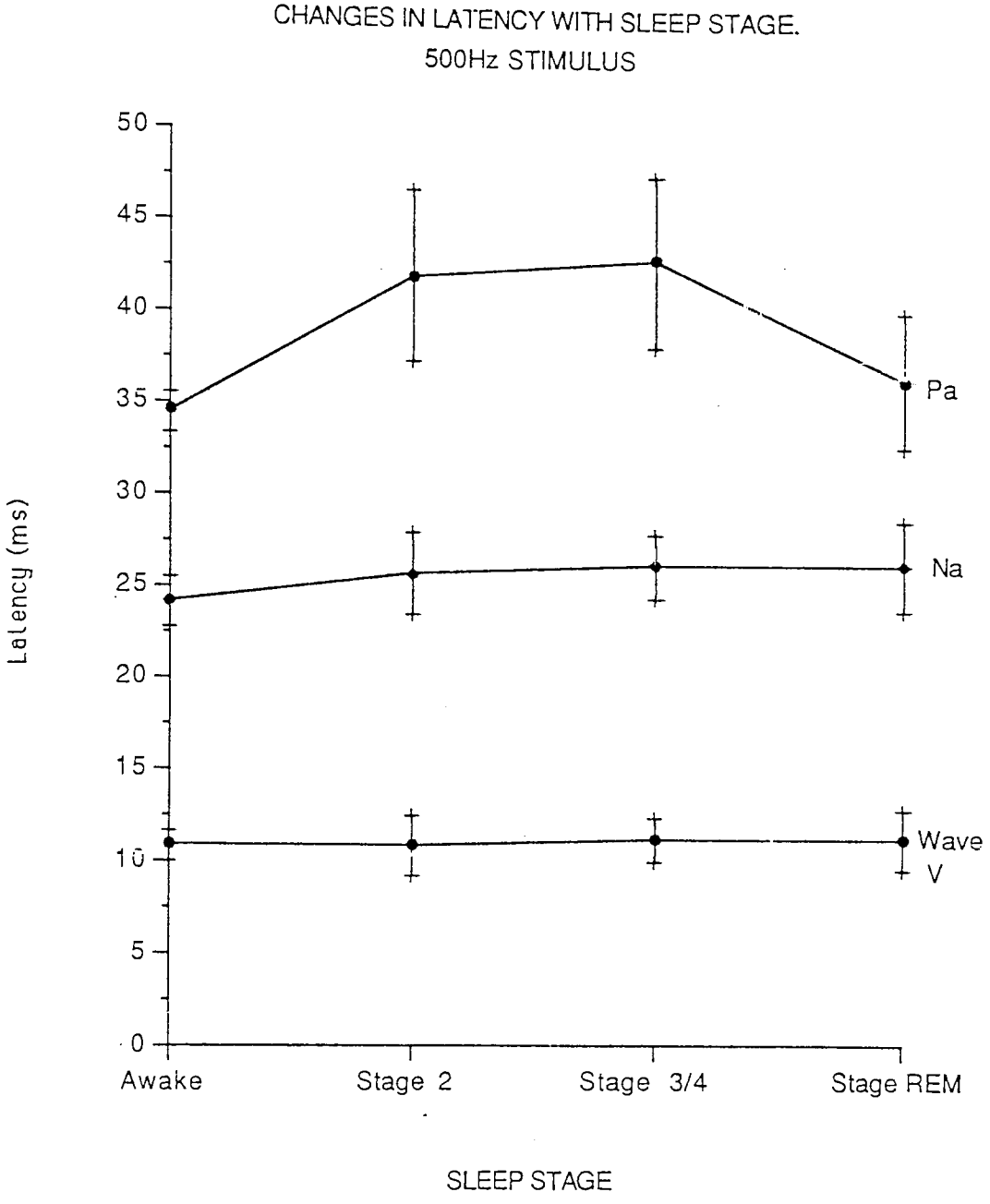

Figure 7.3 Changes in the mean latency of wave V, Na and Pa in wakefulness, stage 2, stage 3/4 and stage REM sleep using 500Hz tone pip stimuli.

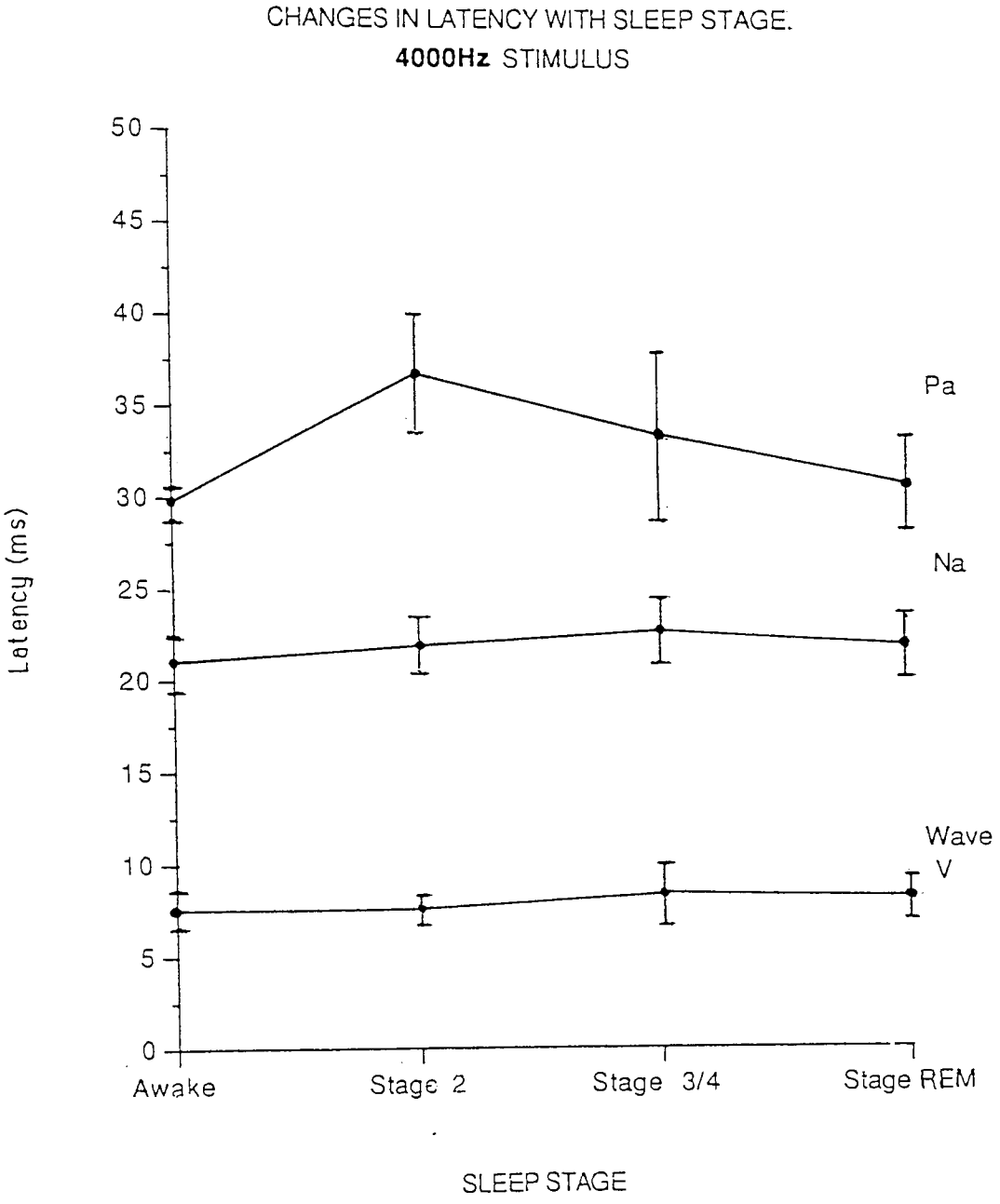

Figure 7.4 Changes in the mean latency of wave V, Na and Pa in wakefulness, stage 2, stage 3/4 and stage REM sleep using 4000Hz tone pip stimuli.

Amplitude changes with arousal level were also recorded for the 40Hz response. The mean amplitudes for each trace were calculated and paired t-tests performed comparing wakefulness, Stage 2, Stage 3/4 and REM sleep. Table 7.2a presents the mean amplitudes, standard deviations and subject numbers for the click, 500Hz and 4000Hz stimuli. Table 7.2b shows the t-test values obtained comparing different levels of arousal and their significance. Table 7.2b clearly shows that there is a significant reduction in 40Hz response amplitude in Stages 2 and 3/4 sleep compared with wakefulness for all stimuli (for click, $p<0.001$; for 500Hz $p < 0.05$ and 4000Hz $p < 0.01$). Furthermore, for the click and 4000Hz stimuli there is also a significant reduction in amplitude in REM sleep when compared with wakefulness (click $p < 0.05$, 4000Hz $p < 0.01$). For the 500Hz stimulus, the value of $t = 2.49$ (significance = 0.055), which implies a probability of 94.5% of rejecting the null hypothesis. This figure just fails to achieve the 95% probability necessary to imply significance.

Turning now to the morphology of the 5Hz MLR and the 40Hz response in sleep and wakefulness, inter-subject variability in response latencies was increased in sleep. This was especially so for the later components of the response in slow wave sleep. The changes, however, were stable and reproducible in each subject with sleep stage. In the following series of figures (7.5 - 7.16), all data (5Hz and 40Hz) for all stimuli in wakefulness, Stage 2 sleep, Stage 3/4 sleep and Stage REM sleep are presented. In all the traces shown, negativity at the vertex is indicated by an upwards deflection. Considering first the 5Hz MLR these results would suggest that in Stages 2 and 3/4 sleep, Pa latency systematically increases and the Nb component become reduced or is absent; in cases where Nb is found to be absent, a broad positive component is formed. In addition, there is an overall reduction in the amplitude of the later part of the response in Stages 3/4 with no clearly defined responses in some cases. In REM sleep, the normal waking configuration and latencies reappear but overall amplitude is reduced. With respect to the 40Hz response, these results suggest that there is a marked reduction in amplitude in all sleep stages in accordance with the findings of other authors (Galambos et al., 1981; Brown and Shallop, 1982; Jerger et al., 1986).

Stimulus		AWAKE	STAGE 2	STAGE 3/4	REM
CLICK	Mean (μV)	1.61	0.86	0.86	0.96
	S.D.	0.29	0.38	0.34	0.31
	n	9	9	8	5
500Hz	Mean (μV)	1.07	0.74	0.51	0.62
	S.D.	0.27	0.38	0.25	0.35
	n	10	9	7	6
4000Hz	Mean (μV)	1.01	0.7	0.61	0.68
	S.D.	0.25	0.21	0.2	0.17
	n	10	10	8	8

Table 7.2a Mean amplitudes of the 40Hz response in wakefulness stage 2, stage 3/4 and stage REM sleep.

Stimulus		t	Sig.	Probability of rejecting null Hypothesis (%)
CLICK	W- S2	5.7	0.0007	99.99
	W- S3/4	7.11	0.0003	99.99
	W- REM	3.71	0.02	98
500Hz	W- S2	2.76	0.03	97
	W- S3/4	4.41	0.004	99.9
	W- REM	2.49	0.055	94.5
4000Hz	W- S2	3.19	0.01	99
	W- S3/4	3.97	0.005	99.5
	W- REM	4.86	0.001	99.9

Table 7.2b Paired t-tests comparing the amplitude of the 40Hz response between arousal levels. W= wakefulness, S2= stage 2 sleep, S3/4= stage 3/4 sleep, REM= Rapid eye movement sleep (sig.= significance).

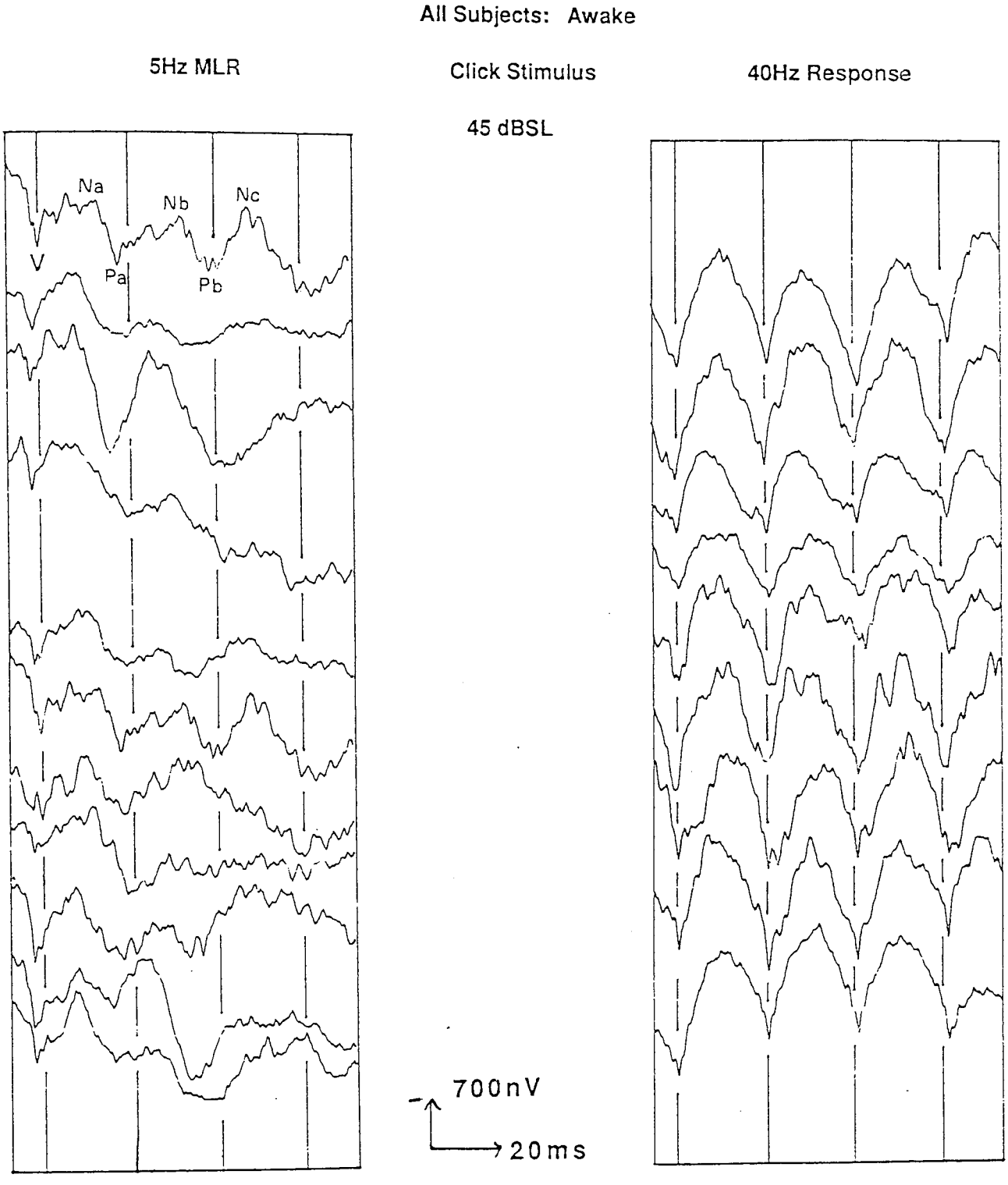

Figure 7.5 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in wakefulness using click stimulation delivered at 45dBSL.

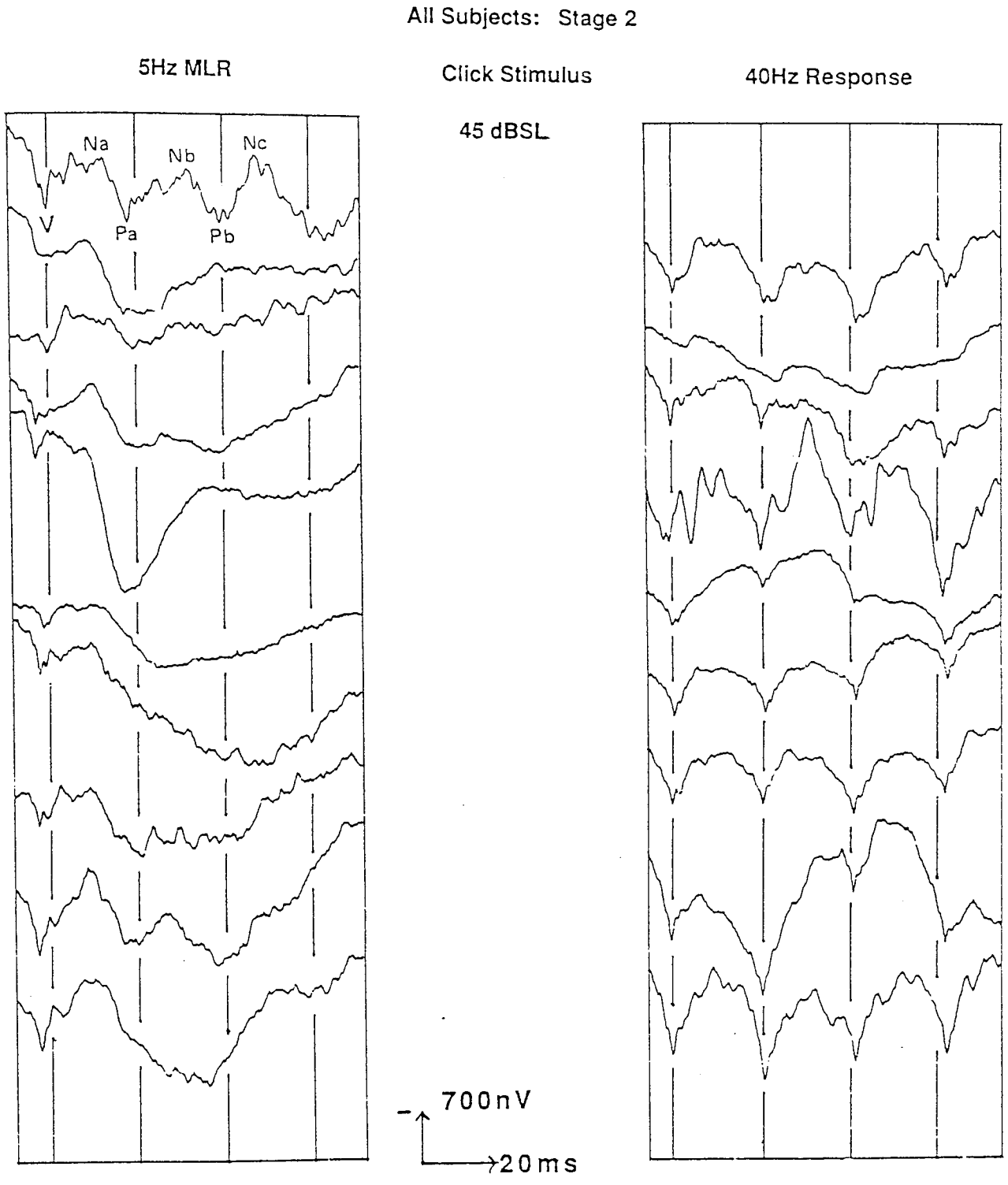

Figure 7.6 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage 2 sleep using click stimulation delivered at 45dBSL.

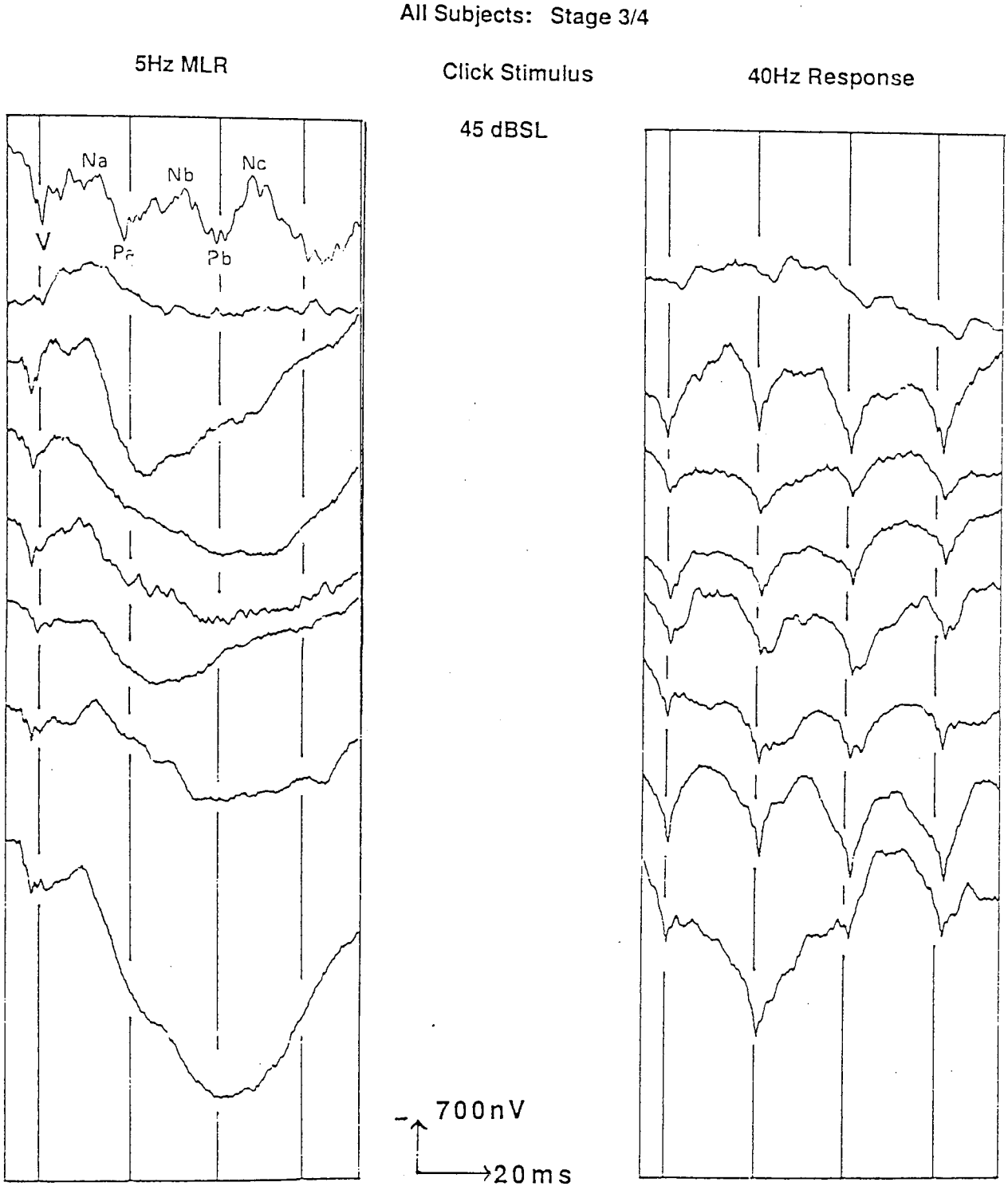

Figure 7.7 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage 3/4 sleep using click stimulation delivered at 45dBSL.

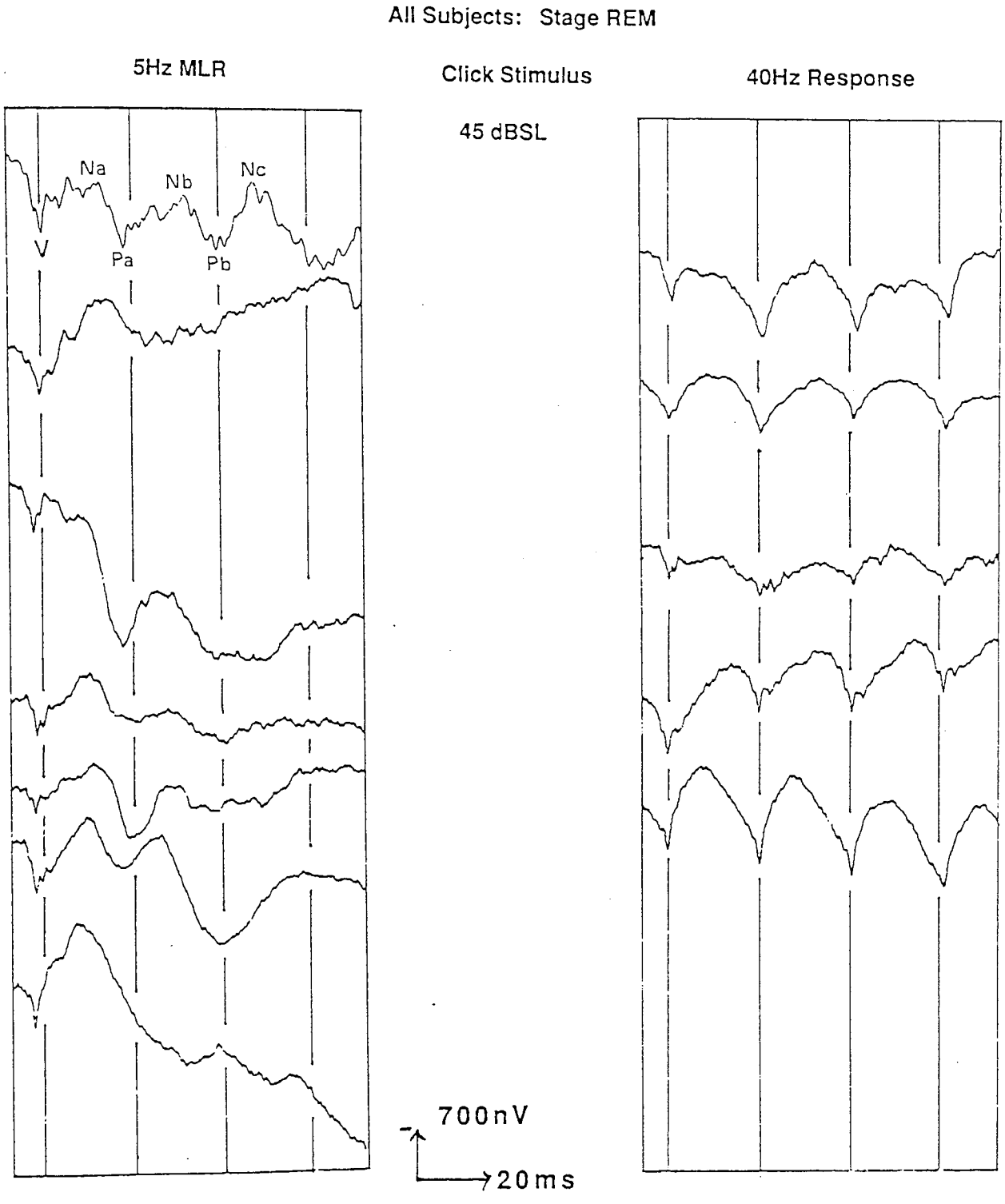

Figure 7.8 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage REM sleep using click stimulation delivered at 45dBSL.

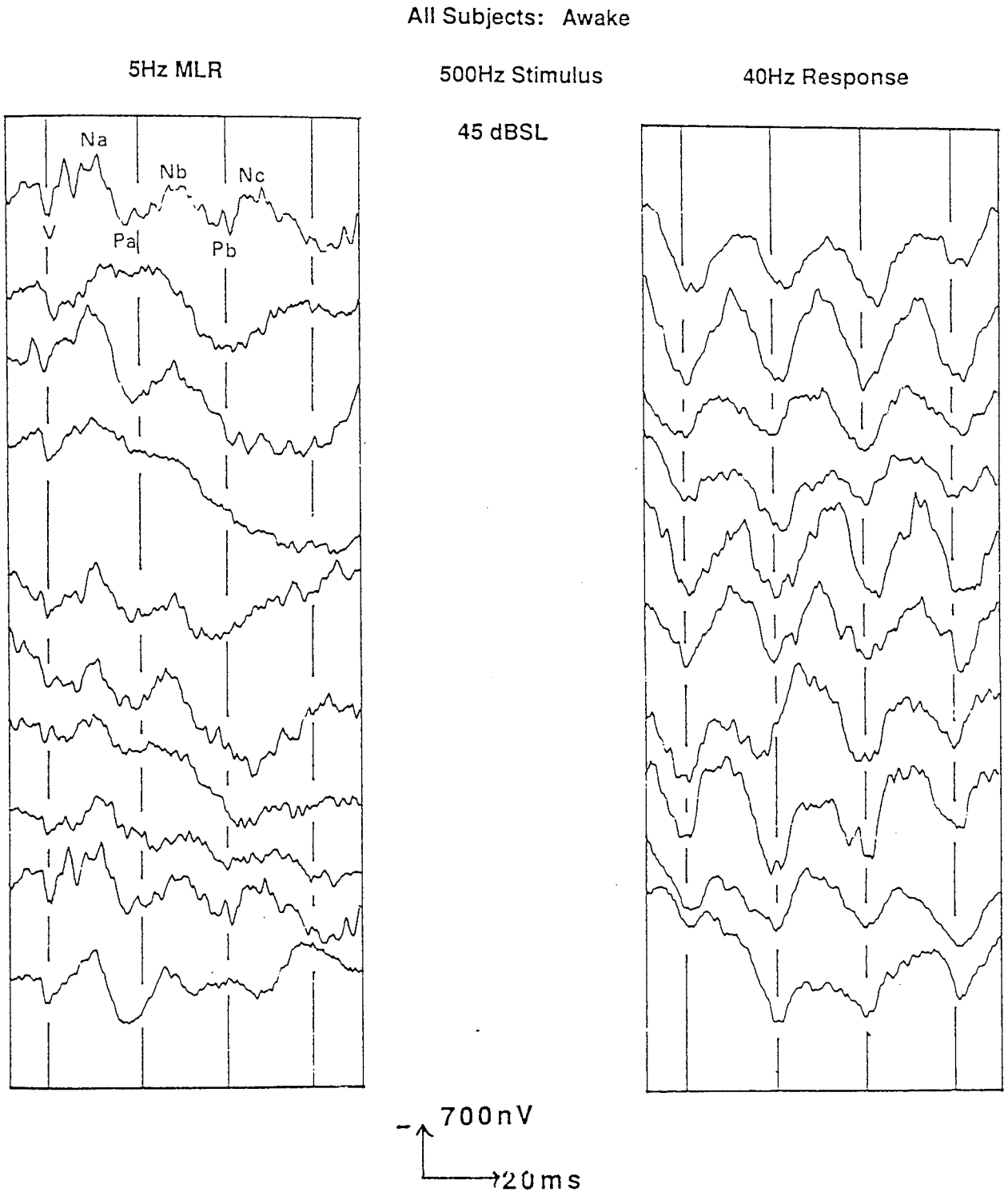

Figure 7.9 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in wakefulness using 500Hz tone pip stimulation delivered at 45dBSL.

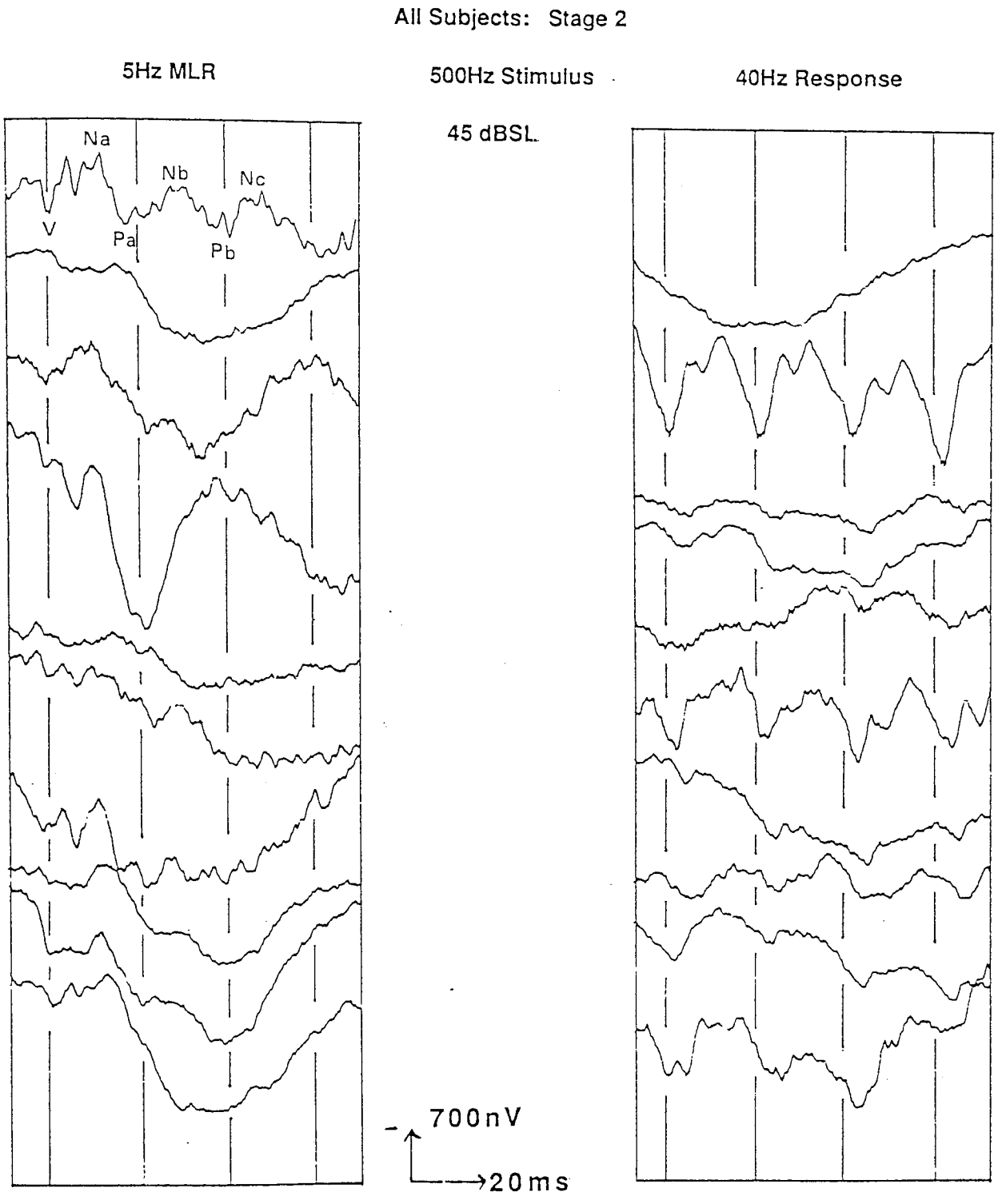

Figure 7.10 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage 2 sleep using 500Hz tone pip stimulation delivered at 45dBSL.

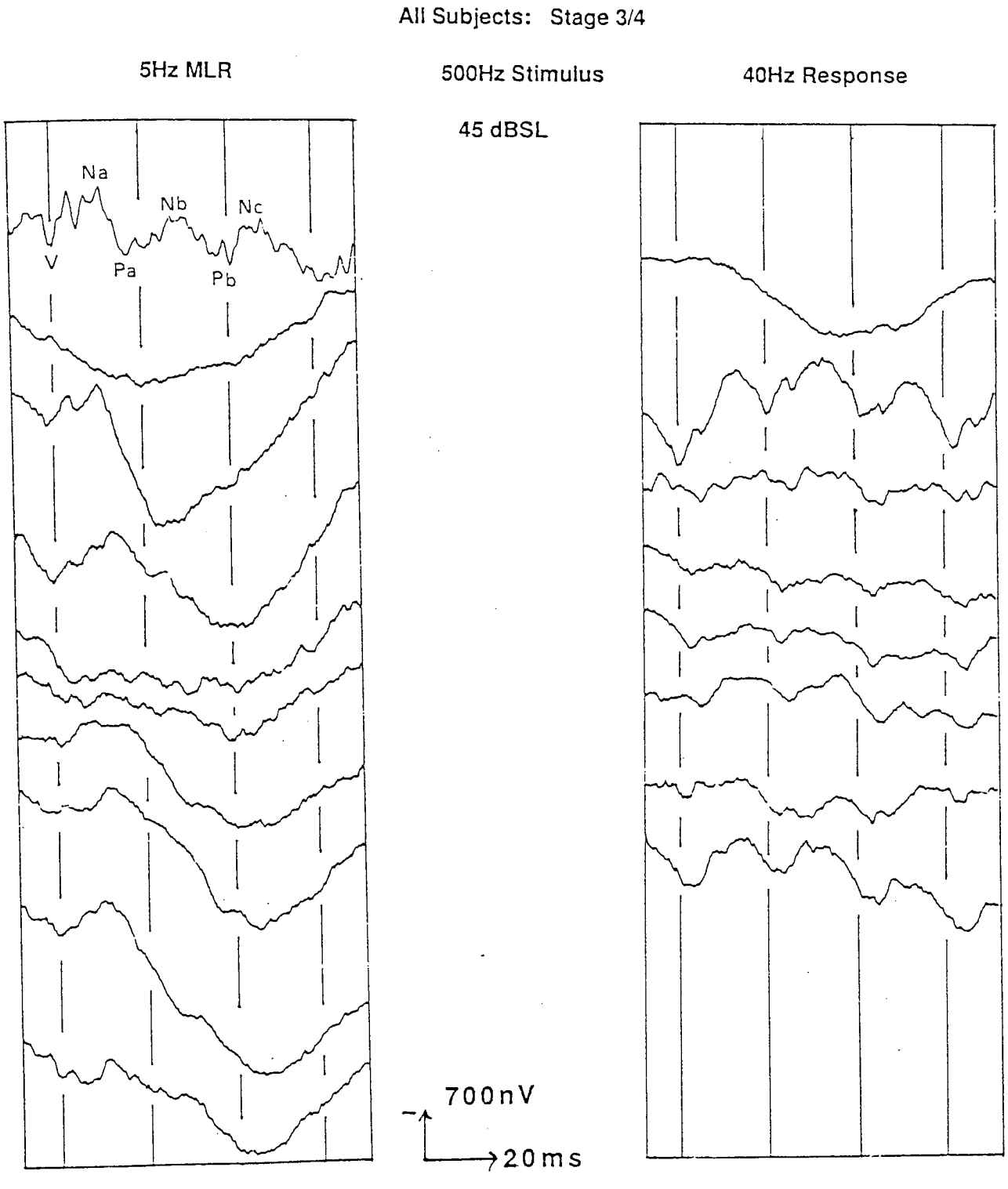

Figure 7.11 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage 3/4 sleep using 500Hz tone pip stimulation delivered at 45dBSL.

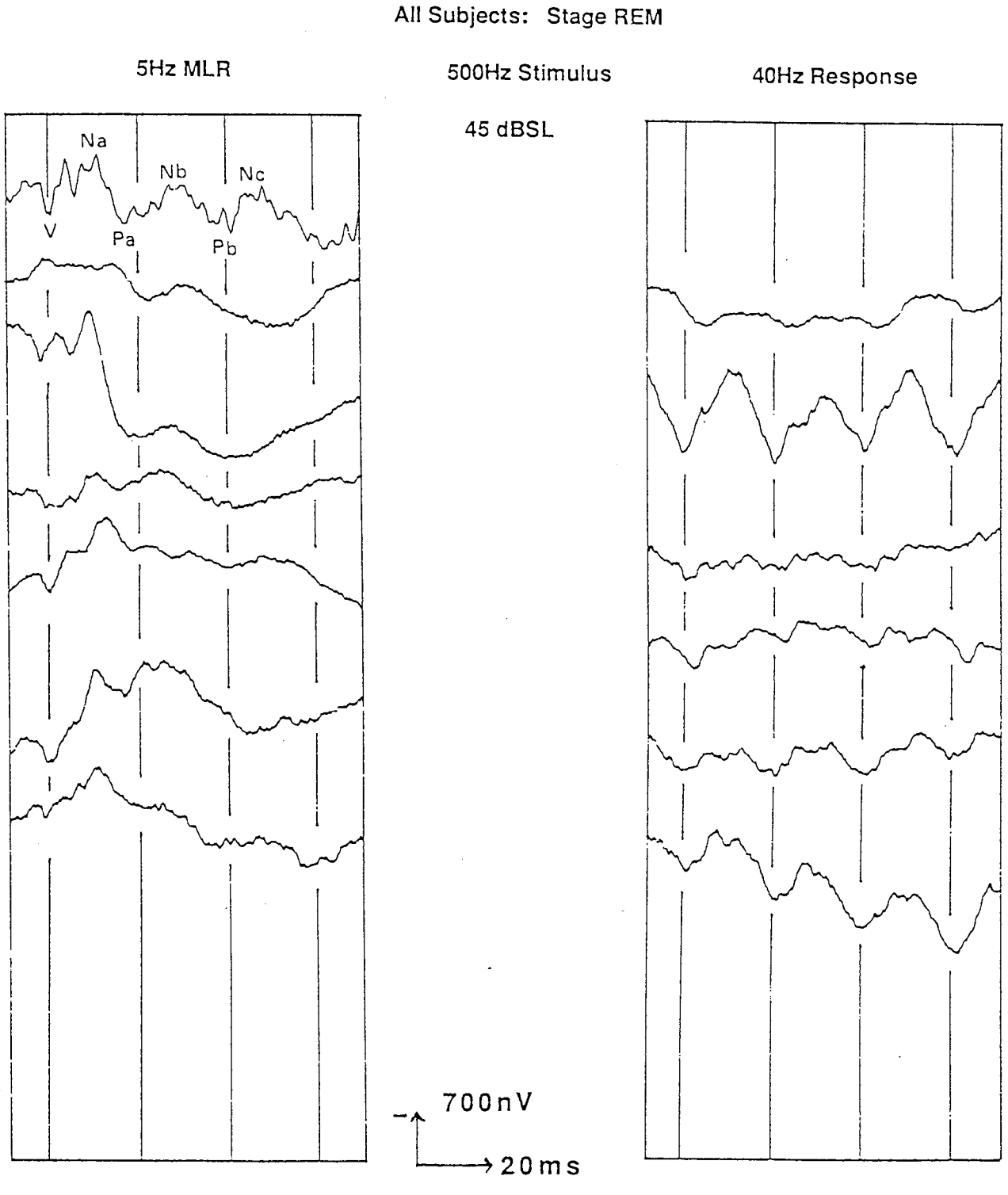

Figure 7.12 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage REM sleep using 500Hz tone pip stimulation delivered at 45dBSL.

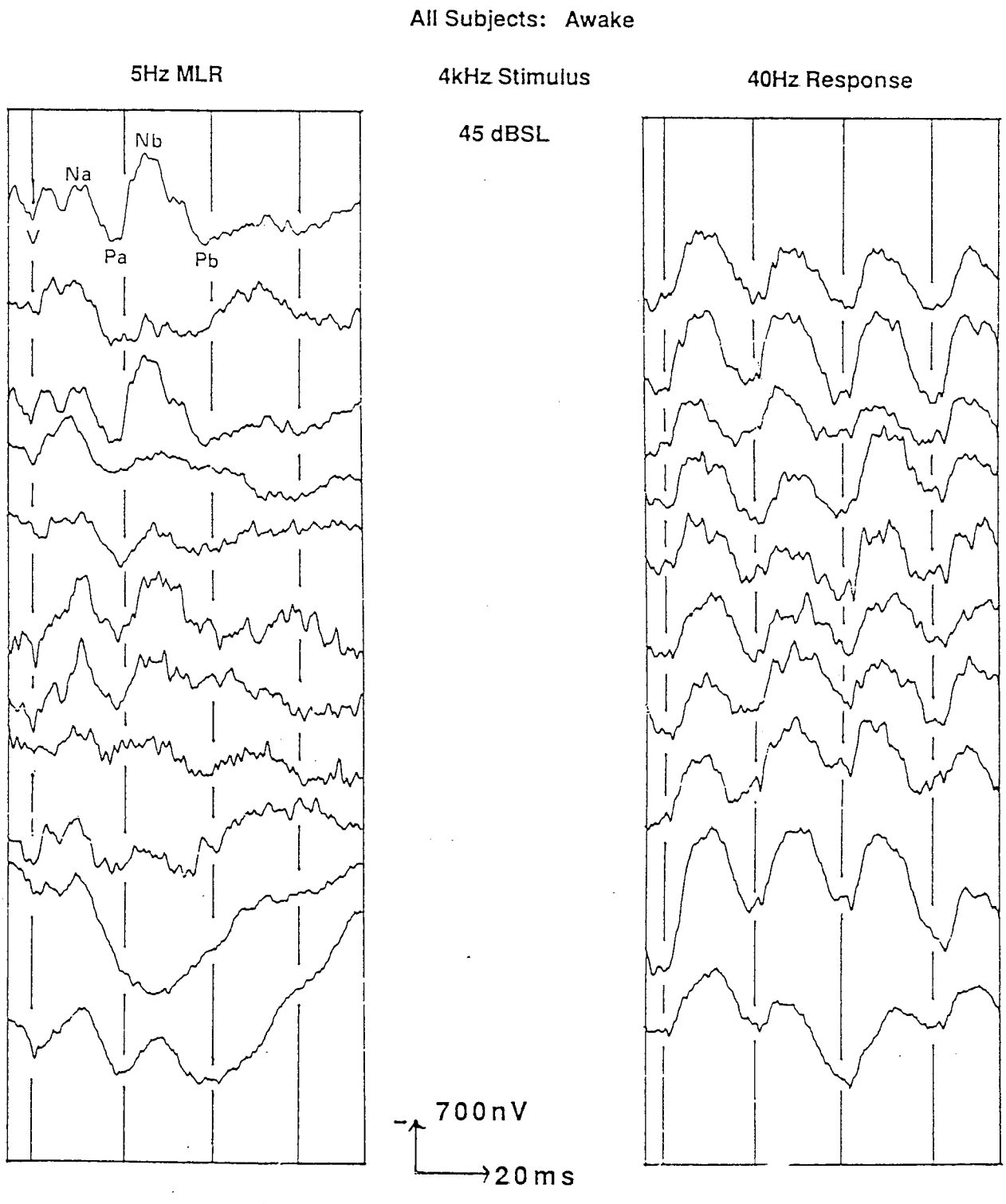

Figure 7.13 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in wakefulness using 4000Hz tone pip stimulation delivered at 45dBSL.

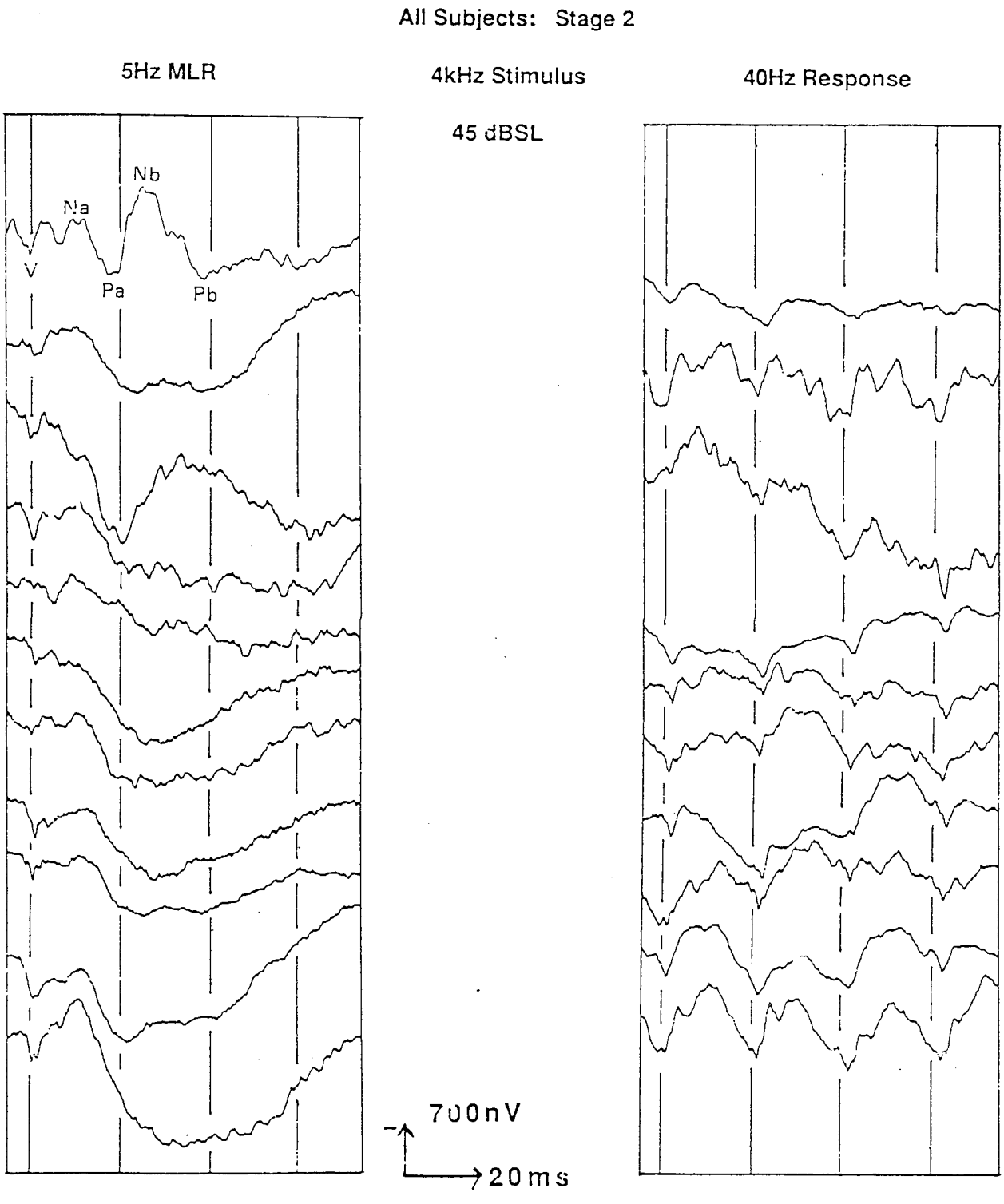

Figure 7.14 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage 2 sleep using 4000Hz tone pip stimulation delivered at 45dBSL.

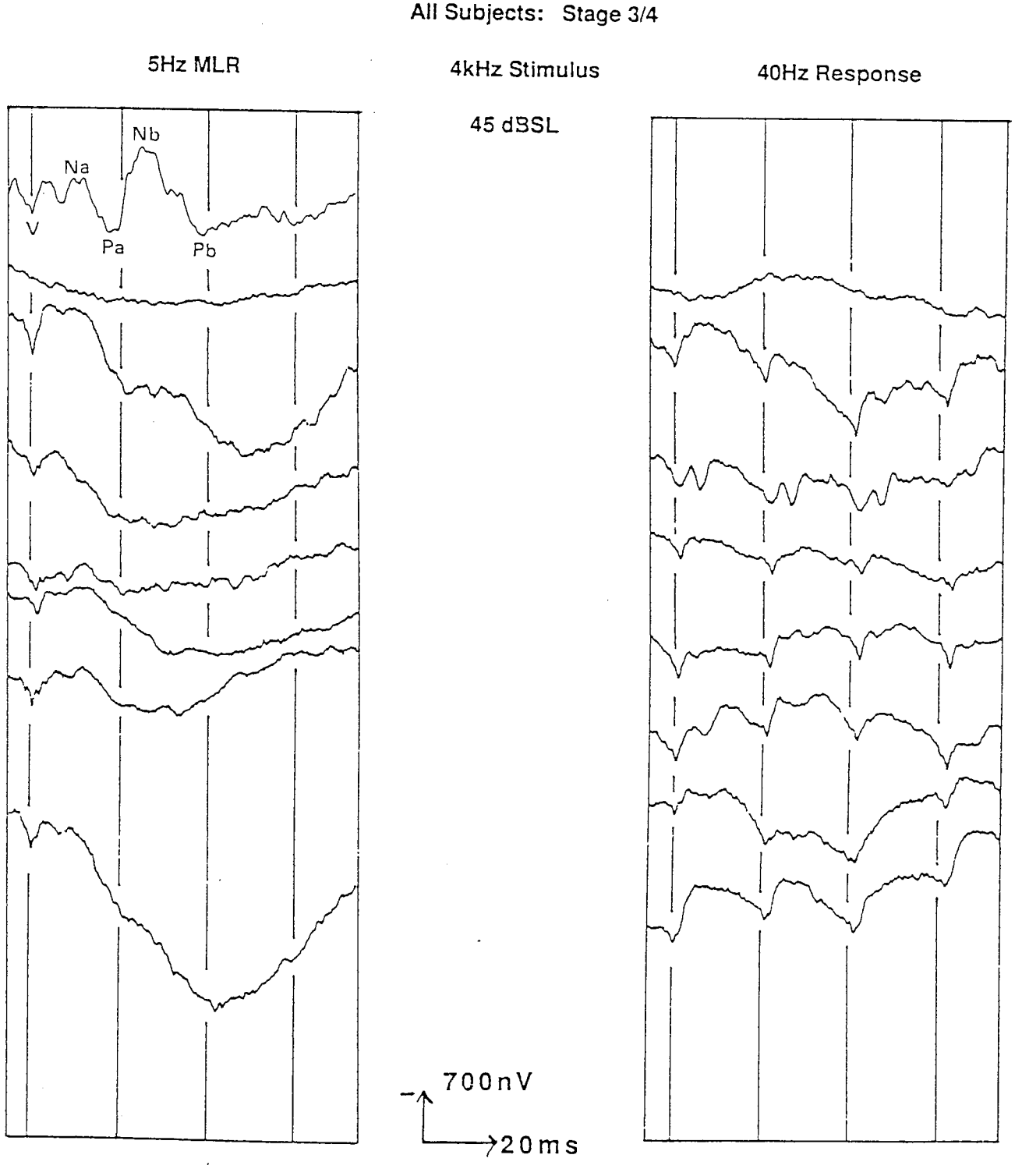

Figure 7.15 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage 3/4 sleep using 4000Hz tone pip stimulation delivered at 45dBSL.

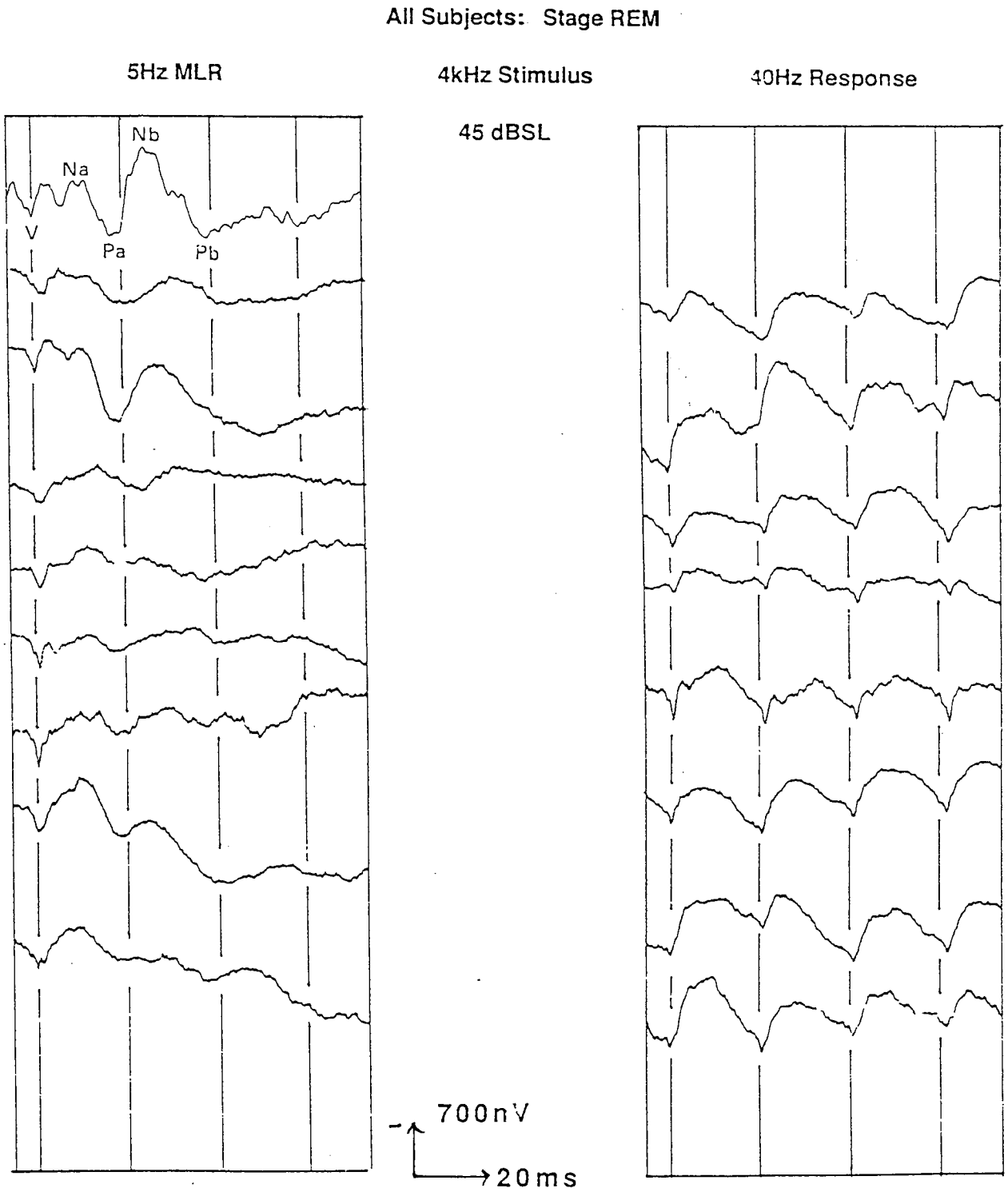

Figure 7.16 The morphology of the 5Hz MLR (left) and the 40Hz response (right) recorded in stage REM sleep using 4000Hz tone pip stimulation delivered at 45dBSL.

The following figures present a more detailed analysis of the changes in the 5Hz MLR and 40Hz responses in individual subjects who exhibited traces which were representative of the subject group. In all these figures, the vertical lines are drawn at the latency wave V of the brainstem response and at following 25 msec. intervals.

Figure 7.17a shows the effects of sleep and sleep stage upon the morphology of the MLR in another experimental subject. In Stage 2 sleep, Pa latency increase significantly. In Stages 3/4 sleep and REM sleep Pa amplitude decreases with no clear later components. Figure 7.17b (right hand side of figure) shows the 40Hz response as being reduced in amplitude in all sleep stages.

In Figure 7.18a, wave V is seen to be stable throughout all stages of sleep and wakefulness. In Stage 2 sleep, Nb appears to be delayed. In Stage 3/4, Nb disappears leaving a single broad positive component. Nb and Pb are discernible again in REM sleep, but it can be seen that the overall response amplitude is reduced in comparison to the waking trace. Figure 7.18b (right hand side of fugure) shows the corresponding effect upon the morphology of the 40Hz response in different stages of sleep. It may be seen that the 40Hz response is of reduced amplitude in Stages 3/4 in comparison to wakefulness.

All middle latency components are clearly seen in wakefulness in this third subject (Fig. 7.19a). However, in Stage 2 and Stage 3/4 sleep, the Nb component is lost and a large single positive is seen of latency intermediate to Pa and Pb. In addition, in Stage 3/4 sleep, the response amplitude is further reduced. In REM sleep, the normal response components are just discernible but response amplitude is greatly reduced. Figure 7.19b (right hand side of figure) shows that the 40Hz response is markedly reduced in amplitude in all stages of sleep and appears only to show mainly four brainstem responses with middle latency activity attenuated to a bare minimum.

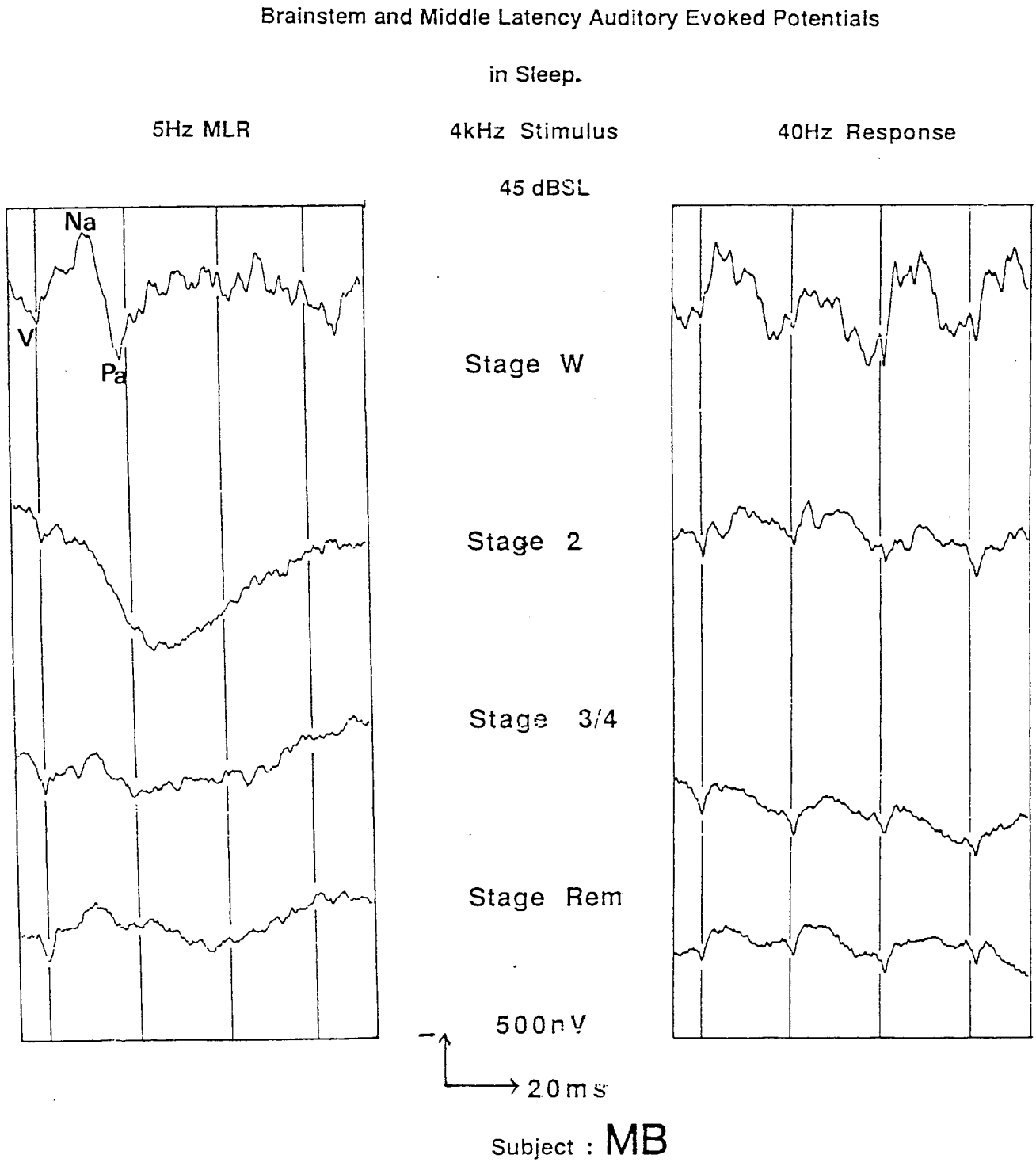

Figure 7.17a Characteristic changes in the 5Hz MLR and 40Hz response (fig7.17b) recorded in one subject (MB).

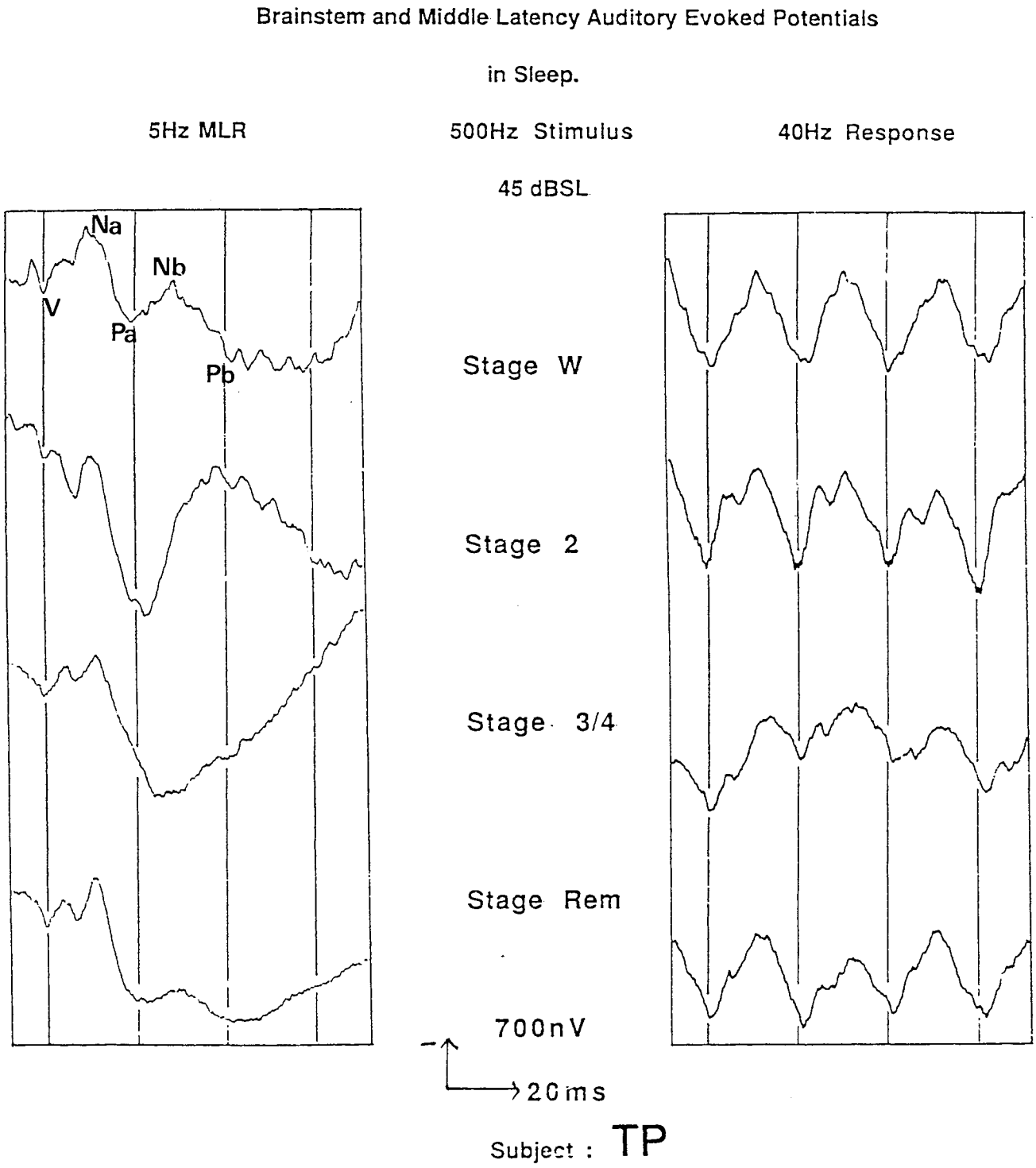

Figure 7.18a Characteristic changes in the 5Hz MLR and 40Hz response (fig. 7.18b right) in one subject (TP).

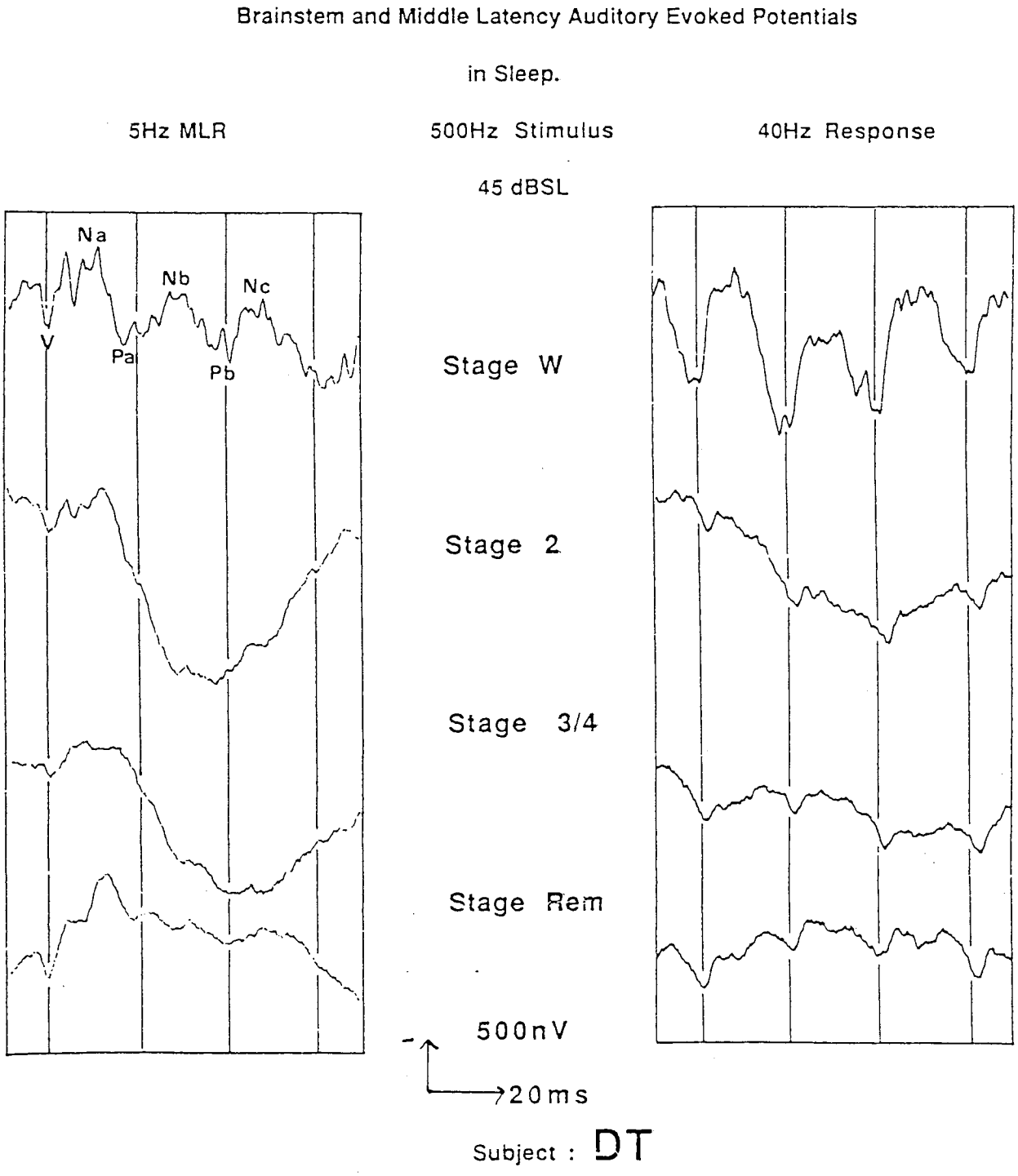

Figure 7.19a Characteristic changes in the 5Hz MLR and 40Hz response (fig. 7.19b) in one subject (DT).

The frequency composition of the MLR (i.e. 40Hz periodicity) is the basis of the steady-state technique (Galambos et al., 1981). In comparing the morphology of the 5Hz MLR recorded in this experiment in different stages of sleep and wakefulness, it would appear that there is a shift in the spectral content (frequency composition) of the response during sleep with an increase in lower frequencies and a reduction in 40Hz activity. Therefore, because of this change, it might be expected that the resulting 40Hz response recorded in sleep would be different from that in wakefulness.

Considering the 40Hz response, it is clear that with the wide bandpass filter setting, the amplitude of these responses is reduced during all stages of sleep. In all subjects, the greatest amount of the 40Hz frequency was present in wakefulness with slow wave sleep causing a reduction in 40Hz (and commensurate rise in lower frequency activity) for the click, 500Hz and 4000Hz stimuli. REM sleep sees an increase in 40Hz sinusoidal morphology present within the MLR transient response, though the waking levels are not reached. With the click stimulus, there is a consistent and marked decline in 40Hz response amplitude through Stages 2 and 3/4 to REM sleep. This illustrates that the superimposition of successive response averages at the 40Hz stimulus repetition rate is achieved most successfully in wakefulness and REM sleep.

In SWS, as the frequency composition of the MLR (transient) changes, so the 40Hz response is less effectively generated. Even in slow wave sleep, there appears to be much less low frequency activity present in the 40Hz response in comparison with the 5Hz MLR transient. This is because the repetition rate of 40Hz effectively imposes its own filter upon the response attenuating activity below this frequency giving the appearance of a steady-state response. However, wide bandpass filtering reveals this to be primarily brainstem activity (wave V) repeated at 25msec. intervals. The 5Hz MLR transient shows very little 40Hz rhythmicity during slow wave sleep which emphasises the loss of later components of the MLR at this level of arousal.

7.4 DISCUSSION.

7.41 Changes in the morphology of the MLR during sleep.

The results of this experiment suggest that the morphology of the MLR changes markedly during sleep when recorded with wide bandpass filter settings. These changes were characterised by a lengthening in the latency of the Pa component in Stages 2 and 3/4 sleep and a loss or drastic reduction in the amplitude of the following Nb negativity. REM sleep saw a return to normal waking MLR morphology in some subjects but with overall response amplitude markedly reduced. All subjects demonstrated changes in sleep but certain subjects also exhibited the formation of a new positivity (of latency intermediate to Pa and Pb) in Stage 3/4 sleep. The loss of the later components of the MLR would appear to cause a shift in the spectral content of the response towards lower frequencies with a loss of the 40Hz rhythmicity present in wakefulness and an increase in the relative abundance of a new frequency maximum centred at a lower frequency.

These findings are in agreement with other published findings in this area. In the past decade, the work of Erwin, Buchwald and colleagues (1981, 1982, 1983, 1986) has also reported changes in the morphology of the MLR in different stages of sleep and the loss of the Pb component during SWS with its reoccurrence in REM sleep. At first glance this would appear to conflict with the work presented in this chapter where it has been claimed that it is the Nb component which is lost. Comparison of Erwin and Buchwald's (1986) work with the results of this chapter will clarify the position. Erwin and colleagues do not label the negative deflections of the MLR but only the wave V, Pa and Pb components. Therefore, Erwin and Buchwald interpret slow wave sleep as causing the loss of the Pb (P1) component whereas it is in fact the negative (Nb) component's disappearance which has caused this change in morphology. This discrepancy is only caused by differences in terminology and therefore Erwin's data are consistent with the results presented here. It would, however, appear to be more correct to describe the changes in the MLR in SWS as a loss of the negativity (Nb) and

not the positivity (Pb). The former description locates the changes as occurring between Pa and Pb whilst the latter could equally well apply to changes in morphology occurring after the Pb component. Section 3.5.3 (pages 110-118) examined the current understanding of the response generators of the MLR. To briefly summarise, animal research has demonstrated decreases in neuronal activity within the reticular activating system (RAS) and certain thalamic nuclei during slow wave sleep (Imeri et al., 1988). Erwin and colleagues have consistently correlated the disappearance of the Pb wave of the MLR to an origin within the RAS and cite its reappearance in REM sleep as the result of increased activity within the RAS. The results of this experiment also indicate similar changes in middle latency response morphology during sleep and therefore an origin for Pb within the RAS cannot be discounted.

MLR morphologies similar to those in this experiment have also been reported in studies examining the effects of anaesthesia (for example, Thornton et al., 1983, 1985; Heneghan et al., 1987). These authors and others have reported dose-related effects of inhalation anaesthetics such as halothane and enflurane (Thornton et al., 1985), isoflurane (Schmidt and Chraemmer-Jergensen, 1986; Heneghan et al., 1987) and fluothane (Prosser and Arsian, 1985), causing increases in latency of Pa ($p < 0.01$) and reduction or loss of the Pb component. Furthermore, these drugs were also reported to increase the latency of waves III and V of the BAEP also in a dose-related manner. Induction agents such as etomidate given I.V. were found to produce similar effects upon the MLR but did not alter peak latencies of BEAP components (Navaratnarajah et al., 1985; Thornton et al., 1985). Madler and Pöppel (1987) recorded MLRs in 30 patients undergoing major cardiovascular surgery. Patients were given flunitrazepam premedication and were induced with etomidate. Muscle relaxation was achieved using pancuronium. Anaesthesia was maintained with 50% nitrous oxide/5% oxygen mixture with bolus doses of fentanyl given prn (no specific doses of these drugs supplied by the authors). Click stimuli were delivered at a rate of 9.3/sec. and responses were compared with those recorded in relaxed wakefulness. Results showed attenuation of response amplitude under anaesthesia, delay in the Pa component and a loss or marked attenuation of Pb in all subjects. Fourier analysis of responses revealed that the principal

power of the responses in wakefulness (centred at 40Hz) shifted to around 10Hz in anaesthetised patients. The similarity of this body of data to the changes in the MLR reported in natural slow wave sleep in this experiment is striking. It might be suspected that the effects of anaesthesia is to suppress thalamic and RAS neurons in a similar way to natural sleep processes.

Interest in the morphology of the MLR during sleep and under anaesthesia is increasing as these components have been suggested as possible indicators of arousal state during surgery (Schmidt and Chraemmer-Jergensen, 1986). The highly emotive issue of awareness under anaesthesia is becoming increasingly a cause for concern with an estimated 7% of patients claiming awareness at operation (Breckenridge and Aitkenhead, 1983). Should the MLR continue to prove a sensitive indicator of arousal level as is suggested by the literature cited above and the data collected in this experiment, then its applications outside audiological threshold assessment would seem appropriate. However, precise investigations of the MLR and 40Hz response is necessary in order to establish and distinguish truly physiological differences with arousal (and anasesthetic) level from artificial distortions caused by methodological factors.

This shift in the frequency composition of the MLR during sleep as a result of the loss of the Nb component in slow wave sleep, has implications for the generation of the 40Hz response. This steady-state potential relies upon the inherent periodicity of the combined BAEP and MLR (25 msec. period) for the superimposition of successive response averages. It follows, therefore, that if there were a shift in the frequency composition of the MLR during sleep (as suggested above), then the 40/sec. stimulus repetition rate would no longer be appropriate for such a phenomenon to occur. This shift in frequency composition of the transient MLR (5Hz) could explain the corresponding reduction in amplitude of the 40Hz response during slow-wave sleep shown in the preceding figures.

Considering these changes in the MLR found in sleep, the associated amplitude reductions in the 40Hz response appears to be caused by a loss of 40Hz periodicity in Stages 2 and 3/4 so that response superimposition does not occur with the 40/sec. repetition rate. Secondly, there is a reduction in response amplitude during REM sleep but with the 40Hz response morphology still persisting. Therefore, in all stages of sleep, the BAEP and the Na component of the MLR seem to form the major part of the composition of the 40Hz response. Thus the 40Hz response recorded in sleep has ceased to be a steady-state potential. There is no superimposition of successive response averages due to the disappearance of the later components of the MLR which results in the loss of the sinusoidal morphology of the response. What is being recorded in sleep would appear to be a succession of brainstem responses (wave V) being evoked to each stimulus. As the 40Hz stimulus repetition rate (by definition) delivers a stimulus every 25 msec., four BAEPs are recorded within the 100 msec. sweep used in this experiment.

The question is now raised as to why these findings have not been reported previously. One of the principal reasons is that middle latency research has been most commonly conducted using narrow bandpass filters with the low filter set at around 10Hz and the high filter regularly set at 100 or 150Hz and sometimes even lower (Goldstein and Rodman, 1967; Mendel and Goldstein, 1069a and b; Mendel et al., 1975). Experimenters who have examined the MLR using wide bandpass filters (Suzuki et al., 1983a and b, 1987; Özdamar and Kraus, 1983; Kavanagh et al., 1984; Kraus et al., 1987, 1988) have also reported that the MLR possesses low frequency activity (at 10Hz and below). However, the work of Suzuki and colleagues and Özdamar and Krause failed to control adequately for level of arousal. Consequently, the frequency composition of the MLR reported by these authors was based on the combined responses recorded in both the waking and/or sleeping states.

The study of brainstem and middle latency responses carried out by Özdamar and Kraus (1983) using wide band filters (3-2000Hz) and reviewed in Chapter 3, illustrates this point. As well as the normal (sinusoidal) middle latency response configuration, they also reported

recording two other normal variants of the MLR waveform. The first possessed no Pb component and in the second, the Nb wave disappeared to produce a single broad positive component. These are strikingly similar changes to those we have observed in sleep. It could, therefore, be suggested that these variations of the MLR most likely reflect differences in level of arousal (see Chapter 3 for full experimental details). Arousal level was not controlled adequately in the Özdamar and Kraus experiment and although the authors state that their subjects were sedated for the duration of testing, responses were recorded either in relaxed wakefulness or in sleep.

Kavanagh and Domico (1986) found a second predominant frequency in the MLR at around 10Hz as well as the familiar 40Hz component in an experiment using bandpass filters of 0.2 to 8000Hz. These authors suggest that this 10Hz component is physiological in origin and is the component wave upon which the Pa and Pb waves of the MLR are superimposed. The results of the present experiment confirm the presence of this low frequency component and would suggest that it is increased in amplitude in slow wave sleep.

Further to the review of literature laid out in Chapter 3, much recent work has not always properly monitored arousal level whilst examining the effects of other subjective variables (such as age and mauration) upon the MLR. Filter bandpass can also be shown to be influencing response detectability in these experiments. Stapells et al. (1988) described morphological changes in the MLR as a function of age. The Stapells experiment (bandpass, 10-1000Hz with 6dB/octave slopes), was conducted upon sleeping children of undisclosed sleep stage and adults who were either awake or asleep. Firstly this means that the isolated or interactive effects of maturation, sleep, sleep stage and wakefulness cannot be separated. Secondly, the choice of 10Hz for the low filter would also have the effect of masking morphological changes in the MLR recorded in sleeping adults. This does not, however, preclude the possibility that maturational factors are also affecting the morphology of the MLR.

7.42 The consequence of narrow bandpass filtration upon the morphology of the MLR.

The separate effects of high and low pass filtration will now be considered. It could be suggested that the setting of the low filter at 10Hz or above may have the consequence of masking the changes in middle latency response morphology reported in this experiment. This hypothesis requires testing with FFT procedures allowing the comparison of digitally filtered responses with those recorded using wide bandpass filters in order to reproduce the experimental procedures favoured by some researchers. The requirements of an adequate FFT program have been discussed in chapter 5. Unfortunately, the Medelec FFT software was incapable of removing trends or introducing a windowing function in order to make these data suitable for frequency analysis. It is great importance to the validity of this data that future work will attempt to repeat this experiment using more powerful equipment able to perform frequency analyses in a reliable manner. The following discussion highlights the necessity for further work and examines the implications of filter distortions upon middle latency and 40Hz recording.

In Figure 7.1 (Introduction section of this chapter) 40Hz response data were presented from a sleeping child using wide and narrow bandpass filter settings within the clinical setting. The choice of a 125Hz high filter had the effect of 'smoothing' the morphology of the 40Hz response by attenuating high frequency components from the response. However, with the 3000Hz high filter, the characteristic sinusoidal morphology of the 40Hz response was found to be lacking with principally a succession of brainstem components (principally wave V) being present. The contribution of the MLR to the composite 40Hz response would appear to be markedly reduced in all stages of sleep in this case and the experimental results of this study corroborate this conclusion. Therefore, the setting of the high filter at 125Hz has had the effect of concealing these changes in 40Hz morphology which occur with sleep and arousal. Although the amplitude of the response is reduced, the use of narrow bandpass filters does

not allow the reason for this reduction to be visualised. Only with wide bandpass filters can the true morphology of the response be seen (ie a succession of four wave V components).

This experiment has illustrated that the middle latency response is clearly affected by changes in level of arousal in terms of latency, amplitude and morphology. The effects of reducing the systems bandwidth could not be directly tested but it is appropriate to explore how the experimental observations from this work coupled with the inferences of other researchers concerning filter bandpass might affect the clinical applications of the MLR and 40Hz response. Stapells et al. (1988) examined the morphology of the MLR and 40Hz response in eighteen infants ranging in age from three weeks to twenty eight months (systems bandpass 10-1000Hz). All infants were tested in natural sleep. Stapells states:

"(In) all infant responses.....the component with the largest amplitude was the wave V to Na deflection. There seems to be no question, therefore, that the slow wave activity in the ABR wave V region is always the major contribution to the MLR, and for some infants this wave V region contains almost the only activity present".

The audiological implications of this are entirely in keeping with the results of this experiment, namely that the MLR is markedly attenuated in sleep and the 40Hz response primarily reflects brainstem activity. This means that the MLR can offer little in audiometric threshold extimation for children in whom sleep is a prerequisite for testing. However, some authors (whilst acknowledging the introduction of distortions with narrow bandpass), have proposed that it might still be advantageous (in terms of response detectability) to record the MLR and 40Hz response in this distorted form (Suzuki et al., 1983a and b; Musiek et al., 1984; Kraus et al., 1987a; Stapells et al., 1988).

Kraus et al. (1987a), supporting this proposition, described how the % detectability of the Na and Pa components of the MLR was significantly increased ($P < 0.01$) in all age groups (normal subjects rangng from 6 months to 20 years) when the low filter was raised from 3Hz (6dB/octave) to 15Hz (12dB/octave). Click stimuli (duration 100μsec.) were delivered at an intensity of 60-70 dBnHL in this experiment. This paper only confirms that the child subjects

(and not necessarily the adults) were sleeping during testing. Kraus' data would appear to suggest that raising the low filter to 15Hz and removing low frequency activity (physiological or otherwise) facilitated response detection of the MLR regardless of possible changes in the response with arousal level. If this enhanced detectability of Na and Pa could be established at lower stimulus intensities, then the higher (> 10Hz) filter setting would appear to be an advantage in audiometric assessment using the MLR in all age groups and at all arousal levels.

Setting the optimum level for the high frequency filter is also open to debate. It was the initial preference for severe high frequency filtering in earlier work which served to mask changes in the MLR in sleep. However, since it has been shown that the principal activity being recorded in sleeping subjects is brainstem, it perhaps would appear preferable to use a high filter setting more in keeping with BAEP recording parameters. Against this, Kavanagh et al. (1984) cautioned that whilst increasing the systems bandwidth from 15-100Hz to 15-3000Hz had little effect on response detection to a 500Hz tone pip near threshold, waveforms were qualitatively easier to identify when high frequency activity was removed from the response. In other words, high frequency activity made responses more difficult to visualise near threshold though the actual estimation of threshold was the same in both cases.

McGee et al. (1988) reported no significant differences in response amplitude or clarity with higher filter settings of 100, 300 and 3000Hz using 60dBnHL click stimuli but did not examine the morphology of the responses near threshold in this work. If the distorted 'MLR' and the 40Hz brainstem response can be detected to tonal stimuli more easily when recorded with a narrow filter bandpass, then this technique would appear to warrant further investigation. However, the dangers of excessive filtering have been strongly emphasised in this experiment and it would surely be in error to return to the era of the sixties and seventies in which important information (such as changes in MLR morphology in sleep) was lost through narrow bandpass filtration.

7.5 CONCLUSIONS.

This experiment has examined the changes in the MLR (recorded to a 5Hz stimulus repetition rate) and 40Hz response during all-night sleep recording using wide bandpass filters to click and tone pip (500, 4000Hz) stimuli. The results indicated that Stages 2 and 3/4 sleep caused significant increases in the latency of the Pa component of the MLR to all stimuli. In addition Stages 3/4 sleep were responsible for removing the Nb component of the MLR within some subjects, the formation of a broad positivity of latency intermediate to the Pa and Pb components. This reduction in the Nb wave resulted in a loss of the familiar sinusoidal morphology of the MLR and a change in the frequency composition of the response away from 40Hz towards 10Hz. REM sleep demonstrated the return of the Nb component to the MLR though the overall amplitude of the response was smaller than in wakefulness.

As the result of the above changes in the MLR transient response recorded during sleep, the 40Hz was reduced in amplitude in all subjects and in all stages of sleep. This was caused by a loss of 40Hz periodicity in SWS and by an overall reduction in amplitude in REM sleep. Therefore, it is concluded that the 40Hz responses recorded in sleep consists primarily of brainstem activity with very little contribution from the MLR components after Na. Due to unavoidable software limitations, the effects of changing filter bandpass could not be properly tested in this experiment. Future work will explore this aspect in greater detail.

Some authors have suggested that clinically speaking, it is possible that the distortions caused by narrow bandpass filtration may be an advantage in audiometric evaluations. However, this experiment has emphasised the precise, physiological nature of the MLR and 40Hz response in sleep which is a necessary first step before clinical applications can be considered.

In addition to the theoretical discoveries made concerning the changes in the MLR during sleep, other clinically relevant questions were raised by this experiment concerning

audiological threshold assessment made with the BAEP using tonal stimuli. It was noted that during sleep, wave V was consistently being recorded to tonal stimuli at an intensity of 45dBSL at both 5 and 40Hz stimulus repetition rates. Particularly noticeable was the detectability of the 500Hz tone pip response made using the 40Hz procedure. This prompted the further investigation of tone pip brainstem responses to see if they could be successfully recorded at lower intensities in sleeping subjects at low and high (40Hz) stimulus rates. These are the experiments which will be described in Chapter 8.

CHAPTER 8

BRAINSTEM AUDITORY EVOKED POTENTIALS TO CLICK AND FREQUENCY SPECIFIC STIMULATION IN NORMAL RELAXED ADULTS.

I) NORMAL RESPONSE CHARACTERISTICS.

II) COMPARISON OF SUBJECTIVE AND EVOKED RESPONSE THRESHOLDS.

8.1 INTRODUCTION.

The original objectives of this thesis were to investigate the MLR and 40Hz responses and to develop the clinical usefulness of these potentials. The results presented in the previous Chapter suggested that far from these responses being stable at all levels of arousal, there are significant changes in the morphology, latency and amplitude of the later components of the MLR especially noticeable in stages 2 and combined 3/4 sleep when using wide bandpass filters. This result has serious consequences for the generation of the 40Hz response which ceases to be a steady-state potential during these stages of sleep but rather primarily consists of brainstem activity. The persistence of the brainstem auditory evoked potential (BAEP) during sleep is well known (Jewett and Williston, 1971; Picton et al., 1974) but a point of interest raised from the previous experiment was the ease with which the BAEP could be detected using tone pip stimuli at the 45dBSL intensity level. The use of click stimuli in generating the BAEP is also well established but less information is known about the

characteristics of the BAEP recorded to tone pips and the use of these potentials in measuring hearing thresholds.

With this in mind, attention was next focussed upon the possibility of developing the brainstem evoked potential in frequency specific assessment. Chapter 4 has described the more restricted use of the BAEP to date in this capacity in comparison to its more common role (i.e. in non-frequency specific assessment using click stimuli). Problems have been encountered in recording BAEPs to tone pip stimuli both in ensuring adequate frequency specificity and also detecting responses at lower stimulus intensities. Alternative strategies of obtaining frequency specific BAEPs have emerged in which more complex stimuli are delivered (for a review refer to Jacobsen, 1985). The value and limitations of these techniques will be discussed at the end of this chapter and these findings put into context with the results shown here.

The potential advantages of frequency specific BAEPs over those generated to clicks is the additional clinical information concerning the precise nature of a patients hearing loss. The click is only able to provide information concerning auditory acuity at frequencies in excess of 2000Hz (Sohmer and Kinarti, 1984). This means that a normal BAEP recording to click stimulus can give little information concerning a low frequency cochlear deficit and an elevated BAEP objective threshold to a click stimulus is insensitive to a patient with normal hearing capabilities at lower frequencies. It is important for the clinician to know if a patient does possess some auditory integrity at a given frequency in order that an appropriate hearing aid may be prescribed.

8.11 Explanation of the structure of this experiment.

This chapter combines data from two experiments. Firstly, twenty subjects were examined in order to determine the normative characteristics of the BAEP recorded to tone pips.

Subsequently, the same twenty subjects were then investigated in order to determine hearing thresholds to tone pip and click stimuli. This threshold data was then compared to similar estimates recorded during an all-night study in four subjects (three of whom were common to both experiments) tested on a separate occasion.

The first part of this chapter describes the morphology, latency and amplitudes of components of the BAEP generated to tone pip stimuli in comparison to click evoked responses recorded as a control. The results of this experiment are then discussed. The second part of the chapter examines the two methods of determining objective hearing thresholds using tone pip and click stimuli.

The first technique records tone pip responses over short epochs in accordance with conventional BAEP methodology. The second technique was developed from the previous experiment (chapter 7) which suggested that detection of tone pip responses may be improved using a 40Hz repetition rate and viewing 100msec. of post-stimulus time when using wider bandpass filters normally reserved for BAEP recording. It was felt that the 100 msec. analysis time and 40Hz stimulus repetition rate provided the experimenter with an improved chance of detecting the wave V component to tonal stimuli because four consecutive responses presented within the same epoch were easier to detect than a single brainstem response viewed over a smaller time window.

As brainstem responses to lower frequency tones are difficult to detect near threshold because of thier low amplitude and uncertain morphology, this comparison is of potential clinical value as the 40Hz protocol may provide a more accurate assessment of subjective hearing thresholds (especially at lower frequencies) than conventional BAEP methodology. One of the aims of this experiment was to test this hypothesis.

8.2 METHODS

8.21 Normal response characteristics of the BAEP recorded to tone pips and click stimulation.

Twenty subjects (male and female) were used in this experiment with an age range of 18-42 years (mean 25 years). No subject had any hearing difficulties nor history of otological disease.

As in the previous experiments, the Medelec Sensor ER84a four channel averager was used (described in Chapter 5). Monaural stimuli were delivered using the Medelec ST-10 unit. The stimuli were alternating tone pips of 5 cycles duration (2 msec. rise/fall and 1 msec. plateau) centred at frequencies of 500, 1000 and 4000Hz and also clicks (generated by 100μsec. square wave pulses). Stimuli were delivered at a repetition rate of 10 per second. Silver/silver chloride electrodes were attached to the vertex and the earlobe ipsilateral to stimulation. An electrode on the forehead served as a ground. All inter-electrode impedances were maintained below 5kΩ. A recording bandpass of 10 to 3000Hz (at 6dB and 12dB/oct slope respectively) was used and the sensitivity of the apparatus was set at 10μV/division. Analysis times of 10 msec. (click stimuli), 20 msec, (4000Hz stimuli) and 30 msec. (1000 and 500Hz stimuli) were chosen in order to adequately visualise BAEP response components. 2048 stimulus repetitions were averaged for each evoked response.

Subjects were asked to relax and encouraged to sleep if possible throughout the test procedure whilst lying in a sound-attenuated room designed specifically for routine clinical audiometric investigation. Stimuli were delivered via an insert ear-piece (described in Chapter 7) in order to provide maximal comfort and hopefully allow the subjects to sleep. The insert earpiece was taped into the ear in order to ensure a consistent level of stimulation. Since the BAEP is unaffected by arousal level (whether relaxed wakefulness or sleep at any stage), it was considered unnecessary to perform detailed sleep stage analysis. However, the ongoing

input activity was carefully monitored throughout the experiment and responses only recorded when subjects were completely relaxed with minimal interference from myogenic potentials. Click, 500, 1000 and 4000Hz stimuli were then presented with each frequency delivered in random order between subjects. Evoked responses were recorded with decreasing stimulus intensities for each of the stimuli and all traces were stored on the Apple IIe microcomputer for off-line analysis. The latency and amplitude of the principal components of the BAEP were measured at different stimulus intensities for subsequent analysis. In addition to the normative aspects of the tone pip BAEP provided by this experiment, objective threshold levels were obtained to all stimuli forming the major part of the second investigation in this chapter.

8.22 Objective threshold assessments recorded using tone pip evoked BAEPs.

The twenty subjects from the above experiment were then combined with the four subjects investigated during all-night sleep in order to assess BAEP thresholds using clicks and tone pips.

The accuracy with which the objective audiogram recorded to tone pips and clicks could approximate to subjective hearing levels was measured by calculating the difference between the subjective and objective thresholds recorded to each stimuli within accuracy of 5dB. Before evoked potentials were recorded, subjective thresholds were determined with all test stimuli by a technician. These results were not revealed to the experimenter until all responses had been recorded in order to eliminate unnecessary experimental bias. Responses were scored positive by the detection of wave V as assessed separately by Dr L.A. Jones and R.J. Baxter. In the case of equivocal responses, the recording was repeated allowing the experimenter to have three separate traces from which to decide if a response

was present or absent. In such cases, a response was only scored as present if a clear waveform was detectable in 2 out of 3 of the traces.

The threshold measurements recorded using the procedure described above was compared to the 40Hz brainstem response recorded in four, normally hearing adult volunteers (three females and one male) aged between 24 and 31 years (mean age 28years) during night-time natural sleep. The following section describes the methods used for this sleep study.

The equipment used to record EEG, EOG and EMG activity was exactly the same as in the previous sleep experiment and the reader is referred to chapter 7 for details. The only modification being the use of 1 - 3000Hz bandpass filters. This alteration in the high pass filter (from 0.3Hz to 1Hz) was considered justified since the 40Hz stimulus repetition rate imposes its own filter upon the response and the 1Hz filter brings the recording methodology more into line with conventional BAEP techniques whilst still maintaining a wide filter bandpass. It had been intended to recalculate the traces after the experiment using the FFT software but this was not possible due to the difficiencies with the program explained in chapter 5. The Medelec Sensor was set to a sensitivity of 50μV/ division to permit averaging to take place in slow wave sleep. As before, 1024 stimulus presentations were averaged for each evoked response. It would have been desirable to record a larger number of averages, but experience in the first sleep study had shown that subjects tend to become restless when sleeping in unfamiliar circumstances and the recording of a larger number of averages was not practical.

Responses were recorded in wakefulness and compared to those found in combined stages 2 and 3/4 sleep (slow wave sleep). It was considered justified to combine stages 2 and 3/4 sleep as the previous sleep study had shown these states to be similar in terms of their effect upon the MLR and 40Hz response. Recording during REM sleep was not included since the first sleep study had demonstrated that the MLR contributed to response morphology during REM and this experiment was interested in recognition of the BAEP without introducing an

added variable. The stimuli used were clicks (100μsec. duration) and tone pips (2 cycles rise/ fall time and 1 cycle plateau) delivered at frequencies centered at 500 and 4000Hz. Stimuli were delivered at repetition rates of 10 and 40Hz. With the 10Hz rate, either 20 or 30 msec. of post-stimulus time was averaged in keeping with established literature concerning tonal BAEP recording (Kodera et al., 1977; Davis et al., 1985; Hyde et al., 1987). When using the 40Hz stimulation rate, 100 msec. of post-stimulus time was averaged. At the beginning of the experiment, subjective thresholds were measured to all three stimuli at both 10 and 40Hz repetition rates. The initial intensity of the stimuli was maintained at 45dBSL until subjects were asleep. Objective threshold estimates were then made by lowering the stimulus intensity until the clear wave V component could not be seen in two out of three separate repetitions at a given intensity. Objective threshold was then taken as the lowest intensity at which a response was recorded consistently with an accuracy of 5dB.

Sleep was continuously monitored throughout the night and scored according to the criteria set down by Rechschaffen and Kales (1968). As in the previous experiment, all EEG, EOG and EMG activity was written out on a Nihon-Koden EEG machine and all evoked potentials were stored on floppy disks on the Apple IIe micro-computer for more detailed off-line analysis.

8.3 RESULTS.

In order to make these data easy to follow, the results of this experiment will be divided into two sections. First, the normative aspects of tone pip brainstem responses (measurements of component latencies, amplitudes, inter-peak latencies and latency - intensity functions) will be presented and then discussed. Subsequently, the threshold data (incorporating the same twenty subjects from the normative work and the four subjects tested during all-night sleep) will be presented and then these data will be discussed. A final discussion/summary at the

end of the chapter will draw together the important findings of this experiment and assess the implications and limitations of this work.

In all the following traces, positivity at the vertex is represented by an upwards deflection according to the convention of Jewett and Williston (1971).

8.31 Normative aspects of BAEP recording to click and tone pip stimuli.

These results relate to the twenty subjects studied in the first experiment. The responses will be described in terms of morphology, the latency and amplitude of the components and the inter-peak latencies for each of the click, 4000Hz, 1000Hz and 500Hz tone pip stimuli. Subsequently, the Latency - Intensity curves for the four stimuli will be presented as this is important in evaluating the frequency specificity of the tone pip stimuli.

Examining first the characteristics of the click response. Although the click evoked BAEP has been well described in the past, it is necessary to establish the nature of this response as a baseline against which the tone pip BAEPs can be compared. Figure 8.1 presents a characteristic trace representing the typical morphology of the BAEP generated to click stimuli at 70dBSL recorded over a 10msec. time sweep. This trace shows five distinct peaks (Jewetts waves I-V) superimposed onto an underlying positive trend.

Table 8.1 shows the means and standard deviations of latency and amplitude for all subjects at the combined intensities of 65 and 70dBSL. These intensities were combined to compensate for the discrepancy in intensity brought about by the experimenter not knowing the subjects' precise subjective threshold in advance of testing and to allow all the subjects to be included into the averages. Amplitude measurements were calculated as the voltage difference from each peak to its following trough. Standard deviations for all components are shown in brackets.

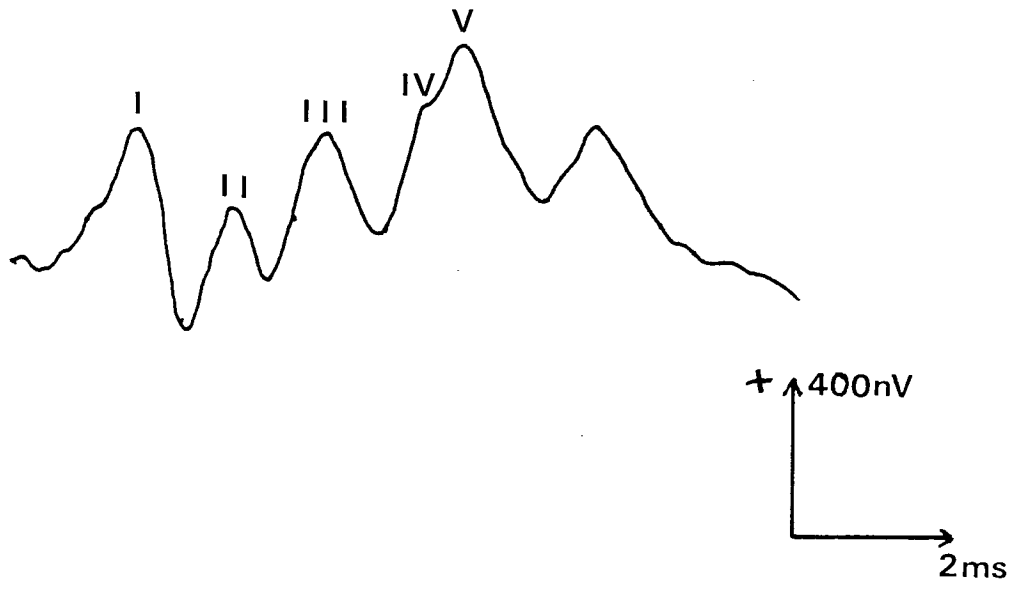

Figure 8.1 A characteristic click evoked BAEP recorded in one representative subject at 70dBSL.

Table 8.1

Wave	*Mean Latency (msec.)*	*Mean Amplitude (nV)*
I	1.7 (±0.10)	220 (±132)
II	2.8 (±0.11)	309 (±87)
III	3.8 (±0.14)	466 (±154)
IV	5.1 (±0.15)	480 (±156)
V	5.88 (±0.17)	324 (±237)

Table 8.1 Mean latencies and amplitudes of the component peaks of the click evoked BAEP at the combined intensities of 65 and 70dBSL.

It is clear from this table that amplitude is a far more variable measurement than latency and also that the later components of the response have higher standard deviations than the earlier peaks. Figure 8.2 shows the morphology of the click evoked BAEP with decreasing stimulus intensity in one representative subject. These responses demonstrate the characteristic decrease in component amplitude and increase in latency which has been well documented by previous workers (Picton et al., 1974). Most noticeable is the disappearence of waves I-IV at stimulus intensities approaching threshold with only the persistence of wave V. Again this phenomenon is well documented but serves to illustrate that wave V is the only reliable component of the BAEP when assessing hearing thresholds.

Measurements of inter-peak latency (IPL) are important in the assessment of the speed of conduction of impulses from the cochlea through the ascending auditory pathway. Table 8.2 presents the mean IPLs (and standard deviations) for the click evoked BAEP for the twenty subjects investigated in this experiment down to an intensity of 45dBSL which was the lowest intensity at which waves I and III were reliably recorded.

The subject numbers (n) within each average are shown in brackets by each intensity.

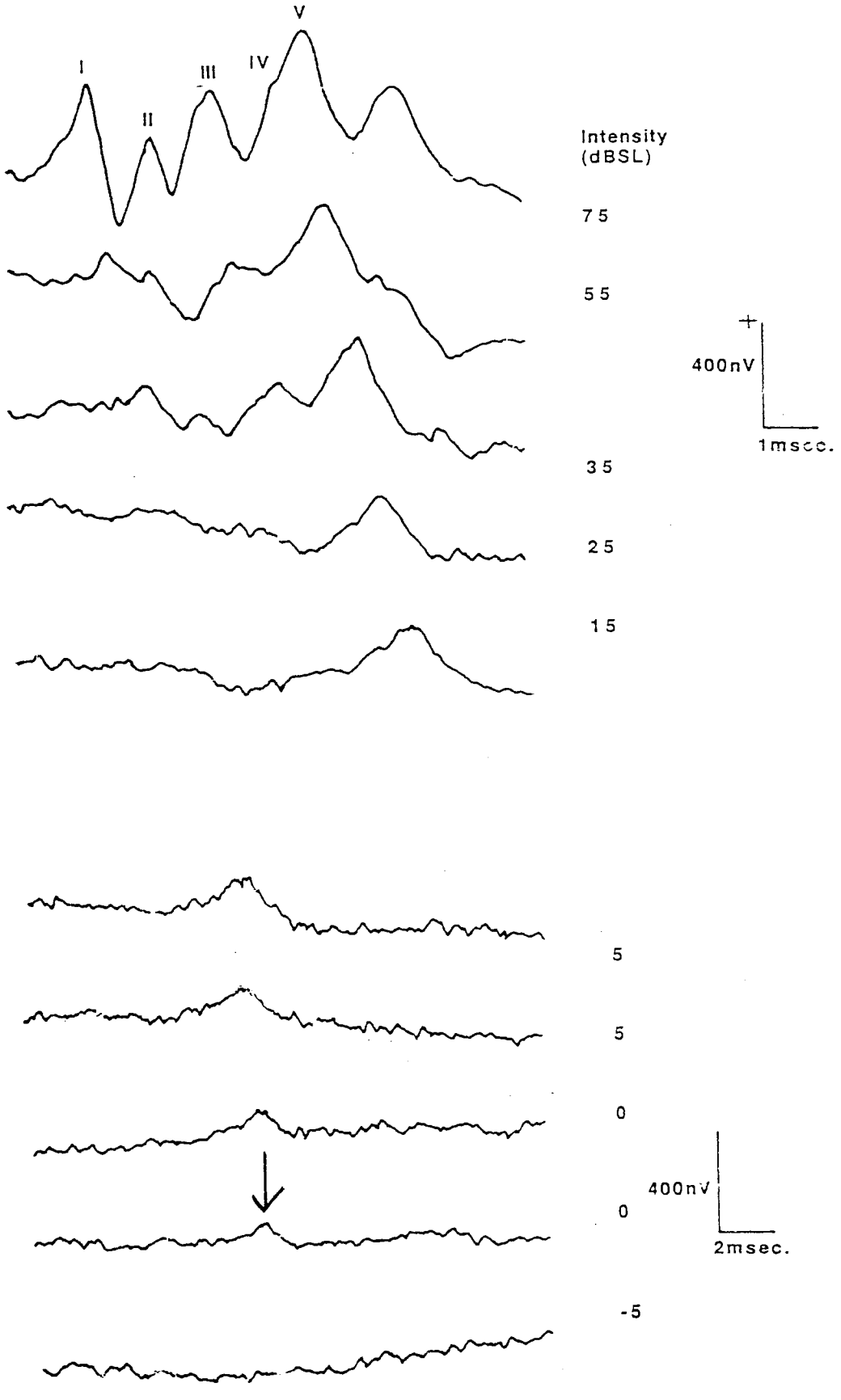

Figure 8.2 Changes in the morphology of the BAEP with decreasing stimulus intensity in one representative subject using click stimulation.

Table 8.2

Intensity (dBSL)	*IPL (msec.)*		
	I-V	*I-III*	*III-V*
80-75 (n=20)	4.10 (±0.16)	2.19 (±0.14)	1.91 (±0.16)
70-65 (n=20)	4.18 (±0.16)	2.10 (±0.12)	2.08 (±0.16)
60-55 (n=20)	3.96 (±0.24)	2.24 (±0.27)	1.72 (±0.29)
50-45 (n=20)	3.68 (±0.26)	1.73 (±0.26)	1.95 (±0.29)

Table 8.2 Inter-peak latencies for the click BAEP (waves I, III and V).

Now that the BAEP characteristics have been described for the click stimulus, attention will now be focussed upon the tone-pip evoked responses and comparisons made between these responses and those obtained to clicks.

Figure 8.3 shows five examples of the BAEP recorded to a 4000Hz tone pip at 70dBSL. The time sweep used for 4000Hz tone pip recording was 20msec. These traces are typical of those recorded in all subjects at high stimulus intensities and serve to give the reader some idea of the normal variability which can be expected when recording this response.

The top two traces show evidence of waves I-III of the BAEP though this was not a universal finding. 7 of the 20 subjects (35%) did not exhibit these early components of the BAEP. The lower traces in fig. 8.3 present these natural variants. By far the most prominent component of the 4000Hz tone pip BAEP is wave V and the negative wave following it (the SN10, Davis et al., 1985).

Table 8.3 gives the means and standard deviations for both latency and amplitude for all subjects at 65 and 70dBSL.

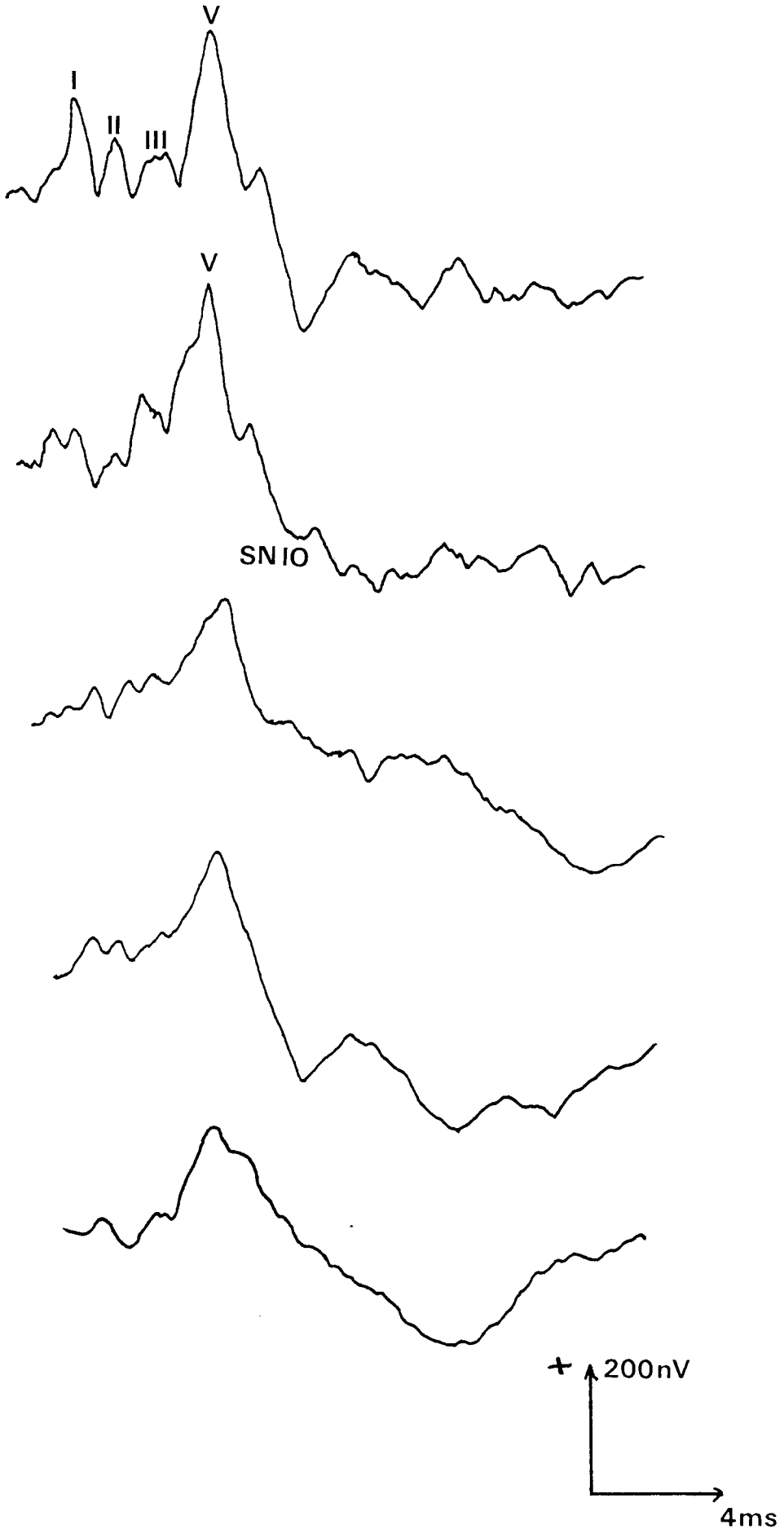

Figure 8.3 Characteristic morphology of the BAEP generated to 4000Hz tone pips recorded at 70dBSL. Five natural variants are shown demonstrating the variability of the response.

Table 8.3

Wave	*Mean Latency (msec.)*	*Mean Amplitude (nV)*
I	2.42 (±0.14)	230 (±82)
II	3.60 (±0.10)	94 (±52)
III	4.84 (±0.17)	112 (±20)
V	6.45 (±0.24)	377 (±125)
SN10	9.80 (±1.1)	

Table 8.3 Mean latencies and amplitudes of the component peaks of the 4000Hz tone pip evoked BAEP at the combined intensities of 65 and 70dBSL.

Figure 8.4 shows the effect of reducing stimulus intensity upon the morphology of the 4000Hz tone pip BAEP. At the highest stimulus intensity, waves I, II, III and V have been labelled but it is clear that the only response component clearly visible at lower stimulus intensities is a single positive deflection (wave V) and the following SN10 negativity. Measurements of inter-peak latency are only possible at the higher intensities using the 4000Hz stimulus. All the components of the response except the large positive SN10 wave become undetectable at intensities lower than 55dBSL. Table 8.4 presents the IPLs for the higher stimulus intensities using the 4000Hz tone pips. The numbers in brackets (n) after each stimulus intensity denote the numbers of subjects within each average.

Table 8.4

Intensity (dBSL)	*IPL (msec.)*		
	I-V	*I-III*	*III-V*
70-65 (n=13)	3.03 (±0.20)	2.42 (±0.16)	1.61 (±0.21)
60-55 (n=8)	4.18 (±0.42)	2.05 (±0.23)	2.13 (±0.38)
50-45 (n=2)	3.72 (±0.33)		

Table 8.4 Inter-peak latencies for the 4000Hz tone pip BAEP.

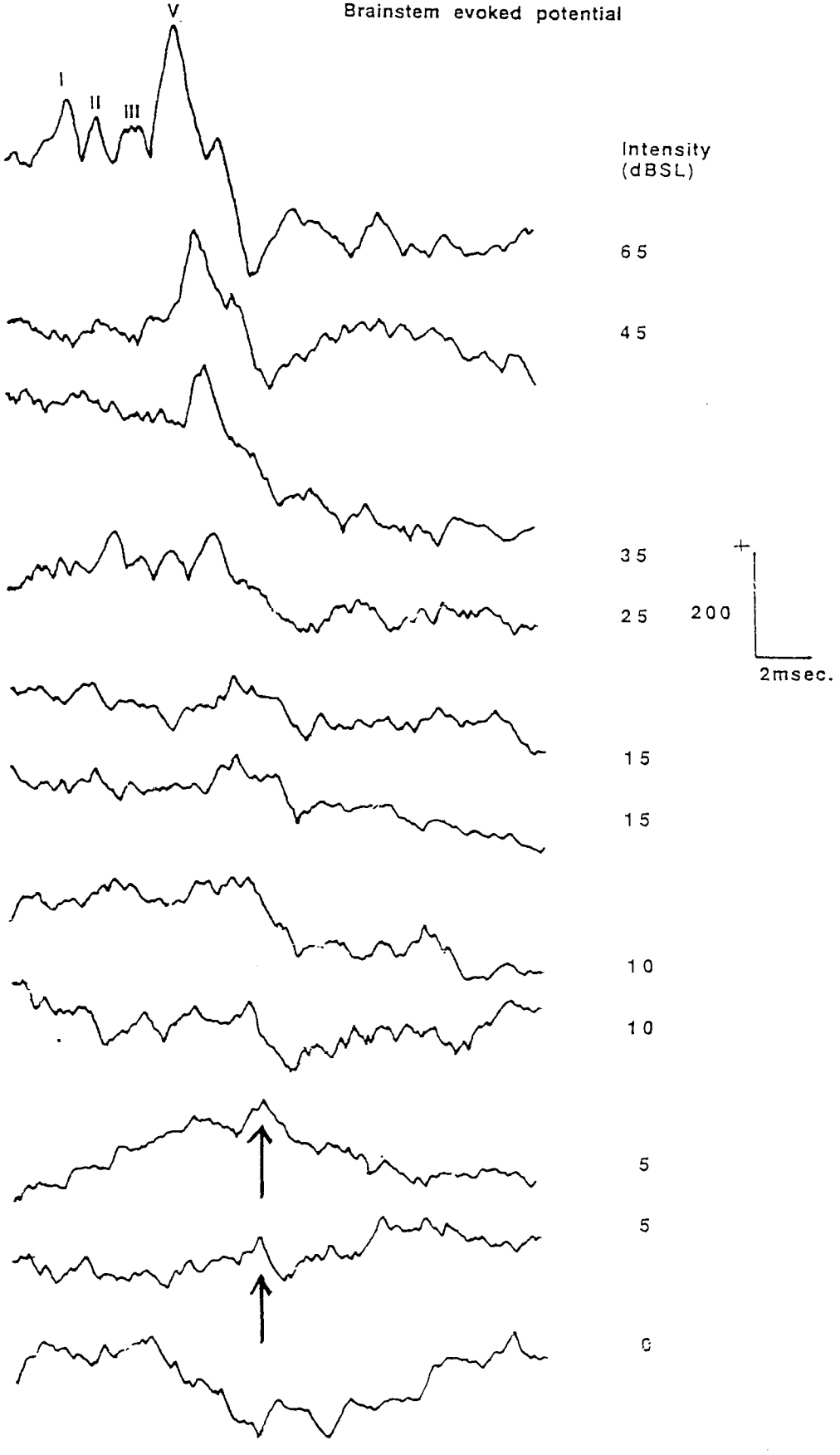

Figure 8.4 Changes in the morphology of the BAEP with decreasing stimulus intensity in one representative subject using 4000Hz tone pip stimulation.

The remaining two stimuli used in this experiment were tone pips of 1000Hz and 500Hz. Figure 8.5 presents three typical responses to 1000Hz tone pips at 70dBSL (the top three traces in this figure). The lower two traces on this figure illustrate the range of normal morphologies which can be encountered depending upon the particular experimental circumstances. All 1000Hz tone pip responses were recorded over a 20msec. time sweep. The fourth trace was recorded from a subject who was asleep and the response shows a clear wave V with very low levels of background noise. The bottom trace illustrates the absolute requirement for adequate subject relaxation and how the response morphology is obliterated if myogenic contamination is allowed to become prevalent. This subject was clearly not sufficiently relaxed and it must be stressed that this trace was rejected. Recording was suspended until the subject had become more comfortable and the 70dBSL response was repeated with a satisfactory outcome. Returning to the typical 1000Hz tone pip responses shown in the top three traces of fig. 8.5. Firstly, it should be noted that the occurrence of waves I, II, III or IV is not apparent in most subjects. Only 2/20 (10%) of subjects demonstrated these earlier components. The interpeak latencies for these two subjects at 70dBSL were: I-V = 4.2 (±0.44); I-III = 2.40 (±0.18) and III-V = 1.81 (±0.41). The lack of earlier components in the majority of subjects clearly was not merely a consequence of inadequate relaxation because even the sleeping subject (shown in the fourth trace) shows no evidence of waves other than the broad wave V- SN10 configuration. Table 8.5 presents the mean latencies and amplitude of the wave V and SN10 components of the 1000Hz tone pip BAEP at 65 and 70dBSL for all subjects. Standard deviations are in brackets.

Table 8.5

Wave	*Mean Latency (msec.)*	*Mean Amplitude (nV)*
V	7.57 (±0.58)	618 (±220)
SN10	10.7 (±0.47)	

Table 8.5 Mean latencies and amplitudes of the component peaks of the 1000Hz tone pip evoked BAEP at the combined intensities of 65 and 70dBSL.

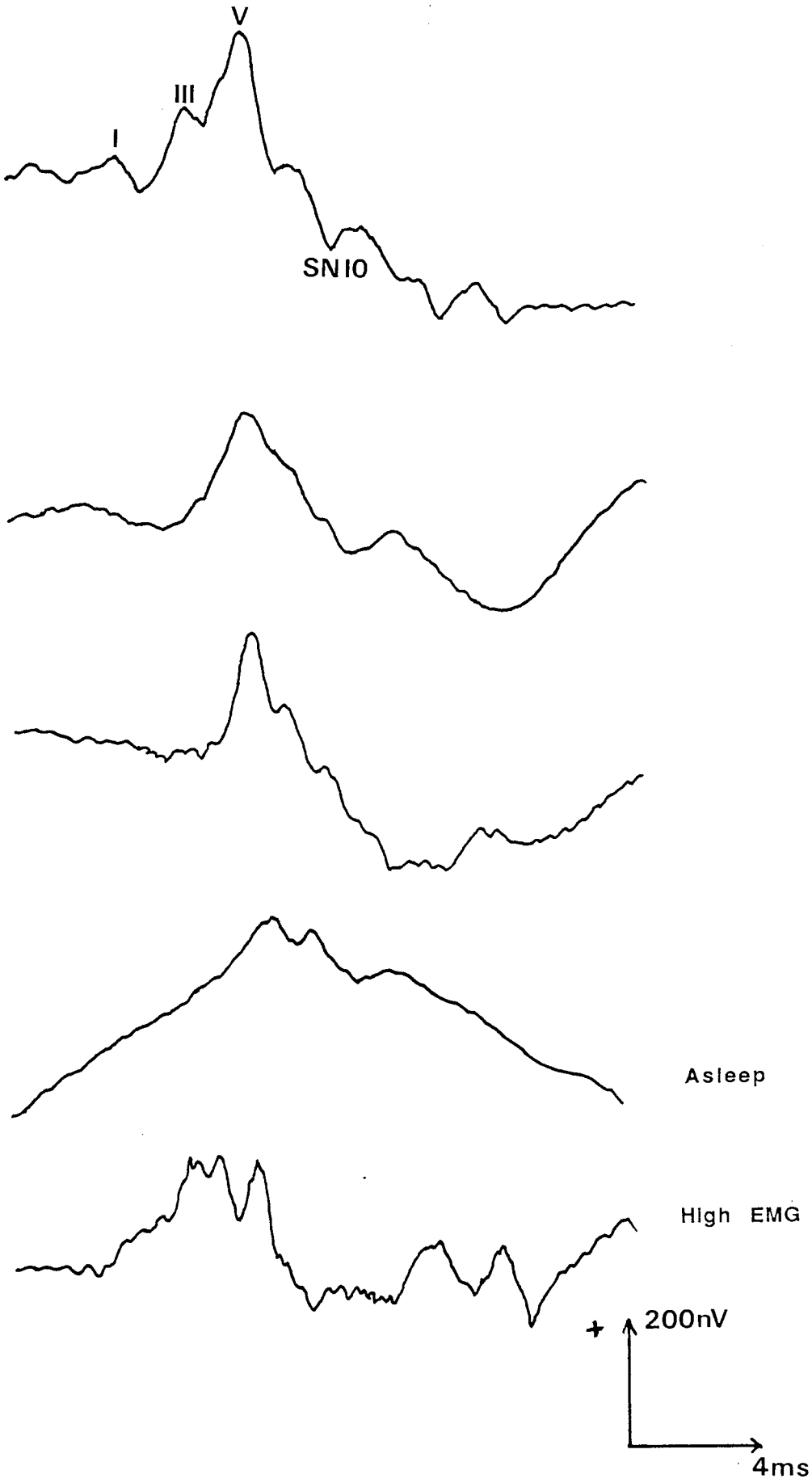

Figure 8.5 Examples of the characteristic morphologies of the BAEP recorded to1000Hz tone pips at a stimulus intensity of 70dBSL. The bottom two traces illustrate the effects of sleep and excessive myogenic activity respectively.

Figure 8.6 shows the effect of reducing stimulus intensity on the morphology of the 1000Hz BAEP response. Most noticeable is the low amplitude of this response at low intensities and this again emphasises the need to pay particular attention in ensuring adequate subject relaxation when recording tone pip brainstem responses.

Figure 8.7 presents five typical variants of the BAEP as generated to 500Hz tone pip stimuli at 70dBSL and a time sweep of 30msec. No earlier components of the BAEP are visible and the wave V - SN10 configuration is the sole indicator of an evoked response. Also of interest is the occurrence of the Frequency Following Response (FFR) in some subjects. This phenomenon was described by Moushegian et al. (1973) and is described in the introductory chapter of this thesis. The FFR is of little use in the determination of objective hearing thresholds (Sohmer et al., 1977) but is often recorded incidentally when using low frequency stimuli at high intensities. Table 8.6 shows the mean latencies and amplitudes (plus standard deviations) for the wave V and SN10 components of the 500Hz tone pip BAEP at 65 and 70dBSL in all subjects.

Table 8.6

Wave	*Mean Latency (msec.)*	*Mean Amplitude (nV)*
V	9.4 (±0.8)	617 (±115)
SN10	15.8 (±1.1)	

Table 8.6 Mean latencies and amplitudes of the component peaks of the 500Hz tone pip evoked BAEP at the combined intensities of 65 and 70dBSL.

Table 8.6 shows that the mean latency of wave V has quite large standard deviations. This is due to the very broad nature of the wave V peak and also the difficulty in locating its apex in the presence of a FFR. Once again, amplitude measurements are less reliable and are of less

Figure 8.6 Changes in the morphology of the BAEP with decreasing stimulus intensity in one representative subject using 1000Hz tone pip stimulation.

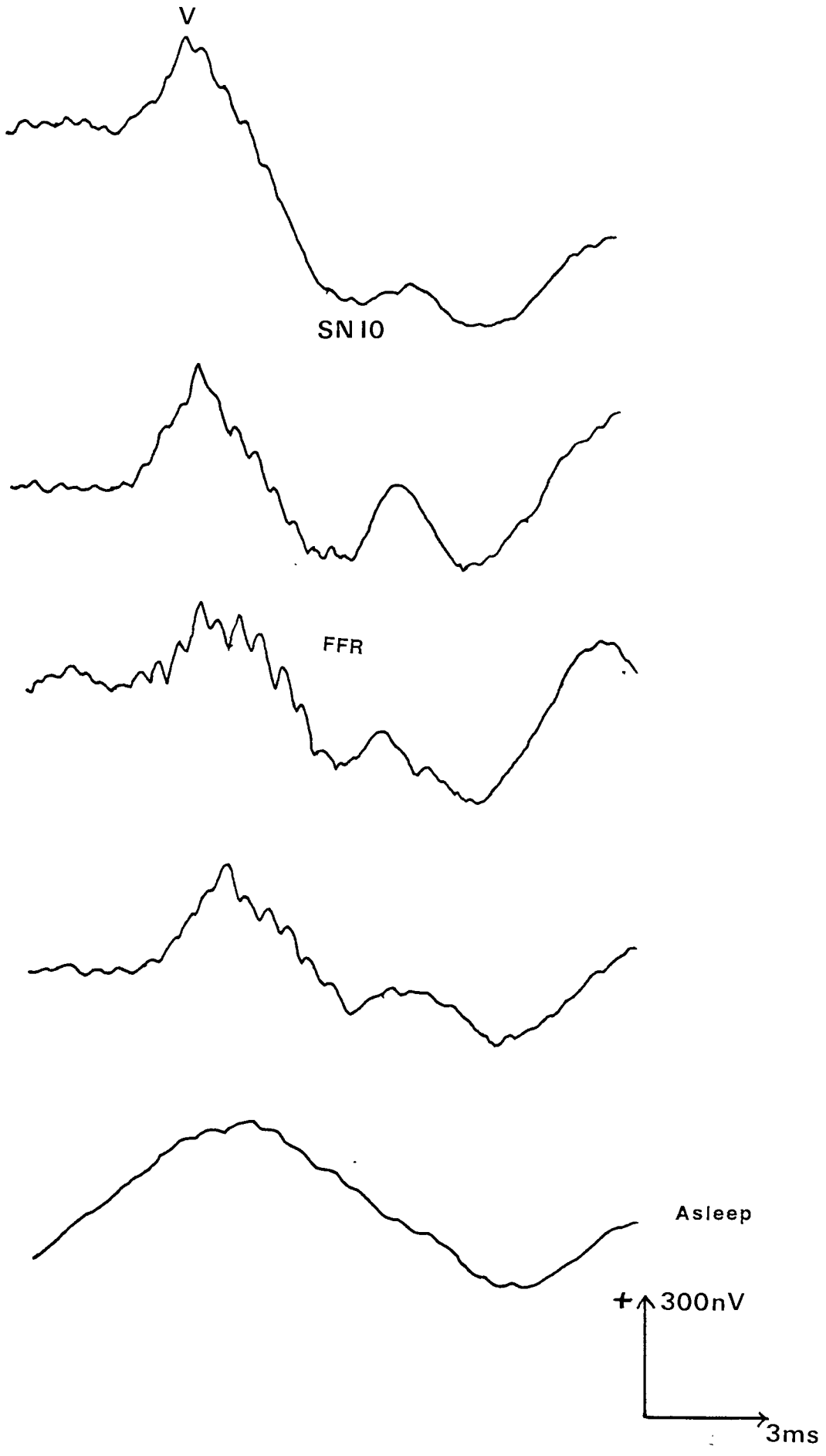

Figure 8.7 Five natural variants of the BAEP recorded using 500Hz tone pips at 70dBSL. The Frequency Following Response (FFR) seen particularly in the middle three traces makes the precise location of wave V difficult.

use in characterising these responses. Figure 8.8 shows the relationship of the 500Hz tone pip BAEP with lowering stimulus intensity. At intensities approaching threshold, the 500Hz responses are hardest to detect due to their vey low amplitude and once again the importance of adequate subject relaxation is emphasised.

Section 8.31 has described the morphology, latencies and amplitudes of the click evoked BAEP and compared this to the BAEP as it is generated to tone pips of 500Hz, 1000Hz and 4000Hz. The normal variability of these responses has been described and also the ways in which components of these responses vary with stimulus intensity. The main conclusion from this is that the wave V component of the click evoked BAEP and the wave V - SN10 configuration of the tone pip responses provides the clearest indicator wave at high intensity and the only indicator wave at low stimulus intensities with which to determine hearing thresholds. The following section will therefore examine more closely the Latency - Intensity relationship of wave V for all the stimuli. Subequently, the characteristics of the BAEP generated to tone pips will be discussed.

8.32 Latency - Intensity curves for click and tone pip stimuli.

Latency - Intensity (L- I) curves give important information about the frequency specificity of stimuli. Therefore, before the effectiveness of the tone pip BAEPs in assessing hearing thresholds can be evaluated, it is first necessary to find out whether these stimuli are frequency specific or whether they are exciting a far larger portion of the cochlear partition than is desirable. Table 8.7 presents the latency - Intensity relationships for wave V for each of the four stimuli used in this experiment. Figure 8.9 represents this information graphically with adjacent intensities (70 with 65dBSL, 60 with 55dBSL etc.) combined in order to simplify the figure. Examination of these latency - intensity (L-I) curves reveals the following information. Firstly, it can be seen that at any given stimulus intensity, the latency of wave V is smallest with the click stimulus and increases with decreasing stimulus frequency. Secondly,

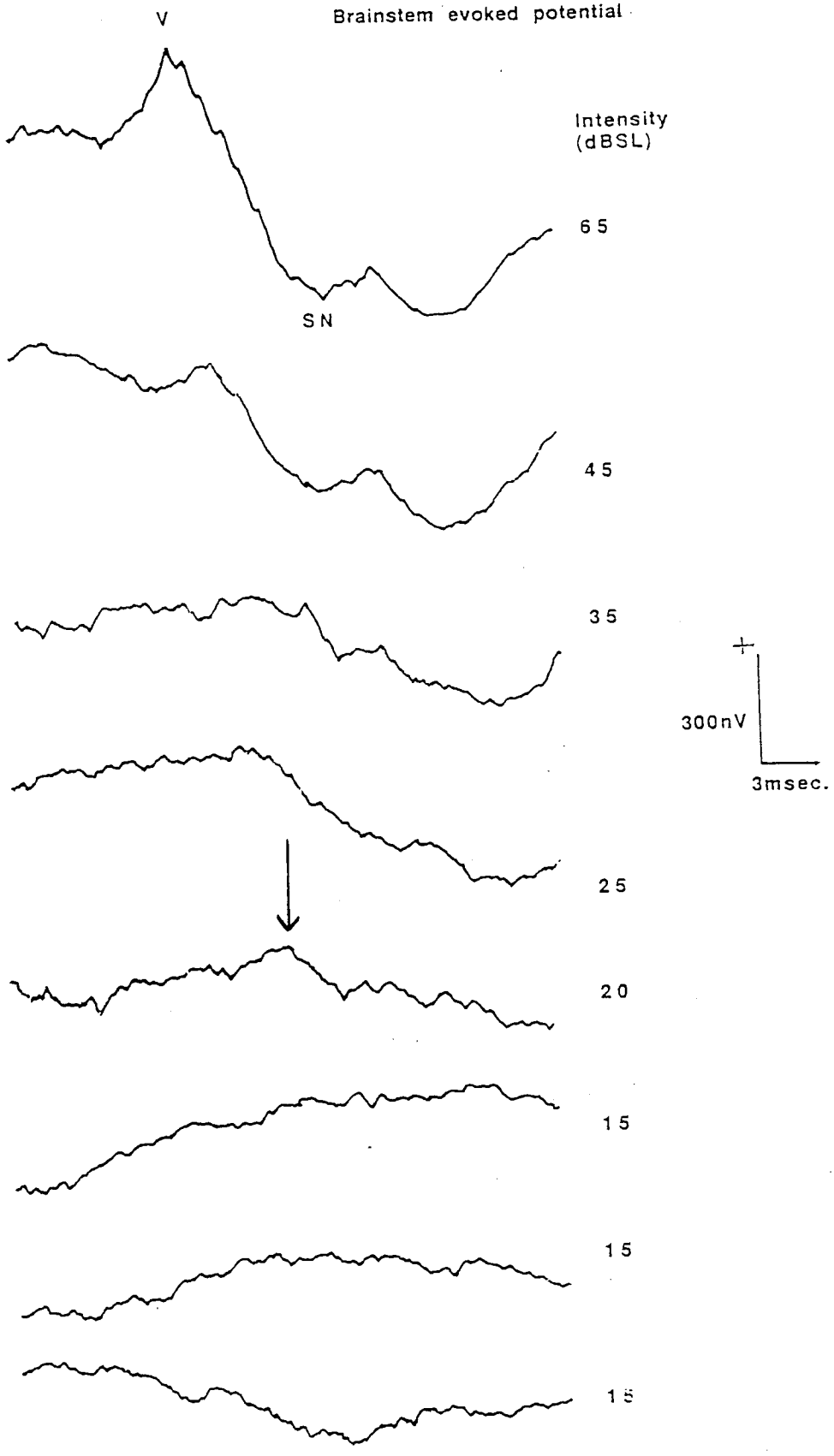

Figure 8.8 Changes in the morphology of the BAEP with decreasing stimulus intensity in one representative subject using 500Hz tone pip stimulation.

Click			4000Hz pip		
Intensity (dBSL)	Mean latency (msec.)	S.D. (±)	Intensity (dBSL)	Mean latency (msec.)	S.D. (±)
67.5	5.88	0.17	67.5	6.45	0.24
57.5	5.9	0.18	57.5	6.82	0.53
47.5	6.43	0.75	47.5	6.82	0.22
37.5	6.77	0.48	37.5	7.13	0.39
27.5	7.29	1.08	27.5	7.61	0.42
17.5	8.15	1.1	17.5	8.92	0.82
7.5	8.21	0.29	7.5	9.18	0.86
-2.5	8.68	0.26	-2.5	9.39	0.51

1000Hz pip			500Hz pip		
Intensity (dBSL)	Mean latency (msec.)	S.D. (±)	Intensity (dBSL)	Mean latency (msec.)	S.D. (±)
67.5	7.57	0.58	67.5	9.37	0.76
57.5	7.83	0.59	57.5	10.1	0.86
47.5	8.82	0.48	47.5	11.3	1.25
37.5	9.85	0.95	37.5	12.29	1.43
27.5	10.75	0.99	27.5	14.1	1.72
17.5	11.77	0.71	17.5	14.4	1.2
7.5	12.6	0.46			

Table 8.7 Mean latencies (and standard deviations) for combined, adjacent intensities (dBSL) for click, 4000Hz, 1000Hz and 500Hz stimuli (see text for details).

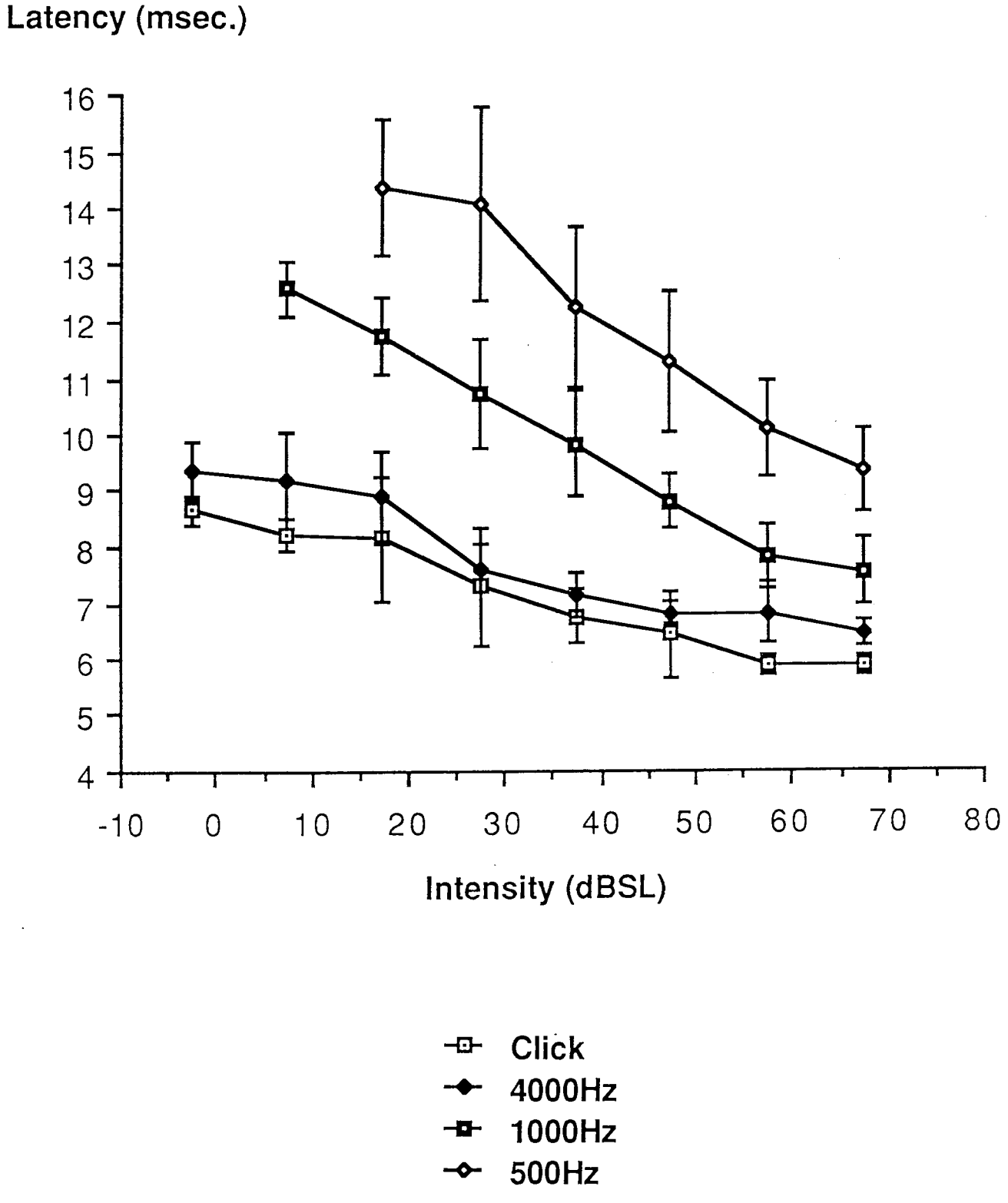

Figure 8.9 Latency-Intensity functions with standard deviations for all stimuli.

it is apparent that the gradient of these lines increases as the frequency of the stimulus falls. Using a *single* line of best fit for each frequency, the mean gradients of these lines are Click = 40μsec./dB; 4000Hz = 50μsec./dB; 1000Hz = 84μsec./dB and 500Hz = 100μsec./dB. Looking more closely at these functions, it could be argued that particularly the click and 4000Hz curves are better modelled by two lines as the rate of latency increase per unit intensity appears smaller at higher stimulus intensities (> 40dBSL) than at lower intensities for these stimuli. Recalculating these gradients but this time applying *two* lines of best fit, the click stimulus has a gradient of 19μsec./dB at intensities greater than 40dB and a gradient of 48μsec./dB below that intensity. Similarly, the 4000Hz L- I function has a gradient of 27μsec./dB (> 35dBSL) and 69μsec./dBSL below that value.

8.4 DISCUSSION.

8.41 Latency and morphology differences in response components of the BAEP with different stimuli.

The aim of this experiment was to compare differences in the latency and morphology of tonally evoked brainstem responses in comparison to click BAEPs. Referring to section 8.3.1, it is clear that click and tonal stimuli generate BAEPs with very different component latencies, amplitudes and morphology.

For ease of comparison, figure 8.10 shows one typical response at 70dBSL for each of the four stimuli used in this experiment. Table 8.8 combines the mean latencies and amplitudes of the component peaks for all stimuli at the combined intensities of 65 and 70dBSL in order that they might be compared more easily.

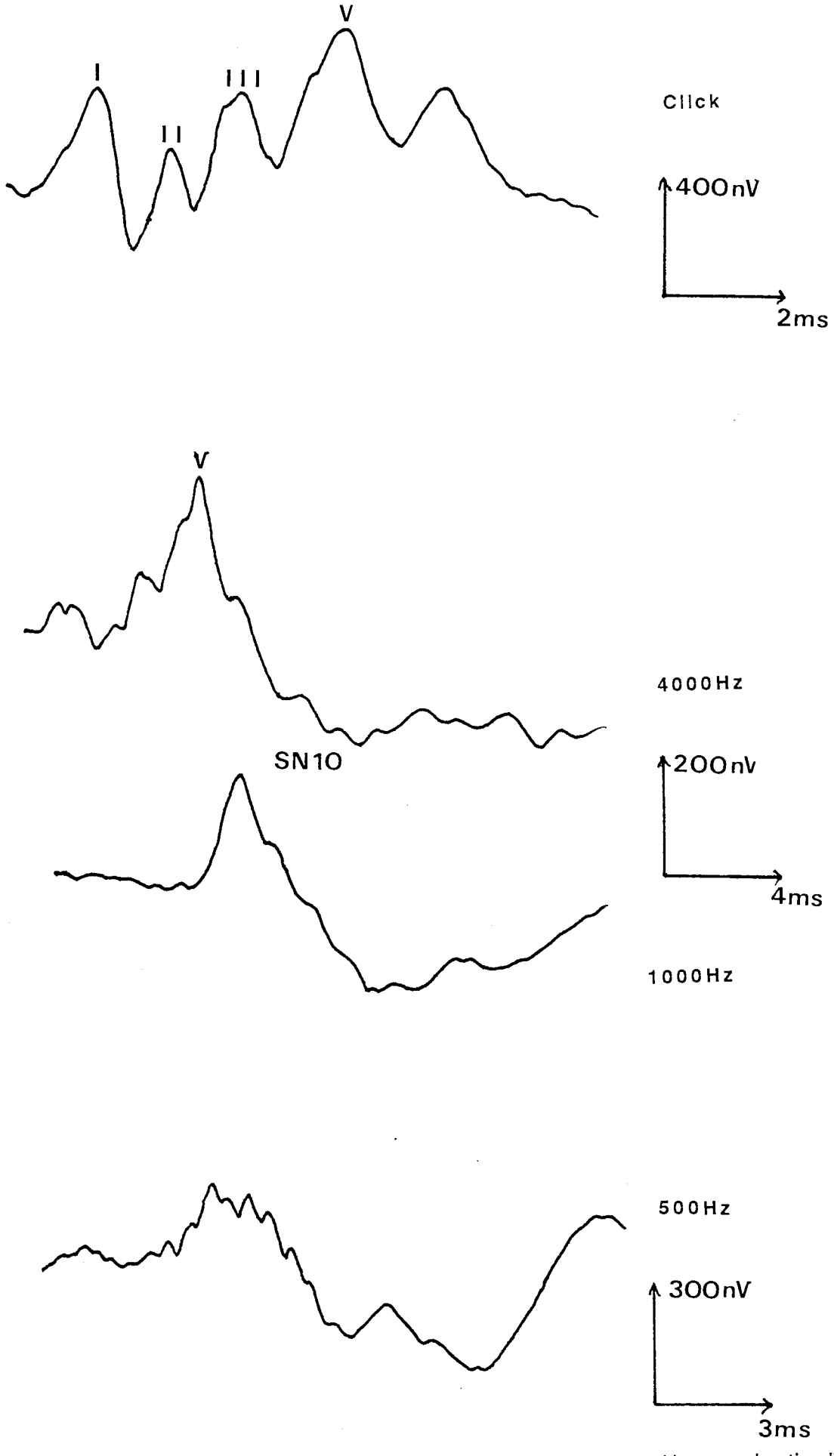

Figure 8.10 Typical responses for click and 4000Hz, 1000Hz and 500Hz tone pip stimuli at 70dBSL.

i) **Click**

Wave	*Mean Latency (msec.)*	*Mean Amplitude (nV)*
I	1.7 (±0.10)	220 (±132)
II	2.8 (±0.11)	309 (±87)
III	3.8 (±0.14)	466 (±154)
IV	5.1 (±0.15)	480 (±156)
V	5.88 (±0.17)	324 (±237)

ii) **4000Hz tone pip stimuli**

I	2.42 (±0.14)	230 (±82)
II	3.60 (±0.10)	94 (±52)
III	4.84 (±0.17)	112 (±20)
V	6.45 (±0.24)	377 (±125)
SN10	9.80 (±1.1)	

iii) **1000Hz tone pip stimuli.**

V	7.57 (±0.58)	618 (±220)
SN10	10.7 (±0.47)	

iv) **500Hz tone pip stimuli.**

V	9.4 (±0.8)	617 (±115)
SN10	15.8 (±1.1)	

Table 8.8 Summary of the mean latencies and amplitudes of the component peak of the BAEP as recorded to clicks and tone pips of 4000Hz,1000Hz and 500Hz.

In summary, amplitude measurements of all components are highly variable and show a great deal of overlap between responses using different stimuli. For statistical significance, amplitude differences between different stimuli would have to be separated by greater than 2.5 standard deviations which is not the case in this experiment. Inspection of the threshold estimates in a typical subject (figs 8.2, 8.4, 8.6 and 8.8) show that the amplitude of the tone

pip responses at low intensities are small and this is especially true of the lower frequency tone pips (1000Hz and 500Hz). With respect to latency and morphology, the click response demonstrates five clear peaks at high stimulus intensity and is easily viewed over a 10 msec. epoch. Lowering intensity causes attenuation of the earlier peaks but wave V persists down to intensities at or approaching threshold (Fig. 8.2). The component peaks of the 4000Hz tone pip BAEP are of longer latency than the click response but the latency variability of the individual peaks are similar to those found with the click evoked BAEP with the later wave V component and the SN10 having the largest variability. The earlier waves are less reliable than with the click BAEP and even the responses at high stimulus intensities only consist of four waves (wave IV not being identifiable) in comparison to the five waves seen with click stimuli at high intensity. The recognition of wave V and the following SN10 negativity is essential in the detection of responses near threshold (fig. 8.4) and due to the smaller amplitude of the 4000Hz tone pip response, subject relaxation is very important .

1000Hz tone pip responses are of longer duration than both the click and 4000Hz responses. In addition, the latency variability of the wave V-SN10 configuration (standard deviation ±0.58) is greater than either for click or 4000Hz stimuli which is due to the broadening of the response peaks which makes precise measurement of these components less accurate. Earlier waves are completely absent from the response and at low stimulus intensities (fig. 8.6) and the wave V - SN10 configuration is small which means a very relaxed or ideally, sleeping subject is required. The 500Hz tone pip response have wave V - SN10 components which are of longer latency than those recorded to any other stimuli tested in this experiment. Recording these responses requires most care on behalf of the experimenter in order for clear responses to be obtained. This often means repeating equivocal responses which tend to occur more with 1000Hz and 500Hz stimuli especially at low intensities of stimulation (fig.8.8).

Section 8.32 examined the latency-intensity curves for click and tone pip stimuli. The aim of this work was to assess the frequency specificity of the different stimuli. Figure 8.9 shows

that wave V latency is inversely related to both intensity and frequency. Secondly, there is little difference between the curves for the click and 4000Hz tone pip stimuli at any intensity. The 1000Hz and 500Hz tone pip latency-intensity curves have steeper gradients (than click or 4000Hz tone pips) which means that the magnitude of the latency difference between these stimuli and the click and 4000Hz tone pip stimuli is greatest at low stimulus intensities. The difference between the latency-intensity curves for the 1000Hz and 500Hz stimuli is greater than 2.5 standard deviations from the click and 4000Hz tone pip curves at intensities less than 40dBSL which suggests that this difference is statistically significant. The reason for the greatest latency differences existing at lower stimulus intensities is probably because the low frequency tone pips (500 and 1000Hz) are less able to activate more basal regions of the cochlea. In other words, the frequency specificity of tone pip stimuli varies as a function of intensity with louder tones causing a greater spread of excitation along the basilar membrane (and hence across frequencies) because of the greater energy that they possess (Davis and Hirsh, 1976; Stapells and Picton, 1981; Stapells et al., 1985). Stapells and Picton (1981) reported an increase of around 1msec. in wave V latency with a 500Hz tone pip in comparison with a 2000Hz pip at 120dBSPL, whereas they found a 3 msec. latency difference between these two stimuli when the intensity was reduced to 70dBSPL. This implies that as intensity is reduced, extraneous frequencies present within the tone pip stimulus gradually become sub-threshold and hence the latency of wave V increases more steeply. This latency difference reflects the increased time required for the lower frequency stimulus to reach the apical region of the basilar membrane, the locus of maximal response for these stimuli (Békesy, 1943). The results reported in this experiment are consistent with these findings and therefore would suggest that frequency specificity of the tonal stimuli increases as intensity falls.

The latency changes in wave V with tonal stimuli presented in the results section and discussed above have important implications for the practical procedures necessary to record tonal BAEPs. In order to properly visualise wave V at intensities approaching audiometric threshold it is clearly necessary to use longer sweep times. The mean latency ranges for the four stimuli used in this experiment were: Click 5.88 msec. at 70-65dBSL to 8.68 msec. at 0- -

5dBSL; 4000Hz 6.45 msec. at 65dBSL to 9.17 msec. at 5dBSL; 1000Hz 7.36 msec. at 70dBSL to 12.6 msec. at 10dBSL and 500Hz 9.24 msec. at 70dBSL to 14.4 msec. at 20dBSL. This demonstrates that in order to be able to detect wave V down to audiological threshold using tone pip stimuli, sweep times of 20 or 30msec. are required in order that wave V and the following SN10 negativity are adequately visualised.

The characteristic morphology of the BAEP as recorded to a click stimulus is well established (Sohmer and Feinmesser 1967; Jewett and Williston, 1971; Picton et al., 1974). However, this experiment and other previous work has shown that the waveform of the BAEP is different when tone pip stimuli are used and the only reliable component of the response is Jewett's wave V. especially at stimulus intensities near audiometric threshold (Suzuki et al., 1977; Kodera et al., 1977; Bauch et al., 1980; Hyde et al., 1987; Riko et al., 1988). The morphology of wave V also changes when tone pip stimuli are used with a decrease in the sharpness and broadening of the wave most apparent with low frequency and low intensity stimuli. Allied to this broadening of wave V, the latency of this component becomes less easy to pin-point accurately and response detection relies far more heavily on the recognition of a general low frequency deflection rather than a discrete peak.

Accompanying the changes in response morphology are changes in the frequency composition of these potentials. It is clear that low frequency stimuli generate responses which rely far more on the detection of low frequency activity for their recognition. This, therefore, raises the question of the most appropriate high pass filter setting in order to see these responses. An evaluation of the commonly used recording filters for BAEP recording is presented in Chapter 4. When click stimulation is used, the value for the high pass filter is commonly set at 30-100Hz (Jewett and Williston, 1971; Picton et al., 1974). However, in tonal BAEP recording, many authors have advocated the use of a filter set at around 10Hz in order that the low frequency activity necessary for response recognition can be seen (Davis, 1876; Suzuki et al., 1977; Kodera et al., 1977; Stapells and Picton, 1981; Davis et al., 1985). In this experiment, a low cut filter of 10Hz was chosen for this reason.

Having now described the characteristics of the BAEP recorded to tone pips, attention will now be focussed upon the use of these responses in the assessment of hearing thresholds. This section will combine two experiments, the first in twenty adult subjects who were relaxed but not necessarily sleeping and the second in four subjects during all-night natural sleep.

8.5 RESULTS.

Comparison of subjective and evoked response thresholds to click and tone pip stimuli using existing BAEP methodology and the 40Hz protocol.

8.51 Conventional BAEP techniques.

The objective thresholds of the twenty subjects used in the experiment described above were then measured. The results were expressed as the difference between the subjects' subjective threshold (S) and the objective threshold (O) as suggested by the evoked responses (the criteria for defining objective threshold was described in the methods section 8.2). A minus sign denotes the objective threshold was greater the subjective threshold. Table 8.9 gives the threshold means, standard deviations and ranges for these twenty subjects. The raw subjective and objective threshold data for the twenty subjects tested in this experiment is provided in table 8.10.

Stimulus	*Mean S-O Threshold difference dBSL(S.D.)*	*Range (dB)*
Click	- 6.0 (±4.8)	-15 to 0
4000Hz pip	- 9.11 (±10.0)	- 30 to 5
1000Hz pip	-19.3 (±10.7)	- 35 to - 5
500Hz pip	-25.8 (±7.1)	- 35 to -15

Table 8.9 BAEP audiometric threshold estimation using click and tone pip stimuli.

	Click Thresholds			4000Hz Thresholds	
Subjective	Objective	Difference	Subjective	Objective	Difference
0	5	-5	20	20	0
0	5	-5	20	20	0
-5	5	-10	15	30	-15
-5	-5	0	15	20	-5
0	10	-10	20	15	5
-5	-5	0	20	25	-5
-5	0	-5	20	25	-5
5	20	-15	20	15	5
-5	0	-5	15	20	-5
0	0	0	20	50	-30
-5	10	-15	15	20	-5
-5	5	-10	20	30	-10
0	5	-5	20	35	-15
-5	0	-5	20	40	-20
0	5	-5	25	30	-5
0	10	-10	20	50	-30
0	0	0	25	30	-5
-10	0	-10	15	15	0
0	0	0	25	25	0
-5	0	-5	15	20	-10
	1000Hz Thresholds			500Hz Thresholds	
Subjective	Objective	Difference	Subjective	Objective	Difference
20	40	-20	20	50	-30
20	40	-20	20	40	-20
15	25	-10	15	30	-15
10	20	-10	15	30	-15
25	35	-10	30	50	-20
15	30	-15	15	30	-15
20	40	-20	15	50	-35
20	40	-20	35	60	-25
10	35	-25	10	40	-30
15	50	-35	15	45	-30
20	45	-25	25	60	-35
15	50	-35	15	50	-35
25	50	-25	25	50	-25
20	40	-20	25	50	-25
25	50	-25	25	40	-15
25	60	-35	25	35	-30
15	40	-25	15	45	-30
20	30	-10	20	55	-35
25	30	-5	35	60	-25
15	40	-25	15	40	-25

Table 8.10 Individual subjective thresholds, objective threshold and threshold differences for all subjects using click, 4000Hz, 1000Hz and 500Hz stimuli.

Histograms were plotted showing the difference between the lowest intensity at which an evoked response could be detected and subjective threshold. Figures 8.11a, b, c, and d present these data. The results of this experiment show that hearing thresholds determined to tone pip BAEPs produced a wider discrepancy between subjective and objective threshold than those obtained to the click stimuli.

8.52 Results of thresholds estimations using the 40Hz protocol.

The all-night sleep study performed in four subjects revealed that the detectability of the BAEP to tone pip stimulation was affected by the choice of analysis time (30 or 100 msec.) and repetition rate (10 or 40Hz). Threshold determinations made using the click stimulus were the same with either protocol. Table 8.11 presents threshold estimates for the four subjects tested using 10Hz (30 msec.) and 40Hz (100 msec.) procedures.

	Stimulus					
	Click		*4000Hz*		*500Hz*	
Rep. rate:	*10Hz*	*40Hz*	*10Hz*	*40Hz*	*10Hz*	*40Hz*
Subject 1	-5	-5	0	-10	-20	-15
Subject 2	-5	-5	-5	-5	-10	-5
Subject 3	-5	-5	-10	-5	-25	-20
Subject 4	-5	-5	-10	-15	-25	-10
Mean	-5.0	-5.0	-6.3	-8.75	-20.0	-12.5

Table 8.11 Subjective-objective threshold differences in non-REM sleep (dB) for the four experimental subjects.

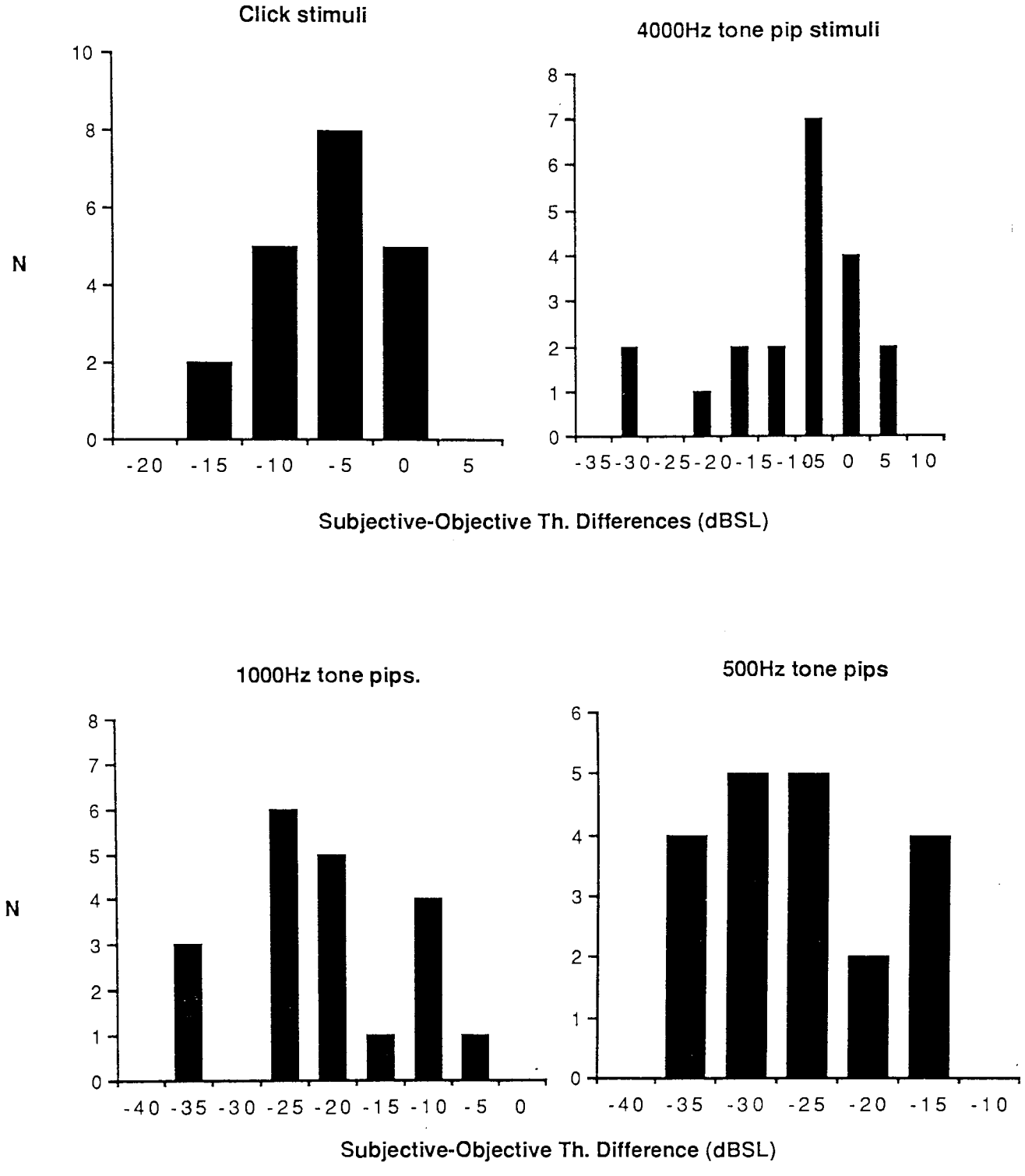

Figure 8.11 Histograms presenting the subjective-objective threshold differences for all subjects and all stimuli using the BAEP.

Figures 8.12-8.15 show the comparative morphologies of the tone pip brainstem threshold estimates as generated by both procedures to the 500Hz stimulus. Figures 8.16-8.19 present the responses generated to the 4000Hz stimulus using the 10Hz and 40Hz methods. Table 8.12 presents the data for the three subjects who took part in both experiments, showing an 8.3dB reduction in threshold estimation using the 40Hz procedure for the 500Hz tone pip stimulus in comparison to the 10Hz BAEP technique either awake or asleep. The click and 4000Hz stimuli demonstrate no clear differences.

8.6 DISCUSSION.

In the twenty subjects tested in the first experiment, it was found that the click stimulus gave the most accurate assessment of threshold both in terms of the absolute difference between subjective and objective threshold and the lowest variability. The data also showed that in a population of normal subjects, the lower the stimulus frequency, the greater the difference between subjective and objective threshold. Whilst the frequency specific responses were not as accurate (in terms of the absolute threshold value) as those recorded to the click stimuli (-6.0dB±4.75), at 4000Hz and 1000Hz mean threshold estimates of -9.11dB (±10.0) and -19.3 (±10.7) respectively would imply that these tone pip responses have some value provided that further work can corroborate these findings and also similar results can be obtained in clinical populations. The mean objective threshold estimate recorded using the 500Hz pip was found to be the furthest away from subjective threshold in this study -25.8dB (±7.1). This result is not unexpected considering the difficulties which arise when stimulating the apical cochlea. However, with all measurements of threshold it is the *consistency* (i.e. low data variability) of the response which is more important than the *absolute* threshold value. The comparatively small standard deviation (i.e. low variability) reported at this frequency would suggest that even at 500Hz, some valid inferences can be drawn concerning hearing thresholds using tonal BAEPs at this frequency.

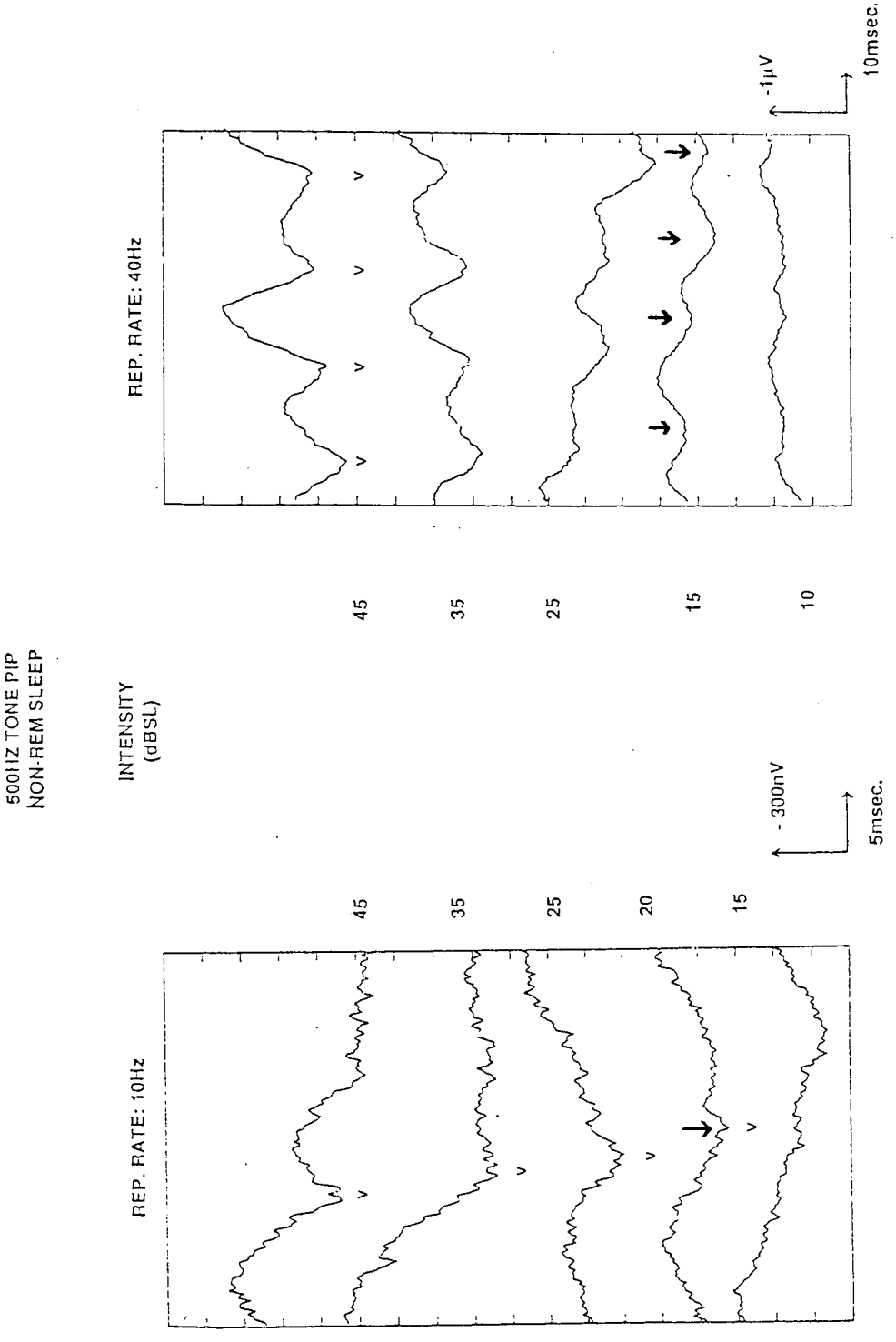

Figure 8.12 10Hz (30msec.) and 40Hz (100msec.) BAEPs in one subject using 500Hz tone pip stimulation.

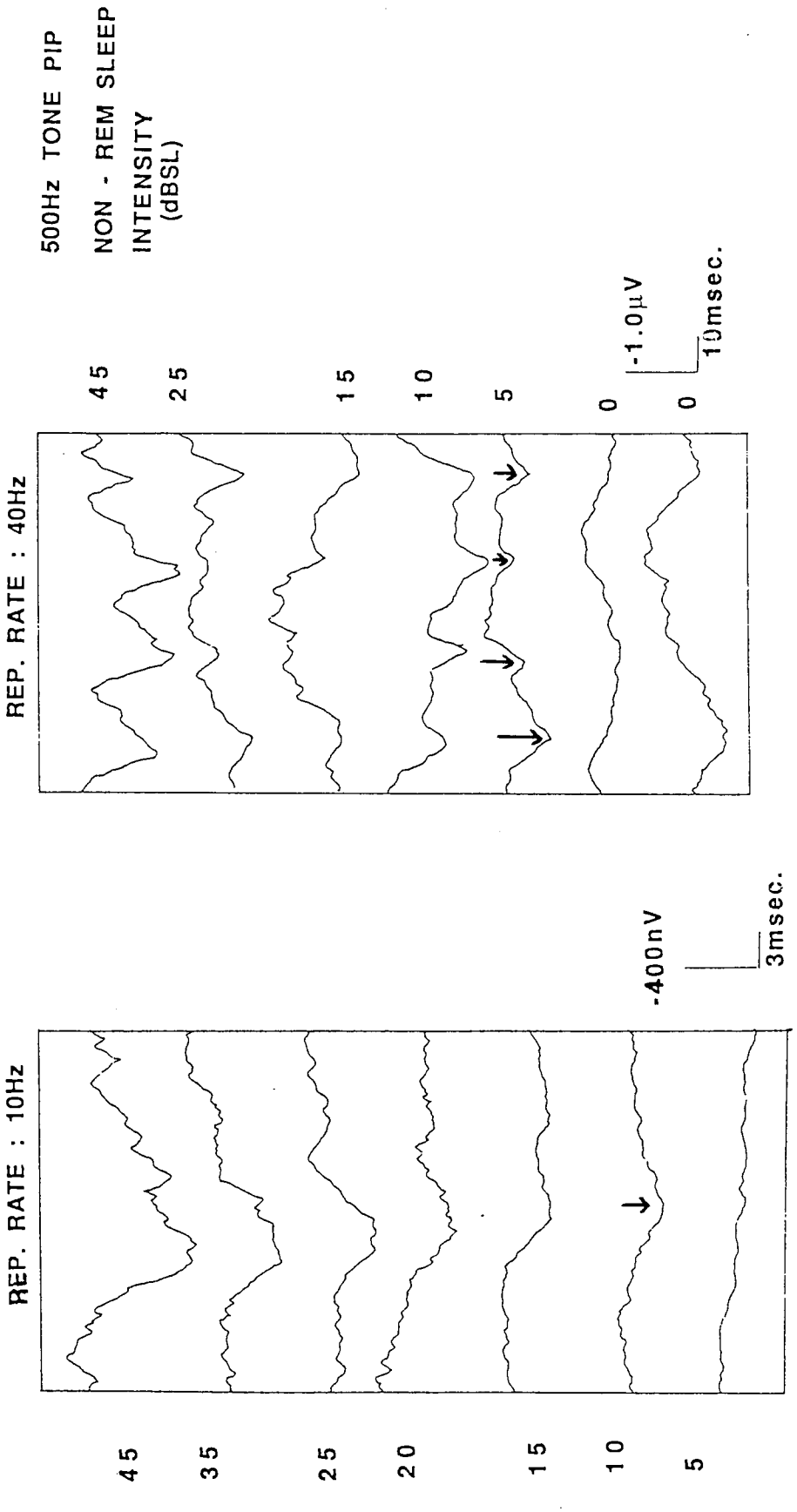

Figure 8.13 10Hz (30msec.) and 40Hz (100msec.) BAEPs in one subject using 500Hz tone pip stimulation.

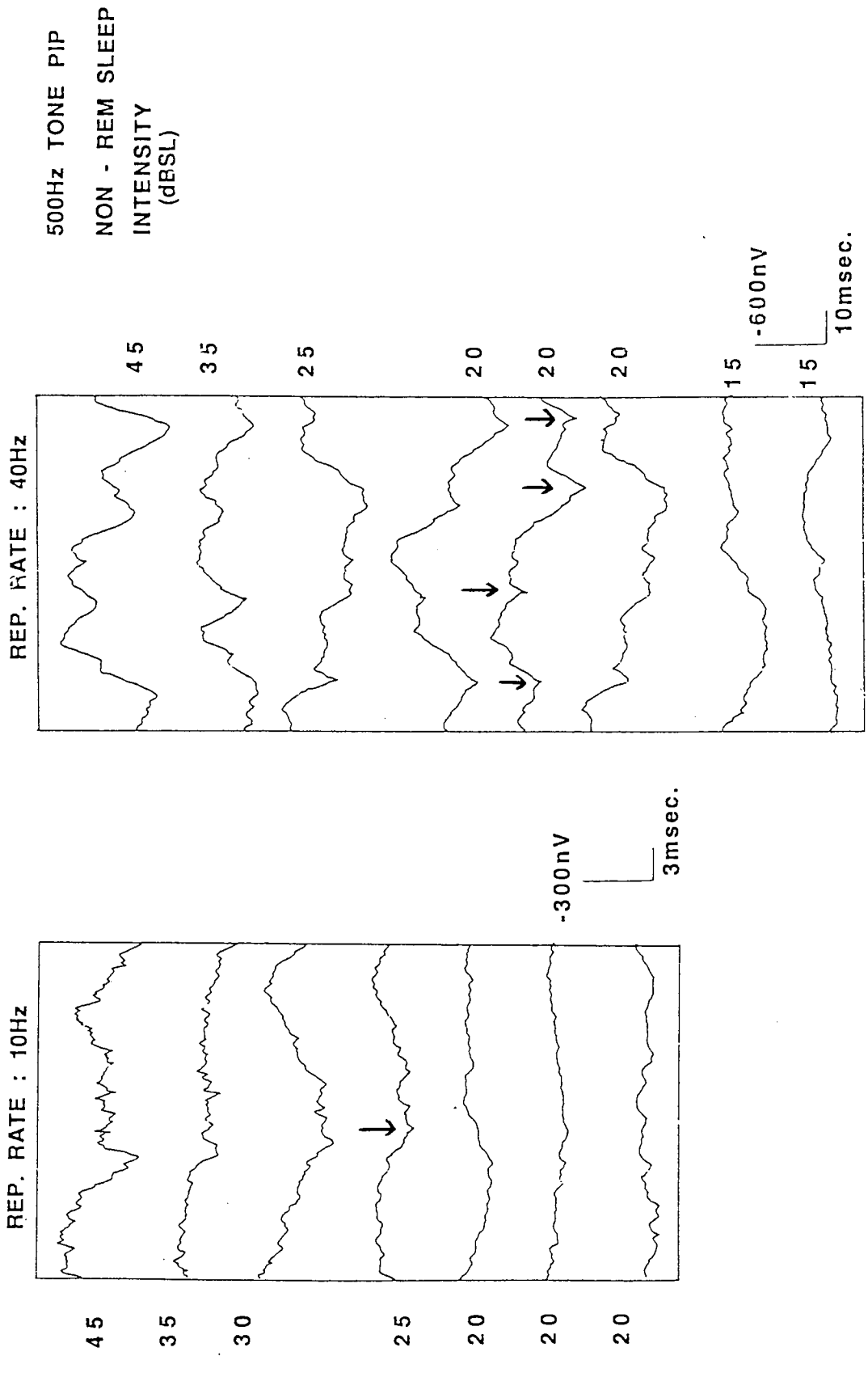

Figure 8.14 10Hz (30msec.) and 40Hz (100msec.) BAEPs in one subject using 500Hz tone pip stimulation.

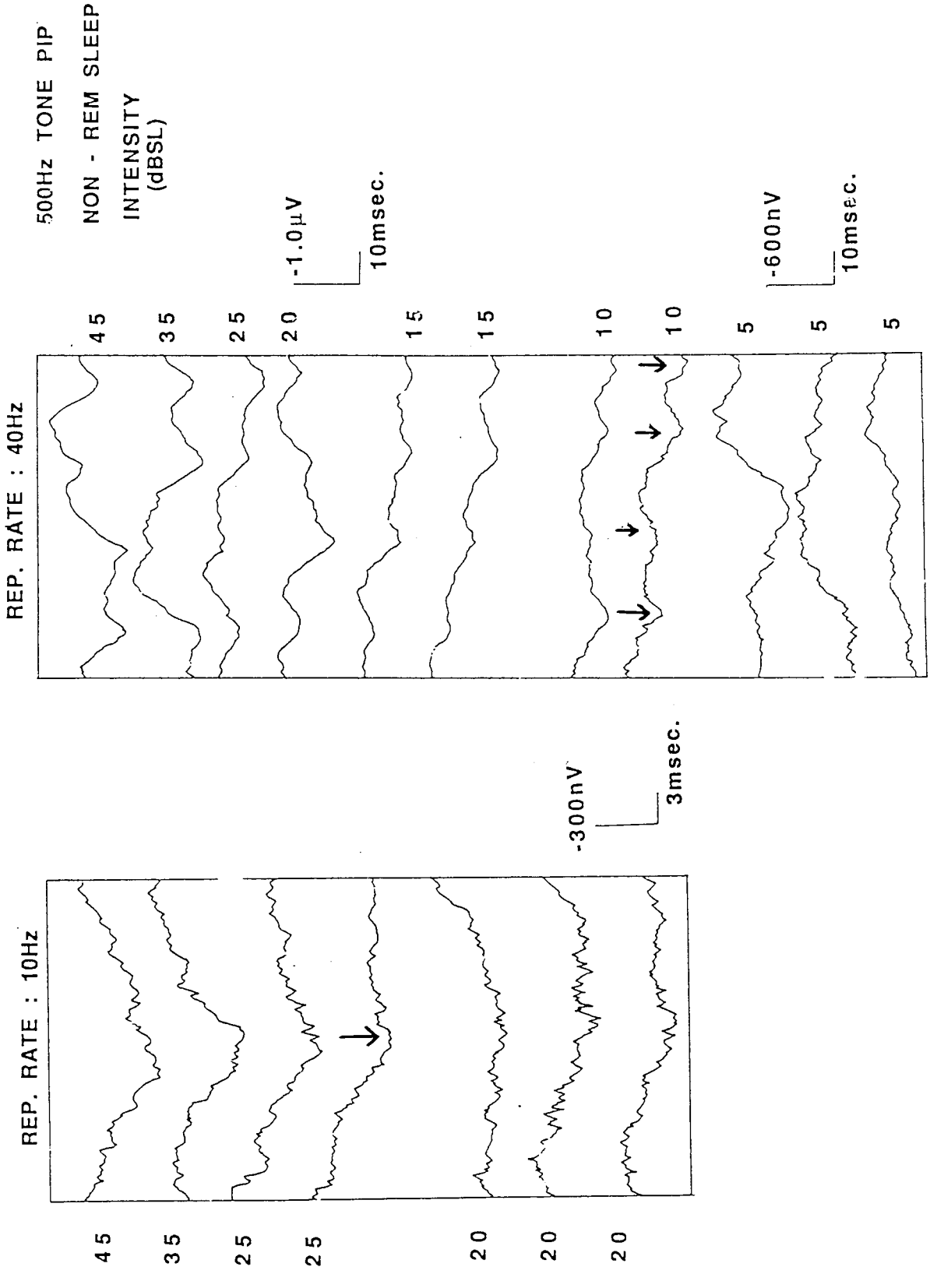

Figure 8.15 10Hz (30msec.) and 40Hz (100msec.) BAEPs in one subject using 500Hz tone pip stimulation.

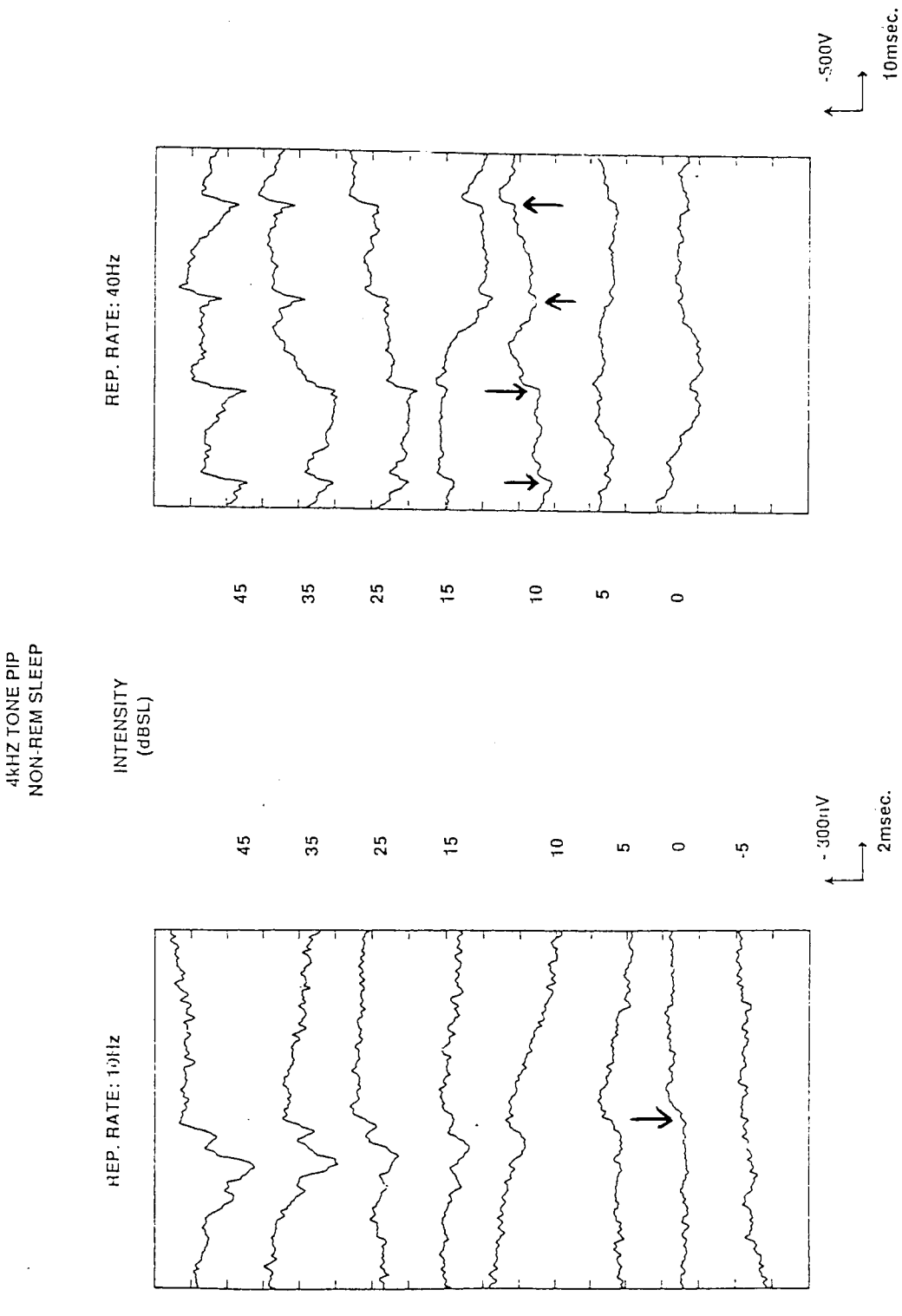

Figure 8.16 10Hz (30msec.) and 40Hz (100msec.) BAEPs in one subject using 4000Hz tone pip stimulation.

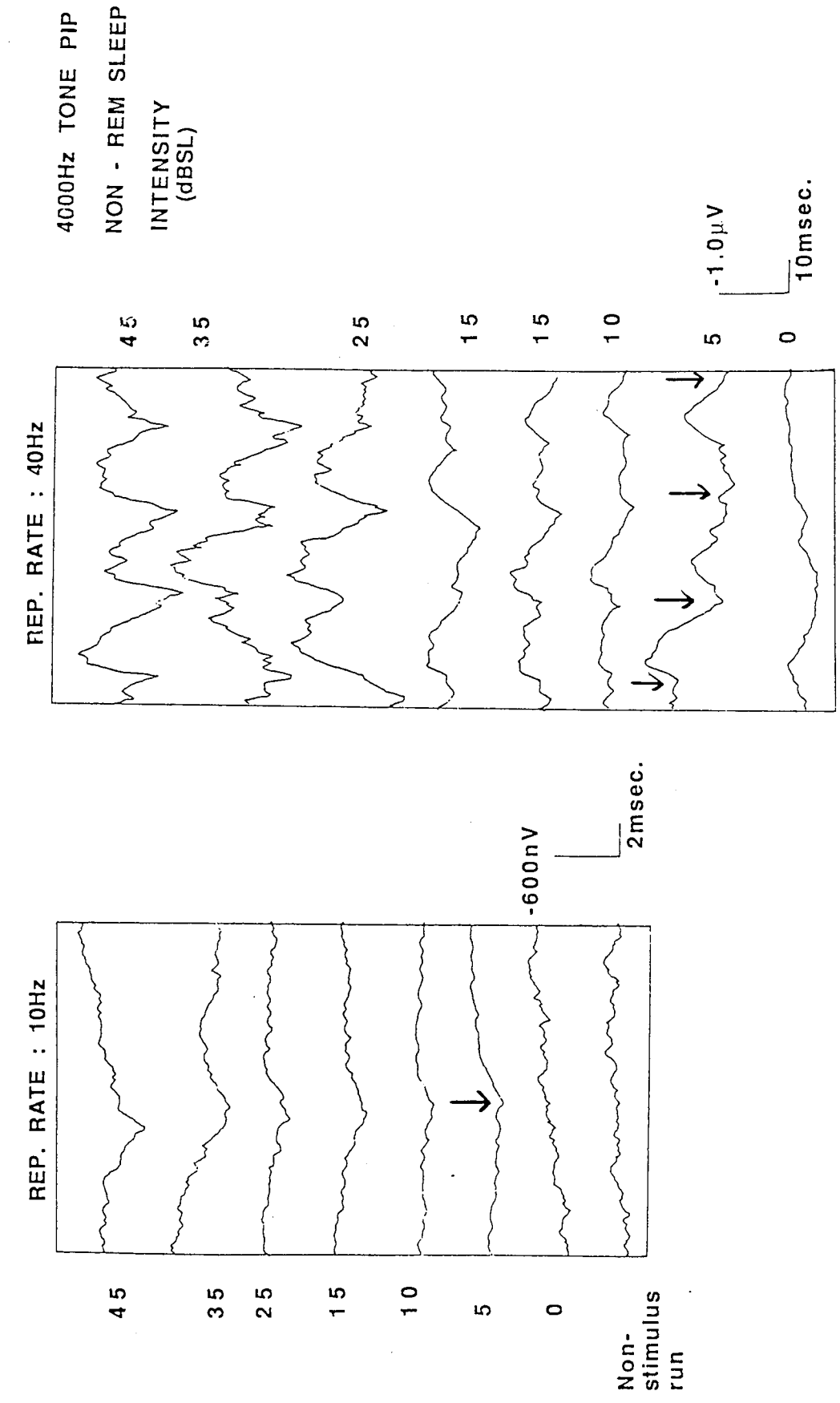

Figure 8.17 10Hz (30msec.) and 40Hz (100msec.) BAEPs in one subject using 4000Hz tone pip stimulation.

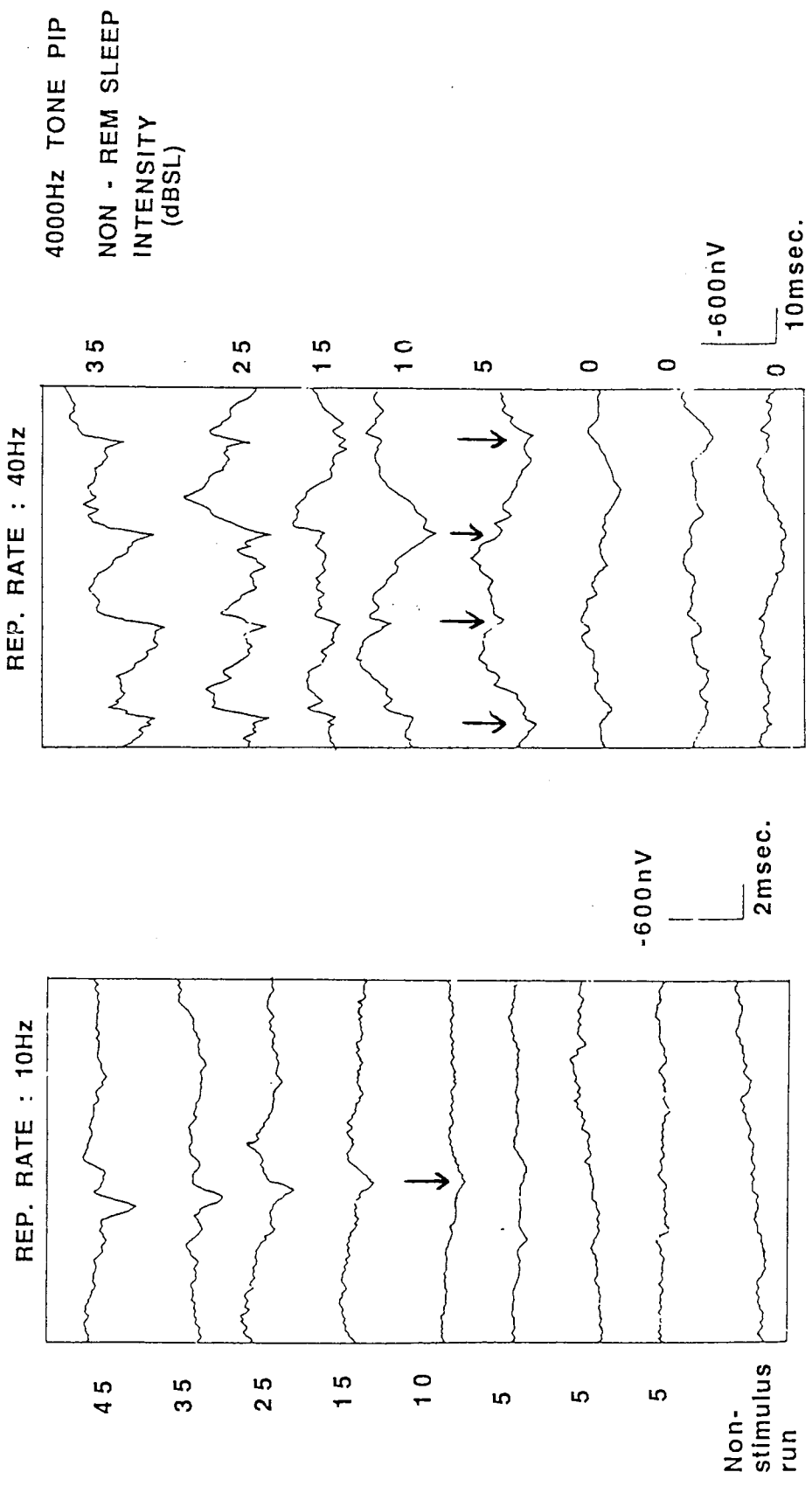

Figure 8.18 10Hz (30msec.) and 40Hz (100msec.) BAEPs in one subject using 4000Hz tone pip stimulation.

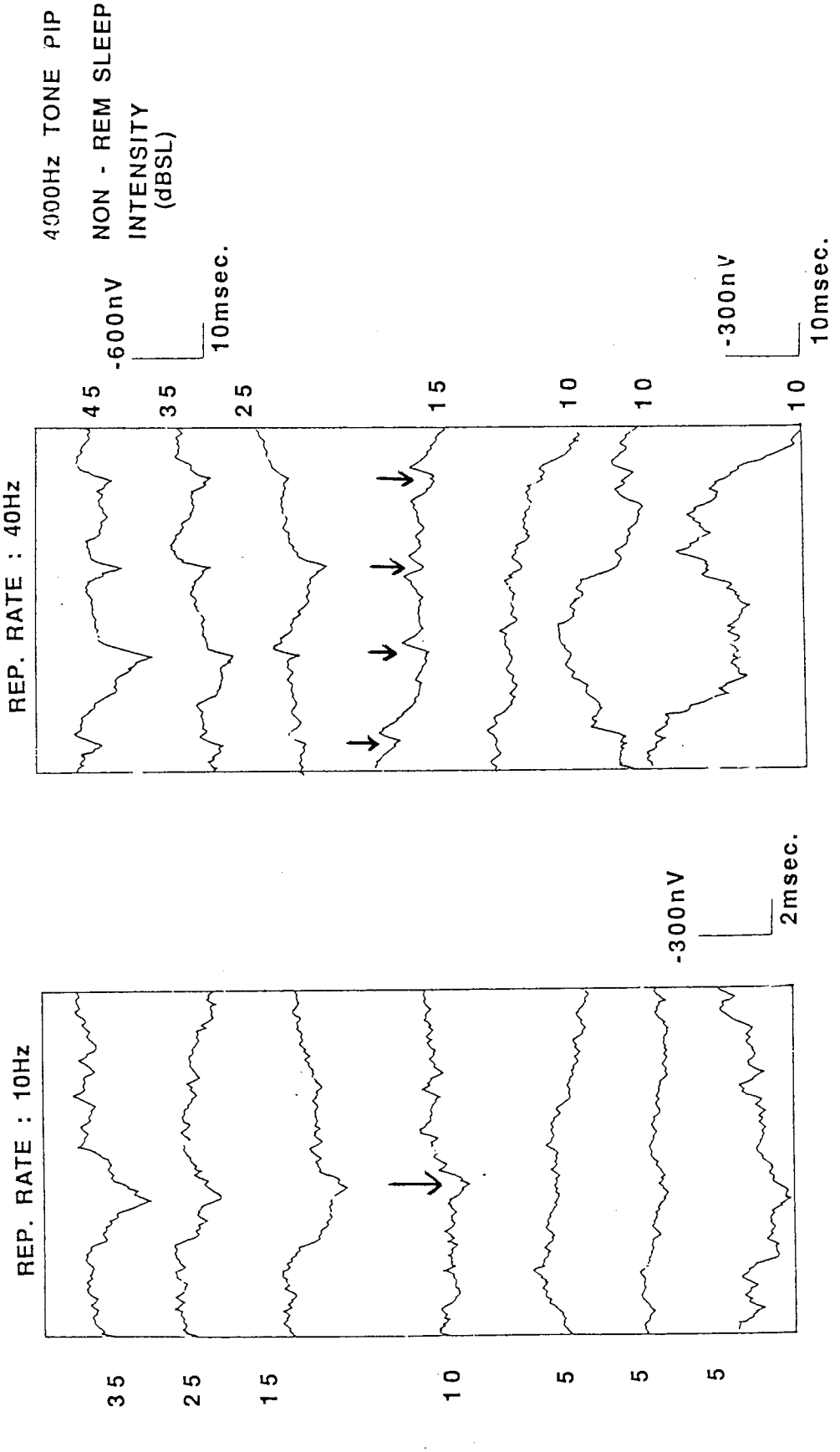

Figure 8.19 10Hz (30msec.) and 40Hz (100msec.) BAEPs in one subject using 4000Hz tone pip stimulation.

Subjective-objective
Threshold difference (dBSL)

500Hz tone pip

Subject	10Hz relaxed	10Hz Asleep	40Hz Asleep
1	-15	-10	-5
2	-15	-25	-10
3	-25	-20	-15
Mean	-18.3	-18.3	-10

4000Hz tone pip

Subject	10Hz relaxed	10Hz Asleep	40Hz Asleep
1	-15	-5	-5
2	-5	-10	-15
3	-20	0	-5
Mean	-13.3	-5	-8.3

Click

Subject	10Hz relaxed	10Hz Asleep	40Hz Asleep
1	-10	-5	-5
2	-5	-5	-5
3	-5	-5	-5
Mean	-6.6	-5	-5

Table 8.12 Combined subjective-objective thrshold differences for three subjects who took part in both experiments.

The reason for this poorer detectability of the tone pip responses compared with the click is primarily due to the less clearly defined response morphologies recorded with these stimuli. In addition, there is a less favourable signal to noise ratio encountered with tonal stimulation because the excitation of localised (frequency specific) regions of the basilar membrane activates a smaller population of neurons. Hence, these responses are smaller than when a click stimulus is used. Thus, at low stimulus intensities, the amplitude of the background activity has a greater influence over response detection, a point which emphasises the need for subject relaxation. The disruption of signal morphology in the presence of increased levels of background activity applies to all stimuli (click or tone pip), but is more evident in tone pip reponse recording than when a broad, non-frequency specific stimulus is used. This study suggested that audiometric threshold estimation gets progressively less accurate as the frequency of the stimulus decreases. Again this reflects the diametrically opposed aims of maximal amplitude and frequency specificity. The rise-times of the tone pip stimuli used in this experiment were 4 msec. for the 500Hz stimulus, 2 msec. at 1000Hz and 0.5 msec. for the 4000Hz stimulus respectively. The click stimulus' total duration was 0.1 msec. The necessary increase in ramp-time to ensure the removal of unwanted acoustic transients and high frequency contaminants serves to progressively decrease the degree of neural synchronisation of cochlear nerve fibres, hence resulting in the production of a smaller response.

Relating these findings to existing experimental literature, the results of this study are in broad agreement with other data. Table 8.13 compares the data presented here with previous research (Kodera et al., 1977; Davis et al., 1985). Kodera and colleagues found a similar correlation between subjective and objective thresholds to the data presented in this study at 1000Hz but a higher degree of accuracy for the 500Hz stimulus. The reduced variability of Kodera's data in comparison with this experiment may be explained in part by the small normative subject sample size (n=10). Davis et al. (1985) presents a large body of clinical data recorded from neonates and infants recorded in sedated sleep. Davis claims that the wave V-SN10 component of the BAEP can normally be recorded down to 10dBnHL to 4000, 2000,

Stimuli:	Click	Mean S-O threshold difference (dBSL) 4000Hz	2000Hz	1000Hz	500Hz
This Expt. n=20	-6.0 (±4.8)	-9.1 (±10.0)	---	-19.3 (±10.7)	-25.8 (±7.1)
Kodera et al. (1977) n=10	---	---	-16.5 (±3.2)	-16.5 (±3.9)	-15.5 (±3.5)
Davis et al. (1985) n=? S.D.=?	---	10dBnHL	10dBnHL	10dBnHL	10dBnHL

Table 8.13 Threshold data from this experiment compared to similar experiments by Kodera et al. (1977) and Davis et al. (1985). See text for details.

1000 and 500Hz stimuli in the majority of cases. The most noticeable methodological difference between the experimental procedures of Davis (1985) and Kodera (1977) and those used in this study is the use of sedation. Sedatives are used to induce sleep and thereby reduce the level of movement artefacts and myogenic activity present in recording. Sedation also helps to ensure a consistent state of relaxation throughout the experimental procedure in which subjects are sleeping continuously and are not prone to fluctuations in background activity. The use of sedation in BAEP recording is based on experiments which have shown that the response is not significantly altered by level of arousal (Amedeo and Shagass, 1973). Davis' data relates to threshold assessments made in children in whom sedation is essential. Kodera et al. (1977) recorded from sedated adult subjects. It was not possible to use sedatives in this experiment, principally due to ethical considerations and lack of qualified medical support necessary for the administration of drugs in research work. In addition, sedating adults in routine clinical practice is unnecessary because the slow vertex response and the 40Hz response are available for frequency specific objective testing.

In summary, the tone pip BAEP thresholds recorded in this experiment show results which are in broad agreement with other workers. The widest discrepancy between subjective and objective threshold is seen particularly with the 500Hz stimulus because the response at low stimulus intensities is of low amplitude and therefore hard to detect. The problem of low response amplitude with low frequency stimuli was re-examined using the 40Hz protocol in sleeping subjects.

These data show that there is little difference in threshold estimation using either 10Hz or 40Hz repetition rates with the click stimuli or the 4000Hz tone pips. However, with the 500Hz tones there is a consistant 5, 10 and even 15dB SL lower threshold estimate when the 40/ sec. repetition rate and 100 msec. analysis time are used in comparison to the more established 10/second procedure. This would appear to indicate that this procedure may be clinically superior for audiometric threshold determinations at this test frequency. This difference was exhibited in all four experimental subjects and reduced the mean threshold

estimate by 8dBSL in comparison with those obtained using the 10/sec. method. Examination of the 500Hz responses (Figs 8.12-8.15) reveals that the shorter analysis time and 10Hz stimulus repetition rate makes visualisation of the response less certain at low stimulus intensities. The possible reasons for the superiority of the 40Hz BAEP at this stimulus frequency are firstly, the 40Hz procedure (using a 100 msec. analysis time) generates a succession of four BAEPs within each sweep. This means that the experimenter is being given four chances to detect the presence of a response. The second advantage of the 40Hz procedure is the 'compression' of the response when viewed over 100 msec. making detection of the wave V- SN10 complex easier than when only 30 msec. of post-stimulus activity is recorded. These advantages appear to only apply to the 40Hz procedure when low frequency stimuli are used. With click or 4000Hz stimuli, the larger amplitude and higher frequency of the response makes detection at low stimulus intensities equally easy with either 10/sec. or 40/sec. methods. Therefore the 40Hz procedure as described in this chapter is indicated to be of comparable accuracy (though not superior) to the 10Hz technique at high stimulus frequencies.

8.61 Tone pip BAEP recording in the clinical setting and the detection of auditory pathology.

This experiment has examined the BAEP as it is recorded to click and tone pip stimuli in normal subjects. It is now necessary to consider how this information might be used to assist in the clinical diagnosis of auditory losses at different frequencies.

Firstly, it is important to understand that the clinical assessment of hearing capabilities either by subjective pure tone audiometry or objective BAEP measurement is based on the assumption that actual cochlea deficits will be manifested in one or both of these tests. It is true to say that changes in the BAEP from the normal and changes in the pure tone audiogram represent two aspects of the overall pathology, but to imply a causal link or direct

dependency of subjective and objective measurements is to over simplify two complex phenomena linking neurophysiological and perceptual processes (Hyde, 1985). A further problem is encountered when trying to relate normative data to responses obtained from patients in whom some auditory pathology is suspected. In normal ears, the tonotopic organisation of VIIIth nerve fibres from high frequencies at the basal turn to low frequencies at the apex, is well understood (Béksey, 1943). However, in pathological states, it is suggested that this fine tuning of auditory neurons is "blunted" and therefore the localisation of frequency specific stimuli upon the basilar membrane is altered (Gorga and Worthington, 1983). Having acknowledged these areas of uncertainty, the data collected in this experiment has indicated that frequency specific BAEPs can be obtained in normal subjects and the limits to which this can be applied to the clinical setting will now be examined.

Examination of the latency-intensity curves for click stimuli can provide information about three different types of hearing loss. Flat losses affecting a broad range of frequencies, steep hearing losses affecting high frequencies and also conductive losses reflecting the disruption of sound impulses through the middle ear with cochlea function intact. Considering flat hearing losses first, Hyde (1985) summarised the data of current authors (Galambos and Hecox, 1978; Yamada et al., 1979; Picton et al., 1981) concerning L - I functions in these patients. Figure 8.20a presents these data which also includes curves showing the effects of varing degrees of conductive losses. The solid lines (flat sensorineural losses) show that as the magnitude of the loss increases, there is an increase in the gradient of the L - I function with 60 and 80dB losses showing a deviation from the normal curve even at the highest stimulus intensities. In contrast, conductive losses of varying degree give rise to L - I curves which are elevated by the same amount at any given intensity, the level of this elevation depending on the severity of the hearing loss. A steep high frequency hearing loss has a different effect on the L- I function (wave V) generated to click stimuli (fig.8.20b). Evidence suggests that the magnitude of the difference between the normal and high frequency deficient cochlea is largest at high stimulus intensities and that this difference is reduced as stimulus intensity is lowered (Don and Eggermont, 1978). This is thought to be

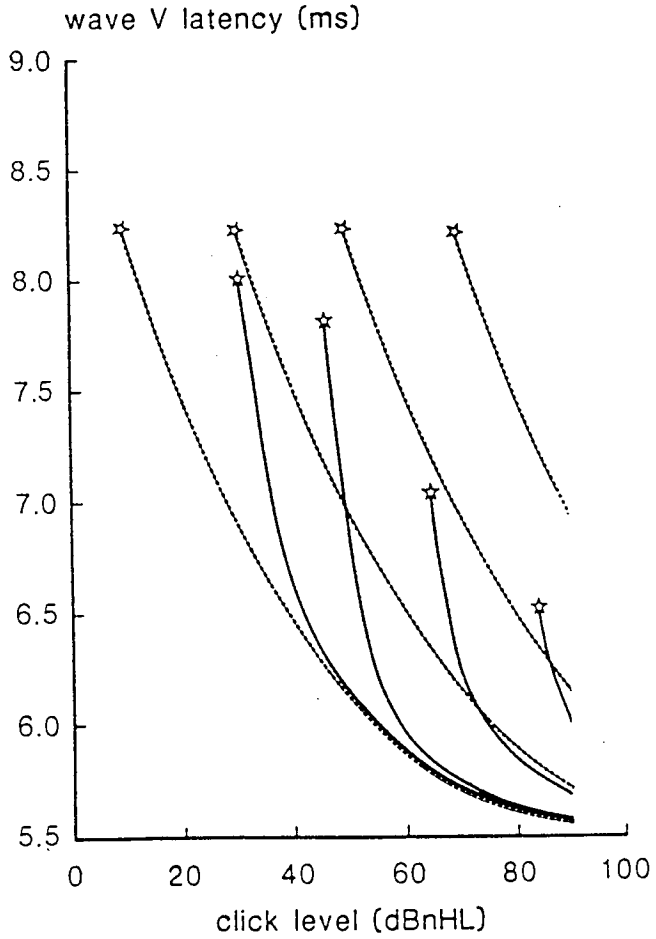

Figure 8.20a A model demonstrating the effect of flat hearing losses on the latency-intensity function for wave V (click stimuli). Dotted curves (left to right) normal ears and ears with 20, 40 and 60dB of flat conductive hearing loss. Solid curves (left to right) 20, 40, 60 and 80dB of flat cochlear hearing loss. BAEP thresholds starred. After Hyde (1985).

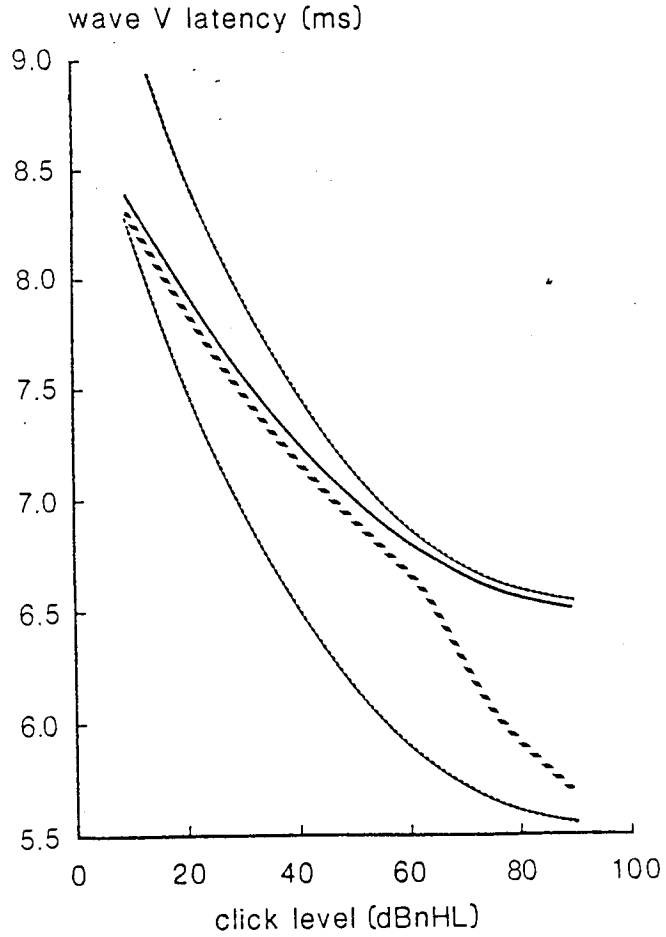

Figure 8.20b A model showing the effects of a high frequency hearing loss on the click latency-intensity curve for wave V. Upper dotted curve: constant latency increase associated with a precipitous high frequency loss. Solid curve: another form of loss which demonstrates a basal shift in cochlear excitation with increasing intensity. Heavy broken curve: possible effect of a moderate high frequency loss. After Hyde (1985).

due to lower intensity stimuli shifting the spread of stimulus energy to lower (unaffected) frequency regions of the basilar membrane. All the possibilities discussed above have been simplified and it should be stressed that data are often very hard to interpret.

Turning now to more frequency specific stimuli. This experiment has looked at the use of unmasked tone pips in generating BAEPs. More complex procedures now exist in which clicks and tones are embedded in masking noise in an attempt to restrict extraneous frequencies. These alternative procedures will be examined separately after the tone pip BAEP data obtained in this experiment has been discussed with respect to its usefulness in the clinical setting. With unmasked tone pip stimuli the most important question is the frequency specificity of the stimulus or more precisely, the *place* specificity of these stimuli upon the basilar membrane. Looking again at the latency - intensity curves (Fig. 8.9) it is apparent that smaller latency differences exist between the four stimuli at high intensity than at lower intensities. This is consistent with a higher degree of stimulus overlap (spread energy) at high intensity which reduces as the intensity decreases (Stapells et al., 1985). Figure 8.9 also shows that the click and the 4000Hz stimuli give rise to very similar L - I functions and that these differ from the 1000Hz curve which is also steeper (84μsec./dB compared with 40μsec./dB for the click) and displaced upwards on the graph. Similarly, the 500Hz curve gives the longest wave V latencies for any given stimulus intensity and has the steepest gradient (100μsec./dB). Stapells et al. (1985) demonstrated a latency - intensity function gradient for 1000Hz (2-1-2 msec.) stimulus of around 84μsec./dB which compares well with the estimate of this value in this experiment. This problem of energy spread at high intensity is not a major factor for determining thresholds in normal subjects because threshold values are sufficiently low to ensure that the stimulus is localised. In the clinical setting there is, however, a major difficulty because high intensity stimuli are necessary in order to elicit responses in defective cochleas and this may result in 'spectral splatter' between test frequencies. In order to confirm this, further experimentation is necessary in patients with known hearing losses in order to see if their auditory profile can be simulated using tone pip BAEPs.

8.62 Other methods of obtaining frequency specific BAEPs.

The preceding discussion has examined the use of unmasked clicks and tone pips in obtaining objective audiograms. Although tone pips show frequency specificity in normal subjects at low stimulus intensities, it is likely that the higher levels of stimulus presentation necessary to determine thresholds in ears with sensorineural hearing losses will cause significant energy spread away from their nominal frequency. This has been the rationale behind techniques which have embedded stimuli (clicks and tones) within masking noise in order to try and diminish the contributions of extraneous cochlear regions to the BAEP at a given frequency. Clicks delivered with notched noise is one such technique which presents masking noise in which one band of frequencies has been attenuated in conjunction with a standard click stimulus (Eggermont and Odenthal, 1974; Pratt and Bleich, 1982; Pratt et al., 1984; Stapells, 1984; van Zanten and Brocaar, 1984). According to these authors, this produces a stimulus with a frequency centered around the frequency of the notch whilst other extraneous frequencies contained within the click are attenuated. Results using this technique have been equivocal with some researchers (Pratt and Bleich, 1982) demonstrating an increase in wave V latency suggestive of frequency specificity with the notched noise paradigm in comparison with clicks presented alone. However, this increase in wave V latency was reported as constant regardless of the frequency of the notch. In contrast, van Zanten and Brocaar (1984) and Stapells (1984) have both reported around a 4 msec. increase in wave V latency as the frequency of the notch was decreased from 4000Hz to 500Hz. Methodological differences have been suggested for this apparent discrepency. In particular, the level (intensity) of masking, the choice of the width of the notch and the most suitable level at which the high pass filter is set. Visual inspection of the data presented in this experiment using unmasked tone pips revealed that the morphology of the tonal BAEP using the 500Hz stimulus is mainly composed of lower frequency waves which would be attenuated by a high pass filter of 100Hz as used by Pratt and Bleich (1982). The complexity of this technique, the length of time needed to record responses and the small amplitudes of responses means that this technique offers little clinical promise to date.

Derived band responses attempt to produce frequency specific BAEPs through the digital subtraction of successive responses to clicks recorded in conjunction with high pass noise with sequentially decreasing cut-off frequencies (Teas et al., 1962). Results have shown that the latency of wave V remains unchanged (in comparison with an unmasked click) with masking in excess of 400Hz but shows a systematic increase in latency (around 4 msec.) as the masking frequency is reduced down to 500Hz (Don and Eggermont, 1978; Parker and Thornton, 1978; Thümmler et al., 1981). This technique assumes that the masking will remove the cochlear response from the masked regions and leave unmasked regions unaffected and has been shown to be successful in modelling hearing losses in patient population (Don et al., 1979). The major problem with subtraction techniques is that the signal to noise ratio of responses derived in this way is reduced (noise increasing by a factor of around 1.4 per subtraction) and therefore the amplitude of the background EEG must be very low in order for these derived responses to be adequately visualised. Secondly, high levels of masking noise can induce temporary threshold shifts (Stapells, 1984). Lastly, the increased recording time necessary for the off-line response processing makes this procedure lengthy in the context of clinical recording. Derived responses have also been obtained using clicks in conjunction with tones (Berlin and Shearer, 1981; Pantev and Pantev, 1982). The rationale behind this technique is that the pure tones would activate frequency specific regions of the basilar membrane and therefore prevent their responding to the clicks. The derived response at a given frequency is then obtained by subtracting the combined click and tone response from the response obtained to the click alone. Similar problems exist with this procedure as with the derived technique described above (i.e. increases in response noise) and results to date remain equivocal.

The use of tone pips delivered alone has been discussed previously. However, other techniques have been developed which combine tone pip stimulation with masking noise. The advantage of using tone pips in notched noise rather than using clicks is that a lower level of masking is required in masking extraneous frequencies outside the desired notch with tones. Notched noise has been shown to have different effects on wave V latency with tones

of low and high frequency (Stapells, 1985). The latency of wave V to tones centred at 2000Hz and 4000Hz was found to be unchanged when presented with and without notched noise though amplitude was reduced in the former case. This is due to the reduced contribution of lower frequency activity with masking which removes the broad component upon which wave V is superimposed. Notched noise significantly increases wave V latency (in comparison with tones delivered alone) when 1000Hz and 500Hz tone pips are used. This is due to the delay induced for the stimulus to reach the apical cochlea and also the loss of higher frequency components of the BAEP which produces a broader wave V complex. This technique has proved successful in modelling hearing losses in patient populations (Picton et al., 1979) and results are also encouraging in children (Alberti et al., 1983; Stockard et al., 1983). Tones presented with high pass noise have also been used to generate BAEPs to low frequency tones with some success (Kileny, 1981; Jacobsen, 1983) though this technique is unsuitable for higher frequencies as there is an unacceptable spread of stimulus energy to lower frequency regions.

In summary, complex procedures using clicks and tones presented with masking have allowed the possibility of improved frequency specificity for the BAEP. Their complexity and the time required for their implementation has unfortunately limited their usage at present.

Of the techniques discussed above, the prevailing view currently is that tones presented with notched noise (20dBSPL) below the peak equivalent of the tone using a stimulus repetition rate of 40Hz and a filter bandpass of 20-2000Hz is optimally suited to recording tone pip BAEPs (Stapells et al., 1985). This response would contain both BAEP and MLR components in waking subjects which would increase response amplitude. However, during sleep, the contribution of the MLR would be markedly reduced (Kavanagh and Domico, 1986; Chapter 7 of this thesis).

8.7 CONCLUSIONS.

This experiment has attempted to further establish normative data for tone pip BAEPs within our Clinical Neurophysiology Unit at Aston University, it has shown that click and tone pip evoked BAEPs differ in terms of their morphology, the latency of components and most significantly, their accuracy in the assessment of objective, audiometric threshold. The morphology of the click BAEP is well established but tone pip responses possess fewer component peaks even at high stimulus intensities with the 1000Hz and 500Hz tone pip responses only possessing the broad wave V-SN10 peak in the majority of subjects. Latency of the response components is inversely related to stimulus frequency which necessitates the use of longer sweep times when viewing tone pip responses. Amplitude was found to be highly variable for all stimuli. The latency-intensity curves suggested that the 500Hz and 1000Hz tone pips were frequency specific at lower stimulus intensities (<40dBSL) and with respect to threshold assessments, the only reliable response component at low stimulus intensities was wave V. Threshold estimations were made for click and tone pip stimuli using conventional BAEP methodology and a 40Hz BAEP protocol. Conventional techniques demonstrated that the smallest differences between subjective and objective threshold were found with click stimuli. Tone pip threshold estimations were most accurate with the 4000Hz stimuli and least accurate with the 500Hz stimuli. The 40Hz BAEP protocol examined click, 4000Hz and 500Hz stimuli and compared threshold estimation using conventional techniques with those obtained using a 40Hz repetition rate and 100msec. time sweep during all-night sleep. Both procedures demonstrated similar threshold estimations for the click and 4000Hz stimuli, but the 40Hz BAEP protocol gave more accurate objective responses at 500Hz than the conventional technique. Although this is an interesting result, it is a preliminary finding and requires confirmation in a larger subject population.

CHAPTER 9

GENERAL DISCUSSION.

9.1 WHAT WERE THE AIMS OF THIS RESEARCH?

This thesis has examined the middle latency and 40Hz auditory evoked potentials. The characteristics of these responses have remained unclear over the three decades since their initial discovery and therefore their clinical utility has been undervalued in comparison with the BAEP and SVR. The aim of this research has thus been to consolidate our basic understanding of MLR and 40Hz and from this basis, suggest how they might be incorporated more widely into audiological electro-diagnosis. The area in which objective audiometry is most lacking is in the accurate frequency specific assessment of auditory threshold recordable at all levels of arousal. This requirement is most marked in the assessment of children and infants where sleep is usually a pre-requisite for testing. This project was undertaken to see if MLR and 40Hz could satisfy this clinical deficiency. As a result of the sleep study (chapter 7), the recording of tone pip BAEPs became the central area of interest owing to the discovery that the MLR was markedly attenuated in sleep and consequently of limited use in the measurement of hearing thresholds in sleeping subjects.

9.2 SUMMARY OF EXPERIMENTAL RESULTS.

The following two sections (9.2 and 9.3) will first summarise the main findings of this thesis and then compare the effectiveness of the various tests.

9.21 Comparing the SVR and 40Hz response in waking adults.

The first experimental chapter (6) was designed to assess the audiometric utility of the 40Hz response in comparison with the more clinically established slow vertex response (SVR). The findings of the study demonstrated that these tests measured audiometric threshold with an equal degree of reliability in alert, waking subjects. However, the data also showed a higher level of variability in both sets of responses than has previously been reported by other authors.

In searching for possible reasons to explain these findings, it was suggested that the choice of an unmotivated student population as subjects did not facilitate experimental compliance. Following on from this observation it was suggested that sitting and alert protocol perhaps was not optimal for recording the 40Hz response. Therefore, some further subjects were tested lying down in a state of relaxed wakefuness. This was found to reduce the subjective - objective threshold difference and improve the signal to noise ratio. This change in procedure made threshold estimations using the 40Hz response and SVR more alike though further work is indicated in order to test this hypothesis more fully.

The main finding from this experiment was that the SVR and 40Hz response may be used interchangeably in the majority of subjects. This implies that if one of these test yields an equivocal or inconclusive result, the other test may be considered as an alternative. Considering the established nature of the SVR and its high level of success in assessing adult hearing capabilities, it is suggested that this test be favoured initially and the 40Hz used (with confidence) in the small number of cases in which the SVR is unsuitable.

9.22 The effects of sleep and sleep stage on the MLR and 40Hz response.

The most significant finding to emerge from this research was the demonstration of clear changes in the MLR during sleep. All-night sleep recording using wide bandpass filters

showed that responses were different (in terms of morphology, latency and amplitude) in all stages of sleep compared to those recorded in relaxed wakefulness. The most marked changes were observed in slow wave sleep, where the later Nb component of the MLR was often seen to greatly reduce in amplitude or even disappear altogether. This had the effect of merging the Pa and Pb components into one broad positivity of intermediate latency in slow wave sleep (SWS). Middle latency responses recorded in REM sleep resembled more those recorded in wakefulness although of reduced amplitude.

These reported changes have serious consequences for the generation of the 40Hz response during sleep. In wakefulness, it is the inherent (40Hz) periodicity of the MLR which is responsible for producing the super-imposition of successive response averages in the 40Hz procedure. This research would therefore suggest that the 40Hz stimulus repetition rate is no longer suitable for generating a steady-state response during sleep, given that this periodicity is lost. The 40Hz response recorded in sleep consists predominantly of brainstem activity with components later than 20 msec. not contributing to waveform morphology.

The use of a 0.3 to 3000Hz filter bandpass was critical in the detection of these changes in the MLR and 40Hz response found during sleep. Narrow filter settings (such as those which have prevailed in much of the original MLR research) have a profound effect upon the morphology of the MLR. Limitations in the FFT software made it impossible to prove conclusively that the MLR is distorted by narrowing the filter bandpass, though comparison with previous literature would suggest that this is the case (Ozdamar and Kraus, 1983; Kavanagh and Domico, 1986). These results would have serious implications for the generation of the 40Hz response which does not appear to be 'steady-state' during slow wave sleep but rather a succession of brainstem components occurring every 25 msec. with middle latency activity attenuated to a minimum.

Although these findings have shown the precise nature of the MLR and 40Hz responses recorded in sleep, they are not necessarily recommendations for the optimum clinical strategy for recording these responses. Since the aim of clinical recording is response

detection at stimulus intensities near audiometric threshold, it has been argued that by removing low frequency activity the detectability of the MLR and 40Hz could be improved (Musiek et al., 1984; Suzuki et al., 1984; Kraus et al., 1987; McGee et al., 1988). This work confirms the variability present in the MLR during sleep but was unable to confirm the improved detectability of these responses using narrow bandpass filters without FFT filter manipulations. The 40Hz response imposes its own low frequency filter by virtue of the high stimulus repetition rate attenuating lower frequencies which means that highpass filter distortions have little influence over these potentials. Regardless of the filter bandpass chosen, the true physiological nature of the MLR and 40Hz response in sleep should not be forgotten: namely the MLR is changed significantly in sleep and the 40Hz response is a series of BAEPs with very little middle latency activity contributing to the response.

The conclusion that the only reliable components apparent in sleeping subjects were the BAEP with very little middle latency activity, led on to an examination of the possible audiometric utility of the BAEP as generated to tone pip stimuli. Chapter 8 sought to first investigate the characteristics of tone pip BAEPs (their morphology, latency, ampltitude and frequency specificity) and then assess frequency specific threshold assessments made with the BAEP: using established recording parameters and also a 40Hz BAEP procedure in sleeping subjects which arose out of the sleep experiment.

9.23 The characteristics of the tone pip BAEP and its role in frequency specific threshold assessment in relaxed wakefulness and in slow wave sleep.

The first part of chapter 8 described the characteristics of the tone pip BAEP (4000Hz , 1000Hz and 500Hz) and compared them to the click BAEP used as a control. Taking each of the tone pips in turn, at high stimulus intensities, the 4000Hz tone pip response resembled the click response (but did not possess wave IV), the component peaks of the response were longer than with the click and amplitude was equally variable with both

stimuli. The latency-intensity curves for click and 4000Hz stimuli were very similar over all stimulus intensities which suggests that the frequency specificity of these stimuli was similar. Using conventional BAEP techniques the mean subjective -objective threshold difference for the click stimulus in relaxed (awake) subjects was 6.0 (±4.8) and for the 4000Hz tone pip stimulus 9.11 (±10.0). This suggests that the 4000Hz tone pip offers no advantage over the click in this capacity. During all-night slow wave sleep, the click once again proved superior in the measurement of hearing thresholds at both 10Hz stimulus repetition rate (click =5dBSL difference, 4000Hz =6.3dBSL difference) and the 40Hz procedure (click=5dBSL difference, 4000HZ =8.75dBSL difference). The 1000Hz tone pip stimuli possessed only a broad wave V-SN10 complex even at high stimulus intensities and this component was of a longer latency than both the click and the 4000Hz response components. The latency-intensity curve for the 1000Hz tone pip had a steeper gradient than the higher frequency stimuli and the latency of the wave V-SN10 configuration was more than 2.5 standard deviations from the click and 4000Hz tone pip stimuli at intensities less than 40dBSL. This suggests that the 1000Hz tones were more frequency specific than the 4000Hz tone pips. Threshold measurements with the 1000Hz stimuli were wider than with the 4000Hz stimuli (1000Hz =19.3±7.1) using conventional BAEP methodology.

The wave V-SN10 component of the 500Hz tone pip responses was longer than for any other stimulus tested at the same intensity. At low intensities, the amplitude of this response was small and hard to define. The latency-intensity curve for the 500Hz tone pip stimuli was steepest of the four stimuli used and showed the greatest difference from the click stimulus particularly at low stimulus intensities. The threshold estimation using conventional BAEP techniques was 25.8dBSL (±7.1) but this was vastly improved using the 40Hz protocol during all-night sleep recording. The threshold difference for the 10Hz (conventional) protocol during sleep was 20dBSL compared with 12.5dBSL using the 40Hz procedure. Thus it appears that sleep induces around 5dBSL improvement in evoked response accuracy and the 40Hz protocol a further 7.5dBSL in comparison to conventional methods in relaxed (awake) subjects. It appears that this method of data acquisition was preferable to existing techniques as it allowed for a succession of

brainstem responses to be seen instead of just a single response. This seemed to be a considerable aid to visual response recognition at 500Hz especially with low levels of stimulus intensity. Further work is needed to corroborate this finding.

9.3 INTERCOMPARISON OF EXPERIMENTAL DATA.

One of the benefits of performing a series of experiments upon a fairly constant subject group, is that certain aspects of these data can be compared across experiments. In this way the SVR, the 40Hz response (both awake and sleeping) and the BAEP can be compared and their effectiveness judged in obtaining good asssessments of audiometric threshold. In table 9.1 group mean data is compared using 500Hz and 4000Hz tone pip stimulation and click stimuli. The procedures compared are the SVR and waking 40Hz response (chapter 6), the tone pip BAEP recorded to stimuli delivered at 10Hz repetition rate in both waking and sleeping subjects and the tone pip BAEP generated to the 40Hz procedure during sleep.

Table 9.1 Mean Subjective -Objective threshold differences for the various audiometric procedures used in this thesis.

	Procedure				
Stimulus	*SVR (alert) (n=21)*	*40Hz response (awake) (n=21)*	*10Hz BAEP (relaxed) (n=20)*	*10Hz BAEP (asleep) (n=4)*	*40Hz response (asleep) (n=4)*
500Hz tone pip	11.2 (±8.4)	14.8 (±9.8)	25.8 (±7.1)	20	12.5
4000Hz tone pip	11.7 (±11.0)	13.1 (±7.2)	9.11 (±10.0)	6.3	8.75
Click	-----	-----	6.0 (±4.8)	5.0	5.0

This table shows a generally good correlation to audiometric threshold for all tests with click stimuli and using 4000Hz tone pips. The most interesting finding is the improvement in 500Hz threshold estimation using the 40Hz BAEP procedure in sleeping subjects described in chapter 8 both over the 10Hz protocol and also the 40Hz response recorded

in waking subjects (chapter 6). The question now arises as to the clinical implications of the research.

Discussing ERA recording in waking subjects first. Considering the results presented in chapter 6, it would appear that the optimal test for the majority of waking adult subjects is the SVR. This long established procedure has proved to be reliable in most cases and provides accurate frequency specific information concerning hearing thresholds. This research and the findings of other workers has indicated that there are however a number of clinical (and normal) cases in which the SVR is unreliable. Such cases include drowsy subjects and those possessing large levels of alpha activity. In these instances, it would appear that the 40Hz response may be used with equal confidence thus providing the clinician with an alternative method of determining hearing thresholds at a range of frequencies. The 40Hz response is optimally recorded in subjects who are lying down comfortably in order to reduce myogenic artefacts to a minimum. This procedure is contrasted to those favoured for the SVR and therefore, if this response is proving inconclusive during an audiological investigation, the clinician is required to interrupt the recording procedure and instruct the subject to lie down before proceeding with 40Hz audiometry.

If, as decribed above, a patient is lying down in a very relaxed state, it is quite likely that drowsiness and even light sleep will ensue. How then will sleep effect the recording of middle latency and 40Hz responses? This question applies equally to audiometry in children and neonates in whom vertex response audiometry is inappropriate. Chapter 7 has conclusively shown that the MLR and 40Hz responses are not unchanged by level of arousal and all that is being recorded in the latter case is a series of brainstem evoked potentials. The possible exception to this is REM sleep when the later components of the MLR may again be seen. The transition into sleep does not however mean that recording using the 40Hz method must cease. Chapter 8 has indicated that the 40Hz BAEP may have a clinical advantage in facilitating detection of frequency specific responses near hearing threshold using lower stimulus frequencies (500Hz) which up until now have proved the most difficult to test using existing techniques. This work has shown that it is

incorrect to term the 40Hz response a *steady-state* potential in sleep and that this phenomena only occurs in waking subjects.

In the research environment, the length of time an experimental procedure demands is not a crucial factor. However, in the interests of efficiency in the clinical setting, maximum information concerning auditory integrity must be obtained in a relatively short period of time. A compromise must therefore be reached between the desire for a detailed clinical profile and the necessary speed of data aquisition. In the light of the results presented in this thesis, the following clinical strategies are suggested in order to obtain frequency specific audiological information.

In adult testing, the SVR is the test of choice providing the clearest, most precise profile of hearing thresholds at different frequencies. Multi- frequency, bilateral testing is possible using the SVR in around two hours in cooperative, waking and alert patients. Should slow vertex potentials prove inaccurate, then the patient may be lain down, told to completely relax or sleep if possible and tested using the 40Hz procedure. The 40Hz response will represent a super-imposition of combined BAEP and MLR activity in waking subjects but a succession of BAEPs in patients that have drifted into sleep. In either case, the 40Hz procedure is able to provide frequency specific information concerning hearing capabilities in suitably relaxed subjects.

In children and neonatal ERA, the key audiological questions are firstly, is the patient deaf? secondly, if so, to what extent? and thirdly, is the hearing loss manifest throughout the entire frequency range or are some 'windows of hearing' preserved? In the great majority of patients, these questions must be answered in sleeping or sedated states. Therefore, the first test of choice for assessing basic audiological functioning is the click evoked BAEP. This test has been shown to be very accurate in reflecting general cochlear functioning. Frequency specificity is also possible using the tonal BAEP but experimental procedures must be adapted in order to visualise the responses. These modifications include viewing 20 or 30 msec. of post-stimulus time instead of the more commonly used 10 msec. for click recording and ensuring the systems bandwidth is wide enough to

include the lower frequency activity prevalent in tonal response recording. Once again, the 40Hz protocol may be an advantage when attempting to assess low frequency hearing capabilities. By viewing 100 msec. of post-stimulus time and stimulating at 40/sec. this research has suggested that it is easier to detect the four BAEPs which are subsequently generated, particularly at low stimulus intensities.

Using frequency specific stimuli in the manner described above, it is suggested that bilateral testing at 500Hz taken in conjunction with the click evoked responses (giving information in the >2000Hz range) could provide an improved clinical profile of hearing capabilities.

9.4 LIMITATIONS OF THIS DATA AND SUGGESTIONS FOR FUTURE WORK.

What cautionary factors must be considered when interpreting the results of these experiments? The most significant limitation was the inevitably small sample sizes in the sleep studies considering the nature of the experiments. These investigations required a total of 150 hours of data acquisition time for the fourteen subjects tested. Constraints of time meant that testing a greater number of people was not feasible. Therefore, in order to strengthen the conclusions drawn from this thesis it is intended to further this research and increase the subject database. In the other experiments (6 and 8), it was possible to use larger subject numbers ($n \geq 20$) as the procedures were not as time consuming (around 2.5 - 3.0 hours/subject). The fact that only four subjects were tested using the 40Hz BAEP protocol means that necessarily this data must be viewed with reservations. As a preliminary study, this work indicated that threshold assessments at 500Hz may be improved using this technique but further work is required in order to confirm or reject this result.

In the light of experimental findings, it would be desirable to conduct future normative work on a broader subject population than simply members of the student body. Members of

the general public (both normally hearing and clinical referrals) tend to have a higher degree of incentive to comply with the experimental requirements of evoked response audiometry. This incentive might be financial or simply borne out of a higher level of compliance within a laboratory environment. Student subjects are a non-representative group of the public in general and without such incentives, tend to become bored and uncooperative more easily.

In addition to strengthening the normative subject database, the next logical step in this area of research is to test the accuracy of frequency specific audiometric assessment using tonal brainstem responses and the 40Hz BAEP procedure in a clinical population of known aetiology. Adult subjects with established hearing losses could be examined in order to test the usefulness of these techniques in comparison with the more established methods (SVR). The development of techniques tested in normal subjects must be validated in clinical populations because of the different properties of defective neurons in sensorineurally impaired cochleas (Gorga and Worthington, 1983). Furthermore, it is important to realise that high stimulus intensities are required when testing deaf ears and this means that frequency specificity of tone pip stimuli may be reduced as indicated by the latency-intensity curves shown in chapter 8. Secondly, sedated children could be assessed using tone pip BAEPs in order to validate the accuracy of these responses in children with no history of auditory abnormality and also those in whom hearing difficulties are suspected. However, this would be more problematic in a child population since no subjective baseline is available with which to compare objective responses. Chapter 8 also described alternative techniques for obtaining frequency specific stimuli involving the use of complex stimuli combining masking noise with the stimulus. It would be interesting in future work to explore the use of these techniques both in terms of their accuracy in measuring hearing thresholds and also their clinical feasibility (ie the time required to record responses).

This thesis also reported changes in the MLR during sleep. These changes appeared to be most noticeable in stage 2 and combined stage 3 and 4 sleep. The loss of the later components of the MLR resulted in what appeared to a be a change in the frequency

composition of the response which had not been reported previously because of the use of narrow bandpass filters. It was the initial intention to use FFT procedures in order to confirm the changes in the frequency composition of the MLR during sleep. However, software limitations made this impossible and therefore, future work will seek to rectify these problems in order that frequency analyses can take place. The FFT can also provide additional methods of analysing the 40Hz steady-state response (as recorded in waking subjects). Phase measurements and in particular phase coherence can provide important information about the 40Hz response and may be a superior method of analysing these responses than relying on visual inspection alone (Jerger et al., 1986; Stapells et al., 1988).

The effects of various anaesthetics upon the components of the middle latency response were discussed in chapter 7. It would be interesting to study the morphology of the MLR in sedated patients and to relate response morphology to level of arousal and depth of anaesthesia. Any selective effects of different anaesthetics could also be studied continuing a currently developing area of research into the MLR (Duncan et al., 1979; Rabe et al., 1980; Cohen et al., 1982; Dubois et al., 1982; Thornton et al., 1983, 1984, 1985, 1987; Prosser and Arslan, 1985; Schmitt and Chraemmer- Jorgensen, 1986). The work of Thornton and colleagues in particular may warrant re-examination in view of the findings presented in this thesis and the reports of other workers (Kavanagh and Domico, 1986). Thornton has reported the presence of later peaks within the MLR under anaesthesia with various inhalation agents (see above references). However, the bandpass consistently chosen for this research by these authors is 25-3600Hz. In the light of the work laid out in this thesis, the choice of a 25Hz highpass filter may be masking physiological changes in the MLR brought about by sleep and sedation. If this were the case, then the reported existence of later components within the MLR may be the result of non-physiological distortions masking the 10Hz component of this response which this thesis suggests is prominent during non-REM sleep. Further work is therefore indicated in order to confirm or refute these findings.

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APPENDICES.

APPENDIX 1

Chapter 7: RAW DATA

The following data presents the individual values of latency and amplitude for wave V and all measurable components of the MLR during wakefulness, stage 2, stage 3/4 sleep and REM sleep using click, 500Hz and 4000Hz stimuli. In all the tables, LAT denotes latency (msec.) and AMP denotes amplitude (nV). Amplitude measurements for the 40Hz response are also included. The values for standard deviation were rounded off to 2 significant figures in all calculations.

			AWAKE									
	Y		Na		Pa			Nb		Pb		
Click 5Hz	LAT		LAT	AMP Y-Na	LAT	AMP Na-Pa	LAT		AMP Pa-Nb	LAT		
JW	7.2		19.6	812	33.6	-896	40.4		266	49.6		
TP	6.4		18.4	770	28.8	-1730	42.8		1130	58.4		
JG	6.8		16.4	630	33.6	-1000	46		322	62		
MD	7.2		20.4	630	32.8	-686	43.6		196	53.2		
MB	8.8		20.8	434	31.2	-686	43.6		378	58		
MR	8.8		21.2	826	32.4	-784	47.6		756	60		
DT	6.8		18.4	1000	31.6	-994	42.8		448	54.8		
PF	6.8		23.2	672	32.8	-1240	45.2		546	58.4		
AE	6.8		19.2	798	28.8	-546	38.4		644	51.2		
AH	6.8		18.4	980	28.8	-938	41.6		126	55.6		
Mean	7.24		19.6	755.2	31.44	-950	43.2		481.2	56.12		
St. Dev.	0.8089499		1.7977764	161.92393	1.8693314	320.96106	2.5549951		286.01986	3.7525458		

Individual latency and amplitude measurements for click stimuli in waking subjects.

AMP Nb-Pb	Nc LAT	AMP Pb-Nc	Pc LAT	AMP Nc-Pc
-350				
-1300				
-952				
-350	67.2	448		
-462	69.2	896	84.4	-1160
-560				
-378	70	938		
-322				
-1630				
-840				
-714.4	68.8	760.66667	84.4	-1160
432.86746	1.1775681	221.75261	0	0

Individual latency and amplitude measurements for click stimuli in waking subjects cont.

			Stage 2 sleep				
		V	Na		Pa		
Click 5Hz	LAT		LAT	AMP V-Na	LAT	AMP Na-Pa	
JW	8.4		17.6	462	39.6	-994	
TP	6.4		20	112	31.2	-1940	
JG							
MD	8.4		24.4	266	40	-812	
MB	6.8		21.2	420			
MR	6.4		20.8	504	35.6	-952	
DT	7.2		21.2	140	31.6	-1000	
PF	6.8		22.4	518	33.2	-826	
AE	6.4		20.4	1160	30.4	-1050	
AH	7.2		22	1520	42	-1700	
Mean	7.1111111		21.111111	566.88889	35.45	-1159.25	
St. Dev.	0.7489911		1.7463896	444.57431	4.2470578	393.88696	

Individual latency and amplitude measurements for click stimuli in subjects in stage 2 sleep.

Nb LAT	AMP Pa-Nb	Pb LAT	AMP Nb-Pb
54.4	742		
54	1410		
42.4	168		
42.8	406	57.2	-700
48.4	681.5	57.2	-700
5.8034473	467.42780	0	0

Individual latency and amplitude measurements for click stimuli in subjects in stage 2 sleep cont.

			Stage 3/4									
		Y		Na		Pa		Nb		Pb		
Click 5Hz	LAT		LAT	AMP Y-Na	LAT	AMP Na-Pa	LAT	AMP Pa-Nb	LAT			
JW	9.6		23.6	560	38.4	-518						
TP	6.4		21.6	700	37.6	-1800						
JG	7.2		16.4	406	32.4	-938						
MD												
MB	6.8		23.6	420	38.4	-658						
MR	6.8		22.4	588	33.2	-826						
DT	8		23.6	154	41.6	-854						
PF	6.8		24.4	546	40.8	-826						
AE	6.4		20.8	364	41.2	-2110		42.8		-28		62.8
AH												
Mean	7.25		22.05	467.25	37.95	-1066.25		42.8		-28		62.8
St. Dev.	1.00871211		2.4119494	157.45138	3.2768125	532.91504		0		0		0

Individual latency and amplitude measurements for click stimuli in subjects in stage 3/4 sleep.

			Stage REM			
			Na		Pa	
Click 5Hz	LAT		LAT	AMP W-Na	LAT	AMP Na-Pa
JW	8.4		19.2	196	34.8	-1230
TP	6.4		20.4	168	30.8	-1700
JG						
MD						
MB	7.2		21.6	784	34.8	-644
MR						
DT						
PF	6.8		22.4	672	32.4	-1
AE	6.8		21.2	952	30.8	-658
AH	6.4		18.4	1330	42	-1660
Mean	7		20.533333	683.66667	34.266667	-982.1667
St. Dev.	0.6831301		1.3792107	408.99946	3.8273867	608.04233

Individual latency and amplitude measurements for click stimuli in subjects in REM sleep.

Nb		Pb		
LAT	AMP Pa-Nb	LAT		AMP Nb-Pb
43.2	71.4	58		-882
46	112	60.4		-434
46	672			
41.6	434	58.4		-1440
57.6	70	72.8		-560
46.88	400.4	62.4		-829
5.6193950	270.39941	6.0728906		388.75314

Individual latency and amplitude measurements for click stimuli in subjects in REM sleep cont.

			AWAKE				
			Na			Pa	
	Y						
500Hz 5Hz	LAT		LAT	AMP Y-Na	LAT	AMP Na-Pa	
1 JW	13.2		27.6	728	35.2	-112	
2 TP	10.4		22.4	896	34.8	-1330	
3 JG	10.8		23.2	574	34.4	-476	
4 MD	10.8		24.4	784	34	-812	
5 MB	10.8		24.8	392	34.8	-658	
6 MR	10		23.6	378	34.4	-504	
7 DT	11.2		23.2	532	32.8	-714	
8 PF	10.4		24	504	36.8	-546	
9 AE	10.8		24	700	33.2	-994	
10 AH							
Mean	10.933333		24.133333	609.77778	34.488889	-682.8889	
St. Dev.	0.8640988		1.3984118	168.01440	1.0958958	325.44958	

Individual latency and amplitude measurements for 500Hz stimuli in waking subjects.

Pb LAT		Nc LAT	AMP Nb-Pb		AMP Pb-Nc	Nb LAT	AMP Pa-Nb
62.4			-1050			42	112
63.6			-1120			46.8	588
64			-798			48	-126
55.6			-574			46.8	392
56.8			-994			44	518
64.4			-1030			44	28
59.2			-490		71.2	308	47.6	448
61.6			-518			50.4	70
54			-322			43.6	756
60.177778			-766.2222		71.2	308	45.911111	309.55556
3.6907626			278.95749		0	0	2.5141574	281.19867

Individual latency and amplitude measurements for 500Hz stimuli in waking subjects cont.

			Stage 2 sleep				
	Y		Na		Pa		
500Hz 5Hz	LAT		LAT	AMP Y-Na	LAT	AMP Na-Pa	
JW	14.4		30	20	42.8	-810	
TP	10.8		23.6	20	38.4	-2180	
JG	10.8		23.2	588	38.8	-1210	
MD	9.6		28.4	28	52.4	-826	
MB	10.4				40.4	-686	
MR	9.6		24.8	300	38.6	-840	
DT	11.6		27.2	406	48	-1800	
PF	11.2		26	238	40.4	-924	
AE	11.2		25.2	230	36.8	-710	
AH	10		23.2	140	44.8	-2430	
Mean	10.96		25.733333	218.88889	42.14	-1241.6	
St. Dev.	1.3169662		2.2627417	182.60367	4.6836311	617.91119	

Individual latency and amplitude measurements for 500Hz stimuli in subjects in stage 2 sleep.

Nb		Pb	
LAT	AMP Pa-Nb	LAT	AMP Nb-Pb
55.2	1800		
50	0	59.2	-406
46.8	20	56	-350
50.666667	606.66667	57.6	-378
3.4615347	843.85359	1.6	28

Individual latency and amplitude measurements for 500Hz stimuli in subjects in stage 2 sleep cont.

			Stage 3/4				
		Y	Na		Pa		
500Hz 5Hz	LAT	LAT	AMP Y-Na	LAT	AMP Na-Pa		
JW	14			36.4	-518		
TP	9.2	24.4	532	40	-1900		
JG	10.8	28	700	38.8	-630		
MD	11.6						
MB	10.4	24.8	84				
MR	11.6	24.8	-240	47.6	-2340		
DT	12.4	29.6	154	49.2	-924		
PF	10.8	27.2	322				
AE	11.2	24.8	252				
AH	10.4	25.6	420	45.2	-1510		
Mean	11.24	26.15	278	42.866667	-1303.667		
St. Dev.	1.2322337	1.7769356	270.81174	4.7352109	669.25572		

Individual latency and amplitude measurements for 500Hz stimuli in subjects in stage 3/4 sleep.

		Stage REM				
	W	Na		Pa		
500Hz 5Hz	LAT	LAT	AMP W-Na	LAT	AMP Na-Pa	
JW	14.4	30.4	42	40.4	-490	
TP	9.6	23.6	672	34.8	-1680	
JG						
MD						
MB	10.4	24.8	476	32.6	-238	
MR						
DT	11.6	28.4	994	36	-448	
PF						
AE	10.8	24.4	1240	32.4	-378	
AH	10	25.6	644	42	-574	
Mean	11.1333333	26.2	678	36.366667	-634.6667	
St. Dev.	1.5902481	2.4083189	379.07607	3.6631802	478.78272	

Individual latency and amplitude measurements for 500Hz stimuli in subjects in REM sleep.

Nb LAT		Pb AMP Pa-Nb	LAT	AMP Nb-Pb
47.2		168		
42.8		266	58.8	-490
43.6		490		
44.533333		308	58.8	-490
1.9136933		134.76894	0	0

Individual latency and amplitude measurements for 500Hz stimuli in subjects in REM sleep cont.

			AWAKE				
		Y	Na		Pa		
	4KHz 5Hz	LAT	LAT	AMP Y-Na	LAT	AMP Na-Pa	
1	JW	8.4	19.2	420	28.8	-840	
2	TP	6.8	21.6	532	29.6	-728	
3	JG	7.2	17.6	672	29.6	-784	
4	MD	8.8	20.8	364	31.2	-756	
5	MB	7.6	21.6	1270	30.4	-924	
6	MR	6.8	20.4	1230	30	-952	
7	DT	7.2	19.6	644	28.8	-756	
8	PF	7.6	20.8	-154	30.8	-56	
9	AE	7.2	21.2	672	29.6	-910	
10	AH						
	Mean	7.5111111	20.311111	627.77778	29.866667	-745.1111	
	St. Dev.	0.6471209	1.2332833	409.93164	0.7774603	255.58493	

Individual latency and amplitude measurements for 4000Hz stimuli in waking subjects.

		Pb			Nc			
Nb		AMP Pa-Nb	LAT	AMP Nb-Pb	LAT	AMP Pb-Nc		
LAT								
	38.4	420	53.2	-266	71.2	42		
	39.2	1030	55.6	-1120				
	42.8	308	54	-252				
	40.8	616	53.6	-448				
	43.6	826	54	-686				
	41.2	630	52.8	-336				
	40.4	224	51.6	-252				
	42.8	28	56.4	-462				
	42	518	53.6	-616				
	41.244444	522.5	53.866667	-523.25	71.2	42		
	1.6378245	306.11068	1.3466007	268.19571	0	0		

Individual latency and amplitude measurements for 4000Hz stimuli in waking subjects cont.

			Stage 2 sleep								
		Y	Na		Pa			Nb			
4kHz 5Hz	LAT		LAT	AMP Y-Na	LAT	AMP Na-Pa	LAT		AMP Pa-Nb		
JW		8	19.6	378	37.2	-588					
TP		6.8	22	-224	32.4	-1170		48.4	1190		
JG		7.2	20	504	33.6	-966					
MD		8.8									
MB		8	20	14	38.8	-1070					
MR		6.8	20.4	280	35.6	-994					
DT		7.6	22.8	392	40.4	-952					
PF		7.2	23.2	252	37.2	-714					
AE		7.2	20.8	434	33.2	-1000					
AH		6.8	19.6	520	42	-2980					
Mean		7.44	20.933333	283.33333	36.711111	-1159.333		48.4	1190		
St. Dev.		0.6248200	1.3063945	230.72254	3.1313627	665.06073		0	0		

Individual latency and amplitude measurements for 4000Hz stimuli in subjects in stage 2 sleep.

			Stage 3/4				
			Na		Pa		
	Y		LAT	AMP Y-Na	LAT	AMP Na-Pa	
4kHz 5Hz	LAT						
JW	12						
TP	6.8		21.2	518	33.2	-1070	
JG	7.2		22.4	-98	30.8	-448	
MD	7.6		23.2	574	39.2	-714	
MB	8		22	392	32.4	-448	
MR							
DT	8.4		24	350	44.8	-868	
PF	7.2		21.2	504	33.6	-532	
AE	6.8		18.4	280	33.2	-1230	
AH							
Mean	8		21.771429	360	35.314286	-758.5714	
St. Dev.	1.6		1.6679451	210.02857	4.5642801	287.21264	

Individual latency and amplitude measurements for 4000Hz stimuli in subjects in stage 3/4 sleep .

Nb LAT	AMP Pa-Nb	Pb LAT	AMP Nb-Pb
49.2	-28		
44.5	-420	59.6	-840
46.85	-224	59.6	-840
2.35	196	0	0

Individual latency and amplitude measurements for 4000Hz stimuli in subjects in stage 3/4 sleep cont.

		Stage REM					
			Na		Pa		
	N		LAT	AMP N-Na	LAT	AMP Na-Pa	
4kHz 5Hz	LAT						
JW	8.8	18		196	28.8	-336	
TP	6.8	20.4		308	29.6	-938	
JG		24.4		490	37.2	-336	
MD	8	21.2		574	29.6	-280	
MB	8						
MR		22.8		406	28.8	-196	
DT	8	22		630	32	-196	
PF	7.2	19.6		784	31.2	-714	
AE	7.2	19.2		574	28.8	-462	
AH	6.8	20.95		495.25	30.75	-432.25	
Mean	7.6	1.9487175		175.55038	2.6790857	247.33265	
St. Dev.	0.6633250						

Individual latency and amplitude measurements for 4000Hz stimuli in subjects in REM sleep.

Nb LAT	AMP Pa-Nb	Pb LAT	AMP Nb-Pb	Nc LAT	AMP Pb-Nc
44.8	336				
41.6	728				
46	280				
48	266		-252		238
43.6	350	54.8	-434	76.4	196
44.4	238	59.6	-350	65.2	217
42.4	70	54	-345.3333	70.8	21
44.4	324	56.133333	74.374428	5.6	
2.0057061	185.64482	2.4729649			

Individual latency and amplitude measurements for 4000Hz stimuli in subjects in REM sleep cont.

Significant t-test values				
1. Click stimulus				
Na component				
	Latency		Amplitude	
	t	Sig.	t	Sig.
Wake-S3/4	3.97	0.0054	2.95	0.02
S2-S3/4	3.54	0.0122	-	-
Pa component				
Wake-S2	2.72	0.0296	-	-
Wake-S3/4	3.89	0.006	-	-
Significant t-test values				
2. 500Hz stimulus				
Na component				
	Latency		Amplitude	
	t	Sig.	t	Sig.
Wake-S2	3.99	0.005	3.37	0.01
Wake-S3/4	3.01	0.023	3.51	0.01
Pa component				
Wake-S2	3.92	0.004	2.84	0.02
Wake-S3/4	2.82	0.04	-	-
Significant t-test values				
3. 4000Hz stimulus				
Pa component				
	Latency			
	t	Sig.		
Wake-S2	6.02	0.0005		
Wake-S3/4	2.71	0.03		

Significant values of Students t-test and level of significance for latency and amplitude of the Na and Pa components of the 5Hz MLR comparing different states of arousal for all stimuli.

	Cl	W	S2	S3/4	REM
1	TP	1.775	1.7	1.25	
2	AE	1.875	1.1	1.03	1.08
3	JG	1.525			
4	MD	.95	.65	.6	.75
5	MB	1.45	.85	.85	.525
6	MR	1.775	.9		
7	PF	1.725	.7	1.3	1.15
8	DT	1.875	.9	.925	
9	AH	1.525	.6	.6	1.3
10	JW		.35	.325	

Amplitude of the 40Hz response at different levels of arousal using click stimuli. Each value is the average of the four component peaks of the response.(uV)

300Hz	W 500Hz	S2 500Hz	S3/4 500Hz	REM 500Hz
JW	1.025			.35
MR	1.475	.975		
JG	1	.35		
MD	.725	.4	.375	.325
PF	1.425	.65	.425	
TP	1.175	1.575	1.05	1.25
MB	1.125	.5	.425	.475
DT	1.225	.725	.425	
AH	.825	.925	.55	.775
AE	.725	.525	.3	.525

Amplitude of the 40Hz response at different levels of arousal using 500Hz stimuli. Each value is the average of the four component peaks of the response. (uV)

4kHz	W 4kHz	S2 4kHz	S3/4 4kHz	REM 4kHz
JW	1.025	.4	.2	.625
TP	1.375	.85	.75	.9
JG	.85	.725	.5	
MD	.75	.7	.625	.575
MB	.95	.5		.35
MR	.7	.525		
PF	1	.775	.725	.75
DT	1.05	.7	.625	.675
AE	1.475	.7	.575	.75
AH	.875	1.125	.85	.825

Amplitude of the 40Hz response at different levels of arousal using 4000Hz stimuli. Each value is the average of the four component peaks of the response.(uV)

APPENDIX 2

SUPPORTING PUBLICATIONS..

1. JONES, L.A. and BAXTER, R.J. (1988) Changes in the auditory middle latency responses during all-night sleep recording. Br. J. Audiol. 22: 279-285.

2. BAXTER, R.J. and JONES, L.A.(1988) Changes in the auditory middle latency responses during all-night sleep recording. Electroenceph. Clin. Neurophysiol. 69 (4): 74P.

3. BAXTER, R.J. and JONES, L.A. (1988) The effect of sleep stage on the morphology and threshold determination of the auditory middle latency responses. 19th Int. Congr. Audiol. Jerusalem, Israel. (Int. Soc. Audiol.). Unpublished abstract.

British Journal of Audiology, 1988, **22**, 279–285

Changes in the auditory middle latency responses during all-night sleep recording

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(*Received 25 January 1988, and in revised form 15 April 1988*)

CHANGES IN THE AUDITORY MIDDLE LATENCY RESPONSES DURING ALL-NIGHT SLEEP RECORDING.

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THE EFFECT OF SLEEP STAGE ON MORPHOLOGY AND THRESHOLD DETERMINATION OF THE AUDITORY MIDDLE LATENCY RESPONSES.

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