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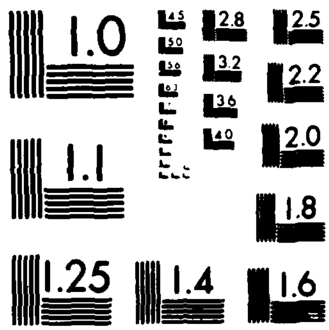

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ABSTRACT

This study evaluated the characteristics of the middle latency response (MLR) and the related steady state evoked potential (SSEP) in a total of 36 neonates. The reports of previous investigators have cast doubt on the existence of both the MLR and SSEP in neonates. The measurements in these studies were obtained, however, using stimulation and recording parameters that are appropriate for adults. Since virtually all other aspects of neonate audition differ significantly from comparable adult attributes, one goal of this study was to determine the appropriate parameters with which to obtain a valid MLR and SSEP in very young children. Other goals of this study included: (1) evaluation of two different algorithms for low-frequency sensitivity prediction using the SSEP; (2) investigation of the stability of the SSEP over repeated trials; and (3) elucidation of the relationship the neonatal MLR to later occurring auditory evoked potentials.

The MLR and SSEP were studied initially with minimal EEG filtering to alleviate the possibility of filter artifact. The evoked responses were investigated at different stimulation rates ranging from one tone burst per second to 40 tone bursts per second. The MLR was observed

THE MLR AND SSEP IN NEONATES

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The Graduate School
Baylor College of Medicine

In Partial Fulfillment of the

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of

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by

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most often at stimulation rates of one to two per second. Only two children had discernable responses at 5 per second; none of the children had repeatable waveforms at 10 per second. The SSEP was observed most frequently when using stimulation rates near 20 per second. These findings were supported by FFT analysis of the respective waveforms. The optimal stimulation rates for the neonatal MLR and SSEP are much slower than the respective rates for adults. Furthermore, MLR waveform morphology was substantially different in neonates. Wave Pa had a broad-based peak and was observed at latencies ranging from 44 msec to 70 msec. This is contrasted to the narrow-based peak and the 25 msec to 35 msec latency range previously reported for adults.

The primary effect of changing the EEG filter band-width was a decrease in the latency of wave Pa as the band-width increased. When the high-pass filter was decreased from 10 Hz to 3 Hz, the addition of significant low-frequency EEG energy to the averaged waveform caused the identification of wave Pa to become increasingly difficult. Although high-pass filtering is necessary to eliminate low-frequency contamination of the averaged waveform, the band-pass should be maintained in such a way that 20 Hz energy remains undistorted.

Prediction of low-frequency sensitivity by visual detection of the SSEP waveforms at different intensity levels was unsatisfactory. This was due to the masking effects of environmental noise on a 500 Hz stimulus. A least-squares linear curve-fitting technique was found to be more suitable. This technique fitted a least-squares line to the 20 Hz FFT amplitude values derived from the averaged waveforms at different intensity levels. The fitted line was extrapolated to zero amplitude to predict 500 Hz threshold. The linear curve-fitting/extrapolation technique predicted normal hearing sensitivity in 10 of 13 children using 512 EEG samples per averaged waveform. When the number of samples was increased to 1024 or 2048, the remaining three children had normal threshold predictions. Equivalent results were obtained when the extrapolation was based on three or four amplitude data points.

The SSEP showed substantial variability over repeated trials. Successive waveforms ranged from large, robust responses to waveforms that were totally indiscernable. An autoregression analysis indicated that the variability was somewhat predictable and cyclic in nature. The amplitude values for each child cycled from one maximum value to the next in four to ten minute periods. These findings indicate that SSEP response verification should be as a function of time instead of a finite number of replicative trials.

Evaluation of the relationship between the MLR and the late auditory potentials revealed substantial variation both in waveform patterns and latencies. Of the three subjects who participated in this experiment, only one had adult-like waveforms. The EEG characteristics that affect the neonate's MLR and SSEP also apply to the late potentials. Consequently, the relationship of the MLR to the late potential is heavily dependent on the level of activity at the respective generator sites.

Perhaps the greatest implication of this study is the introduction of a method to determine shape of audiogram. The SSEP to low-frequencies may supplement the ABR to provide both low- and high-frequency audiometric information. In turn, the increased detail in the diagnostic audiologic information will enhance habilitation efforts in prescribing hearing aids and designing appropriate language intervention strategies for children found to have hearing impairment.

DEDICATION

This dissertation is dedicated to the patients, parents, and staff of the Neonatal Intensive Care Unit, Wilford Hall United States Air Force Medical Center, Lackland Air Force Base, Texas.

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CHAPTER I

INTRODUCTION

Audiologists recognize the devastating effects of hearing loss on speech and language acquisition in young children. Advocates of early identification of hearing loss have strongly urged the development of sensitive, efficient test procedures. One primary group for whom these efforts are focused is children in the neonate intensive care unit (NICU). These children are considered high risk candidates for hearing loss because of factors generally associated with pre-mature birth or because of congenital anomalies. The prevalence of hearing loss in NICU children has been estimated from 2.5% to 8.0% in contrast to the 0.25% to 0.5% prevalence among normal term babies. The most frequent factors contributing to hearing loss are transplacental infections inducing pre-mature labor, low Apgar scores, neonatal asphyxia, respiratory distress syndrome, acidosis, ototoxic antibiotics, intracranial hemorrhage, and congenital malformations. Unfortunately, the items in this list often occur in combination rather than in isolation. Interactions among these factors generally produce synergistic effects.

At birth, the NICU children range in gestational age from 25 weeks to 42 weeks. Due to recent advancements in neonatology, a larger proportion of the younger children are surviving the sequelae of pre-mature birth. Consequently, more children of 34 to 36 weeks conceptual age (gestational age plus the post-partum age) are being discharged to home. Since many of these children are lost to hearing follow-up after discharge, the most advantageous time to screen for hearing loss is while they are in the NICU. These children have, therefore, become prime targets for hearing screening efforts.

Indeed, significant progress has been made in recent years to develop sensitive, efficient screening procedures. Most of these evaluative tools, however, provide detailed, frequency specific information for children aged three to six months and older. Only three test procedures are generally used with children under three months of age: 1) behavioral observation, 2) Crib-O-Gram, and 3) auditory brainstem response (ABR).

Audiologists have used various forms of behavioral observation for many years to rule out moderate and severe hearing loss. This type of hearing screening is often conducted informally with hand claps or uncalibrated noise-makers, or formally with "calibrated" instruments emitting sounds of known frequency composition and approximate intensity. Behavioral responses in neonates are generally limited to widening of the eyes and gross limb movements to high intensity sounds. Since this basic reaction to loud sounds is reflexive in nature, the presence or absence of a response offers no qualitative information about hearing sensitivity. Moreover, changes in behaviour which is time-locked to an acoustic stimulus usually occurs only 20-25% of the total number of trials making accurate interpretation of the observations quite difficult. Furthermore, there are many variables that influence a child's response over which the examiner has no control. A partial list includes: 1) the degree of contrast between stimulus characteristics and the environmental noise; 2) the child's general state of wellness and alertness at the time of test; and 3) the variability in the qualitative nature of each child's reaction to a given stimulus. Collectively, the factors listed above make behavioral observation audiometry the least informative of the evaluative tools for neonates.

The Crib-O-Gram was developed on the premise that changes in behavior in response to acoustic stimulation can be automatically recorded. It was designed for the purpose of screening large numbers of children with a minimum number personnel and relatively inexpensive equipment. Each apparatus has three basic components: 1) An acoustic stimulus section; 2) motion detectors; and 3) a graphic output of the child's responses. Stimulus activation, inter-stimulus intervals, and response recording are micro-processor controlled. In addition, later models also use the micro-processor to automatically score the results. The stimulus section presents only a high frequency signal (3 kHz warble tone or narrow band noise) at a fixed level of approximately 92 dB SPL. Consequently, many investigators feel that these instruments are limited to the identification of children with at least moderate hearing impairment. Some individuals have reported failure to identify children with hearing loss less than 45 dB or with sloping audiometric configurations. Furthermore, the efficiency of these devices in the NICU is questionable. Recent publications suggest that up to 20% of the children must be retested due to ambiguous results. Although this technique is somewhat more objective than behavioral observation audiometry, the quantity and quality of information obtained for each child is approximately the same. Since a substantial proportion of NICU children have sloping high-frequency hearing loss, the results from these automatic recording devices must be evaluated with extreme caution.

The ABR is cited as the most useful for neonate hearing screening. This technique can be used reliably to evaluate hearing threshold with children 35 weeks conceptual age and older. The principle upon which the ABR is recorded is a volume conduction of neural activity. To achieve sufficient activation of these neurons, the ABR requires a very short duration stimulus. Efforts to employ longer duration, more frequency-specific stimuli have resulted in degraded and often uninterpretable waveforms.

Studies of ABR characteristics have shown that the ABR is most highly correlated with the frequency range of 1000 Hz to 8000 Hz. Therefore, interpretation of ABR results must be limited to this region of the audiogram. Consequently, audiologists cannot predict low frequency sensitivity and the configuration of the audiogram by using only the ABR.

In contrast to the ABR, other evoked potential measurements do offer frequency-specific information. The middle latency response (MLR) has somewhat more liberal stimulus requirements to obtain a well-defined waveform. Whereas the ABR requires a broad-frequency, click-like stimulus, the MLR can be elicited by frequency-specific tone pips. Consequently, the MLR offers valuable low-frequency information that the ABR cannot. Several investigators have reported an MLR in neonates which was similar in latency and morphologic characteristics to the adult response. The validity of this findings, however, has recently been challenged by several other investigators. Using stimulation rates of eight to eleven per second, they demonstrated that the waveform which appeared to be an MLR disappeared when the EEG filters were opened widely. Consequently, they speculated that the MLR waveform observed in the earlier reports is nothing more than filter artifact. Despite the early, optomistic reports on the MLR, it never gained popularity as a clinically applicable tool. The advent of these recent criticisms have further decreased the MLR's appeal as a frequency specific diagnostic tool.

Late auditory evoked potentials have the least stringent stimulus requirements to obtain frequency-specific information. In an awake, attending adult, the late potentials convey accurate threshold information for both low- and high-frequencies. However, the waveform amplitude is highly dependent on subject state. The waveform decreases in amplitude or, at times, disappears when the subject is sleeping. This particular property of late potentials make their use with infants tenuous, at best. Infants must generally be tested while asleep due to overwhelming muscle artifact when the child is awake and moving. The late auditory potential is not recommended, therefore, to assess peripheral sensitivity in neonates.

The steady state evoked potential (SSEP) was recently developed as a frequency specific predictor of hearing thresholds in adults. It is a very robust reponse which can be observed to within 5 to 10 dB of auditory threshold for frequencies between 250 Hz and 4000 Hz. More recently, several investigators have attempted to expand application of the SSEP to infants. They reported observing waveforms comparable to the adult data when using the same stimulating and recording parameters. Application of the SSEP in the neonate population, however, has been criticized by other researchers. The SSEP is thought to be closely related to the MLR with regard to neurological derivation since they have many common characteristics. Of particular interest, therefore, is the question regarding EEG filter effects on the waveform. When highly filtered, the neonate SSEP, obtained with 40 per second stimulation rate, appears very much like the adult response. As the filters are widened, the waveform becomes nothing more than the ABR wave V. Consequently, the presence of the SSEP in neonates is strongly questioned.

In summary, the ABR is the most widely accepted objective tool for determining hearing thresholds in neonates. When the ABR predicts normal hearing sensitivity, the prediction carries minimal probability of error. When the ABR predicts peripheral hearing loss, however, the qualitative accuracy of the prediction is less than adequate. Since this technique offers no information regarding low frequency sensitivity and slope of audiometric configuration, a supplemental method is needed to give a more complete description of peripheral hearing abilities.

It is interesting that both the MLR and SSEP are used with neonates according to the parameter guidelines established for adults. Several lines of evidence suggest that this may be inappropriate. First, measurement of acoustic reflex responses in neonates requires different recording parameters than used with adults. The reflex is virtually impossible to record when using a 220 Hz probe tone. Several studies have established that the reason for this phenomenon is that the resonant characteristics of the neonate middle ear are very different from adult middle ears. As a result, a 220 Hz probe tone will fail to record the minor impedance changes associated with stapedius muscle contraction. In contrast, probe tones between 800 Hz and 1800 Hz greatly facilitate observation of impedance changes from reflex contraction.

Second, wave V latency of the ABR is much longer in neonates than adults. If the recording parameters were constant for both adults and infants, then the neonate wave V would often occur beyond the end of the recording period. Consequently, to ensure accurate recording of wave V in neonates, clinicians increase the time period during which neural activity is recorded.

Third, minor reductions in rate of stimulation have a significant effect on ABR waveform morphology, especially in pre-term infants. For example, slowing the stimulus presentation rate from 10 per second to 5 per second is particularly effective for improving wave I identification by increasing peak definition and waveform amplitude. Concommitantly, stimulation rate affects the V/I amplitude ratio due to alteration in wave I. In contrast, slowing stimulation rate below 10 per second has minimal effect on wave I in adults.

Fourth, neuromuscular coordination is quite undeveloped in neonates. Behavioral hearing tests must use totally different criteria for detection of hearing loss in the newborn population than for older infants. If criteria that were appropriate for four to six month old infants were used with neonates, then virtually every child would fail hearing screenings. Consequently, the choice of stimuli and the target response must focus on the age of the child.

These examples illustrate that virtually all aspects of neonatal audition posess characteristics unique to that population. It is plausible, therefore, that MLR and SSEP parameters established for adults are inappropriate for neonates. A re-examination of the MLR and SSEP in neonates is justified to determine the optimum stimulus and recording parameters. Consequently, the goal of this study was to investigate in greater detail MLR and SSEP responses in neonates. This project was divided into five major areas of investigation. The first area determined the most appropriate stimulation rates for the neonate MLR and SSEP; the second area evaluated the basic characteristics of the neonate MLR as a function of band-pass filter width; the third area evaluated how well the SSEP predicted low-frequency hearing sensitivity; the fourth area investigated the stability of the SSEP as children cycled through periods of wakefulness and sleep; the fifth area examined the relationship of the neonate MLR to later occurring auditory evoked potentials.

CHAPTER II

LITERATURE REVIEW

Behavioral Observations

It is firmly established that neonates do not respond well to discreet frequency auditory stimuli (Taylor and Mencher, 1972; Eisenberg, 1976; Gerber and Mencher, 1979). Eisenberg (1976) reported that the rate of infant response varies according to the complexity of the stimulus. Taylor and Mencher (1972), Gerber and Mencher (1979), and Gerber, Lima, and Copriviza (1983) have each shown that newborns respond more often to unfiltered white noise than to narrow bands of noise. At best, however, the response rate is 25%-30% to sounds presented at levels near 90 dB SPL (Gerber et al., 1983). The lack of frequency specific measurements, and the high stimulation levels required for responses, severely limit usefulness of behavioral observation methods for predicting thresholds and audiometric contours.

Crib-o-gram

The crib-o-gram was designed to eliminate observer bias in judging the presence of a response and to screen large numbers of newborn infants with minimal cost and manpower (Simmons and Russ, 1974; Simmons et al., 1979). The apparatus consists of a sound source, a motion detection device, a micro-processor control circuit to score the results, and a recorder. A similar device has been developed in Europe, the Linko-Bennett Auditory Response Cradle (Bennett, 1979), and in Israel, the Accelerometer (Shenhav and Eliachar, 1983). The instruments present band-passed noise filtered between 2600 Hz and 4300 Hz or narrow band noise centered at 3000 Hz at levels between 85 dB and 92 dB SPL. Each respective unit monitors time-locked changes in the child's motor activity in response to the stimuli. In general, if the child responds at rates between 20% and 30% over approximately 20 trials, the unit scores him as having passed the screen.

The crib-o-gram instruments are intended to find children with hearing loss greater than 45 dB (Miller and Simmons, 1984). As is the case with behavioral measurements, the high frequency stimuli, combined with the intense presentation levels, limit the usefulness of this technique for defining thresholds, particularly for low frequencies. Consequently, when hearing impaired children are detected by this technique, the instrumentation and test protocols do not permit definition of either degree of hearing loss or audiometric slope.

Acoustic Reflex Measurements

Niemeyer and Sesterhenn (1974) and Jerger and his co-workers (1974) devised methods to predict categories of hearing based on acoustic reflex measurments. In addition, Jerger et al. (1974) reported that audiometric slope could be predicted with reasonable accuracy by comparing reflex thresholds elicited by pure tones to those elicited by high-pass and low-pass filtered noises. Since these reports were published, several investigators have developed techniques to improve the accuracy of hearing sensitivity predictions and the frequency specificity of the predictions (Baker and Lilley, 1976; Handler and Margolis, 1977; Rizzo and Greenberg, 1979). The findings of most acoustic reflex investigations in neonates, however, have fueled substantial controversy regarding characteristics of the acoustic reflex in the neonate population. Consequently, these predictive techniques have yet to be applied successfully in neonates.

Keith (1973) was the first to systematically evaluate acoustic reflexes in neonates. He used a Madsen ZO-70 immittance bridge with a 220 Hz probe tone to monitor reflexes in 40 normal, term infants. Using tone bursts of 500 Hz and 2000 Hz to elicit the reflex, Keith reported observable reflexes in 30% of the children and absent reflexes for 26% of his subjects. In the remaining children any possible reflex activity was obscured by gross body movements in response to the tonal stimuli.

Bennett (1975) examined 98 infants age 5 to 218 hours. He used a Barany noise box with approximately 106 dB SPL output to produce reflex activity and recorded immittance changes with a 220 Hz probe tone. Bennett obtained reflexes in 28% of the neonates between 5 hours and 20 hours of age. The percentage of measurable responses declined to approximately 18% for infants who were 20 to 218 hours old. He attributed the initial peak in response rate to hyper-responsiveness of the elicited reflex during the first hours of life. These findings also suggested that absence of the reflex in neonates does not signify concommittant hearing loss.

Crowell and his collegues (1980) used a standard immittance meter (American Electromedics 83) and a 220 Hz probe tone to record reflexes in 63 babies between 1 and 101 days old. Their stimuli consisted of tones at octave intervals from 500 Hz to 4000 Hz, wide band noise, high-pass and low-pass filtered noise. Only ten percent of the ears tested demonstrated contralateral reflexes to one or more stimulus. In contrast, 79% of the children demonstrated ipsilateral reflexes.

Stream and his co-workers (1978) attempted to study the emerging characteristics of the acoustic reflex in neonates. Their subject sample consisted of 152 ears of 90 children whose ages ranged from 3 to 132 hours. Using a commercial device similar to Crowell et al. (1980), they recorded acoustically elicited reflexes in seven of 152 ears (4.6%) to one or more tonal stimuli between 500 and 4000 Hz. Like Bennett (1975), they asserted that absence of the reflex in neonates does not necessarily suggest hearing loss.

Barajas and his collegues (1980) examined the acoustic reflex as a method of hearing screening in 26 ears of 25 subjects age 24 to 144 hours. They employed a Grason Stadler 1721 otoadmittance meter to record contralateral reflexes and a Grason Stadler 1722 otoadmittance meter to record ipsilateral reflexes. Both instruments used a 220 Hz probe tone. To elicit contralateral reflex activity, stimuli consisted of 1000 Hz tones and wide band noise presented between 95 and 110 dB SPL. Only 1000 Hz tones presented at 95 dB SPL were used to activate the reflex ipsilaterally. In contrast to Crowell et al. (1980), Barajas et al. reported that ipsilateral stimulation failed to elicit reflex activity in any child. With contralateral stimulation, they observed reflexes in 7.7% of the ears for noise and 4.4% for tonal activating signals. The reflex was clearly absent for 4.4% of the ears tested with wide band noise and 20.6% using tonal stimuli. The remaining responses were obscured by behavioral responses to the sounds. They concluded that stapedial reflex testing is not efficacious for screening hearing in neonates.

Keith and Bench (1978) expressed concern about neonatal behavioral responses interfering with acoustic reflex measurements. They hypothesized that repeated stimulus presentations would result in habituation of the behavioral response, leaving only stapedius muscle activity. They evaluated their hypothesis on 20 clinically normal neonates with ages between 8 and 192 hours. The apparatus was a commercial immittance bridge with a 220 Hz probe tone. The reflex eliciting signals were 1000 Hz tones, wide band noise, and 2600 Hz low-pass filtered noise presented to the ear contralateral to the probe ear at levels from 95 to 110 dB SPL. Regardless of the number of stimulus presentations, Keith and Bench were unable to habituate the behavioral reactions. They measured unambiguous stapedial reflex activity in only 5% of the total number of trials.

McCandless and Allred (1978) were troubled by the low incidence of stapedial reflexes reported in earlier studies. Consequently, they evaluated 53 infants, first testing them at 18 hours post-partum, and then at regular intervals over the first six weeks of life. They used tones from 500 Hz to 4000 Hz to elicit reflexes and an otoadmittance meter with both 220 Hz and 660 Hz probe tones to record reflexes. Almost 79% of their subjects demonstrated strong reflexes during the first hours of life; 89% had reflexes by 48 hours post-partum. Measurements made during the second week revealed that every child had reflex responses to one or more stimulus frequencies. The overwhelming majority had measurable reflexes for 500 Hz and 1000 Hz signals. In addition, McCandless and Allred reported that probe tone frequency had significant influence on measurement of the reflex. They found that the 660 Hz probe tone had much greater sensitivity to impedance changes than the 220 Hz probe tone. For example, 4% of the neonates had measureable reflexes at 48 hours using a 220 Hz probe tone; whereas 89% demonstrated reflex activity using a 660 Hz probe tone. They attributed the effect of probe tone frequency on acoustic reflex measurements to a difference in resonant characteristics of the neonatal external ear canal.

Weatherby and Bennett (1980) examined in greater detail the effect of probe tone frequency on stapedial reflex measurements. Their subjects were 44 normal neonates ranging in age from 10 to 169 hours. Using only a white noise stimulus, they recorded reflex activity with probe tones from 220 to 2000 Hz in approximately 200 Hz intervals. Weatherby and Bennett reported that none of the infants demonstrated reflexes with a 220 Hz probe tone. In contrast, all neonates had recordable reflexes for probe tones from 800 Hz to 1800 Hz. Mean reflex thresholds for white noise signals varied from 63.5 dB SPL for 1400 Hz probe tone to 77.3 dB SPL for 400 Hz probe tone. Like McCandless and Allred (1978) they attributed the absence of measurable reflexes at 220 Hz probe tone to a substantial difference in resonant characterictics between neonatal and adult ears.

Himelfarb, Popelka, and Shannon (1979) elucidated the source of the probe tone effect on recording middle ear immittance changes in neonates. They performed susceptance and conductance tympanometric measurements at 220 Hz and 660 Hz in 34 infants age 8 to 96 hours. Their results indicated that the newborn middle ear system has positive sign reactance. That is, the system is mass dominated as opposed to stiffness dominated in adults. Moreover, reactance values are often smaller than resistance values, again, in contrast to adults. A major contributor to these transmission characteristics is the neonatal eardrum. The low impedance of the eardrum effectively shunts the higher impedance of the middle ear system. Consequently, small changes in immittance such as caused by the reflex cannot be seen when using a low frequency probe tone. However, small changes in immittance should be observable with a high frequency probe tone.

To demonstrate this point, Bennett and Weatherby

(1982) evaluated stapedial reflexes in 28 infants 4 to 8 days old using a 1200 Hz probe tone. Reflex activating signals were tones from 250 Hz to 4000 Hz, high-pass and low-pass filtered noise, and wide band noise. Eighty-nine percent of the children demonstrated reflex activity to wide band noise. The lowest number of reflexes were obtained for 500 Hz and 1000 Hz activating signals (61% each). Mean reflex thresholds ranged from 73 dB SPL for wide band noise to 105 dB SPL for 500 Hz. The high percentage of measurable reflexes are sharply contrasted to the results of earlier studies using 220 Hz probe tones.

Very few studies have specifically applied hearing threshold prediction techniques to neonatal subjects. Newman, Stream, and Chesnutt (1974) used the Niemeyer and Sesterhenn (1974) and Jerger et al. (1974) methods of predicting hearing loss and audiometric slope in both neonates and infants. They found, however, that lack of measurable reflexes prohibited use of the prediction methods.

Himelfarb, Shannon, Popelka, and Margolis (1978) evaluated the applicability of three hearing prediction techniques in 21 normal neonates 8 to 96 hours old. The prediction techniques were those of Niemeyer and Sesterhenn (1974), Jerger et al. (1974), and the bivariate plot method (Handler and Margolis, 1977). They used 220 Hz susceptance changes to monitor reflex activity. These investigators found that the Niemeyer and Sesterhenn and Jerger et al. methods were not applicable due to an average 9 dB difference between reflex thresholds for tones and noise. The bivariate plot procedure predicted normal results for six infants and abnormal thresholds for 21 infants.

Although Bennett and Weatherby (1982) were able to observe reflexes in almost every child using a 1200 Hz probe tone, they had a substantial number of children with absent reflexes for 500 Hz and 1000 Hz activating signals, essential frequencies for predictions of hearing loss. Therefore, despite the usefulness of stapedial reflex measurements for predicting hearing loss in older children and adults, the reflex seems to have limited value in neonates. One problem is the interference to recordings by behavioral reactions to reflex activating signals (Keith, 1973; Keith and Bench, 1978). Efforts to habituate the behavioral responses have not been successful (Barajas et al. 1981) leaving this as a potential problem when initial signal intensities are 95 dB SPL or greater.

Another factor limiting clinical application of reflex measurements is maturation of the middle ear system. Numerous investigators have reported low impedance measurements when using a 220 Hz probe tone (Keith, 1973; Stream et al., 1978; Himelfarb et al., 1979; Crowell et al., 1980; Weatherby and Bennett, 1980). These findings are due to a highly compliant ear drum (Himelfarb et al., 1979) necessitating use of a high frequency probe tone. Bennett and Weatherby (1982) found that a high frequency probe tone (1200 Hz) greatly facilitated the ability to record reflexes for all activating signals.

Despite the enhancement of high frequency probe tones, a substantial number of children failed to demonstrate reflex activity for 500 Hz and 1000 Hz activating signals (Bennett and Weatherby, 1982). This suggests the possibility of neurological immaturity causing elevated thresholds, a further effect of the middle ear transmission characteristics, or an interaction between these two factors. Regardless of the mechanism, the substantial number of missing reflexes at 500 Hz and 1000 Hz severely limits the usefulness of this tool for hearing prediction.

Evoked Potentials

Evoked potentials have become extremely valuable for assessment of hearing function. They are categorized as auditory brainstem response (ABR), middle latency response (MLR), and slow-wave or late auditory potentials based on the post-stimulus latency at which the respective waveforms occur. The ABR is seen from 1 to 10 msec; the MLR waveforms occur from 10 to 80 msec; and the late potentials are seen between 80 and 500 msec.

Late Auditory Potentials

Mapping studies have indicated that late auditory potentials arise from the frontal cortex (Davis and Zerlin, 1966; Davis, 1976). The exact anatomical areas of the cortex which contribute to the averaged response are unknown. In adults, the waveforms consist of a series of positive and negative peaks that vary in latency according to stimulus intensity. The frequency composition of these waveforms is greatest in the 10-14 Hz range, requiring EEG filter settings generally from 1 to 30 Hz. Of the three categories of evoked potentials, late potentials have the least stringent stimulus requirements. Tone pips with durations up to 30 msec can be used to elicit responses (Davis, 1976). This capability offers substantial frequency specificity for hearing assessment. In adults, the waveforms have been observed within 10 dB of behavioral threshold for various frequency tone pips. However, waveform amplitude is highly dependent on subject state (Davis, 1976, 1981; Skinner and Glattke, 1977). Sleep can produce 30 dB shifts in response thresholds resulting in significant errors in hearing sensitivity predictions

(Mendel, Hosick, and Windman, 1975). However, it is well established that neonate EEG and sleep patterns are totally different from those seen in adults (Spehlmann, 1981). It was reasonable, therefore, that several researchers explore late auditory potentials as a possible method of hearing prediction in infants.

McRandle, Smith, and Goldstein (1974) evaluated late potentials in 10 normal newborns 36 to 72 hours old. They found that, similar to adults, the waveforms were highly dependent on the state of the child. Of the waveforms they successfully recorded, the peak latencies were much longer than noted in adults. When the babies slept, large amplitude low frequency EEG components often obliterated major late potential peaks. Approximately one-half of their evoked potential recordings resembled the control, no-sound recordings. Arlinger and Walker (1975) reported similar results in infants ranging in age from one day to seven months.

Hume and Cant (1977) attempted to predict hearing thresholds in 88 children less than three years of age. They found that 11 of the 12 substantial errors in threshold prediction were with children under 12 months. Six of these errors were associated with the use of sedation to induce sleep.

Skinner and Glattke (1977) and Davis (1976, 1981) each stated that, in their clinical experiences, late auditory potentials were not efficacious for use in young children. Skinner and Glattke found that the stability of the waveform diminished sharply in children. Davis (1981) reported that the pediatric responses varied according to stage of sleep. Consequently, he recommended against using late auditory potentials to evaluate hearing sensitivity in children under three years of age.

Joseph, Lesevere, and Dreyfus-Briscoe (1976) found EEG patterns to be very unstable in 17 infants between 29 and 43 weeks conceptual age. Premature infants showed EEG frequency dominance in the beta range (16-20 Hz). In contrast, full-term infants had EEG frequency dominance in the alpha range (8-13 Hz). Several children who were at the dividing age between premature and full-term also demonstrated an intermediate frequency dominance (15-16 Hz). In addition, bursts of high amplitude (greater than 50 uV) waves of 1-3 Hz often occur simultaneously on both sides of the head and last four to five seconds (Spehlmann, 1981). All of the infants had large spatial regions (greater than 2 cm) of either inactivity or unsynchronized activity. Therefore, the instability of the EEG frequency patterns combined with the high amplitude, low-frequency bursts of EEG noise are among the primary factors that severely limit the use of late auditory potentials to predict hearing thresholds in neonates.

Middle Latency Response

The middle latency response (MLR) consists of a series of waves between 10 and 80 msec pose-stimulus. Geisler, Frishkopf, and Rosenblith (1958) first reported the MLR in humans as having an onset latency of approximately 20 msec. The most prominate peak, wave Pa, occurred at approximately 30 msec after stimulus onset. Later studies have shown that the MLR is a robust response that is influenced to a much lesser degree by sleep and sedation than the late potential (Mendel, 1974; Mendel, Hosick, and Windman, et al., 1975; Ozdamar and Krause, 1983). The MLR is elicited by either clicks or frequency-specific tone pips and has been used successfully in hearing threshold prediction in adults (Geisler, Frishkopf, and Rosenblith, 1958; McFarland, Vivion, and Goldstein, 1977; Ozdamar and Kraus, 1983). The amplitude of the waveforms, particularly wave Pa, is largest for low-frequency stimuli (250-500 Hz) and becomes somewhat smaller as tone pip frequency is increased (McFarland, Vivion, and Goldstein, 1977; Thornton, Mendel, and Anderson, 1977) possibly reflecting spatial areas of stimulation along the basilar membrane (Davis, 1976).

The exact anatonical origins of the MLR are unknown. Parving, Salomon, Elberling, and Larson (1980) reported the case of a 76 year old man with bilateral temporal lesions manifesting themselves as auditory agnosia. MLR in this person was normal bilaterally for both latency and waveform morphology. Based on cerebral blood flow and evoked potential results, they concluded that the transverse gyrus of the temporal lobe is not primarily responsible for generation of the MLR.

Ozdamar, Kraus, and Curry (1982) presented a case with bilateral subarachnoid hemorrhage affecting the temporal lobe and thalamo-cortical fibers. Their patient had a normal ABR but absent MLR bilaterally. From these results they proposed that the origins of the MLR are the primary auditory cortex and the thalamic radiations.

The low-frequency response characteristic suggests that the MLR is a product of post-synaptic potential activity as opposed to the high frequency action potentials of the ABR. Response symmetry over both hemispheres plus largest amplitude when the active electrode is on the vertex suggest bilateral generation of wave Pa (Ozdamar, Kraus, and Curry, 1982).

Engle (1971) was the first to evaluate the MLR in newborn infants. He observed waveforms in eight of 24 children in the newborn nursery. Repeat testing resulted in disappearing waveforms in five of the eight infants. Only three children had stable, repeatable waveforms.

McRandle, Smith, and Goldstein (1974) examined the influence of stimulation rate on the MLR in neonates. They presented click stimuli at 4.5 and 9.0 per second to 10 babies 36 to 72 hours old. The most stable responses with the largest amplitudes occurred in response to the 4.5 per second stimulation rate.

Mendel, Adkinson, and Harker (1977) studied the latency and amplitude components of the MLR in infants. Their subjects were 18 infants ranging in age from one to eight months. Tone pips with a frequency of 1000 Hz were presented at a rate of 6.0 per second. Latency of the positive and negative peaks, especially wave Pa, decreased with increasing age. Latency of wave Pa averaged 26.7 msec for the one month old infants and 24.2 msec for the children eight months old. The amplitude of wave Pa showed comparable changes with age, becoming larger in older children. In addition, they noted that MLR waveforms could be identified in the majority of infants at 30 dB.

Wolf and Goldstein (1978) found that the early peaks of the MLR were more prominent in five neonates 24 to 96 hours old. Moreover, only the ipsilateral recordings were recognizable as middle latency components. Contralateral recordings revealed repeatable waveforms only at moderate intensities that had no resemblance to the expected MLR. They also found that MLR waveforms could be visually identified at 30 dB nHL in all five children and at 10 dB nHL in three children.

In a follow-up study, Wolf and Goldstein (1980) reported that the MLR was beneficial for obtaining low-frequency information regarding hearing sensitivity. They presented 500 Hz and 3000 Hz tone pips to 20 normal neonates 26 to 82 hours old. Although the overall amplitude of the responses in these children was smaller than seen for adults, the amplitude for 500 Hz tone pip MLR was substantially larger than for 3000 Hz tone pip MLR. They concluded that the small amplitude responses from 3000 Hz stimulation make the prospects of predicting high-frequency hearing poorer than for low-frequency hearing.

Mendelson and Salamy (1981) described maturational effects on the MLR from prematurity through adulthood. They presented 60 dB nHL clicks at a rate of 9.7 per second to 15 premature infants (31 to 37 weeks conceptual age), 15 full-term babies (12 hours to 4 days), 15 children (3 to 4 years), and 15 adults (24 to 39 years). To their surprise, they found no significant latency changes with age except for wave Po. Response amplitude increased from prematurity through childhood, then declined in adulthood.

Despite these apparant successes in obtaining the

MLR in neonates, Davis (1976) and Skinner and Glattke (1977) stated that the MLR was not successful in determining hearing thresholds in their pediatric populations. Substantial proportions of their normal children failed to demonstrate recognizable waveforms at low and moderate intensities.

Recently, considerable attention has been focused on EEG filtering effects on MLR waveforms. The studies cited above used narrow analog filtering (25 Hz to 175 Hz or less) to obtain MLR recordings. The narrow band pass was designed to minimize the influence of high amplitude, low-frequency and moderate amplitude, high-frequency EEG contamination of the averaged waveform (Davis, 1976). Scherg (1982) and Kavanagh, Harker, and Tyler (1984) demonstrated that such narrow analog filtering produces significant distortion of the MLR waveform. Low-pass filtering smoothed the waveform but extended the latency of wave Pa by 5 msec. High-pass filtering increased the amplitude of Nb-Pb and decreased Pa amplitude and latency. Increasing the slope of the analog filter produced almost a complete phase reversal of the Na-Pa-Nb complex. These results suggest that amplitudes, latencies, and perhaps the presence of some waves are highly dependent on filtering characteristics (Suzuki, Hirabayashi, and Kobayashi, 1984).

Suzuki and his colleagues (1983a, 1983b, 1984) conducted a series of studies designed to elucidate optimal filtering for the MLR in children and adults. Using digital, zero phase shift filters, they found that the primary energy of the MLR in adults is between 30 Hz and 50 Hz. In contrast, the primary energy of the MLR in children 1 to 7 years is approximately 20 Hz. Consequently, children require a lower high-pass filter than traditionally used. The previous studies that examined the MLR in children often used high-pass filters of 25 Hz to 35 Hz. Suzuki et al. reported that wave Pa disappeared in children as the high pass filter approached 40 Hz. Conversely, if too little high-pass filtering was used, large amplitude, low-frequency EEG components totally obscured wave Pa. When the filters were optimally adjusted, they noted substantial variability in the latency and morphology of wave Pa which was attributed to unstable low-frequency brain activity. The mean wave latency for children was 40.16 msec. This latency value was significantly longer than reported for adults (30.7 msec) or in previous studies for children (approximately 25 msec) (Mendel Adkinson, and Harker, 1977; Wolf and Goldstein, 1978; Mendelson and Salamy, 1981).

The effects of EEG filtering on MLR waveforms in very young children were studied further by Okitsu (1984) and Kileny (1984). Okitsu (1984) presented clicks at the rate of 8 per second to 20 children age 4 months to 3 years.

Using band pass filters of 20 to 300 Hz, he observed wave Pa in only 33% of the recordings. Using clicks delivered at 9.1 per second, Kileny (1984) reported that the MLR disappeared in an 8 month old child as the EEG filters were opened from 30-100 Hz to 5-1500 Hz. In a second child 18 days old, wave Pa appeared to shift in latency from 25.6 msec to 41 msec with comparable filter changes. Furthermore, the morphology of wave Pa degraded from a sharply defined peak to a very broad, low amplitude peak.

The findings of these recent studies reveal that MLR characteristics are substantially different between children and adults. The primary differences are the concentration of EEG energy in the MLR, the EEG filtering requirements, and the uncertainty of whether the MLR actually exists in very young children. More investigation is needed to determine the exact characteristics of the MLR in children before it can be used reliably to evaluate hearing sensitivity.

Auditory brainstem response

Since Jewett and Williston (1971) first described an auditory evoked neural response that appeared between 1 and 10 msec, numerous reports have expounded on the value of the auditory brainstem response (ABR) for neurological evaluation and hearing prediction. The ABR is characterized by six or seven vertex-positive peaks labeled with Roman numerals I through VII. Wave V is generally the most prominent wave due to its relatively large amplitude. Moller and Janetta (1983) reported that wave I is believed to represent the whole nerve action potential at the level of the cochlea. Wave II also arises from the auditory nerve after the nerve exits the internal auditory canal. Waves III and IV are assumed to have their source in second- and third-order neurons of the ascending auditory pathway. They attribute the neural generator of wavd V to the lateral lemniscus and the slow negative peak following wave V to the inferior colliculus.

Using unfiltered and unmasked stimuli, ABR recordings reflect activity in the basal portion of the cochlea, primarily in the 1000 Hz to 8000 Hz region (Coats and Martin, 1977; Coats, 1978; Jerger and Mauldin, 1979; Yamada, Kodera, and Yagi, 1979; Borg and Lofqvist, 1982). Consequently, the ABR offers little low frequency information without substantial manipulation in stimulation and recording conditions.

Stockard and Westmoreland (1981) outline several technical factors which are very important to obtain valid and reliable recordings, particularly from neonates. Among these are state of the child with specific reference to muscle contamination of the response; earphone placement;

environmental ambient noise; stimulus phase, rate, and intensity; chronological age; and neurological maturation. Each of these variables influence the quality of the ABR recording and, in turn, hearing threshold predictions. Perhaps the most important factors are the age of the child and concommitantly, the degree of neurological maturation.

Starr, Amlie, Martin, and Sanders (1977) evaluated the ABR in 42 premature and full-term infants (25 to 44 weeks conceptual age) to define maturation of the peripheral and central neural components of the response. They presented clicks at a rate of 10 per second at levels between 75 dB and 25 dB nHL. The premature babies below 29 weeks had an ABR only at 75 dB. As age increased, the ABR was observed at correspondingly lower levels. Maturation of the ABR proceeded at the same rate for intra-uterine and extra-uterine environments. Despite great variability, response amplitude increased as gestational or conceptual ages increased. Similar findings were reported by Morgan and Salle (1980) and Picton, Stapells, and Campbell (1981). In addition, Picton and his colleagues found that wave I in the neonates was much larger and longer in latency than in adults. Conversely, wave V had approximately the same amplitude as in adults although it had a longer latency. They attributed the longer latency for wave I to maturation of the high frequency region of the cochlea or immaturity in transmission between hair cells and nerve fibers.

Schulman-Galambos and Galambos (1975) reported that wave V latency increased by 0.4 msec with each 10 dB of attenuation in children from 34 to 42 weeks gestational age. This finding is similar to observations made in adults. Furthermore, wave V latency decreased systematically 0.3 to 0.5 msec per week with increasing gestational age. Waveform replications showed that wave V latencies were similar over repeat trials with an average 0.16 msec difference and a maximum difference of 0.32 msec from test to retest. Stage of sleep in these children had no systematic effect on the ABR.

Mjoen and Qvigstad (1983) assessed the efficacy of recording ABRs during the first 30 minutes after birth, 2 hours after birth, and 48 hours after birth. They used 60 dB clicks presented to 20 normal newborns. Repeatable waveforms could not be identified in any child during the first 30 minutes due to extreme activity. After 2 hours they could identify waveforms in nine children; and after 48 hours, repeatable waveforms were recorded in 17 children.

Salamy and Mckean (1976) obtained recordings from 158 infants ranging in age from 16 hours to 1 year. They used a click rate of 15 per second at 55 dB nHL to examine peripheral transmission (stimulus onset to wave I) and central transmission (wave I to wave V) latency characteristics. The newborns had an average wave I latency of 2.12 msec (SD 0.35 msec), wave V latency of 7.06 msec (SD 0.38 msec), and I to V interwave interval of 5.12 msec (SD 0.29 msec). Inter-subject variability was much greater than intra-subject variability. Although wave I reached adult latency by 6 weeks of age, the I to V interwave interval did not reach adult values until the children were 1 year old. Adult morphology replaced the infantile response at 3 to 6 months.

Barajas, Olaizola, Tapia, et al. (1981) evaluated wave V responses in 10 ears of children age 24 to 144 hours. Their stimulus was a single cycle of a 1000 Hz sinusoid presented at 20 per second in 10 dB steps from 60 dB nHL to 30 dB nHL. They recorded wave V at 30 dB for all children. The mean latencies for each intensity ranged from 7.5 msec at 60 dB to 8.8 msec at 30 dB.

Although most studies focused on wave V, it is not the only prominent feature to identify the presence of an ABR. Weber (1982) and Hooks and Weber (1984) discovered that wave III had larger amplitude and was more readily identifiable than wave V in a significant percentage of their premature infants between 32 and 44 weeks conceptual age.

The ability to record the ABR at levels of 30 dB and below in neonates made ABR testing a promising method for hearing evaluation early in life (Davis, 1981; Barajas, Oliazola, Tapia, et al., 1981; Stein, 1984). Indeed, numerous investigations have examined the efficacy of using the ABR to screen neonate hearing, especially children in the neonatal intensive care units (NICU).

Mokotoff, Schulman-Galambos, and Galambos (1977) evaluated the ABR as a hearing screening device in 81 children between 36 weeks conceptual age and 15 years. Whenever possible, the ABR results were compared with previous or follow-up audiologic evaluations. The ABR correlated well with behavioral thresholds and acoustic reflex predictions of hearing sensitivity except in a few cases of suspected middle ear problems. In those children, there existed the strong likelihood of low-frequency hearing loss which the ABR would not detect.

Schulman-Galambos and Galambos (1979) performed ABR measurements on three groups of children. The first group consisted of 220 normal newborn infants from 7 to 72 hours old. Attempts to determine ABR threshold revealed that repeatable waveforms could be obtained at 20 dB nHL for all infants but at 10 dB for only a few children. None of the children had results consistent with hearing loss. The second group of children was 75 neonates in the NICU. These infants were born at 37 to 40 weeks gestational age and evaluated at 1 to 14 weeks post-partum. Of these children, four (5.3%) were shown to have severe hearing impairment. The third group consisted of 325 NICU survivors who were examined at 1 year of age or older. Twenty-seven of these children overlapped with group two. Four new cases were found with significant hearing loss bringing the total prevalence of hearing loss for NICU children to 2.4%. They concluded that if a child passed the NICU screen, he/she is unlikely to develop severe auditory impairment thereafter. In a follow-up study (Schulman-Galambos and Galambos, 1979) they evaluated 273 premature infants who were at risk for hearing disorders with ABR measuremets. The prevalence of hearing loss for this group was 2.14%. Consequently, they recommend ABR testing on all NICU infants prior to discharge.

In a study of 108 NICU infants from 26 to 42 weeks gestational age, Despland and Galambos (1980) found 11 children with hearing loss for an prevalence of 10.2%. In a corresponding report (Galambos and Despland, 1980), they evaluated the risk factors which produced abnormal ABR results. These included asphyxia, low birth weight, acidosis, intracranial hemorrhage, coma, genetic anomalies of the heart or face, and respiratory distress syndrome. The administration of ototoxic medication in prophylactic doses was not a major contributor to the risk factors.

Galambos, Hicks, and Wilson (1982) continued the study of Galambos and Despland (1980) to determine the prevalence of hearing loss in a larger sample. They screened 890 NICU babies with ABR just prior to discharge. Approximately 15% (141 children) of the sample failed the screening. Follow-up evaluations revealed that 3.7% of the total sample had bilateral hearing loss. Approximately 1.8% of the sample had hearing impairment sufficient to warrant hearing aid use.

Jerger, Hayes, and Jordan (1980) reported their clinical experience with auditory brainstem testing in pediatric assessment. They performed ABR measurements on 167 children age 4 days to 83 months as a cross-check to confirm behavioral or impedance results. The children were referred as high risk for hearing loss or to confirm hearing loss. Jerger and his colleagues proposed that one must consider the presence of concommitant central nervous system (CNS) disorder in high risk infants in order to interpret ABR results accurately. Fifty-four percent of their sample had normal sensitivity or no worse than a mild hearing loss. Twenty percent had moderate to severe hearing impairment; and 25% had profound hearing loss. Approximately one-third of the moderate to severe and profound hearing impaired children also manifested some degree of CNS involvement which could have influenced ABR interpretation.

Stein, Ozdamar, and Schnabel (1981) used the ABR to evaluate hearing sensitivity in 82 children who were either suspected or labeled deaf and blind. The children, age 12 days to 20 years, displayed no behavioral responses to sound. ABR results indicated that 43% of the children had normal sensitivity; 32.9% had no demonstrable ABR; and almost 20% of the children fell into the 30 dB to 70 dB threshold range. Three children had severe neurological involvement which made interpretation of the ABR for hearing loss ambiguous.

Cevette (1984) described ABR screening results obtained from 745 children. Approximately 21% showed signs of peripheral hearing loss prior to discharge. Follow-up testing indicated that approximately 2% of the original sample had sufficient hearing loss to require amplification. Interestingly, two children that had normal ABR thresholds displayed low-frequency sensorineural hearing loss on follow-up testing.

The ABR has been highly recommended as an effective method to screen for hearing loss in neonates (Schulman-Galambos and Galambos, 1979; Barajas, Olaizola, Tapia, et al., 1981; Davis, 1981; Stein, 1984). However, it is not the panacea of hearing assessment that can be used reliably and effective in every case. Central nervous system abnormalities affecting the brainstem auditory pathways can cause substantial ambiguity in test interpretation (Jerger, Hayes, and Jordan, 1980; Stein, Ozdamar, and Schnabel, 1981). Furthermore, ABR data convey little or no information below 1000 Hz (Jerger and Mauldin, 1979). Consequently, as shown by Cevette (1984), normal ABR thresholds may be displayed in the presence of significant low-frequency hearing loss. The lack of ABR frequency-specificity has been criticized as a major inadequacy of the test paradigm (Mokotoff, Schulman-Galambos, and Galambos, 1977; Davis, 1976). The ABR not only fails to detect hearing loss confined to the low-frequencies, but also offers no information regarding slope of audiogram in the infants found to have hearing loss. Several investigators have responded to the need for increasing the frequency-specificity of the ABR through derived responses, notched-noise masking, examination of a slow-negative wave that occurs after wave V, and by using tone pip stimuli.

Tone pip stimuli. Wood, Seitz, and Johnson (1979) obtained ABRs from 10 normal listeners 22 to 47 years old. Stimuli consisted of 500, 1000, 2000, and 4000 Hz tone pips. As the tone pip frequency decreased, the ABR became more difficult to identify. At 500 Hz, six subjects had recognizable waveforms at 30 dB. Only four subjects displayed identifiable responses at 10 dB.

Suzuki and Horiuchi (1981) attempted to determine optimum rise times for tone pips eliciting ABRs. They presented 2000 Hz and 500 Hz tone pips to eight normal adults age 21 to 34 years. Tone pip rise times varied from 10 msec to 0.5 msec; stimulus intensities ranged from 50 dB to 15 dB nHL. They found that rise times of 1.5 msec for 2000 Hz and 3 msec for 500 Hz were the best suited to obtain consistent, reliable waveforms.

Maurzi, Paludetti, Ottaviani, and Rosignoli (1984) evaluated ABR thresholds for 1000 Hz and 500 Hz tone pips in 19 normal adults. They observed a single, large, low-frequency wave, presumably wave V, which occurred 2.5 to 3.0 msec later than the click-evoked wave V. For 1000 Hz tone pip, a recognizable waveform was seen in each subject at 30 dB. However, only 52.6% or the subjects had a response at 20 dB. The response rate for the 500 Hz tone pip was considerable less than for 1000 Hz. Approximately 74% of the subjects had a response at 30 dB. The rate fell to 32.6% at 20 dB. The tone pip thresholds were 10 to 30 dB worse than behavioral thresholds at the respective frequencies.

Kileny (1981) studied the frequency-specificity of 500 Hz and 1000 Hz tone pip ABRs in 20 normal hearing adults (26 to 30 years old), eight children (1 to 5 years old), and eight persons with precipitous hearing loss above 1000 Hz. He found that unmasked tone pips had similar latencies to click stimuli suggesting similar sites of neural activation along the basilar membrane. He obtained additional responses using high-pass filtered masking (98 dB/octave) with cut-off frequencies of 2000 Hz for the 1000 Hz tone pip and 1500 Hz for the 500 Hz tone pip. When masking was used, the tone pip elicited ABRs predicted low frequency thresholds with reasonable accuracy in the hearing impaired subjects.

Stapells and Picton (1981) investigated the frequency specificity of the brainstem responses to tones with different rise times. Tones of 500 Hz and 2000 Hz were presented alone or in the presence of notched noise. The rationale for this study was that if the notched noise caused the response to change, the response to the tones alone was mediated by nerve fibers in more basal areas of the cochlea. They found that tone pips were not frequency specific at moderate intensities. Furthermore, 500 Hz tone pips were not frequency specific at low intensities with rise times as long as 2 msec.

Hayes and Jerger (1982) examined the predictive accuracy of the ABR to 500 Hz tone pips in 30 normal adults 23 to 32 years old, 20 children 4 to 12 years old, and 37 hearing impaired children 4 to 16 years old. ABRs to tone pips were observed at 10 dB in all normal subjects. In most hearing impaired subjects, the 500 Hz tone pip overestimated threshold by up to 40 dB. The extent of overestimation varied according to the audiometric contour of the pure tone behavioral thresholds. Generally, steeper audiometric slopes resulted in larger errors.

Derived responses. A stimulus paradigm that combines tone pips or clicks with high pass masking noise has been used to isolate discreet areas of the cochlea (Don and Eggermont, 1978; Don, Eggermont, and Drachman, 1979). Consecutive ABRs are obtained with high-pass noise differing in cut-off frequencies by one-half to one octave. The waveforms are then subtracted from each other to yield a "derived" response for narrow bands throughout the cochlea. Measurement of thresholds for the derived responses results in reasonably accurate estimation of the audiogram (Don, Eggermont, and Brachman, 1979). Despite its accuracy, this technique has two major problems. First, the high-pass filters for sufficient masking require slopes that approach 100 dB per octave. Moreover, the signal averager must have the capability to store and subtract waveforms. These pieces of equipment are seldom found in most clinical environments due primarily to cost. Second, the derived response technique requires several hours to complete. The time requirement makes this technique impractical for most clinical situations, particularly with children or in the NICU environment.

Notched noise. Van Zantan and Broccar (1984) attempted to make the ABR more frequency-specific by using click stimuli that were partially masked by notched noise. Their subjects were seven normal hearing adults 20 to 32 years old. The clicks were presented in noise with notch widths of 5/3 octave centered at 500, 1000, 2000, and 4000 Hz. Latency of wave V decreased monotonically with increasing center frequency and with increasing stimulation levels. Frequency-specific ABR thresholds were within 20 dB of behavioral thresholds for each subject.

Pratt, Ben-Yitzhak, and Attias (1984) performed a similar study with both normal hearing and hearing impaired adults. Click-elicited ABRs were obtained from 10 normal listeners (21 to 33 years) and 10 listeners (19 to 33 years) with high frequency sensorineural hearing loss. Pink noise was filtered by two 96 dB per octave filters to produce one-half octave notches centered at frequencies from 500 Hz to 8000 Hz. They found no meaningful correlations between predicted and actual thresholds at all test frequencies. They concluded that, in its present form, the use of one-half octave notched noise does not yield audiologically relevant information.

Stockard, Stockard, and Coen (1983) attempted to use the notched noise technique in 486 premature and full-term infants. Tone pips at 1000 Hz and 4000 Hz were presented with noise which had a 1500 Hz notch centered at 1000 Hz and 4000 Hz, respectively. They found that the amplitudes were smaller and the thresholds were higher for the 1000 Hz stimuli than for the 4000 Hz tone pips thus limiting their use for hearing prediction.

Although the concept of notched noise is intuitively appealing, these studies demonstrate that the test paradigm is inadequate for prediction of mid-frequency (Stockard, Stockard, and Coen, 1983) or low-frequency (Pratt, Ben-Yitzhak, and Attias, 1984) hearing thresholds, especially in the presence of high frequency sensorineural hearing loss.

Slow negative 10 (msec) response. Suzuki, Hirai, and Horiuchi (1977) and Davis and Hirsh (1979) introduced a new technique that used low-frequency tone pip stimuli and examined the slow negative ABR wave that occurred between 8 and 15 msec (SN-10). These investigators reported promising results, citing observations of the SN-10 within 10 to 15 dB of behavioral threshold for both normal and hearing impaired listeners.

A more recent study by Klein (1983) examined the SN-10 in seven normal listeners using tone pips from 250 Hz to 4000 Hz. He found that tone pips from 500 Hz to 4000 Hz were adequate to obtain a frequency-specific SN-10. The 250 Hz tone pip yielded little useful information.

Hawes and Greenberg (1981) investigated SN-10 characteristics to tone pips in 20 normal infants 48 to 72 hours old. The stimuli were 500, 1000, and 2000 Hz tone pips presented at 60, 40, and 20 dB nHL. The frequency of occurrance for the SN-10 diminished rapidly as the stimulus frequency decreased. For 2000 Hz tone pips, the SN-10 was observed in 85% of the trials at 20 dB. In contrast, SN-10 to a 500 Hz tone pip was observed in 35% of the recordings at 20 dB.

The low-frequency region of the audiogram is the area of greatest need for assessment in infants. Although the ABR is well accepted by most audiologists as an evaluative tool for hearing sensitivity above 1000 Hz, attempts to improve the ABR's ability to assess low-frequency sensitivity have been less than adequate. One reason for lack of success is the trade-off between frequency specificity and the requirement for synchronous activation of multiple neurons. As the rise-decay characteristics and duration of the tone pip become longer to increase the frequency-specificity, the tone pip's ability to synchronize neural activity is severely compromised. A second reason for lack of success is the time and equipment requirements for some masking derivation paradigms. At present, neither requirement can be met in most clinical settings. Despite early optimistic reports, improving the quantity and quality of frequency-specific ABR waveforms remains a challenging task.

Steady State Evoked Potential

Galambos, Makeig, and Talmachoff (1981) recently introduced a new concept in evoked potential testing, the steady state evoked potential (SSEP). Originally called the 40-Hz event related potential, the SSEP is described as a consolidation, or superimposition, of successive negative and positive waves that comprise the middle latency response. The stimuli to elicit the SSEP and the recording paradigm are very similar to those used for the MLR. When stimuli are presented at approximately 40 per second, the resulting waveform resembles a 40 Hz sine wave. The amplitude of the SSEP is much larger than for the traditional MLR. For low-frequency tone pips, the response amplitude rises quickly at levels slightly above threshold permitting observation of waveforms within 10 dB of the behavioral threshold. Although the optimal stimulation rate varied slightly from one individual to another, all but one person in their adult sample had the largest amplitude response in the 35 to 45 per second range of stimulation.

Lesner, Lynn, and Poelking (1983) examined the reliability of the SSEP to predict hearing thresholds at 500 Hz and 1000 Hz. They presented 500 Hz and 1000 Hz tone pips to 20 adults (mean age 55 years) who had thresholds for at least two frequencies in each ear worse than 20 dB. Their results indicated that the 500 Hz SSEP was substantially more accurate than the 1000 Hz SSEP in predicting thresholds when using a visual scoring paradigm. Errors for 500 Hz ranged from 0 dB to 20 dB. Errors for 1000 Hz varied from 1 dB to 45 dB. The 95% confidence interval suggested that the SSEP could predict 500 Hz thresholds within 14 dB in contrast to 31 dB for 1000 Hz.

Stapells, Linden, Suffield, et al. (1984) performed a systematic study of the SSEP to confirm the original findings of Galambos and his co-workers and to explore other characteristics of the SSEP. Similar to the Galambos report, they found that amplitude of the response for most subjects was greatest with stimulation rates of 40 to 45 per second. Amplitude for 10 and 60 per second stimulation rates were less than half the amplitude at 40 per second. Individual maximum amplitudes showed greater variability than reported by Galambos, occurring at stimulation rates of

20, 30, 40, 45, and 50 per second. Fast Fourier Transform (FFT) measurements paralleled the peak to peak amplitude values. Both functions were linear down to threshold. Moreover, they also noted that the SSEP could be recorded to within a few decibels of the behavioral threshold.

The SSEP appeared as the most promising of any measure to date, for low-frequency hearing threshold prediction. Galambos, Makeig, and Talmachoff (1981) and Stapells, Linden, Suffield, et al. (1984) each reported that response amplitude increased as a function of decreasing stimulus frequency. Stapells and his colleagues stated that the 500 Hz response amplitude was almost double the 4000 Hz amplitude. Lesner, Lynn, and Poelking (1983) found that the larger amplitude at 500 Hz made the waveforms easier to recognize visually. Consequently, the 500 Hz data had fewer predictive errors than 1000 Hz. The large response amplitude for 500 Hz tone pips makes the SSEP particularly attractive to complement the ABR in infants for more complete hearing threshold predictions (Stapells, Linden, Suffield, et al., 1984).

Shallop and Osterhammel (1983) were the first to report on SSEP predictions in neonates. They compared the click-evoked SN-10, click-evoked SSEP, and 500 Hz-evoked SSEP in 35 normal newborns (mean age 4.4 days). The SN-10 had a mean threshold of 28 dB; SSEP to clicks had a mean threshold of 33 dB; and the SSEP to 500 Hz tone pips had a mean threshold of 37 dB. Interestingly, the peak to peak amplitudes for all three responses were nearly identical at the various intensities. The amplitude difference noted earlier in adults for high-frequency (clicks) and low-frequency (500 Hz tone pips) stimuli were absent.

Kileny (1984) studied this phenomenon further in an 8 month old infant. The amplitudes of the SSEP and the traditional MLR were the same, suggesting that a superimposition of MLR waveforms was not occurring. As the analog filters were opened from 30-100 Hz to 5-1500 Hz, the MLR to clicks (stimulation rate 9.1/second) and the SSEP to clicks (stimulation rate 40/second) virtually disappeared. The SSEP peaks observed under the narrow band filtering conditions were merely highly filtered ABRs. There appear to be significant differences, therefore, between the adult SSEP and the infant SSEP.

It is interesting that the few studies to examine the MLR or the SSEP in infants have used the same stimulation and recording parameters as in adults. Two lines of evidence suggest that this approach may be erroneous. First, the adult SSEP is based on the periodicity of the MLR waveforms. Waves Po (wave V), Pa, and Pb have an interpeak interval of approximately 25 msec. This periodicity makes the waves appropriate for superimposition to an acoustic stimulus presented at 40 per second (Galambos, Makeig, and Talmachoff, 1981). Suzuki, Kobayashi, and Hirabayashi (1983) confirmed that the primary energy in the adult MLR waveform is 40 Hz. This finding corresponds well to the 25 msec peak periodicity of the waveform components. In contrast, a frequency analysis of the MLR in young children revealed that the energy peak was approximately 20 Hz. If the SSEP is indeed a superimposition of successive peaks, it is plausible that 40 Hz is not the optimal stimulation rate for young children.

Second, pediatric MLRs obtained with zero phase shift digital filtering indicated a mean latency for wave Pa at 40.16 msec and a standard deviation of 5.40 msec (Suzuki, Hirobayashi, and Kobayashi, 1984). This latency value is much larger than any reported previously. Moreover, analog filtering distorted the pediatric waveform to a much greater extent than the adult waveform creating the possibility of erroneous amplitudes and peak latencies. The findings of Suzuki and his colleagues suggest that pediatric recordings of either MLR or SSEP must be obtained with EEG filters that will pass 20 Hz energy undistortedly. Most of the recordings for pediatric MLRs were obtained with high-pass filters from 25 Hz to 35 Hz. Shallop and Osterhammel (1983) obtained SSEP responses with high-pass filters of 30 Hz. Although Kileny (1984) lowered his high-pass filter to 5 Hz, it is plausible that no response was observed due to the 40 per second stimulation rate. Therefore, the evidence presented by Suzuki, Hirabayashi, and Kobayashi (1984) suggest that stimulation and recording parameters used successfully in adults are not appropriate in young children.

Purpose of the Project

The goal of this project was to develop a technique which could be used with reasonable reliability and validity to predict low-frequency hearing sensitivity in neonates. The basis for developing this technique was derived from the concept of the SSEP (Galambos, Makeig, and Talmachoff, 1981) and the MLR findings of Suzuki, Hirabayashi, and Kobayashi (1984) suggesting that present stimulus and recording parameters are not appropriate for use in neonates. To approach this goal, however, it was necessary to divide the project into five experiments. The first experiment was designed to establish the optimum stimulation rate using minimal EEG filtering to obtain a valid MLR and SSEP in neonates. The purpose of the second experiment was to determine the effect of band-pass filtering on the neonate MLR. The third experiment was designed to examine the variability of the low-frequency threshold predictions. The fourth experiment examined the stability of the neonatal

SSEP as a function of the sleep/wake cycle. The fifth experiment was designed to elucidate the relationship of the MLR to the late auditory potentials.

CHAPTER III

METHODS AND PROCEDURES

Subjects

The subjects in this study were 10 adults and 36 children. The children (19 boys and 17 girls) were patients in the neonate intensive care unit (NICU) at Wilford Hall United States Air Force Medical Center, San Antonio, Texas. Each child participated in one or more portions of this project. Their gestational ages at birth ranged from 24 to 42 weeks. At the time of test, their conceptual ages (gestational age plus post-partum age) ranged from 28 to 44 weeks. The children were selected on the basis of availability and degree of infirmity. Children who were critically ill or had severe central nervous system disorders were excluded from this study.

All of the premature infants were administered prophylactic doses of gentamycin and ampillicin for a minimum of three days to rule out sepsis. Galambos and Despland (1980) reported that this practice was not a risk factor for hearing loss, and it was not considered as such for this project. However, any child who had the administration of ototoxic medications beyond the prophylactic period for active treatment of a medical disorder became a candidate for increased risk of hearing loss. In all, nine infants were considered at risk for hearing loss due to the disorder that placed them in the NICU or the form of medical treatment for an otologically unrelated disorder. Four infants had moderate respiratory distress syndrome; one child had elevated cytomegalovirus titers; one infant had osteogensis imperfecta. One child was born at 32 weeks gestation with "CHARGE" association (Pagon et al., 1981). CHARGE is an acronym that describes an association of anomalies including Coloboma, cardiac disorder (Heart), choanal Atresia, mental Retardation, Gonadal dysgenesis, and sensorineural hearing loss (Ears). These disorders may occur in isolation or in combination. Examination of this child revealed coloboma, cardiac disorder, and choanal atresia. Four of these high risk children plus two others received significant doses of gentamycin and ampicillin for treatment of sepsis or to minimize the possibility of infection from a surgical wound. Of the remaining children, ten infants experienced premature birth due to maternal illness (hypertension, diabetes, or epilepsy). The etiology of premature birth in the other 17 children was unknown. The medical condition of the 27 infants who were at low risk for hearing loss was very good. In general, they were considered normal, premature infants growing up under medical supervision.

In addition to the children, ten normal hearing adults also participated in this project. Their ages ranged from 21 to 32 years. The adults participated in this project to provide normative threshold values for the evoked potential stimuli. The adult subjects were selected on the basis of availability and willingness to participate in the project. Criteria for selection included: 1) hearing sensitivity from 250 to 8000 Hz equal to or less than 15 dB HL in both ears; 2) normal middle ear function as displayed by acoustic immitance measurements; 3) acoustic reflex thresholds at 95 dB HL or less for 500, 1000, and 2000 Hz; 4) negative history of otologic or neurologic disorders; and 5) normal auditory brainstem response.

All subjects were unpaid volunteers. Informed consent was obtained from each adult. Prior to signing the consent form, one or both parents of the children were informed of the overall purpose of the project and the portion of the study in which their child would participate. Furthermore, the attending physician for each child was consulted for approval before the child was included in the study.

Apparatus

Pure Tone Thresholds

Pure tone thresholds were obtained from the adult subjects with a standard clinical audiometer (Grason-Stadler 1701). The acoustic signals were transduced by a dynamic earphone (Telephonics TDH-49) encased in a Teledyne model 51 supra-aural cushion. Testing was performed in a double-wall, sound attenuating audiometric test suite with a suitable acoustic environment.

Immittance Measurements

Acoustic immittance measurements were obtained with two instruments. For the adults, pressure-compliance functions (tympanograms) and acoustic reflex measurements were performed with an immittance meter (Amplaid model 702) with a 226 Hz probe tone. The acoustic signals to elicit stapedial reflex responses originated in the audiometer complement of the immittance meter and were transduced by a dynamic earphone (Telephonic TDH-49) in an MX41/AR cushion. Since the neonate group had middle ear characteristics different from the adults requiring a higher frequency probe tone, they were evaluated with a second immittance unit with two probe tone frequencies. An otoadmittance meter (Grason-Stadler 1720B) was employed to obtain pressure-compliance functions in the neonate subjects of experiments 3, 4, and 5. Tympanograms were obtained with both 220 Hz and 660 Hz probe tones to ensure normal middle ear function.

Evoked Potentials

Evoked potential measurements were performed for the neonates with a dual-channel Bio-logic System 7 evoked potential unit. Electrode application sites were scrubbed with an abrasive gel to maintain electrode impedance below 10,000 ohms. Four gold electrodes were filled with EEG conductive paste and affixed to the vertex (active), each earlobe in the adults and each mastoid in the children (reference), and forehead (ground). An EEG amplifier provided differential amplification with total gain varying from 50,000 to 200,000:1. Band-pass filtering for ABR testing was 300 Hz-3000 Hz. Band pass filtering for middle latency response (MLR) and steady state evoked potential (SSEP) measurements varied according to experimental conditions and will be described in subsequent sections. A 60-Hz notch filter was an integral part of the software program and was engaged for all evoked potential measurements. The amplified EEG signals were delivered to a specially adapted micro-computer (Zenith model 100) which converted the analog input into digital values and then performed signal averaging. Artifact rejection excluded input voltages larger than 42 microvolts for gain of 50,000:1, 21 microvolts for gain of 100,000:1, or 11 microvolts for gain of 200,000:1. A total of 2048 to 4096 sweeps over a 20.48 msec epoch were averaged for the ABR. Unless otherwise noted, 512 sweeps over a 102.4 msec epoch were averaged for MLR and SSEP waveforms. The ongoing EEG activity and the averaged waveforms were displayed on an RGB color monitor. The data were stored on magnetic disk for later analysis. Permanent records of the waveforms were printed with a graphics plotter (Tandy CG-115).

A micro-computer software program executed triggering for the averager and controlled timing and envelope parameters for the acoustic stimuli. The acoustic signals originated in a stimulus generator and were routed to TDH-49 earphones mounted in MX41/AR cushions. For ABR measurements, square wave clicks of 200 microsecond duration were presented to all subjects at the rate of 11.1 per second. For all other evoked potential measurements the stimuli were 500 Hz tone bursts with 3 msec rise/fall times and 0 msec plateau. Stimulus repetition rate varied according to test condition.

In experiment 1, comparative SSEP waveforms were obtained from one neonate with a standard clinical evoked potential unit (Nicolet CA 1000). EEG signals were amplified (Nicolet HGA-200A) by a factor of 10,000:1, band-pass filtered from 5 Hz to 1500 Hz, and routed to the clinical averager for summation and display. Triggering for the signal averager was supplied by the tone pip generator (Nicolet model 1002). The time base and the stimulus characteristics were the same as those described for the Bio-logic system. The signals were attenuated (Nicolet model 1007) and transduced in TDH-39 earphones in MX41/AR cushions. Unlike the Bio-logic unit, the CA 1000 had no magnetic disk storage capabilities. Consequently, waveforms were plotted throughout the test session on an X-Y plotter (Houston Instruments HRC-11E).

Calibration

All calibration on the clinical audiometer and the audiometer complement to the Amplaid immittance bridge were performed in accordance with American National Standards Institute (ANSI, 1969) specifications. The measurements were obtained with an audiometric calibrator (Tracor model RA310), a condenser microphone (Knowles BL1802), and 6cc coupler (NBS-9A). Both the Amplaid 702 and the Grason-Stadler 1720B bridges were calibrated prior to testing for accuracy of manometer readings, frequency, and sound pressure level of the probe tone.

Normalized hearing level (nHL) values for the tone pip and click stimuli of both evoked potential units were obtained from a jury of 10 normal listeners. Behavioral thresholds were obtained for 500 Hz tone pips presented at

1.1, 10.1, 20.1, 30.1, and 40.1 per second and for clicks presented at 11.1 per second. Median threshold values for each condition served as the calibration value for 0 dB nHL.

A Fast Fourier Transform (FFT) procedure analyzed the SSEP responses obtained from the Bio-logic unit. The averaged waveforms from experiment 1 were analyzed with a spectral resolution of 9.76 Hz. The waveforms from experiment 3 were subjected to a Hanning window transformation prior to the FFT analysis to make them more suitable for the FFT procedure for the purpose of threshold prediction. This transformation removed any low-frequency influence that could contaminate the analysis and ensured that the FFT was obtained on a periodic waveform. However, by performing this transformation, the spectral resolution was reduced to 19.52 Hz. (Note: The value for the FFT frequency components were rounded to the nearest 10 Hz interval throughout this paper for convenience of reporting). To accomplish the transformation, the digital points that comprised the waveform were multiplied by the cosine function Y=.5*(1+(Cos(PI))). Since the waveform was displayed across 256 data points, the values of PI were incremented in 128 steps for the first half of the waveform and decremented in 128 steps for the last half of the waveform. This curvilinear function had values that ranged from 0 to 1. The portion of the waveform that occurred at 0 msec and 102 msec were multiplied by a factor of 0. As the waveform data points moved medially along the 102 msec epoch, the multiplication factors increased such that the portion of the waveform at 51 msec was multiplied by a factor of 1. After transforming the waveform data, the "windowed" waveform was subjected to the FFT analysis.

FFT power (amplitude) values were converted from arbitrary units to microvolts by obtaining amplitude values from discreet frequency sinusoids with known input voltages. The sinusoidal output of a function generator (Hewlett Packard, model 3311A) was connected to an audio-frequency microvolter (General Radio, model 546-C). The output of the microvolter (0.1 microvolt) was routed to a triangular electrode array consisting of active, reference, and ground electrodes interconnected by three 10,000 ohm resistors. The EEG amplifier increased the voltage input by a factor of 50,000:1 and band-passed the signal through filters set at 10 Hz-1000 Hz. The micro-computer collected a sample of each sine wave over a single 102.4 msec epoch. An FFT analysis of the sine wave served as the basis for conversion to microvolts. This procedure was used for sinusoids of 20 Hz, 30 Hz, and 40 Hz. The conversion values in microvolts were multipled by appropriate factors to make them applicable for amplifier gains of 100,000 through 200,000:1.

The function generator and the microvolter were also used to examine EEG filter characteristics. Single frequency sine waves between 6 Hz and 3000 Hz were routed to the micro-computer through the electrode/amplifier configuration. For this procedure, however, an FFT analysis was not performed. Instead, peak-to-peak amplitudes of each sine wave were recorded. The band-pass filter characteristics for all filter settings used in this project were thus evaluated.

To ensure similarity of filter and amplifier characteristics for each channel, a pulse generator (General Radio model 1217-C) supplied square wave pulses simultaneously to both EEG amplifier channels. The pulse generator was triggered by the audio stimulus output of the Bio-logic evoked potentials unit. Square wave pulses of 50 msec duration were routed to the differential amplifiers through two triangular electrode arrays similar to that described for the FFT value to microvolt amplitude conversion procedure.

Calibration of peak-to-peak amplitude waveform measurements and examination of EEG amplifier characteristics were completed on the CA 1000 averager with a Nicolet model 200 calibrator. Standard procedures prescribed by the Nicolet Corporation were implemented for the calibration procedure.

Procedures

After one or both parents signed the consent form, the peripheral sensitivity of each child who participated in this project was evaluated by ABR. A latency-intensity function was established for both ears of each child to determine threshold. Following replication of each waveform, the signal intensity was decreased in 10 dB or 20 dB steps from 70 dB nHL to a final intensity of 30 dB nHL. Environmental noise in the NICU precluded testing below this level. If repeatable waveforms were not observed at a given intensity, the signal level was increased in 5 dB or 10 dB steps until a response was recognized and replicated. Between 2048 and 4096 sweeps using a 20.48 msec epoch were collected for each waveform.

The MLR and SSEP studies were divided into five experiments. Experiment 1 examined the effects of stimulus rate on the averaged waveform in order to determine an optimum rate for the MLR and the SSEP. The second experiment was designed to examine analog filter effects on the MLR in neonates. Experiment 3 evaluated the efficacy of predicting low frequency threshold sensitivity using the ABR as the basis of comparison. Experiment 4 studied the stability of the SSEP as a function of the sleep/wake cycle. Experiment 5 addressed the relationship between wave Pa of the MLR and the late auditory potentials.

Experiment 1

The purpose of this study was to determine the optimum stimulation rate for the neonate SSEP. Twelve children ranging in age from 28 weeks to 44 weeks conceptual age participated in this experiment. Trains of 500 Hz tone pips were presented monaurally at 70 dB nHL. Tone pips were presented at 1.1 and 2.1 per second, and in increments of 5 per second from 5.1 to 40.1 per second. In all, 10 stimulus rate conditions were evaluated. Recordings made with the Bio-logic evoked potential unit used band-pass filters at 10 Hz-1000 Hz. To ensure that the rate results were not unique to a particular apparatus, duplicate rate recordings were made on one child with the a Nicolet CA 1000 averager. In this case band-pass filters were 5 Hz-1500 Hz. For both instruments, 512 sweeps of a 102.4 msec epoch comprised the averaged waveform. The optimum stimulus rate derived from these results was employed for subsequent SSEP studies.

Experiment 2

This experiment was designed to examine the effect of band-pass filtering on the MLR in neonates. Two stimulus conditions were used: a stimulation rate of 8.0 per second and a stimulation rate of 1.7 per second. For both rates, EEG band-pass filters were 10 Hz-100 Hz, 10 Hz-300 Hz, 10 Hz-500 Hz, 3 Hz-100 Hz, 3 Hz-300 Hz, 3 Hz-500 Hz. Eleven children ranging in age from 29 weeks to 44 weeks conceptual age participated in one or both rate conditions. Tone pips of 500 Hz were presented monaurally for each child. Signal intensity was maintained at 70 dB nHL for each condition. A total of 512 samples of evoked activity were collected for each averaged waveform.

Experiment 3

This experiment evaluated the efficacy of the SSEP for predicting low frequency hearing sensitivity for 13 children from 32 weeks to 44 weeks conceptual age. Tone pips of 500 Hz were presented at the optimum stimulation rate as indicated by experiment 2. The tone pips were presented monaurally from 70 dB nHL to 30 dB nHL in 10 dB steps. Band-pass filters were 10 Hz-1000 Hz. A total of 512 sweeps was collected for each average. In addition, a portion of this experiment focused on the effect of sample size on threshold prediction. A subset of four children had threshold predictions made with 512 sweeps, 1024 sweeps, and 2048 sweeps per average. The averaged waveforms were subjected to a Hanning window transformation. The "windowed" waveform was then evaluated by an FFT analysis. The FFT frequency component corresponding to the optimum stimulation rate was plotted as a function of intensity and fitted with a least-squares line of best fit. The least-squares line was extrapolated to zero amplitude to predict threshold.

Experiment 4

The purpose of this study was to examine the stability of the SSEP as a function of the sleep/wake cycle in neonates. SSEPs were obtained monaurally from five children with an age range of 32 weeks to 44 weeks conceptual age. Series of 500 Hz tone pips were presented at a level of 70 dB nHL at the optimum stimulus rate derived from experiment 2. Averaged waveforms, each the result of 512 sweeps, were collected continuously over a two hour period. This time period was sufficient to allow each child to cycle through the stages of sleep and wakefulness two or three times (Spehlmann, 1981). Each waveform was subjected to FFT analysis for variations of amplitude and phase in successive samples over the two-hour testing period.

Experiment 5

This experiment was designed to elucidate the relationship of the MLR to later vertex potentials. Three infants (34, 37, and 37 weeks conceptual age) from whom the MLR had been obtained previously participated in this study.

Late auditory potentials were obtained with time bases of 512 msec, 1024 msec, and 2048 msec. Differential amplification of EEG activity was band-pass filtered from 1 Hz to 1000 Hz. A total of 64 tone pips of 500 Hz were presented monaurally at the rate of one tone pip every two seconds at 70 dB nHL. Response validation was accomplished by replication of the waveform. Latency and amplitude of each replicated peak of the late auditory potential were measured.

CHAPTER IV

RESULTS AND DISCUSSION

The overall goal of this project was to find an efficacious method to predict low frequency hearing sensitivity in neonates. To reach this goal, the project was divided into a series of five experiments. The first experiment determined an optimum stimulation rate for the middle latency response (MLR) and the steady state evoked potential (SSEP) using minimal EEG filtering. Experiment two examined the effects of band-pass filtering on the MLR. The third experiment evaluated the variability of low-frequency SSEP threshold predictions using a 500 Hz tone burst. The fourth experiment investigated the stability of the SSEP waveforms during the wake/sleep cycle. The last experiment examined the relationship of the neonatal MLR to the late auditory potentials.

Experiment 1

This first experiment was designed to determine an optimum stimulation rate for both the middle latency response (MLR) and the related steady state evoked potential (SSEP). EEG filtering was maintained at 3 Hz to 1000 Hz to minimize the possibility of filter artifact on the averaged waveform. Twelve children ranging in age from 29 weeks to 44 weeks conceptual age participated in this experiment. Figures 1a and 1b show typical results observed for these children. On the ipsilateral recording, Po (ABR) and the large negative Na are readily identifiable at stimulation rates of 1.1 and 2.1 per second. A large positive wave, possibly Pa, had relatively poor peak replication at 1.1 per second but somewhat better replication at 2.1 per second. In contrast to the ipsilateral results, the contralateral recordings at 1.1 and especially at 2.1 per second showed remarkably well formed responses corresponding with wave Pa. The primary characteristic of this averaged response was a broad-based waveform with a maximum amplitude at approximately 50 msec. Marked degradation of the waveform occurred for both ipsilateral and contralateral recordings at stimulation rates of 5.1 and 10.1 per second. At 15.1 per second, the evoked waveform began to show organization again with a replicable peak at approximately 72 msec. The 20.1 per second results showed a well organized response for both the ipsilateral and contralateral recordings that resembled a 20 Hz sinusoid. Although some waveform replication persisted at stimulation rates greater than 20.1 per second, the quality of the recordings became progressively poorer until, at 40.1 per second, the presence of a response was virtually indiscernable.

In order to evaluate the effects of stimulation rate

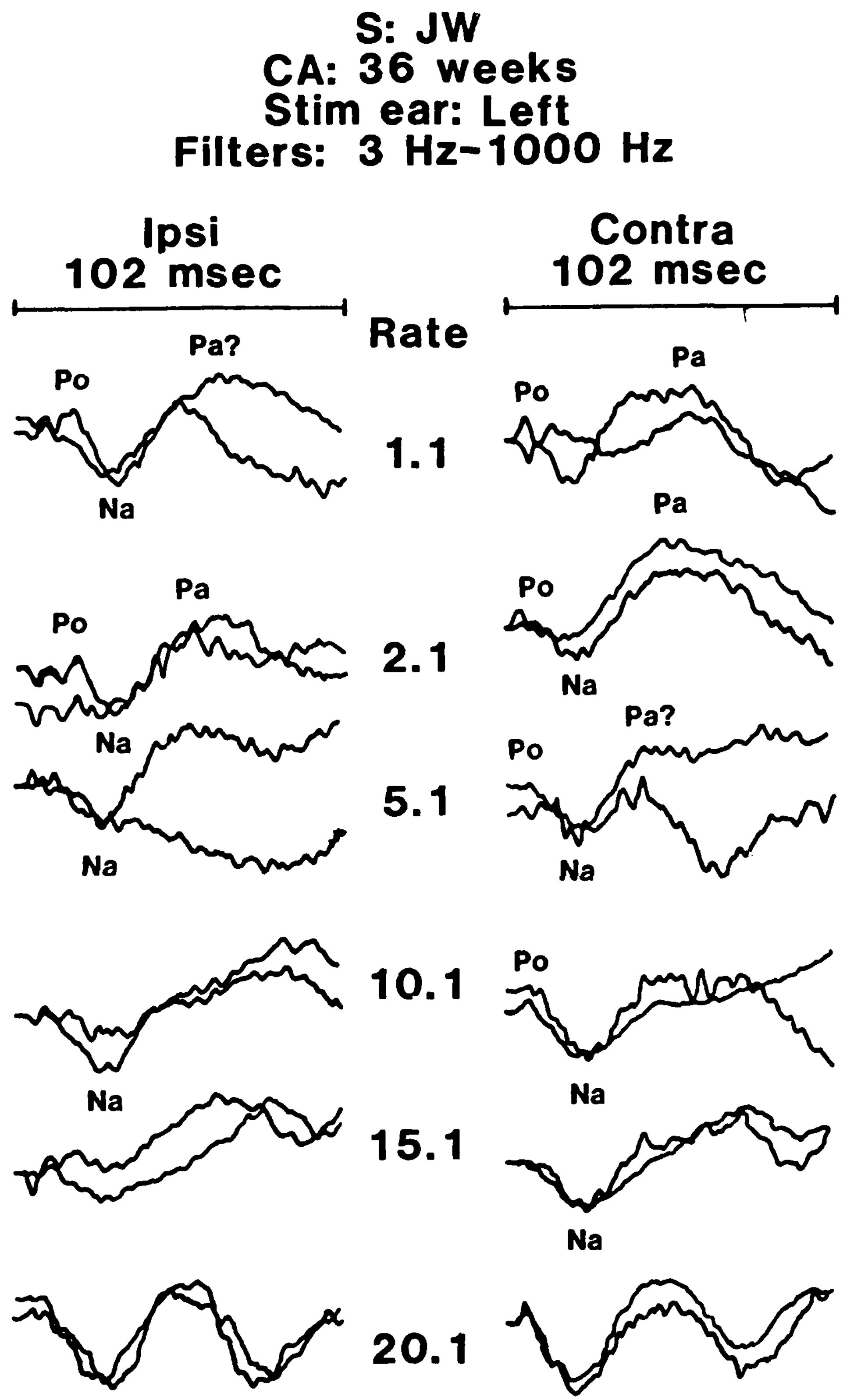


Figure 1a. Averaged waveforms for ipsilateral and contralateral recordings at different stimulation rates.

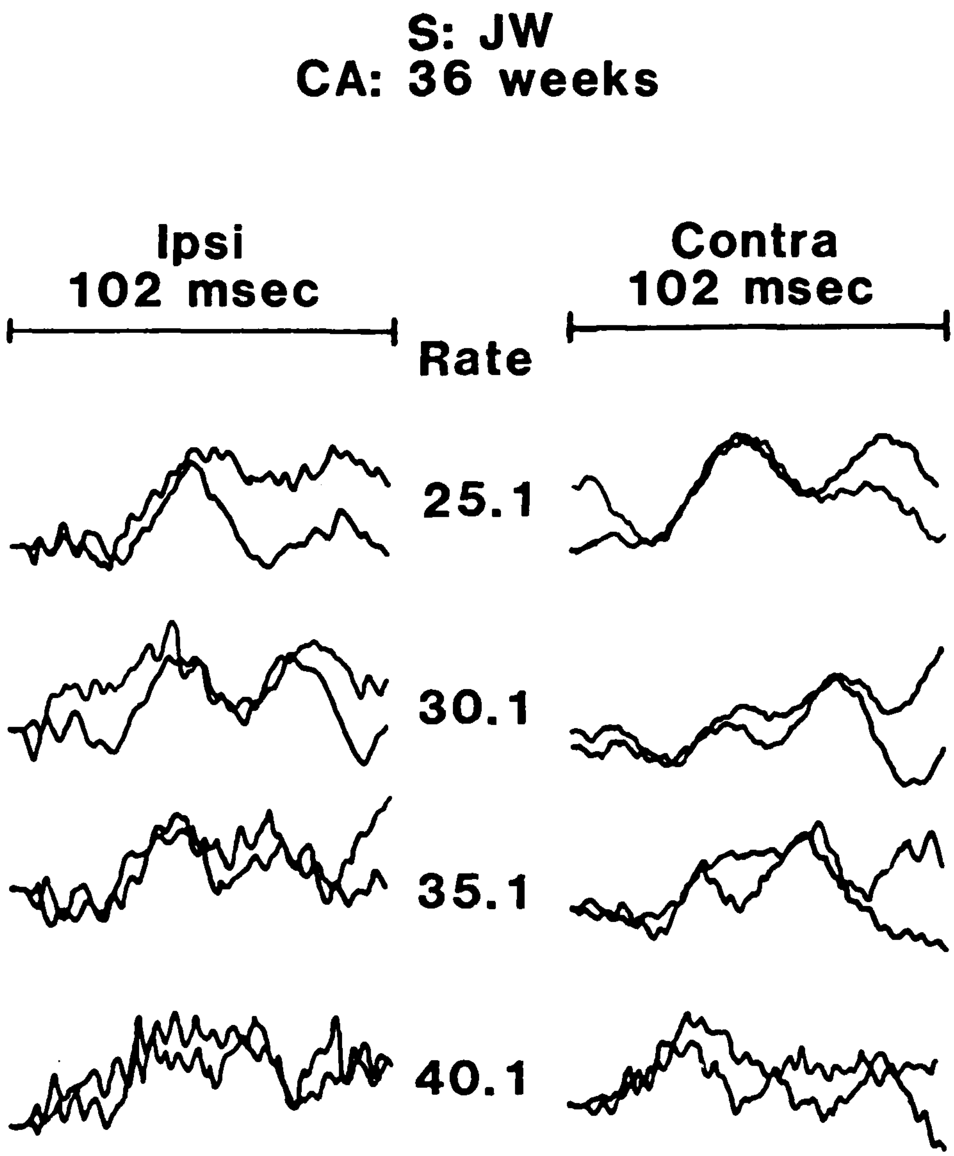

S: JW
CA: 36 weeks
Ipsi
102 msec
Contra
102 msec
Rate
25.1
30.1
35.1
40.1

Figure 1b.

on the waveform morphology of each child, the respective recordings were submitted to a panel of three judges. Each judge was an audiologist with experience in evoked potential measurements who had not previously participated in this project. Their task was to select the stimulation rates which produced the most robust (i.e. largest amplitude) and most replicable recordings from either the ipsilateral or contralateral channels. Responses at more than one stimulation rate indicated that, in the judge's opinion, the waveform recordings were of equal quality. Their results are shown in Table 1 and Figure 3. For the MLR, the majority of the children had the best recordings at stimulation rates of one and/or two tone bursts per second. Two children had recognizable waveforms at a stimulation rate of five per second, while two other children failed to show an MLR at any stimulation rate. Ten children at five per second and all twelve children at 10 per second failed to demonstrate a recognizable MLR. At faster stimulation rates, the judges selected 20 per second and 25 per second most often as optimal stimulus repetition rates. All three judges agreed that 15 per second was an optimal rate for subject DP. Only one judge selected 15 per second for subject SC. The general consensus for this subject, however, was that the waveforms did not show sufficient replication for a determination of optimal stimulation rate above two per second. Somewhat similar determinations were

Table 1. Determination of optimal stimulation rates made by a panel of three judges. The values in each cell represent the number of judges that selected the respective stimulation rate as producing a robust and replicable waveform.

Subject	Rate (TB/sec)									
	1	2	5	10	15	20	25	30	35	40
SR	3	0	0	0	0	3	0	0	0	0
JW	0	3	0	0	0	3	3	1	0	0
SC	0	3	0	0	1	0	0	0	0	0
RA	2	0	0	0	0	1	2	0	0	0
NG	1	0	3	0	0	1	3	0	0	0
SJ	0	2	3	0	0	3	2	0	0	0
GL	0	0	0	0	0	3	3	0	0	0
DL	0	3	0	0	0	2	3	3	0	0
KM	3	2	0	0	0	3	2	0	0	0
DP	0	3	0	0	3	0	0	0	0	0
SP	0	0	0	0	0	3	3	0	0	0
AO	0	0	0	0	0	3	0	0	0	0
Total	9	16	6	0	4	25	21	4	0	0

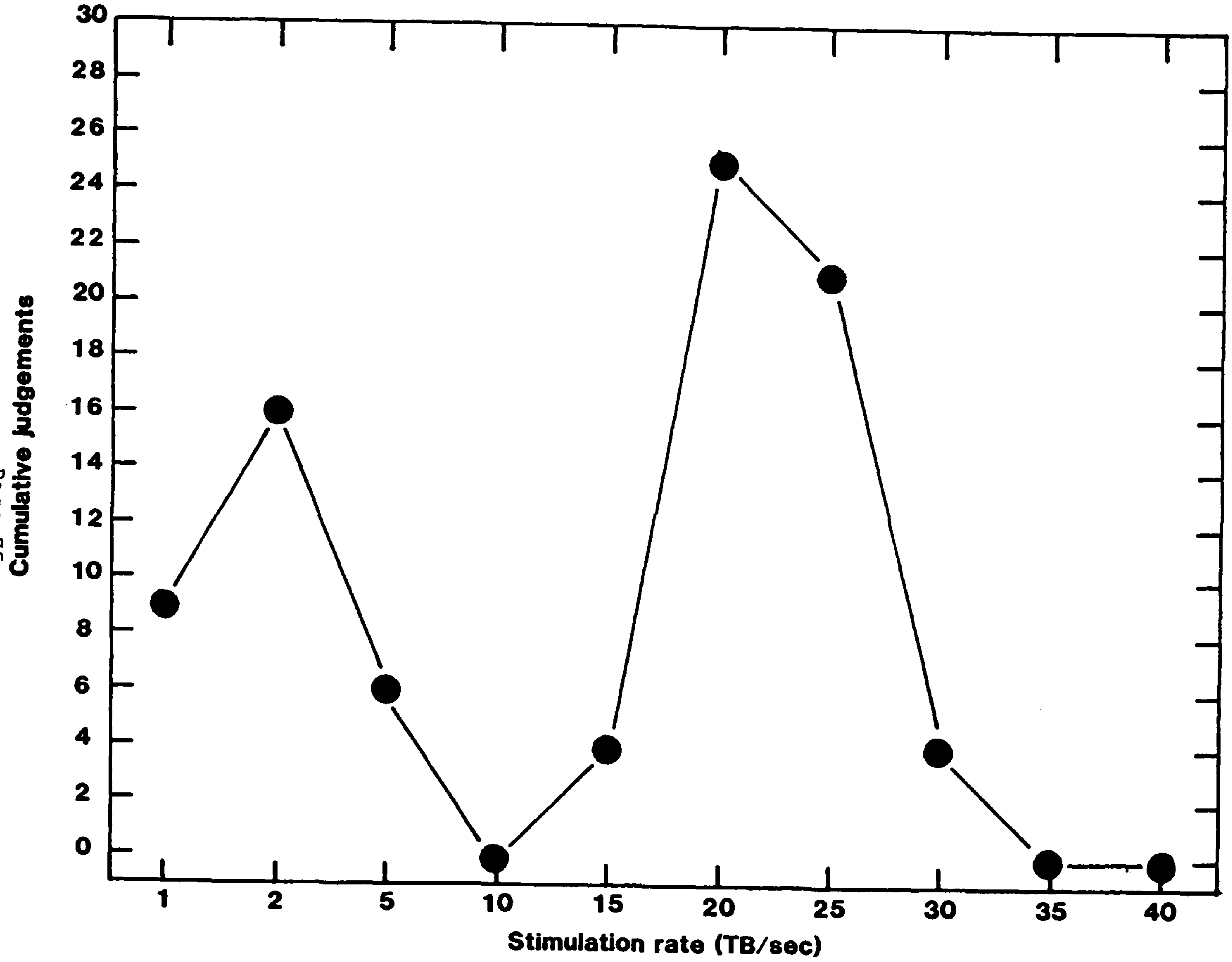


Figure 2. Cumulative judgements of the stimulation rates which produced the most repeatable and largest amplitude waveforms. The judgements were made by three audiologists who are familiar with auditory evoked potential techniques. The evoked potential waveforms of 12 children were evaluated.

made for 30 per second. That is, the three judges agreed that the recordings at 30 per second were very robust for subject DL. Only one judge made a similar determination for subject JW. None of the judges found the waveforms obtained with stimulation rates of 35 per second or 40 per second to be robust and/or replicable.

In summary, several findings were observed consistently across subjects for the MLR. First, the peak latency of wave Pa ranged from 44 msec to 68 msec. This is significantly longer than the range of latencies (25 msec to 35 msec) found in adults (Ozdamar and Kraus, 1983). Second, the optimum stimulation rate for the MLR generally varied between one and two per second. Except for two subjects, the morphology of the averaged waveform often became degraded at stimulation rates faster than two per second. This finding is also sharply contrasted to adult data in which stimulation rates of five to eleven per second still produced a waveform of excellent quality (Geisler et al., 1958; Thornton et al., 1977). In general, the neonatal MLR obtained with stimulation rates of 5.1 and 10.1 per second was very poorly organized and not easily replicable.

For the SSEP, a stimulation rate near 20.1 per second repeatedly produced an averaged waveform with relatively large peak-to-peak amplitudes and a morphology that resembled a 20 Hz sinusoid. Some children had averaged responses that were of near equal quality with regard to amplitude and morphology at 15.1 and 20.1 per second or at 20.1 and 25.1 per second. One child in particular had waveforms of approximate equal quality at 20, 25, and 30 per second. In general, however, as the stimulation rate exceeded 25.1 per second, the waveform recordings were increasingly degraded. At 40.1 per second, none of the familiar characteristics of the adult SSEP could be observed. In most children, only one or two small amplitude peaks would replicate over the 102 msec time base. The four large amplitude peaks that are often observed in adults were consistently absent in these children.

To ensure that the results represented in Figures 1a and 1b were not due to instrumentation artifact, the stimulation rate study was repeated for one subject using a Nicolet CA1000 evoked potential system. The electrode montage, the instrumentation components, and the recording procedures were comparable to those described for the Bio-logic System 7 unit. The EEG band-pass filter settings were 5 Hz to 1500 Hz (12 dB/octave slope). The averaged waveform results are displayed in Figures 2a through 2d. At a stimulation rate of 1.1 per second, a large amplitude wave corresponding to wave Pa occurred in the ipsilateral recording at a latency of 70 msec. At 2.1 per second, a large waveform was seen at the same latency in one tracing, but did not replicate. Compared to 1.1 per second results, the morphology of the averaged waveforms was severely

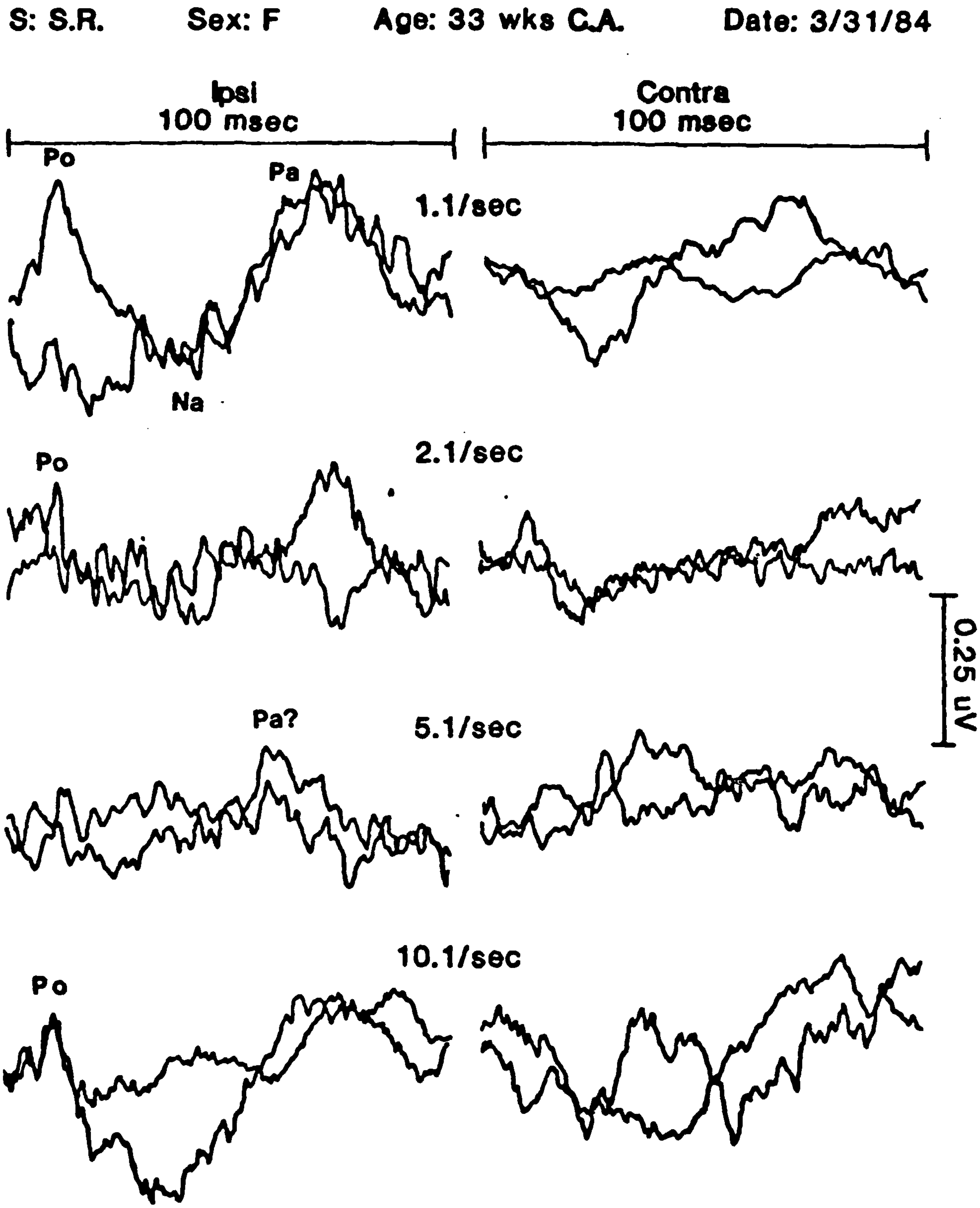


Figure 3a. Averaged waveforms for the ipsilateral and contralateral recordings. These data were obtained with a Nicolet CA1000, filter settings of 5 Hz to 1500 Hz, and a 500 Hz tone burst at 70 dB nHL.

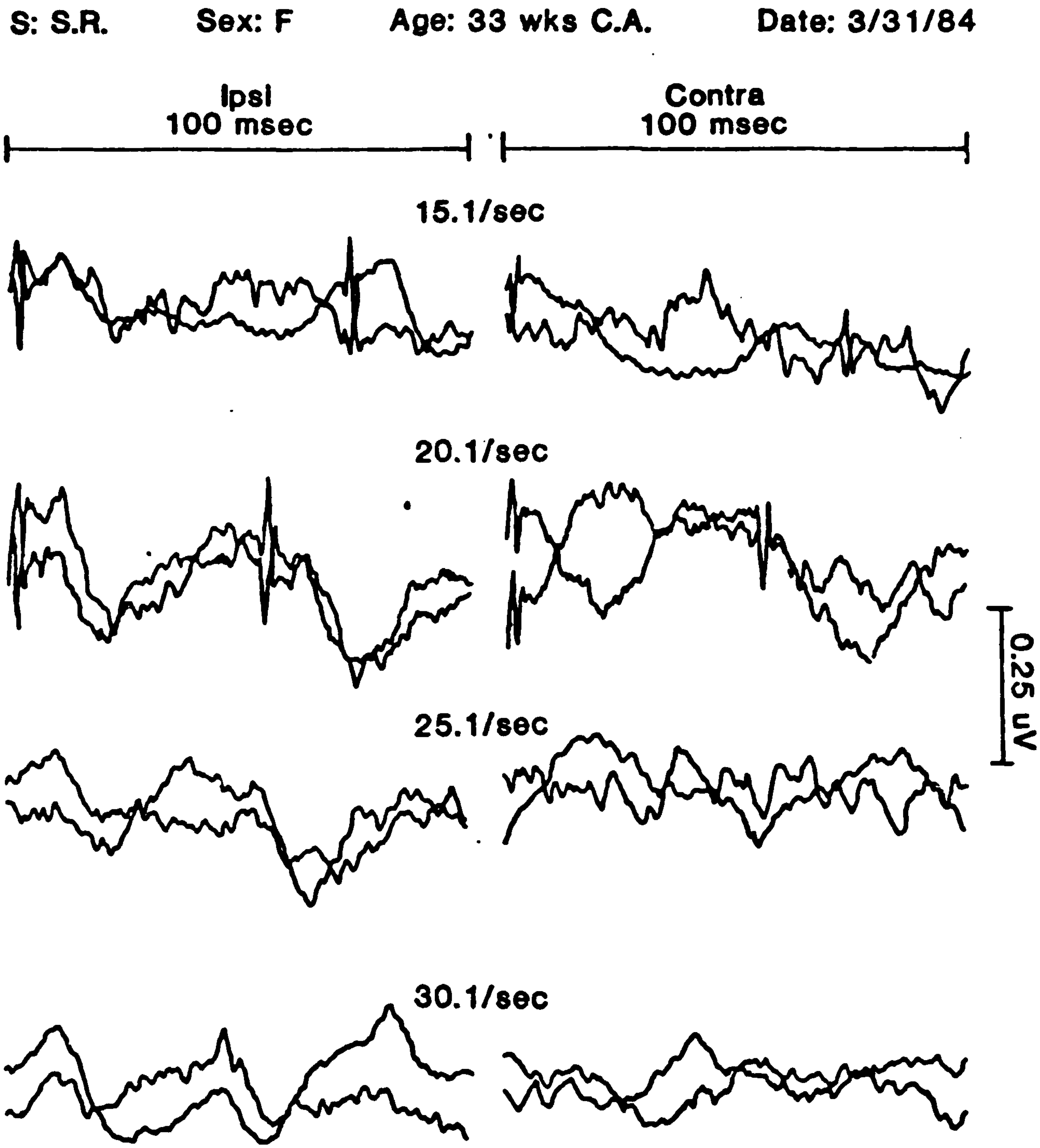
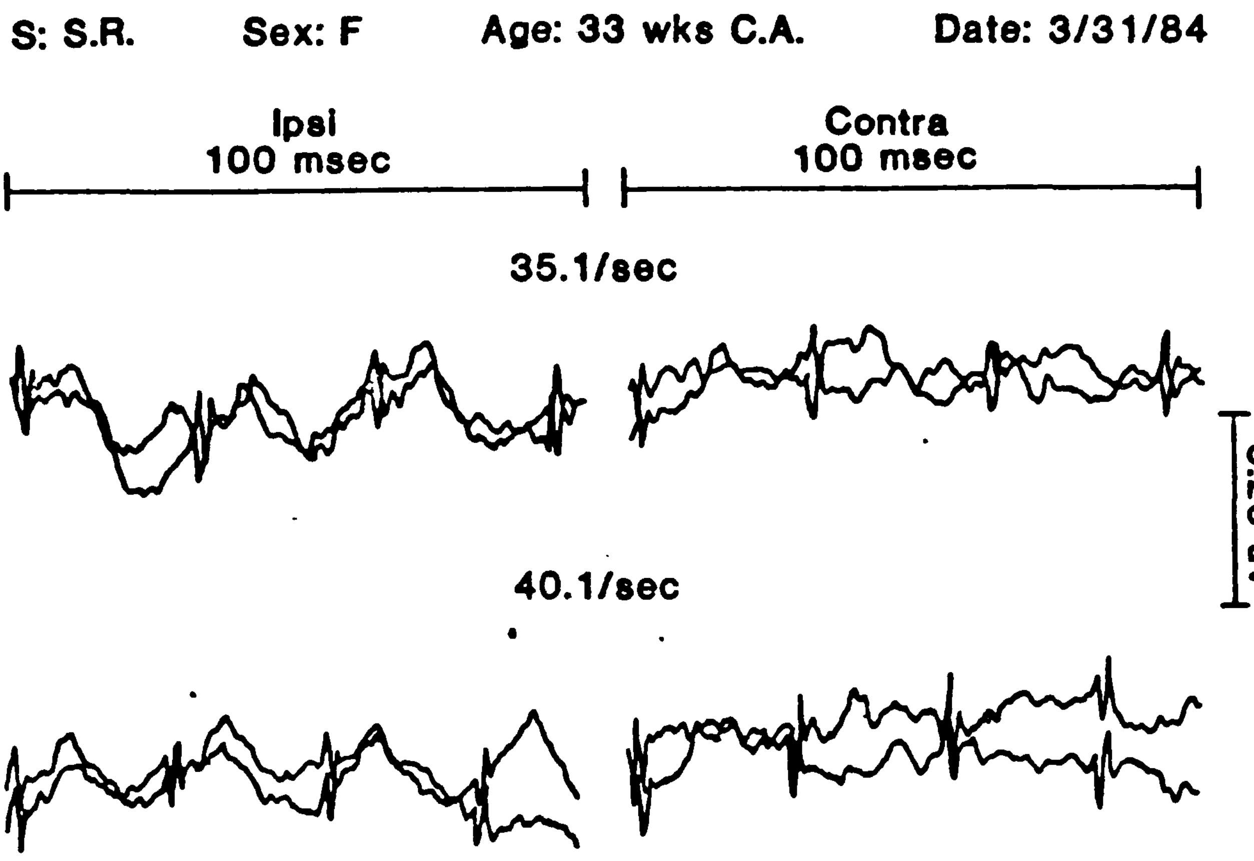

S: S.R.
Sex: F
Age: 33 wks C.A.
Date: 3/31/84
Ipsi
100 msec
Contra
100 msec
15.1/sec
20.1/sec
25.1/sec
30.1/sec
0.25 uV

Figure 3b.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Sex: F
Age: 33 wks C.A.
Date: 3/31/84
Ipsi
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Contra
100 msec
35.1/sec
0.25 uV
40.1/sec

Figure 3c.

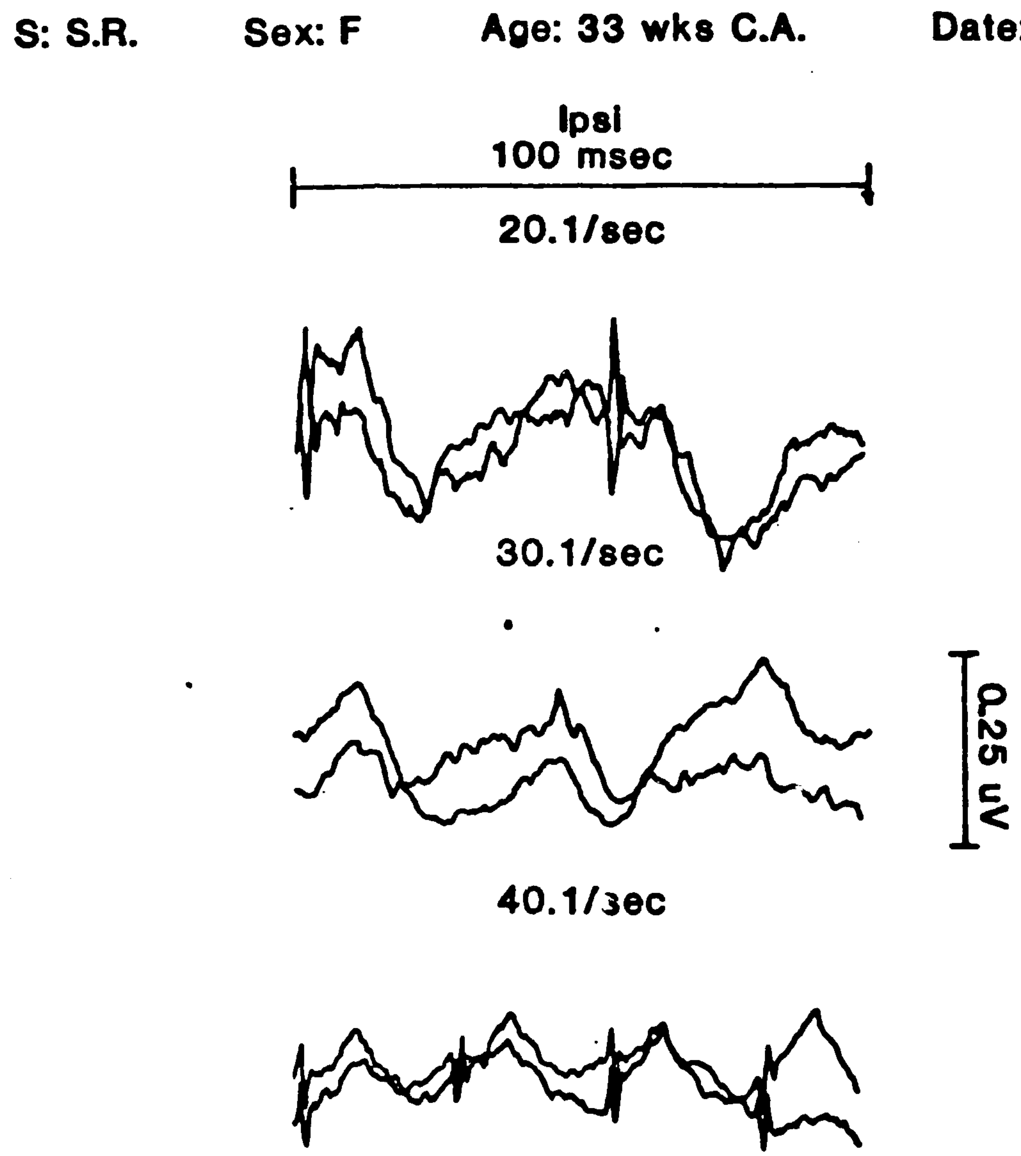
S: S.R.
Sex: F
Age: 33 wks C.A.
Date: 3/31/84
Ipsi
100 msec
20.1/sec
30.1/sec
0.25 uV
40.1/sec

Figure 3d.

AD-A158 007 THE MIDDLE LATENCY RESPONSE (MLR) AND STEADY STATE EVOKED POTENTIAL (SSEP) IN NEONATES(U) AIR FORCE INST OF TECH WRIGHT-PATTERSON AFB OH R C FIFER MAY 85 2/2

UNCLASSIFIED AFIT/CI/NR-85-100D F/G 6/16 NL

END

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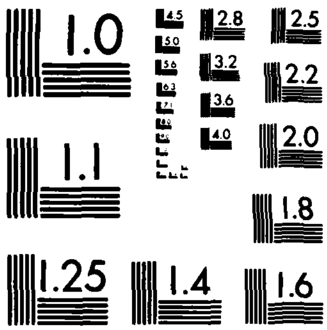

MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

degraded at 5.1, 10.1, and 15.1 per second. Similar to the previous recordings, a stimulation rate of 20.1 per second produced a robust waveform resembling a 20 Hz sinusoid. For stimulation rates greater than 20.1 per second, peak replication persisted, although the amplitude of the response diminished with each successive increment in stimulus rate. At a driven rate of 40.1 per second, the only recognizable components were replications of the ABR at 25 msec intervals. The large negative peak followed by the slow positive wave that was seen in the 20.1 per second data was not observed. Figure 2d emphasizes the difference between the 20.1, 30.1, and 40.1 per second waveforms. These waveforms illustrate that the peak to peak amplitudes diminished with concommittent increases in stimulation rate. Consequently, at 40.1 per second, the remaining waveform is a relatively low amplitude driven ABR. The contribution of the middle latency component to the overall amplitude seen at 20.1 per second was virtually eliminated at 40.1 per second.

In contrast to the contralateral waveforms in Figures 1a and 1b, the contralateral recordings for this child showed very poor organization at all stimulation rates except 20.1 per second. At 20.1 per second, waveforms that resembled the ipsilateral response were recognized although the negative peak at approximately 25 msec latency showed a phase reversal in one tracing.

The overall pattern of results was similar between the two evoked potential recording units. A large, slow wave Pa was observed only at very slow stimulation rates. When measured in five per second steps, the optimum stimulation rate for the SSEP was 20 per second for both units. The MLR and SSEP were recorded, therefore, with confidence that the responses were not a function of instrumentation artifact unique to a particular system.

The averaged waveforms collected with the Bio-logic evoked potential system were subjected to a Fast Fourier Transformation (FFT) analysis to obtain the relative amplitudes of the various frequency components. The results for the ipsilateral recordings at 20 Hz, 30 Hz, and 40 Hz, averaged across 12 children are shown in Figure 4. The ordinate of Figure 4 is the amplitude of the frequency component in microvolts. The abscissa is the stimulation rate at which the respective component was measured. FFT information for 10 Hz was omitted since that frequency component consistently had a large amplitude contribution to the averaged waveform, regardless of the stimulation rate. The amplitudes of frequency components greater than 40 Hz were always near the instrumentation noise level and contributed little to the interpretation of these results.

The 20 Hz amplitude data in Figure 4 showed a tri-modal configuration with an initial peak at a stimulation rate of 1 per second followed by a decline in

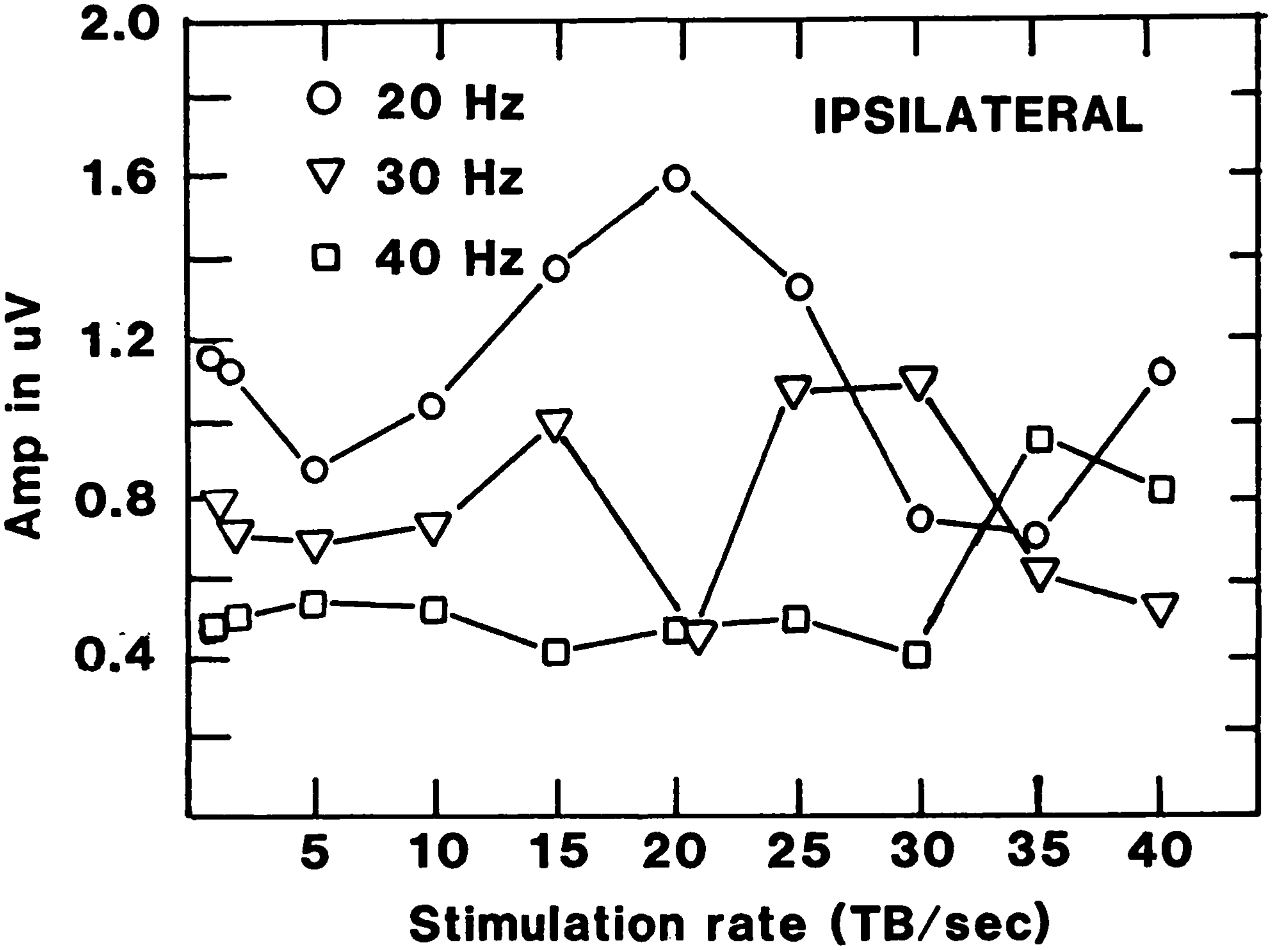

Figure 4. FFT amplitude values for the ipsilateral recording as a function of stimulation rate for the 20 Hz, 30 Hz, and 40 Hz components. These data were averaged across 12 children.

amplitude to 5 per second. The amplitude then increased to reach a maximum value at 20 per second, declining to another trough at 30 and 35 per second, then increasing at 40 per second. In contrast, the 30 Hz and 40 Hz components failed to equal the maximum 20 Hz values regardless of the stimulation rate. The average maximum amplitude for 20 Hz was 1.60 microvolts obtained at 20 per second. For 30 Hz, an average maximum value of 1.10 microvolts was obtained at 30 per second. And for 40 Hz, the largest mean amplitude was 0.96 microvolts at 35 per second. The ipsilateral FFT analysis correlated well with the empirical waveform results indicating that the optimal stimulation rates ranged from 15 to 25 per second with an overall largest amplitude response at 20 per second.

The contralateral FFT results (Figure 5) are similar to the ipsilateral results although smaller in overall peak amplitude for each frequency component. The 20 Hz data showed an initial peak at 1 per second followed by a sharp decrease in amplitude at 2 per second. From 5 through 25 per second, the 20 Hz function showed a broad, less well defined peak in contrast to the ipsilateral data. Maximum amplitude was still noted, however, at 20 per second with a value of 1.40 microvolts. The 30 Hz amplitudes reached a maximum of 1.06 microvolts at 30 per second. The 40 Hz FFT results had a maximum amplitude of 0.84 microvolts at 10 per second. At 40 per second, the 40 Hz FFT amplitude was 0.65

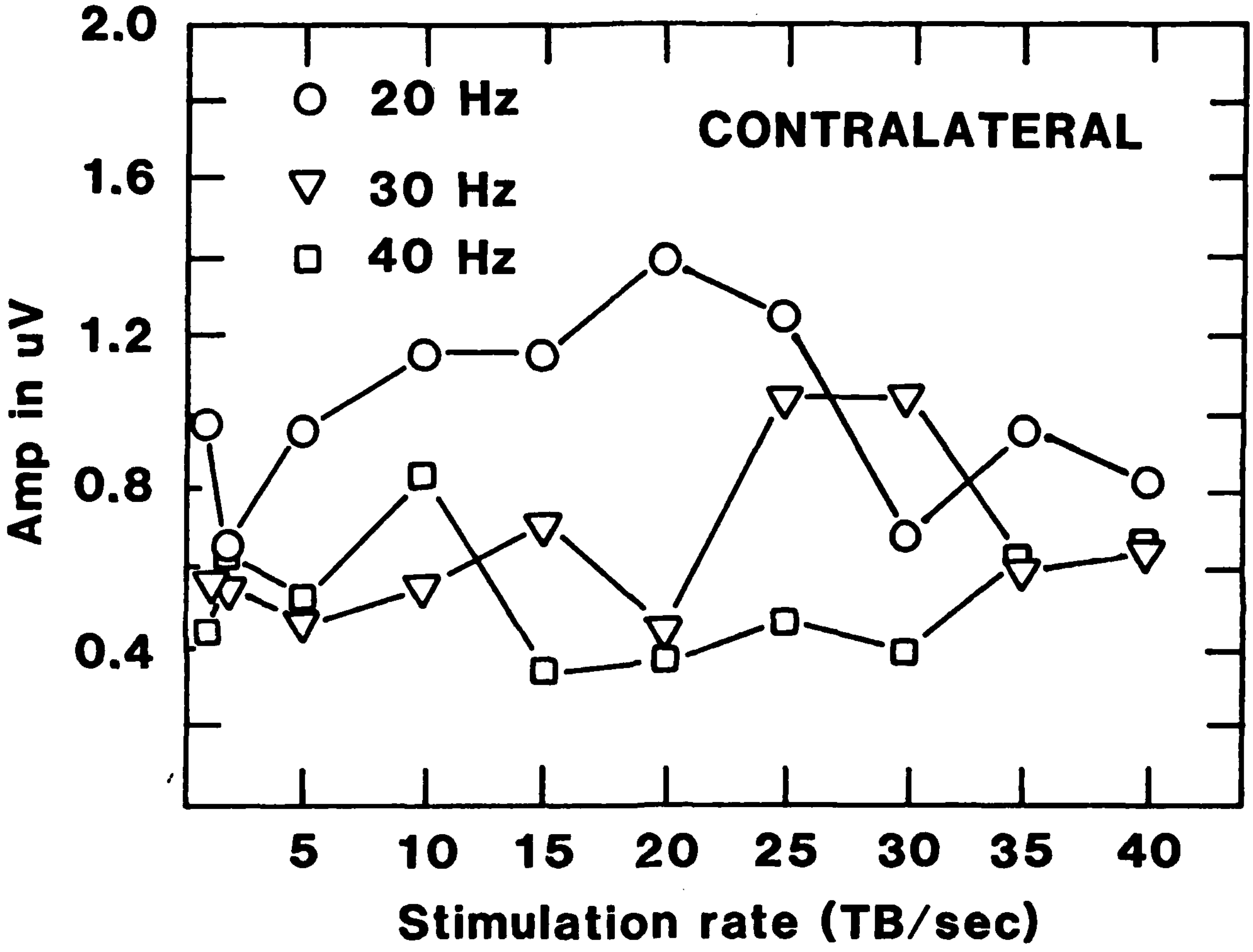

Figure 5. FFT amplitude values from the contralateral recording for the 20 Hz, 30 Hz, and 40 Hz components averaged across 12 children.

microvolts. Although 20 Hz is the dominant energy component in the contralaterally recorded waveforms, the absence of a sharply defined amplitude peak as seen in the ipsilateral analysis suggests that, in general, the distinct characteristic of an "optimum" stimulation rate for the SSEP is less evident in the contralateral recording.

In summary, the overall results of experiment one indicate that the MLR and the SSEP are best obtained at stimulation rates much slower than those typically used with adults. The MLR was generally observed at rates of one and two per second. The optimum stimulation rates for the SSEP were near 20 per second. These findings are contrasted to five to 11 per second and the 40 per second optimum rates for the MLR and SSEP, respectively, in adults. To ensure the absence of instrumentation artifact, the study was replicated on a different evoked potential system with equivalent results. The FFT analysis of the component amplitudes revealed that the 20 Hz component at a stimulation rate of 20 per second was larger in amplitude for both the ipsilateral and contralateral recordings than the 30 Hz or 40 Hz components at any stimulation rate.

Experiment 2

Experiment 2 was designed to examine the effects of band-pass filter width on the averaged waveform. Two stimulus conditions were used: a stimulation rate of 8.0 per second or a stimulation rate of 1.7 per second. These rates were selected on the basis that a rate of 8.0 per second is comparable to the typical adult stimulation rate, and a rate of 1.7 per second was found in experiment 1 to be in the range of stimulus repetitions that produced a repeatable middle latency waveform. For both rates, the stimulus was a 500 Hz tone burst presented at 70 dB nHL. Data were collected at the respective rate for a minimum of six filter conditions. Eleven children participated in this experiment in one or both conditions. These children ranged from 29 weeks to 44 weeks conceptual age. The low-pass EEG filters varied from 100 Hz to 3000 Hz. The high-pass filters were 3 Hz and 10 Hz. A total of 512 samples of EEG activity across a 102 msec time base were summed to produce the averaged waveform.

Figure 6 shows results obtained from a 39 week conceptual age infant using a stimulation rate of 8.0 per second. The averaged waveform for the filter band-pass of 10 Hz to 100 Hz revealed a large positive peak at 70 msec that was similar in appearance to wave Pa in experiment 1. However, as the low-pass filter was increased to 500 Hz, the well-defined peak disappeared and was replaced by a flat, broad waveform. When a 3 Hz high-pass filter was combined with a 100 Hz low-pass filter, a distinct wave Pa failed to appear. Band-pass filter settings of 3 Hz-300 Hz and 3 Hz-500 Hz produced a positive peak at 48 msec. This peak

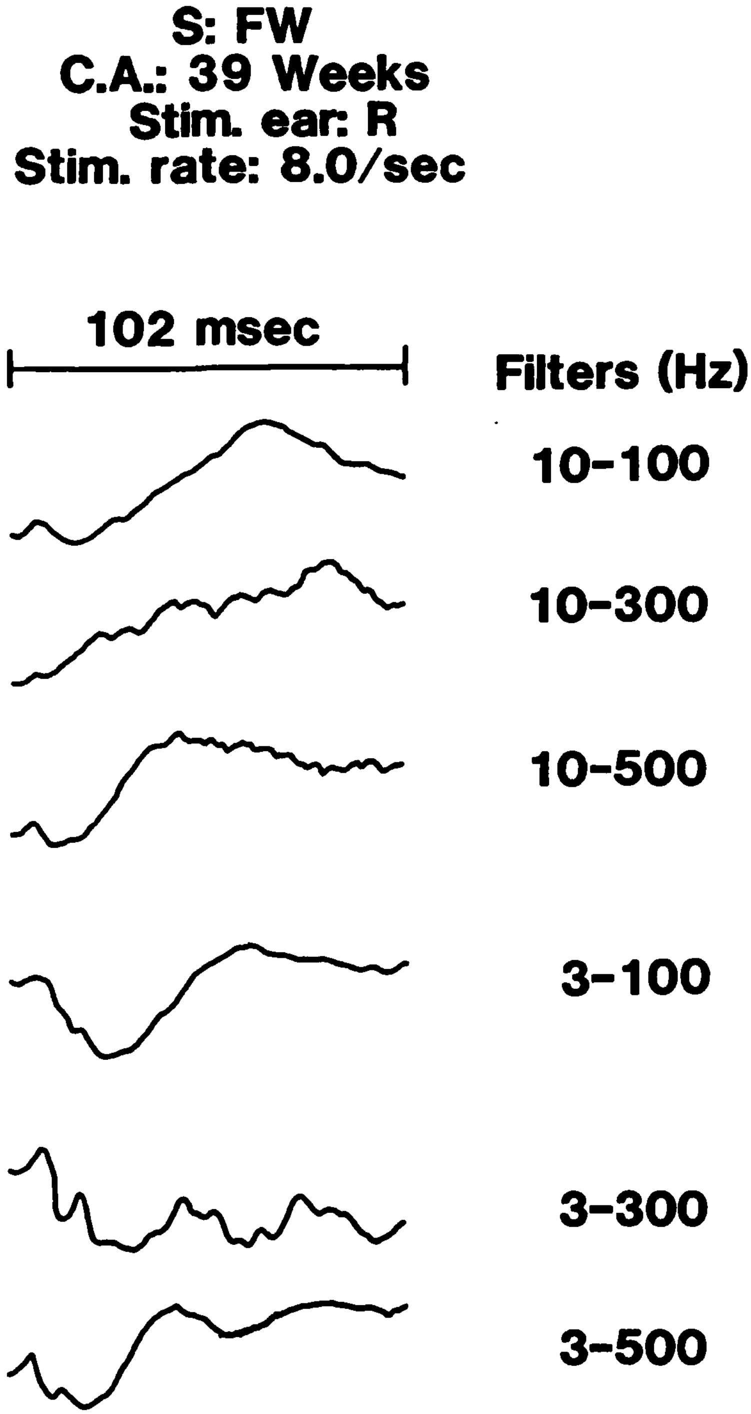

Figure 6. The effect of band-pass filtering on the MLR using a stimulation rate of 8.0 per second.

occurred much earlier than the waveform in the 10 Hz-100 Hz tracing and could not be replicated under other filter conditions. Furthermore, the morphology of this waveform was significantly different from the characteristic waveforms obtained in experiment one. Consequently, it was difficult to state with any degree of certainty that the peak observed at 48 msec was actually wave Pa.

Figure 7 displays results obtained from another child (S:GL) with a stimulation rate of 1.7 per second. In contrast to the waveforms in Figure 6, these results show a large, distinct peak (wave Pa) at approximately 50 msec that is remarkably stable, regardless of the low-pass filter setting. As the low-pass filter increased from 100 Hz to 3000 Hz, the primary effect on the ipsilateral waveform was a decrease in peak latency for Pa from 52 msec to 48 msec. The contralateral recording also revealed a consistent Pa at similar latencies, although the quality of the recorded waveform was more variable than the ipsilateral tracing. Included in this figure is a no-sound, control run for both channels to emphasize the difference in waveform morphology. The no-sound tracing for the contralateral channel particularly shows a marked contrast to the stimulation recording at comparable band-pass filters. Due to patient care needs and subsequent discharge, 3 Hz high-pass filter information could not be obtained for this child.

Dual channel recordings for both 10 Hz and 3 Hz

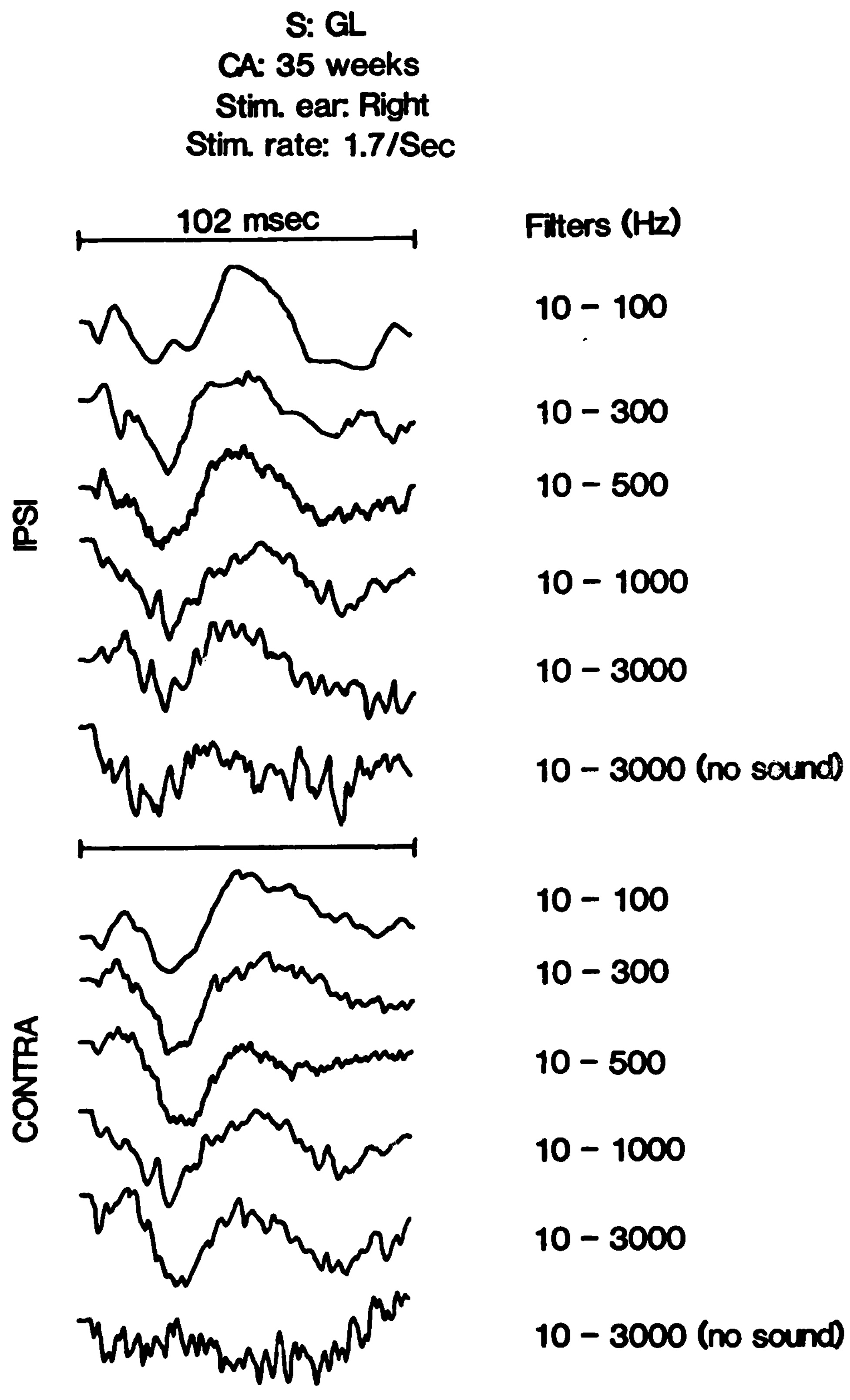

Figure 7. The effect of band-pass filtering on the MLR using a stimulation rate of 1.7 per second.

high-pass filters are shown in Figure 8. The averaged responses obtained with each band-pass width using a 10 Hz high-pass filter produced a remarkably consistent wave Pa. Similar to the previous figure, the primary effect of increasing the low-pass filter was to decrease the peak latency of Pa from 53 msec to 49 msec. Decreasing the high-pass filter to 3 Hz introduced a substantial low frequency component in the averaged waveform, thus broadening the peak of wave Pa. Despite the broader peak, wave Pa was still identifiable even with a low-pass filter of 500 Hz.

Table 2 shows the effects of the band-pass filters on the peak latency of wave Pa for all 11 subjects. For the subjects who received tone bursts at a rate of 8.0 per second, the table indicates that wave Pa was increasingly difficult to identify as the width of the filter band-pass increased. This was particularly true when the high-pass filter was 3 Hz. With one exception, a positive waveform corresponding to wave Pa was identified for each child at a band-pass setting of 10 Hz to 100 Hz. In contrast to the faster rate, stimulating at a rate of 1.7 per second produced a large positive peak corresponding to wave Pa at each filter condition. Although the peak latencies showed variability from one condition to the next, the overall effect for the 1.7 per second rate was a slight decrease in peak latency as the band-pass width increased.

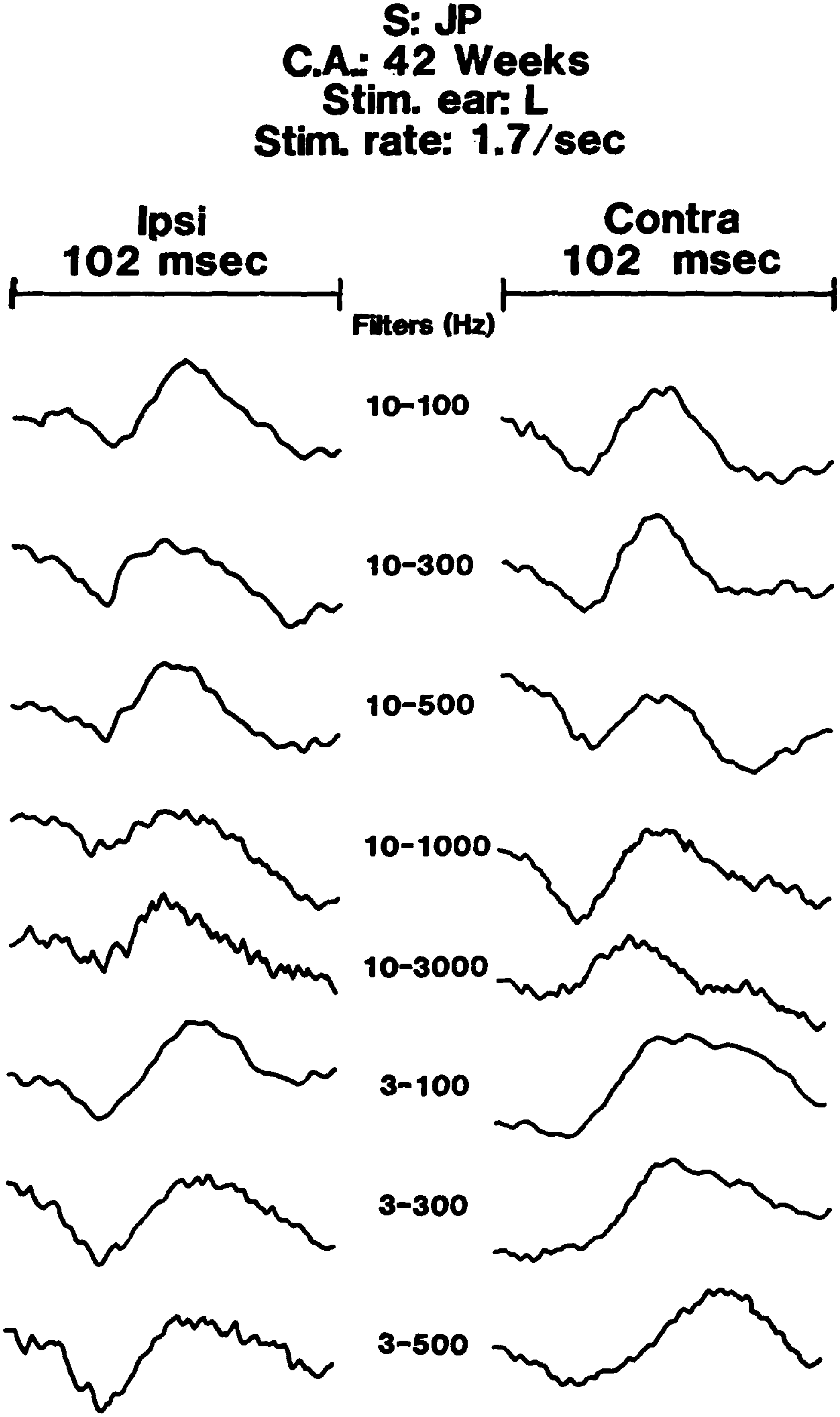

Figure 8. The effect of band-pass filtering on the MLR for 10 Hz and 3 Hz high-pass filters.

Table 2. Latency in msec of wave Pa at different EEG band-pass filter settings. Evoked responses were obtained with 500 Hz tone bursts presented monaurally at 70 dB nHL. Only one filter condition could be evaluated with subject SR due to patient care needs. "++": waveforms were elicited using a stimulation rate of 8.0 per second. "+": waveforms were elicited using a stimulation rate of 1.7 per second. "*": the band-pass filter condition was not evaluated. "-": wave Pa was not identifiable.

	Band-pass filters (Hz)							
Subject	10-100	10-300	10-500	10-1000	10-3000	3-100	3-300	3-500
OL++	46	46	44	*	*	52	54	54
JE++	-	40	38	*	*	66	-	-
IF++	54	48	48	*	*	77	-	-
CJ++	45	44	-	*	*	-	-	-
LL++	46	46	42	*	*	-	-	-
FW++	65	-	-	*	*	-	-	-
HM++	55	-	-	*	*	-	-	-
FW+	49	43	43	*	*	60	45	45
JP+	53	46	50	51	49	60	63	54
GL+	47	52	48	56	48	56	52	54
HG+	61	68	54	51	51	71	56	54
SR+	*	*	*	50	*	*	*	*

Note: Subject FW was evaluated for both rate conditions.

Experiment 3

The purpose of experiment 3 was to use the optimum stimulation rate information for the steady state evoked potential (SSEP) from experiment 1 in the evaluation of two different algorithms for threshold prediction. While monaural tone bursts were presented at the rate of 20.1 per second, SSEP waveforms were collected from 15 ears at intensities ranging from 70 dB nHL to 30 dB nHL. The two basic algorithms for threshold prediction were: 1) Visual identification of responses based on waveform replication; and 2) extrapolation of threshold values using a least-squares line-fitting extrapolation technique on the 20 Hz FFT amplitude data points. Evaluation of the extrapolation method was accomplished in two stages. The first stage determined the number of amplitude points corresponding to the various stimulus intensities that was necessary to produce a reasonable prediction value. The second stage ascertained whether the sample size per waveform average (i.e. 512 vs 1024 vs 2048) had a significant effect on the predicted threshold in a small subset of children. Predicted thresholds within the range of +30 dB to -20 dB were accepted as normal values.

Figure 9 shows an example of waveforms used in the visual tracking method for response identification. In the ipsilateral recording, waveforms showing reasonable replication were obtained from 70 dB nHL to 50 dB nHL. The morphology of the waveform at 40 dB nHL failed to show adequate replication. Similarly, the 30 dB nHL and the no-sound control run had little resemblance to the responses at higher intensities. Despite differences in peak-to-peak amplitudes due to a graphic scaling subroutine in the computer's software program, the results from the contralateral recordings revealed positive and negative peaks at similar latencies on replicate tracings down to 30 dB nHL. Based on the contralateral tracings, therefore, threshold for this child was predicted to be 30 dB nHL or below which is consistent with normal hearing sensitivity.

Despite these findings, the visual detection method was generally inadequate since most children did not display repeatable waveforms at 30 dB nHL. Recall that each child was tested in the neonatal intensive care unit. The noise associated with the constant activity in the unit was sufficient to mask the 500 Hz tone burst stimulus at low intensity levels. The sound pressure levels for the 500 Hz octave band averaged 60 dB, ranging from 52 dB during the evening hours to 66 dB during shift change or patient care crisis. The largest percentages of repeatable waveforms were at 70, 60, and 50 dB nHL with decreasing percentages at 40 and 30 dB nHL. The effect of the environmental noise on the auditory stimulus and the resultant waveform prompted evaluation of an alternate method for threshold prediction.

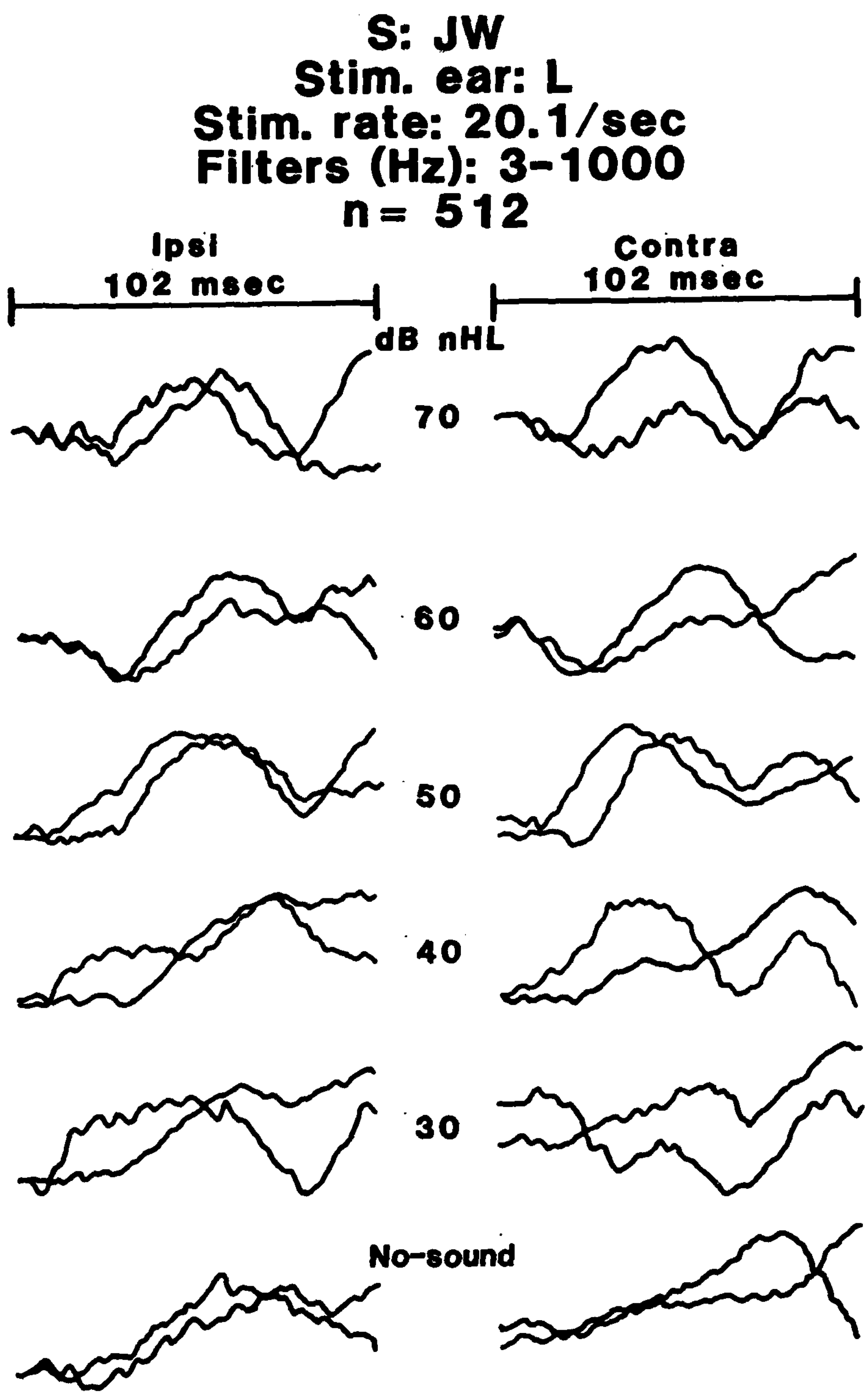

Figure 9. SSEP waveforms obtained at intensities ranging from 70 dB nHL to 30 dB nHL and a no-sound control run.

Since the FFT data in figures 3 and 4 indicated that the 20 Hz amplitude information was the most robust for use in an extrapolation technique, 20 Hz amplitude values were plotted initially for 70 dB nHL, 60 dB nHL, and 50 dB nHL and submitted to a linear regression analysis. Later, 40 dB nHL amplitude points were added to the analysis. This type of prediction technique relies heavily on two assumptions. First, a reasonable linear relationship exists between the intensity of the stimulus and the amplitude of the waveform. Second, the intensity level that corresponds to zero amplitude represents auditory threshold for that stimulus. Evidence to support these assumptions has been found in preliminary research using 40 Hz information for the SSEP in adults (Jerger, personal communication). Figure 10 shows an example of the least-squares extrapolation technique. The 20 Hz FFT amplitude points at 70, 60, 50, and 40 dB nHL were submitted to a least-squares regression analysis. The line of best fit (regression line) intersected the X-axis at 10.9 dB nHL. Consequently, the predicted threshold at 500 Hz for this child was 10.9 dB nHL.

Table 3 summarizes the prediction results using 70, 60, and 50 dB nHL amplitude information on the total group. Of the 13 children who had normal sensitivity based on ABR results, ten had normal low-frequency threshold predictions in the interval between 30 dB nHL and -20 dB nHL using the extrapolation technique on 512 sweeps per average. The

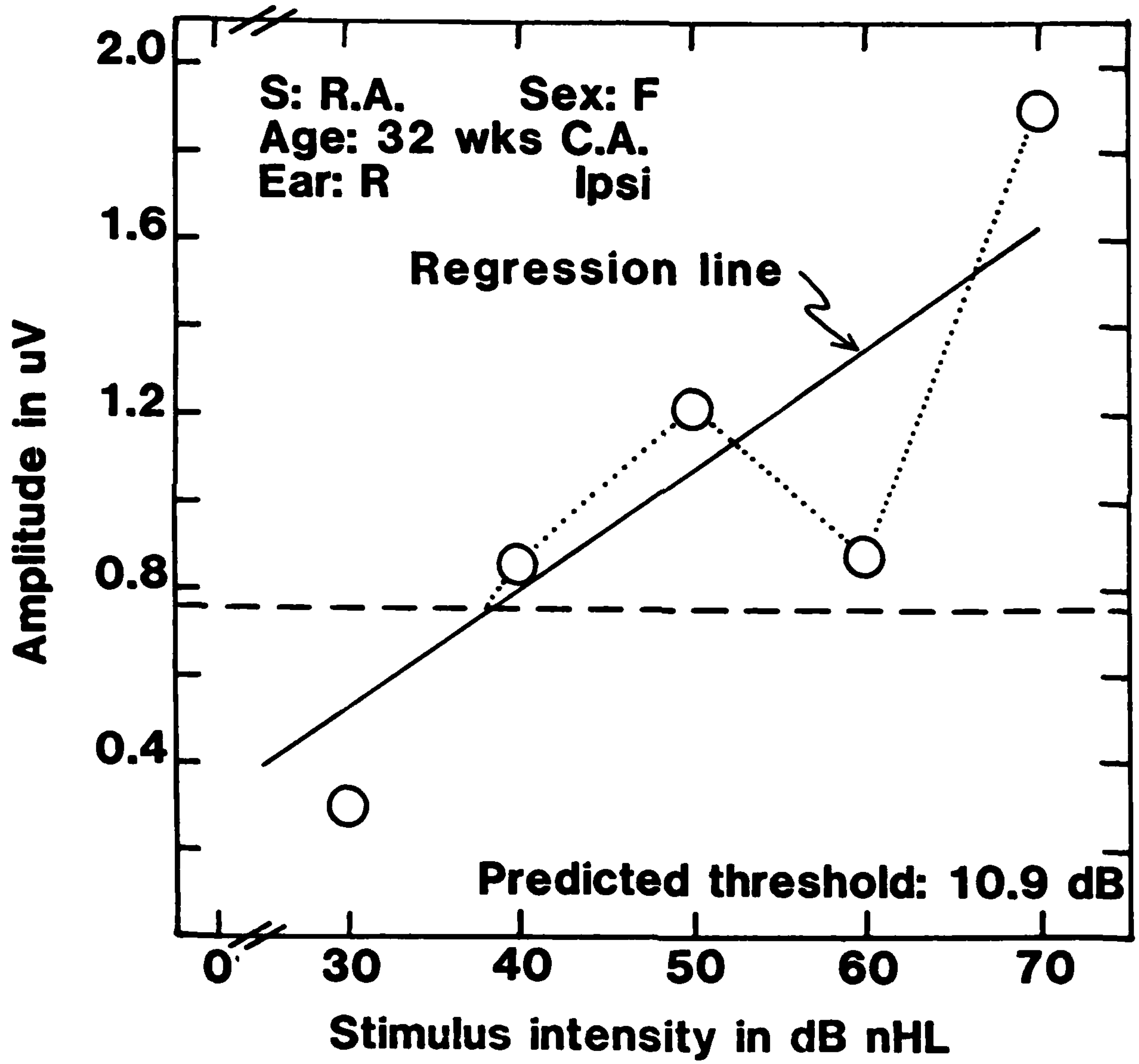

Figure 10. Five hundred Hertz threshold prediction using a least-squares extrapolation technique.

Table 3. Three point predicted thresholds at 500 Hz based on either the ipsilateral or contralateral recording. Threshold values were obtained by submitting 20 Hz FFT power (amplitude) data points at 70, 60, and 50 dB nHL to a linear regression analysis and extrapolating the least-squares line to zero amplitude.

Subject	Number of sweeps per average 512	1024	2048
RA	22.4		
MP	84.6	4.4	8.5
JW1	-20.2		
JW2	-443.2	15.0	-16.1
NS	15.9		
SR	27.2		
MS	14.4		
CD	-391.3	21.1	17.6
SJ	11.5		
GL	3.4		
AL	24.8	-19.2	24.9
DL	22.3		
KM	-17.1		

three children with widely deviant predictions each had waveform amplitudes that varied unpredictably with stimulus intensity. The extreme negative values represent a gradual decrease in amplitude with decreasing stimulus intensity. The subject with a large positive value had waveform amplitudes that increased slightly as stimulus intensity decreased. Together, the amplitude values of these waveforms reflect significiant influence of background EEG activity and possible variance of the waveform amplitude on repeat averages. However, increasing the sample size to 1024 or 2048 sweeps produced a more appropriate threshold prediction for each child with an aberrant value for 512 sweeps. Consequently, all children had normal threshold prediction values under one or more conditions when using only three data points.

Similar results are shown in Table 4 for a four-point regression analysis. The values shown in this table are the predicted thresholds using the 20 Hz FFT amplitude data at 70, 60, 50, and 40 dB nHL. These data show that the same children who had normal threshold predictions from the three point analysis also had normal predictions with the four point analysis. Similarly, the children with abnormal threshold predictions in Table 3 also had abnormal predictions in Table 4. For the children with abnormal threshold values, increasing the number of sweeps per average to 1024 or 2048 sweeps produced normal

Table 4. Four-point predicted thresholds at 500 Hz as indicated by either the ipsilateral or contralateral recording. Threshold values were obtained by submitting 20 Hz FFT power (amplitude) data points at 70, 60, 50, and 40 dB nHL to a linear regression analysis.

Subject	Number of sweeps per average 512	1024	2048
RA	26.7		
MP	151.8	19.8	-8.0
JW1	8.6		
JW2	-89.8	7.3	7.2
NS	16.8		
SR	27.2		
MS	26.4		
CD	-24.4	26.5	17.4
SJ	-0.5		
GL	20.2		
AL	-18.0	-355.4	-13.9
DL	3.0		
KM	-2.0		

predictive values in all cases except one (S:AL, n=1024). Examination of the printed waveforms for this subject indicated extremely noisy tracings for both ipsilateral and contralateral recordings, especially at the lower intensities. The extreme negative threshold prediction suggested that the variability in this child's recordings interfered with the orderly change in waveform amplitude as the stimulus intensity decreased.

A t-test was performed on the predicted thresholds derived from the three point extrapolation and the four point extrapolation techniques. An alpha level of 0.05 was the level of significance. The results indicated no significant difference between the two methods of threshold prediction ($t=0.60$, $df= 40$, $p>0.35$). Since both tables contained significant outliers among the data points that could adversely influence the t statistic, the t-test was repeated with the data pairs containing outliers eliminated. Despite the reduction in variance, the t-test failed to suggest a significant difference between analysis methods ($t=0.35$, $df=34$, $p>0.35$).

These results suggest that the linear curve-fitting extrapolation method of threshold prediction offers great potential for evaluation of low-frequency hearing sensitivity in neonates. Furthermore, the line-fitting extrapolation method appears to be a viable alternative to the more common visual detection method while avoiding many of the difficulties associated with visual identification of the waveform.

EXPERIMENT 4

The purpose of experiment 4 was to evaluate the stability of the SSEP as neonates progressed through the stages of sleep and wakefulness. Five children ranging in age from 32 weeks to 44 weeks conceptual age participated in this project. The procedure used to gather the SSEP data was to collect repeated samples over a time period that was sufficiently long to permit each child to cycle, repeatedly, through the various stages of sleep. Children of this age range have essentially three states (Spehlmann, 1981): wakefulness, active sleep (corresponding to REM sleep), and quiet sleep (corresponding to stage 4 sleep). Spehlmann (1981) reported that infants of this age group completely cycle through all stages of sleep and wakefulness every 35 to 40 minutes. Each child was successively tested, therefore, over a two hour period to ensure several sleep/wake cycles. Since each waveform required approximately two minutes for averaging, a total of 60 waveforms were collected for ipsilaterally and contralaterally for every child. The data were analyzed by plotting the averaged waveforms and evaluating the amplitude (power) values of the 20 Hz FFT component.

Figures 11a through 11f show the waveform series for

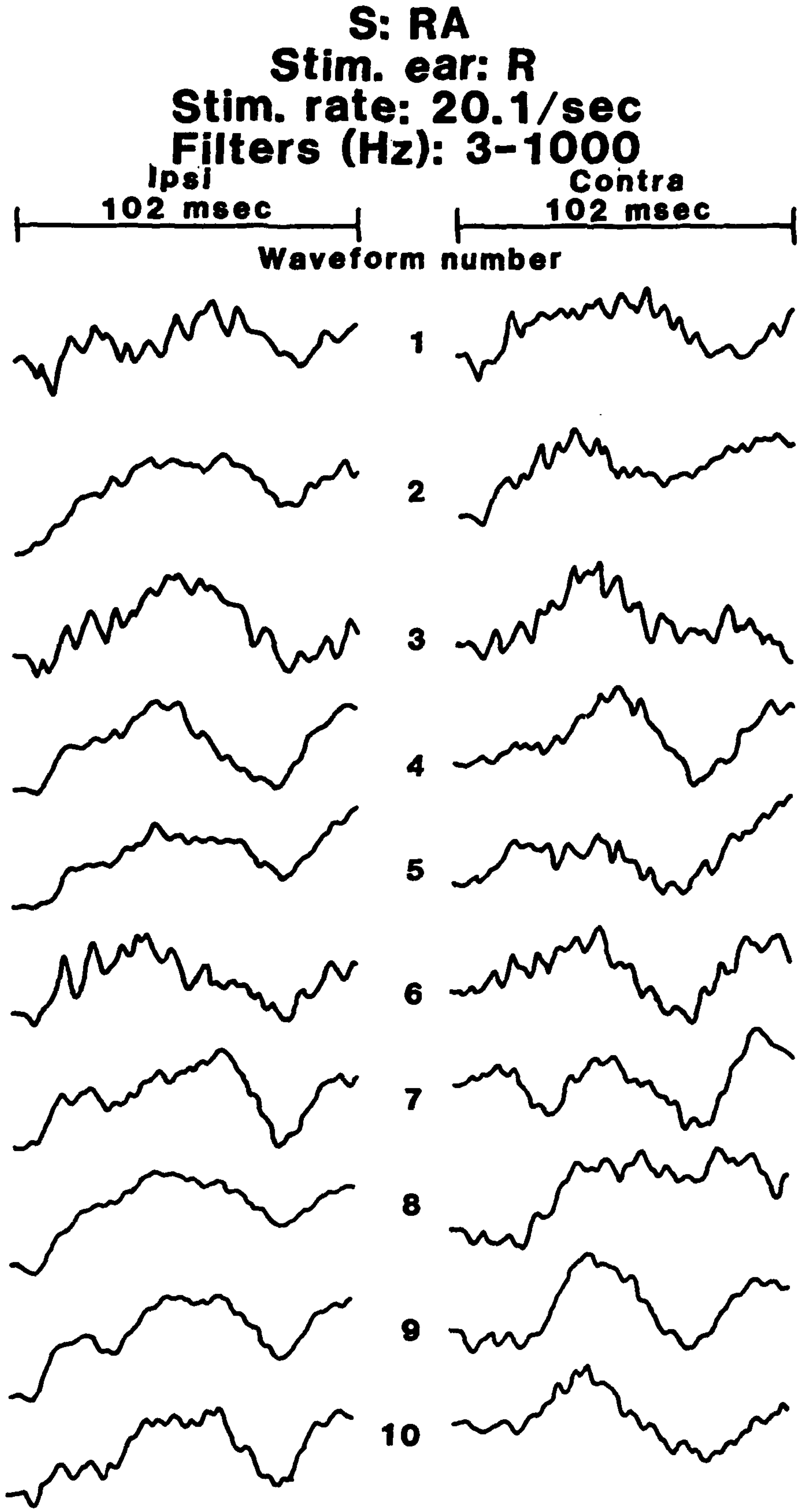

Figure 11a. Consecutive recordings of averaged waveforms for a child cycling through sleep/wake periods.

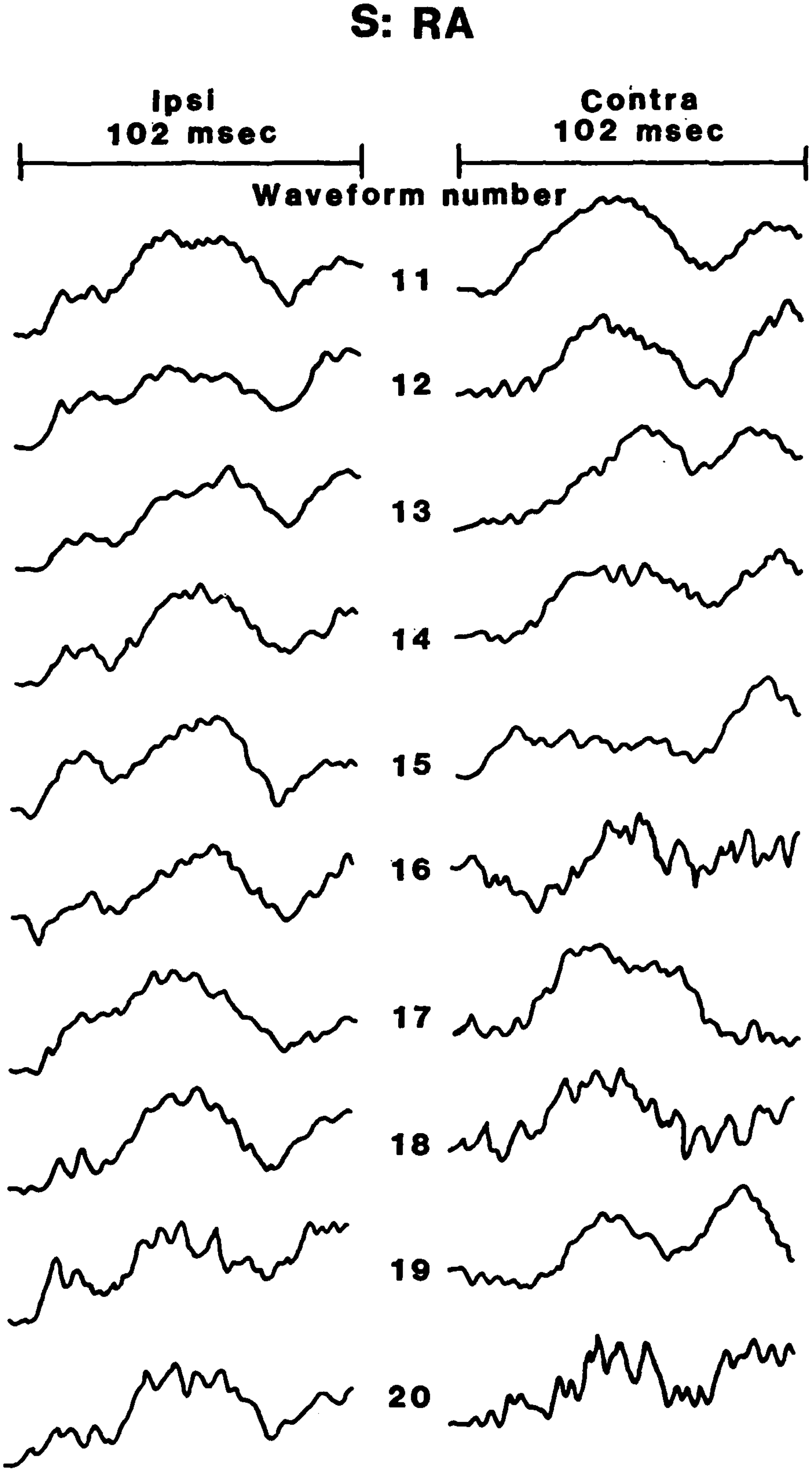
S: RA
Ipsi
102 msec
Contra
102 msec
Waveform number
11
12
13
14
15
16
17
18
19
20

Figure 11b.

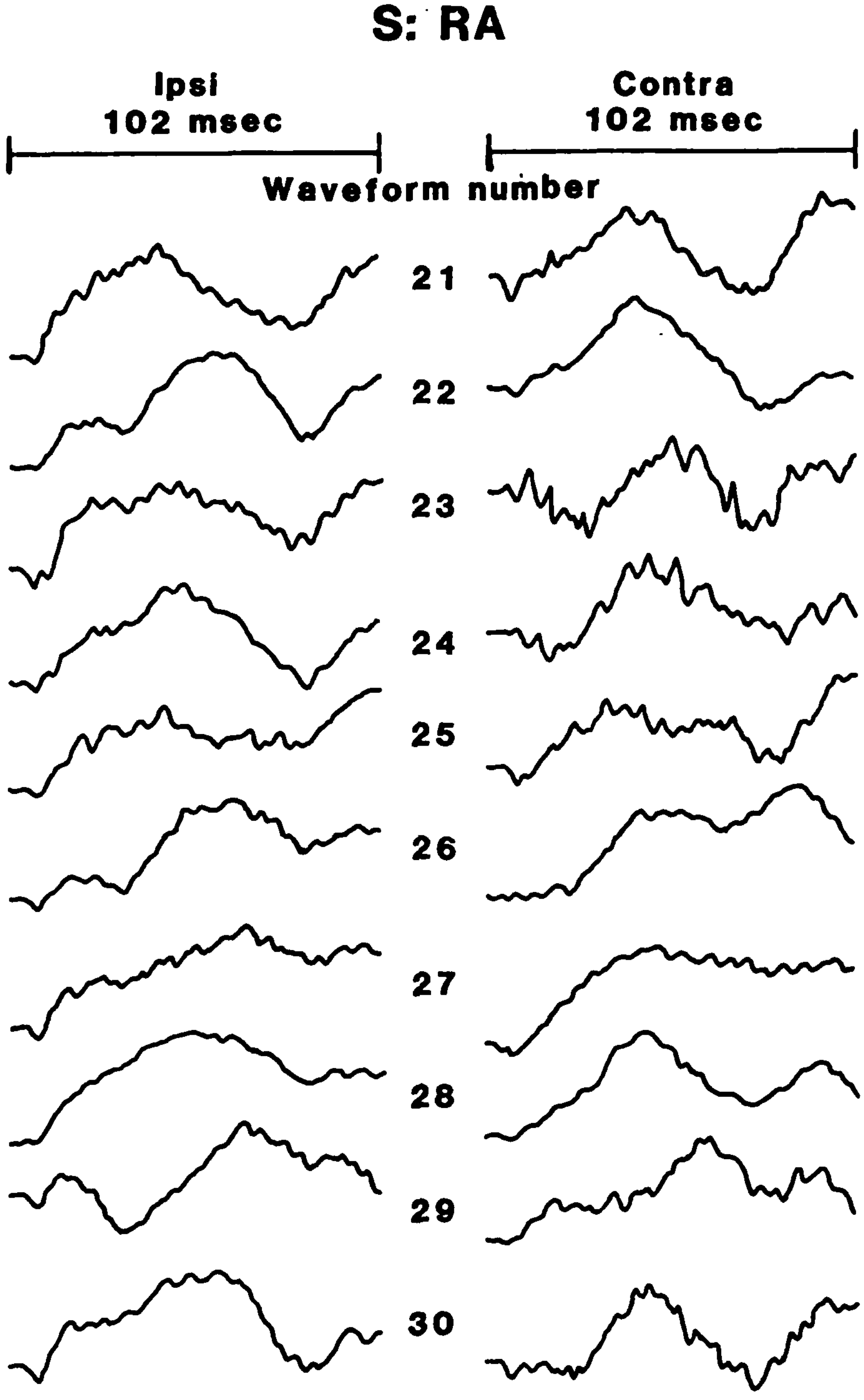
S: RA
Ipsi
102 msec
Contra
102 msec
Waveform number
21
22
23
24
25
26
27
28
29
30

Figure 11c.

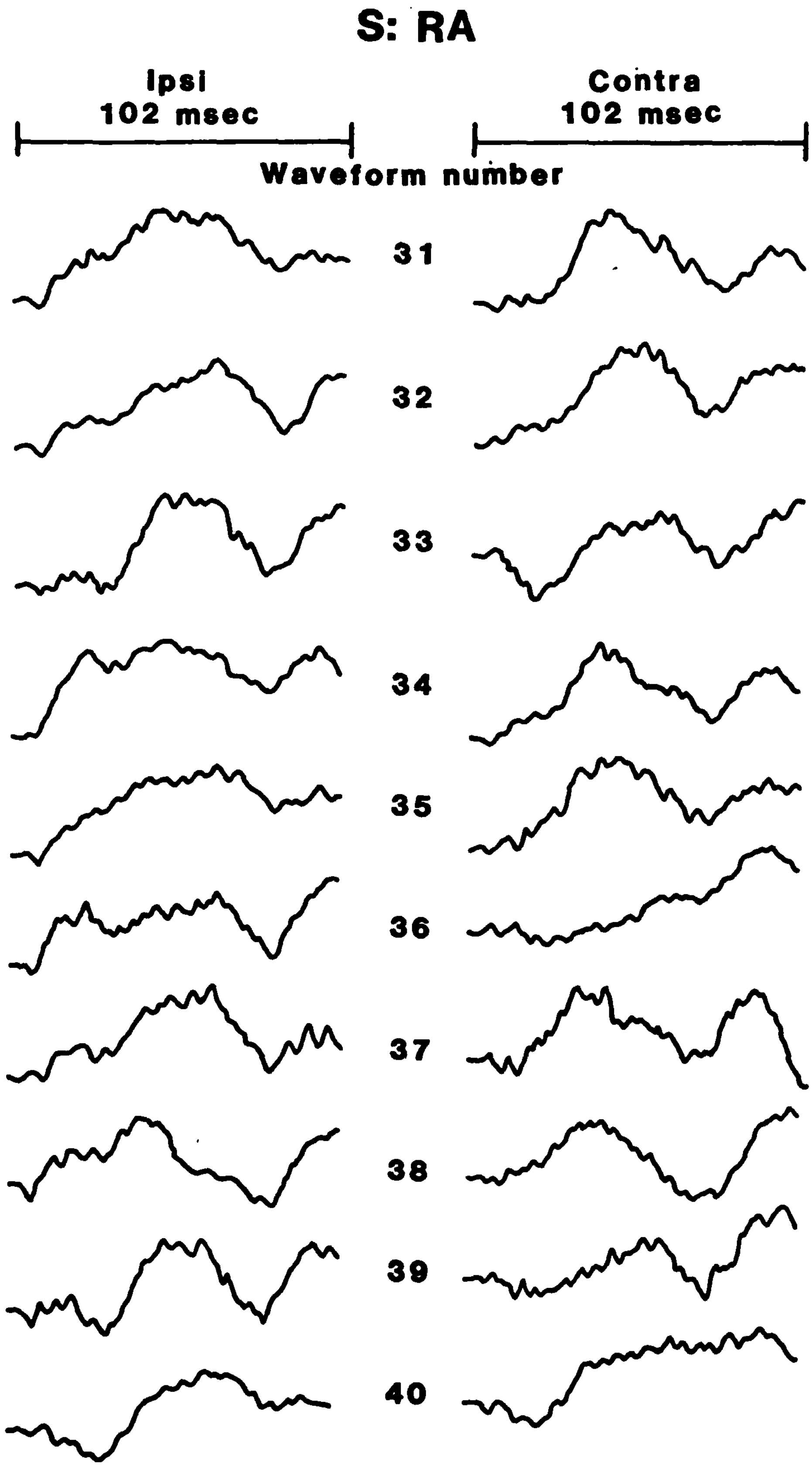
S: RA
Ipsi
102 msec
Contra
102 msec
Waveform number
31
32
33
34
35
36
37
38
39
40

Figure 11d.

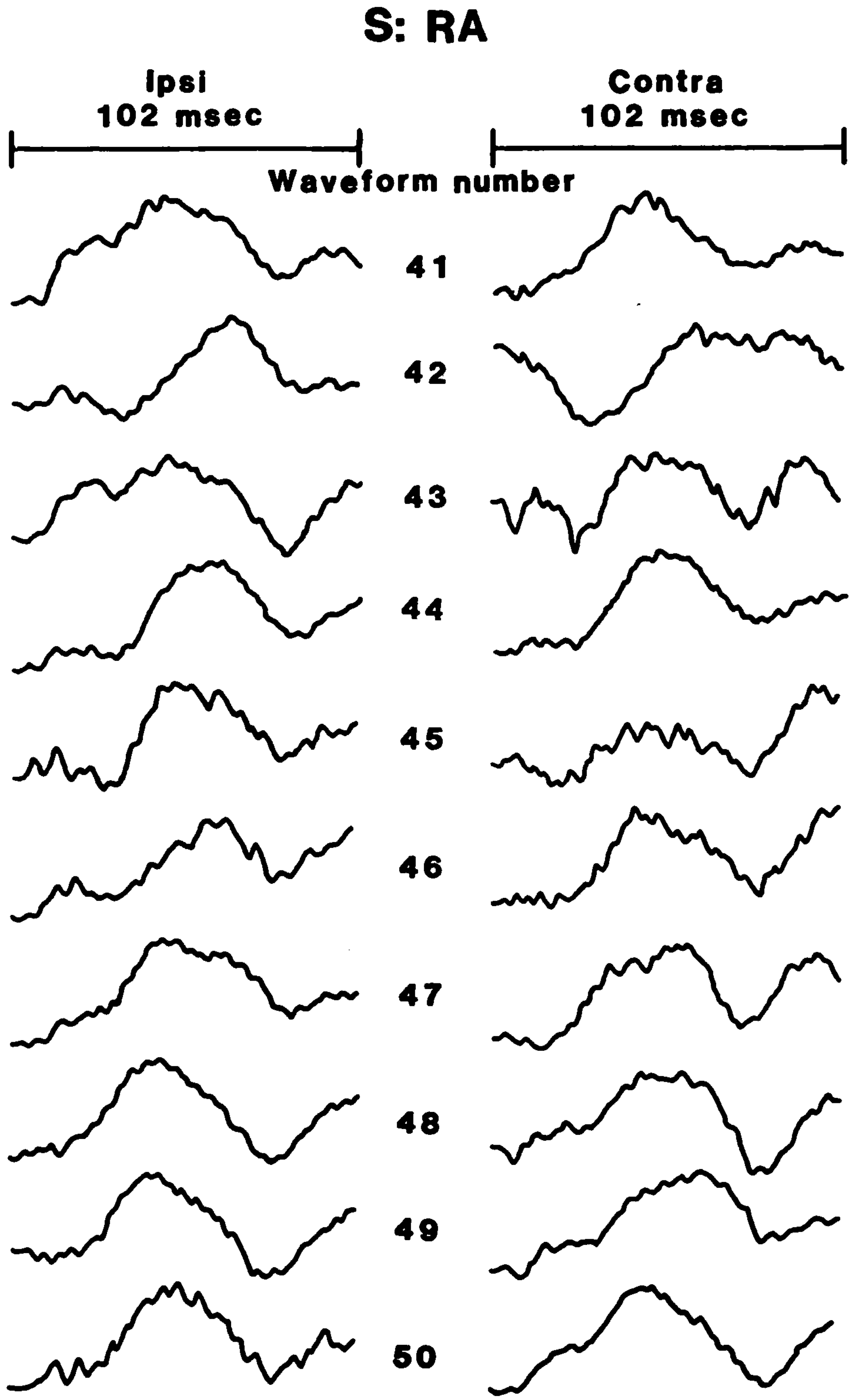
S: RA
Ipsi
102 msec
Contra
102 msec
Waveform number
41
42
43
44
45
46
47
48
49
50

Figure 11e.

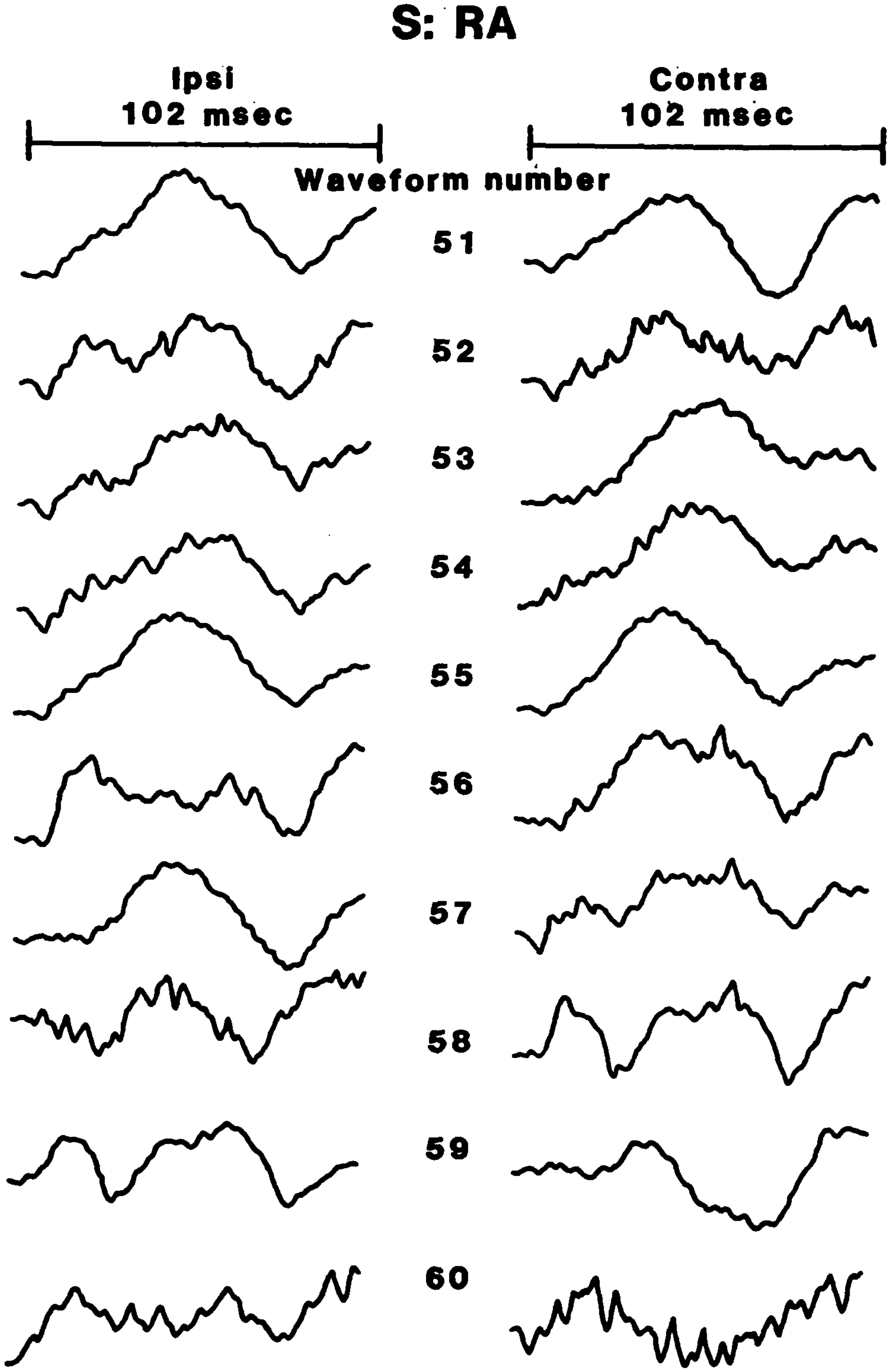
S: RA
Ipsi
102 msec
Contra
102 msec
Waveform number
51
52
53
54
55
56
57
58
59
60

Figure 11f.

subject RA. These figures reveal substantial variability in waveform morphology from one waveform tracing to the next. For the ipsilateral channel, consecutive responses demonstrated good repeatability only for waveform numbers 14 through 20 and 47 through 51. The primary characteristic of these waveforms was a prominent peak at 65 msec. Similar morphology was seen in other individual waveforms but was not observed as a consistent trend among consecutive responses.

Waveforms recorded from the contralateral channel in figures 11a through 11f also show great variability in morphology. In contrast to the ipsilateral recordings, the main feature of these waveforms consisted of two peaks, one occurring at 45 msec and the other at approximately 90 msec. Furthermore, the waveforms from this channel maintained a greater degree of stability than those recorded ipsilaterally. That is, the primary characteristics of these waveforms were seen more often in consecutive series in the contralateral than in the ipsilateral recordings.

In general, the waveforms shown in figures 11a through 11f are highly representative of the results from the other four children. In each series of averages, a maximum of five consecutive waveforms duplicated well. Then the trough-to-peak amplitudes diminished rapidly such that an identifiable waveform was no longer observed. One child (subject SJ) demonstrated bilateral variances in peak latencies that corresponded with the waveform amplitudes. That is, as the amplitude diminished, the peak latency increased. The latency variances were particularly evident for the ipsilateral recordings where the most prominent peak ranged from 43 msec to 63 msec. Similar to subject RA (figures 11a through 11f), each child had substantial morphological differences between the ipsilateral and contralateral recordings. The ipsilateral tracings had one prominent peak, whereas the contralateral tracings often had two peaks. The first peak of contralateral recording occurred earlier than the primary peak of the ipsilateral waveform. Even in cases where the contralateral tracing had only one positive wave, its latency was generally earlier than the corresponding ipsilateral wave.

An FFT analysis was performed on each series of 60 waveforms in order to obtain the amplitude value at 20 Hz. The results of the waveform amplitudes for the ipsilateral and contralateral recordings were remarkably similar for all five subjects and are shown for subject AL in figures 12 and 13, respectively. The most striking feature in each figure is the great variation in the 20 Hz amplitude over the complete series of trials. Since each data point represented the amplitude value in two minute intervals, these results suggest that the amplitudes assume a cyclic nature with a period ranging from four to 10 minutes. That is, a time interval of four to 10 minutes was required to

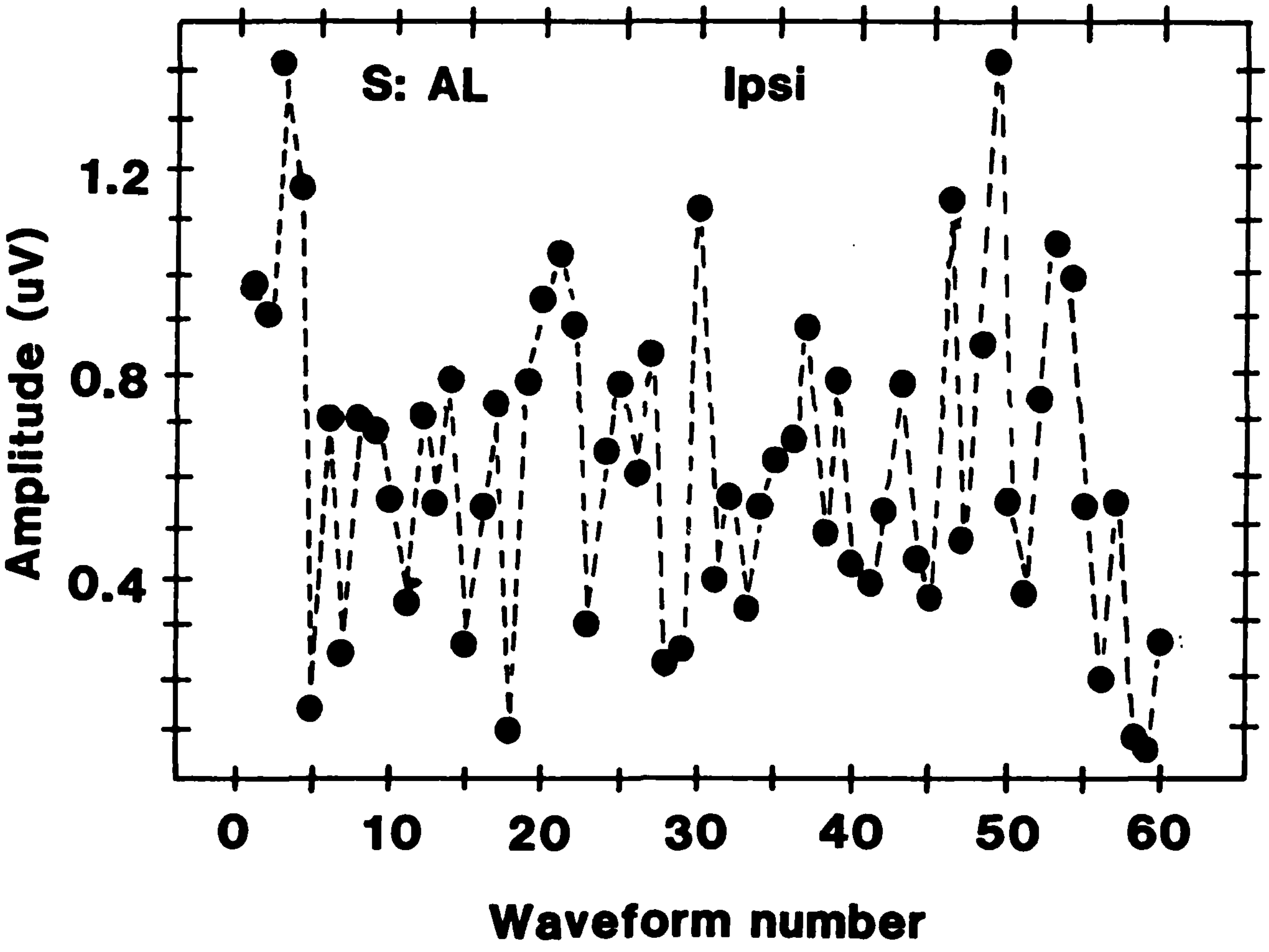

Figure 12. Amplitude of the FFT 20 Hz component obtained from the ipsilateral channel for 60 consecutive waveform averages.

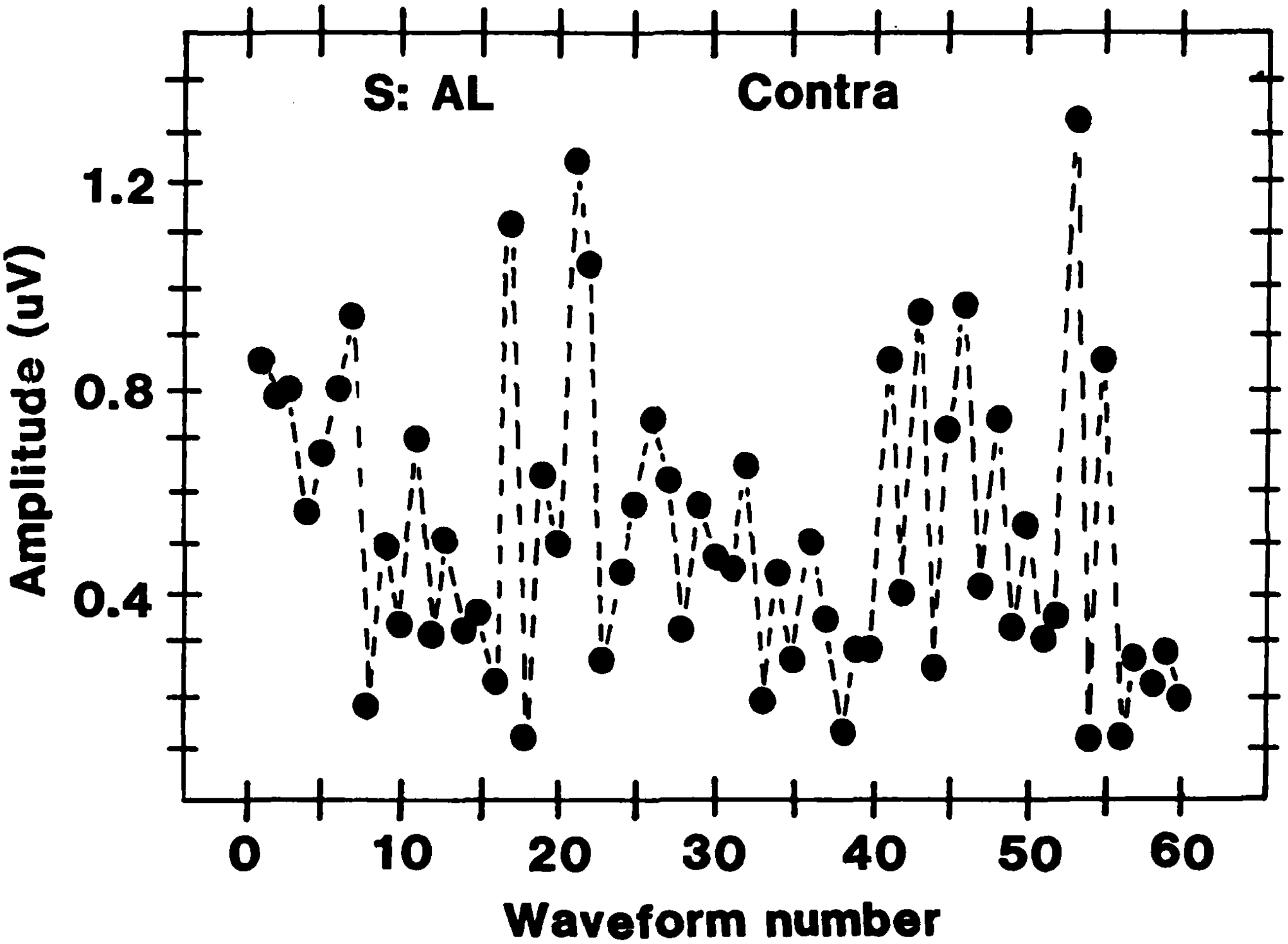

Figure 12. Amplitude of the FFT 20 Hz component obtained from the contralateral channel for 60 consecutive waveform averages.

cycle from one minimum value to the next minimum value. These empirical observations were supported by autoregression analysis. An autoregression analysis is a regression of a variable on a time-shifted version of itself. Consequently, this mathematical modeling procedure predicts values based on data points which occurred earlier in time. The efficiency of this model varies depending on the time interval used to make the predictions. For data points that show substantial variance and the absence of any organized patterns, each value is best predicted by the preceding adjacent data point. In contrast, values that are cyclical in nature are best predicted by data points that precede by a fixed time interval. The data in table 5 indicate that, for the ipsilateral recordings, each amplitude value was best predicted by a data point that occurred six to 10 minutes earlier. For the contralateral recordings, the most efficient autoregression model was achieved by using amplitudes values spaced four to eight minutes apart. These results suggested that the 20 Hz amplitude values cycled in a predictable manner from one minimum or maximum value to the next.

As seen in figures 11a through 11f, the minimum and maximum amplitudes occurred in different trials suggesting independence between the two hemisphere recordings. Table 6 contains a summary of the amplitude information for the ipsilateral and the contralateral channels. Mean amplitudes

Table 5. Optimum time intervals in minutes that produced the most efficient autoregression models of 20 Hz FFT values for 60 consecutive SSEP recordings. Each series of recordings was collected from children progressing through wake/sleep cycles over a two hour period. The optimum time intervals were obtained with a forward stepwise autoregression analysis using intervals (lags) between data points ranging from 2 minutes to 12 minutes.

	Optimum Lag Time (minutes)	
Subject	Ipsilateral Recording	Contralateral Recording
AL	6	4
SJ	8	8
MP	10	4
RA	10	8
JW	10	4

Table 6. Summary of the FFT 20 Hz amplitude data for five children from whom 60 consecutive waveform averages were obtained during sleep and wakefulness. The waveforms were elicited by 500 Hz tone bursts presented at 70 dB nHL.

Subject	Ipsi Amp.	Ipsi S.D.	Contra Amp.	Contra S.D.	r
S.J.	0.57	0.18	0.62	0.21	0.31
A.L.	0.63	0.32	0.52	0.29	0.39
R.A.	0.83	0.38	1.14	0.47	0.49
M.P.	0.97	0.37	0.88	0.41	0.24
J.W.	0.85	0.30	0.59	0.29	0.07

for the ipsilateral channel ranged from 0.57 uV to 0.97 uV. The grand mean was 0.70 uV with a standard deviation of 0.31 uV. Similarly, mean amplitudes for the contralateral channel ranged from 0.52 uV to 1.14 uV. The grand mean was 0.84 uV with a standard deviation of 0.33 uV. A Student's t-test for significant difference indicated that two of the five subjects had significantly larger amplitudes for one channel ($p<0.05$). The remaining three subjects demonstrated a trend toward larger amplitudes on one channel although the difference did not reach statistical significance.

The low correlation coefficients between the ipsilateral and contralateral amplitude values in table 6 suggest a substantial degree of independence in the amplitudes recorded from the two channels for each subject. That is, as the magnitude of the 20 Hz amplitude changed in one channel, the 20 Hz amplitude from the other channel often failed to show a corresponding change in magnitude. This finding is supported by the results in figures 11a through 11f. The waveforms demonstrating large 20 Hz components appeared unpredictably on each channel, seldomly occurring in corresponding ipsilateral and contralateral recordings.

One possible reason for the difference in mean amplitude values between channels was the placement of the vertex electrode. The precise position of the vertex electrode was uncontrolled in the majority of children due to open fontenelles or fixed head position from respirator attachment. As a result, the vertex electrode was periodically located slightly lateral to the Cz position in many of these children. Since minor differences in electrode position on an extremely small head could intuitively cause significant changes in amplitudes, the possibility of this phenomenon was examined in greater detail in one child. A total of 60 two-channel averages were obtained for each of the following vertex electrode placements conditions: affixed precisely in the Cz position (CzM), one centimeter to the right of Cz (CzR), and one centimeter to the left of Cz (CzL). The right ear was stimulated with a 500 Hz tone burst at 70 dB for all test conditions. Total test time, including feeding and other nursing requirements, was approximately eight hours.

Table 7 shows the summary amplitude data for each condition. Although the ipsilateral amplitudes were consistently larger than the contralateral values, the differences failed to reach statistical significance at the 0.05 level of confidence. Due to the significant correlations observed between the ipsilateral and contralateral recordings for each condition, a one-way analysis of variance was obtained separately for the ipsilateral and contralateral channels, respectively. Although the mean data suggested that locating the vertex electrode one centimeter to the right of midline (CzR)

Table 7. Summary of the FFT 20 Hz amplitude data for subject R.A. from whom 60 consecutive waveform averages were obtained during sleep and wakefulness under three conditions of vertex electrode position. The right ear was stimulated for all conditions. CzM: vertex electrode placed in the Cz position; CzR: vertex electrode placed one centimeter to the right of Cz; CzL: vertex electrode placed one centimeter to the left of Cz.

Electrode Position	Ipsi Amp.	Ipsi S.D.	Contra Amp.	Contra S.D.	r
CzM	0.64	0.34	0.56	0.29	0.75
CzR	0.84	0.29	0.73	0.33	0.33
CzL	0.70	0.30	0.63	0.31	0.61

Table 8. One-way analysis of variance tables comparing the amplitude means for three electrode positions (CzM, CzR, CzL). The results from each channel were analyzed separately due to large correlation coefficients observed between the ipsilateral and contralateral recordings for the CzM and CzL positions.

Ipsilateral Channel

Source	SS	df	MS	F	p
Factor	1.28	2	0.64	2.06	ns
Trials	17.46	57	0.31		
Total	18.74	59			

Contralateral Channel

Source	SS	df	MS	F	p
Factor	0.88	2	0.44	1.47	ns
Trials	16.82	57	0.30		
Total	17.70	59			

produced larger amplitudes than placement in either the CzM or the CzL positions, the analysis of variance results shown in table 8 failed to suggest a significant main effect. These results suggest, therefore, that the location of the vertex electrode on a very small head does not have a significant overall effect on the 20 Hz amplitude component of the averaged waveform. Moreover, changing the placement of the vertex electrode failed to influence significantly the amplitude relationship between the simultaneously recorded ipsilateral and contralateral waveforms.

EXPERIMENT 5

Experiment 1 showed that the primary peak (wave Pa) of the MLR occurs much longer in latency than comparable waveforms in adults. Since the latency relationship of the MLR to the ABR was substantially different in neoates, it was of interest to also investigate the relationship of the MLR to the late auditory potentials. The purpose of this experiment, therefore, was to examine the relationship of the middle latency response to the late auditory evoked potentials. Three children, 34, 37, and 37 weeks conceptual age, respectively, participated in this experiment. Each subject had also participated in one or more of the previous experiments. Waveforms were averaged over three time bases: 512 msec, 1024 msec, and 2048 msec. Data were obtained for at least two of the three children for each time base.

Figure 14 (Subject AL) shows long latency responses for a 512 msec time base. Neither channel revealed repeatable waveforms on the order of the traditional morphology often observed in adults. The ipsilateral channel showed a low-frequency wave with a peak at aproximately 300 msec and a single, replicable peak at 450 msec. The contralateral channel showed only a negative peak at 100 msec.

In contrast to the results for subject AL, subject JW (figure 15) had a wave Pa at 50 msec and a positive peak at 200 msec (P200). Similar findings were observed in the 1024 msec waveform. The same waveforms are preserved at their appropriate latencies. Replicable peaks could not be observed beyond P200. Replicable waveforms were absent in the 2048 msec time base.

In figure 16, subject CD's results failed to show repeatable waveforms in either the ipsilateral or contralateral channels for either the 1024 msec or the 2048 msec time bases. Due to the subject's nursing requirements at the time of test, 512 msec waveforms could not be obtained.

These results show substantial variability in the MLR/late potential relationship. Subject AL and subject CD failed to demonstrate waveforms that resembled the late potential. Only subject JW demonstrated recognizable waveforms. The degree of variability observed in these

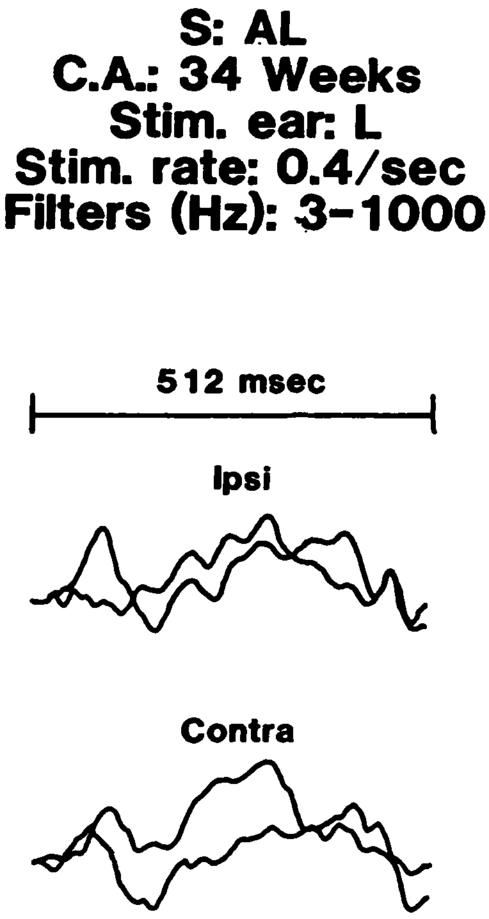

Figure 14. Late auditory potentials obtained from subject AL over a 512 msec time base.

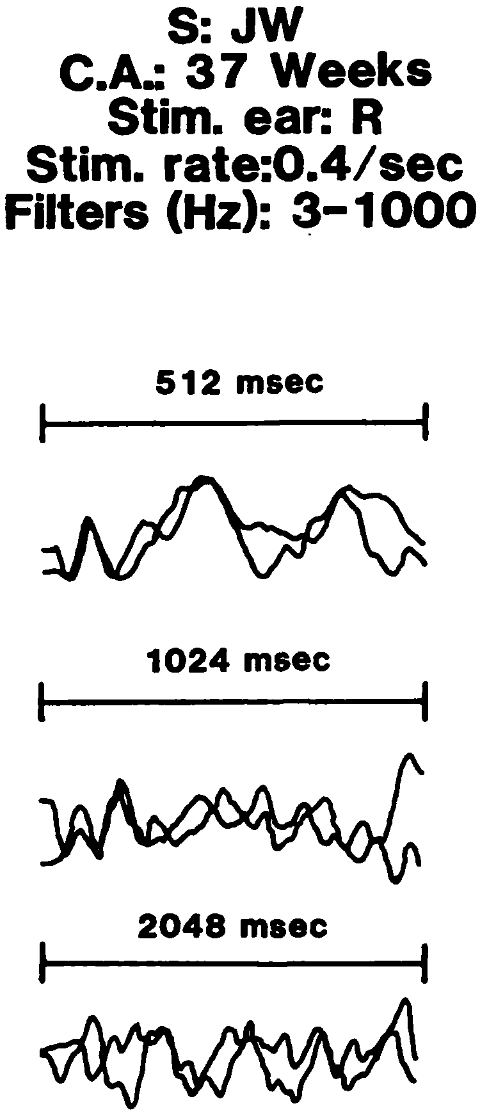

Figure 15. Long latency auditory potentials obtained from subject JW over a 512 msec, 1024 msec, and 2048 msec time base. Only the ipsilateral channel recordings are shown.

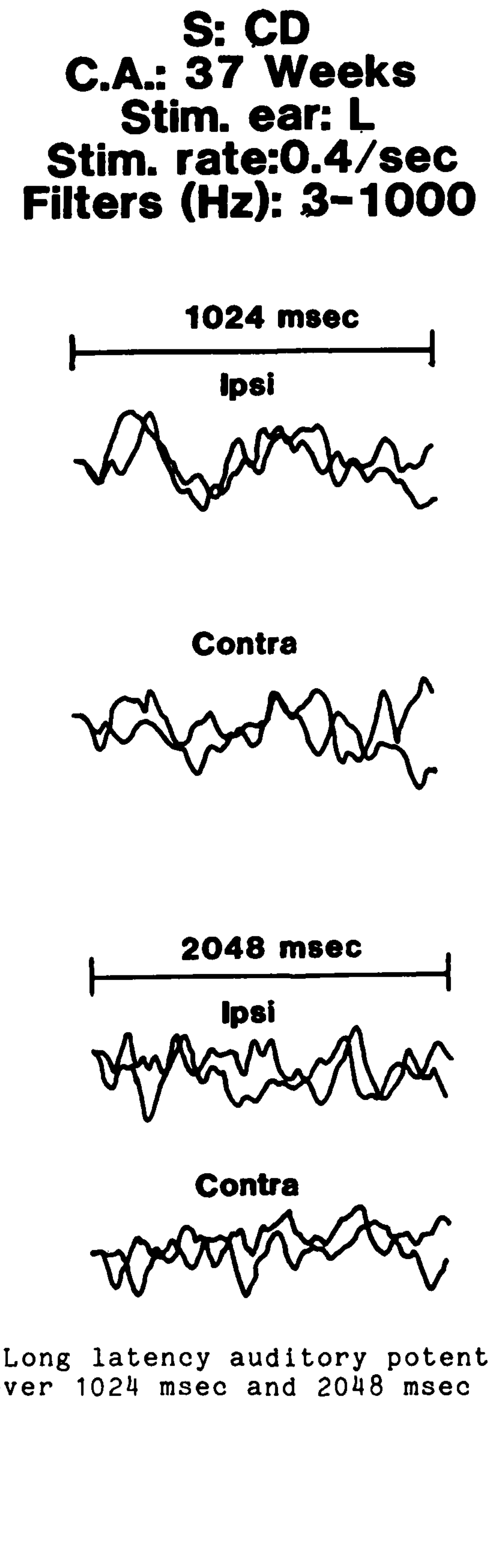

Figure 16. Long latency auditory potentials obtained from subject CD over 1024 msec and 2048 msec time bases.

recordings is consistent with the findings of Joseph et al. (1982) in using the late potential to predict hearing sensitivity. They reported significant variability in the latencies and morphology of the waveforms. Given a caudal to rostral development of the central nervous system and the effects of sleep on the late potential, it is not surprising that the response would be virtually absent in two of the three children.

DISCUSSION

The results of these collective experiments indicate that neonates do have a middle latency response and a related steady state evoked potential. Furthermore, the SSEP successfully predicted low-frequency threshold for 10 of the 13 children using 512 samples per waveform average. Normal low-frequency thresholds were predicted for the remaining 3 children when the number of samples per average was increased to 1024 or 2048. The characteristics of both the stimulation parameters and the averaged waveforms in neonates are apparently very different from those traditionally noted for adults. The peak latencies for wave Pa varied from 44 msec to 68 msec. These values are much larger than the 25 msec to 35 msec range for Pa in the adult. The basic morphology of the neonate waveform was also quite different from the corresponding waveform in the adult. Whereas the adult Pa usually shows a narrow-based peak, the neonate results revealed a broad-based waveform and a comparatively rounded peak. Furthermore, these children often demonstrated a better quality MLR recording from either the ipsilateral or the contralateral channel. The waveform amplitude and morphology were seldom of equal quality in simultaneous recordings from the two channels. It has been well established that the adult recordings show nearly identical waveforms from the ipsilateral and contralateral channels. Lastly, the neonate MLR is extremely rate dependent and was observed only at stimulation rates of one to two tone bursts per second. Adults tolerate stimulation rates of five to 11 per second without severe degradation of the MLR response.

WAVEFORM MORPHOLOGY

The differences in MLR characteristics between neonates and adults reflect an immature neurological system. Qualitatively similar differences have been well documented for the neonate auditory brainstem response (Schulman-Galambos and Galambos, 1975; Salamy and MeKean, 1976). Although the morphology is similar, the ABR waveform latencies are prolonged by adult standards. As the infant matures during the first 18 months of life, the latencies approach adult values. Moreover, the intensity levels at which the ABR can be observed are somewhat restricted until the child approaches 35 weeks conceptual age

(Schulman-Galambos and Galambos, 1975).

The primary maturational factor associated with neonatal ABR latency and intensity characteristics is a lack of VIIIth nerve action potential and synaptic synchrony. Since the MLR is thought to be derived from post-synaptic activity at the levels of subcortical auditory radiations and the auditory cortex (Parving et al., 1980, Ozdamar et al., 1982), it is not surprising that the neonate MLR would be of substantially longer latency and broad-based morphology. Given that neurological systems mature in a caudal to rostral direction, the generators of the MLR develop more slowly than the generators of the ABR.

RATE DEPENDENCY OF THE MLR

The caudal to rostral maturational trend may also contribute to the rate dependency of the MLR. Very slow rates of stimulation allow the neurons to cycle through long refractory periods as they repolarize in preparation for subsequent action potential discharge. If stimulation occurs at rates that do not allow complete repolarization of the neuron, each succeeding action potential becomes smaller in amplitude until the neuron no longer has the ability to initiate an action potential. In the case of the neonate whose central nervous system is still undergoing myelination, the refractory phenomenon may interact with the inter-stimulus interval (stimulus rate) in a manner that decreases the magnitude of synchronous activity required to recognize an evoked response. The results in experiment one indicate that stimulus rates having inter-stimulus intervals less than 500 msec were detrimental to adequate recording of the MLR. Consequently, the rate dependency of the MLR may be at least partially caused by an interaction between inter-stimulus interval and refractory periods of a very immature auditory system.

RATE DEPENDENCY OF THE SSEP

The principle of waveform phase relationships also applies toward the steady state evoked potential results. In adults, a predominant theory regarding generation of the SSEP is a superimposition of successive waveform (Po, Pa, Pb, Pc). Since each interpeak interval is approximately 25 msec, a stimulation rate of 40 per second would maintain the proper phase relationships to produce the steady state evoked potential. In contrast to adult waveforms, neonates have only one truely dominant peak, wave Pa, which occurs at an average latency of approximately 50 msec (see figures 1a and 2a). If superimposition of this waveform is required to produce the SSEP, a stimulation rate near 20 per second would be most appropriate to maintain the proper phase relationships to create the driven waveforms. The phase relationships of the superimposed waveforms at higher rates of stimulation would result in a partial or complete cancellation of the MLR component of the SSEP. The rate study for the MLR indicated that a degradation of waveform morphology and amplitude occurred at rates greater than 25 per second.

As shown in figure 2d, the SSEP waveform at 20 per second consisted of a large amplitude wave on which the ABR was identifiable as a relatively small part of the overall waveform. At 30 per second and 40 per second, the contribution of the MLR component decreased such that by 40 per second, only the ABR remained on an otherwise flat baseline. Suzuki and Kobayashi (1984) found similar results in children aged three to seven years. Thus, it appears that the phenomenon seen in the neonate group extends to older children. For this reason, the superimposition theory of SSEP waveform generation is intuitively appealing since older children have a central auditory system that is more advanced in myelination than neonates.

Despite its attractiveness, the superimposition theory fails to explain the severe degradation of the waveform at stimulation rates of five and 10 per second. Since the base of wave Pa always covered a span of less than 50 msec, the interstimulus at five and 10 per second should have been sufficiently long to prevent degradation of the response due to out-of-phase summations. It is plausible, therefore, that a strong interaction exists for the SSEP between refractory effects and waveform superimposition. This is supported by the comparative amplitude versus rate data for children and adults reported by Suzuki and

Kobayashi (1984). The Na-Pa amplitude obtained at a stimulation rate of 10 per second was virtually identical for both the children and the adults. However, at the respective optimum stimulation rates for the SSEP, the increase in amplitude for the children was approximately 50% of the magnitude of amplitude growth for the adults. This could only be attributable to a breakdown in the synchronous activity at higher rates in the children. the most plausible explanation for this phenomenon is a partial interference in the refractory characteristics.

BAND-PASS FILTER EFFECTS ON THE MLR

The effects of band-pass filtering indicated that the width of the band-pass had only a modest effect on the waveforms. These results are reported with two qualifications. First, the stimulation rate was within the range of one to two per second; and second, the high pass filter was maintained below 20 Hz. Kileny (1984) reported that the MLR disappeared in two children age 18 days and 8 months as the filters were opened from 30 Hz to 1500 Hz. His stimulation rate, however, was nine tone bursts per second. The waveforms in the present study were severely degraded in morphology at a stimulation rate of 10 per second. Consequently, the most significant observation from Kileny's report was that a very narrow band-pass filter (30 Hz to 100 Hz) has the ability to artifactually create a waveform resembling Pa. As the high-pass filter was reduced to 5 Hz, the artifact peak disappeared. The present results suggest, however, that the true MLR failed to appear due to the high stimulation rate.

Suzuki et al. (1984) discuss the effects of filtering and its importance for obtaining the MLR in children. They reported significant variability in the unfiltered middle latency responses. The MLR waveforms showed greatest stability when a digital high-pass filter was at 20 Hz. High-pass analog filtering also produced the most stable responses at 20 Hz, but introduced distortions in the amplitudes and latencies of the waveforms. Since 20 Hz high-pass filtering was not available, the two high-pass settings that were investigated in the present study were 3 Hz and 10 Hz. The results of experiment two showed relatively stable responses at 10 Hz. A high-pass filter at 3 Hz allowed high-amplitude, low-frequency energy to reduce the stability of he MLR waveform. This was most apparent in the latter portion of waveform in figure 8.

These results, combined with Suzuki's report, illustrate the need for digital filtering in MLR testing of neonates. Infants in the range of 29 weeks to 43 weeks conceptual age have spontaneous EEG activity in the 3 Hz to 7 Hz range that can approach 45-50 uV in amplitude (Spehlmann, 1981). They also have a significant amount of 12 Hz to 16 Hz energy (Joseph et al., 1976). These components are sporadic in occurrence, often lasting four to six seconds, and arising in widely differentiated regions across the scalp (Joseph et al., 1976). These frequency components significantly influence the averaged waveform, thus decreasing the stability of the amplitude and morphology characteristics. The potentially contaminating EEG components require elimination by filtering (Suzuki et al., 1984) to produce the most robust waveform. This situation, however, presents a minor delimma. To prevent contamination of the 20 Hz component by an analog filter, the high-pass setting must be near 10 Hz. This setting will eliminate much of the 3 Hz to 7 Hz energy, but will pass the random 12 Hz to 16 Hz activity. Therefore, the most effective way to obtain an uncontaminated MLR in neonates is by using a digital filter at 20 Hz to eliminate unwanted low-frequency energy and prevent waveform distortion (Scherg, 1982; Suzuki et al., 1984).

LOW FREQUENCY THRESHOLD PREDICITON

Traditionally, the auditory evoked potentials have been identified on the basis of visual identification of replicable waveforms. While this technique is often satisfactory for a very robust response that is obtained in a well controlled environment, it is less than optimal for a variable response that is measured in an uncontrolled environment. The results from experiment one and two of this study and from other investigations (Joseph et al., 1976; Cooper et al., 1980; Spehlmann, 1981; Suzuki et al., 1983; Suzuki et al., 1984) strongly suggest that the neonate MLR and SSEP are quite varable depending on the test conditions. Furthermore, the test environment for this study was the neonate intensive care unit (NICU). This type of environment is uncontrolled for electrical interference, background noise, and miscellaneous distractions. When testing in the NICU, it is important to establish the most efficient procedures to maintain minimum patient contact time, to minimize possible extraneous interence, and to increase the accuracy of the hearing threshold predicton. A level of 30 dB is normally accepted as the maximum intensity for ABR measurments by which to predict normal hearing sensitivity (Despland and Galambos, 1980). It is not unreasonable to establish the same criterion for a low-frequency threshold prediction. If using visual identification of the waveforms in th NICU environment to rule out hearing loss, however, a criterion level of 30 dB for a low-frequency stimulus may result in a substantial number of hearing loss predictions. A 500 Hz tone burst was significantly affected by the background noise in this study. The percentage of children with repeatable waveforms decreased as the stimulus intensity level decreased below 50 dB nHL. Consequently, an alternative method was needed that eliminated the need for visual identificaion of waveforms at 30 dB nHL. One alternative approach was to use an extrapolation technique for the SSEP based on an amplitude-intensity relationship at moderate levels of intensity. This procedure relied on two assumptions. First, a reasonably linear relationship exists between the 20 Hz component amplitude of the SSEP and the stimulus intensity. Second, zero amplitude corresponds to threshold. The first assumption was derived from preliminary investigations of the 40 Hz SSEP in adults (Jerger, personal communication). Using the boundary criteria of +30 dB nHL to -20 dB nHL and a normal ABR threshold as the standard, 10 of the 13 children in this study had normal threshold predictions. The remaining 3 children had normal predictions when the number of samples per waveform average was increased to 1024 or 2048. These results are encouraging with regard to supporting the assumption that the 20 Hz amplitude component of the SSEP maintains a reasonably linear relationship with the stimulus intensity. In each child high frequency hearing loss had been ruled out by the observation of an ABR response at 30 dB nHL. Since the probability of a low-frequency hearing loss without concommittant high-frequency involvement is minimal, each child was expected to have a normal low frequency threshold prediction. Indeed, the majority of children did have normal theshold predictions with 512 EEG samples per average.

Significant response variability was demonstrated in the children with abnormal threshold predictions. The magnitude of prediction error in these subjects was very large reflecting the random amplitude values at each intensity level. That is, despite the apparent replication of the waveform morphology, the amplitudes of the 20 Hz component failed to show an orderly relationship to the stimulus intensity. Increasing the number of samples per average generally produced more appropriate threshold predictions. One source for the amplitude variability was revealed by the fourth experiment regarding the effects of sleep.

RESPONSE VARIABILITY OF THE SSEP

The most significant finding of experiment four was that the variability of the 20 Hz amplitude was cyclical in nature. The amplitudes had minimal values that were roughly equivalent to the EEG noise level. The values increased to maximum amplitude and decreased again to minimum levels on an average of every seven minutes. A secondary finding was that the ipsilateral and contralateral hemispheres acted independently with regard to maximum and minimum amplitude values. That is, the amplitude values seldom reached maximum or minimum values simultaneously for both channels.

One explanation for cyclical variability in amplitude is the effect of stage of sleep on the auditory MLR. Mendel (1974) reported that the amplitude of wave Pa decreased as the stage of sleep progressed from the extremes of REM sleep to stage IV sleep. Children in the age group of this study have essentially two stages of sleep, a stage that corresponds REM sleep (active sleep) and a stage that corresponds to stage IV sleep (quiet sleep). Consequently, the large swings in amplitude could be attributed to the extreme variations in sleep stage.

It is unlikely that the large variance in amplitude is attributable only to stage of sleep. Full term newborns have sleep cycles that consist of approximately 25 minutes of active sleep and 20 minutes of quiet sleep. Transitions in the EEG patterns between active and quiet sleep stages are very rapid and distinct. The rhythmical transitions between active and quiet sleep cannot clearly be distinguished in premature infants (Joseph et al., 1976; Spehlmann, 1981). In other words, the cycles between active and quiet sleep fail to show clearly marked transitions in children of the age group in this study. Therefore, although stage of sleep may influence these results, it is unlikely that these transitions can explain the large variations in amplitude in figures 12 and 13.

A more likely explanation is the basically immature characteristic of the neonate EEG. Premature infants have large spatial regions (>2 cm) of either inactivity or unsynchronized activity (Joseph et al., 1976). These periods of inactivity often last up to three minutes in the very young premature infant (circa 28 weeks conceptual age) and are separated by 20 second bursts of activity. The neural activity usually occurs simultaneously over both hemispheres although the frequency content is often different for each hemisphere. As the infant approaches term equivalency, the inactivity/activity ratio decreases as the quiet periods become progressively shorter (Spehlmann, 1981). However, it is not until the infant reaches 43 weeks conceptual age that the EEG becomes continuous (Joseph et al., 1976). The 20 Hz component typically showed two to four minutes of relatively small amplitudes followed by two to four minutes of substantial larger amplitudes. Hence, these periods of neural inactivity have the potential to contribute greatly to the variability observed in the evoked potential amplitudes in experiment four.

The cyclical nature of the 20 Hz amplitude suggests that the method of evaluating the waveform repeatability based on one or two replicative runs is not valid with premature infants. The concept of waveform verification must change from the number of repeat averages to the time period over which the averages were obtained. That is, replicative runs should be obtained over an approximate seven minute period in order to judge by visual identification the presence of a response.

The low correlation for amplitude values between the ipsilateral and contralateral channels is consistent with the independence of the EEG spectral content for each channel (Spehlmann, 1981). Despite the simultaneous bursts of EEG activity across both hemispheres, significant qualitative differences have been reported in the frequency composition of the recorded waveforms. In like manner the recorded auditory evoked potential waveforms generally showed little similarity between channels. Other investigators have reported similar findings. Wolf and Goldstein (1978) and Okitsu (1984) found that the MLR in newborns and young infants was recognizable only in the ipsilateral channel. They could not obtain contralaterally recorded waveforms. In contrast to these reports, contralateral waveforms were observed in the present study. However, they often required serial recordings to be verified. Moreover, the morphology of the ipsilateral and contralateral SSEP waveforms were different. The maximum amplitudes occurred at a different latency in each channel. The response amplitude was seldom equal for corresponding recordings. Typically one channel had larger mean amplitudes. The differences noted in table 6 ranged from 0.05 uV to 0.31 uV. These findings correlated well with the EEG characteristics of the premature infant and suggest that the test strategy commonly used with adults must be altered substantially to obtain neonatal MLRs and SSEPs.

RELATIONSHIP OF THE MLR TO LATE AUDITORY POTENTIALS

The last experiment examined the relationship of the neonatal MLR to the late auditory evoked potentials. The adult late potentials are characterized by positive waves at approximately 80 msec (P1), 200 msec (P2), and 350 msec (P3) (Polich and Starr, 1983). The morphologies found in the present study revealed substantial variation both in waveform patterns and latencies. Subject AL (figure 14) had a small amplitude peak at 210 msec and 480 msec in the ipsilateral channel only. The contralateral channel failed to show replicable waveforms. In contrast, subject JW (figure 15) had a P1 at 88 msec and a P2 at 226 msec. Subject CD (figure 16) showed a poorly formed P1 at 98 msec and an N1 at 177 msec in the ipsilateral channel. Like subject AL, contralateral waveforms could not be obtained. The general pattern of these results is consistent with the concept of a very immature central auditory neural system. The EEG characteristics that affect the premature neonate's MLR and SSEP also apply to the late potentials. Consequently, the relationship of the MLR to the late potential is heavily dependent on the level of activity at the respective generator sites. Of the three subjects who participated in this experiment, only one (subject JW) had adult-like waveforms. The remaining two subjects failed to show waveform morphologies that were similar to the adult late response.

CHAPTER V

CONCLUSIONS

The results of this study support four major conclusions. First, the characteristics of the neonatal middle latency response (MLR) show virtually no resemblence to corresponding adult waveforms. Whereas wave Pa of the adult MLR generally occurs from 25 msec to 35 msec, the neonatal wave Pa was found in the range of 43 msec to 70 msec. The morphology of the respective waveforms are also quite different. The adult tracings typically show a distinct peak with a relatively narrow base. The recordings in this study demonstrated a more rounded peak and a very broad based waveform. Another characteristic difference was the rate dependency of the MLR. Most of the children had recognizable MLRs at stimulation rates of one to two per second. Occassionally, repeatable tracings were noted at a rate of five tone bursts per second. However, the majority of children demonstrated marked degradation of the waveform morphology at five per second, and none of the children displayed recognizable waveforms at a rate of 10 per second. This particular characteristic is in sharp contrast to the corresponding stimulation rates for adults. That is, tone bursts are typically presented to adults at rates of five to 11 per second without degradation of the waveform. Similarly, the optimum rate for the steady state evoked potential (SSEP) was much slower in neonates than in adults. Whereas the optimum stimulation rate for adults is near 40 per second, the optimum stimulation rate for neonates was near 20 per second. Each of these characteristics of the neonatal MLR and SSEP are consistent with an immature central auditory nervous system. The findings of this study are consistent in principle with previous reports regarding auditory brainstem response (ABR) characteristics in neonates (Schulman-Galambos and Galambos, 1975; Starr et al., 1977), late audiory potentials in neonates (McRandle et al., 1974; Arlinger and Walker, 1975), and MLR studies in slightly older children (Suzuki et al., 1983a, 1983b, 1984). In contrast to early studies of the neonatal MLR, this auditory response is not at all similar in latency and morphological characteristics to the adult MLR.

Second, EEG band-pass filtering has the potential to greatly influence the averaged waveform. Experiment 2 showed reasonable stability of the waveform as the low-pass filter increased. Decreasing the high-pass filter from 10 Hz to 3 Hz introduced a low-frequency wave that periodicially made wave Pa difficult to identify. Consequently, some degree of high-pass filtering is required to minimize low-frequency contamination of the waveform. That is especially important in neonates since their EEG is rich with low-frequency energy (Joseph et al., 1976). However, the high-pass filter must not exceed the point that 20 Hz EEG energy levels are significantly compromised. The FFT analysis in experiment 1 as well as previous results by Suzuki and his collegues (1983a, 1983b, 1984) indicated that 20 Hz energy must be band-passed with minimal distortion to ensure the highest quality MLR and SSEP recordings. A high-pass filter setting of 10 Hz was generally found to be adequate for this purpose.

Third, the results of experiment 3 support the concept of a reasonably linear relationship between the stimulus intensity and the amplitude of the 20 Hz FFT component of the SSEP. The relationship allowed the amplitude values to be submitted to a linear regression analysis to derive a least-squares line of best fit. The least-squares line was then extrapolated to zero amplitude for low-frequency threshold prediction. In 10 of 13 children, normal sensitivity was predicted when using only 512 EEG samples per waveform. Increasing the samples to 1024 or 2048 resulted in normal predictions for the remaining 3 children. The least-squares extrapolation technique offers greater objectivity in the prediction of threshold by removing potential judgemental biases often found in the visual detection method. Furthermore, the technique permits data collection only at moderate intensities, minimizing the detrimental masking influences of environmental noise on low-intensity, low-frequency tone bursts. Although the margin of error for predicting actual thresholds is currently unknown, this method provides a reasonable approach for determining shape of audiogram. That is, the SSEP to low-frequency tone bursts estimates low-frequency sensitivity while the ABR estimates high-frequency sensitivity.

Fourth, the SSEP is quite variable with regard to morphology and amplitude over successive recordings and the morphology of the ipsilateral versus contralateral tracings. Similar to the MLR findings and the rate dependency of both the MLR and the SSEP, the variability observed with these children probably reflects a very immature central nervous system. The variability over successive trials and between simultaneously recorded ipsilateral and contralateral recordings is consistent with previous reports on EEG characteristics in children of comparable ages (Spehlmann, 1981). Consequently, the data for the threshold predictions may need to be collected as a function of time instead of the usual method based on one or two replications of the original waveform.

Perhaps the greatest implication of this study is the introduction of a method to determine shape of audiogram. The SSEP to low-frequencies may supplement the ABR to provide both low- and high-frequency audiometric information. In turn, the increased detail in the diagnostic audiologic information will enhance habilitation efforts in prescribing hearing aids and designing appropriate language intervention strategies for children found to have hearing impairment.

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