AGE RELATED CHANGES IN MLR

REG. NO.M9612

An Independent Project submitted as part fulfilment of First Year M.Sc, (Speech and Hearing), Mysore.

All India Institute of Speech and Hearing, Mysore

May 1997

DEDICATED TO

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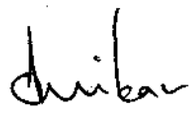
CERTIFICATE

This is to certify that this Independent Project entitled **AGE RELATED CHANGES IN MLR** is the bonafide work in part fulfilment for the degree of Master of science (Speech and Hearing) of the student with Register No.M9612.



Mysore
May, 1997

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CERTIFICATE

This is to certify that this Independent Project entitled AGE RELATED CHANGES IN MLR has been prepared under my supervision and guidance.

Mysore
May, 1997

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DECLARATION

This Independent Project entitled AGE RELATED CHANGES IN MLR is the result of my own study under the guidance of Mrs.Vanaja C.s. Lecturer in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore and has not been submitted earlier at any University for any other diploma or degree.

Mysore
May, 1997 Reg. No.M9612

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INTRODUCTION

Along with the progress in science and technology, the methods involved in audiological testing have also progressed a great way, starting from the simple pure tone audiometry to the recent more sophisticated approaches such as measurement of oto-acoustic emissions and auditory evoked potentials.

Auditory evoked potentials (AEPs) are used in the assessment and monitoring of audiologic, otologic and neurologic disorders. Although clinical use is still evolving, these are methods that promise to provide more focal information about site/level of lesion.

In general it is expected that AEP measurement, methods and procedures will continue to develop and be refined as knowledge of the AEP generators expands and as clinical needs evolve. The auditory evoked potentials can be sub-divided on the basis of where and when they occur. When a signal is introduced into the ear there are immediate electrical responses in the inner ear. As the signal is propagated along the auditory pathway, more time elapses between introduction of a stimulus and occurrence of the response. Early AEPs that occur in the first 10 milli secs, after the introduction Of a signal are believed to originate in the

brain stem and are called auditory brain stem response. AEPS occurring from 10 to 50 millisecs in latency are called auditory middle latency response (MLR) and probably originate in the auditory cortex (Geisler, et al. 1958).

Picton, et al. (1974) described the various components of the human auditory evoked potentials including the MLR. The MLR is characterized by several scalp or vertex negative and positive peaks (as shown inFig. 1) including N18 (Na), P30 (Pa) and P50 (Pb or P1). The approximate interpeak latency of the most prominent peak of the ABR (Wave V) and Pa is 25 ms. (Goldstein and Rodman, 1967).

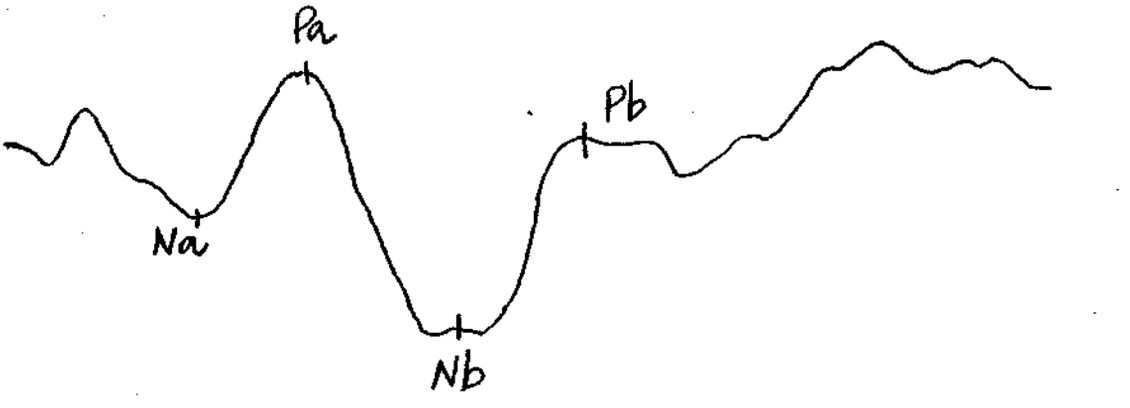


FIG 1

Researcher's argue over the fact that MLR may be of neurogenic or myogenic origin. In addition to the neural generators, several scalp muscles produce sonomotor reflexes that may contribute to the MLR. At relatively high stimulus intensities, several reflexes originating from scalp musculature occur within a post stimulus latency range of 7.50 ms. Therefore Bickford, et al. (1964) concluded that MLR was a purely myogenlc rather than mixed or neurogenic scalp-recorded response. However, Geisler (1964) felt that only the amplitude of the response was affected by muscle and that the basic of the response was neural.

In 1983, Kilen, et al. observed that MLRs at a moderate intensity level (60 dB nHL) ere usually not associated with a postauricular muscle reflex in 12 patients. Muscle paralysis induced by pancuronium brought about minimal changes in MLR configuration and peak latencies.

The variables affecting MLR can be grouped as factors related to stimuli, procedure and subject. Some of the variables related to stimuli are type, frequency, intensity, number of stimuli and rate of stimuli. Recording parameters include place of electrode and filter characteristics. Subject related factors include age, gender, sleep, drugs, anaesthesia and muscle tone.

It appears that response filtering, stimulus repetition rate and sleep stage all significantly influence the amplitude, latency and/or the detectability of Pa in children (Kraus, et al. 1987).

MLR is less dependent than the ABR on neural synchrony, (Vivion, et al. 1980). MLR has advantages in the clinical assessment of low frequency hearing, since those nerve fibres show poorer synchrony.

It has been demonstrated in adults that the MLR will accurately reflect low frequency hearing thresholds (Zerlin and Naunton, 1974).

MLR in children, is of chief interest, however, because an accurate electrophysiologic measure of low frequency hearing thresholds is essential to the appropriate management of hearing loss in children too young to be tested by behavioral audiometric methods. MLR can also be used clinically in the assessment of cochlear implant function, the assessment of auditory pathway function and the localisation of auditory pathway lesions.

It is of utmost importance that normative data are collected before using the MLR on clinical population as a lot of variables can affect MLR. Many attempts have been made to compare MLR waveforms of neonates, young children and adults. Numerous studies have demonstrated that the MLR is obtained inconsistently in children (Engel, 1971; Skinner and Glattke, 1977; Okitsu, 1984; Hirabayashi, 1979; Suzuki, et al. 1983 a; Kraus, et al. 1985; Stapells, et al. 1988). Most of these studies have focussed on wave Pa, which is reliable and robust in adults.

From birth to adolescence, the detectability of wave Pa increases monotonically, from 20% at birth to 90% at 12 years of age (Kraus, et al. 1985).

The response follows a systematic developmental course, and the trend of increased detectability with age exists regardless of whether the child is normally developing or has any of a wide range of neurologic, cognitive, or speech and language disorders. A trend of increased MLR detectability with age has also been observed in the more controlled context of an animal model (Kraus, et al. 1987; Kraus, 1988). Thus both human and animal data suggest that a systematic developmental process underlies the detectability of MLR waves.

Generators involving the primary auditory thalamus cortical pathway are responsible for the robust MLR typically seen in adults and are always active {Kraus, et al. 1988). Other inconsistently active generators such as the reticular formation and the non-primary auditory pathway also contribute to the response. Without the primary pathway contribution the response comes and goes depending upon the patient's level of alertness.

In adults, it is the primary thalamo - cortical pathway, that imparts stability to the response, making it consistently detectable regardless of sleep stage. In children, this system is only partially developed, not reaching maturity until puberty. The observed MLR is then dominated by the other, more labile generators. There is evidence that myelinization of the human thalamo-cortical pathway and sensory cortex continues untilpuberty (Yakovlev and Lecours, 1967; Rabinowicz et al. 1977).

The systematic development of MLR components observed in humans is consistent with such a maturational process (Kraus, Smith, and Reed, 1985). Therefore development of the temporal lobe and the auditory thalamo-cortical pathway may account for increases in detectability with age.

Clinical Utility

The MLR is used clinically in the electrophysiologic determination of hearing thresholds in the lower frequency range. It is used as a measure of establishing threshold because of its frequency specificity. It has been established that the MLR threshold will be within 10-30 dBnHL of behavioural measure (Madell and Goldstein, 1972; Vivion, Wolf, Goldstein, et al. 1979; Frye-Osier, Vivion et al. 1980). It has been demonstrated in adults that the MLR will accurately reflect low frequency hearing thresholds (Zerlin and Naunton, 1974; Scherg and Volk, 1983). MLR in children is of chief interest, however, since an accurate electrophysiologic measure of low frequency hearing the holds is essential to the appropriate management of hearing loss in children too young to be tested by behavioural audiometric methods.

MLR can also be used as a means of neurootological diagnosis. It gives us information about the integrity of auditory pathways when considered along with other auditory evoked potentials.

The hearing-impaired show a slight increase in amplitude and reduction in latencies of MLR, according to McFarland et

al. (1977); Robinson and Rudge (1977) reported significant latency delays but no amplitude abnormalities in multiple sclerosis patients. A normal Pa component was noticed in bilateral temporal lobe infarction (Parring et al. 1980). MLR in mentally handicapped does not show any significant differences in detect ability of Na and Pa but BR has better repeatability in such cases (Smith et al. 1983).

Harker and Backoff (1981) while studying acoustic neuroma cases, noticed a general increase in latency. The cases with large tumors showed low false negative responses compared to cases with small tumors. So these researchers suggest that MLR can be used as a predictive tool for size of tumors.

MLR can also be used as an objective index of cochlear implant function (Gurali, 1985). Electrical MLR is providing useful with cochlear implant patients in the pre-operative assessment of surviving neural elements of the central auditory system and as an objective measure of threshold and comfort level settings post-operatively.

The present study aims at studying age related variations in MLR waveforms, comparing young normal children with adults.

The present study aims at studying :

1. The amplitude, latency and morphology of the MLR waveform at various intensities of the MLR waveform.

2. Comparing the MLR waveforms of normal young children (7-10 years) and adults (18-35 years).

REVIEW OF LITERATURE

The middle latency response (MLR) was one of the first auditory evoked potentials to be discovered. Monitoring of spontaneous bio-electric activity from the central nervous system and recording this from the human scalp was first described by Berger (1929). After ten years Davis gave effects of auditory stimulation on human brain wave (Davis, 1939). These effects were termed as electroencephalic responses. The process of extracting stimulus related bio-electric events from the ongoing EEG activity set the stage for future clinical development in various aspects of what was called as electric response audiometry (ERA) by Davis (1976).

Classification (Davis and Owen (1985) have classified AEP based on their latency and origin as

Response	Latency range	Origin
Cochlear	0-4 msec	Cochlea
Early	2-15 msec	Cranial nerve VIII and brain stem
Middle	15-50 msec	Brainstem, mid-brain and cortex
Late	50-300 msec	Primary and secondary auditory cortex

One of the important auditory evoked responses is the middle latency response. The AMLR is observed in a time

period between about 12 msec, and 50 msec. As typically recorded with one non-inverting electrode on the scalp of the head (in the midline at the vertex or high forehead location, or on the side of the head approximately midway between the ear and the vertex) and another (inverting) electrode near the ear(s), AMLR waves appear with positive voltage plotted upward. Following nomenclature introduced by Goldstein (1967), each positive voltage wave is labeled with an upper case "P" and each negative voltage wave is labeled with an upper case "N". The sequence of waves is denoted alphabetically in lower case (eg. Na, Pa, Nb and Pb). This system for labeling AMLR waves is now almost universal. Some AMLR waveforms will show a small positive wave before Pa, usually labelled "Po". It is likely that Po is actually not a true component in the AMLR - that is, not a neurogenic component (arising from the nervous system), but rather a reflection of postauricular muscle activity (Goldstein, 1967).

Although auditory components in the EEG were discovered earlier using rather simple superimposition methods, the AMLR was the first AER to be recorded with computer averaging techniques (Geisler, Frishkopf and Rosenblith, 1958).

Geisler et al. (1958) said MLR originated from the cortex. They came to this conclusion because of the following reasons. Repeated evaluation in the same subject gives the same results :

- MLR can be recorded from a wide area of scalp.
- Bilateral response is evoked even on a monoaural stimulation.
- Symmetrical placement of electrodes show same response.
- Latencies are comparable to onset latency of somatosensory and visual systems.

Ruhm et al. (1967) recorded MLRs from the exposed cerebral cortex of humans and found MLRs with similar intensity and morphological characteristics. They said this indicate that MLR is a neurogenic response. Harket et al. (1967); Celesia et al. (1968), Celesia and Puletta (1969, 1971) support these findings.

Rome (1981) listed a few reasons as to the non-agreement about site of origin.

- The electrodes are placed away from the neural generators
- Ipsilateral and contralateral pathway are present.

- Simultaneous activity of generators.
- Overlapping activity of multiple sites.

All these factors would make it difficult to come to a decision about the exact point of origin of MLR in the brain.

A large number of studies have been carried out on humans (Wood and Woolpaw, 1952; Vaugha and Ritter, 1970; Picton, et al. 1974; Celesia, 1976; Picton, et al. 1974; Celesia, 1976; Goff et al. 1977; Cohen, 1982; Ozdamar and Stein, 1982; Ozdamar et al. 1982) and on animals (Arezzo et al. 1975; Kaga et al. 1980; Norman et al. 1981) to determine the area of origin of MLR. However a general consensus is still lacking.

Geisler et al. (1958); Picton et al. (1974); Davis (1976b) report origin of earlier components of MLR that is No, Po, Na to be the medial geniculate body and poly sensory nuclei of thalamus while later portions originate from a wide area of association cortex. Okitsu et al. (1977) say that origin of peak Po may be different from that of the later Na and Pa. Picton and Smith (1978) found similarity between animal cortical responses and human MLRs which reflect activation of thalamus and cerebral cortex.

Buchwald et al. (1981) localised origin of Pa to medial rostral, mid brain retlicular formation and projection of thalamus. Po was localized to primary auditory cortex. Hashimoto (1982) attributed the origin of No, Po, Na to post synaptic activity from inferior colliculus. When multiple coronal electrode array was used, Pa was found to be at the level of sylvian fissure. This is suggestive of a dipole source in the superior temporal plane (Cohen, 1982). Kaga et al. (1980) in an experiment with animals showed the anterior part of contralateral primary auditory cortex to be the generator site of Pa. Even though Pa is widespread over human scalp, latencies may slightly differ for different electrode locations. If hemispheric asymmetry is seen, it may indicate some diagnostic condition (Kraus, et al. 1982). Amplitude of Na and No were found to be evenly distributed across surface of head by Paccioretti et al. 1987).

Uchida et al. (1979) conducted an experiment in cats under general anaesthesia. The effect of unilateral and bilateral median geniculate body destruction was noted. According to them, the generation of MLR is from upper level of superior colliculus. The Na component is due to contralateral median geniculate body (MGB) while Pa is a compound response from a wide area.

FACTORS AFFECTING MLR

There are two types of parameters which affect the MLRs. They are exogenous factors and endogenous factors. Exogenous factors are - factors which are related to stimuli, instrument used for the test and recording parameters like filter characteristics etc. Endogenous factors are subject related factors such as sleep, drugs, anaesthesia, muscle tone etc.

Stimulus related factors are -

1. Type of stimulus
2. Intensity of stimulus
3. Frequency of stimulus
4. Number of stimulus
5. Rate of stimulus presentation
6. Rise-fall time and duration

Types of stimuli

There are different stimuli using which MLR can be elicited. They are tone pips, tone bursts, filtered clicks, unfiltered clicks, logans etc.

The initial studies of MLR were carried out using clicks as stimuli. Zerlin et al. (1971) advocated the use of l/3rd octave filter clicks. They reported that filtered clicks elicited clearer waveforms than tone burst. Zerlin and Naunton (1974); Zerlin, et . al. (1973); have reported that clicks evoke greater amplitude changes compared to tone burst. Kilney and Shea (1986) found that clicks evoked well defined and easily identifiable MLR. Also the amplitude of Na and Pa were larger than when tone bursts were used.

On the other hand Kupperman and Mendel (1974) preferred use of gated tone bursts with a rise time of 2.5 msec and a duration of 2 msec. Using either of these stimuli, that is, filtered clicks or gated tone bursts, it was possible to obtain frequency specific stimuli in the range of 500-8000 Hz.

Maurizi et al. (1984) compared MLR waveforms of tone pips and clicks. The results indicated that tone pips provided more frequency specificity than clicks. Pa, Na, Pb and Nb showed greater latency but smaller amplitude for tone pips. This they attributed to asynchrony of response evoked by tone pips.

Tonal stimuli are found to give frequency specific responses compared to clicks (Moushegian, et al. 1973; Kupperman and Mendel, 1974; McFarland, et al. 1977; Thornton, et al. 1977). Low frequency tone bursts are found effective in obtaining response from adults who are awake (Musiek and Geurkink, 1981).

Electrical stimulation can also be used for recording. No significant difference between latencies of electrically and acoustically evoked waveforms in guinea pigs have been reported (Burton, Miller, and Kileny, 1989). In profoundly deaf ears electric MLRs were present. Latency of most prominent positive peak was similar around 20-30 ms. to the latency of acoustic MLR (Kemink, Kileny and Arbon, 1989).

Intensity of **the** stimulus :

As the stimulus intensity increases, amplitude of the MLR wave increases (Goldstein and Rodman, 1967; Mendel, 1974; Thornton, et al. 1974; Picton et al. 1977). Ozdamar and Kraus (1983) reported that amplitude of middle component levels off at about 50-60 dB. Goldstein and Rodman (1967) found that though the latencies appeared stable the peaks become less well defined as the stimulus intensity reached threshold. Kupperman and Mendel (1974) reported of absence

of systematic growth in amplitude with an increase in intensity of tone pipes.

At higher intensity levels, the waveform may change suddenly. Thornton (1975) has attributed this to inclusion of myogenic components.

Frequency of stimulus :

Clicks do not seem to yield as distinct a middle latency response as do tone bursts (Kiang, et al. 1963; Bickford et al. 1964).

Latency for each peak reduces with increased stimulus frequencies. Further, linear changes in amplitude are noted for early peaks with increase in stimulus frequency.

Kupperman (1970) demonstrated that the middle component was more dependent on the stimulus type, than the stimulus frequency.

Rise-fall time duration

MLR is considered an 'onset' response, i.e. it depends upon the onset of stimulus. Use of faster rise time gives

more consistent and clearer responses. Skinner and Antinoro (1971) found that rise time greater than 25 msec, did not produce suitable response.

Clicks have a faster rise time than tone pips or tone bursts. They elicit waveforms which have larger amplitudes (Zerlin et al., 1973; Zerlin and Naunton, 1974).

There is no effect on MLR waveform with change in decay time as it is a "on response".

Kupperman and Goldstein (1974) used a 1000 Hz, 50 dB SL tone burst, rise times of 5, 10, 15 and 25 msec with duration of 20-40 msec, were used. The early components of MLR are not affected by a combination but later waves show an increase in amplitude when 25 msec, rise-decay time was used.

When the rise-day time or duration was increased, latency rised of 1-3 msec was noticed for all MLR peaks. At the same time, there was an overall reduction in amplitude at all intensity levels (Vivion, Hirsch, Feye-Osier and Goldstein, 1982).

Rate of stimuli

Stimulus rate is nothing but the number of times it is repeated per unit of time.

Mendel (1973) has reported that a change in repetition rate has little effect on the amplitude of the response. A change in repetition rate from 1-16 stimuli per second has no effect on middle latency response amplitudes (McFarland, et al. 1975). However, when repetition rate is increased beyond 16/sec. a reduction in the overall amplitude may be seen (Goldstein et al. 1972; McFarland, et al. 1979).

McRandle et al. (1974) found a number of 250 stimuli sufficient with a stimulation rate of 4.5/sec and 512 stimuli with a rate of 9/sec.

Jerger et al. (1987) reported that MLR may undergo rapid adaptation and augmentation at rates of 1/sec and 2.5 sec. A majority of studies have used repetition rates of 9/sec (Mendel, 1977). The majority of investigators of the AMLR and clinicians applying AMLR have used a stimulus rate in the 8-11 sec, range.

There is no standard or invariably correct number of sweeps (stimulus repetitions) in AER measurement. The larger the signal and/or the smaller the amount of noise, the fewer repetitions are necessary, and vice versa with comparable amounts of noise, then, more repetitions will be needed for the typically smaller short-latency responses.

NUMBER OF STIMULI :

The MLRs are usually obtained after 400-500 stimulus presentation although. McFarland, Vivion, Wolf and Goldstein (1978) manage to obtain clear recordings after only 125 stimuli. Hortwitz and Larson and Sances (1966) have stated that between 200-400 stimuli should be presented to obtain an average response. Lawe, Kupperman and Goldstein used, 1024 stimuli to obtain an average. Increasing the number of stimuli, increases the amplitude of the wave form. But several authors say that increasing the number of stimuli from 1000 to 4000 does not increase the ease of identification of MLR. McRandle et al. (1974) found a number of 256 stimuli sufficient with a stimulation rate of 4.5/sec and 512 stimuli with a rate of 9.6/sec.

Effect of masking: Monoaural vs binaural stimulation:

In general, amplitude for the AMLR Pa component is smaller for true binaural recordings than for the sum of monaural responses (Dobie and Norton, 1980; Skinner and Shimota, 1973; Peters and Mendel, 1974; Ozdamar, Kraus and Grossmann, 1986).

Woods and Clayworth (1985) found evidence of a binaural difference waveform in AMLR recordings from 12 normal subjects. They observed that wave Pa amplitude values were about 20% larger and latencies about 1.5 msec, longer for binaural versus monaural stimulation. Na amplitude was larger and latency shorter when recorded with an inverting electrode on the stimulus - contralateral mastoid versus an ipsilateral location.

There was little inverting electrode effect on the Pa component amplitude or latency. The actual binaurally stimualted AMLR Pa amplitude was smaller than the amplitude for the summed monaural condition.

In comparing AMLRs for monaural versus binaural stimulation, it is very important to eliminate the possible influences of post auricular muscle artifacts. These

artifacts are more likely to be present in the binaural condition, due to greater stimulus intensity, and if present, they will preclude valid monaural versus binaural data analysis.

Stimulus intensity does not appear to Influence the likelihood or magnitude of AMLR binaural interaction. This is taken as evidence that stimulus cross over effects are not a concern in Bl studies of AMLR (Dobie and Norton, 1980).

However, masking noise presented to the contralateral ear during monaural stimulation does significantly increase amplitude of major AMLR components, based on experimental findings in guinea pig (Ozdamar, Kraus and Grossman, 1986). Generalisation of animal findings to humans is, of course not necessarily possible.

Recording parameters :

Place of electrode :

There are basically two kinds of electrode arrays. Ipsilateral mastoid (-) to high forehead (+) and ipsilateral mastoid {-) to vertex (+). According to Kavanagh and Clark

(1989) both these arrays have equal efficacy in recording ABR and MLR in open as well as closed filter conditions.

Mastoid to high forehead array was preferred by several authors (Beattie, et al., 1983; Bettie, 1984; Hall et al. 1984; Suzuki, et al. 1981).

The forehead placement is usuallypreferred because it eliminates placement of electrode gel in hair. The forehead placement is usually preferred because -

- it moves electrode away from ear phone head band which can cause discomfort and dislodgement of electrode.
- it allows easy achievement of low electrode impedance.

Beatti, et al. (1986) says that this array remit in 34% reduction in response amplitude. The mean Po-Na amplitude is found larger in forehead electrode array. Mean Na-Pa and Pa-Nb amplitude is larger in vertex array.

The amplitude of Nb-Pb was small and ill defined in both cases. Cohen (1982) and Wood and Woolpaw (1982) also report that the maximum evoked amplitude is obtained on the midscalp anterior to Cz. But very little difference in waveform or magnitude between these two electrodes has been reported by Suzuki, et al. (1981).

The trend in AMLR measurement, however, is clearly toward multiples calp sites for non-inverting electrodes. Rationale for this measurement is stated in relation to suspected neurogenerators and clinical correlations for AMLR.

Filter Characteristics

Filtering is usually used in AMLR recording, to reduce the unwanted influence of low-frequency EEG activity as a source of noise in the response. Filter settings, especially the high-pass filter cut-off frequency are an extremely important variable in AMLR measurement (Jerger, Chamiel, Glaze and Frost, 1987; Kileny, 1983).

Scherg (1982 b) simulated analog filtering digitally, using a 24 dB/octave slope and assessed filter effects on AMLR waveform morphology. Low pass analog filtering, as expected, tended to produce a very smooth waveform and increased latency for components Na, Pa and Nb. High pass filtering however, resulted in the most marked waveform distortion.

Increasing the high pass filter setting from 1 Hz actually was associated with greater amplitude of some

components due to filter oscillations generated by earlier components. Latency of Pa shortened as the high pass cut-off was reduced from the wide setting (1 Hz) and by 40 Hz, there was a polarity reversal of the Pa component. Greater waveform distortion is observed with steeper filter slopes.

Further extending the cut off frequency of the high-pass filter downward below 15 Hz may however, not always be desirable in clinical AMLR measurements. In a study of AMLR recordings in 217 patients ranging in age from 6 days to 20 years, Kraus, Reed, Smith, Stein, and Cartee (1987) found that the likelihood of observing the Na and Pa components was greater for a high-pass filter setting of 15 Hz (12 dB/octave slope) than for one of 3 Hz (6 dB/octave slope). These authors attributed the more favourable findings with the 15 Hz cut off to effective reduction of unwanted low EEG activity (20 Hz and below), which, in children at least, can obscure the AMLR (Suzuki, Hirabayashi and Kobayashi, 1983).

Spectral analysis shows that the major power in the AMLR, at least in normal-hearing adults, is in the 30-50 Hz region (Kavanagh and Domico, 1986; Suzuki, Kobayashi, and Hirabayashi, 1983). With digital filtering techniques, all AMLR components are observed with a high pass frequency cut off of 30 Hz. As the cutoff frequency is increased from 30

to 50 Hz. amplitude of the Na and Pa components decreases but at about 40 Hz, the Pb component disappears.

This suggests that later components of the AMLR are composed of somewhat lower frequency energy. Witha high pass cut off frequency above 60 Hz, the entire AMLR disappears.

One additional noteworthy feature of AMLR spectrum is apparent variability among normal adult subjects, with subjects having peaks at different frequencies within the response spectrum. It is quite possible, as demonstrated by Kavanagh and Domico (1986), for two subjects to each have a distinct AMLR with an unfiltered AMLR and yet, with a 30 Hz analog or digital high pass filter cut off, for one subject to show no AMLR while the other does.

The influence of subject characteristics, such as age (young or old), or gender, on AMLR spectrum and susceptibility to filter effects is not known.

Endogenous factors:

Sleep:

Maturational sleep studies

There is general agreement that sleep does not impede Pa detectability in adults as it does in children. Some studies

have reported the absence of any sleep effects on adult MLRs (Mendel and Goldstein, 1969; Mendel, 1974; Mendel and Kupperman, 1974). while others have reported sleep related amplitude and latency changes (Okitsu, 1984; Osterhammel, Shallop and Terkildsen, 1985; Brown, 1982) . There are variations in methodology used in these studies. Erwin and Buchwald (1986), who showed that Pa amplitude is virtually unaffected during stage 4 sleep in adults, obtained their data at slow stimulation rates, while the changes observed by Osterhammel et al. (1985) were observed with faster stimulation rates.

Developmental sleep stage studies by Feinberg and Carlson (1968) show a decrease in detectability of wave Pa in stage 4 sleep as well as an increase in wakefulness with age during the period of a night's sleep. These changes may account in part, for the systematic increasing detectability of wave Pa with age. Still, even within stage 4, detectability improves with age. This improved detectability combined with decreased time in stage 4 sleep may account for the dramatic differences in Pa detectability seen between infants and adults.

Latencies of major peaks remain constant across different stages of sleep. Amplitudes are larger during REM1 and 2 stages than 3 and 4 (Mendel and Goldstein, 1971). Sleep deprivation has little effect on MLR (Mendel and Goldstein, 1969b). Light sedation does not diminish the overall response (Kupperman, Mendel, 1974; Mendel and Hosick, 1975). They reported that MLR *in* fairly slabic during early stages of sleep (Mendel and Hosick, 1975). They further observed that there was no change in MLR due to drug induced sleep. Another investigation by (Brown and Shallop, 1982) showed that the amplitude of Pb and Pc of MLR are reduced during sleep. As stages of sleep deepen, latencies of peaks except Po gradually increase and amplitude decreases. During sleep Na shows one of the double peaks Nal and during stage of wavefulness, Na2 is seen.

Effect of deep sleep on MLR is not much in adults as in children (Okitsu, Shibahana, 1981). Pa can be easily detected in awake children and early stage of sleep. During stage 4 detectability is poor (Kraus et al. 1985). The MLR threshold was 40 dB higher in children who were asleep, than when they were awake (Kankkumen and Rosenthal, 1985).

Body temperature :

Kileny, Dodson and Gelfand (1983) monitored hypothermic; patients undergoing open heart surgery with MLR. Hall (1987) has applied MLR in monitoring patients undergoing hyperthermia (increased body temperature) treatment for advanced cancer. There is evidence of decreased latency yet reduced amplitude of the Pa component in some patients as body temperature is elevated from normal levels (about 37 degree celcius) to 42.2 degree celcius. This is not, however, a consistently observed finding.

Anaesthetic agents :

Anaesthetic agents produce differential effects on AERs; MLR, LLR which involve multisynaptic non-lemniscal pathways are sensitive to suppression by anaesthetic agents. Unfortunately, much of the information on the relationship between anaesthesia and these extra lemniscal AERs was obtained from clinical experience with humans (Pradhan and Galambos, 1963; Smith and Kraus, 1987). Drugs like Fentanyl, Enflurane and Fluothane were found to have differential effects on MLR amplitude and latency (Kileny, Dodson and Gelfand, 1983; Thornton et al. 1981; Prosser and Arslan, 1985).

Maturational changes :

Most aging brains show a group of structural changes which are progressive in nature. The electric potentials picked up from the brain may Mimic these changes in terms of their waveform morphology and latencies.

Visco et al. (1987) recorded MLR in 64 premature infants, followed upto, 32 weeks conceptional age (CA). The MLRs were analyzed for the components Po, Na and Pa, and the interpeak latency difference Na-Po. , The detectability rate of Po and Na reached 80-90% at about 30 weeks CA. Pa reached the highest rate of about 60% at 52 weeks CA. They concluded that MLRs were obtainable as early as 25 weeks CA and that MLR therefore reflected an early functioning structure in the auditory pathway, with the most prominent changes in latency and amplitude values occurring before and around term date.

Hiromi Veda (1990) examined ABRs and MLRs for click and/or 500 Hz tone pip stimuli in infants (36-44 weeks conceptional age) admitted to the NICU and measured the threshold and detectability of these responses-wave Po, Nal, Na2 for MLR measurement. Thresholds of MLRs for click stimuli were almost equal to those of ABRs for click stimuli. On the other hand, thresholds of MLRs for 500 Hz tone pip

stimuli were slightly worse than ABRs for click stimuli, the average differences being less than 10 dB wave Po, Na, Na2 are the best threshold indicators of MLRs in infants, but wave Pa was still unstable and the detectability was less than 30%.

There are, however, differing opinions about the detectability of wave Pa in children and neonates. Mendel et al. (1977), McKandle et al. (1974) and Mendelson and Salamy (1981) have emphasized that wave Pa can be recognized even in infants and neonates. On the other hand, Engel (1971) and Rotteveel et al. (1987) suggested the detectability of wave Pa to be almost 0% in neonates.

Mendelson, Salamy (1981) recorded MLRs from 60 subjects in four age categories, 15 premature infants, 15 full term newborns, 15 children and 15 adults, and the waveform, latency and amplitude were compared across the age groups. Results indicated that significant age effects were evident for amplitude but not latency. Amplitude of components, Po, Pa and Pb were found to increase until 3-4 years of age, and decline in adulthood. Significant age effects on latency were found only for Po, which is postulated to be synonymous with wave V of the brain stem response. The absence of age

effects on middle component latencies is quite surprising and this raises questions about the generator sources for middle components.

Okitsu (1984) compared the detectability of each peak in waking children (3 years) with that of each peak in sleeping children (4 months-3 years 3 months). There was little difference in the detectability of the Po peak between the two test conditions, and the Na peak was only about 10% lower in sleeping subjects than in waking ones. However, a considerable decrease in the detectability of the Pa peak was found during sleep. Later peaks, such as Nb and Pb peaks, which are usually elicited in waking adults, could scarcely be found in children, either in the sleeping or in the wakeful state. Po-Na may be the most suitable index for electric response audiometry in young children.

Kobayashi et al. (1983) compared MLR waveforms of adults and young children. A digital high- pass (HP) filtering technique was applied to the responses in 26 young children aged 1-7 years and a adults with normal hearing aged 21-35 years. The two major differences that existed in the MLR configurations between adults and young children was firstly. Pa in the responses from adults was consistently recognised with HP filtering upto 50 Hz, while Pa in young children was

effectively detected only with 20 Hz HP filtering. When the HP filter was set at 30 or 40 Hz, Pa markedly decreased in magnitude or effectively disappeared. Secondly, Pa was identified in most of the adult responses, with a latency ranging from 55 to 65 ms, particularly with HP filtering at 30 Hz. On the other hand, it was not visually distinguished in the responses from young children with any HP filter setting.

Mendel and Goldstein (1969) examined the early components of the averaged electroencephalic response (AER) in eight normal hearing adults (22-26 years) over a single, sleepless 24-hour span, using 1024 clicks at the rate of 9.6/sec. Electroencephalic activity was recorded from an electrode on the vertex referred to the left earlobe. The response pattern was very stable, characterized by a polyphasic configuration with mean peak latencies of (Po) 13.3 msec, (Na) 22.0 msec, (Pa) 32.3 msec, and (Nb) 45.1 msec. At the conclusion of the 24 hour span, three of the subjects were tested with the same stimuli during various stages of sleep. the early components of the AER remained consistent even during sleep.

Thus MLRs of children are found to differ substantially from that of adults (Suzuki et al. 1983; Kraus, et al. 1984 b). Under appropriate measurement conditions-namely a slow stimulus rate (1 to 2/sec) and non-restrictive filter settings (10-300 Hz) a true MLR is sometimes recordable in neonates and young children. An infant MLR is not reliably recorded for stimulus rates exceeding 5/sec (Fifer and Sierra-Irizarry, 1988).

At the slower rate, latency of Pa component is usually in the 50 msec range, or twice the expected adult latency value, although it may be further delayed in very young but normal infants (Fifer and Sierra-Irizarry, 1988). Kraus et al. (1985) say that detectability of Pa increases systematically from birth to adolescnce.

Several investigators (Davis, 1976a; Mendel, 1977; Wolf and Goldstein, 1980) concluded that MLR can be used as an auditory diagnostic tool for the very young children.

Many studies have been done on children, the results of which revealed that there are differences in the waveforms obtained from children compared to adults. So there is a need for studying the normal variations in the MLR waveform before using it to diagnose pathological conditions.

METHODOLOGY

Subjects :

The experimental group of this study consisted of 60 subjects, thirty adults and thirty children. Group I consisted of thirty adults, fifteen males and fifteen females, between the age range of 18-30 years.

Group II consisted of thirty children, with 10 children in each of the three age intervals 7-8 years, 8-9 years and 9-10 years. All subjects chosen had normal hearing.

Subject selection criteria :

1. Subject should not have any otological or neurological problems.

2. Subject should not have any psychological problems and should have average intelligence.

3. General health should be good at time of testing.

4. Subject should be able to relax and sit without any extraneous movements for duration of testing.

Equipment :

Electrophysiological test equipment was. Biologic-Navigator EP.

Test Environment :

1. The experiment was carried out in a sound treated rooms.

PROCEDURE

Instructions :

Subjects were instructed to sit comfortably on the chair and relax. They were briefed with the information that the electrodes would be placed and then the earphones. They were instructed that they would hear tone bursts in one ear only and that no voluntary response was required. Subjects were asked to avoid extraneous movements of head, neck and jaw for the duration of the test. They were asked to be alert during the test period and not to fall asleep. Instructions were given in a language that was familiar to the subjects.

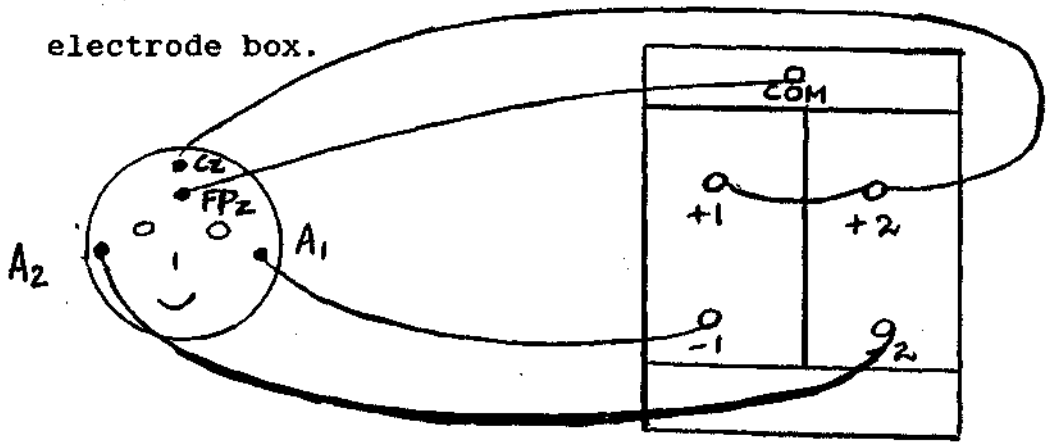
Electrode placement :

Four electrodes were used in this study. All were checked for continuity. The area of placement of electrode

was cleaned by rubbing the surface with cotton dipped in rectified spirit and skin preparing paste. This was done till the surface appeared red indicating vascularity. Appropriate amount of gel was used to stick the electrodes in their respective positions. They were secured in place by a piece of plaster.

The first electrode was placed on the vertex (C2), second on forehead (Fp2) and the third and fourth on mastoid region behind the auricle The electrode on vertex served as non-inverting electrode, electrode on forehead serves as common electrode and electrodes on mastoid served as inverting electrodes.

Figs.here shows connection of electrodes into the electrode box.



Site:	Head box :
Forehead (F2)	com.
Vertex (C2)	1+2 (linked)
Left ear mastoid (A1)	1-
Right mastoid (A2)	2-

Impedance matching areas carried out as directed in the manual and it was ensured that that impedance at all electrodes was < 5K and interelectrode impedance was < 2K. Earphones were then placed without dislodging the electrodes. Blue earphone was used for the left ear and red to the right ear. Earphone diaphragm was placed directly over the ear canal so that accurate stimulus intensity levels were delivered to the ear.

Stimulus parameters : stimulus parameters used for adults was as follows :

i) Stimulus :Rarefacting tone burst
ii) Frequency - 500 Hz
iii) Rise time 10.0
iv) Plateau - 20.00
v) Rate 7.7/s
vi) Band pass -3-100 Hz
vii) Sample number - 500.

Similar parameters were used for children, except for the rate, which was reduced to 3.1/sec.

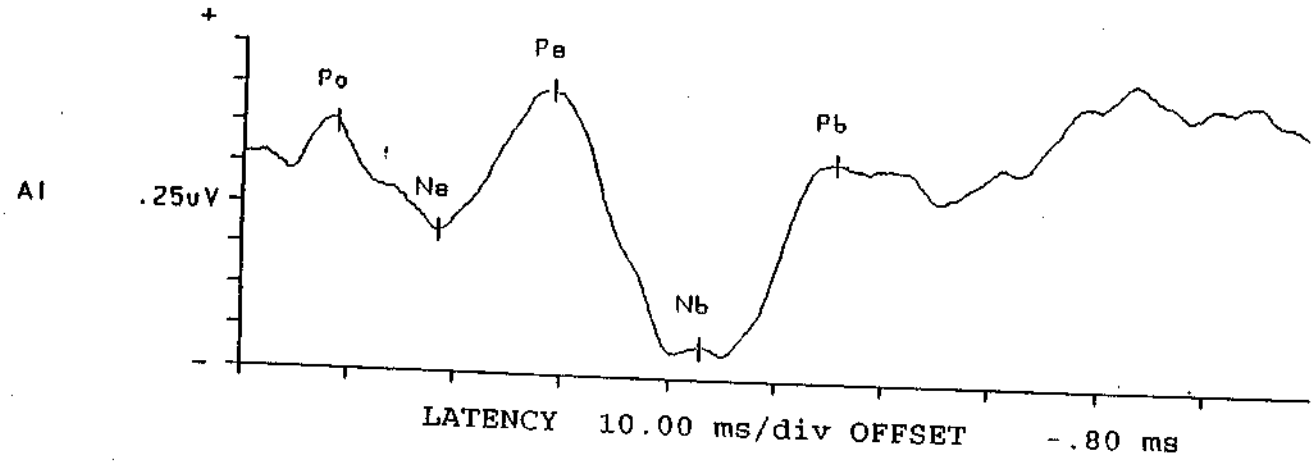
The MLR waveform was recorded from only one ear. Equal number of right to left ears were tested which was randomly

selected. The test begun at an intensity of 60 dB nHL. The lowest intensity at which a clear waveform could be obtained was found out.

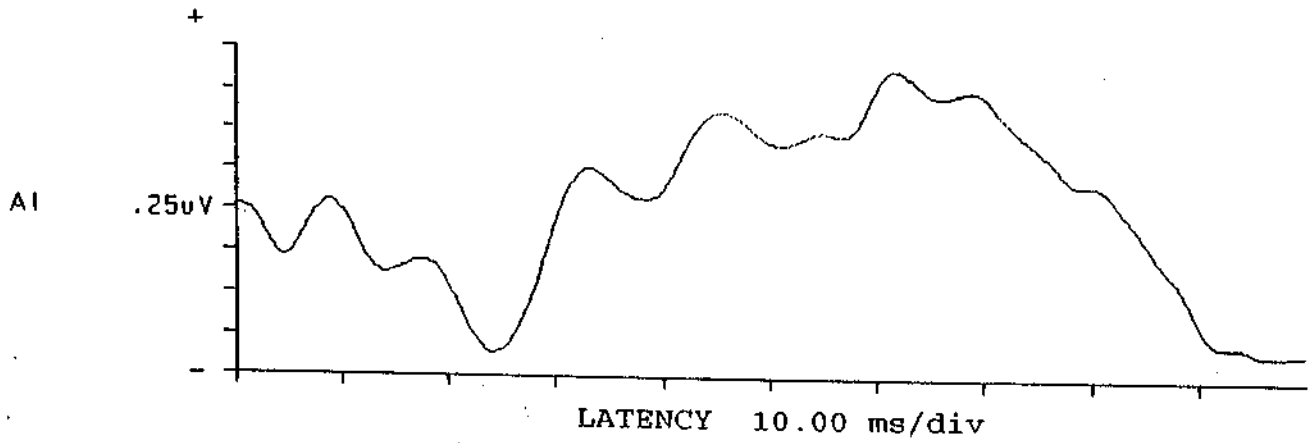
The MLR waveforms obtained by the subjects were stored and later analysed for their peak latencies (Na-Pa, Nb and Pb) at different intensities.

The MLR waveforms obtained for children and adults were compared.

MLR WAVEFORM ELICITED AT 60 dBnHL
A NORMAL 23 yr OLD ADULT FEMALE



MLR WAVEFORM IN A 7yr OLD NORMAL FEMALE CHILD ELICITED AT 60 dBnHL.



RESULTS AND DISCUSSION

MLR waveforms were elicited at 60 dBnHL, 40 dBnHL and 20 dBnHL for adults and children. The following Tables A, B, C, and D summarises the changes in peak latencies and amplitude at different intensities for Na, Pa, Nb and Na Pa respectively.

Table A: Na peak latency

Int.	Mean A	SD A	Min.A	Max,A.	Mean C	SD C	Min.c	Max.c
60	25.35	4.57	11.70	36.47	30.15	7.16	20.28	46.80
40	28.44	4.37	16.38	39.39	31.82	7.43	20.28	47.58
20	31.00	5.09	22.62	46.41	33.03	6.86	24.76	53.04

Table B: Pa Peak Latency

Int.	Mean A	SD A	Min.A	Max,A.	Mean C	SD C	Min.c	Max.c
60	34.85	4.72	21.84	41.14	41.13	7.40	27.49	53.04
40	36.71	4.68	27.10	45.63	39.64	6.90	30.03	53.82
20	39.97	5.95	27.69	57.91	42.98	6.85	32.37	61.42

Table C: Nb Peak latency

Int.	Mean A	SD A	Min.A	Max.A.	Mean C	SD C	Min.c	Max.c
60	42.65	5.14	31.98	51.09	50.61	6.88	32.56	61.62
40	44.87	5.80	31.00	58.50	45.83	7.37	35.49	60.25
20	48.05	6.05	40.17	62.98	50.24	6.33	38.41	67.67

Table D: Na-Pa amplitude

Int. A	Mean A	SD A	Min.A A	Max.A. A	Mean C	SD C	Min.c A	Max.c A
60	1.26	0.64	0.16	1.83	0.92	0.49	0.18	1.88
40	0.73	0.43	0.22	2.02	0.84	0.47	0.16	1.80
20	0.68	0.43	0.11	1.64	0.76	0.37	0.19	1.44

As shown in Tables A, B and C the peak latency value! Na, Pa and Nb lengthened as the intensity decreased in adults. These results are in correlation with findings o: the study done by Goldstein and Rodman, (1967), which stated that as stimulus intensity level increases from behavioural threshold up to about 40-50 dB SL, latency systematically decreases. Them for higher intensity levels, latency remain relatively constant.

This change was however not consistent in children.

It was also observed from Table D that for adults an children there was a definite and consistent decrease i amplitude with decrease in intensity. This finding again wa in correlation with the study done by Goldstein and Rodman (1967), they indicated that amplitude increases steadily fro over the intensity range of 0-70 dBSL.

The mean peak latencies and amplitude at 60 dBnHL (ipsilateral) was also compared between 7 years, 8 years, 9 years and adult group to study the age related changes in ms.

The following Tables la, b, 2 a, b and 3 a, b summarizes the results.

Table la: Peak latency Na.

	7 years	8 years	9 years	Adults
Mean	34.30	31.30	28.80	25.35
SD	8.28	5.45	5.90	4.57
Minimum	21.64	22.23	20.28	11.70
Maximum	41.14	46.80	35.10	36.47

Table lb: t-test scores

Groups compared	t-scores
7-8 vs. 8-9 years	- 6.66
8-9 vs. 9-10 years	11.22**
7-8 vs. 9-10 years	5**
Adults vs.children	-.50

* significant at 0.05 level.
** significant at 0.05 level and 0.01 level

Table la compares the mean peak latency of Na both for children of 7 years, 8 years and adults elicited at 60 dBnHL (ipsilateral). As seen from the Table, the mean peak latency for Na peak appeared at 34.30 ms for 28.80 ms for 9 years and 25.35ms for adults. It indicated a definite and consistent

decrease in Na latency as the age increased. The Na peak could be identified for 28 of the adult subjects and 25 of the children at 60 dBnHL.

Table lb depicts the t-scores obtained when the respective groups were compared.

As seen the difference in peak latency of Na was statistically significant in the age groups. 8-9 vs 9-10 years and 7-8 vs 9-10 years but not in 7-8 vs 8-9 years. There was no statistically significant in Na peak latency between adults and children.

Table 2a: Peak Latency Pa and NaPa amplitude

	7 years	8 years	9 years	Adults
Mean	40.01	45.14	37.47	34.85
SD	7.14	6.36	6.86	4.72
Minimum	27.49	33.15	28.27	21.84
Maximum	48.75	53.04	48.55	41.14
NaPa Amplitude (Mean)	0.98	0.95	0.60	1.26

Table-2b: t-test scores.

Groups compared	t scores for latency	t scores for amplitude
7-8 vs. 8-9 years	-10.91	0.84
8-9 vs. 9-10 years	17.04**	0.71
7-8 vs. 9-10 years	5.40**	0.76
Adults vs.children	-48.30	2.12*

* - Significant at 0.05 level
** - Significant at 0.05 level and 0.01 level.

Tables 2a compares the mean latency for Pa for both adults and children of 7 years, 8 years, 9 years. The mean latency for Pa falls at 40.01 ms for 7 years, 45.14 ms for 8 years, 37.47 ms for 9 years and 34.85 ms for adults. Again the mean latency for Pa indicated a decrease in latency with increase in age except at 7 years which indicated a latency value lesser than 8 years old. Pa could be identified in all of the adult subjects except one and all of the children except two at 60 dBnHL.

Table 2b indicated t-scores for groups compared. There was no significant difference between the mean latency for Pa for adults and children. There was a significant difference between the mean latency for Pa for 7-8 vs 9-10 years and 8-9 vs 9-10 years.

The mean Na Pa amplitude was more in adults when compared to children and the difference was statistically

significant at 0.05 level. However the change in amplitude with increase in age was not consistent in children.

Table 3a: Peak latency Nb

	7 years	8 years	9 years	Adults
Mean	48.53	52.75	47.69	42.65
SD	4.63	6.75	8.40	5.14
Maximum	39.39	37.44	32.56	31.98
Maximum	56.74	61.62	57.33	51.09

Table 3b: t-scores

Groups compared	t-scores
7-8 vs. 8-9 years	-8.97
8-9 vs. 9-10 years	10.12**
7-8 vs. 9-10 years	1.68
Adults-children	-5.10

The mean Nb peak latency showed a statistically significant difference between 8-9 vs.9-10 years.

Table 4: Comparing adult males vs.femlaes.

	Mean		SD		Minimum		Maximum		t-score
	(M)	(F)	(M)	(F)	(M)	(F)	(M)	(F)	
Na	25.26	25.43	5.21	3.80	11.70	18.52	36.47	31.20	-.10
Pa	35.58	34.17	4.9	4.52	21.84	24.38	41.14	40.75	.80
Nb	41.91	43.3	5.92	5.04	35.68	31.98	51.09	50.50	-.68
Na -pa	0.78	0.84	0.40	0.52	0.19	0.16	1.79	1.83	-.35

Table-5: Comparing children males vs females.

	Mean		SD		Minimum		Maximum		t-score
	(M)	(F)	(M)	(F)	(M)	(F)	(M)	(F)	
Na	26.15	32.16	7.64	8.53	21.64	20.28	39.78	46.80	.85
Pa	39.60	47.47	6.05	8.58	27.49	28.27	49.72	53.04	-2.84
Nb	50.80	50.46	4.58	8.41	41.34	32.56	56.74	61.62	.12
Na -pa	1.00	0.91	0.64	0.39	0.18	0.33	2.33	1.88	.42

Table 4 compares the mean, SD, range and t-scores for Na, Pa, Nb and NaPa between adult males and females.

The peak latencies at Na and Nb were consistently longer for females than for males but the difference was not statistically significant. Pa latency was shorter for females compared to males. Amplitude of the female population was greater than the male population but the difference in amplitude was not statistically significant.

The finding that the amplitude was greater in females was in correlation with the results of the study done by Palaskas, Wilson and Dobie (1989). They reported that the MLR components tend to be shorter in latency and larger in amplitude in female versus male subjects, the difference do not always reach statistically significance (Ozdamar, Kraus, 1983). Table 5 compares the mean, SD, range and t-scores for Na, pa, Nb and NaPa between children males and females. Again females showed a lengthening of latencies at the peak Na and Pa. Peak latency for Nb was shorter for females than for males. Unlike adult population, the amplitude of the males was more than that of females. But the differences obtained in peak latencies and amplitude was not statistically significant.

In a study conducted by Mendelson, Salamy (1981), they reported that significant age effects were evident for amplitude but not latency.

Mendel et al. reported that although MLR may be recorded in infants, the detectability of Pa increases systematically from birth to adolescence. The primary thalamo-cortical pathway is only partially developed in children, not reaching maturity until puberty. Here is evidence that myelinization

of the humans thalamo-cortical pathway and sensory cortex continues until puberty (Yakovlev and Lecours, 1967). The systematic development of MLR components observed in humans is consistent with such a maturational process (Kraus, Smith and Reed, 1985).

SUMMARY AND CONCLUSION

AEPs occurring from 10 to 50 millisecs in latency are called auditory middle latency response (MLR). The main components of MLR are Na (18 ms), Pa (30ms) and Pb (50 ms).

30 adults with normal hearing between the age range of 18 years - 30 years and 30 children with hearing within normal limits, 10 in each age group of 7-8 years, 8-9 years and 9-10 years were taken. The aims of the study were as follows:

(1) To study the latency, amplitude and morphology of the MLR waveform at different intensities.

(2) To compare for any significant difference in waveform between children and adults.

The MLR waveforms were elicited for 60 dBnHL, 40 dBnHL and 20 dBnHL using an electrophysiological unit (Biologic Corporation System, Navigator). It was observed that Na, Pa and Nb could be identified in a majority of the subjects at 60 dBnHL consistently.

The data was subjected to the following statistical analysis, mean, standard deviation, range and t-test. The results indicated that there was a significant difference between adults and children for amplitude (NaPa) but not for latency.

There was a significant difference for Na and Pa peak latency between 8-9 years vs. 9-10 years and 7-8 vs 9-10 years age groups and Nb peak latency between 8-9 years vs.9-10 years age groups.

There was no significant difference in latency and amplitude of peaks between males and females for adults and children, though females consistently showed longer latencies than males in both adults and children.

In conclusion, the results of the above study showed that there was no significant difference observed in terms of latencies between the adult group and the children group.

However, there was a difference in the mean peak latencies of Na, Pa and Nb between adults and children. Hence it is important to study the MLR, in terms of peak latency and amplitude, in normals first before administering it on the clinical population.

Limitations of the study

1. Number of subjects used was small.
2. It was difficult to keep the children alert, since the test procedure was very long, and this could be one of the possible reasons for a greater intra-subject variability in children.
3. Multiple electrode placement that could have yielded better results was not used.

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