Diagnosis of hearing loss in newborns : clinical application of auditory steady-state responses

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DIAGNOSIS OF HEARING LOSS IN NEWBORNS

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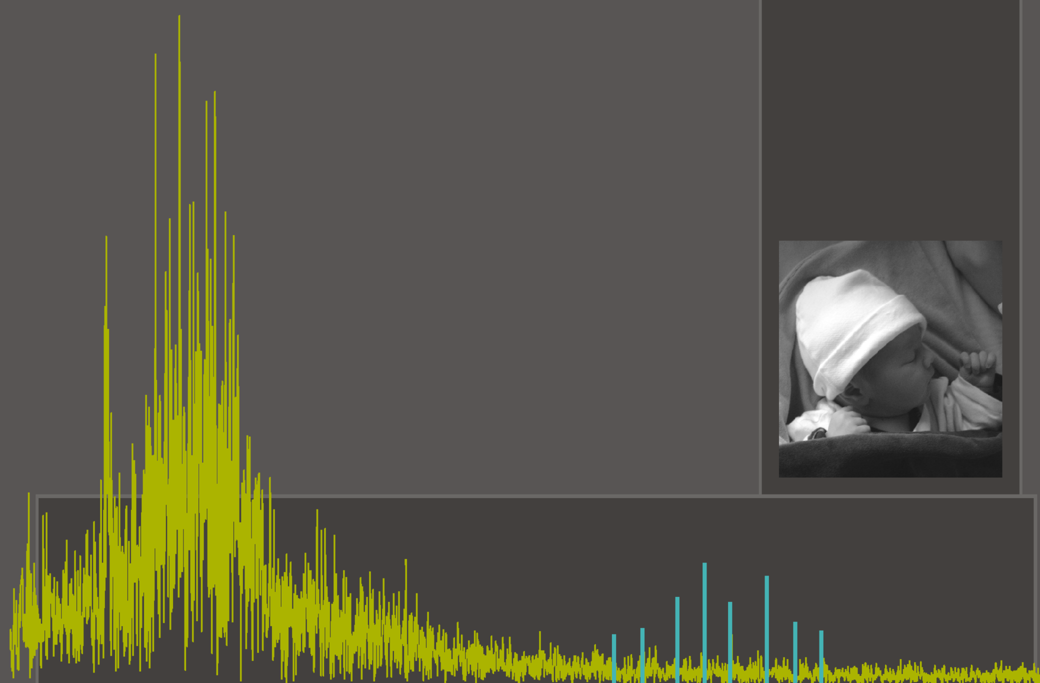

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Clinical application of auditory steady-state responses

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Thesis submitted in fulfillment of the requirements for the degree of
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Promotor: Prof. Dr. J. Wouters

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Voor Maarten en June

Voorwoord

Een doctoraatsproject is een hele uitdaging. Gelukkig stond ik er niet alleen voor, maar heb ik kunnen rekenen op de hulp van familie, vrienden en collega's. Ik zou dan ook graag iedereen die mij bijgestaan heeft oprecht willen bedanken.

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En dan zijn er mijn twee liefste schatten, Maarten en June. June, mijn kleine meid met zo’n grote impact op mijn doen en laten. Haar vrolijke babbeltjes, ondeugende lachjes en lieve zoenen laten mij iedere keer weer echt thuiskomen en mijn zorgen relativeren. Maarten, ondertussen al 10 jaar mijn steun en toeverlaat, heeft mij altijd liefdevol bijgestaan. We vormen een goed team, en dankzij z’n goede zorgen, flexibele houding en humoristische kijk heb ik dit project tot een goed einde kunnen brengen. Daarom draag ik dit proefschrift op aan Maarten en June.

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Chapter 1

Screening and diagnosis of hearing loss in children

The ability to hear and process sounds is crucial for an appropriate development of speech, language and cognitive abilities. To reduce the handicap of hearing loss in children, it is important to detect the hearing loss early and to provide effective rehabilitation. Therefore, since 1998, hearing of all newborns in Flanders (Belgium) is screened by the Flemish public agency Kind & Gezin. If the outcome of the screening does not indicate normal hearing, the infant is referred for further diagnosis. The implementation of this screening program has lead to a new, very young patient population for audiologists and ENT physicians. The hearing status of the referred infant has to be determined more quantitatively, but standard behavioral techniques are not yet applicable at young age. Hearing assessment has to rely on objective physiologic techniques that are not influenced by sleep or sedation.

The most commonly used objective technique to assess hearing in infants is the click-evoked auditory brainstem response (ABR). This technique, however, is restricted to the prediction of a general degree of hearing loss. In case of frequency-dependent hearing loss, the ABR could be misinterpreted. Furthermore, for general diagnostic purposes and for efficient fitting of hearing aids, it is vital to obtain hearing thresholds at different audiometric frequencies. For several decades, one has tried to improve the frequency and place specificity of the ABR by altering stimulus, noise masking and recording parameters. Some approaches were quite successful, but the long test duration and demanding test procedure have hampered a general application of these techniques within the European clinical practice.

Besides these ABR techniques, auditory steady-state responses (ASSRs) have been investigated as an objective technique to assess hearing thresholds at different frequencies. This technique uses continuous rather than transient stimuli and enables the recording of responses to several carrier frequencies simultaneously, which could reduce test duration. Experimental studies have shown that the ASSR can be used to predict frequency-specific hearing thresholds. Although research results were very promising, at the start of this project it was not clear how this technique could be introduced in clinical practice and systematically used in certain patient populations.

This research project is carried out to provide an answer to the necessity, due to the general neonatal hearing screening in Flanders, of a clinically useful objective method to obtain frequency-specific hearing thresholds for diagnostic and therapeutic purposes. The clinical application of ASSR, as a follow-up diagnostic, is studied in the neonatal population, to guarantee an adequate rehabilitation in order to reduce the consequences of hearing loss. The audiological research as presented in this thesis has been a prerequisite for the current application of ASSR at the ENT Department of the University Hospitals UZ Leuven.

In this introductory chapter, human hearing is described, as well as the impact of hearing loss on children. An overview of the current screening program and follow-up diagnostics in Flanders is given. The objectives of this research project and an outline of this dissertation are specified in the last section.

1.1 Hearing and hearing loss in children

1.1.1 Anatomy and physiology of the auditory system

The peripheral auditory system can be divided in three main parts: the outer ear, the middle ear and the inner ear (see Figure 1.1).

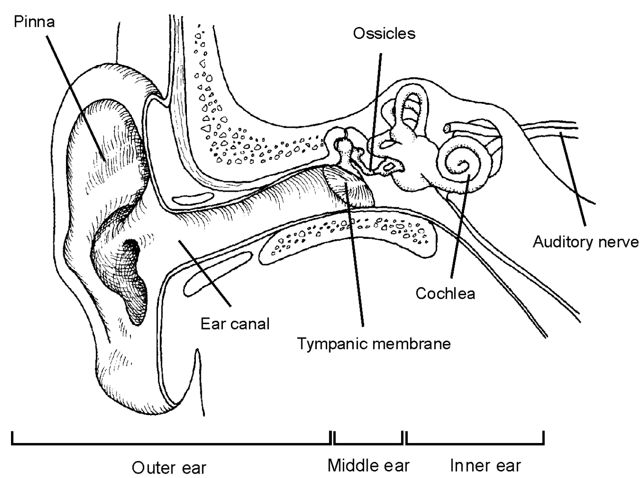


Figure 1.1: Schematic representation of the peripheral ear, adapted from Seikel et al. (2000).

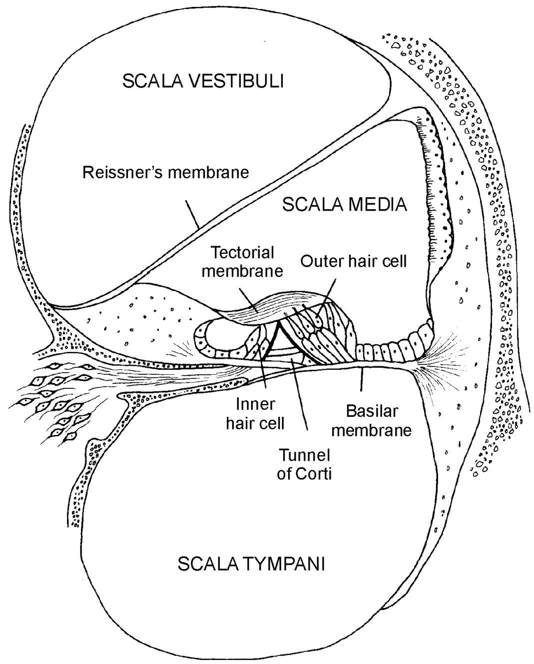


Figure 1.2: Cross section of the cochlea, adapted from Seikel et al. (2000).

The outer ear consists of the pinna and the ear canal. The tympanic membrane marks the boundary between the outer and the middle ear. The middle ear is a small space and contains three of the smallest bones of the body, the malleus, the incus and the stapes. The footplate of the stapes is embedded in the oval window, a membranous window opening to the inner ear. The inner ear houses the sensors for balance (the vestibular system) and hearing (the cochlea).

Figure 1.2 presents a cross section of the cochlea and shows the longitudinal division into three scalae. The sensory apparatus for hearing is located in the scala media, which is intermediate between the scala vestibuli and the scala tympani. The organ of Corti is situated on the basilar membrane and contains hair cells, which are the receptor cells. The tectorial membrane overlays the hair cells.

Hearing is the result of a complex sequence of events. Sound energy enters the outer ear through the ear canal and causes the tympanic membrane to vibrate. At the tympanic membrane, acoustical energy is transformed into mechanical energy. In the middle ear, these mechanical vibrations are transmitted by the three ossicles to the oval window. This induces motion in the fluids of the cochlea, which causes a wave-like movement of the basilar membrane and the structures attached to it.

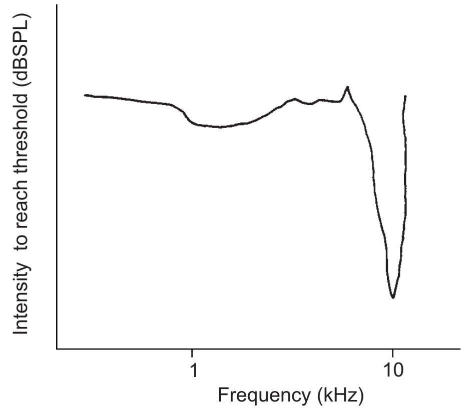


Figure 1.3: Schematic representation of a tuning curve of an auditory nerve fiber. The frequency at which the threshold of the fiber is lowest is called the characteristic frequency. Adapted from Seikel et al. (2000).

Through this, the hair cells are moved relative to the tectorial membrane and the hairs on top of the hair cells are bent. The displacement of the hairs leads to excitation of the hair cells, which leads in turn to the generation of action potentials in the neurons of the auditory nerve. In this way, the mechanical vibrations are converted into electrical events transmitted to the central nervous system by the auditory nerve (Northern & Downs, 1991; Pickles, 1988).

The inner ear provides the first level of auditory processing of an acoustical signal. It performs spectral and temporal analysis: it extracts the various frequency components and identifies basic temporal aspects of the signal (Seikel et al., 2000). The intensity and frequency of the vibrations are transmitted by traveling waves along the basilar membrane in the cochlea. The cochlea has a tonotopic arrangement, meaning that the pattern of movement of the basilar membrane depends on the frequency of the stimulus. Hair cells that respond to high frequencies are located in the basal turn of the cochlea, while hair cells that are tuned to lower frequencies are found more apical (Pickles, 1988).

The auditory nerve fibers respond better to some frequencies than to others. This can be illustrated by the tuning curve, which is a graphic representation of the acoustical stimulus intensity necessary to evoke a response in a specific auditory nerve fiber as a function of frequency (see Figure 1.3). The sharper the tuning curve, the greater is the frequency selectivity. The ‘tail’ in the lower frequencies shows that the nerve fiber will also fire at lower frequencies than its characteristic frequency, but only at higher intensity levels. Besides frequency selectivity, the nerve fibers show phase-locking (Rose et al., 1967). Neural firings tend to occur at a particular phase of the stimulating waveform, so that there is temporal regularity in the firing pattern of a neuron in response to a periodic stimulus.

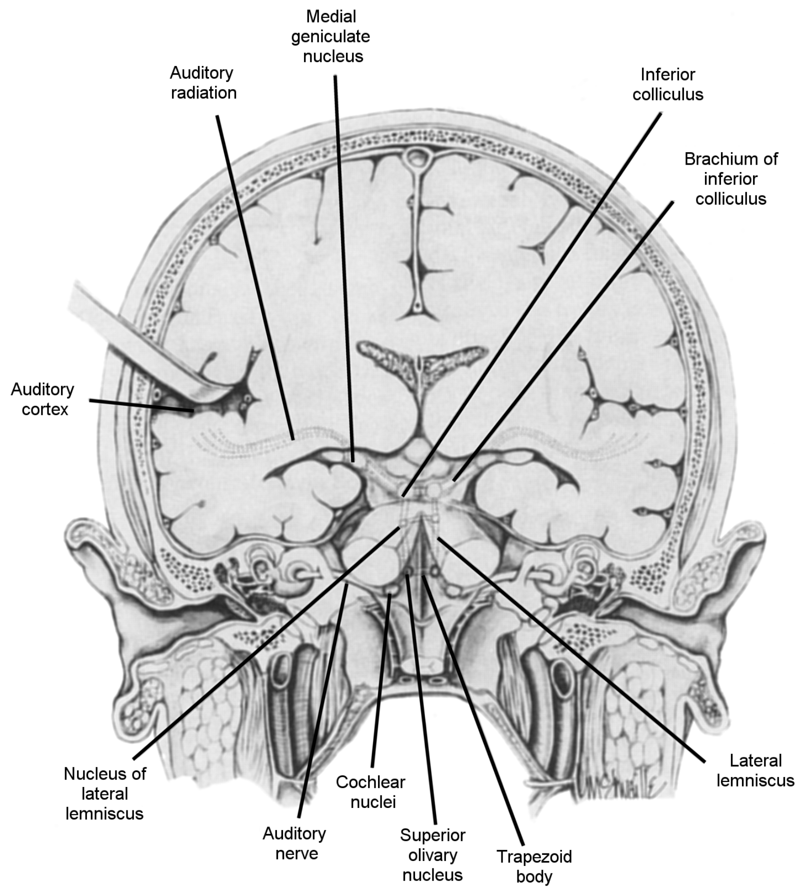


Figure 1.4: Ascending auditory pathways. Adapted from Nolte (1988).

The cochlea and the auditory nerve represent only the first stage of information extraction of the auditory signal. Electrical events are transmitted to neurons at higher levels of the auditory system for further extraction of information. The responses of these neurons are more complex and not yet fully understood. The most important ascending pathways and nuclei from the cochlea to the auditory cortex are shown in Figure 1.4.

The human auditory mechanism has a frequency range from 20 to 20000 Hz, and can differentiate small increments in frequency and intensity. It can listen to a signal embedded in background noise and to rapid sequences of sounds, which is all required for optimal speech understanding (Seikel et al., 2000). At birth, the form and function of the inner ear, the cochlea, is completely developed. The central auditory pathway, however, is less mature than the peripheral auditory structures (Jiang & Tierney, 1995). The auditory pathway is myelinated by the 29th week of gestation, but the density of the myelin sheath continues to increase until about 1 year after birth (Moore et al., 1995). Moreover, synchrony of neural discharge is immature (Jiang & Tierney, 1995). Maturation of auditory processing proceeds through the early childhood, concurrent with the developing speech and language skills.

1.1.2 Types of hearing loss

When a hearing loss is diagnosed, three attributes are described: the type, the degree and the configuration of the hearing loss. The type of hearing loss refers to what part of the auditory system is damaged. When sound is not conducted efficiently through the outer and middle ear a conductive hearing loss is present, meaning the sound level is reduced. This type of hearing loss can often be corrected by medicine or surgery. When the inner ear or the auditory nerve pathway is damaged, a sensorineural hearing loss occurs. Sounds are not only attenuated, but also distorted. This type of hearing loss is permanent and cannot be corrected with surgery or medication. A conductive hearing loss can occur in combination with a sensorineural hearing loss. This is called a mixed hearing loss.

The degree of hearing loss refers to the severity of the loss. Most commonly used categories are normal hearing (0-25 dBHL), mild hearing loss (26-45 dBHL), moderate hearing loss (46-70 dBHL), severe hearing loss (71-90 dBHL), and profound hearing loss (more than 90 dBHL).

The configuration or the shape of the hearing loss refers to the extent of hearing loss at each frequency. Possible configurations are high-frequency hearing loss, low-frequency hearing loss, flat hearing loss and a cookie-bite configuration. A bilateral hearing loss affects both ears, a unilateral hearing loss only one ear. In a symmetrical hearing loss the degree and configuration is the same in each ear, in contrast with asymmetrical hearing loss. A hearing loss can be fluctuating, stable or progressive. If it is present at birth it is congenital, if it develops later it is acquired. This research project mainly focuses on the objective assessment of the degree and configuration of congenital sensorineural hearing loss.

1.1.3 Impact of hearing loss

Permanent bilateral hearing loss affects at least one in a thousand newborns (Mehl & Thomson, 2002; Dalzell et al., 2000; Mason & Herrmann, 1998). The prevalence of hearing loss in infants at the Neonatal Intensive Care Unit (NICU) and those with other specific risk factors is even 10 to 20 times higher than in the general population of newborns. Hearing loss in children is a silent, hidden handicap. If undetected and untreated, it can lead to delayed speech and language development, learning problems, social and emotional problems (Northern & Downs, 1991).

The development of the auditory nervous system relies, in part, on auditory input. The longer auditory language stimulation is delayed because of an undetected hearing loss, the less efficient will be the language facility, because there is a critical period for the development of language (Northern & Downs, 1991). By identifying hearing loss at birth, the early plasticity of the brain can be assessed for auditory learning.

In 1998, Yoshinaga-Itano and colleagues (1998) showed that children whose hearing losses were identified by 6 months of age demonstrated significantly better receptive and expressive language skills than did children whose hearing losses were identified after the age of 6 months. All of the children received early intervention services, including the fitting of hearing aids, within an average of 2 months after identification. This language advantage was evident across age, gender, socioeconomic status, ethnicity, cognitive status, degree of hearing loss, mode of communication and presence/absence of other disabilities. Moeller et al. (2000) investigated the relationship between age of enrolment in intervention and language outcomes at 5 years of age in a group of hearing-impaired children. Regardless of degree of hearing loss, early-enrolled children performed comparably to their hearing peers. These studies have shown that early identification of hearing loss and early intervention are crucial to maximize the development of receptive and expressive language abilities and communicative competence.

1.2 Early hearing detection and intervention

1.2.1 International recommendations

Since undetected congenital hearing loss has such a big impact on the general development of infants, the American Joint Committee on Infant Hearing (JCIH) was established in 1969. The working group was composed of representatives from audiology, otolaryngology, pediatrics, and nursing. The main responsibility of the JCIH was to make recommendations concerning the early identification of children with, or at-risk for hearing loss and newborn hearing screening. Initially, they recommended identification of infants at risk for hearing loss according to a list of high-risk criteria and audiological testing of these infants. The list of risk criteria has been extended throughout the years. Table 1.1 presents the list, which was part of the 1994 Position Statement.

Table 1.1: Risk factors that identify those neonates (birth through age 28 days) who are at risk for sensorineural hearing impairment (Joint Committee on Infant Hearing, 1995).

1.	Family history of hereditary childhood sensorineural hearing loss
2.	In utero infection, such as cytomegalovirus, rubella, syphilis, herpes and toxoplasmosis
3.	Craniofacial anomalies, including those with morphological abnormalities of the pinna and ear canal
4.	Birth weight less than 1500 grams
5.	Hyperbilirubinemia at a serum level requiring exchange transfusion
6.	Ototoxic medications, including but not limited to the aminoglycosides, used in multiple courses or in combination with loop diuretics
7.	Bacterial meningitis
8.	Apgar scores of 0 to 4 at 1 minute or 0 to 6 at 5 minutes
9.	Mechanical ventilation lasting for 5 days or longer
10.	Stigmata or other findings associated with a syndrome known to include a sensorineural and / or conductive hearing loss

However, risk factor screening identifies only 50% of infants with significant hearing loss (Mauk et al., 1991; Mehl & Thomson, 2002). The need to detect *all* infants with hearing loss in the first few months of life was ratified in the Position Statement of the JCIH in 1994 (Joint Committee on Infant Hearing, 1995). In the ensuing years, not only the feasibility of universal newborn hearing screening was demonstrated, but also the importance of early intervention for infants with hearing loss. In 2000, the committee endorsed screening of all neonates' hearing using objective physiologic measures (Joint Committee on Infant Hearing, 2000). The following guidelines were recommended:

- All infants should have access to hearing screening before 1 month of age.
- In case of failed hearing screening, an appropriate audiological and medical diagnosis should be made before the age of 3 months.
- All infants with confirmed permanent hearing loss should receive multidisciplinary intervention by the age of 6 months.

In response to these recommendations general or hospital-based newborn hearing screening programs have been introduced in many regions around the world with a high coverage. The targeted hearing loss for screening programs is permanent bilateral or unilateral, sensorineural or conductive hearing loss, averaging 30 to 40 dB or more in the frequency region important for speech recognition, approximately ranging from 500 to 4000 Hz.

Two physiologic measures have been successfully implemented for universal newborn hearing screening, namely otoacoustic emissions (OAEs) and ABR. Both technologies are non-invasive recordings of physiologic activity that underlie normal auditory function and that are easily carried out in neonates. OAE responses are generated within the cochlea by the outer hair cells, and therefore OAE evaluation will not detect neural or retrocochlear dysfunction. The ABR reflects activity of the cochlea, the auditory nerve and auditory brainstem pathways. Most screening technologies use automated response detection and only answer the question of a hearing loss greater than the targeted hearing loss with a pass or refer.

The efficiency of a hearing screening technique can be expressed by the sensitivity and specificity. The sensitivity of a test is the probability of a positive test (a refer) among infants with hearing loss. The sensitivity should be near 100%, since all infants with hearing loss should be detected. The specificity of a test is the probability of a negative test (a pass) among infants with normal hearing. A low specificity means that many normal-hearing infants are referred for further audiological evaluation. These false positive screening results cause unnecessary parental distress and increased workload at referral centers, which should be avoided.

In the first screening protocols, referral rates were sometimes very high, up to 10% and more, although the incidence of congenital hearing loss (unilateral and bilateral) is about two in a thousand. The JCIH recommended a referral rate after the screening process of 4% or less. Therefore, most screening programs use a two-step screening procedure. If an infant does not show a clear response on the initial test, a second test is carried out, soon after the first. If this second test also shows no clear response, the infant is referred to more specialized medical services, for further audiological evaluation. ABR and OAEs are used sequentially, or one test is repeated. Due to advances in technology and training methodology, referral rates (and false alarm rates) were significantly reduced, to rates even below the recommended 4%.

In 1996, before the implementation of a newborn hearing screening program, Harrison and Roush (1996) reported an average age of identification of 30 months in the United States. Although children with severe or profound hearing loss may be identified earlier, children with mild to moderate losses were often not identified until school age. By the introduction of early hearing detection and intervention programs, hearing loss should be identified before the age of 1 month.

After a failed hearing screening, an extensive audiological and medical evaluation has to ascertain the hearing status of the referred infant. According to the JCIH (2000), the audiological assessment must consist of a test battery, including developmentally appropriate behavioral and physiologic measures. It must include an electrophysiological measure of threshold using frequency-specific stimuli. Every infant with confirmed hearing loss should be referred for otologic and other medical evaluation, in order to determine the etiology of the hearing loss.

All infants with the targeted hearing loss are at risk for delayed communication development and should receive early intervention services (Bess et al., 1998). These intervention services should be designed to meet the individualized needs of the infant and family, including addressing acquisition of communicative competence and social skills. Hearing aid selection and fitting should be provided as soon as possible after confirmation of the hearing loss (Joint Committee on Infant Hearing, 2000).

1.2.2 Screening and follow-up of hearing loss in Flanders

Flanders was one of the first regions in the world where early auditory screening was systematically offered to all babies, approximately 60000 per year (Van Kerschaver & Stappaerts, 2002). Universal newborn hearing screening has been implemented since 1998. Newborns are screened free of charge by the Flemish organization Kind & Gezin (‘Child & Family’), which is a suborganisation of the Flemish Ministry of Welfare and Health and whose purpose is to promote welfare and health of all children. To this end, all mothers who have just given birth receive visits from a nurse and are invited to preventive consultations for babies, in which the child is examined, advice is given and vaccinations are carried out.

The screening is carried out at the age of about 4 weeks and is fully integrated into the normal program of basic preventive care. This means no additional time or additional staff is needed for the hearing screening and the target group can easily be reached. Screening of all newborns before hospital discharge is very difficult to achieve because of the decreasing hospitalization period after giving birth and the increasing number of home births. In addition, the number of referrals is higher shortly after birth. From psychological point of view, there are also reasons to postpone the screening test for a few weeks. The first weeks are, after all, crucial to the process of parental bonding with the new baby. Concerns about possible disabilities may disrupt this process.

The ALGO test is used for screening. This test is based on automated ABR and shows a “pass” result if there is 99.98% certainty of good hearing and a “refer” if that certainty is not achieved. The test can be carried out by one person and requires only limited practical training. If the first ALGO cannot assure normal hearing for both ears, a second test is performed within 48 hours of the first test, in the presence of the welfare baby clinic medical officer. If this second test can again not ascertain normal hearing, the baby is referred for extensive diagnosis (see Figure 1.5).

In 2002, screening was offered to 99.41% of the newborns and 96.38% was effectively screened. The small difference is due to refusals by parents. The refer rate after the first ALGO test was 0.52%. Almost half of the retested babies passed the second test. In total, 143 babies were referred for further diagnostic evaluation. This is 0.26% of the total group of tested infants. These refer rates are far below the recommended 4%. Hearing loss was confirmed by diagnostic tests in approximately 80% of these babies. Four out of 10 had a unilateral hearing loss, 6 out of 10 a bilateral hearing loss. The incidence of bilateral hearing loss of more than 40 dB was 0.1% (Van Kerschaver & Stappaerts, 2004). The number of false negative screening results is difficult to evaluate. A few infants that passed the screening were diagnosed with hearing loss at later age. These could be false negative screenings or cases of acquired hearing loss.

Not all infants could be reached by the general screening program. During the first years of this screening project, it appeared that especially the babies that spent time after birth at the Neonatology Department and the NICU were missed. However, the incidence of hearing loss in this target group is very high (2-8%) (van Straaten et al., 2003; Yoshikawa et al., 2004; Prieve et al., 2000). Especially the use of ototoxic medication carries an additional risk. In 2002, 609 babies stayed at the Neonatology Department of UZ Leuven. Of this group, 159 babies or 26% were missed by the general hearing screening program. Therefore, since 2003, screening is performed at the NICU of UZ Leuven before hospital discharge by audiologists of the ENT Department. This screening consists of click-evoked ABR recordings at 70 and 80 dBpeSPL, corresponding to levels of 40 to 50 dB above the normal-hearing threshold. If the screening at the NICU cannot be carried out, for instance if the baby is transferred to another hospital, or if it is discharged from the hospital before the screening can take place, the baby is referred to the general screening program of Kind & Gezin (see Figure 1.5).

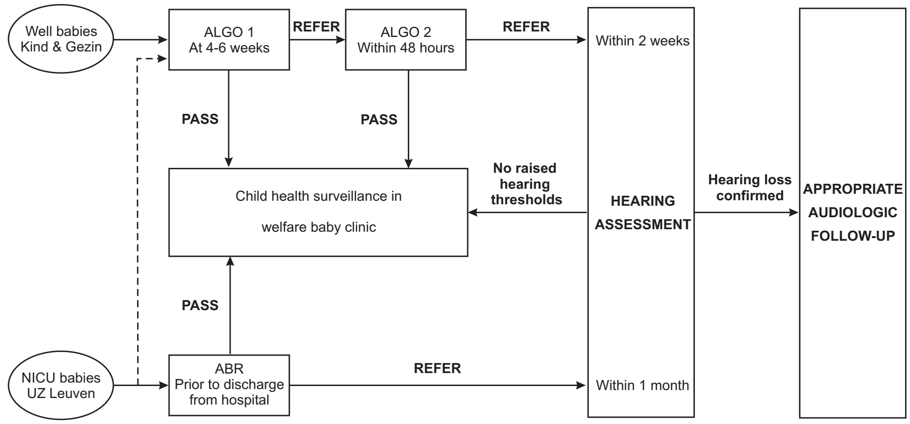


Figure 1.5: Decision chart of the general screening protocol for well babies in Flanders, combined with the screening at the NICU of UZ Leuven. The dashed arrow represents a back-up scenario, in case the screening at the NICU fails. The baby is then referred to the general ALGO screening.

If the screening cannot guarantee normal hearing, the infant is referred to one of the 22 specialized referral centers in Flanders for further audiological and medical diagnosis within two weeks. First the hearing status of the infant is examined by means of audiological tests. At the start of this research project, the diagnostic test battery at the ENT Department of UZ Leuven consisted of tympanometry to investigate the middle ear status, OAEs to assess the function of the hair cells, and click-evoked ABR threshold measurements to determine the degree of hearing loss for a broadband stimulus. If the hearing loss is confirmed, in a second phase additional specialized tests are carried out to define the etiology of the hearing loss. Immediately, the multidisciplinary rehabilitation begins.

All results of the general screening program, as well as the NICU screening are collected in a central database by the ALGO-coordinator of Kind & Gezin. Referral centers send reports on the diagnostic evaluation and rehabilitation on regular basis. This centralization of information ensures an optimal circulation of the referred infants through the different stages from screening to rehabilitation and guarantees a very low loss-of-follow-up.

Before the implementation of this ALGO screening program, hearing-impairment in children in Flanders was tested by the Ewing-test at the age of 9 months. However, the sensitivity and specificity were low and rehabilitation generally started only at the age of 2 years. The last few years, newborns are screened at 4 weeks of age and referred within two weeks of a positive screening result. This means that audiologists and ENT physicians are confronted with a new, very young patient population. As the referred infants are only a few weeks or months old, reliable behavioral responses are not yet attainable. Objective physiologic techniques, like ABR, which are not influenced by sleep or sedation, have to be applied to predict the hearing thresholds. Whereas behavioral hearing tests can provide frequency-specific information, the click-evoked ABR can only predict a general degree of hearing loss, which could result in a faulty diagnosis in case of frequency-dependent hearing loss. The JCIH recommends an electrophysiological technique, which uses frequency-specific stimuli. For general diagnostic purposes, as well as for an efficient fitting of hearing aids it is important to obtain hearing thresholds for different audiometric frequencies. In digital hearing aids, the amplification can be adjusted separately in different frequency bands, to compensate the hearing loss at that particular audiometric frequency. Also in infants with a severe to profound hearing loss, who are candidates for a cochlear implant, it is important to determine the residual hearing in order to provide appropriate amplification with hearing aids in anticipation to the cochlear implantation. Experience of the first 5 years of this screening program has stressed even more that an objective frequency-specific threshold technique is needed for adequate follow-up and rehabilitation of the very young referred children.

1.3 Objective diagnosis of hearing loss: auditory evoked potentials

To define the hearing ability of a patient without its active participation or cooperation, objective hearing tests can be applied. The use of objective techniques is required in patients that cannot or do not want to give adequate responses. A patient’s ability to cooperate is influenced by the mental or physical capabilities. In case of non-organic and simulated hearing loss, an objective test can reveal the real hearing thresholds. Since the worldwide introduction of hearing screening in newborns, the need for objective audiometric techniques to quantify hearing thresholds has increased.

1.3.1 General principles

Objective hearing tests are usually related to a physiologic response. Auditory Evoked Potentials (AEP) are based on recordings of brain activity associated with auditory stimulation. The central nervous system generates spontaneous, random electrical activity in the absence of sensory stimulation, which can be recorded with surface electrodes from the scalp in the electroencephalogram (EEG). The human EEG was first described by Berger (1929). In addition, Davis et al. (1939) noted that the EEG altered with auditory stimulation in human. The recording of AEPs is based on the assumption that there is an exact temporal relationship between the presentation of auditory stimuli and the resulting neural response patterns (Jacobson, 1994). The AEPs reflect electrical potential fields that consist of summated electrical activity for thousands of neurons. The amplitude of AEPs directly depends on temporal synchronization of neural activity. AEPs are optimally generated by action potentials arising almost simultaneously from many neurons within a specific anatomic region (Hall, 1992). In general, the amplitude of the AEP is related to the intensity of the stimulus. The more intense the stimulus, the larger the average evoked response to a certain point. The growth in amplitude of the wave is accompanied by a decrease in latency (the time after the stimulus at which the AEP occurs) of the peak components.

The auditory evoked potentials that are clinically useful can be separated into three types on the basis of their latencies. Short-latency potentials occur within the first 10 ms after the presentation of a transient stimulus, middle-latency potentials occur at latencies from 10 to 60 ms and long-latency potentials occur at latencies between 50 and 500 ms. Auditory evoked potentials with latencies up to 50 ms are essentially the result of the progressive transmission of auditory neural activity through the ascending auditory pathway, including the ear and the auditory cortex. Long-latency potentials are generated by numerous higher brain centers that receive input from the auditory system (Moller, 1994).

The instrumentation required for AEP testing consists of two main parts: an auditory stimulator to provide the necessary sounds to evoke the response that is picked up with surface electrodes on the scalp, and a signal amplifier and processor to record and display the response (Mason, 1993). Through technical manipulations the neural activity related to the auditory stimulus can be extracted from the ongoing EEG, which contains many unwanted potentials (e.g. spontaneous EEG, muscle activity and internal instrumentation noise). Since the signal or the AEP is much smaller than the noise, the signal-to-noise ratio (SNR) has to be enhanced by differential recording, amplification, filtering, artifact rejection and averaging techniques.

Differential recording and amplification

Many noise components in the EEG take similar values at various points on the head. The AEP components, however, usually show marked variations across the head. Thus by measuring differences in potentials at two or more points instead of absolute potentials, the noise components will partially cancel (Hyde, 1994). For a single differential recording channel, three electrodes are required: the noninverting, the inverting and the common electrode. The noninverting electrode is usually positioned over an area of high response activity, on the vertex or high on the forehead. The inverting electrode is placed over an area of low response activity.

The differential preamplifier subtracts the activity at the inverting electrode from that at the noninverting electrode and multiplies this difference with the gain factor. The common electrode is required as an electrical reference point for the preamplifier.

Filtering

The aim of filtering is to suppress those frequency components of the EEG that contain particularly high amounts of noise energy and to pass energy at other frequencies. For AEP, commonly a combination of a high-pass and a low-pass filter is used, resulting in band pass filtering. Since the signal and noise spectra for most AEPs overlap strongly, the SNR enhancement achievable by filtering is modest (Hyde, 1994).

Artifact rejection

An artifact in an AEP recording is electrical activity that is not part of the response and that should not be included in the analysis of the response. Artifacts can be electromagnetic and originating from an external source or electrophysiologic, originating from the patient, such as potentials related to patient movement (Hall, 1992). These extreme values or outliers, that exceed a chosen preset voltage, can be removed from the recorded data sample before this is sent on to the signal averager by means of artifact rejection.

Averaging

After amplification and filtering of the recorded signal, waveforms are averaged in the time domain. In this way, random noise activity can partially be cancelled out, while the AEP remains stable. This ameliorates the SNR maximally by the square root of the number of averaged recordings.

1.3.2 The click-evoked auditory brainstem response

Until now, the most widely used objective technique to assess hearing thresholds in young infants and difficult-to-test patients in clinical practice has been the click-evoked ABR. This technique is based upon recordings of EEG-signals of synchronously firing auditory neurons as a response to acoustical clicks. Click stimuli provide a sufficiently short rise time to ensure a synchronous neural burst from the auditory system (Hecox et al., 1976). The ABR is optimally recorded differentially from the vertex to the ipsilateral mastoid, with an electrode on the contralateral mastoid serving as ground. The ABR typically consists of five peaks (usually labeled by Roman numerals) that appear during the first 10 ms after the transient stimulus (Jewett & Williston, 1971). With decreasing intensity of the presented stimulus, peak V remains identifiable the longest. This peak is used to define the ABR threshold. With ABR, the ascending auditory pathway can be evaluated up to the inferior colliculus (Moller, 1994).

The major advantage of ABR is the ability to estimate the degree of hearing loss in a relatively short testing time. This technique however, has a few shortcomings. First, there is lack of frequency specificity over the auditory spectrum. The rapid onset and the broad frequency spectral content of the click stimulus result in activation of a wide area of the basilar membrane in the cochlea (Picton et al., 1994; Stapells & Oates, 1997). Detailed information concerning the type and degree of hearing loss as a function of frequency cannot be provided. ABR correlates best with hearing sensitivity in the 2000-4000 Hz region. However, ABRs to clicks receive contributions to the response from a wide area of the basilar membrane and could be misinterpreted when a hearing-impairment is restricted to a particular frequency region. The loss will often be missed or the degree of the loss will be substantially underestimated (Stapells & Oates, 1997). The click-ABR threshold is better thought of as the equivalent of a speech awareness threshold. However, for accurate fitting of hearing aids and for general diagnostic purposes, all frequencies between 125 and 8000 Hz are important, and it is vital to get a quantitative measure of the frequency-specific hearing thresholds in infants. Second, the maximum presentation level of a click is limited, which makes it difficult to differentiate between severe and profound hearing losses. Third, the response detection is based on visual inspection of the waveforms. For adequate response detection, decision-making of an experienced clinician is required.

1.3.3 Frequency-specific ABR

A number of techniques have been developed for retrieving frequency-specific information from the ABR. These techniques include different stimulus paradigms as well as different signal processing techniques.

Tone burst ABR

The most straightforward approach is the use of brief tones or tone bursts (Beattie & Torre, 1997; Conijn et al., 1993; Kodera et al., 1977; Purdy et al., 1989; Suzuki et al., 1977). As shown in Figure 1.6, clicks produced by passing a 100-µs square wave through an earphone, have a broad frequency spectrum. In contrast, tone bursts have their concentration of energy at the nominal frequency of the tone and sidebands of energy at lower and higher frequencies.

Davis and colleagues (1984; 1985) suggested the use of '2-1-2 cycle' tone bursts, with rise and fall times equal to two cycles of the stimulus frequency and a plateau time equal to one cycle. This stimulus is a good compromise between frequency specificity and sufficient synchronization capability of the stimulus. Reasonably accurate estimates of the pure-tone behavioral audiogram can be obtained by presenting tone bursts. However, these techniques are quite demanding and time-consuming, since obtaining the results for each audiometric frequency will take the same amount of time as for one click-evoked ABR (Stapells & Oates, 1997). Moreover, there is some question about the spread of energy around each of these transient, sudden onset signals. When stimulus intensity is increased, the spread of excitation to lower- and higher-frequency regions will be greater.

To elicit short-latency responses brief stimuli are most effective, but frequency specificity depends upon the duration of the stimulus. This relation between precision in frequency and precision in time is especially problematic at lower frequencies (Davis et al., 1984). To obtain a sufficiently narrow bandwidth of the acoustical stimulus, the rise times are large and not effective in synchronizing neural discharges at moderate stimulus intensities (Kramer & Teas, 1979; Laukli & Mair, 1986). Moreover, low-frequency tone bursts of higher intensity elicit ABRs which include strong contributions originating from the more basal regions of the cochlea (Beattie & Kennedy, 1992). To restrict the regions of the basilar membrane that are capable of contributing to the ABR, the use of noise masking paradigms is necessary.

Noise masking paradigms

Noise masking techniques have been suggested to improve the frequency specificity and place specificity of the response. The noise, which is presented simultaneously with the click or tone burst, restricts the regions of the basilar membrane that are capable of contributing to the ABR, by selectively masking certain regions that are outside the region to be stimulated.

Masking with high-pass noise prevents auditory nerve fibers with characteristic frequencies higher than the cutoff frequency from contributing to the ABR. It gives reliable estimates of hearing sensitivity at 500 Hz (Purdy et al., 1989), but is inappropriate for middle- and high-frequency tones because it does not prevent the spread of energy to frequencies below the tone frequency. A better approach, which improves the frequency specificity of the response to tonal stimuli of all frequencies, is the use of notched-noise masking (Stapells & Oates, 1997; Beattie et al., 1992; Beattie & Kennedy, 1992; Abdala & Folsom, 1995). Stimuli are presented simultaneously with broadband noise, which has been band-rejected or ‘notched’. These notches, typically one octave wide, represent those spectral regions from which stimulus-evoked activity can effectively contribute to the recorded ABR. Notched-noise masking can be used with clicks and tone bursts. However, when the stimulus is made frequency-specific, the response amplitude becomes small. To extract the response from the background noise a long test duration is required.

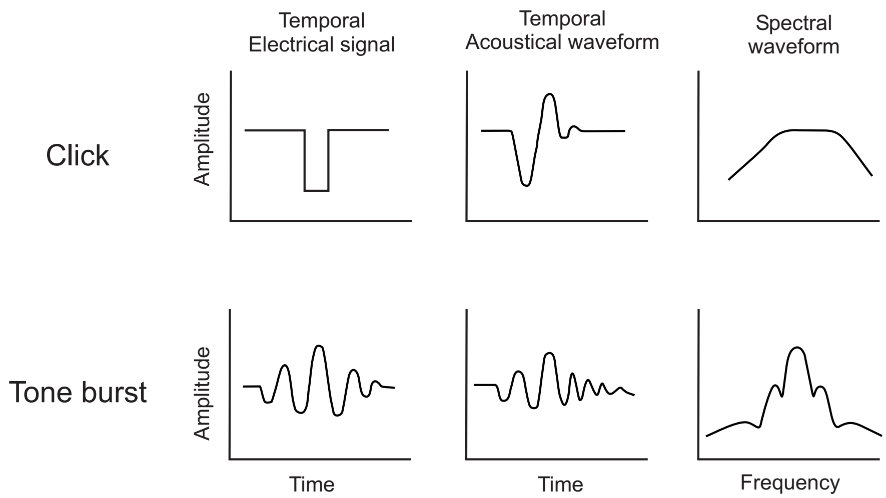


Figure 1.6: Representation of two types of stimuli used in AEP measurement. The electrical signal, the temporal waveform of the acoustical signal and the spectrum are shown diagrammatically. Adapted from Hall (1992).

Derived responses can be used to investigate the cochlear contributions to ABRs to clicks or tone bursts (Oates & Stapells, 1997). In this technique, electrophysiological responses are recorded to a stimulus in quiet and then simultaneously with broadband noise of sufficient intensity to completely mask the response. This broadband noise is then high-pass filtered, and the evoked potential is recorded for clicks presented simultaneously with ipsilateral high-pass filtered noise with different cutoff frequencies, e.g. separated by one octave. The response in high-pass noise at one cutoff frequency is subtracted from the response obtained in the presence of high-pass noise with a higher cutoff frequency. The result is a derived response, representing the narrow-band contributions to the response from portions of the basilar membrane located between the two cutoff frequencies.

The use of masking noise results in unknown technical or physiologic variables (Hall, 1992). Even though hair cells in a portion of the cochlea may be activated by a masking noise, it is conceivable that these or other hair cells in the same region still might be responsive to the transient stimulus. Moreover, the extent and the effect of masking noise spread into the stimulus frequency region is unknown, as well as the interactions between masker and stimulus.

Although tone burst ABR in combination with noise masking paradigms have been extensively researched throughout the years (Stapells et al., 1995; Beattie &

Kennedy, 1992; Picton et al., 1979; Purdy et al., 1989; Stapells et al., 1990), the common use of these techniques in the European clinical practice has been hindered. Reasons for this are the long recording time, the demanding test procedure and the need for step-by-step interpretation by highly skilled clinicians.

ABR evoked by chirps

More recently, the use of chirp signals is proposed to obtain larger wave-V amplitudes. High-frequency stimuli cause maximum displacement at the basal regions of the basilar membrane, whereas low-frequency stimuli cause maximum displacement closer to the apex. It takes the peak of the traveling wave approximately 10 ms to travel from the base to the apex, so the neural response to a broadband stimulus such as a click will be spread out in time (Bell et al., 2002). The rising frequency chirp was designed to compensate for these frequency-delay characteristics of the basilar membrane (Dau et al., 2000). In a chirp stimulus, the low frequencies occur before the high frequencies. So theoretically, traveling-time differences should be cancelled and all points on the basilar membrane should reach maximum displacement simultaneously for that chirp, producing a synchronous neural response across the corresponding bundle of auditory nerve fibers. According to Dau et al. (2000) responses elicited by a broadband chirp show a larger wave-V amplitude than do click-evoked responses. This indicates that the use of chirps enables the inclusion of activity from lower-frequency regions, whereas with a click, the contribution of these lower-frequency regions is limited because of a decreased synchrony.

Wegner and Dau (2002) investigated the frequency specificity of the chirp-evoked ABR. When high-pass noise was presented in addition to a broadband chirp, larger wave-V amplitudes were elicited than when a click was presented. However, when notched-noise was used with a one-octave wide notch, the gain in synchrony within the frequency-regions of one octave was not sufficient for the chirp to produce significantly larger response amplitude than the click. A low-frequency chirp elicited larger response amplitude than a tone burst. According to Bell et al. (2002) the ABR evoked by frequency-specific chirps is closer to the behavioral hearing threshold than the ABR evoked by tone bursts without masking. However, it was not as close as for tone bursts in notched-noise.

These results are promising and the chirp might be valuable for clinical applications, particularly in tests where the click stimulus has been used so far (Fobel & Dau, 2004). A disadvantage of chirps is the fact that the stimulus is designed based on theoretical models and therefore not necessarily optimal for any given individual subject. Probably significant variation may occur from subject to subject in the cochlear response time between frequency regions. Moreover, the ABR evoked by chirps has only been investigated in normal-hearing adults, in a restricted number of studies. Further research is needed to assess the possibility of determining frequency-specific hearing threshold estimates by means of the ABR evoked by chirps in clinical practice.

1.3.4 Auditory steady-state responses

The last few years, auditory steady-state responses (ASSRs) have been investigated as a possible technique for objective evaluation of frequency-specific hearing thresholds. ASSRs are the periodic electrical responses of the brain to repeating auditory stimuli (Stapells et al., 1984; Maiste & Picton, 1989). The frequency components of the ASSR maintain constant in amplitude and phase over prolonged time periods (Regan, 1989). The potentials can be elicited by amplitude- and/or frequency-modulated pure tones or noise. The resulting EEG-signal contains energy at the modulation frequency.

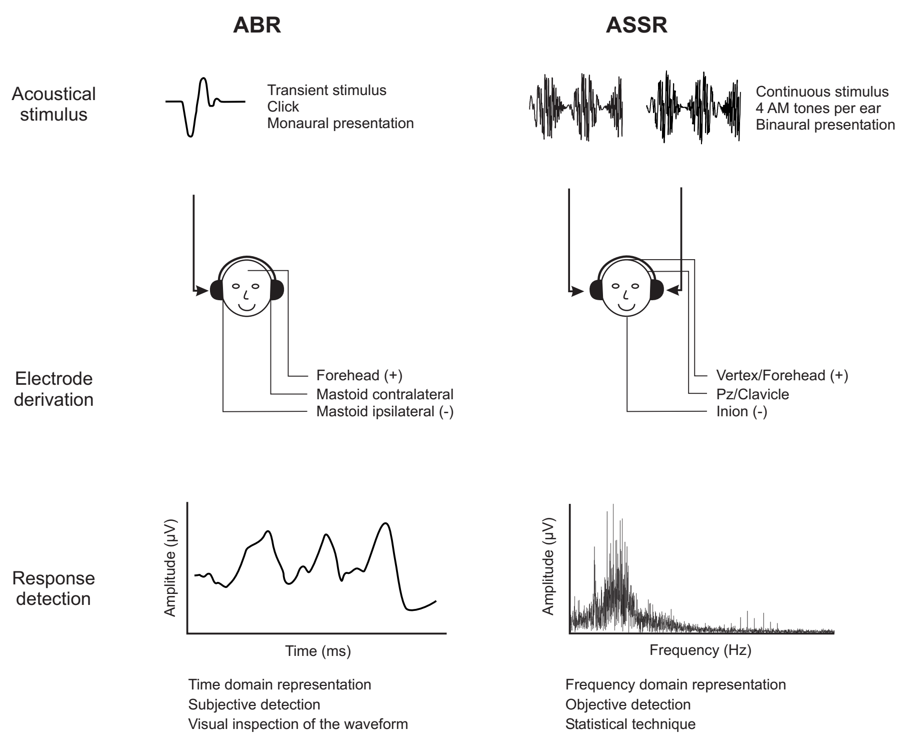


Figure 1.7: Schematic overview of the differences between ABR and multiple-stimulus ASSR.

Compared to the click-evoked ABR, currently most used in clinical practice for objective threshold evaluation, the ASSR technique has some interesting features:

- Modulated tones contain energy at a much smaller frequency range and therefore activate a more limited part of the cochlea, which results in a more place-specific response. This enables frequency-specific estimation of hearing thresholds.
- The continuous nature of the stimuli allows a higher maximum stimulation level compared to click stimuli. For click-ABR, the maximum presentation level is 130 dBpeSPL, corresponding to hearing losses of approximately 90 dB. Continuous ASSR stimuli can, depending on the test set-up, be presented at a maximum presentation level of 130 dBSPL. This corresponds to hearing losses of approximately 115 dB. The extended range of the ASSR could allow differentiation between total hearing loss and useful residual hearing.
- Responses can be detected in the frequency domain with an objective response detection method.
- The ASSR technique offers the possibility to record the responses to several carrier frequencies in both ears simultaneously, by modulating each signal at a different modulation frequency (Lins & Picton, 1995). Since each response would occur exactly at the modulation frequency, these multiple-stimulus ASSRs can be separated in the frequency domain. This technique could reduce the test duration by a factor of two to three (John et al., 2002), which is important in view of the clinical application.

A comparison between the ABR and the multiple-stimulus ASSR technique is shown in Figure 1.7. Both techniques differ with regard to stimulus type (transient versus continuous), stimulus presentation (single-stimulus monotic versus multiple-stimulus dichotic), electrode derivation and response detection method (subjective in the time domain versus objective in the frequency domain).

More details on the ASSR technique can be found in Chapter 2.

1.4 Research objectives

Internationally, the interest in ASSR has strongly increased. Experimental studies have shown that the ASSR technique could be used to assess frequency-specific hearing thresholds, but it was not clear how this could be applied to the clinical practice, especially in very specific patient groups. Few studies of the ASSR have been carried out on clinical populations and no agreement exists about the optimal ASSR test parameters for a clinical setting. However, the accuracy of the estimated hearing thresholds depends on the methods and parameter settings used.

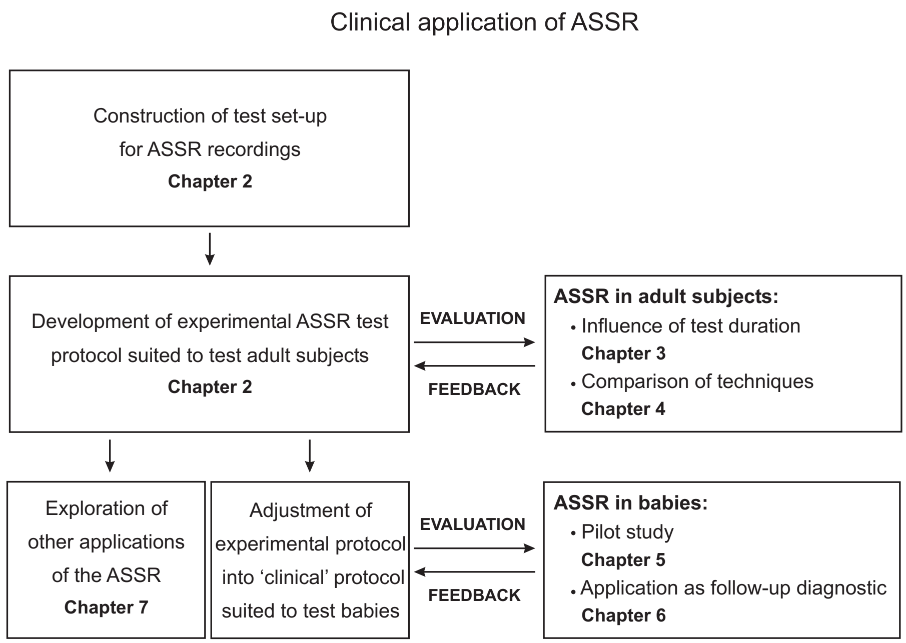


Figure 1.8: Overview of the research project and thesis outline.

In this research project, the clinical application of ASSR is studied in the neonatal population as a follow-up diagnostic after the hearing screening. In general, the research objectives were to develop and validate a clinical protocol for the use of ASSR in patients that cannot or do not want to give adequate or reliable behavioral responses. The ultimate goal of the objective audiometry researched in this work, is the generation of precise and accurate frequency-specific audiograms based upon electrophysiological recordings. For the clinical feasibility on a large scale, four hearing thresholds in both ears should be assessed within a test duration of about 1 h, without the need for a general anesthetic.

More specific the following objectives were aimed for (see Figure 1.8):

- To build and evaluate a robust experimental test platform for recording auditory steady-state responses for research and clinical applications.
- To compare and critically evaluate two ASSR techniques, a monaural single-stimulus approach and a binaural multiple-stimulus approach, under similar circumstances.
- To develop an ASSR test protocol that is suitable for testing adults in an experimental setting and to evaluate this protocol in normal-hearing and

hearing-impaired adults taking into account total test duration and its relation with the accuracy of the hearing threshold estimates.
- To adjust this experimental ASSR test protocol in order to make it applicable for clinical use and for testing sleeping babies at the ENT Department and to evaluate this clinical test protocol in a small group of babies.
- To test very young babies referred after a failed hearing screening in natural sleep, to interpret their hearing impairment and to compare ASSR, ABR and behavioral hearing thresholds in a large sample of babies.
- To assess the feasibility of other applications of the ASSR technique that could increase the clinical value of ASSR.

1.5 Thesis outline

In Chapter 2, an overview is given on the basic features of the ASSR technique. Subsequently, the ASSR test set-up and the stimulus and recording parameters, as utilized in this research, are described.

In Chapter 3, we evaluate the influence of test duration on the precision of the hearing thresholds estimated by dichotic multiple ASSRs. High precision of the threshold estimate as well as a reasonable test duration are crucial regarding the clinical applicability of a technique. In this work, we first compared the ASSR thresholds with the corresponding behavioral hearing thresholds (BHTs) while varying the maximum number of recorded sweeps per intensity level between 16, 32 and 48, which agrees with about 5, 10 and 15 min. Moreover, an intensity step-size of 10 dB was compared with a step-size of 5 dB in the threshold test procedure. Finally, a possible decrease of the quality of the recordings, caused by restlessness or tension after a long test duration, was investigated.

In Chapter 4, the single-stimulus and multiple-stimulus ASSR approach are compared in the same subjects and in a quiet test environment. First, the ability of both techniques to predict hearing thresholds by means of ASSR over a wide intensity range within a total test time of 1 h was evaluated. Second, the influence of prolonging the test duration was assessed. And third, the test-retest reliability of both techniques was examined.

Chapter 5 describes the first results of the dichotic multiple-stimulus ASSR technique in babies in clinical practice. Hearing thresholds of 10 infants between 3 and 14 months of age with suspected hearing loss, referred to UZ Leuven, were estimated. Click-evoked ABR and dichotic multiple-stimulus ASSR were carried out in the same test session, under general anesthesia. Behavioral hearing thresholds were obtained in later test sessions, if they could be obtained at all. BHTs, ABR and

ASSR threshold values were compared. Moreover, the relation between precision of hearing threshold estimates obtained with ASSR and test duration was investigated.

In Chapter 6, the clinical applicability of the dichotic multiple-stimulus ASSR technique is investigated in a large sample of newborns and infants at risk for hearing loss (n=60). First, ASSRs were recorded in normal-hearing high-risk infants younger than three months of age and adults. The responses were directly compared concerning amplitude, SNR and ASSR thresholds. Moreover, age effects within the group of infants were evaluated. A better insight into the differences between infant and adult ASSRs will optimize the interpretation of ASSR results in different patient groups. Second, ASSR thresholds were assessed in a group of infants with a wide range of hearing threshold levels and were compared with ABR and BHTs. The precision that can be achieved when estimating hearing thresholds by means of ASSR was investigated. The possibility of testing babies in natural sleep was evaluated and practical considerations regarding the clinical use of ASSR are discussed.

In Chapter 7, we give an overview of other possible applications of the ASSR technique. ASSR thresholds are measured with the bone-conductor and in sound field. Moreover, the ASSR technique is applied in patients with non-organic hearing loss.

Chapter 8 comprises a general discussion of the results of this research. We end with an overview of the future research directions.

1.6 Conclusions

In this research project, we investigated the clinical application of the ASSR technique as an objective technique to predict hearing thresholds in young children. To introduce this work, we gave an overview of the anatomy and physiology of hearing, and the impact of hearing loss in children. The current state of screening and diagnosis in Flanders was explained. Finally, the objectives and the outline of this dissertation were described.

Chapter 2

Auditory Steady-State Responses

In this chapter, we briefly describe most important features related to auditory steady-state responses, as an objective means to assess hearing. The aim of the first section is to provide a better insight in the ASSR technique, and to clarify our choice for the multiple-stimulus approach at higher modulation rates. In the second section, we deal with the experimental set-up that was assembled at the start of this project and used in the studies described in further chapters.

An extensive overview of the current state of our knowledge concerning human auditory steady-state responses can be found in the review article of Picton et al. (2003).

2.1 Theoretical background on the auditory steady-state response

2.1.1 Terminology

When a low-frequency sinusoidal stimulus is presented to the ear, auditory nerve fibers discharge at preferred phases of the signal. This phenomenon has been termed phase-locking of the discharge (Rose et al., 1967). The frequency following response (FFR) is a scalp potential that reflects this phase-locking of the auditory nerve fibers to the stimulus frequency for frequencies up to at least 1000 Hz (Batra et al., 1986). The FFR, however, is not useful for assessing hearing thresholds, since it requires moderate to high stimulus intensities. Moreover, the limited frequency range is not sufficient to assess the frequency range most important for speech understanding (500 to 4000 Hz).

When amplitude-modulated (AM) sinusoids are presented to the ear, the auditory neurons fire synchronously (i.e., phase-lock) in response to the low-frequency envelope of the high-frequency signals that are amplitude-modulated (Moller, 1974). The scalp potential in response to sine AM tones has been termed the amplitude modulation following response (AMFR) (Kuwada et al., 1986) or the envelope following response (EFR) (Dolphin & Mountain, 1992). By varying the carrier frequency, populations of neurons with different frequency sensitivities can be excited.

In what follows, the more general term auditory steady-state response (ASSR) is used. A steady-state response occurs when the frequency components of the response remain stable in amplitude and phase over time (Regan, 1989). Whereas transient responses (e.g. ABR) are evoked by stimuli that occur infrequently, steady-state responses are evoked by repetitive stimuli that are presented continuously or at a stimulus rate that is fast enough to cause an overlap of the consecutive responses.

2.1.2 Physiological model

To understand the principle of ASSR, we consider how the cochlear transducer works (see Figure 2.1). The transfer function of the hair cell and the auditory nerve fiber can be described as compressive rectification of the signal waveform (Lins et al., 1996; Lins & Picton, 1995).

An AM tone has energy at the frequency of the carrier and at two sidebands separated from the carrier by the modulation frequency. This means that these sounds activate only a limited part of the cochlea, centered around the carrier. The spectrum of the stimulus does not contain energy at the modulation frequency. When this sound is captured by the ear, a frequency place analysis is performed in the cochlea. Higher frequencies activate the basilar membrane close to the oval window, while lower frequencies activate regions further along the basilar membrane. The hairs on the inner hair cells bend, causing polarization and depolarization of the hair cells. Only depolarization causes the auditory nerve fibers to transmit action potentials. The output of the cochlea thus contains a rectified version of the acoustic AM stimulus, which does have a spectral component at the frequency at which the carrier was modulated. This spectral component can be used to detect the response of the cochlea to the carrier.

The signal is not only rectified, but also compressed. Larger depolarization of the inner hair cell causes faster firing rates in the auditory nerve fibers. Though, the transfer function is non-linear and saturates with high levels of depolarization of the inner hair cell.

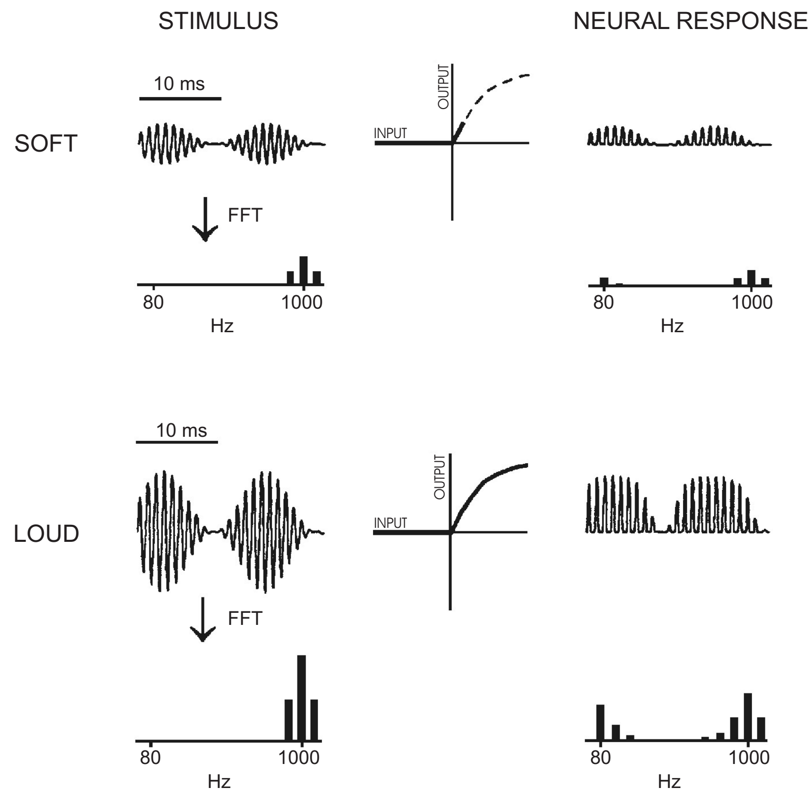


Figure 2.1: Simple model for the principle of compressive rectification. The top row represents the events following the presentation of a low-intensity stimulus. The bottom row represents the events following the presentation of a high-intensity stimulus. The stimulus (left) and the neural response (right) are represented both in the time domain and in the frequency domain. The rectification causes the output of the cochlea to have a spectral component at the modulation frequency. At loud intensities, the response envelope becomes distorted. Adapted from Lins et al. (1995).

2.1.3 Stimulus parameters

ASSRs can be evoked by various kinds of stimuli, like clicks, tone bursts and sinusoidally amplitude- and/or frequency-modulated tones. The advantage of modulated tones in contrast with clicks and tone bursts is the narrower spectrum, centered around the carrier frequency. Since frequency specificity is such a major issue in the search for a better objective technique, we will focus on sinusoidally modulated tones in what follows. Parameters that can vary are the carrier frequency, the modulation rate and the depth of amplitude and/or frequency modulation.

Carrier frequency

The carrier frequency determines which area on the basilar membrane in the cochlea is activated. All octave frequencies that are usually assessed in audiometric tests, between 125 and 8000 Hz, could be used for the recording of ASSR. Due to timing restrictions, only a limited number of stimuli will be assessed, mostly at frequencies between 500 and 4000 Hz because of the importance for speech understanding.

Modulation frequency

The modulation rate of the presented stimulus is a defining characteristic of the ASSR. The ASSR has been investigated over a wide range of rates between 2 and 450 Hz (Picton et al., 1987; Kuwada et al., 1986; Rees et al., 1986). As the ASSR appears in the EEG, the amplitude of the ASSR, measured as the amplitude at the modulation rate, is the sum of the signal amplitude and the residual EEG noise. In general, the ASSR amplitude decreases with increasing modulation rate (see Figure 2.2). In certain regions, however, there is an enhancement of the response above the general decline, more specific around 40 Hz and 90 Hz.

The detectability of the ASSR depends on the characteristics of the EEG. EEG signals arising from the brain consist of several simultaneous oscillations, which have traditionally been subdivided into frequency bands such as delta (1-3 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (about 14-30 Hz) and gamma (around 40 Hz). The brain signals are related to alertness, level of attention, and degree of mental effort. However, when recorded from the scalp, the EEG itself is intermixed with other electrical activity from the scalp muscles, the eyes, the skin, and the tongue. The amount of EEG activity also decreases with increasing frequency, with the activity being most prominent at frequencies below 25 Hz. Therefore, although the response amplitude decreases with increasing modulation rate, the signal-to-noise ratio may actually increase (Picton et al., 2003).

To determine hearing thresholds by means of ASSRs, the ASSR should be recognizable at intensity levels just above threshold. Initially, the ability of the 40-Hz response to assess hearing was studied, since in adults the most prominent responses are obtained at presentation rates around 40 Hz. Galambos and colleagues (1981) were the first to note that the 40-Hz event related potential could have an application in clinical hearing testing. They observed that the response was present at sound intensities very close to the hearing threshold and that response amplitude rises with intensity increase. However, it appeared that the 40-Hz response was influenced by sleep and sedation (Cohen et al., 1991; Plourde & Picton, 1990). Furthermore, it is difficult to record in children (Stapells et al., 1988; Maurizi et al., 1990) because the 40-Hz component results from the overlap of the short latency with the middle latency response, which has a much longer developmental timetable.

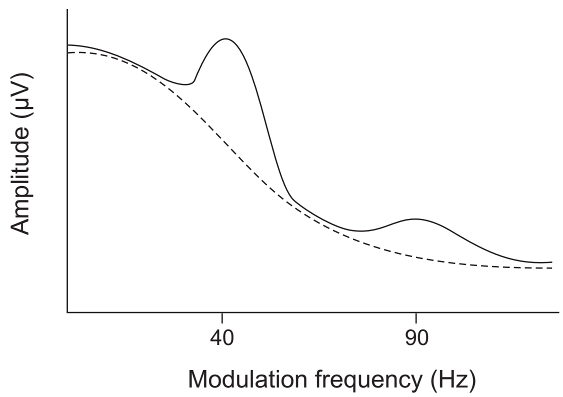


Figure 2.2: Schematic representation of the amplitude of the auditory steady-state response (solid line) and the noise level (dashed line) as a function of modulation frequency for amplitude-modulated tones.

Since neonates are the most important target population for this kind of objective technique, research continued and it was shown that ASSRs can also be evoked at modulation rates between 80 and 110 Hz. These responses are smaller than the 40-Hz responses, but less influenced by sleep (Plourde & Picton, 1990; Cohen et al., 1991) and reliably measurable in children (Aoyagi et al., 1994; Aoyagi et al., 1993; Cohen et al., 1991; Rickards et al., 1994; Rance et al., 1995), since they represent neural phase-locked responses from the lower portion of the auditory nervous system, just like an ABR. Several studies have shown that this ASSR at higher modulation rates could be a useful technique for objective audiometry (Aoyagi et al., 1994; Aoyagi et al., 1993; Cohen et al., 1991; Rickards et al., 1994; Rance et al., 1995). Since this study concentrates on evoked potential measures in infants, and the 40-Hz ASSR is not reliably recordable in this target group, we focus on the higher modulation rates.

Amplitude and/or frequency modulation

The most commonly used stimuli to evoke ASSRs are sinusoidally amplitude-modulated (SAM) tones. The advantage of this type of stimulus is the simple spectrum, containing energy only at the carrier frequency and the carrier frequency plus and minus the modulation frequency (see Figure 2.3). The depth of modulation is defined as the ratio of the difference between the maximum and minimum amplitudes of the signal to the sum of the maximum and minimum amplitudes. As the depth of modulation is increased, the spectral energy at the carrier frequency decreases and the energy at the sidebands increases. When the depth of modulation is 100%, the amplitude at the sidebands is one half that at the carrier frequency. The amplitude of the ASSR increases as the depth of modulation increases.

Frequency-modulated (FM) tones can also elicit ASSRs (Picton et al., 1987; Maiste & Picton, 1989). Frequency modulation depth is defined as the difference between the maximum and minimum frequencies divided by the carrier frequency. The response to frequency modulation increases in amplitude with increasing depth of modulation. However, as the amount of FM increases the frequency specificity of the stimulus decreases.

A combination of AM and FM elicits larger responses than simple AM or FM tones (Cohen et al., 1991; John et al., 2001b). This mixed modulation (MM) involves changing the amplitude and the frequency of the carrier at the same modulation rate. Apparently, the AM and FM components generate independent responses that add together. If a phase delay of -90° is added to the frequency modulation, the stimulus reaches maximum amplitude and maximum frequency at the same time (John & Picton, 2000). This type of stimulus is often used to elicit ASSRs for audiometric purposes. The amount of FM is kept limited, mostly between 10 and 25%. In this way, the stimulus is still quite frequency-specific and remains within one critical band.

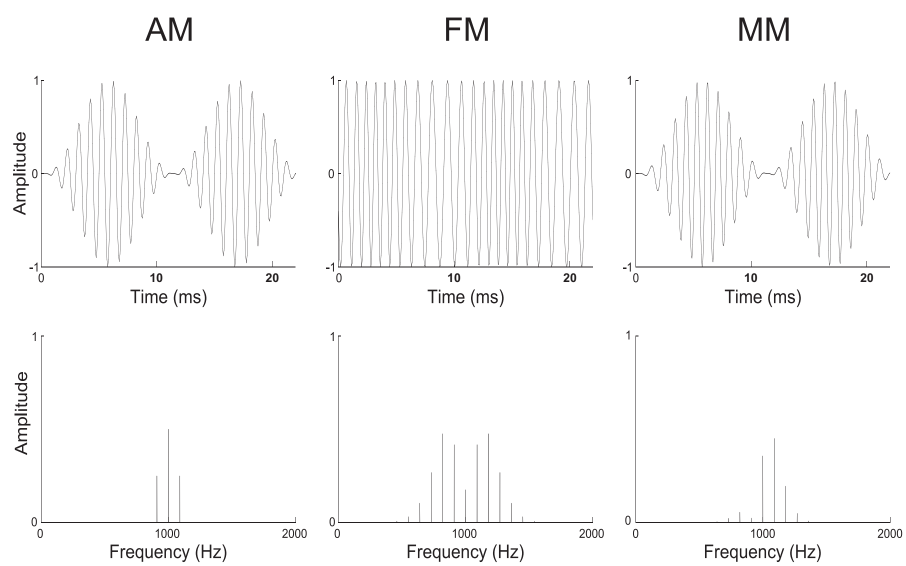


Figure 2.3: Stimuli used to evoke auditory steady-state responses. The stimuli are presented in the time domain (upper part) and in the frequency domain (lower part). Three types of sinusoidally modulated tones are shown: an amplitude-modulated tone (AM) with a depth of modulation of 100%, a frequency-modulated tone (FM) with a depth of modulation of 50% and a mixed-modulated tone (MM) that is modulated in amplitude (100%) as well as in frequency (20%). All signals consist of a carrier frequency of 1000 Hz that is modulated at a rate of 90 Hz.

2.1.4 Recording of EEG activity and response detection

For ASSR recordings, the inverting electrode is mostly placed at the vertex (Cz) or at the high forehead. The noninverting electrode is placed at the ipsilateral mastoid in case of monaural stimulus presentation or at the neck in case of dichotic stimulus presentation. A substitute for the neck position can be the inion (Oz). This electrode position results in lower noise levels, which can increase the SNR. The place of the reference electrode is more variable: the contralateral mastoid, the side of the neck, the clavicle or Pz.

While the signals are presented, the EEG is recorded. DA conversion of the acoustic signal and AD conversion of the EEG signal must be perfectly synchronized. EEG recordings are typically stored in epochs. An epoch of data is created every time the input buffer is filled. The input and output buffer need to have equal duration and to start and end at the same time. These epochs can be combined to sweeps (see Figure 2.4).

Time and frequency domains

Whereas transient responses are best identified in the time domain by inspection of the waveforms and by interpretation of amplitudes and latencies of peaks and troughs, ASSRs are easier to detect in the frequency domain. In the frequency domain, a response is measured as the amplitude and phase at a particular frequency and objective response detection techniques can be utilized. ASSRs are therefore double objective:

- The response generation is objective; the patient does not have to respond subjectively.
- The response detection is objective; the clinician does not have to judge the presence of a response subjectively.

The recorded EEG activity can be transformed from the time to the frequency domain with a Fast Fourier Transform (FFT). The FFT provides values for both amplitude and phase at each of the frequencies in the spectrum.

Improving the signal-to-noise ratio

As in other evoked potential applications, ASSRs are recorded in conjunction with other EEG activity or ‘noise’ and the SNR is an important aspect. The SNR can be improved with similar efficiency by either averaging the data in the time domain or using the data to increase the duration of the sweep which will be submitted to FFT analysis (John et al., 1998). Averaging together repeated recordings reduces the level of activity in the recording that is not time-locked to the stimuli. Increasing the duration of the activity submitted to the FFT increases the frequency resolution of the analysis. Provided the stimulus frequencies are precisely locked to the recording frequencies, increasing the sweep duration thus reduces the noise level, by distributing the power across more FFT bins, without affecting the amplitude of the response, which is represented within a single FFT bin. Another approach to enhance the SNR is the use of artifact rejection protocols. Recordings wherein the noise level is excessively high (usually because of movement or swallowing) are selectively rejected prior to averaging, which increases the efficiency of the averaging process (John & Picton, 2000). If an epoch is rejected, the next epoch that was not rejected was used in its place when linking the epochs of data into sweeps (see Figure 2.4).

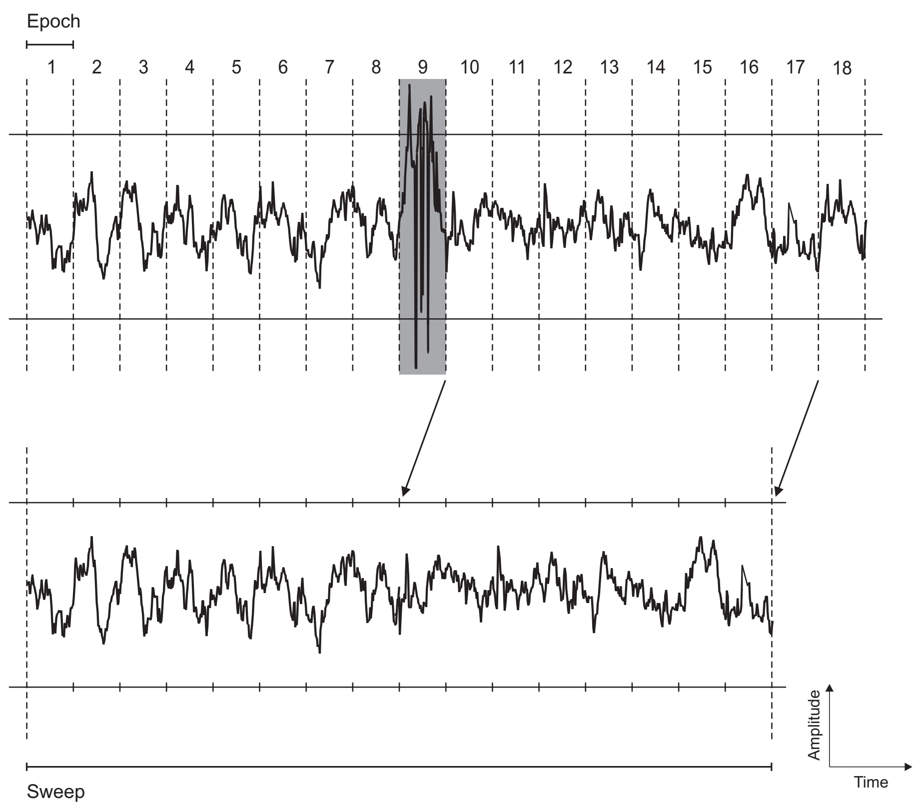


Figure 2.4: Schematic representation of an EEG-recording in the time domain. When an entire sweep is recorded, an FFT analysis computes the spectrum. When the next sweep is recorded, it is added to the prior sweep in the time domain and the result is again submitted to FFT analysis. The horizontal lines represent the artifact rejection limits. The artifact rejection protocol operates only on sections of the recording sweep or epochs. In the 9th epoch, the EEG energy exceeds this preset voltage and consequently the epoch is rejected. In this example, 16 epochs are linked together to form a sweep. If an epoch is rejected, the next epoch is used in its place.

Objective response detection methods

As a steady-state response is characterized by its phase and amplitude, both measures can be used to assess the presence or absence of a response. A detection algorithm can be based on the similarity of a measurement across replications or based on the difference between a measurement at the frequency of stimulation (signal) and other measurements (noise) in the spectrum (Picton et al., 2001). The two most applied techniques are phase coherence and the F-technique. Phase coherence assesses similarity in phase across replications. The probability is calculated that the set of response angles, at any given time during the recording, could have arisen in the absence of a response component at the modulation frequency. A response is considered reliable if its phase remains stable over time rather than varying randomly (Stapells et al., 1987; Rance et al., 1995). The *F*-technique evaluates whether the amplitude and phase of the response at the frequency of stimulation are different from the noise at adjacent frequencies (Lins et al., 1996).

2.1.5 Neural sources of ASSR

The exact generators of the ASSR are not yet fully understood. However, distinct generators have been suggested for ASSRs evoked at low (25-55 Hz) and high (80-400 Hz) modulation frequencies because of the differential effect of state of arousal and different latencies. At high modulation frequencies, the ASSR is not dependent on state of arousal (Cohen et al., 1991; Aoyagi et al., 1993). In contrast, low-frequency ASSR amplitudes are sensitive to the subject's behavioral state (Kuwada et al., 1986). During sleep or sedation, the amplitude decreases dramatically. This suggests a cortical generator.

ASSRs evoked by high modulation frequencies have a short latency (7-9 ms). In contrast, at low modulation frequencies ASSRs have a latency of about 30 ms. The source which generates the high-frequency ASSR probably resides in the brainstem and the source which generates the response at low modulation frequencies is probably cortical. According to Kuwada et al. (1986) the latencies of the two generators are similar to those observed in inferior colliculus and cortical neurons. A dipole source analysis (Herdman et al., 2002) pointed out that at modulation frequencies of 88 Hz, the greatest activity occurred in the brainstem, and subsequent cortical activity was minor. At 39 Hz, activity occurred in the brainstem as well as in cortical sources in the left and right temporal plane.

Different generators thus respond selectively to different modulation frequencies. A possible neural basis for this selectivity is provided by the responses of auditory neurons to amplitude-modulated tones. Animal studies of locally recorded evoked potentials or single-unit studies show that at successively higher structures in the auditory system, neurons seem to prefer progressively lower rates of modulation (Kuwada et al., 1986).

Testing patients using ASSRs to AM tones modulated between 70-100 Hz would suggest normal auditory function or hearing sensitivity up to the level of the brainstem. Dysfunction further along the auditory pathway may not be resolved unless slower rates are used (Herdman et al., 2002).

2.1.6 Frequency specificity

The frequency specificity of the ASSR is not only related to stimulus characteristics, but also to the response pattern of peripheral and central auditory structures. Frequency specificity can be divided into acoustic specificity, place specificity and neural specificity (Picton et al., 2003).

The acoustic specificity defines how well the stimulus energy is concentrated within certain frequencies in the spectrum. A sinusoidal AM tone has spectral energy at the carrier frequency and at two sidebands, separated from the carrier frequency by the modulation frequency. Place specificity relates to the portion of the cochlear partition that is activated by the stimulus and contributing to the response. The traveling wave causes an activation pattern of the basilar membrane. The point of maximal activation can be considered the specific place for that tonal frequency. However, spread of activation can occur to regions of the basilar membrane other than this specific place. Finally, neural specificity has to be considered. Neural specificity is illustrated by the tuning curve of the auditory nerve fibers (see Figure 1.3). In a normal functioning ear, the curve shows a narrow tip at the characteristic frequency. In case of cochlear hearing loss, however, the tuning curves are quite different. The tip of the tuning curve can be attenuated and distorted, meaning that the difference in threshold to fire at the characteristic frequency and at other frequencies has decreased. In these pathological auditory nerve fibers, the response that occurs to a single stimulus at its characteristic frequency might not occur in the presence of other stimuli of lower frequency that activate the response area of the cell and thereby mask its response to stimuli at its characteristic frequency. Therefore, one has to be careful in testing patients with hearing impairment due to cochlear dysfunction. Certain discrepancies can exist between the pure-tone audiogram and responses obtained using multiple simultaneous stimuli (John et al., 1998).

2.1.7 Electromagnetic artifacts

In the recording of ASSRs, electromagnetic artifacts could arise (Picton & John, 2004). When currents are converted into sound by an acoustic transducer, electromagnetic fields are generated. These fields can be picked up by the EEG recording electrodes. As stimulus and response overlap in time, the aliased stimulus energy could be taken as a response. If the transducer is linear, the electromagnetic field will contain only the frequencies that are present in the signal. One would expect little problem in recording ASSRs, since stimulus frequencies are different from the response frequency. A sinusoidal amplitude-modulated stimulus after all does not contain spectral energy at the modulation frequency, which is used for response detection. However, due to the aliasing effect (Picton & John, 2004) and non-linearities in the transducers and the recording system, artifacts may come about with high-intensity air-conducted stimuli or moderate-intensity bone-conducted stimuli (Gorga et al., 2004; Small & Stapells, 2004).

Aliasing occurs whenever a signal is sampled at a frequency that is lower than twice the signal frequency (see Figure 2.5). The signal is seen at a frequency equal to the absolute difference between its frequency and the closest integer multiple of the sampling frequency. When ASSRs are recorded with an AD conversion of 1000 Hz, signal frequencies above 500 Hz may be aliased into the spectrum. When a 2000-Hz carrier modulated at 80 Hz is presented, the energy at the carrier frequency will be aliased into the spectrum at 0 Hz (2*1000 – 2000). However, the energy at the side bands separated from the carrier frequency by the modulation frequency (1920 and 2080 Hz) are aliased into the spectrum exactly at the modulation frequency (2*1000 – 1920 and 2080 – 2*1000) which is used for response detection.

Apart from aliasing, a recording system is not perfectly linear. This can directly introduce artifactual energy at the modulation frequency. The occurrence and size of the artifacts is difficult to predict, because it depends on several factors, such as the intensity and frequency of the stimulus, the distance between the transducer and the recording circuits, the geometry of the electromagnetic field and the recording circuits, and the electrode montage. Bone-conduction transducers will cause more artifacts than air-conduction transducers, and earphones more than insert phones (Picton & John, 2004).

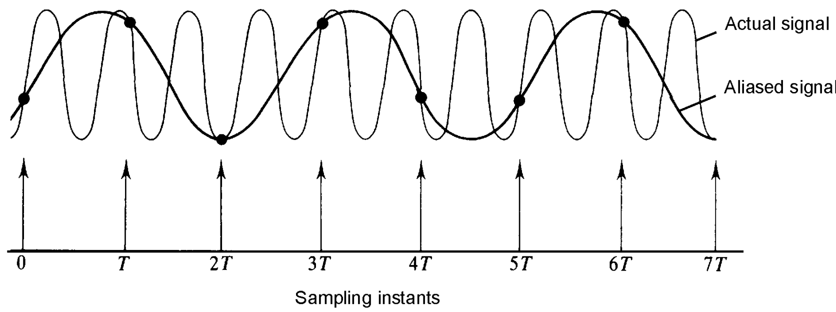


Figure 2.5: An example of aliasing in the time domain. The two signals have the same values at the sampling instants, although their frequencies are different. The actual signal is higher than twice the sampling frequency and is consequently aliased to the absolute difference between the signal frequency and the integer multiple of the sampling rate closest to the signal frequency. From Ifeachor and Jervis (1993).

A number of solutions are suggested to avoid electromagnetic artifacts. The most evident solution to avoid aliasing is changing the sampling rate. If the sampling rate is not an integer multiple of the carrier frequencies, the stimulus energy is aliased to frequency regions other than the modulation frequencies. In this way the aliased energy does not hinder the response detection (Picton & John, 2004). However, the choice of an appropriate sampling rate is limited, since it is essential that the AD and DA buffers have an identical duration and remain synchronized during the recording. Another possibility to avoid artifacts is the use of stimuli with frequency spectra that do not alias back to the response frequencies, such as beats or SAM tones with alternating stimulus polarity (Picton & John, 2004; Small & Stapells, 2004). Finally, shielding of cables and transducers can decrease the electromagnetic interference.

2.1.8 Multiple-stimulus ASSR

The possibility of recording steady-state responses to multiple simultaneous stimuli was first demonstrated for visual stimuli. Regan and Cartwright (1970) showed that steady-state responses to simultaneous visual stimuli can be recorded and analyzed independently if each stimulus is modulated at a different rate. Lins & Picton (1995) demonstrated the possibility of using multiple auditory steady-state responses to assess hearing at different frequencies and in both ears.

Principle

To enable the assessment of hearing at multiple frequencies in both ears simultaneously, various carrier frequencies are presented, all modulated at a different modulation frequency (see Figure 2.6). When this combined stimulus is presented to the ear, the carrier of each stimulus activates a different segment of the basilar membrane and thus stimulates a different group of inner hair cells and nerve fibers. The responses to each carrier frequency in each ear can be separated by assessing the spectral component at the modulation frequency, specific to that particular carrier. The modulation frequencies serve as labels of the carriers, to recognize their evoked responses (Lins et al., 1996).

If the carriers that constitute the combined stimulus are separated by one octave or more, there is little overlap of the activated areas on the basilar membrane, at least at low and moderate intensities. At low intensities the response is therefore specifically mediated by the hair cells and nerve fibers in one region of the basilar membrane. Intense stimuli, however, will interact more than weaker stimuli because the bandwidth of the cochlear filter enlarges with increasing sound pressure level (Lins & Picton, 1995; Lins et al., 1996).

Modulation frequencies for different carrier signals can be very close, provided the Fourier analysis has a sufficient resolving power. Separating the modulation frequencies by only 1.3 Hz does not attenuate the response (John et al., 1998).

Limitations of multiple-stimulus ASSR

The multiple-stimulus approach could significantly reduce test duration compared to the traditional single-stimulus approach, increasing the efficiency of steady-state audiometry. However, any reduction in amplitude of the response, caused by the simultaneous presentation of the stimuli has to be less than the reduction in the EEG noise provided by the increased time available for recording the responses (John et al., 1998). Loss of amplitude could be the result of interactions between stimuli with a different carrier frequency due to overlap of the activation patterns on the basilar membrane (Picton et al., 2003) or through neural interactions in the central nervous system (Lins & Picton, 1995). When two amplitude-modulated tones are presented simultaneously, the envelope response to the low-frequency carrier can be attenuated by the high-frequency carrier and the responses to high-frequency carriers can be enhanced when presented together with low-frequency stimuli. This is opposite to what would be expected from the general principles of masking and may be related to effects like suppression (John et al., 2002).

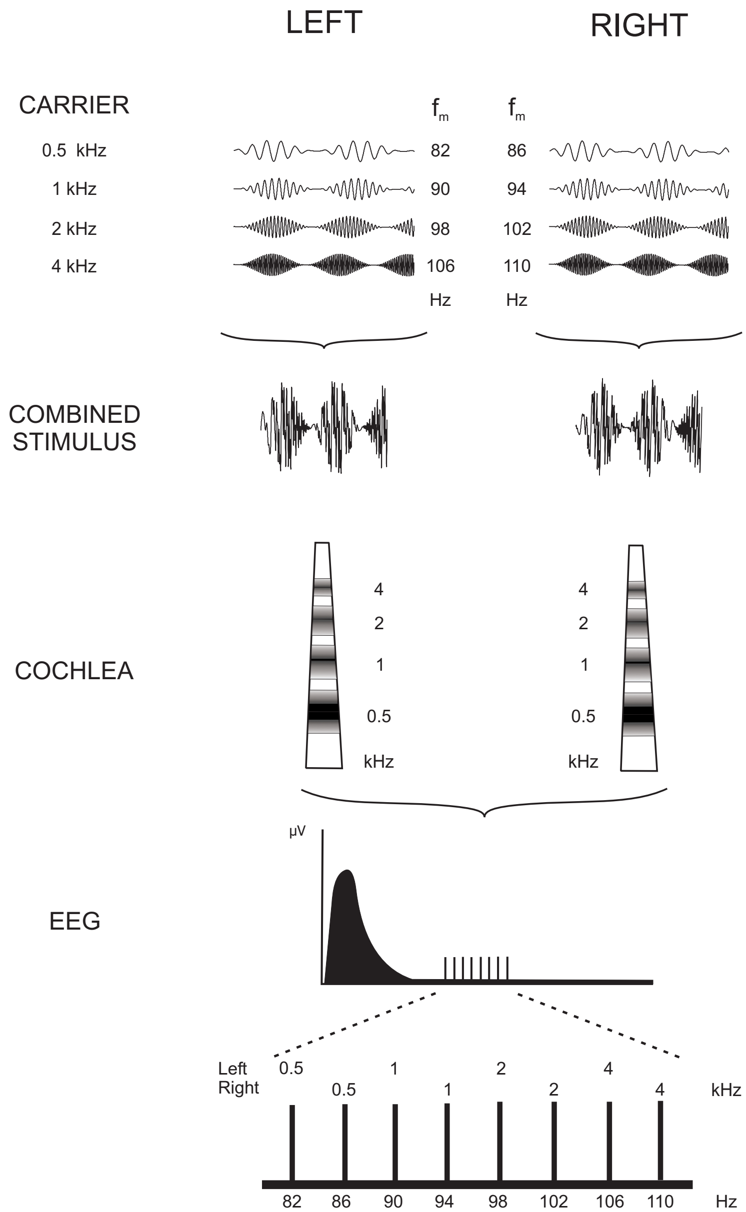


Figure 2.6: Principle of dichotic multiple-stimulus auditory steady-state responses. A combined stimulus that consists of four carrier frequencies, each modulated at a different modulation frequency is presented to each ear. On both basilar membranes, only the regions around the carrier frequency are stimulated, since the presented signals do not contain spectral energy at the modulation frequencies. As a result of the compressive rectification process, the neural response does contain energy at the modulation frequencies. Moreover, the response to each carrier can be separated in the frequency domain, since it occurs exactly at the modulation frequency.

At higher intensity levels, overlap of the activation patterns on the basilar membrane is broader. This results in an increased interaction between stimuli with a different carrier frequency (Picton et al., 2003). John et al. (1998) noticed greater interactions between the stimuli when the intensity was increased to 75 dBSPL.

At modulation frequencies around 40 Hz much greater interactions are shown than at higher modulation frequencies. This indicates that the interaction between adjacent frequencies is greater at higher levels of the auditory system (Picton et al., 2003). Consequently, the multiple-stimulus technique is not useful at these lower modulation frequencies (John et al., 1998).

The multiple-stimulus technique would be most effective if responses to the different carriers would be equal in amplitude. Test duration will increase if not all responses reach significance, since it takes longer to determine that a response is absent than it does to recognize that a response is present. For instance, in case of a sloping audiogram configuration, many intensity steps will have to be assessed and there will be several intensities at which at least one response is absent. Consequently, in these cases the advantage of the multiple-stimulus technique will be attenuated, but not completely removed (John et al., 2002).

2.2 Test set-up Lab. Exp. ORL

In this section, we describe the experimental test platform for recording auditory steady-state responses, which was built at the Lab. Exp. ORL, as well as our choice of stimulus and recording parameters. This test set-up remained basically the same for all studies described in Chapter 3 to 7 of this dissertation.

2.2.1 ASSR stimulus presentation

Eight stimuli were simultaneously presented, four to each ear. Sine waves at carrier frequencies of 500, 1000, 2000 and 4000 Hz were 100% amplitude-modulated and 20% frequency-modulated. Simultaneous modulation in both amplitude and frequency results in larger responses compared to simple amplitude modulation (John et al., 2001b). The frequency modulation was phase-shifted by -90° to ensure that the tone reached maximum frequency at the same time as it reached maximum amplitude (John & Picton, 2000). Modulation frequencies were approximately 82, 90, 98 and 106 Hz for the left ear and 86, 94, 102 and 110 Hz for the right ear (see Table 2.1). The carrier and modulation frequencies were adjusted, so that there were an integer number of cycles within one recording section or epoch (see Table 2.2). For simplicity, from now on the frequencies are expressed without decimals.

Table 2.1: ASSR stimulus parameters. Carrier and modulation frequencies are expressed without decimals.

	Left				*Right*			
Carrier frequency (Hz)	500	1000	2000	4000	500	1000	2000	4000
Modulation frequency (Hz)	82	90	98	106	86	94	102	110
AM percentage	100	100	100	100	100	100	100	100
FM percentage	20	20	20	20	20	20	20	20
FM phase	-90	-90	-90	-90	-90	-90	-90	-90

The eight signals were calibrated separately in dBSPL, using a Sound Level Meter (Brüel & Kjaer 2260) in combination with a 2-cc coupler (Brüel & Kjaer DB 0138). Calibration in terms of sound pressure level makes comparison of the results of audiological assessment with the electroacoustical performance of a hearing aid easier (Munro & Lazenby, 2001).

The maximum presentation level was 100 or 110 dBSPL, dependent on the study. At this intensity level, no non-linearities were observed in the acoustical signal and a 15-min presentation of this stimulus would not damage the subject's ear. The spectrum of the signal was examined in one-third octave bands with the sound level meter. In all one-third octave bands, intensity increased linearly up to a stimulus level of 110 dBSPL.

2.2.2 ASSR recording parameters

Data were recorded in epochs containing 1024 data points. Artifact rejection limits were set in such a way that about 5-10% of the epochs was rejected, in order to eliminate potentials due to artifacts from muscles or movement. This corresponded to limits between 15 and 20 µV. The epochs were linked together to form a sweep, which lasted for 16.384 seconds.

In the digitizing step, initially an analogue-to-digital conversion rate of 1000 Hz was used. However, during the experiments we noticed that artifacts occurred at high intensity levels. To reduce these artifacts, from then on a sampling rate of 1250 Hz was utilized. Therefore, the carrier and modulation frequencies slightly changed, as well as some recording parameters (see Table 2.2). However, the sweep length and thus the frequency resolution of the FFT were kept equal, to facilitate post-hoc data analyses for recordings made with different sampling rates. The frequency resolution of the FFT was 0.061 Hz.

Table 2.2: Stimulus and recording parameters for AD sampling rates of 1000 versus 1250 Hz.

		Sampling frequency 1000 Hz		*Sampling frequency 1250 Hz*	
		Carrier frequency (Hz)	Modulation frequency (Hz)	Carrier frequency (Hz)	Modulation frequency (Hz)
Stimulus parameters	LEFT	500.00	82.031	500.488	81.787
		1000.00	89.844	999.756	90.332
		2000.00	97.656	1999.512	97.656
		4000.00	106.445	4000.244	106.201
	RIGHT	500.00	85.937	500.488	85.449
		1000.00	93.750	999.756	93.994
		2000.00	101.562	1999.512	102.539
		4000.00	110.352	4000.244	109.863
Recording paramters	Epoch length	1.024 s		0.819 s	
	Epochs per sweep	16		20	
	Sweep length	16.384 s		16.384 s	
	DA factor	32		20	

2.2.3 Experimental set-up

ASSR recordings were made with an experimental setup in a soundproof room with a Faraday cage. The background noise level in the sound booth was 12.1 dB(A). A schematic overview of the test room is shown in Figure 2.7.

During the recordings, the test leader was seated in a control room in front of the sound booth. The patient was lying down on a bed in the soundproof room. The acoustical stimuli were generated via a National Instruments AT-MIO-16E-10 (for ISA bus) or 6040E (for PCI bus) board in the PC. A clinical audiometer, Madsen Orbiter 922, was used to control the overall stimulus intensity of the left and right channels. The level for the ASSR stimuli for the two ears was controlled by separate channels of the audiometer and could be adjusted independently. All four frequencies in one ear, however, were presented at the same level. The acoustical stimuli were presented to both ears by means of ER-3A insert earphones with ER3-14D, ER3-14E or ER3-14B ear tips (see Figure 2.8). These insert phones offer more comfort and prevent collapse of ear canals in babies. Moreover, interaural level attenuation is increased compared to supra-aural headphones.

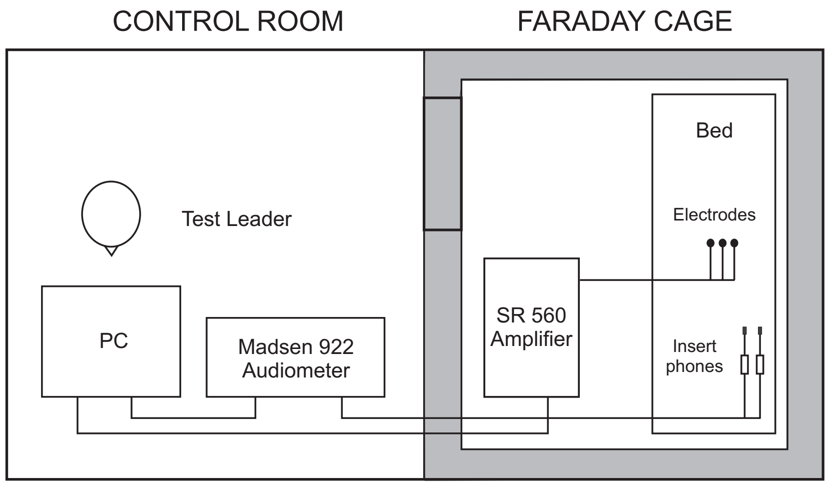


Figure 2.7: Schematic overview of the test room with Faraday cage.

The EEG was recorded with surface electrodes (see Figure 2.8). In adults, silver-silver chloride recording electrodes were placed at the vertex (Cz) and at the inion (Oz), with a ground electrode in between at Pz. This electrode derivation has a lower noise level and a higher signal-to-noise ratio (SNR) than other configurations (van der Reijden et al., 2001). In infants, the noninverting electrode was placed at the forehead instead of the vertex to avoid the fontanel region. The inverting electrode was placed at the inion and the ground electrode at the clavicle. The skin was abraded with Nuprep abrasive skin prepping gel. A conductive paste was used to keep the electrodes in place and to obtain inter-electrode impedances of less than 5 kΩ at 30 Hz. Only in a few cases, impedances were between 5 and 10 kOhm. The electrodes were connected to a Stanford Research Systems SR560 amplifier, which has a very low noise level. The EEG was amplified 50000 times and band pass filtered between 30 and 300 Hz (6 dB/octave). The output of the amplifier was digitized by the National Instruments board and further processed by the PC.

The MASTER software was used to generate the stimuli and record the electrical responses (John & Picton, 2000). This software was designed to record multiple auditory steady-state responses. Stimulus presentation and recording of the EEG are synchronized. During the recordings, the EEG is shown in the time domain and in the frequency domain. The presence or absence of a response is determined by a combination of averaging of the responses, FFT and the F-ratio. Stimulus and recording parameters can be adjusted and recorded data can be saved and reviewed.

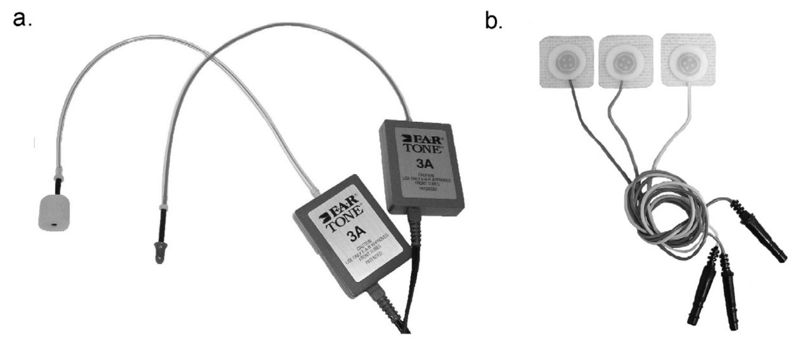


Figure 2.8: ER-3A insert phones with different types of ear tips (a) and disposable silver-silver chloride recording electrodes (b).

Prior to the measurements, the noise inherent to the recording system was investigated. The inverting and noninverting electrode were directly connected (impedance 250 Ohm) and a recording of 8 sweeps was made. The noise level, calculated as the average amplitude of the frequency bins ranging from 77 to 115 Hz (5 Hz below and above the range of modulation frequencies), was 0.9 nV. The amplitude spectrum of the noise is shown in Figure 2.9.

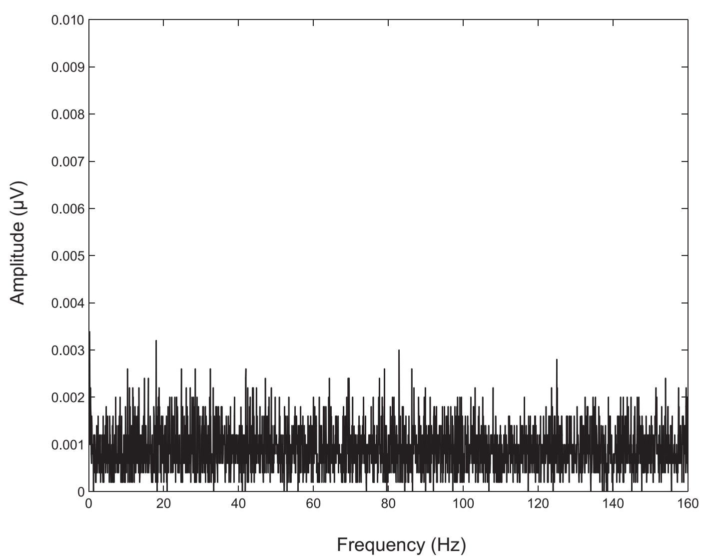


Figure 2.9: Amplitude spectrum of the system noise, after averaging 8 sweeps, recorded with an electrode impedance of 250 Ohm.

2.2.4 Test procedure

For each stimulus intensity, 8 to 48 EEG recording sweeps were averaged, corresponding to approximately 2.5 to 15 min, including rejected epochs. Response waveforms were added in the time domain, and the result was submitted to FFT analysis. The level of significance of the responses was monitored after each sweep. The probability that the amplitude of the signal was within the distribution of the noise amplitudes of 120 neighboring frequency bins (approximately 3.7 Hz on both sides) was evaluated using *F*-ratio statistics (John & Picton, 2000). The significance level was set at $p<0.05$.

ASSR thresholds were always determined for four frequencies in both ears at 10-dB precision. A threshold was defined as the lowest intensity level where a significant response was obtained. Moreover, a threshold was only accepted when confirmation was found at an intensity level 10 dB above the threshold. If no significance was achieved at this higher intensity level, a false positive response was assumed. The raw data of all recordings were saved for further analysis.

Figure 2.10 illustrates a threshold procedure in a normal-hearing adult. Frequency spectra are shown for recordings at different intensity levels. At 30 dBSPL, responses to all eight presented stimuli were easily to detect and the recording could be ended after 16 sweeps. Closer to threshold, the maximum number of sweeps had to be recorded, since not all eight responses reached significance. At the lowest intensity level, no significant responses could be recorded. According to these data, ASSR thresholds could be determined at 30 dBSPL for 500 Hz left (modulation frequency of 82 Hz), at 10 dBSPL for 2000 Hz right (modulation frequency 102 Hz) and at 20 dBSPL for the other stimuli.

2.2.5 Evaluation of electromagnetic artifacts

At high intensity levels, artifacts might occur. Recently, ways to reduce sampling artifacts were systematically explored. Small & Stapells (2004) recorded ASSRs to high-intensity air-conduction stimuli in hearing-impaired subjects that could not hear the stimuli. At AD rates of 1000 Hz and 1250 Hz, they only recorded artifactual responses for a 1000-Hz carrier presented at 120 dBHL. No artifacts were recorded when alternated stimulus polarity was used. Gorga et al. (2004), however, report artifacts at an average level of 100 dBHL for all carrier frequencies, using a sampling rate of 1000 Hz. Occasionally, artifactual responses even occurred at levels as low as 85 dBHL.

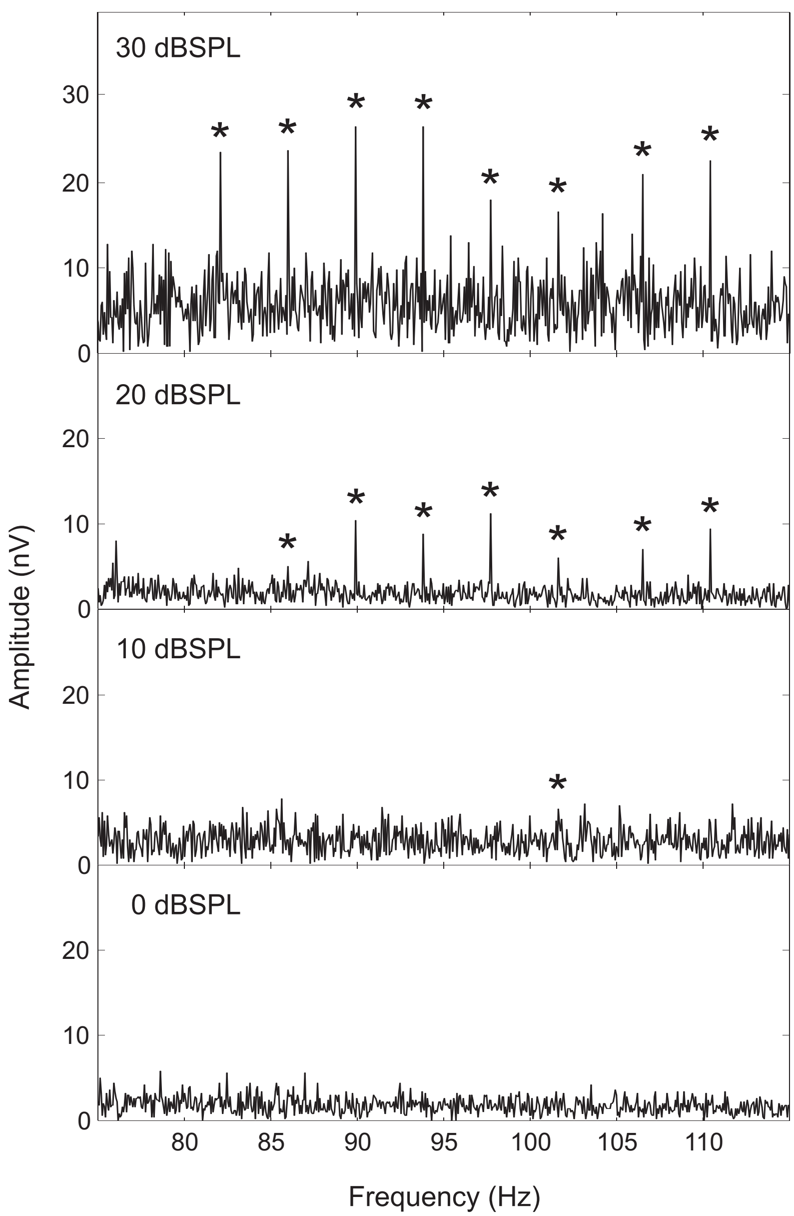


Figure 2.10: Frequency spectra of ASSR recordings at different intensity levels in a normal-hearing adult. The modulation frequencies were 82, 90, 98 and 106 Hz for the left ear and 86, 94, 102 and 110 Hz for the right ear for 500, 1000, 2000 and 4000 Hz respectively. The asterisks indicate the significant responses. At 30 dBSPL, all eight responses were significant after 16 sweeps, and therefore the recording was stopped. At the other intensity levels, the maximum number of 48 sweeps was recorded since not all responses reached significance. ASSR thresholds are defined as the lowest intensity level where a significant response could be recorded.

As the occurrence of artifacts depends on many factors, we made an analysis of the artifacts that could arise with our test set-up in patients that were not able to hear the presented stimuli. Amplitudes at the modulation frequencies are compared to the noise at the adjacent frequencies. If the *F*-test shows a significant result at the modulations frequencies, this was judged to be an artifact, since it can not be a physiologic response to the sound.

At a sampling rate of 1000 Hz, ASSRs were recorded in a deaf infant. Significant responses occurred at 110 dBSPL for carrier frequencies of 1000, 2000 and 4000 Hz for both ears. The mean amplitude of the artifactual responses was 11 nV, with a maximum of 24 nV. At 100 dBSPL, significant responses occurred only at 1000 and 2000 Hz, only in one ear. The largest artifact was 9 nV for the 1000-Hz carrier. At 90 dBSPL, no significant responses were found. Average noise levels of these recordings were below 3 nV after 40 sweeps of 16.384 s.

At a sampling rate of 1250 Hz, ASSRs were recorded in two adults with a profound hearing loss and with the tubes of the insert phones occluded. In this way, the patients were unable to hear the stimuli at the maximum stimulus level. Recordings were made at 90, 100 and 110 dBSPL in both ears of the two patients for four carrier frequencies. At each intensity level, significance of these 16 responses was judged after a recording time of approximately 9 min. At 110 dBSPL, three out of 16 responses were significant. The largest artifactual response found was 9 nV. At 100 dBSPL, significance occurred in two out of 16 cases. Most sensitive for artifacts seemed to be the responses to 1000 and 4000 Hz signals. At 90 dBSPL, no artifacts were recorded.

Artifacts are smaller using a sampling rate of 1250 Hz instead of 1000 Hz, though not fully eliminated. This shows that apart from the aliasing problem, nonlinearities in the test set-up cause artifacts. Especially the cable of the transducers creates artifacts. We can conclude that data presented in the next chapters below 100 dBSPL are free of artifacts. At higher intensity levels, artifacts may have been present. However, in case of doubt about the origin of the responses, a second recording was carried out with the insert phones not in the patient’s ear. If responses were still significant, these data were not interpreted as thresholds and were indicated as no-response for further analyses. During the recordings, the transducer cables and the EEG recording electrodes and cables were separated in space and impedances were as low as possible.

2.3 Conclusions

In this chapter, we briefly explained most important features of the ASSR. For the objective assessment of hearing thresholds in babies, modulation rates around 90 Hz have to be applied, since ASSRs at lower frequencies are not reliably recordable in babies and are influenced by sleep and sedation. Moreover, in this research the multiple-stimulus technique was used, because this can reduce test duration, which is a major issue when testing babies.

Chapter 3

Hearing assessment by recording multiple auditory steady-state responses: the influence of test duration

Luts, H. & Wouters, J. 2004. International Journal of Audiology, 43 (8), 471-478.

Abstract

In this study, we investigated the influence of test duration on the precision of the hearing threshold estimated by recording multiple-stimulus auditory steady-state responses (ASSRs). High precision of the threshold estimate as well as a reasonable test duration are crucial regarding the clinical applicability.

ASSR thresholds at four frequencies in both ears were assessed in 10 normal-hearing and 10 hearing-impaired subjects. First, the precision of the estimated hearing thresholds was compared for ASSR recordings of 5, 10 and 15 min per intensity level, corresponding to total test durations of approximately 30, 55 and 70 min for hearing-impaired ears. Second, an intensity step size of 10 dB was compared to a step size of 5 dB. Third, a possible decrease of the quality of the recordings, caused by restlessness or tension after a long test duration, was investigated.

The mean difference scores (and standard deviations) between the ASSR threshold and the behavioral hearing threshold (BHT) averaged over the four frequencies were 15 ± 10, 12 ± 9 and 11 ± 8 dB after recordings of 5, 10 and 15 min respectively. The corresponding Pearson correlation coefficients were 0.93, 0.95 and 0.96. Increasing the length of the separate recordings increases the precision of the estimates, independent of tested frequency. A compromise between test duration and precision will have to be made. With recordings of approximately 10 min and a total test duration of approximately 1 h, four hearing thresholds in both ears can be estimated with a standard error of the estimate of 8 dB. A recording at an additional intensity level to obtain ASSR thresholds at 5 dB accuracy instead of 10 dB does not improve the precision of the hearing threshold estimate. Moreover, a long test duration has a negative effect on the SNR.

3.1 Introduction

A first requirement towards the clinical application of dichotic multiple-stimulus ASSRs, is the development of an appropriate test protocol. Two crucial factors in the evaluation of a test protocol are the precision of the obtained test results, and test duration. In clinical practice, the precision of the predicted hearing thresholds needs to be high, but test duration is limited.

Recently, the dichotic multiple-stimulus ASSR technique has been evaluated in different groups of subjects with different test protocols. Mean difference scores between ASSRs and behavioral hearing thresholds ranged from 5 to 15 dB (Herdman & Stapells, 2001; Perez-Abalo et al., 2001; Dimitrijevic et al., 2002). If these mean difference scores are known, they can be taken into account in the estimation of the hearing threshold. The accuracy of this estimate, however, is particularly defined by the variability of the difference scores, represented by the standard deviation. Dependent on study and subject group standard deviations ranged from 7 to 16 dB (Herdman & Stapells, 2001; Dimitrijevic et al., 2002; Perez-Abalo et al., 2001). The results of these studies depend, to a great extent, on the test method used. Several factors affect the accuracy of the estimated thresholds: the response detection method, the significance level, the stimulus type, the level of arousal of the subjects, ambient noise levels, and the duration of each recording. No agreement exists about the most optimal test settings. Especially test duration per intensity level varies considerably, ranging from 4 to 17 min.

Stimulus parameters have been studied in previous research. It is known that ASSRs in infants are best recorded at modulation frequencies around 90 Hz (Cohen et al., 1991). Moreover, a greater response is obtained when a combination of amplitude and frequency modulation is used compared to simple amplitude modulation (Cohen et al., 1991; John et al., 2001b; John et al., 2004). Carrier frequencies between 500 and 4000 Hz are generally assessed, since these frequencies are most important for speech understanding. With regard to the recording parameters, however, less research has been done. It is known that averaging responses together and increasing the duration of the sweep submitted to Fourier analysis, can reduce the overall noise level (John et al., 1998). Both processes result in an increase of the total test duration, but the effect on the predicted hearing thresholds has not been examined.

In this study, we investigated the influence of an increased test duration on the precision of the hearing thresholds estimated by means of dichotic multiple ASSRs. The total test duration is determined by the length of the individual recording sweeps, by the number of sweeps that are recorded per intensity level and by the number of intensity steps that have to be taken to define the threshold. In this work, we first compared the ASSR thresholds with the corresponding BHT while varying the number of recorded sweeps per intensity level between 16, 32 and 48, which corresponds to about 5, 10 and 15 min. Second, an intensity step size of 10 dB was compared with a step size of 5 dB in the threshold test procedure. This additional recording at 5-dB precision again increases the total test duration. Third, a possible decrease in the quality of the recordings, caused by restlessness or tension after a long test duration, was investigated.

3.2 Methods

3.2.1 Subjects

Table 3.1: Behavioral hearing thresholds in dBSPL of the 10 HI subjects for the modulated pure tones used for ASSR testing.

	Left ear				*Right ear*			
Subject	*500 Hz*	*1000 Hz*	*2000 Hz*	*4000 Hz*	*500 Hz*	*1000 Hz*	*2000 Hz*	*4000 Hz*
1	30	30	65	100	10	10	30	60
2	35	55	85	100	50	65	85	90
3	50	55	55	60	50	50	55	55
4	60	70	75	75	55	70	75	80
5	75	60	70	75	70	70	70	85
6	45	55	65	70	50	55	60	65
7	45	55	75	85	45	50	70	85
8	25	32	40	100	30	45	55	100
9	30	35	55	60	25	35	60	70
10	35	30	50	95	30	25	55	70

Ten normal-hearing (NH) and 10 hearing-impaired (HI) volunteers participated in the study. The ages in the NH group varied from 22 to 32 years. The hearing thresholds were less than 30 dBSPL for audiometric frequencies between 500 and 4000 Hz. The mean pure-tone average (PTA) was 14 dBSPL. In the HI group, the ages ranged between 45 and 75 years. Hearing thresholds are presented in Table 3.1. The mean PTA was 51 dBSPL. Six ears had a flat hearing loss (difference between low and high frequencies less than 20 dB), eight ears a mild sloping hearing loss (difference of 25-45 dB) and six ears a steep hearing loss (difference of 50 dB or more). These subjects were selected from the patient population of UZ Leuven. The average age of the NH and HI subject group differs, but ASSRs do not change significantly with increasing age in adulthood (Picton et al., 2003).

3.2.2 Experimental design

3.2.2.1 Stimulation and recording parameters

The ASSR testing parameters are described in section 2.2.

3.2.2.2 Test procedure

First, BHT were determined for 500, 1000, 2000 and 4000 Hz, with a 5-dB up and 10-dB down search method. The ASSR thresholds obtained later were compared with the corresponding BHTs. To make this comparison clear, BHTs were obtained in the same experimental conditions as used for the ASSRs, with insert phones and modulated sinusoids, calibrated in dBSPL. In 14 ears, a comparison was made between BHTs determined with pulsed pure tones and that determined with modulated sinusoids. A paired samples t-test showed a difference between both measures of 0.5 dB, which is statistically (p=0.406) and clinically not significant. Therefore, we considered the use of the modulated sinusoids for behavioral audiometry to be justified, although pure tones are generally used.

After this behavioral test, the objective ASSR recordings were started. In the NH group, recordings were made with tin-plated copper electrodes with a diameter of 3 cm. In the HI group, disposable neonatal 3M 2282E electrodes were used. In five NH subjects, a comparison was made between the experimental tinned copper electrodes and clinically used disposable electrodes 3M 2282E. For large scale clinical testing, the tinned copper electrodes are not appropriate. Therefore, a recording of 16 sweeps was carried out at 55 dBSPL with both types of electrodes. A repeated measurements analysis of the results of ten ears shows that there is no significant difference between the different types of electrodes what concerns noise level, amplitude and SNR.

The subject was asked to lie down on a bed with eyes closed and to relax or sleep. Despite reduction of response amplitude during sleep, detection efficiency does not decrease (Cohen et al., 1991). The lights were switched off. To check if the position of the subject was comfortable, an exploratory recording was carried out at the start of the test session. The main goal of this was to find the most relaxed position of the head and neck before the threshold measurements were started. The EEG was recorded during eight sweeps (130 s). Noise levels were checked, and further measurements were started in case the noise level was below 12 nV. If the noise level was too high, the subject was positioned differently and the EEG recording was repeated, until a better noise level was achieved.

Recordings were started at intensity levels of 55 dBSPL for the NH group and 70 dBSPL for the HI group. The maximum presentation level was 100 dBSPL. Recordings were carried out in multiples of 16 sweeps. If responses for all stimuli were significant after 16 sweeps, recordings were stopped, on the assumption that the responses would stay significant after 32 and 48 sweeps. If not all responses were significant after 16 sweeps, 32 or 48 sweeps were recorded. If significance was not reached after averaging 48 sweeps, it was assumed that there was no response. After each multiple of 16 sweeps, the test leader noted if the responses reached significance for the eight stimuli. In this way, it was possible to determine what the thresholds for the different stimuli would be after recordings with maximum numbers of sweeps of 16, 32, or 48. A recording of 16 sweeps lasted for a minimum of 4.4 min, but taking into account the 5-10% rejected epochs, this resulted in approximately 5 min. Thirty-two and 48 sweeps corresponded to about 10 and 15 min.

Because of timing restrictions, the eight thresholds for each subject were defined at 10-dB precision. However, the benefit of an additional recording to define the ASSR threshold at 5-dB precision was evaluated. In both groups, one extra recording was made to estimate the threshold at 1000 Hz in both ears at a precision of 5 dB. Since this recording was close to the threshold, it was mostly required to measure 48 sweeps. This means a maximum increase in test duration of 15 min.

At the intensity level of 55 dBSPL, responses to all frequencies should have reached significance within 16 sweeps in the NH group. This was a reference measure that was compared with regard to amplitude, noise level and SNR with a similar measure at the end of the test session. In this way, we could check the influence of a long measurement duration on the quality of the recorded signal.

3.2.3 Data analyses

Hearing thresholds at four frequencies were defined in both ears of 10 NH and 10 HI subjects. In total, 160 ASSR thresholds were compared with the corresponding BHTs; difference scores (ASSR – BHT) are presented. All ASSR thresholds were measured at a precision of 10 dB unless otherwise specified. The BHTs were defined at 5-dB precision.

Statistical analyses were carried out with the 10.0 SPSS software. Difference scores after recordings of 16, 32 and 48 sweeps were compared with regard to frequency by means of a repeated-measures analysis of variance (ANOVA). The linear relationship between ASSR thresholds and BHTs was evaluated using Pearson correlation coefficients and linear regression analyses. R^2 describes the amount of variance of the dependent variable (BHT) that is accounted for by the independent variable (ASSR threshold). *t*-Tests were carried out to compare the noise level of the exploratory recordings at the start of the test session in the NH and HI group and the noise level, amplitude and SNR after the recording of 55 dBSPL at the start and at the end of the test session. An ANOVA with repeated measures was conducted to compare thresholds obtained after 5-dB or 10-dB intensity steps in both groups.

3.3 Results

A minimum of two and a maximum of four recordings of eight sweeps were carried out in order to find the most comfortable position with an optimal noise level. For each subject, the recording with the lowest noise level was selected. The mean noise levels and standard deviations of these recordings were 10.4 ± 3.5 nV and 11.9 ± 2.7 nV for the NH and HI groups respectively. An independent-samples t-test showed no significant difference between both groups.

3.3.1 Comparison of 16, 32 and 48 sweeps

Figure 3.1 shows the distributions and the cumulative distribution of the differences found between the objective ASSR thresholds and the corresponding BHTs after recordings with maximum numbers of sweeps of 16, 32 and 48. Both plots show only a small difference between the 48 and 32 sweeps condition. For the cumulative distribution the difference between the curves of 32 and 48 sweeps is never larger than 5%. In contrast, the curve of 16 sweeps is up to 15% lower than that of 32 sweeps and up to 20% lower than that of 48 sweeps at a difference score of 15 dB. In total 160 thresholds were examined. The number of missing and outlying values increased with decreasing number of sweeps (see Table 3.2). All missing values occurred in the HI group. In these cases, no ASSR was found at the maximum presentation level of 100 dBSPL. The average BHTs that corresponded to the missing ASSR thresholds were 83, 85 and 88 dBSPL after 16, 32 and 48 sweeps respectively.

Table 3.2 shows the mean difference scores and standard deviations between the ASSR thresholds and the BHTs for both groups of subjects and four separate frequencies. The differences become smaller after a longer test duration and are lower in the mid-frequencies. This is also illustrated in Figure 3.2. The differences (and standard deviations) between the ASSR thresholds and the BHTs averaged over both groups (40 ears) and averaged over the four frequencies were 15 ± 10 dB, 12 ±

9 dB and 11 ± 8 dB after 16, 32 and 48 sweeps respectively. The corresponding Pearson correlation coefficients were 0.93, 0.95 and 0.96.

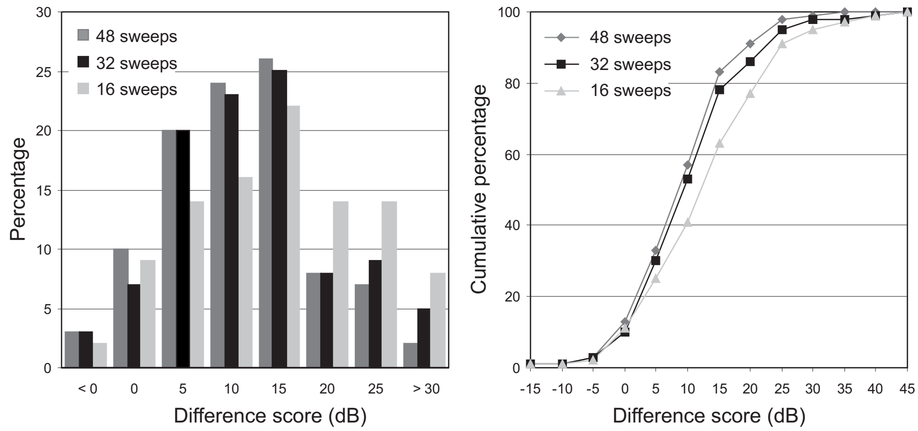


Figure 3.1: Distribution and cumulative distribution (in percentages) of the raw difference scores between the ASSR threshold and the corresponding BHT after recordings with maximum numbers of sweeps of 48, 32 and 16 for the 40 tested ears and all tested frequencies. Missing values are omitted (*n*=149 for 48 sweeps, *n*=145 for 32 sweeps and *n*=144 for 16 sweeps).

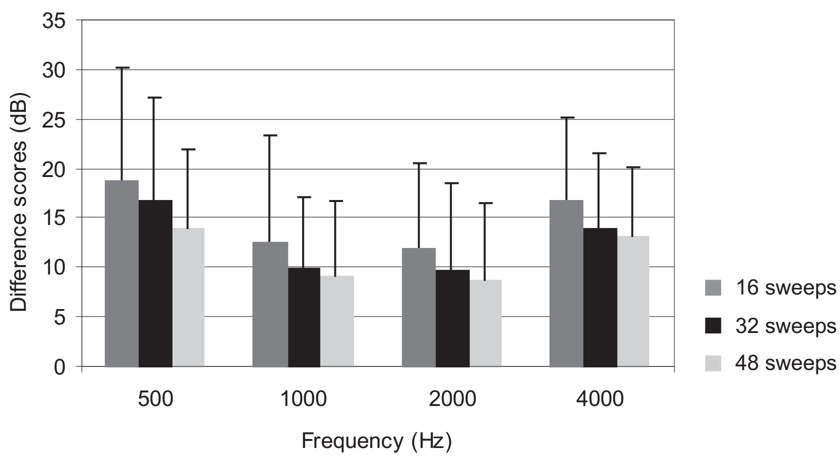


Figure 3.2: Average difference scores (ASSR threshold minus BHT) in dB and the standard error of the mean after recordings with maximum numbers of sweeps of 16, 32 or 48 are shown for each frequency. The results of 40 ears are averaged.

Table 3.2: Mean differences (in dB) and standard deviations between the BHT (measured at 5-dB precision) and the corresponding ASSR threshold (measured at 10-dB precision) for 20 NH and 20 HI ears after recordings with maximum numbers of sweeps of 16, 32 and 48.

	Normal-hearing			*Hearing-impaired*		
Frequency	*16 sweeps*	*32 sweeps*	*48 sweeps*	*16 sweeps*	*32 sweeps*	*48 sweeps*
500 Hz	15 ± 9	13 ± 8	12 ± 7	23 ± 12	20 ± 12	15 ± 9
1000 Hz	10 ± 11	7 ± 7	7 ± 7	15 ± 10	13 ± 7	11 ± 8
2000 Hz	12 ± 7	9 ± 7	9 ± 7	12 ± 10	11 ± 11	9 ± 9
4000 Hz	18 ± 9	15 ± 8	13 ± 7	14 ± 8	13 ± 7	13 ± 8
Total	13 ± 10	11 ± 8	10 ± 7	17 ± 11	14 ± 10	12 ± 9
Missing values	$n = 0$	$n = 0$	$n = 0$	$n = 16$	$n = 15$	$n = 11$

A two-way repeated measures ANOVA was carried out on the difference scores for the factors test duration (16, 32 and 48 sweeps) and frequency (500, 1000, 2000 and 4000 Hz). Missing ASSR-values were replaced by a threshold of 105 dBSPL. There is a main effect for test duration (lower bound, $p \leq 0.001$, observed power 100%) and frequency (lower bound, $p=0.011$, observed power 74%). The interaction effect between these factors is not significant (lower bound, $p=0.395$). Pairwise comparisons (with Bonferroni adjustment for multiple comparisons) for the factor test duration show significant differences between the three conditions ($p \leq 0.004$). With regard to test frequency, the difference scores of the mid-frequencies are significantly smaller than those of the low and high frequencies ($0.005 \leq p \leq 0.029$).

Linear regression analyses were conducted to evaluate the correlation between the BHT and the ASSR threshold. The linear regression coefficients for the different measurement conditions (16, 32 and 48 sweeps) are given in Table 3.3. There was a good spread of the data over the intensity range. Accuracy in predicting hearing thresholds was high. R^2 or the variance of the BHT that was accounted for by its linear relationship with the ASSR threshold can also be found in Table 3.3. After estimation of the hearing thresholds with the linear regression equation, the standard error of the estimate was only 8 or 9 dB, for all frequencies with the same regression equation. Finally, Table 3.3 shows the distribution of the absolute differences between the estimated hearing thresholds and the BHTs. For the above regression analyses, the missing values were excluded. If we add these missing values to the data, assuming an ASSR threshold at 105 dBSPL, and conduct the regression analysis, R^2 becomes 0.94, 0.92 and 0.90 for 48, 32 and 16 sweeps respectively.

Table 3.3: Results of linear regression analyses after a maximum number of sweeps of 16, 32 or 48 for the individual recordings.

Maximum number of sweeps	*Intercept b_0 (dB) (standard error)*	*Slope b_1 (standard error)*	*R^2*	*Standard error of the estimate*	*≤ 10 dB*	*≤ 15 dB*	*≤ 20 dB*
16	-8.67 (1.36)	0.85 (0.03)	0.87	9 dB	76%	90%	96%
32	-7.36 (1.17)	0.87 (0.02)	0.90	8 dB	83%	95%	97%
48	-7.40 (1.04)	0.91 (0.02)	0.92	8 dB	84%	95%	99%

In the regression equation $\boldsymbol{y = b_0 + b_1 x}$, $\boldsymbol{y}$ represents the BHT, $\boldsymbol{x}$ the ASSR threshold, $\boldsymbol{b_0}$ the intercept (in dB) and $\boldsymbol{b_1}$ the slope. Regression coefficients (and standard errors), $\boldsymbol{R^2}$, the standard error of the estimate and the distribution of the absolute differences between the estimated hearing thresholds and the BHTs are shown. Data of 20 NH and 20 HI ears are used for the regression analyses.

The time needed to define hearing thresholds at 10-dB precision for four frequencies in both ears with a maximum of 48 recorded sweeps was on average 55 min for the NH subjects and 75 min for the HI subjects. For the NH group, recordings were made at five or six intensity levels in order to find the four thresholds for both ears. At higher levels, 16 sweeps sufficed to obtain eight significant responses. For the HI subjects, four to seven intensity steps were necessary. At most intensity levels, the maximum number of sweeps had to be recorded because not all responses became significant, as a result of the sloping audiograms. A reduction in the maximum number of sweeps would reduce the test duration, especially in cases of sloping hearing losses. For 32 sweeps, the test duration for HI subjects would be reduced to, on average, 50-55 min. A maximum of 16 sweeps would result in an average test duration of 25-30 min.

During the recordings, the exact number of sweeps at which significance of the responses was reached was noted. Strict rules were followed: the response had to stay significant until the end of the recording; limited periods of significance did not count. At intensities of 20 dBSL, 50% of the responses became significant within nine sweeps (about 150 s), and 80% within 40 sweeps; at 25 dBSL, 50% reached significance within five sweeps (approximately 80 s) and 80% within 18 sweeps; and at 30 dBSL, 50% reached significance within four sweeps and 80% within 11 sweeps.

Figure 3.3 shows the median number of sweeps that was required to reach significance at a certain intensity level, expressed in dBSL, for the different carrier frequencies. The error bars indicate the interquartile range. Seventy-five percent of the data lies below the upper limit. At 30 dBSL significance was reached very fast for 1000, 2000 and 4000 Hz. For 1000 and 2000 Hz the interquartile range was still rather limited at 20 dBSL. Closer to threshold, variability of the data was very large, making it impossible to predict thresholds based on the number of sweeps needed to reach significance.

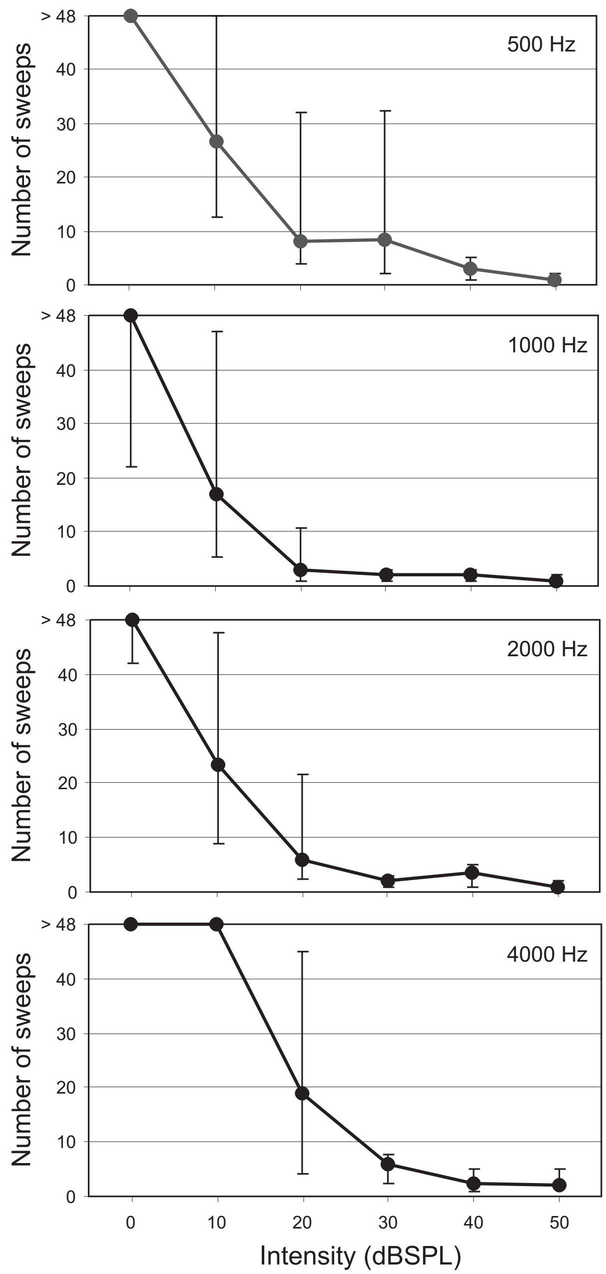


Figure 3.3: The median number of sweeps required to reach a significant response, as a function of intensity level expressed in dBSL. Data of 20 NH and 20 HI ears were included. The error bars indicate the interquartile range, containing 50% of the data. If no significant response was obtained after 48 sweeps, this was indicated as '>48'. In this way, all data were included for analysis.

3.3.2 5-dB Intensity steps

In both subject groups, one extra measurement was performed to estimate the hearing threshold for 1000 Hz at 5-dB precision. The difference between the ASSR threshold and the BHT at 1000 Hz was reduced with 2 dB, and became 7 ± 8 dB. A one-factor repeated measures ANOVA showed that this difference is significant (p<0.001) and independent of the subject group (p=0.757). Nevertheless, the variance of the BHT at 1000 Hz that was accounted for by the ASSR threshold at 1000 Hz measured at 5-dB or 10-dB precision was identical. R^2 was in both cases 0.93.

In 19 out of 40 cases, this recording reached significance, resulting in a lower ASSR-threshold. The recording reached significance within 16 sweeps in only six cases, and it reached significance within 32 sweeps in an additional three cases. This means that the recording near threshold lasted in all the remaining cases for 48 sweeps or about 15 min.

3.3.3 Effects of long test duration

In the NH group, a recording of 16 sweeps at 55 dBSPL was carried out at the start and at the end of the test session in order to compare the noise level, amplitude and SNR of the response after a long testing duration (Table 3.4). The average time between both measurements was 100 min. Averaged over the four carriers, a significant difference was found with a paired samples t-test for the noise level (p<0.001), the amplitude (p=0.012) and the SNR (p<0.001) between the start and the end of the test session. It was observed that after a long test duration some subjects could not sleep and became restless. This particularly applied to the noise level that increased with 24%. Response amplitudes decreased by only 7%.

Table 3.4: Mean noise level, amplitude and signal-to-noise ratio (SNR) and standard deviations for the first and last recording (of an approximately 100-minutes test) of 16 sweeps at 55 dBSPL in 20 NH ears averaged over the four carrier frequencies.

	First measure	*Last measure*
Noise level (nV)	6.3 ± 1.4	7.8 ± 3.2
Amplitude (nV)	55.4 ± 21.8	51.5 ± 20.7
SNR (dB)	18.5 ± 3.8	16.3 ± 4.7

3.4 Discussion

The results of this study show that the number of collected sweeps or the test duration has an influence on the precision of the threshold estimates when multiple ASSRs are recorded. An increase in length of the ASSR recordings from approximately 5 min to 10 or 15 min decreases the difference between BHTs and ASSR thresholds, independent of test frequency. A recording at an additional intensity level to obtain ASSR thresholds at 5-dB accuracy instead of 10-dB accuracy does not improve the precision of the hearing threshold estimate.

In the estimation of individual hearing thresholds, mean differences can be taken into account. With regard to the precision of this estimate, the variation of these difference scores is of more importance. The longer the measurement, the lower the noise level and the higher will be the SNR. Except for the mean difference between ASSR and BHT becoming smaller, the standard deviation decreases with increasing test duration. The results of this study are comparable to those of other studies. Mean differences, standard deviations and Pearson correlations of the 48-sweep condition correspond to values reported by Herdman and Stapells (2001) and Dimitrijevic et al. (2002) who defined ASSR thresholds after recordings with maximum numbers of sweeps of 48 and 64 respectively.

The test duration in the study of Perez-Abalo et al. (2001) is comparable to the 16-sweep condition, although the variability of the reported results is higher than in the present study. Standard deviations are higher (between 10 and 11 dB for NH adults and between 14 and 16 dB for HI children), correlation coefficients are lower (between 0.7 and 0.8), and standard errors of the estimate are higher (between 14 and 15 dB). Several procedural differences could be responsible for this discrepancy. First, the acoustical noise level in the test rooms was above the standard for permissible ambient noise (ANSI, S3.1-1999). Second, 95% amplitude-modulated tones were presented. This will result in smaller responses compared to stimuli that are modulated simultaneously in both amplitude and frequency (John et al., 2001b).

In a clinical setting, test duration as well as precision are important issues. There are limits to acceptable test duration, especially for the testing of babies, the target population for the use of objective physiologic techniques, although high precision should be aimed for. In HI subjects, four to seven intensity steps are needed to define four thresholds for each ear. This has to be multiplied by a recording time of 5, 10 or 15 min. Since movement and stress can disrupt the recordings, children need to be tested during sleep, and anesthesia or sedation may be required. Taking into account the average duration of sleep after chloral hydrate sedation, a maximum test duration of 1 h should be aimed for (Reich & Wiatrak, 1996). Therefore, recordings of 10 min are most appropriate. Recordings lasting 15 min each are clinically not advisable, since the difference in precision from that obtained with 10-min recordings is small. The standard error of the estimate after linear regression analysis was 8 dB for both conditions. As shown in Figure 3.4, recordings lasting only 5 min still provide reasonably precise estimates. Nevertheless, at middle and high intensities, the plot is fairly scattered and more values are missing, which affects the accuracy of the estimated thresholds.

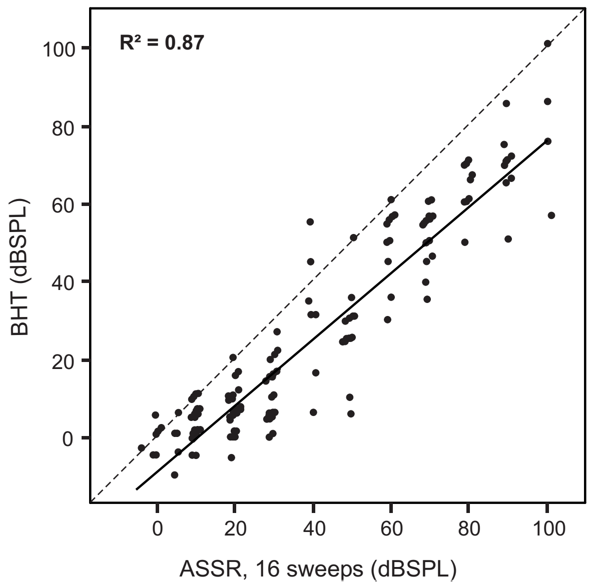


Figure 3.4: Scatterplot of the ASSR threshold estimated after recordings of 16 sweeps and the BHT averaged over the four frequencies, for 20 NH and 20 HI ears. Overlapping data have been adjusted by 2% to resolve all points in the plot. The dashed line represents the line of equality.

A step size of 10 dB for the ASSR turned out to be sufficient. Intensity steps of 5 dB resulted in a smaller difference between the BHT and the ASSR threshold (2 dB in our study), but did not make the estimate more precise. Moreover, it has most effect on the threshold after a 15-min recording, which is clinically least interesting. In case of sloping hearing losses, the aim of 5-dB precision may lead to an increase in test duration of up to 60 min.

In addition to this, a long test duration has a negative effect on the SNR. Some subjects were unable to sleep. Movement, stress or tension resulted in higher noise levels, which had a disruptive effect on the recording of ASSRs. More epochs were rejected. This noise problem will not apply to sedated children. As well as the increasing noise levels, response amplitudes significantly decreased. Whether or not this is a consequence of some form of neural adaptation after a long test duration should be further investigated. This measurement shows the importance of subject relaxation during the recordings.

The difference scores for the carrier frequencies 1000 and 2000 Hz are lower than those for 500 and 4000 Hz. The relative difficulty in threshold detection at 500 Hz has been extensively described in previous studies. The most likely explanation for this phenomenon is the greater intrinsic jitter, due to neural asynchrony (Perez-Abalo et al., 2001; Dimitrijevic et al., 2002). An elevation in threshold for the 4000-Hz carrier has also previously been reported (Picton et al., 1998; Herdman & Stapells, 2001; Dimitrijevic et al., 2002). This could be caused by interference of the simultaneously presented low-frequency sounds with the high-frequency response. Further experiments comparing single- and multiple-stimulus recordings, combined with noise-masking paradigms, should provide more clarity concerning the possible interactions and/or masking effects between combined stimuli and responses.

According to John et al. (1998), one has to be careful in testing multiple-stimulus ASSR in patients with hearing impairment due to cochlear dysfunction. Tuning curves are often distorted and a neural response might occur at stimulus frequencies other than the characteristic frequency. Especially at higher intensity levels, more interactions could occur between responses to the different stimuli in the cochlea. Certain discrepancies can therefore exist between the behavioral audiogram for single modulated tones and thresholds obtained using multiple simultaneous stimuli. This would particularly be evident in sloping hearing losses. In the current study, difference scores in the HI group are similar or bigger than in the NH group. Standard deviations of the difference scores tend to be higher in the HI group compared to the NH group. This could be the result of the increased interaction between the responses due to the hearing loss. Other possible causes are the greater diversity in BHTs in the HI group, different shapes of hearing loss, and the higher stimulation level needed with severe hearing losses. Moreover, NH subjects were more familiar with the test leader and the environment than were the HI subjects. This could lead to a higher noise level in the HI group and thus a worse SNR. The increased standard deviation in HI subjects has also been reported by Perez-Abalo et al. (2001) and Dimitrijevic et al. (2002). In contrast with our results, previous studies (Rance et al., 1995; Lins et al., 1996; Picton et al., 1998) have reported smaller difference scores between ASSR and BHT with increasing hearing loss.

At high intensity levels, electromagnetic artifacts could occur (Picton & John, 2004; Small & Stapells, 2004), especially at a sampling rate of 1000 Hz, as used in the present study. The maximum presentation level was 100 dBSPL and all subjects had residual hearing at all tested frequencies. If artifactual responses had been present, one would expect difference scores to be smaller in HI subjects compared to NH subjects. Moreover, at high intensity levels one would expect significant ASSRs below the BHTs, resulting in negative difference scores. Since this was not the case, we assume the presence of artifacts to be minor.

In this study, recordings were always stopped after a fixed number of sweeps (16, 32 or 48). The noise level was not taken into account. No weighted averaging was applied, and phase information was not used to determine whether a response was present or not. This decision was based only on a simple F-ratio technique applied to amplitude information in the frequency domain. More complex signal-processing techniques may make response detection easier and may further shorten the test duration (Van Dun, 2005).

3.5 Conclusions

When multiple-stimulus ASSRs are being recorded, increasing the length of the separate recordings increases the precision of the hearing threshold estimate. A compromise between test duration and precision will have to be made. With recordings of approximately 10 min and a total test duration of approximately 1 h, the correlation between ASSRs and BHTs is 0.95, and estimates of four hearing thresholds in both ears can be made with a standard error of the estimate of 8 dB.

Chapter 4

Comparison of MASTER and AUDERA for measurement of auditory steady-state responses

Luts, H. & Wouters, J. 2005. International Journal of Audiology. In Press.

Abstract

Two approaches to assess auditory steady-state responses (ASSRs) are compared under similar test conditions: a monaural single-stimulus technique with a detection method based on phase coherence (AUDERA) and a binaural multiple-stimulus technique using the F-test (MASTER).
ASSR thresholds at four frequencies were assessed with both methods in both ears of 10 normal-hearing and 10 hearing-impaired adult subjects, within a test duration of 1 h. The test-retest reliability and the influence of prolonging test duration are assessed.
For the total subject group, the multiple-stimulus technique outperforms the single-stimulus technique. In hearing-impaired subjects, however, both techniques perform equally well. Hearing thresholds can be estimated with a standard error of the estimate between 7 and 12 dB dependent on frequency. About 55% of the estimates are within 5 dB of the behavioral hearing threshold (BHT), and 94% are within 15 dB. Prolonging the test duration improves the performance of both techniques.

4.1 Introduction

The past 10 years, two major approaches to determine objective hearing thresholds by means of the ASSR have been thoroughly investigated: first, a monaural single-stimulus approach, with short recording times per trial and a response detection method based on phase coherence (Aoyagi et al., 1999; Cohen et al., 1991; Rance & Briggs, 2002; Rance et al., 1998; Rance et al., 1995; Rickards et al., 1994; Rance & Rickards, 2002) and second, a binaural multiple-stimulus technique with long recording times per trial and a response detection based on an *F*-test (Dimitrijevic et al., 2002; Herdman & Stapells, 2001; Lins & Picton, 1995; Herdman & Stapells, 2003; Perez-Abalo et al., 2001; Luts et al., 2004; Luts & Wouters, 2004). Besides the difference in number of stimuli simultaneously presented and the response detection paradigm, variations in subject group, test environment and total test duration make a comparison of the results of these studies difficult. Therefore, it is hard to determine whether both approaches produce similar results or whether one technique is more accurate and/or faster than the other. In the meantime, both techniques became commercially available, and therefore the question towards the most reliable and accurate technique emerged. Little research has been done directly comparing the two methods.

In this study, the single-stimulus and multiple-stimulus ASSR approach were compared in the same subjects and in a quiet test environment. First, the ability of both techniques to predict hearing thresholds over a wide intensity range within a total test time of 1 h was evaluated. Second, the influence of prolonging the test duration was assessed. Third, the test-retest reliability of both techniques was examined.

4.2 Methods

4.2.1 Subjects

Ten NH and ten HI volunteers participated in the study. The NH subjects varied in age between 21 and 28 years. Hearing thresholds were better than or equal to 20 dBSPL at all octave frequencies between 500 and 4000 Hz. Mean PTA was 7 dBSPL. In the HI group the ages varied between 18 and 73 years. These subjects had cochlear hearing loss and were selected from the patient population at the ENT Department of UZ Leuven. Hearing thresholds ranged from 10 to more than 110 dBSPL. The mean PTA was 63 dBSPL.

4.2.2 Experimental design

4.2.2.1 Stimulation and recording parameters

The software for the multiple-stimulus ASSR recordings, the MASTER (Multiple Auditory STEady-state Responses), was developed by and based on the research of John and Picton (2000) at the Rotman Research Institute, University of Toronto. For the single-stimulus approach, a GSI AUDERA device of Grason-Stadler was used. The equipment manufactured by ERA Systems, Ltd., based on research at the Department of Otolaryngology, The University of Melbourne, served as a prototype for the AUDERA device. For the sake of simplicity in what follows both systems will be referred to as the MASTER and the AUDERA system. Parameter settings for both systems were selected, as far as possible, as proposed by the developer and/or manufacturer. As a consequence, there are some differences in test parameters between both systems (see Table 4.1).

Table 4.1: Comparison of test parameters for the MASTER and AUDERA technique.

	MASTER	*AUDERA*
Software version	MASTER 1d	SSEP GSI version 2
Stimulus presentation	Multiple-stimulus, binaural	Single-stimulus, monaural
AM / FM	100% AM, 20% FM	100% AM, 20% FM
Modulation rates	Left 82, 90, 98, 106 Hz and Right 86, 94, 102, 110 Hz for 500, 1000, 2000, 4000 Hz	Test protocol '> 10 years ASLEEP' : Left and right 74, 81, 88, 95 Hz for 500, 1000, 2000, 4000 Hz Test protocol '> 10 years AWAKE' : Left and right 46 Hz for all carriers
Transducers	Insert earphones (ER-3A)	Insert earphones (GSI TIP-50)
Calibration	dBSPL	dBHL
Maximum level	100 dBSPL	100 dBSPL (or 94.5, 100, 97 and 94.5 dBHL)
Starting level	50 dBSPL for NH, 70 dBSPL for HI	50 dBHL for NH, 70 dBHL for HI
Trial duration	2.5 - 15 min	40 - 107 s
Response detection	F-test (p<0.05)	Phase-coherence (p<0.01)
Electrode position	Vertex, inion, Pz (common)	Left and right mastoids, high and low forehead (common)

AM, amplitude modulation; FM, frequency modulation; NH, normal hearing; HI, hearing impaired.
The frequency modulation depth is defined as the difference between the maximum and minimum frequencies divided by the carrier frequency.

For both systems, the eight separate signals were calibrated with a Brüel & Kjaer Sound Level Meter 2260 and a 2-cc coupler DB0138. The EEG was monitored using silver-silver chloride electrodes. Impedances were less than 5 kOhm, with the exception of a few cases where impedances were between 5 and 10 kOhm.

The MASTER system

The MASTER system consisted of the test set-up as described in section 2.2 and included the MASTER software to generate the stimuli and record the responses. As usual, epochs were linked together to form a sweep, which lasted for 16.38 seconds. For each stimulus intensity, 8 to 48 EEG recording sweeps were averaged.

The AUDERA system

Individual stimuli were presented monaurally. The system incorporates a noise threshold warning that depends on the modulation frequency in use and that is defined in the test protocol. Two different test protocols were used. If possible, the protocol '>10 years ASLEEP' was applied, which used high modulation rates and a low noise criterion. In case the EEG noise level was too high and recordings were all characterized as 'noise', the protocol '>10 years AWAKE' was selected, which included a low modulation rate (46 Hz) and a high noise threshold. Three types of results can occur. A noise result occurs when no response is found after 64 samples and when the EEG exceeds the noise threshold limit. A random result occurs when no response is found and the EEG does not exceed the noise threshold level. If a significant response is found, a phase-locked result occurs, regardless of the noise level.

The presence or absence of a response was determined automatically using a detection criterion, which looked for non-random phase behavior. This was equivalent to the phase coherence technique described by Jerger et al. (1986) and Stapells et al. (1987), and as further described in Cohen et al. (1991) and Rance et al. (1995) (see also section 2.1.4). Calculations are performed on each EEG sample. Up to 64 samples are analyzed for each trial, with a trial being defined as a tone frequency-intensity combination. In each EEG sample, the magnitude and phase of the EEG activity corresponding to the tone modulation frequency is quantified. A phase-locked or random response is determined on the basis of statistical analysis. The analysis algorithm will automatically halt stimulation and data sampling when the probability level $p<0.01$ is achieved or after a maximum of 64 samples.

4.2.2.2 Test procedure

All experiments were carried out in a double-walled soundproof room with Faraday-cage (see Figure 2.7). MASTER and AUDERA thresholds were obtained in separate test sessions. In the beginning of each test session, behavioral hearing thresholds were determined in the same experimental conditions as for the ASSR, for MASTER and AUDERA separately, with insert phones and modulated sinusoids, at 5 dB accuracy with the Hughson-Westlake method. The later obtained ASSR thresholds are compared to the corresponding BHTs. After this behavioral test, the objective ASSR recordings were started. The subject was asked to lie down on a bed with eyes closed and to relax or sleep. Lights were switched off. ASSR thresholds were assessed for 500, 1000, 2000 and 4000 Hz in 10-dB steps. Recordings were started at an intensity level of 50 dBSPL/dBHL for the NH group and 70 dBSPL/dBHL for the HI group. The maximum presentation level was 100 dBSPL. A threshold was defined as the lowest intensity level at which a response was judged to be significant or when a phase-locked response was obtained. 'Noise' epochs or trials were excluded from all further evaluation. In total, 160 ASSR thresholds were compared to the corresponding BHTs for MASTER as well as for AUDERA. Difference scores (ASSR – BHT) are presented, in order to cancel out differences in calibration and in BHTs between test sessions.

Thresholds were calculated after different lengths of total test duration. For the MASTER system, recordings were carried out in multiples of 8 sweeps. If responses for all stimuli were significant after a multiple of 8 sweeps, recordings were stopped. If significance was not reached after averaging 48 sweeps, a no-response was assumed for any one frequency. It was calculated what the thresholds for the different stimuli would be after recordings of maximum 16, 24, 32, 40 or 48 sweeps. A recording of 8 sweeps lasted minimal 2.2 min, but taking into account the rejected epochs, this resulted in approximately 2.5 min. The maximum duration of a recording was 48 sweeps, which corresponded to about 15 min or more in case of excessive noise levels. Maximum 32 and 16 sweeps were recorded at 90 and 100 dBSPL respectively, to avoid over-stimulation. Total test duration was calculated for different lengths of the individual recordings.

AUDERA thresholds were defined after short and long test sessions. In a short test session, only one EEG-recording with a good noise level was made for each tone frequency-intensity combination, resulting in a random or phase-locked response. In a long test session, recordings just below the threshold level obtained in the short test (thus with a random result) were repeated and in case of phase-locking intensity was lowered until a new threshold was defined. Thresholds for the long test were thus equal to or better than the thresholds obtained in the short test. As well for MASTER as for AUDERA, the total test duration does not include the time needed to prepare the patient, to place the electrodes and to find a comfortable position of the patient. Noisy measurements or rejected epochs during the threshold seeking procedure are included in the calculation of the total test duration, to assure a realistic estimate of the test duration.

Besides the comparison of ASSR and behavioral thresholds, the test-retest reliability was assessed for both techniques. MASTER and AUDERA thresholds (and the corresponding behavioral thresholds) were retested in extra test sessions in three NH and three HI subjects in the exact same way as described above.

4.2.3 Data analyses

Statistical analyses were carried out with the 10.0 SPSS software. In a first step, the test duration was calculated for the different test procedures and the procedure with the most comparable total test duration for MASTER and AUDERA was sought. For this test procedure, difference scores (ASSR – BHT) were calculated. For both techniques, the linear relationship between ASSR thresholds and BHTs was evaluated using Pearson correlation coefficients and linear regression analyses. Hearing threshold estimates will not be based on previously published data, since procedural and environmental variations may have an influence on the results. Predictions will be made based on the data of this study only. Frequency-specific regression equations will be used, because carrier frequency affects the ASSR response (John et al., 2002). The standard error of the estimate indicates how large the typical error is in predicting Y from X. It is the standard deviation of the expected values for the dependent variable. The R^2 describes the amount of variance of the dependent variable Y (behavioral threshold) that is accounted for by the independent variable X (ASSR threshold).

Paired samples *t*-tests were applied to compare MASTER and AUDERA concerning difference scores (ASSR – BHT) and test duration. Correlation coefficients for the relationship between the ASSR and BHTs in HI subjects were compared between AUDERA and MASTER with the Fisher's z_r transformation. The influence of test duration was evaluated for the two techniques separately, by comparing the difference scores that resulted from the different test procedures.

The differences between the test and retest results were compared with a paired samples *t*-test. Test-retest reliability was assessed by calculating the variability of difference scores, measured as the within-subjects standard deviation of the difference scores (σ_w) with the formula

$$\sigma_w = \sqrt{\frac{1}{2}\sum_{i=1}^{n}\frac{(x_{i1} - x_{i2})^2}{n}}$$

where x_{i1} is the i^{th} difference score (ASSR – BHT) of the first ASSR session, x_{i2} is the i^{th} difference score of the second ASSR session (the retest) and n is the total number of difference scores to compare. For six subjects and eight threshold comparisons per subject, n is 48.

4.3 Results

BHTs measured with the MASTER and the AUDERA set-up for NH and HI subjects are reported in Figure 4.1. For a clear comparison, AUDERA thresholds are corrected to dBSPL. Both measures are highly correlated ($r \geq 0.96$ for all frequencies). The average within-subject differences are within 2 dB for 500 and 1000 Hz and within 1 dB for 2000 and 4000 Hz. The overall within-subject difference is 0 dB with a standard deviation of 7 dB.

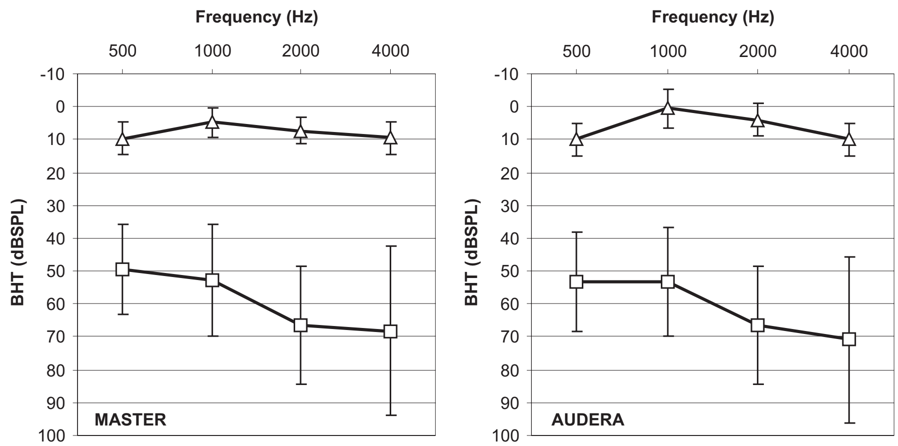


Figure 4.1: Average behavioral hearing thresholds and standard deviations in dBSPL for the normal-hearing (triangles) and hearing-impaired (squares) subjects, measured at the start of the test session with the MASTER and the AUDERA set-up.

The average total test duration for the MASTER test with trials of maximum 16, 24, 32, 40 and 48 sweeps and for the long and short AUDERA test is given in Table 4.2. For AUDERA, the test duration is shorter for the HI compared to the NH. In contrast, test duration with the MASTER system is considerably longer for the HI. However, none of these differences is statistically significant. For both approaches, the variation is larger in the HI group. The longer test duration and greater variability in HI subjects with the MASTER technique is a consequence of the multiple-stimulus approach, which takes more time in sloping audiogram configurations compared to the flat audiograms of the NH subjects, since a higher number of intensity steps needs to be tested.

Table 4.2: Average total test duration, in minutes, for the MASTER test with trails of maximum 16, 24, 32, 40 or 48 sweeps and for the short and long AUDERA test. For the total subject group the short AUDERA test corresponds best with the 24 sweeps MASTER.

	MASTER					*AUDERA*	
	16 sweeps	24 sweeps	32 sweeps	40 sweeps	48 sweeps	short	long
NH	32 ± 7	45 ± 10	58 ± 13	69 ± 17	79 ± 19	46 ± 12	61 ± 10
HI	39 ± 9	55 ± 13	70 ± 17	82 ± 20	95 ± 24	42 ± 16	55 ± 19
Total	36 ± 9	50 ± 12	64 ± 16	76 ± 19	87 ± 22	44 ± 14	58 ± 15

Because a short test duration is important towards the clinical applicability of a technique, the short AUDERA test will be compared to the best matching MASTER condition. In the HI group, the correspondence is best for the 16 sweeps condition and in the NH group for the 24 sweeps condition. However, because it is not advisable to average results of different test protocols, the mean test duration of the total subject group was taken into account. The MASTER 24 sweeps condition corresponds best for the total subject group. The mean within-subject difference between the short AUDERA test and the MASTER 24 sweeps is 6 min, but this difference is statistically not significant (p=0.174).

4.3.1 Short test duration

Each AUDERA test session was started with the ASLEEP protocol. In eight NH and only three HI subjects, ASSR recordings could be carried out at higher modulation rates. At least four recordings (a few minutes), which were characterized as noise, were carried out before switching over to the AWAKE protocol. These recordings were not included in the calculation of the total test duration in contrast with other noise measurements that were included.

On average 35 trials were carried out for the AUDERA test to define four thresholds in both ears. This corresponds to 4 to 5 trials per frequency. MASTER thresholds were all defined at modulation rates between 80 and 110 Hz. A test duration of 45 to 55 min corresponds to 6 or 7 intensity steps lasting for 24 sweeps or approximately 7.5 min each.

For both systems, 160 pairs of BHTs and ASSR thresholds were compared. In instances where BHTs or ASSR responses were absent at the audiometric limits, these comparisons were not included in further data analysis. For both approaches, BHTs as well as ASSR responses were absent in 3 cases. In 5 instances for AUDERA and in 9 instances for MASTER, BHTs were present, but ASSR responses were absent. In these cases, BHTs were on average 86 dBSPL for AUDERA (range 69-96 dBSPL) and 88 dBSPL for MASTER (range 70-100 dBSPL). The elimination of these few cases with missing data (about 6% of the total) was not considered to have a significant effect on the overall findings.

The mean differences between the measured ASSR thresholds and the corresponding BHTs are reported in Table 4.3.

Table 4.3: Mean difference scores and standard deviations (in dB) of the ASSR threshold (measured at 10-dB precision) and the corresponding behavioral threshold (measured at 5-dB precision) for 20 normal-hearing (NH) and 20 hearing-impaired (HI) ears after a test duration of on average 50 and 44 min for MASTER and AUDERA respectively.

		500 Hz	*1000 Hz*	*2000 Hz*	*4000 Hz*	*Total*
MASTER	NH	24 ± 11	17 ± 9	14 ± 7	21 ± 11	19 ± 10
	HI	17 ± 12	12 ± 8	17 ± 8	19 ± 12	16 ± 10
	Total	21 ± 12	14 ± 8	16 ± 7	21 ± 11	18 ± 10
AUDERA	NH	48 ± 21	40 ± 21	33 ± 10	30 ± 20	38 ± 20
	HI	20 ± 8	14 ± 7	13 ± 7	14 ± 13	15 ± 9
	Total	34 ± 21	27 ± 20	24 ± 13	23 ± 19	27 ± 19

The relationship between BHTs and ASSR thresholds for 20 NH and 20 HI ears is shown in Figure 4.2. The data have been fitted with regression lines. Regression equations are shown in Table 4.4, together with the correlation coefficients calculated for each of the carrier frequencies, R^2 and the standard errors of the estimate. The use of linear regression for these AUDERA results is ambiguous, since the relation between ASSR thresholds and BHTs is not linear. The prediction should be based on a different regression equation for NH and HI subjects. However, if these objective techniques are used for threshold prediction in clinical practice, it is not known beforehand if the patient is normal-hearing or hearing-impaired.

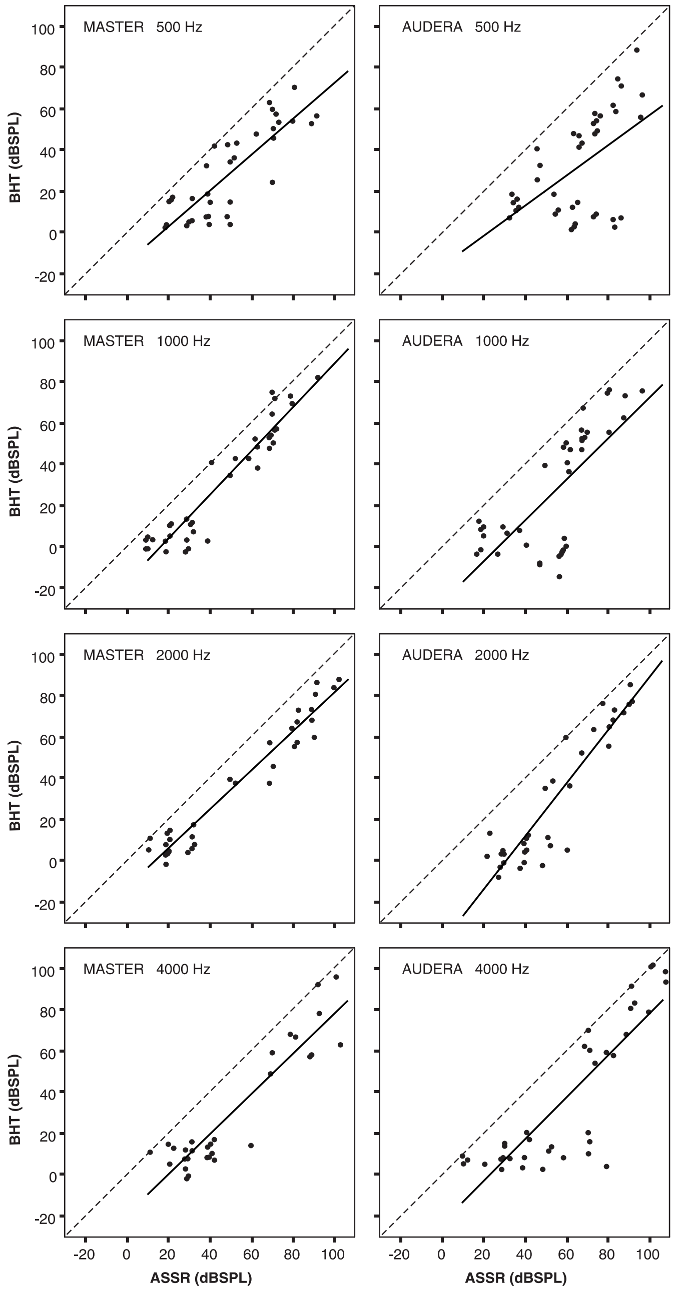


Figure 4.2: Scatter plots of the ASSR thresholds (after test durations of on average 50 and 44 min) as a function of the corresponding behavioral hearing thresholds (BHT) for 20 normal-hearing and 20 hearing-impaired ears per frequency. Points are jittered for 5% to show overlapping of the data. Behavioral hearing thresholds and ASSR thresholds determined with the AUDERA set-up are corrected to dBSPL. The dashed lines represent the lines of equality.

Table 4.4: Comparison of the 24 sweeps MASTER and the short AUDERA test for the total subject group. Frequency-specific regression equations, Pearson correlation coefficients, R^2 and the standard error of the estimate are given.

	Frequency (Hz)	*Regression equation*	*Correlation*	R^2	*Std. error of the estimate (dB)*
MASTER	500	BHT = -14.29 + 0.87 * ASSR	0.83	0.69	12
	1000	BHT = -16.45 + 1.05 * ASSR	0.95	0.91	8
	2000	BHT = -12.63 + 0.94 * ASSR	0.97	0.95	7
	4000	BHT = -19.33 + 0.97 * ASSR	0.93	0.86	11
AUDERA	500	BHT = -17.21 + 0.73 * ASSR	0.54	0.29	21
	1000	BHT = -26.74 + 0.99 * ASSR	0.72	0.52	20
	2000	BHT = -39.28 + 1.28 * ASSR	0.92	0.85	12
	4000	BHT = -22.85 + 1.01 * ASSR	0.85	0.71	19

Table 4.5: Distribution of the absolute differences between the predicted hearing thresholds and the behavioral hearing thresholds for the total subject group (NH + HI) and for the hearing-impaired group alone (HI). Behavioral hearing thresholds are predicted based on the formulae in Table 4.4 for the total subject group and in Table 4.6 for the hearing-impaired group.

	NH + HI		HI	
	MASTER	*AUDERA*	*MASTER*	*AUDERA*
≤ 5 dB	41%	25%	56%	54%
≤ 10 dB	70%	42%	78%	81%
≤ 15 dB	90%	59%	94%	94%
≤ 20 dB	97%	72%	97%	99%
> 25 dB	0%	19%	0%	1%

An overall correlation coefficient of 0.926 and 0.766 is obtained with the MASTER and AUDERA approach respectively. The formulae in Table 4.4 can be used to predict BHTs from ASSR thresholds. The distribution of the absolute behavioral prediction errors, obtained by subtracting the predicted BHT from the actual BHT, is given in Table 4.5.

For the total subject group, the raw difference scores of MASTER are on average 10 ± 18 dB lower than those of AUDERA. This difference is highly significant (paired samples *t*-test, $p \leq 0.001$). The difference between the correlation coefficients was evaluated using the Fisher z_r transformation. Probabilities for the differences were 0.014, ≤0.001, 0.016, 0.129 for 500, 1000, 2000 and 4000 Hz respectively, and $p \leq 0.001$ for the difference between the overall correlation coefficients. For the total subject group, the MASTER technique outperforms the AUDERA technique.

By visual inspection of the regression plots and based on the results in Table 4.3, it becomes clear that there is a discrepancy between the AUDERA results of the NH and the HI group. For all frequencies, the difference scores are significantly higher in the NH group than in the HI group (independent samples *t*-test, *p* always <0.01). Moreover, variability of the difference scores is higher and data points are more scattered in the NH group. This deteriorates the results of the total subject group for the AUDERA approach. For the MASTER technique, difference scores are not significantly different between NH and HI subjects for all frequencies (*p* always >0.05).

4.3.2 Hearing-impaired subject group

Raw difference scores between ASSR thresholds and BHTs for the HI group, as given in Table 4.3, are not significantly different between MASTER and AUDERA (paired samples *t*-test, mean difference is 0 ± 11 dB, $p=0.957$). Table 4.6 shows the regression equations based on the data of the HI group only. Frequency-specific correlations for AUDERA are all equal to, or slightly higher than, those for MASTER. The largest difference is apparent at 500 Hz. The data range at this frequency is rather small, which affects the correlation coefficient, especially for the MASTER data. The difference between the correlation coefficients was evaluated using the Fisher z_r transformation. Probabilities for the differences were 0.124, 0.749, 0.952, 1.000 for 500, 1000, 2000 and 4000 Hz respectively. The overall correlation coefficient between the estimated thresholds and the real BHTs is 0.879 and 0.896 for MASTER and AUDERA respectively. These are also not significantly different ($p=0.682$).

The behavioral prediction errors range from -18 to 34 dB for AUDERA and from -18 to 25 dB for MASTER, the standard error of the estimate is 8.4 dB for AUDERA and 8.6 dB for MASTER. The distribution of the absolute behavioral prediction errors in the HI group is given in Table 4.5, and is very similar for both techniques. More than 50% of the predicted hearing thresholds is within 5 dB of the real hearing threshold and 94% is within 15 dB. The mean absolute behavioral prediction error is 6 ± 6 dB for both techniques.

Table 4.6: Comparison of the 24 sweeps MASTER and the short AUDERA test for the hearing-impaired subject group. Frequency-specific regression equations, Pearson correlation coefficients, R^2 and the standard error of the estimate are given.

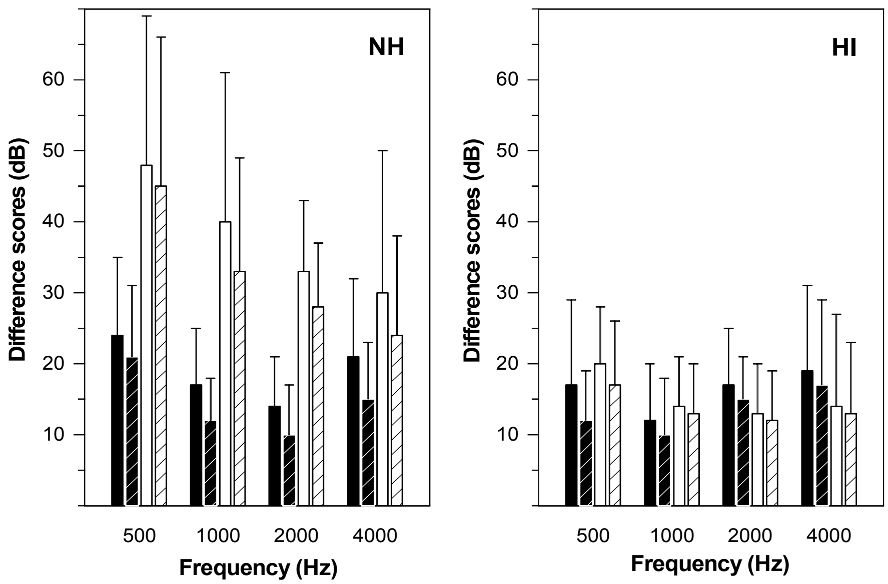
	Frequency (Hz)	*Regression equation*	*Correlation*	*R²*	*Std. error of the estimate (dB)*
MASTER	500	BHT = -16.43 + 0.48 * ASSR	0.64	0.41	9
	1000	BHT = -17.12 + 1.08 * ASSR	0.89	0.80	8
	2000	BHT = -17.06 + 1.00 * ASSR	0.89	0.79	8
	4000	BHT = -27.17 + 1.10 * ASSR	0.88	0.78	12
AUDERA	500	BHT = -8.82 + 0.84 * ASSR	0.86	0.74	8
	1000	BHT = -7.39 + 0.90 * ASSR	0.91	0.83	7
	2000	BHT = -15.96 + 1.04 * ASSR	0.90	0.80	8
	4000	BHT = -28.10 + 1.20 * ASSR	0.88	0.78	12

4.3.3 Increase of test duration

MASTER thresholds were calculated for different maximum numbers of collected sweeps per intensity. Mean difference scores and standard deviations gradually decrease from 21 ± 10 dB after 16 sweeps to 15 ± 9 dB after 48 sweeps in the NH group and from 18 ± 11 dB to 13 ± 9 dB in the HI group.

It was sometimes very difficult to prolong the AUDERA test, especially in the HI group, because noise levels increased and exceeded the noise criterion. Thus, recordings were characterized as ‘noisy’. This problem rather typifies the commercial implementation of the technique than the technique itself. In the NH group, the increase in test duration had a larger effect compared to the HI group. Difference scores and standard deviations decrease. Averaged over the four frequencies the mean difference scores decrease from 38 ± 20 dB to 33 ±17 dB in the NH group and from 15 ± 9 dB to 14 ± 8 dB in the HI group.

Mean difference scores per frequency for different test protocols, separated for the NH and HI subject group, are depicted in Figure 4.3. The graph clearly shows the difference between MASTER and AUDERA for the NH subjects and the similar results obtained in the HI group.



MASTER 24 sweeps MASTER 48 sweeps AUDERA short AUDERA long

Figure 4.3: The influence of test duration for the normal-hearing (NH) and hearing-impaired (HI) subject group. Bars show the mean difference between the ASSR threshold and the corresponding behavioral hearing threshold. Error bars show one standard deviation of the mean. MASTER is represented in black, AUDERA in white. Solid bars represent the 24 sweeps MASTER and the short AUDERA test, which have a comparable test duration. Shaded bars represent the 48 sweeps MASTER test of on average 87 min and the long AUDERA test of approximately 60 min.

4.3.4 Test-retest reliability

Test-retest reliability was assessed for AUDERA and MASTER. Difference scores (ASSR – BHT) of the test and retest were compared with a paired samples *t*-test. Table 4.7 shows the mean differences between the test and retest results and the associated standard deviations. As a reference, BHTs of the test and retest were compared. None of the differences were significant.

To define the reliability, the variability defined as the within-subjects standard deviation of the difference scores was calculated (see also Table 4.7). The reliability is higher for MASTER. However, for AUDERA there is a big difference between both subject groups. The variability is 13 dB in the NH group in contrast with 8 dB in the HI group. Moreover, there is a large effect of test duration, especially in the

NH group. The variability decreases to 9 dB and 7 dB for the NH and HI group respectively. For MASTER, the reliability is comparable between the subject groups and also between the different lengths of recordings.

Table 4.7: Comparison of the test and retest of the 24 sweeps MASTER and the short AUDERA test. Difference scores (ASSR – BHT) of the test and retest are compared with a paired samples *t*-test. Variability of the difference scores is given.

	Mean difference (dB)	*Significance (2-tailed)*	*Variability (dB)*
ASSR MASTER	-1 ± 9	0.489	6
ASSR AUDERA	0 ± 16	0.901	11
BHT MASTER	1 ± 4	0.243	3
BHT AUDERA	0 ± 6	0.726	4

4.4 Discussion

In this study, a single-stimulus and multiple-stimulus ASSR approach were compared in similar test conditions. For the total subject group, which consisted of 10 normal-hearing and 10 hearing-impaired subjects, the MASTER approach predicted behavioral hearing thresholds with more accuracy than the AUDERA technique in the same amount of testing time. MASTER could predict hearing thresholds in NH and HI subjects with a similar accuracy. For AUDERA, however, results were very different for both groups. Performance was better in HI subjects. When comparing the MASTER and AUDERA technique for HI subjects only, similar results were obtained. BHTs could be predicted based on the ASSR thresholds with a standard error of the estimate of 7 to 12 dB dependent on frequency. About 55% of the estimations was within 5 dB of the real behavioral threshold, 94% was within 15 dB. Clearly, the composition of the subject group had a big influence on ASSR results obtained with the AUDERA set-up. Outcomes obtained in NH subjects cannot always be used to predict performance in HI subjects, although this often has been done in ASSR research. Additionally, one has to be cautious when using adult data for predicting performance in young children.

4.4.1 Estimating hearing thresholds

Previous studies have investigated multiple-stimulus ASSR thresholds in normal-hearing (Dimitrijevic et al., 2002; Herdman & Stapells, 2001; Perez-Abalo et al., 2001) and hearing-impaired adults (Dimitrijevic et al., 2002). Reported variability of the results (standard deviations of the difference scores) is comparable to the current data. The difference scores, however, are lower than in the present study. The lower difference scores in Perez-Abalo et al. (2001) are probably the result of elevated behavioral hearing thresholds that are the consequence of the high environmental noise levels. In that study, behavioral hearing thresholds of normal-hearing subjects were on average 16 dB higher than in the current study. In the studies of Dimitrijevic et al. (2002) and Herdman & Stapells (2001) test duration was considerably longer, which may have influenced the difference scores. The correlation coefficients in our study are very similar to those reported in Dimitrijevic et al. (2002). The longer test duration apparently affects particularly the difference score, and to a smaller extent the variability of the data. This has also been observed in the current study. Extending the test duration from 16 to 48 sweeps per trial in this study has changed the difference scores and standard deviations from 21 ± 10 dB to 15 ± 9 dB. For the multiple-stimulus technique, difference scores are elevated for 500 and 4000 Hz. This has also been reported in previous studies (Herdman & Stapells, 2001; Dimitrijevic et al., 2002).

As can be deduced from the studies of Rance and colleagues (Rance et al., 1995; Rance et al., 1998; Rance & Briggs, 2002), single-stimulus ASSR results can vary substantially, dependent on the degree of hearing loss. Composition of the subject group will thus be a determining factor. Rance & Briggs (2002) compared behavioral hearing thresholds and ASSR thresholds in subjects with moderate to profound hearing loss. Correlations coefficients ranged from 0.81 to 0.93. This agrees well with the correlations found in the HI subjects of the present study. For the total subject group of normal-hearing and hearing-impaired subjects, correlation coefficients are lower in the present study. In Rance et al. (1995), however, subjects with hearing thresholds ranging from normal to profound were tested and correlations ranged from 0.97 to 0.99. This is due to the relatively limited number of subjects with hearing thresholds below 10 dBHL in contrast to the normal-hearing group tested in the current study. Particularly in this group, ASSR thresholds measured with the AUDERA are extremely variable. Moreover, the very wide range of ASSR levels in Rance et al. (1995), from approximately 20 to 120 dBHL, has also a positive effect on the correlation coefficient.

4.4.2 Different parameter settings

In this study, the total test duration of both techniques was kept approximately equal. Since the multiple-stimulus technique is estimated to be two to three times faster than a single-stimulus approach using the same MASTER system (John et al., 2002) and MASTER and AUDERA perform equally well in HI subjects within the same test duration, AUDERA appears to be relatively faster. For NH subjects, however, AUDERA performs worse. These differences between MASTER and AUDERA may, in part, be caused by different parameter settings. In general, the manufacturer's advice was followed as much as possible, since this was considered the optimal way to use the device and this is how it will be used by most clinicians who purchase the device. In this way, the total MASTER approach was compared to the total AUDERA approach. Besides the number of signals simultaneously presented, the techniques compared in this study also differ on other parameters, such as stimulus levels, modulation rate, electrode montage, response detection algorithm and test duration per tone frequency-intensity combination.

First, the AUDERA set-up was calibrated in dBHL by the manufacturer and the MASTER set-up was calibrated in dBSPL. Consequently, stimulus levels for both systems were not equivalent. However, according to the ISO 389-2 for insert phones dBHL levels are within 0 to 5.5 dB of the dBSPL levels for frequencies between 500 and 4000 Hz. Moreover, ASSR thresholds were always compared to behavioral hearing thresholds in the same units (dBHL or dBSPL) and difference scores were calculated. In this way, issues related to calibration and to differences in hearing level at the time of testing were eliminated. Second, for AUDERA, an alternative test protocol was used in cases of excessive noise levels, which included a slower modulation rate and a higher noise criterion. This disparity in modulation rates complicates the interpretation of the results, since the modulation rate has an influence on the activated intracerebral generator (Herdman et al., 2002), on the size of the response and on the effect of sleep or drowsiness (Cohen et al., 1991). However, the comparison of 40-Hz or 80-Hz modulation frequencies is beyond the scope of this study. The 40-Hz modulation rate was only used in case of noise levels that exceeded the noise criterion and this would bias the results of the comparison. Third, the electrode montage was different for MASTER and AUDERA. In ASSR research, electrode positions typically used in case of monaural stimulation include the mastoid position and, in case of binaural stimulation, electrodes are placed on the midline. According to van der Reijden and colleagues (2001) a significantly larger SNR was found for the Cz-inion derivation compared to the Cz-ipsilateral mastoid derivation for the 90-Hz modulation rate. Fourth, the response detection method was different for both approaches. According to Picton et al. (2001), the difference between detection protocols based on both phase and amplitude and phase alone is small, so this cannot explain the big difference between MASTER and AUDERA in the NH group. And finally, a very important factor to explain this difference is the test duration for each tone-frequency combination that was relatively larger for the MASTER approach. In HI ears, ASSRs above threshold are relatively larger compared to NH ears and thus faster to detect. This could be the result of recruitment (Picton et al., 2005). Detecting ASSRs at threshold level in NH subjects might require larger EEG samples and consequently a longer test duration.

4.4.3 Advantages and disadvantages

Both techniques to determine hearing thresholds have shown strengths and weaknesses in functionality. The main differences are related to high EEG noise levels, sloping audiogram configurations, and testing subjects with small or no hearing-impairment.

High EEG noise levels

In case of restless patients and high EEG noise levels, the MASTER approach is most advantageous since recordings can be prolonged in order to decrease the noise level and increase the signal-to-noise ratio. In this way, it is always possible to carry out the recordings at modulation frequencies of 80 Hz, also in restless patients. The AUDERA technique allows repeating trials that are too noisy, but this does not influence the noise level or the quality of the measurement. This difference is not related to the single- or multiple-stimulus approach, but rather to the way it is implemented in the software.

In this study, carried out in a double-walled soundproof Faraday cage room, it was often not possible to record at 80 Hz with AUDERA in hearing-impaired subjects (in 7 out of the 10 subjects) because the noise level exceeded the default noise criterion, even in subjects that were asleep. In these cases, the 46-Hz modulation rate was applied. This could be a substantial problem when testing sleeping children since the detection of 40-Hz responses have been found to be affected by sleep (Cohen et al., 1991) and inconsistent in young children (Stapells et al., 1988; Aoyagi et al., 1993; Kraus et al., 1985; Maurizi et al., 1990). The noise criterion seemed too strict for this subject group. It might be advisable to adjust the noise criterion, although this could deteriorate the results.

Sloping audiogram configuration

An advantage of the single-stimulus approach is that audiogram configuration has no influence on test duration. With a multiple-stimulus approach, test duration is considerably lengthened in case of sloping audiogram configurations, when the intensity of frequencies in the stimulus cannot be adjusted separately. First, it is often required to record the maximum number of sweeps per intensity level in hearing-impaired subjects, since often one or more responses do not reach significance. And second, more recordings will have to be registered since the intensity range that has to be tested will be broader. Alternatively, by presenting different stimuli simultaneously, each frequency will be presented at more intensity steps than strictly needed, which can serve as an additional verification of the thresholds. This might positively affect the reliability.

Subjects with small or no hearing-impairment

Both techniques can accurately predict hearing thresholds in hearing-impaired adult subjects. In normal-hearing subjects, however, the AUDERA technique comes short. Since ASSR assessments are in the first place designed to use in hearing-impaired children, as a follow-up to general neonatal hearing screening, this might not seem a problem. However, false positive referrals have to be traced, and therefore it is important that also normal hearing can be assessed. Moreover, the lower modulation frequencies that often had to be applied in this study are not appropriate to test children. In patients with low EEG noise levels, where the hearing loss was first diagnosed with e.g. ABR and normal hearing can be ruled out, the AUDERA can be used to accurately predict the audiogram.

4.5 Conclusions

Both approaches, MASTER and AUDERA, as implemented in commercial products, make it possible to accurately predict frequency-specific hearing thresholds in hearing-impaired adult patients within a clinically acceptable test duration. Hearing thresholds can be predicted with a standard error of the estimate between 7 and 12 dB dependent on frequency. For MASTER and AUDERA, test-retest accuracy is high and performance is improved by prolonging the test duration. The AUDERA is less suited for testing subjects with normal hearing or limited hearing loss. Moreover, EEG noise levels often exceed the noise criterion of the 80-Hz test protocol of AUDERA. This could be a problem when testing sleeping children. The composition of the subject group has a big influence on the results of ASSR studies.

Chapter 5

Objective assessment of frequency-specific hearing thresholds in babies: a pilot study

Luts, H., Desloovere, C., Kumar, A., Vandermeersch, E., & Wouters, J. 2004. International Journal of Pediatric Otorhinolaryngology, 68, 915-926.

Abstract

The objective of this study was to report on our first clinical experience using dichotic multiple-stimulus auditory steady-state responses (ASSRs) as an objective technique to estimate frequency-specific hearing thresholds in hearing-impaired infants.

A comparison was made between the click-evoked auditory brainstem response (ABR), auditory steady-state responses and behavioral hearing thresholds (BHTs). Both ears of 10 infants between 3 and 14 months of age were tested. ABR and ASSRs were recorded during the same test session. ABR was evoked by 100 µs clicks. ASSR thresholds were derived after separate recordings of approximately 5, 7.5 and 10 min to compare the influence of test duration. BHTs were defined in later test sessions as soon as possible after the ASSR test, dependent on medical and developmental factors.

For the subjects tested in this study, 60% of ABR thresholds and 95% of ASSR thresholds for 1000, 2000 and 4000 Hz were found at an average age of 7 months. Only 51% of frequency-specific BHTs could be obtained but on average 5 months later. The correlation of ASSRs and BHTs was 0.92. The mean differences and associated standard deviations were 4 ± 14, 4 ± 11, -2 ± 14 and -1 ± 13 dB for 500, 1000, 2000 and 4000 Hz respectively. The average test duration was 45 min for ABR (one threshold in both ears) and 58 min for ASSR (four thresholds in both ears). By reducing the duration of the separate recordings of ASSR, the precision of the hearing threshold estimate decreased and the number of outlying and missing values increased.

In conclusion, multiple-stimulus ASSRs offer the possibility to estimate frequency-specific hearing thresholds in babies in a time-efficient way.

5.1 Introduction

The target population for objective measures based on electrophysiological recordings are babies and children with suspected hearing loss, who cannot give reliable behavioral responses to auditory stimuli. In this patient group, it is of high importance for the speech and language development to provide adequate amplification as soon as possible. However, most clinical ASSR studies are carried out in adult subjects, with or without hearing loss. The number of studies to investigate the accuracy of hearing threshold prediction in babies and children is limited. The single-stimulus monotic ASSR technique has been evaluated in large groups of hearing-impaired infants at the University of Melbourne (Rance & Briggs, 2002; Rance et al., 1998; Rance & Rickards, 2002; Rance et al., 1995). However, the single-stimulus technique used in these studies differs considerably from the dichotic multiple-stimulus technique, notably with regard to response detection method and recording time per intensity level (for a comparison of both techniques see Chapter 4).

Thresholds obtained with the multiple-stimulus ASSR technique have been evaluated in normal-hearing babies up to 12 months of age (Lins et al., 1996; Savio et al., 2001) and in hearing-impaired children older than 6 years (Perez-Abalo et al., 2001; Swanepoel & Roode, 2004; Picton et al., 1998). To our knowledge, no threshold data are available yet of dichotic multiple-stimulus ASSR testing in hearing-impaired infants younger than one year, although the need for a frequency-specific objective technique is greatest in this target group.

In this chapter, we report on our first clinical experiences with the dichotic multiple-stimulus ASSR technique in young infants. Therefore, hearing thresholds of 10 infants between 3 and 14 months of age with suspected hearing loss, referred to UZ Leuven, were estimated. Based on the results of a previous study (see Chapter 3), a clinical ASSR protocol was developed, which should enable the assessment of a four-frequency audiogram with a reasonable accuracy (a standard error of the estimate of 8 dB) within 1 h. Click-evoked ABR and dichotic multiple-stimulus ASSR were carried out in the same test session. Behavioral hearing thresholds were obtained in later test sessions (at older age), if they could be obtained at all. First, BHTs, ABR and ASSR threshold values were compared. Second, the relation between precision of hearing threshold estimates obtained with ASSR and test duration was investigated. Test duration is an important issue in the search for a reliable objective technique and will be crucial for a more general clinical application of this technique in newborns.

5.2 Methods

5.2.1 Subjects

All infants referred to UZ Leuven for ABR testing under general anesthesia from November 2001 through July 2002 were included in the study (see Table 5.1). Ten infants were tested. Their ages ranged from 3 to 14 months at the time of ABR and ASSR testing, with an average of 7 months. All infants had undergone hearing screening by means of automated ABR at 4 weeks of age. Two babies passed the screening but needed an evaluation of their hearing at a later age because of risk factors. Seven babies failed the hearing screening for both ears, one baby failed in one ear. A first ABR was carried out within 2 weeks of the screening. For various reasons, a follow-up sedated ABR was needed. For this research, ASSR testing was added on to this sedated ABR.

Table 5.1: Overview of the population.

Subject	*Sex*	*Age (months)*	*Screening Left*	*Screening Right*	*Risk factors Medical details*
1	f	7	pass	pass	chemotherapy
2	f	4.5	refer	refer	twins, birth weight less than 1500 grams
3	f	5.5	refer	refer	unknown
4	m	13.5	refer	refer	metabolic disease, blind, developmentally retarded
5	f	10	refer	refer	unknown
6	f	3	refer	pass	cytomegalovirus
7	f	14.5	refer	refer	partial agenesis of the cochlear nerve
8	f	6	refer	refer	mechanical ventilation ≥ 5 days, craniofacial anomalies
9	m	4	refer	refer	unknown
10	m	4.5	pass	pass	cytomegalovirus

Sex (f, female; m, male), age in months, results of hearing screening at 4 weeks of age and risk factors or medical details of importance are shown.

Hearing tests are only carried out under general anesthesia if other attempts to obtain audiometric data failed. Classic sedation e.g. with chloral hydrate is known to be unreliable in this age group because of either too short or prolonged sedation. Kau et al. (1987) showed that the best results for an ABR examination were obtained when general anesthesia was first administered followed by intravenous midazolam. General anesthesia was induced with intramuscular ketamine, followed by a continual infusion of midazolam and clonidine, products known not to affect auditory evoked potentials (AbdulJawad et al., 2001; de Bruin et al., 1999; Hotz et al., 2000). The infants were continuously monitored during the ABR test for heart rate, blood pressure, oxygen saturation, temperature and respiratory rate. They were not intubated and neither was a larynx mask used. They breathed spontaneously, if necessary with added oxygen via a mask. During the ASSR testing, oxygen saturation was monitored with a battery run saturation meter.

The use of the supplementary ASSR testing was approved by the Committee of Medical Ethics of Clinical Research of the K.U.Leuven. This research project was in accordance with the Helsinki Declaration. Informed consent was obtained from a parent to conduct an additional audiometric test, namely the ASSR.

5.2.2 Experimental design

5.2.2.1 Stimulation and recording parameters

An overview of the ASSR test set-up and stimulus and recording parameters can be found in section 2.2.

The ABR was recorded with a Madsen ERA 2260 brainstem evoked response audiometer. Clicks of 100 μs in duration were presented at a rate of 21 per second with alternating polarity. For the recording of the ABR, Kendall silver-silver chloride electrodes were placed at the forehead and the mastoids. Electrode impedance was always smaller than 5 kOhm at 30 Hz. Filter settings of 100 to 3000 Hz (6 dB/octave) were applied. Data were collected in time windows of 12 ms. At each presentation level 2000 sweeps were averaged.

Click signals were calibrated in dBpeSPL for ER-3A insert phones with a 2-cc coupler (Brüel & Kjaer DB 0138), an amplifier (Brüel & Kjaer 2610) and a 50-MHz scope meter (Fluke 97). As a reference, ABR thresholds were assessed in 20 normal-hearing adult ears (hearing thresholds less than 20 dBHL for 1000, 2000 and 4000 Hz) for ER-3A insert earphones. The average ABR threshold was 41 dBpeSPL. This means that the maximum stimulation level of 130 dBpeSPL was approximately 90 dB above the normal-hearing threshold. In this subject group, the mean pure-tone threshold at 2000 Hz was 3.5 dBHL for insert phones.

Frequency-specific behavioral hearing testing of the infants was carried out in later test sessions, as soon as behavioral responses to auditory stimuli could be assessed. Time of testing differed among infants. For the infants where frequency-specific behavioral testing yielded usable data (for 7 out of 10 infants), results were obtained up to twelve months later. For one infant (subject 3) behavioral thresholds could be obtained at the age of 5.5 months. Developmental age and medical status were determining factors. Tests were carried out at an average age of 11.5 months. Behavioral observation audiometry (BOA) or visual reinforcement audiometry

(VRA) was carried out using a clinical audiometer with EAR-Tone 3A insert phones or in free-field conditions with a Kenwood LS-34 loudspeaker. In both cases, warble tones were presented. Behavioral thresholds obtained in free-field were compared to evoked potential thresholds of the best ear. Thresholds were defined in dBSPL. A 5-dB up and 10-dB down search method was used. Tests were carried out in a sound-attenuated room.

5.2.2.2 Test procedure for ABR and ASSR testing

All subjects received otoscopic examination by an ENT physician. Cerumen was removed if necessary. In case of suspicion of abnormal middle ear function, tympanometry was carried out.

ABR recordings were always carried out first. Electrodes were applied, electrode impedance was measured and thresholds were defined for both ears. Then new electrodes were applied for ASSR testing. Thresholds for four frequencies in both ears were determined. For both techniques, the acoustical stimuli were presented by means of ER-3A insert earphones.

Due to timing restrictions, ABR and ASSR thresholds were defined at 10-dB precision. ABR testing was started at 100 dBpeSPL. Responses were determined by visual inspection of the ABR waveforms. The stimulus level was decreased with 10 dB until no wave V could be detected. The threshold was defined at the lowest level at which an ABR was present. ASSR thresholds were determined with a 10-dB up and 20-dB down method. Starting intensity was 60 dBSPL. A threshold was defined as the lowest intensity level where a significant response was obtained. The maximum presentation level was 110 dBSPL.

ASSR recordings were carried out in multiples of 8 sweeps. If responses to all stimuli were significant after 8 sweeps, recordings were stopped. If one or more response was not significant after 8 sweeps, 16, 24 or 32 sweeps were recorded. In most cases, the maximum number of sweeps had to be recorded because of differences in threshold between both ears and the different carrier frequencies. If significance was not reached after averaging 32 sweeps, a non-response was assumed. After 16, 24 and 32 sweeps, the test leader noted if the eight responses were significant or not. In this way, it was possible to determine what the thresholds for the different stimuli would be after recordings with a maximum number of sweeps of 16, 24 or 32. A recording of 8 sweeps lasted minimally 2.2 min but taking into account the 5 to 10% rejected epochs, this resulted in approximately 2.5 min.

5.2.3 Data analyses

In all ears, ABR-measurements were carried out. ABR thresholds were compared to the ASSR threshold at 2000 Hz. ASSR thresholds were compared to the available corresponding BHT-information.

Differences between thresholds were compared with paired-samples *t*-tests. The linear relationship between two variables was evaluated using Pearson correlation coefficients and linear regression analyses. R^2 describes the amount of variance of the dependent variable (BHT) which is accounted for by the independent variable (ASSR threshold). Statistical analyses were carried out with the 10.0 SPSS software.

5.3 Results

Results of the 20 tested ears are shown in Table 5.2. In total 20 ABR and 77 ASSR thresholds were assessed. The remaining three ASSR thresholds could not be assessed because of time constraints. In eight cases out of 20 no ABR threshold and in 10 cases out of 77 no ASSR threshold was found at the maximum presentation level. This meant that 12 ABR and 67 ASSR thresholds were included in further analyses. In 7 out of 10 infants, frequency-specific BHTs were obtained, resulting in 41 thresholds.

5.3.1 Comparing ABR and ASSR thresholds

ABR thresholds were compared to the ASSR thresholds at 2000 Hz, since the spectrum of the click stimulus contains most energy at frequencies around 2000 Hz. Twelve threshold comparisons were made. The Pearson correlation coefficient was 0.77 (p=0.004). The scatter plot (Figure 5.1) shows a linear relationship between the two variables. Linear regression analysis was used to evaluate the correlation between the ABR threshold and the ASSR threshold at 2000 Hz. Only 58% of the variance of the ABR threshold was explained by its linear relationship with the ASSR threshold. The intercept was 34.5 dB and the slope 0.76. There was one outlying value of the left ear of subject 2. When this value is omitted, the Pearson correlation becomes 0.93 ($p \leq 0.001$). The linear regression equation would have an intercept of 23.6 dB and the slope would become 0.88.

In eight ears, no ABR threshold could be defined. Even at 130 dBpeSPL no peak V could be identified. For each of these ears, ASSR thresholds were found for 1000 and 2000 Hz. In total 23 ASSR thresholds could be defined, varying from 40 to 110 dBSPL.

Table 5.2: Thresholds obtained with three different audiometric test methods for both ears of 10 infants

Subject	*Test*	*Age (months)*	*Left*				*Right*			
			500 Hz	*1000 Hz*	*2000 Hz*	*4000 Hz*	*500 Hz*	*1000 Hz*	*2000 Hz*	*4000 Hz*
1	ASSR	7	40	20	10	40	70	60	60	80
	ABR	7			40				70	
	BHT	19	50	35	25	35				
2	ASSR	4.5	50	40	30	30	60	40	40	70
	ABR	4.5			110				-	
	BHT	12	30	25	30	25				
3	ASSR	5.5	-	110	110	90	-	90	95	100
	ABR	5.5			-				-	
	BHT	5.5	120	120	-	-	125	90	125	125
4	ASSR	13.5	-	110	90	-	80	80	90	90
	ABR	13.5			-				80	
	BHT									
5	ASSR	10	-	90	85	110	-	80	90	90
	ABR	10			-				-	
	BHT									
6	ASSR	3	-	100	100	-	-	100	80	100
	ABR	3			-				-	
	BHT	8	120	100	105	115	95	90	85	105
7	ASSR	14.5	100	100	80	-	110	80	100	100
	ABR	14.5			110				120	
	BHT	15.5	95	80	70	80	95	70	80	85
8	ASSR	6		80	80	70	80	80	60	70
	ABR	6			100				80	
	BHT	9.5	75	70	70	65		70	60	60
9	ASSR	4		50	30	50		30	30	30
	ABR	4			40				40	
	BHT									
10	ASSR	4.5	50	30	20	20	40	30	20	20
	ABR	4.5			40				50	
	BHT	11					50	40	30	35

When no threshold was found, this was indicated with '-'. When thresholds were not measured, the space was left blank. ABR thresholds are indicated at 2000 Hz because correlation of ABR thresholds and BHTs is highest at 2000 Hz. In subject 1, 2 and 10 BHTs are measured in free-field conditions. Thresholds are indicated at the best ear.

ASSR, Auditory steady-state response in dBSPL; ABR, Auditory brainstem response evoked by clicks in dBpeSPL; BHT, Behavioral hearing threshold in dBSPL.

5.3.2 Comparing BHTs and ASSR thresholds

In seven infants, reliable frequency-specific BHTs were obtained. In three infants, (subject 1, 2 and 10) tests were carried out in free-field conditions and thresholds were consequently not ear-specific. BHTs were compared to the ASSR thresholds of the best ear. In four other infants insert phones were used, so that ear-specific information could be obtained. In total, 41 thresholds in 11 ears were assessed. In six cases, no corresponding ASSR threshold could be found at the maximum presentation level. In one case, the ASSR threshold was not assessed. When no ASSR could be recorded at 110 dBSPL, the BHT was between 80 and 125 dBSPL, with an average of 109 dBSPL.

In total, 34 BHTs could be compared to the corresponding ASSR thresholds. The mean difference between both measures was 0.9 dB (SD 12.8 dB). This difference was not significant (p=0.691). Difference scores ranged from –30 to 20 dB. Of the absolute differences 68% were within 10 dB, 94% were within 20 dB. The scatter plot in Figure 5.2 shows a linear relationship between the ASSR threshold and the BHT. The three data points in the right upper corner are of subject 3. BHTs were higher than expected. This could be explained by the young age at which behavioral testing was carried out. The infant was only 5.5 months old. Actual hearing thresholds will probably be lower than these minimum response levels. Nevertheless, a clear linear relationship could be observed. Frequency-specific correlations (and associated p-values) were 0.92 (p=0.029), 0.93 ($p \leq 0.001$), 0.91 ($p \leq 0.001$) and 0.93 (p=0.001) for 500, 1000, 2000 and 4000 Hz respectively. The overall Pearson correlation was 0.92 ($p \leq 0.001$). Linear regression analysis resulted in a slope of 0.89 and an intercept of 6.8 dB. R^2 was 0.84. Difference scores (and SD) for the separate frequencies were 4 ± 14 dB, 4 ± 11 dB, -2 ± 14 dB and -1 ± 13 dB for 500, 1000, 2000 and 4000 Hz respectively. The time delay between both measures was between 0 and 12 months, with an average of 5 months.

5.3.3 Test duration

Comparing BHTs and ASSR thresholds after recordings of maximum 16, 24 or 32 sweeps (corresponding to 5, 7.5 and 10 min) showed that the precision of the hearing threshold estimate changed. A decrease in test duration was associated with an increase in the difference scores between BHTs and ASSR thresholds and an increase in the standard deviations (see Table 5.3). The linear relationship between BHTs and ASSR thresholds represented by the Pearson correlation coefficient decreased, which dramatically affected R^2. The number of missing and outlying values increased. In Figure 5.3, the distribution of the absolute difference scores between the ASSR threshold and the corresponding BHT is shown. After recordings of 32 sweeps, 10 out of 77 values were missing and two difference scores exceeded 20 dB. After 24 sweeps, 10 values were missing but five difference scores were higher than 20 dB. After 16 sweeps, 13 values were missing and six difference scores exceeded 20 dB. The maximum difference was 30 dB after recordings of 32 and 24 sweeps and 55 dB after 16 sweeps.

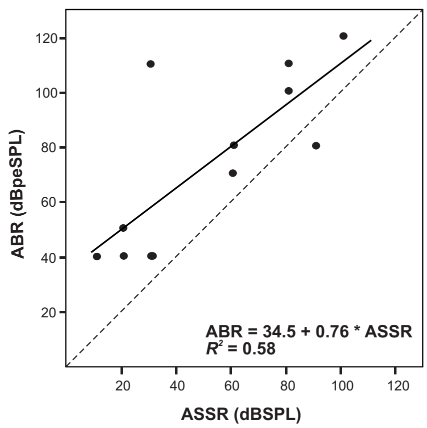


Figure 5.1: Scatter plot for the ASSR threshold at 2000 Hz and the ABR threshold. Results of 12 ears are included. The regression equation and R^2 are shown in the plot. The line of equality is represented by the dashed line.

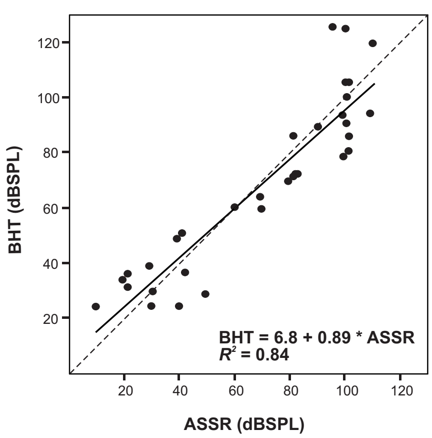


Figure 5.2: Scatter plot for the ASSR threshold and the corresponding BHT. Results of 34 threshold comparisons are included. The regression equation and R^2 are shown in the plot. Points are jittered for 3% to show overlapping of the data. The line of equality is represented by the dashed line.

Table 5.3: Relation between BHTs and ASSR thresholds after separate recordings of maximum 16, 24 and 32 sweeps.

	16 sweeps	*24 sweeps*	*32 sweeps*
Mean difference score ± SD	7 ± 17 dB	4 ± 14 dB	1 ± 13 dB
Pearson correlation coefficient	0.83	0.89	0.92
R^2	0.69	0.80	0.84

Defining the ABR threshold in both ears took on average 45 min (standard error of the mean of 2 min). ASSR thresholds after recordings of maximum 32 sweeps at 4 frequencies in both ears were on average determined in 58 min (standard error of the mean of 4 min). The average difference between both measurements was 14 min (p=0.005). In this extra time, thresholds were defined at 4 frequencies for both ears with an extended range compared to ABR. However, the recording time of ABR is linked to the click rate, which could be increased.

If only a maximum of 16 or 24 sweeps would be recorded (corresponding to 5 and 7.5 min), the average total test duration would be about 30 and 45 min respectively.

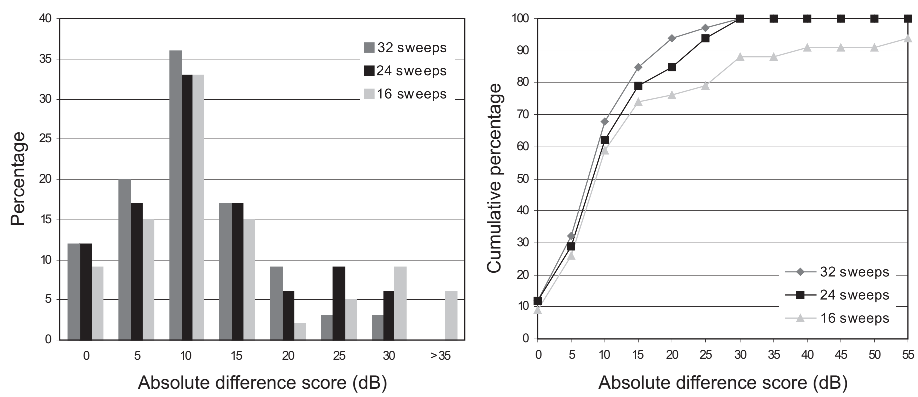


Figure 5.3: Distribution and cumulative distribution of the absolute difference scores between the ASSR threshold and the corresponding BHT after recordings with a maximum number of sweeps of 32, 24 and 16 for the 20 tested ears and all tested frequencies.

5.4 Discussion

The results of this study indicate that the dichotic multiple-stimulus ASSR technique can provide reliable estimates of BHTs in babies, within a reasonable testing time. We have been able to obtain ABR thresholds in 60% of the cases, ASSR thresholds in 84% of the cases averaged over the four frequencies and in 95% of the cases for 1000, 2000 and 4000 Hz. Approximately 5 months after ASSR testing, only 51% of the BHTs could be determined.

5.4.1 Hearing threshold estimates

Several studies have been conducted to evaluate the dichotic multiple-stimulus ASSR technique in adults and children. However, the target group for this objective audiometric test are infants younger than 1 year. Due to the introduction of neonatal hearing screening programs, the group of young children requiring audiometric evaluation is growing and standard behavioral techniques cannot always be applied. No previous study was published about the feasibility of dichotic multiple ASSRs in young hearing-impaired children.

The current study showed a very strong relation between BHTs and ASSR thresholds. Difference scores between BHTs and ASSR thresholds were between -2 and 4 dB. This is lower than reported for adults (Lins et al., 1996; Dimitrijevic et al., 2002; Perez-Abalo et al., 2001). If the size of the discrepancy between ASSR and BHT is known, BHT can be predicted from ASSR results. A more important issue is the variability of the results or the standard deviation of the mean discrepancy. In the present study, standard deviations ranged from 11 to 15 dB. This is slightly higher than reported in studies with adult subjects (Lins et al., 1996; Perez-Abalo et al., 2001; Dimitrijevic et al., 2002). The lower difference scores and higher standard deviations are probably due to the fact that there is a higher variability of the BHTs in young children. The correlation of 0.92 in this study corresponds to the one reported for adults in Dimitrijevic et al. (2002). Thresholds obtained with the dichotic multiple-stimulus ASSR technique provide a good basis for the fitting of hearing aids.

In a few studies, thresholds have been obtained in young hearing-impaired children with a monaural single-stimulus ASSR technique (Rance et al., 1995; Rance & Briggs, 2002; Cone-Wesson et al., 2002a; Rance & Rickards, 2002). Variability of the results differs between those studies, but this is of course related to several methodological factors. Cone-Wesson et al. (2002a) report standard deviations between 14 and 15 dB. In Rance & Briggs (2002) standard deviations vary between 6 and 17 dB, dependent on degree of hearing loss. Although the same test methods are used in the studies of Rance and Cone-Wesson, there are rather large differences between the reported correlation coefficients. Consequently, R^2 or the amount of variance of the dependent variable (BHT) which is accounted for by the independent variable (ASSR threshold) differs even more between the different studies. Correlations between ASSR and BHT reported by Cone-Wesson et al. (2002a) range from 0.77 to 0.88. Dependent on subject group, Rance and colleagues found correlations between 0.81 and 0.93 (Rance & Briggs, 2002) and between 0.96 and 0.99 (Rance et al., 1995; Rance & Rickards, 2002).

Correlations found in the present study are relatively high in view of the small data set, even for the frequency-specific comparisons. Moreover, correlations between ASSRs and BHTs are clearly higher when the same carrier frequencies are compared than when different carriers are compared. This indicates that ASSR provides information about audiometric configuration.

The difference scores are largest in the lower frequencies, but standard deviations are similar. These elevated thresholds at 500 Hz were also found in other studies (Lins et al., 1996; Perez-Abalo et al., 2001; Dimitrijevic et al., 2002). This discrepancy may be related to issues of neural synchrony. There is likely more phase dispersion in the neurons responding to the low-frequency sounds caused by the slowly changing stimulus and the broader region of activation on the basilar membrane. The phase dispersion would decrease the time-locked summation of responses (Dimitrijevic et al., 2002).

The weakness of this study may be the small number of subjects. In addition, the BHTs in some subjects are rather minimum response levels than real hearing thresholds and are therefore more variable. These factors will have a negative effect on the results. Nevertheless, a strong relation was found between ASSRs and BHTs.

Tests were carried out under general anesthesia, because it was a very specific subject group of difficult-to-test children. A study of Rance and colleagues (1995) showed that the relationship between behavioral thresholds and ASSR thresholds is not influenced by subject state. No significant difference was found between subjects in natural sleep, under the sedative chloral hydrate or under a general anesthetic. Of course, there are important practical implications. Testing during natural sleep is preferred and is most feasible in babies younger than 3 months. Because of the general neonatal hearing screening, it should be possible to carry out the ASSR testing between the age of 1 and 3 months.

5.4.2 Test duration

As shown in this study, the precision of a hearing threshold estimate based on ASSR recordings in infants is enhanced by prolonging the test duration. This is due to the signal-to-noise ratio enhancement obtained by averaging separate recordings.

Moreover, a smaller number of non-responses will occur. This is in accordance with the results found in adults, as presented in Chapter 3. Although a short test duration is crucial in clinical practice, a high degree of precision should be aimed for. Therefore, a compromise should be found between precision and test duration.

In this study, realistic recording times are reported instead of theoretical estimates. In clinical practice, hearing thresholds of a patient are unknown. As a consequence, more intensity steps may be needed. Moreover, testing babies in clinical practice involves more practical difficulties than testing adults in an experimental setting. These factors will result in an increased recording time.

5.4.3 Comparison of ABR and ASSR

Clicks have a broad frequency spectrum and therefore the click-evoked ABR may reflect contributions to the response from a wide area of the basilar membrane. When a hearing impairment is restricted to a particular frequency region, the click-evoked ABR will often miss the loss or substantially underestimate the degree of the loss. Consequently, for individual patients, the click-ABR should not be used as an estimate for the 2000 Hz threshold (Stapells, 2000). However, on average and for a large group of patients with hearing loss, click-evoked ABR thresholds correlate best with hearing sensitivity at 2000 Hz. Therefore, in this study, ABR thresholds are compared to BHTs and ASSR thresholds at 2000 Hz.

The relation between ABR and ASSR has only recently been investigated. Vander Werff and colleagues (2002) compared the 2000 Hz ASSR with the click-evoked ABR in children from 2 months to 3 years old. They report a correlation coefficient of 0.96. In this study, a correlation of only 0.77 was found. There was one outlying value (see below). If this value is omitted, a correlation of 0.93 can be reached, which corresponds more to the correlation mentioned by Vander Werff et al. (2002). Since the ABR is absent or worse than would be expected from BHTs in auditory neuropathy, correlation of ABR with 2000 Hz BHTs or 2000 Hz ASSR thresholds will be influenced by the presence or absence of these special cases. Although click-evoked ABR is the most widely used evoked potential technique to estimate hearing thresholds, the relationship between hearing thresholds and ABR is not unambiguous. Previously reported correlation coefficients between behavioral hearing thresholds and ABR vary from only 0.48 (Jerger & Mauldin, 1978) to 0.70 (Stapells & Oates, 1997) and 0.75 (Gorga et al., 1985). Van der Drift et al. (1987) even report a correlation of 0.91.

Besides the frequency-specificity, the ASSR technique has a number of advantages over the click-evoked ABR, as described in section 1.3.4.

5.4.4 Auditory neuropathy

In one case (subject 2) no ABR could be recorded at the right ear and a threshold of 110 dBpeSPL was found at the left ear, though ASSRs were clearly present at lower intensities and noticeable correspondence existed between the ASSR thresholds and the behavioral hearing thresholds. The ABR and ASSR thresholds were obtained at 4.5 months of age. The first reliable behavioral responses could be obtained 7.5 months later, at 12 months of age. The discrepancy between ABR and ASSR could be due to the disorder 'auditory neuropathy' (Starr et al., 1996). Patients with auditory neuropathy have absent or severely abnormal auditory brainstem responses but have preserved cochlear outer hair cell function as shown by normal otoacoustic emissions or cochlear microphonics. In this infant, we were not able to measure reliable otoacoustic emissions or cochlear microphonics, so we can only speculate on this being a case of auditory neuropathy. Nevertheless, there is a clear discrepancy between the behavioral hearing thresholds and ASSR on one hand and ABR on the other hand.

To detect an ABR response in the time domain, synchronous onset responses of a large population of auditory nerve fibers to the transient stimulus are required. For ASSR recording and analysis in the frequency domain, the response of the auditory system only needs to be phase-locked to the modulation envelope of the stimulus (Rance et al., 1999). Depending on the severity of neural dyssynchrony and the place of the deficit in the auditory path, both ABR and ASSR recordings can be affected or only the ABR. Some cases of auditory neuropathy have been studied with single-stimulus ASSR by Rance et al. (1999) and Rance and Briggs (2002). In these studies ASSR thresholds were found, but the authors concluded that ASSR alone has no predictive value for hearing levels in children with auditory neuropathy. However, discrepancy between ABR and ASSR thresholds may be an indication for auditory neuropathy, which may be confirmed by otoacoustic emission or cochlear microphonic testing.

5.5 Conclusions

This study indicates that the dichotic multiple-stimulus ASSR technique can reliably estimate frequency-specific hearing thresholds in very young infants in a time-efficient way. In view of the recent developments concerning universal newborn hearing screening, the ASSR technique could form a follow-up diagnostic test with widespread clinical application.

Chapter 6

Clinical application of dichotic multiple-stimulus auditory steady-state responses in high-risk newborns and young children

Luts, H., Desloovere, C., & Wouters, J. 2005. Audiology & Neuro-Otology. Accepted for publication.

Abstract

Experience with dichotic multiple-stimulus auditory steady-state responses (ASSRs) in clinical practice is described. ASSR thresholds were assessed in a sample of 60 high-risk newborns and young children between birth and 4 years of age. Amplitudes and signal-to-noise ratios (SNRs) of the ASSR were compared between normal-hearing infants and adults. Age-related changes within a group of infants younger than three months of age were investigated. A comparison was made between ASSR, the click-evoked auditory brainstem response (ABR) and behavioral hearing thresholds (BHTs) in infants with a wide range of hearing threshold levels. Mean ASSR thresholds for normal-hearing infants at an average corrected age of 12 days were 42 ± 10, 35 ± 10, 32 ± 10 and 36 ± 9 dBSPL for 500, 1000, 2000 and 4000 Hz respectively. Compared to adults, these thresholds were elevated by on average 11 dB and SNRs were 1.7 times smaller. However, based on ASSRs reasonably accurate estimations could be made of behavioral hearing thresholds obtained at a later age (median delay of 7 months). The predicted thresholds were in 61% of the cases within 10 dB of the corresponding behavioral thresholds, and in 83% of the cases within 15 dB. In less than one hour, thresholds at four frequencies per ear could be obtained. The optimal age of testing is between one week and three months corrected age. The dichotic multiple-stimulus ASSR technique is a valuable extension of the clinical test battery for hearing-impaired children, as a follow-up diagnostic after the neonatal hearing screening.

6.1 Introduction

Since the introduction of the neonatal hearing screening program in Flanders, Belgium, infants are referred at a younger age and the need for anesthesia during objective testing has diminished, because tests can be carried out in natural sleep. The possibility to record ASSRs without sedatives would increase the clinical value of the technique. Results of the previous study indicated that the ASSR technique could be used to assess hearing in young infants. The aim of the current study was to extend our findings to younger infants, shortly after the hearing screening, in order to avoid the need for sedatives and to investigate age effects within the infant group.

The last few years, the number of clinical ASSR studies in adults and children has increased and devices to record ASSR have become commercially available. However, little research has been done in hearing-impaired neonates and the question remains whether ASSR should be included in the standard pediatric test battery and whether ASSR can replace ABR or rather complements it. The single-stimulus ASSR has been evaluated in hearing-impaired adults, children and babies (Rance et al., 1995; Rance & Rickards, 2002; Stueve & O'Rourke, 2003; Cone-Wesson et al., 2002a; Vander Werff et al., 2002). For the multiple-stimulus ASSR technique, it has also been shown that there is a strong relationship between ASSR and behavioral hearing thresholds (BHT) in adults and older children (Perez-Abalo et al., 2001; Swanepoel & Roode, 2004; Picton et al., 1998). However, data are very limited for hearing-impaired infants (Luts et al., 2004) and, to our knowledge, no threshold data are available on the dichotic multiple-stimulus ASSR in babies at risk for hearing loss younger than three months of age. Since ASSRs are smaller in normal-hearing babies (compared to adults) as shown by Lins et al. (1996) it is not clear how this affects the clinical efficacy of ASSR when used in this population. However, the Joint Committee on Infant Hearing (2000) recommends further diagnosis after a failed hearing screening to be completed before the age of three months, so this is the patient group that needs a frequency-specific objective technique the most.

In this chapter, we describe our experience with the dichotic multiple-stimulus ASSR technique in clinical practice, in a large number of newborns and infants at risk for hearing loss. Firstly, ASSR amplitudes, SNRs and thresholds obtained from high-risk infants younger than three months of age were compared to those of adults. These infants were considered to be normal hearing on the basis of OAE and ABR tests. Moreover, age effects within this group of infants were evaluated. A better insight into the differences between infant and adult ASSRs will optimize the interpretation of ASSR results in different patient groups. Secondly, ASSR thresholds were assessed in a group of infants with a wide range of hearing threshold levels and were compared with ABR and BHTs. The precision that can be achieved when estimating hearing thresholds by means of ASSR was investigated. The possibility of testing babies in natural sleep was evaluated and practical considerations regarding the clinical use of ASSR are discussed.

Table 6.1: Description of the subject group.

		Natural sleep	*Induced sleep*
Number of infants successfully tested:		30	23
Chronological age range (days):		8-177	104-1521
Premature infants:		12	4
Risk factors:			
	Ototoxic medication	9	2
	Low birth weight (<1500 g)	7	2
	In utero infections (e.g. CMV)	6	3
	Family history	5	1
	Hyperbilirubinemia	5	1
	Mechanical ventilation > 5 days	3	2
	Craniofacial anomalies	1	1
	Bacterial meningitis	0	2
	Postnatal asphyxia	2	0
	Stigmata associated with syndrome	2	0

6.2 Methods

6.2.1 Subjects

Initially, a group of 60 infants was studied. In 53 infants (28 boys and 25 girls) ASSR recordings were successful and data were included in the study. A test was considered successful if at least two out of eight ASSR thresholds could be determined. In 47 infants, at least five ASSR thresholds could be assessed. ASSR recordings did not succeed in six infants that were planned for testing in natural sleep, but did not sleep for a sufficiently long time or not at all. Two of the six were older than 5 months. One child tested under anesthesia was spastic, resulting in exceeding noise levels.

All 53 tested subjects were at risk for hearing loss (see Table 6.1) and/or failed hearing screening carried out by the Flemish public agency Kind & Gezin or at the NICU of UZ Leuven. Thirty infants were tested in natural sleep, shortly after a failed hearing screening. Their median chronological age was 37 days. The other 23 infants were tested under general anesthesia. Their median age was 9 months and 3 weeks. Threshold data of 10 of these infants were in part reported in Chapter 5. The distribution of the chronological age for both groups is depicted in Figure 6.1. When correcting the age for prematurity, 21 babies were younger than 1 month.

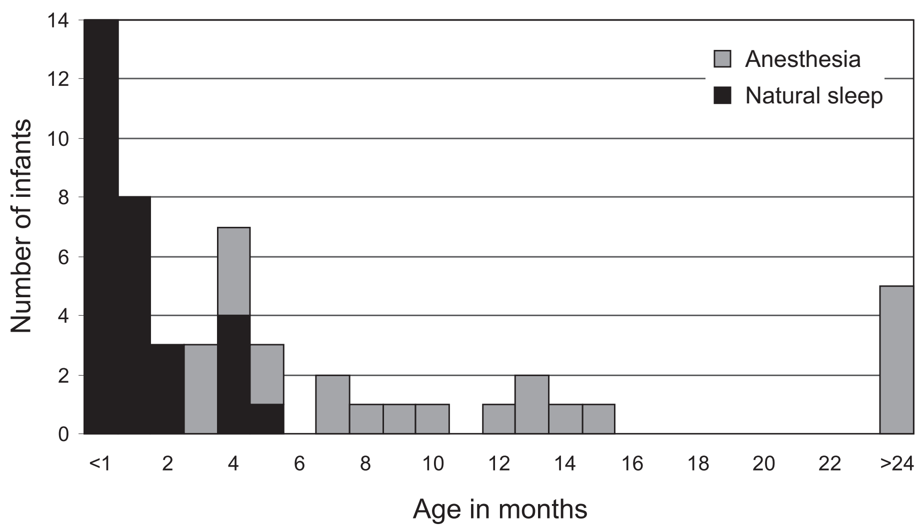


Figure 6.1: Distribution of the age (in months) at the day of ASSR testing. Ages are not corrected for prematurity.

Recordings of both ears of 10 normal-hearing adults were used to compare with the infant data. These adults participated in a previous study (Chapter 4). They varied in age between 21 and 28 years. Hearing thresholds were better than or equal to 20 dBSPL at all octave frequencies between 500 and 4000 Hz. During the ASSR recordings, they were encouraged to relax and if possible fall asleep.

The ASSR testing was approved by the Committee of Medical Ethics of Clinical Research of the Katholieke Universiteit Leuven. This research project was in accordance with the Helsinki Declaration.

6.2.2 Experimental design

6.2.2.1 Stimulation and recording parameters

The ASSR test set-up is described in section 2.2. Detailed information about the click-evoked ABR and behavioral audiometry can be found in section 5.2.2.

6.2.2.2 Test procedure

All subjects received otoscopic examination by an ENT surgeon. Cerumen was removed if necessary. Tympanometry was carried out in most infants with a Madsen Zodiac 901 Middle-Ear Analyzer with a probe tone of 226 Hz.

Under general anesthesia, ASSR recordings were always combined with ABR measurements in the same test session. Hearing tests were only carried out under general anesthesia if other attempts to obtain audiometric data failed. More details on the anesthesia can be found in section 5.2.

In natural sleep, transiently evoked otoacoustic emissions (OAEs) were assessed with an Otodynamics Echoport ILO292. Based on the presence of OAEs, normal-hearing infant ears were selected for further analyses of normal ASSRs. ASSR measurements were usually started after feeding. Data were only included if there was no evidence of middle ear pathology and no evidence of auditory neuropathy. Middle ear pathology was assessed by otoscopic examination of an ENT-physician as well as by tympanometry. If both assessments showed normal results, the infant was included in the study. An indication for auditory neuropathy was the presence of OAEs in cases where the ABR was absent or severely abnormal. Progressive hearing loss was not ruled out.

For ASSR, neonatal 3M 2282E recording electrodes were placed at the forehead and at the inion, with a ground electrode at the clavicle. Thirty-two sweeps were collected for each stimulus intensity. Recordings were only carried out during sleep, no noise criterion was used. Artifact rejection limits were set in a way that maximum 5 to 10% of the recordings were rejected. Exceptionally, recordings had to be ended before 32 sweeps were reached because the infant became restless. ASSR thresholds were determined at 10-dB precision. A threshold was defined as the lowest intensity level where a significant response was obtained. Because of clinical constraints, 20 dBSPL was accepted as minimum presentation level. If no response could be detected at the maximum intensity level, the ASSR threshold was interpreted as being >110 dBSPL and the threshold procedure was considered successful, since recordings at all required intensity levels were completed. Raw data of all recordings were saved for further analysis.

Behavioral audiometry was performed in 21 infants in later test sessions, as soon as behavioral responses to auditory stimuli could be assessed. Time of testing differed among infants, determined by developmental age and medical status. The median age at behavioral hearing testing was 14 months. The median time delay between ASSR and BHT was 7 months, the maximum time delay was 26 months. Visual reinforcement audiometry (VRA) was performed. Warble tones were presented through EAR-Tone 3A insert phones or in free-field conditions, using a clinical audiometer. Thresholds were defined in dBSPL at 5-dB precision. Behavioral thresholds obtained in free-field are compared to evoked potential thresholds of the best ear. The clinicians performing the VRA test often had knowledge of the ASSR thresholds, which could have influenced the results.

6.2.3 Data analyses

Statistical analyses were carried out with the 10.0 SPSS software. To compare the data of normal-hearing adults and infants, the percentage of significant responses per intensity level was explored. Amplitude spectra were calculated, based on raw data of the EEG-recordings using MATLAB 6.5. Noise levels and SNRs were compared as a function of intensity level and test duration with a two-way analysis of variance (ANOVA). The influence of age was assessed by comparing SNR values at two intensity levels for three age groups with a two-way ANOVA. For the comparison of techniques, mean difference scores and standard deviations were calculated. The linear relation between two variables was analyzed by means of Pearson correlation coefficients, R^2, and linear regression analyses. Absolute prediction errors were computed by taking the absolute value of the difference between the estimated hearing threshold and the behavioral hearing threshold.

6.3 Results

ASSR testing was successful in 104 ears of 53 infants (in two infants only one ear was tested). In total 358 ASSR thresholds, 54 ABR thresholds and 108 BHTs were determined. Otoacoustic emissions were assessed in 54 ears. The average test duration for ASSR was 54 min (range 40 – 75 min) under anesthesia and 44 min (range 20 – 68 min) in natural sleep. The success rate of ASSR testing in natural sleep was 83%, on average 6 out of 8 hearing thresholds were estimated.

6.3.1 Comparing normal-hearing infants and adults

Responses recorded in high-risk infants younger than three months of age and adults were directly compared concerning ASSR thresholds, amplitude and SNR. Thirty infant ears tested in natural sleep showed OAEs present and were presumed to be normal hearing. The average corrected age of these infants was 12 days (range -23 to 70 days), 65% were prematurely born. Due to clinical constraints, not all four carrier frequencies could be assessed for every infant and 20 dBSPL was the lowest presentation level. In total, 90 normal-hearing ASSR thresholds were determined. Mean ASSR thresholds were 42 ± 10, 35 ± 10, 32 ± 10 and 36 ± 9 dBSPL for 500, 1000, 2000 and 4000 Hz respectively. In 20 normal-hearing adult ears ASSR thresholds measured with the same test set-up were 34 ± 7, 18 ± 8, 20 ± 7, 29 ± 12 dBSPL, for 500, 1000, 2000 and 4000 Hz respectively. The differences between infant and adult normal-hearing ASSR thresholds are significant for all frequencies. The adult thresholds are on average 11 dB lower than the infant thresholds ($p \leq 0.001$).

Figure 6.2 represents the percentage of significant responses at different intensity levels for infants and adults. The plots are based on all recordings obtained in the normal-hearing infant and adult group. As not all intensity levels were assessed in each subject, the number of recordings may differ between intensity levels. For 500 Hz, the percentage significant responses is clearly lower than for the mid frequencies for infants as well as for adults. At 20 dBSPL, about 5% of the responses are significant in both subject groups, this is equal to the significance level of the *F*-test used for response detection ($p<0.05$). At higher intensity levels, there is a great discrepancy between adults and infants, which maintains even at 50 dBSPL. For the higher frequencies, the difference between adults and infants is the largest at low intensity levels and decreases at higher levels. Averaged over all frequencies (see lower graph) the difference between adults and infants is still significant at 50 dBSPL (independent samples *t*-test, $p=0.005$).

Because of timing restrictions in the infant group, ASSR testing was often limited to three or four intensity steps, with 20 dBSPL being the lowest level. In the adult group though, more intensity steps were taken, sometimes as low as 0 dBSPL, since test duration is not such a limiting factor in this population. However, several reasons indicate that this restriction in the infant group will have only a limited effect on the threshold data. First, the number of significant responses at 20 dBSPL is rather low in infants, except at 2000 Hz. As the slopes of the curves in Figure 6.2 are quite steep at lower intensity levels (also in adults), the number of significant responses at 10 dBSPL, and thus the number of thresholds below 20 dBSPL, would have been very low, even at 2000 Hz. Second, the ASSR thresholds can be compared to the intensity level at which 50% of the recorded responses reached significance, calculated based on the graphs in Figure 6.2. These 50% significance levels are shown in Table 6.2, as well as the deviation relative to the ASSR thresholds that are defined as the lowest level at which significance was reached. The average deviation is 5 dB for infants as well as for adults, which is to be expected since the step-size of the ASSR threshold test procedure was 10 dB. In infants, the number of significant responses at 20 dBSPL is the highest at 2000 Hz. At this frequency, the deviation is also the largest, which could indicate that recordings at lower levels would have resulted in lower thresholds. However, the deviation averaged over all frequencies is equal for adults and infants, although adults were tested at lower intensity levels. Third, the difference in 50% significance level between the adult and the infant group averaged over all frequencies is 11 dB, which corresponds exactly to the average difference observed between infant and adult normal-hearing ASSR thresholds. This is again an indication that the infant ASSR thresholds are realistic estimates.

Table 6.2: The intensity level (in dBSPL) at which 50% of the recordings showed a significant response, as calculated from Figure 6.2. Between brackets the deviation from the ASSR threshold (defined as the lowest level at which a significant response is reached) is given. This deviation is on average 5 dB. The overall difference between infants and adults is 11 dB, which corresponds to the average difference between infant and adult normal-hearing ASSR thresholds.

Group	*Carrier frequency (Hz)*				
	500	1000	2000	4000	Total
Infants	41 (1)	32 (3)	23 (9)	29 (7)	31 (5)
Adults	31 (3)	13 (5)	15 (5)	22 (7)	20 (5)

The average amplitude spectra were calculated for eight binaurally normal-hearing infants and adults, tested at 30 and 50 dBSPL. Figure 6.3 depicts the spectra after recordings of 16 sweeps at 50 dBSPL. Figure 6.4 shows the spectra after recordings of 32 sweeps at 30 dBSPL. The main aim of these figures is to show the difference between adult and infant spectra. The average spectra are the result of a point-by-point average of eight individual spectra. Noise levels and amplitudes are thus average values. In a single recording, the average noise level is similar, but the variation of the noise is larger. An exemplary spectrum of a recording of 32 sweeps at 30 dBSPL for a single infant is depicted in Figure 6.5. Table 6.3 shows the mean amplitudes and standard deviations for both ears of the infants and adults that were included in Figure 6.3 and Figure 6.4. Variability of the amplitudes is large in both subject groups. Averaged over all carrier frequencies, the ASSR amplitudes in infants are 3 to 4 times smaller than in adults. The average noise level between 77 and 115 Hz, however, is also smaller. For the recording of 16 sweeps at 50 dBSPL, the noise level was 7.7 and 3.9 nV for adults and infants respectively. For the recording of 32 sweeps at 30 dBSPL, the noise level has decreased to 5.1 and 3.0 nV. As a result, the average SNR for adults is 1.7 times the SNR for infants, as well for a recording of 32 sweeps at 30 dBSPL, as for 16 sweeps at 50 dBSPL. When the recording time for infants at 50 dBSPL is doubled to 32 sweeps, the SNR is still 1.3 times smaller than the SNR for adults. This difference in amplitudes and signal-to-noise ratios can explain the lower number of significant responses for infants seen in Figure 6.2.

Table 6.3: Mean amplitudes (in nV) and standard deviations for both ears of eight normal-hearing infants and adults for ASSR recordings at 30 and 50 dBSPL.

Intensity	*Number of sweeps*	*Group*	*Carrier frequency (Hz)*				
			500	1000	2000	4000	Total
30 dBSPL	32	Infants	4 ± 2	6 ± 4	8 ± 3	6 ± 3	6 ± 4
		Adults	10 ± 7	25 ± 8	24 ± 9	11 ± 7	17 ± 10
50 dBSPL	16	Infants	9 ± 6	12 ± 7	11 ± 5	8 ± 5	10 ± 6
		Adults	32 ± 15	51 ± 18	45 ± 15	22 ± 11	37 ± 18

The effect of recording length on noise levels, calculated as the average of 120 noise bins centered around the signal bin, and SNRs is further analyzed in infants, in order to assess the benefit of increasing test duration in this subject group. The average difference in noise levels for recordings of 16 and 32 sweeps was 1.1 nV. Although this difference seems small, it is highly significant ($p \leq 0.001$). This decreasing noise level influences the SNR. The SNRs were analyzed with a repeated measures analysis of variance, with within-subject factors intensity (30 and 50 dBSPL) and number of recorded sweeps (16 or 32). The main effects of intensity and number of sweeps were highly significant ($p \leq 0.001$), there was no interaction effect ($p=0.608$). The average increase in SNR from 30 to 50 dBSPL was 4.4 dB. Doubling the recordings from 16 to 32 sweeps increases the SNR by on average 2.6 dB. Theoretically, doubling the length of a recording decreases the noise level by the square root of 2, which results in an SNR increase of 3 dB. Since a significant response requires an SNR of 4.8 dB or more, it is certainly recommended to increase the length of the recordings at threshold level.

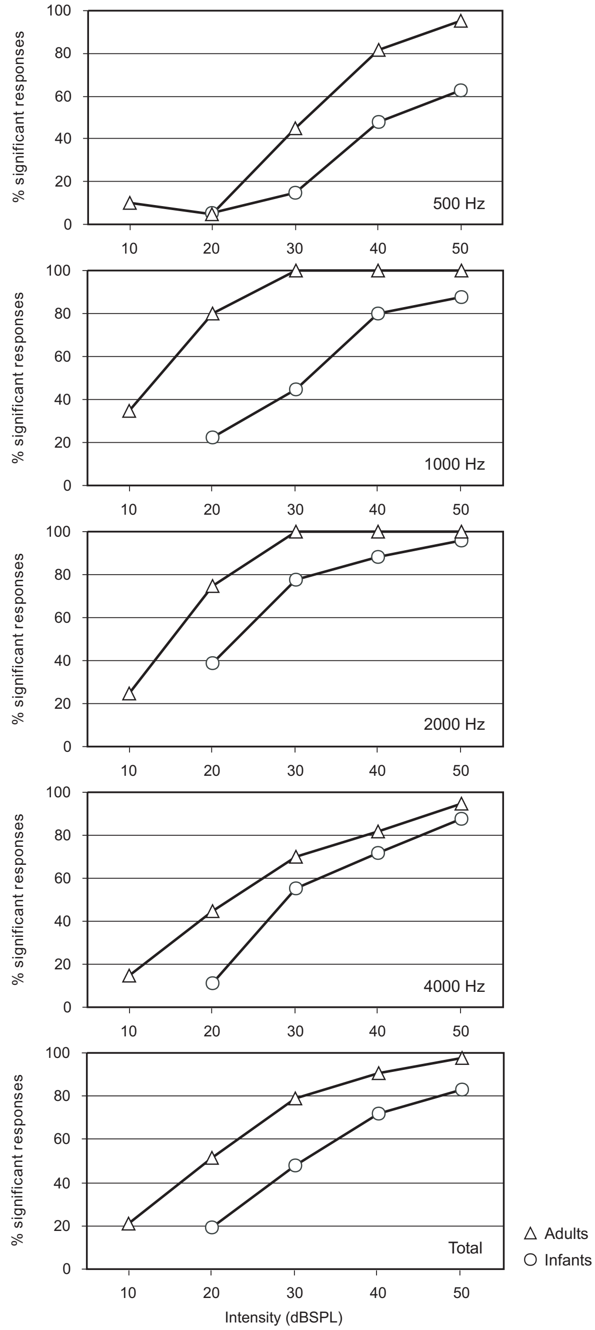


Figure 6.2: Percentage of significant responses at different intensity levels after recordings of maximum 32 sweeps for 500, 1000, 2000 and 4000 Hz and the average of all carrier frequencies. Circles represent 30 normal-hearing infant ears and triangles 20 normal-hearing adult ears. For the infant group, the minimum presentation level was 20 dBSPL because of clinical constraints.

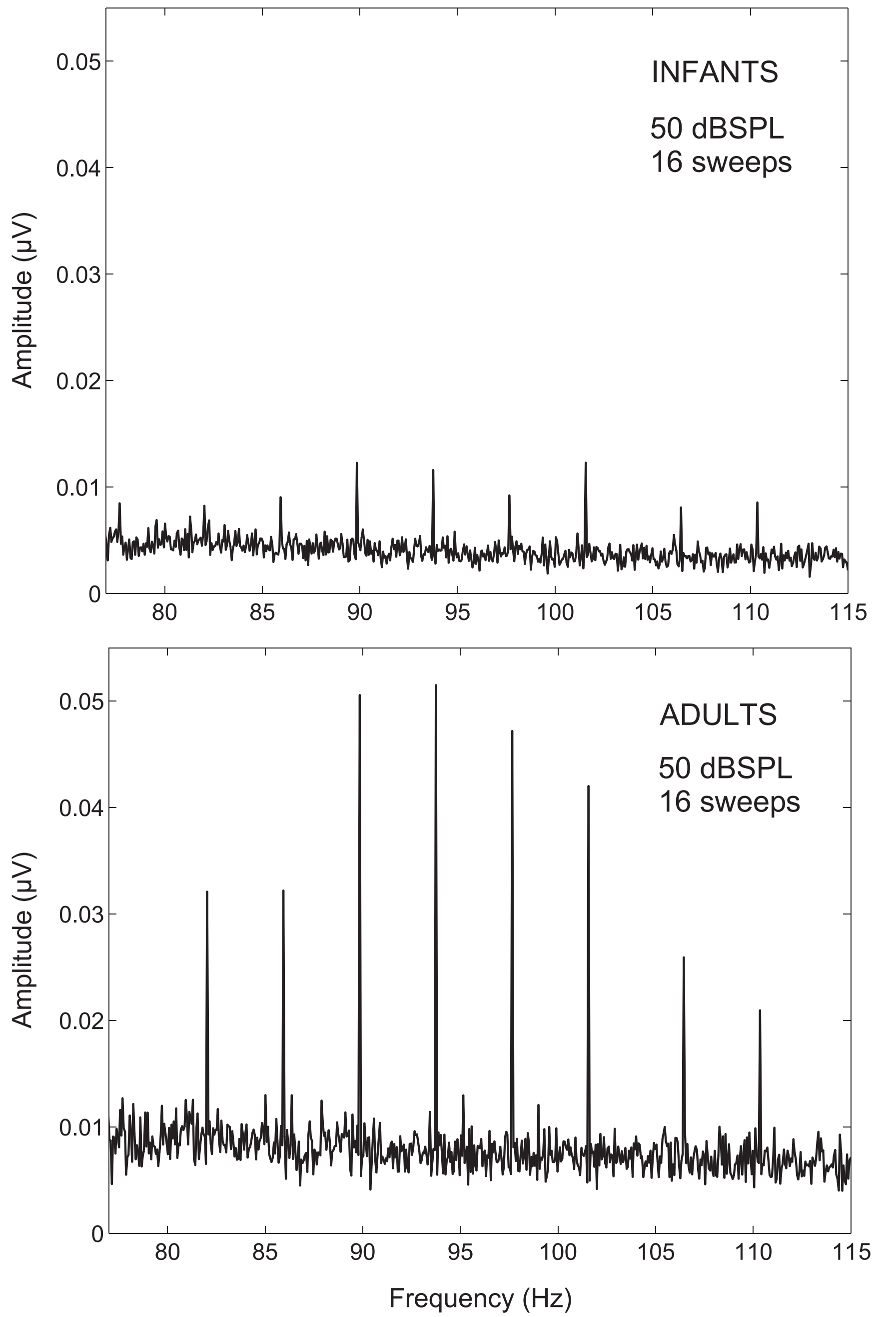


Figure 6.3: Averaged amplitude spectrum at 50 dBSPL for eight normal-hearing infants and adults (both ears) after recordings of 16 sweeps.

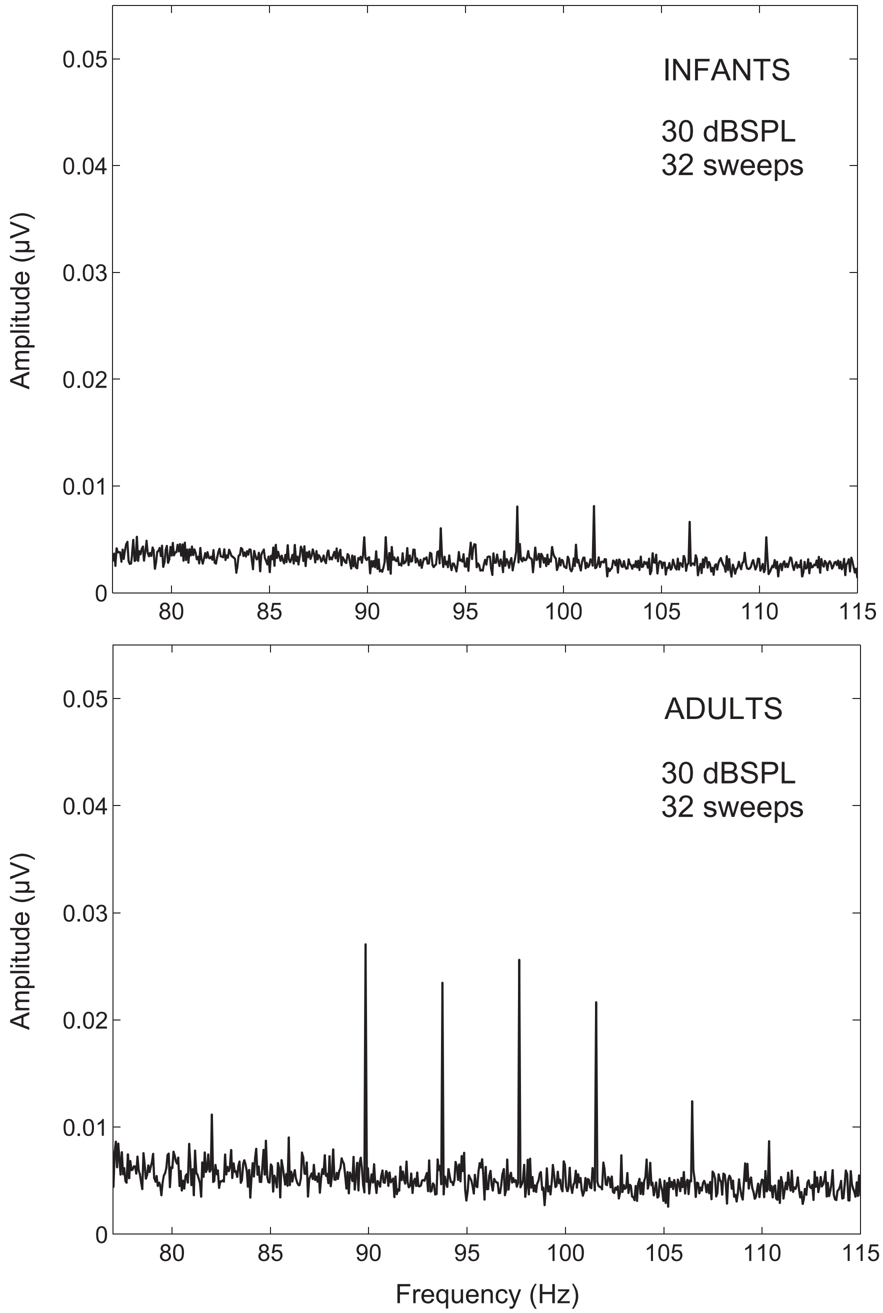


Figure 6.4: Averaged amplitude spectrum at 30 dBSPL for eight normal-hearing infants and adults (both ears) after recordings of 32 sweeps.

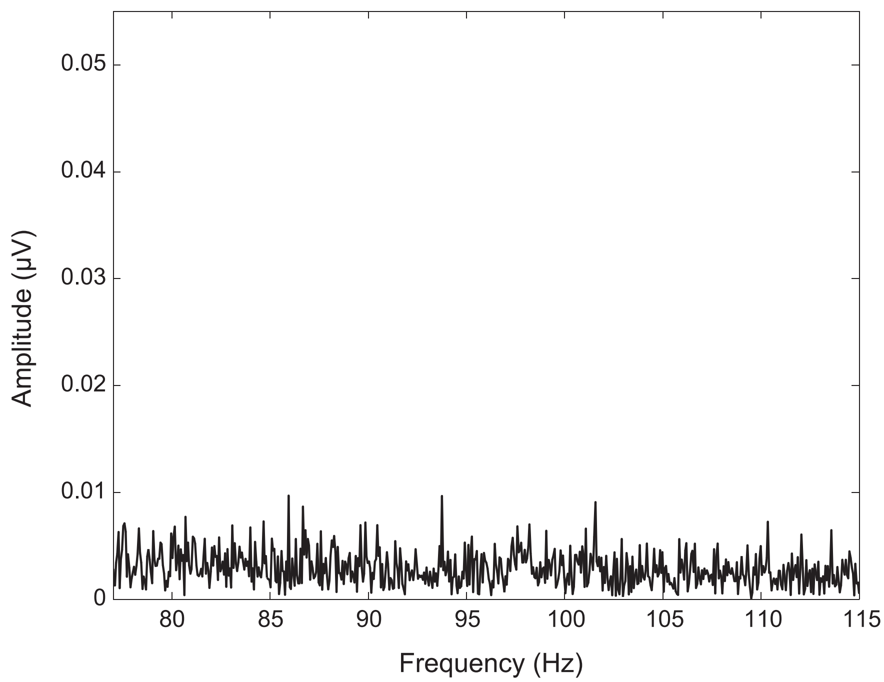


Figure 6.5: Exemplary amplitude spectrum at 30 dBSPL for a normal-hearing infant (both ears) after a recording of 32 sweeps.

Many infants tested in this study were prematurely born. Since the referral protocol is the same for preterm and term–born babies and further diagnostic testing is always planned as soon as possible after the failed hearing screening, ASSR testing is, in some infants, performed at a very young age. As neural maturation is not yet completed in these infants, the question raised whether this early testing would affect the detectability of the ASSR. Therefore, the influence of age on the SNR was investigated. Instead of chronological age, postconceptional age (PCA) was considered. In this way, prematurity is taken into account. An increase in SNR during the first few weeks or months after birth would be an indication to postpone ASSR testing, at least in premature infants. The normal-hearing infant group (30 ears) was divided in two, the youngest and the oldest infants. The infants of the first group (14 ears) were younger than 41 weeks PCA (range 36 to 40 weeks). Term-born babies will normally be tested after they reached this age. The youngest infants were compared with infants older than 41 weeks PCA (16 ears) (range 41 to 50 weeks) and with adults (16 ears). The SNR at 50 and 30 dBSPL, averaged over the four carrier frequencies, is plotted as a function of age in Figure 6.6. The SNR increases with increasing age, especially at 50 dBSPL. A two-way ANOVA was carried out with the factors intensity (30 and 50 dBSPL) and age group (2 infant groups and 1 adult group). There is a main effect of intensity ($p \leq 0.001$) and age group ($p \leq 0.001$). The interaction between both factors is not significant ($p=0.395$). At 50 dBSPL, the SNR is 41% larger in older infants than in the youngest group. Even at near-threshold level, at 30 dBSPL, there is an increase of 17%. The growth in SNR with increasing intensity is larger in the older infants.

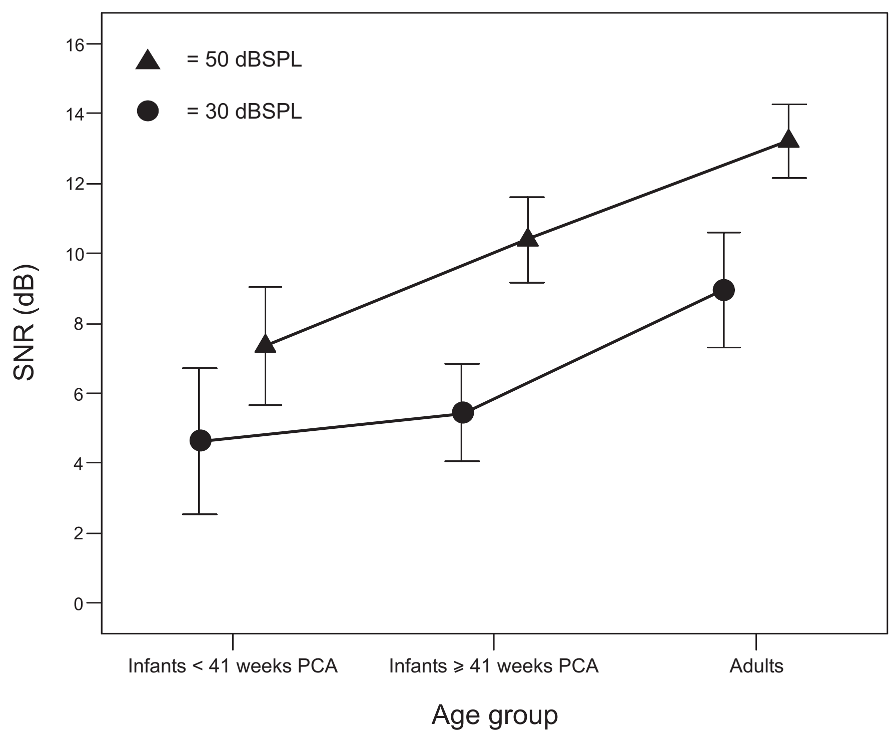


Figure 6.6: The signal-to-noise ratio (SNR) of the ASSR as a function of age group. The age of the infants is expressed as postconceptional age (PCA). The error bars indicate the 95% confidence interval of the mean SNR. Triangles represent the SNR at 50 dBSPL and circles at 30 dBSPL. Results are based on recordings of 32 sweeps, except for adults at 50 dBSPL, where only 16 sweeps were recorded.

6.3.2 Threshold comparisons

In 30 ears of 21 infants, behavioral hearing thresholds could be defined. In each ear, a maximum of four threshold comparisons could be made. In 84 instances, the

ASSR threshold as well as the BHT could be determined. The relation between ASSR thresholds and BHTs is depicted in Figure 6.7. Table 6.4 presents the average difference scores between ASSR and BHTs, the Pearson correlation coefficients and the linear regression equations. After estimation of the BHTs by means of frequency-specific linear regression analyses, 35% of the absolute prediction errors are within 5 dB, 61% are within 10 dB and 83% within 15 dB. In 64 instances, no ASSR threshold could be determined at the maximum output level of 110 dBSPL. In 19 of these cases, BHTs could be assessed and the average BHT was 93 dBSPL. Most missing ASSRs occurred at 500 Hz (39%) and 4000 Hz (30%).

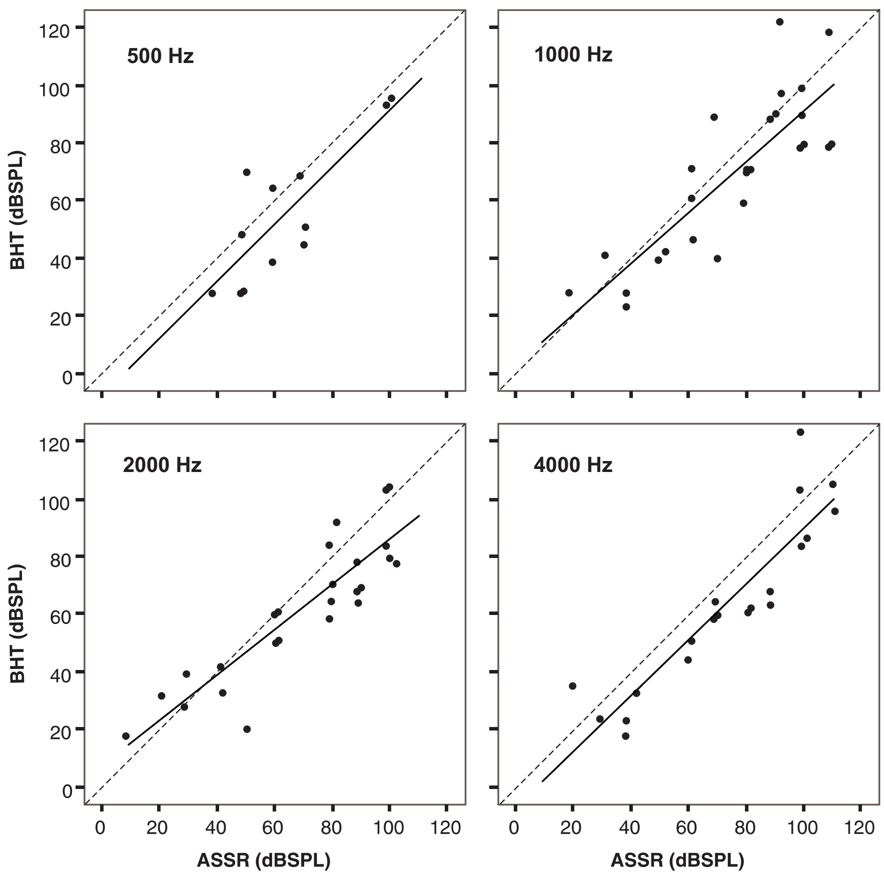


Figure 6.7: The linear relation between ASSR thresholds and BHTs is shown in a scatter diagram. The regression lines as well as the lines of equality (dashed lines) are presented. Data points are jittered to show overlapping of the data.

The mean difference score between ASSR and BHTs for infants tested in natural sleep (10.0 ± 12.6 dB, n=17) and under general anesthesia (7.0 ± 13.5 dB, n=67) was not significantly different (independent samples t-test, p=0.412). This study, however, does not allow the systematic assessment of the influence of general anesthesia on the ASSR. The children tested under anesthesia were older than the infants tested in natural sleep. Since age influences the amplitude and SNR of the ASSR, it is impossible to distinguish age effects and anesthesia effects. For the same reason, the influence of age was evaluated only in infants tested in natural sleep.

ABR thresholds were assessed in 54 ears, a threshold was found in 31 ears. If an ABR was present, between 2 and 4 (out of 4) ASSR thresholds were found, with an average of 3.5. The correspondence between ABR and ASSR at 500, 1000, 2000 and 4000 Hz, as assessed by the calculation of R^2, was highest at 2000 Hz (R^2=0.83). Therefore, this comparison is further explored. If no ABR was found at the maximum output level, ASSR thresholds at 2000 Hz were found in 60% of the ears and varied from 80 to 110 dBSPL. The mean difference of the paired comparison between the ABR threshold (in dBpeSPL) and the ASSR threshold at 2000 Hz (in dBSPL) was 14 dB with a standard deviation of 11 dB. The Pearson correlation was 0.91. At other frequencies, the correspondence was lower, which particularly affects the standard deviation of the difference scores, which was thus the lowest at 2000 Hz.

Table 6.4: Comparison of ASSR and ABR with BHTs. Mean difference scores (ASSR – BHT and ABR – BHT) and standard deviations, Pearson correlation coefficients and the linear regression equation are given. ASSR thresholds are measured in dBSPL, ABR thresholds in dBpeSPL. The click-ABR was compared to the 2000 Hz BHT.

	Frequency (Hz)	*Mean Difference ± St. Dev. (dB)*	*Pearson Correlation*	*Regression Equation*
ASSR	500	8 ± 13	0.82	BHT = -7.8 + 1.0 * ASSR
	1000	6 ± 15	0.84	BHT = 2.8 + 0.9 * ASSR
	2000	7 ± 13	0.89	BHT = 7.2 + 0.8 * ASSR
	4000	9 ± 12	0.91	BHT = -7.1 + 1.0 * ASSR
	Overall	8 ± 13	0.87	BHT = 0.5 + 0.9 * ASSR
ABR	Click	24 ± 10	0.94	BHT = -1.1 + 0.7 * ABR

In 15 ears, the ABR threshold (dBpeSPL) could be compared to the BHT (dBSPL). The correspondence between ABR and BHTs at 500, 1000, 2000 and 4000 Hz was assessed by calculating R^2. Similarly to the comparison of ABR and ASSR, R^2 was highest at 2000 Hz (R^2=0.89) and this comparison was further investigated. Results are given in Table 6.4.

6.3.3 Risk factors

All infants tested in this study were likely to have hearing loss, indicated by a failed hearing screening or the presence of one or more risk factors associated with hearing loss. Eighteen infants had bilaterally normal hearing, based on the presence of OAEs or an ABR threshold better than or equal to 50 dBpeSPL. Nine of them (50%) were born prematurely. They were referred after a failed hearing screening (mostly unilateral) based on auditory brainstem responses carried out during their stay at the NICU. The false positive referrals of the hearing screening carried out at the NICU are probably in part the result of maturation issues. Evoked potential testing, which indicated normal hearing, was performed later. Development of click-evoked ABR occurs rapidly during the first 3 months after birth and continues up through 1 year of age (Jiang & Tierney, 1995).

Five of the normal-hearing infants (28%) had cytomegalovirus infection (CMV). Preventive testing was performed, since CMV is known to cause delayed onset hearing loss or progressive hearing loss (Fowler et al., 1999). In four other infants with CMV, a severe to profound hearing loss was diagnosed. In three of them, both ears were affected and they received a cochlear implant.

Within the group of infants that were not bilaterally normal hearing, ototoxic medication and low birth weight, both related to prematurity, and family history of hereditary childhood hearing loss were the most common risk factors. Eight out of 11 referred infants who received ototoxic medication and five out of six infants with family history of hearing impairment appeared to have some degree of hearing loss.

6.4 Discussion

6.4.1 ASSRs in normal-hearing infants at age < 3 months

ASSR thresholds were investigated in normal-hearing high-risk infants, showing elevated thresholds relative to adults. Previous studies have reported multiple-stimulus ASSR thresholds for normal-hearing well babies. Lins et al. (1996) report ASSR thresholds of 45 ± 13, 29 ± 10, 26 ± 8 and 29 ± 10 dBSPL in infants between 1 and 10 months of age. In our study, thresholds are slightly higher for 1000, 2000, and 4000 Hz. Infants were in general younger, often born prematurely, and high-risk. This difference in high-frequency thresholds could support the hypothesis that auditory function is mature in newborns for lower-frequency stimuli and immature for higher-frequency stimuli (Sininger et al., 1997). However, compared to normal-hearing adults, ASSR thresholds in infants are elevated, also at 500 Hz.

Savio et al. (2001) also report ASSR thresholds in normal-hearing babies, but ambient noise levels were very high (62 and 65 dB(A)), which makes results difficult to compare with the present study. Thresholds are between 49 and 67 dBSPL for infants from 0 to 6 months of age. A common observation is the smaller response or the higher ASSR threshold for low-frequency stimuli compared to the threshold for high-frequency stimuli. A possible explanation is a desynchronization of the neurons generating the responses because of a jitter in the transmission time between the cochlear receptors and the neural generators. This results in a decrease of the amplitudes of the recorded signals (Lins et al., 1996). A similar elevation in threshold has been reported for the 500 Hz ASSR in adults and older children (Perez-Abalo et al., 2001; Dimitrijevic et al., 2002; Luts & Wouters, 2004) and for the 500 Hz tone-evoked ABR in infants (Stapells et al., 1995).

In Cone-Wesson et al. (2002b), ASSR thresholds are obtained with a monaural single-frequency ASSR recording technique in a group of normal-hearing infants. Mean ASSR thresholds are reported of 44, 34, 29, and 44 dBSPL for 500, 1000, 2000 and 4000 Hz respectively (dBHL values are converted into dBSPL according to the ISO 389-2 for insert phones). Since short recording times were used in comparison to the present study, one would expect higher difference scores, analogues to what is reported in adults (Picton et al., 2003). However, threshold values are comparable. This can in part be explained by the difference in age between both subject groups. The mean corrected age of the infants tested by Cone-Wesson and colleagues (2002b) was 8 weeks in contrast to the infants tested in the present study that were only 12 days corrected age. As the SNR increases during these first weeks after birth, normal-hearing ASSR thresholds will decrease.

6.4.2 Age-related changes in ASSR

In a number of prematurely born infants, ASSR testing was performed at a very young age. The influence of this early testing on the detectability of the ASSR within these first few weeks or months after birth was assessed. Since noise levels are higher in adults compared to infants, SNRs were compared instead of amplitudes. SNRs take these noise levels into account and are, moreover, more directly related to the response detection. Within the infant group, an increase in SNR was observed with increasing age. In the age group older than 41 weeks PCA, SNRs at 50 dBSPL were 41% larger compared to the youngest group and thus responses were easier to recognize. John et al. (2004) recorded ASSRs at 50 dBSPL in newborn infants (within 3 days of birth) and older infants (within 3-15 weeks of birth). Response amplitudes in older infants were on average 40% larger than for the newborn infants. Due to this increase in amplitude and SNR, it is advisable to postpone ASSR testing, especially in prematurely born infants, until they are between one week and three months of corrected age, as also suggested by John et al. (2004). In this age group, the success rate of testing in natural sleep is high and the use of sedatives can be minimized.

Savio et al. (2001) also reported developmental changes in the monaural multiple-stimulus ASSR. They tested well babies between birth and 12 months of age, whereas the current study assessed high-risk infants younger than three months of corrected age and compared these data with adult ASSRs. Moreover, background noise levels were very high and intensities were corrected by normal adult hearing thresholds (between 34 and 51 dBSPL) and expressed in dBnHL. In the present study, ambient noise levels were very low and intensities are expressed in dBSPL. Therefore, the response detectability as well as ASSR thresholds are difficult to compare with the present study. However, both studies have observed an age related change in ASSR, although in different subject groups. Pethe et al. (2004) tested children between the ages of 2 months and 14 years with the single-stimulus ASSR. At 50 dBnHL, the amplitude slightly increased with age, but the increase in SNR was not significant. Taking into account the results of the present study and of Savio et al. (2001), this could indicate that the largest increase in SNR takes place in the first year of life. However, the SNRs in the study of Pethe et al. (2004) were in general very low, partly caused by the very short test duration and high noise levels.

6.4.3 ASSR versus behavioral hearing thresholds

For a correct interpretation of ASSR test results, it is important that the average difference and standard deviation between the ASSR threshold and the BHT is known. This difference is dependent on subject group, age, hearing loss, carrier frequency, test duration, and test environment. Difference scores and standard deviations for a group of high-risk neonates and young children were investigated in the present study. The mean difference scores (ASSR – BHT) are similar for all carrier frequencies tested.

Since ASSR thresholds in normal-hearing infants are on average 11 dB higher than in adults, one would expect the difference scores to be higher. However, compared to adult data difference scores are lower and standard deviations are higher (Dimitrijevic et al., 2002; Perez-Abalo et al., 2001; Luts & Wouters, 2004; Lins et al., 1996), which implies that hearing threshold estimates are less accurate. This reflects several factors. First, BHTs in these young infants are rather minimum response levels (MRL) than hearing thresholds. Parry et al. (2003) determined normative data for MRL in normal-hearing young infants. VRA was carried out using insert phones with warble tone stimuli. Mean MRLs for 500, 1000, 2000 and 4000 Hz were 21, 13, 10 and 11 dBSPL (dBHL values are converted into dBSPL according to the ISO 389-2). Behavioral hearing thresholds may thus be elevated in this very young subject group, which decreases the difference scores (ASSR – BHT). Second, there may be a time delay between the ASSR test and the behavioral test. Hearing thresholds may have changed meanwhile, which will especially influence the standard deviation of the difference scores. Moreover, the sound pressure at the eardrum may decrease because of the growing ear canal volume. This will mainly have an effect on the difference scores that will decrease. Finally, maturation of the auditory system influences the ASSR results. Since maturation is not equal between subjects tested in this study, the ASSR results will be more variable. Despite these influencing factors, correlations of BHT with ASSR and ABR are high in these young infants, and hearing thresholds can be estimated with reasonable accuracy. Taking into account age and real ear SPL could ensure a more optimal estimation of hearing thresholds by means of ASSRs. However, difficulties related to the behavioral data collection are inherent to this kind of research.

No previous threshold data are available on the dichotic multiple-stimulus ASSRs in hearing-impaired newborns. Few studies, however, were carried out in infants and children. In Luts et al. (2004) a small sample of young infants at risk for hearing loss were tested. Reported standard deviations and correlation coefficients are comparable to the present study. Perez-Abalo et al. (2001) recorded ASSRs in children aged 6 to 15 years. Differences between ASSR and BHT were 13 ± 15, 7 ± 15, 5 ± 14 and 5 ± 16 dB for 500, 1000, 2000 and 4000 Hz respectively. Correlation coefficients ranged from 0.70 to 0.83. Difference scores are comparable to the results of the present study. However, standard deviations are slightly higher and correlation coefficients are lower. This weaker relationship between ASSR and BHT can be explained by the facts that the overall acoustical noise level in the recording rooms was very high (65 and 71 dBSPL) and recording times were very short (average total recording time = 21 minutes). In Swanepoel et al. (2004) a small sample of children aged 10 to 15 years, with severe to profound hearing impairment was tested. Difference scores are comparable to the current study. Standard deviations and correlation coefficients are lower (between 0.58 and 0.74), probably in part due to the small data sample and the restricted range of threshold levels. A general trend is the increase in standard deviation in infants compared to adults, which implies a less accurate prediction.

ASSR thresholds have been assessed in young children at risk for hearing loss with a monaural single-frequency recording technique (Rance & Rickards, 2002; Cone-Wesson et al., 2002a). The reported regression formulae are quite different from those found in the present study. Rance & Rickards (2002) and Cone-Wesson et al. (2002a) found slopes greater than 1, whereas in this study the slopes are close to 1. A similar trend can be found in adult data. The origin of this difference, is clearly explained by Picton et al. (2003). Regression equations are affected by the level of residual noise as well as the amount of recruitment. In subjects with mild or no hearing loss, brief recordings will result in higher physiological thresholds. Consequently, the number of ears with mild or no hearing loss in proportion to the number of ears with severe or profound hearing loss will influence the regression formulae (Luts & Wouters, 2005).

6.4.4 ABR or ASSR thresholds?

A high correlation of 0.91 was found between the click-evoked ABR and the 2000 Hz ASSR. This is slightly lower than the correlation of 0.96 reported by Vander Werff et al. (2002) for a comparable infant group. The 2000 Hz BHT can be predicted with a slightly higher accuracy by a click-evoked ABR than by a 2000 Hz ASSR. Advantages of ASSR are the frequency-specificity, the objective response detection method and the continuous nature of the stimulus. The maximum output level is less limited and it allows to present the stimuli through hearing aids without too much distortion, which could be interesting to estimate the aided hearing thresholds (Picton et al., 1998). The ABR, however, has also a number of advantages. The average test duration for one ear is shorter than for ASSR. In some cases, it can be handy to have a quick idea about the general level of hearing loss in a short test duration. However, for ASSR both ears are tested simultaneously and thus thresholds are only known for both ears after completing the whole test procedure. In some infants, it will be very difficult to test both ears simultaneously. This can be because of practical difficulties, e.g. because they only sleep on their side, or because of large differences in hearing thresholds between both ears which requires masking of the contralateral ear. In these cases, ABR could be more practical, since test duration doubles for ASSR.

It is always advisable to combine several tests, certainly in case of hearing loss. Otoscopy, tympanometry, otoacoustic emissions and auditory evoked potentials should at least be assessed. If possible, the combination of ASSR and ABR is advised, since results of one test can be confirmed by the other. In clinical practice, it will often not be possible to carry out both tests. Then ASSR is preferred as follow-up diagnostic test because of the objective response detection and the frequency-specificity of the estimated thresholds.

The aim of the present study was to investigate whether the implementation of ASSR can ameliorate the current clinical situation. Therefore, we chose to compare ASSR with the click-evoked ABR and not with tone-evoked ABR, since the click-evoked ABR is more commonly used in clinical practice. It is possible to obtain frequency-specific threshold estimates using tone-evoked ABR, but this technique is time-consuming since results for each audiometric frequency will take the same amount of time as that for a click-evoked ABR (Stapells & Oates, 1997).

6.4.5 Testing ASSR in infants

The assessment of ASSR during natural sleep is possible in more than 80% of the babies and can contribute to a more precise quantification of hearing thresholds shortly after birth. This high success rate in natural sleep increases the clinical applicability. However, ASSR amplitudes were three to four times smaller in infants than in adults and thus less recognizable. This of course hampers the response detection and is certainly disadvantageous for the test duration. Especially the low-frequency ASSR is very difficult to detect in infants.

Since ASSR amplitudes and SNRs are very small in young infants, a sufficiently long recording time is indispensable. Moreover, testing during sleep is essential. Noise resulting from movement and opened eyes is very disturbing for an adequate response detection. In this study, a quite fixed test protocol was handled. A trial duration of 32 sweeps or on average 10 minutes (including rejected epochs) was chosen, since this appeared to be most optimal in adults (Luts & Wouters, 2004). This is a good starting-point. In a clinical setting, recordings can be stopped before the 32nd sweep is attained if all responses reached significance. This could save some time. However, in infants significance of all eight responses occurs not often, especially since the 500 Hz response is so difficult to detect. In children more than in adults, it is important to be flexible and to increase the trial duration depending on the circumstances. By increasing test duration, noise levels decrease which has a positive effect on the SNR. Reasons to prolong test duration are restless patients and thus high noise levels, or *p*-values that are between 0.20 and 0.05 and that tend to decrease during the course of the recordings. This could indicate that a small response is present but that the noise is too high to recognize it. When the baby is calm and amplitudes remain small and consequently *p*-values are high, prolonging the test will in most cases not influence the results. Unfortunately, not all ASSR systems provide the flexibility to increase the recording time. In case of contradictory results, it can be advisable to repeat a recording after checking the position of the earplugs and electrode impedances. For interpretation of the ASSR results, one has to be cautious when using predictions based on adult data, because of differences in ear canal volume and elevated ASSR thresholds in babies.

In contrast with most other studies, the tested subject group was very diverse. Forty percent of the infants tested in natural sleep were prematurely born and 30% received ototoxic medication during their stay on the NICU. Although this group does not represent the average infant group, it is highly representative for the target group of objective audiometric tests.

6.5 Conclusions

Dichotic multiple-stimulus ASSRs can be assessed in clinical practice in high-risk neonates and can provide reasonably good estimates of hearing thresholds. For a successful use of the ASSR technique, several guidelines have to be followed. Since ASSR amplitudes are very small, tests have to be performed during sleep and testing duration per trial has to be sufficiently long, preferably 10 minutes or longer, in order to decrease the noise level and to optimize the SNR. In this way, thresholds at four frequencies in both ears can be assessed within one hour. The optimal age of testing (corrected for prematurity) is between one week and three months, as SNR values are higher than in younger infants and the success rate of obtaining at least 2 ASSR thresholds in natural sleep is more than 80%, reducing the need for sedatives or anesthesia. Normal-hearing ASSR thresholds in infants younger than 3 months of age are elevated by on average 11 dB compared to adult thresholds. Rather than substituting the click-evoked ABR, the ASSR technique can supplement it and can extend the clinical test battery for hearing-impaired children to allow a robust and precise diagnosis of the auditory status.

Chapter 7

Other applications of auditory steady-state responses

A number of pilot studies were performed to investigate whether the ASSR technique is suitable for other applications. Aside from estimating hearing thresholds with insert phones, stimulus presentation through a bone oscillator and in sound field were investigated. Moreover, the application of ASSR in patients with non-organic hearing loss was assessed.

7.1 Experiment 1: Bone-conduction stimulation

Sounds can reach the cochlea through two pathways. A first pathway is via air-conduction. Sound waves enter the external ear canal and vibrations are transmitted via the tympanic membrane and the ossicles to the fluids in the cochlea. A second is the bone-conduction pathway. Since the cochlea is encased in the bones of the skull, vibrations to the skull create fluid motions in the cochlea. The generation of action potentials in the neurons of the auditory nerve, as a result of the excitation of the hair cells in the cochlea is the same for the air- and bone-conduction pathway. Bone-conducted vibrations bypass the external and the middle ear. By comparing the sound transmission of air-conducted sound versus bone-conducted sound, conductive and sensorineural hearing losses can be distinguished. Only two prior studies have described difference scores (ASSR – BHT) for bone-conducted ASSR. In both studies, the bone-conductor was placed on the forehead and both ears were occluded with insert earphones. However, at our department, it is customary to assess unmasked bone-conduction thresholds with a mastoid placement and unoccluded ears and therefore this study was carried out. ASSR thresholds were determined for stimuli presented through the bone conductor and compared with the behavioral thresholds for the same bone-conducted stimuli.

7.1.1 Materials and methods

A group of 10 normal-hearing adults (2 men) was tested. Their ages ranged from 21 to 51 years. Air-conduction hearing thresholds for pure tones were better than 20 dBHL for octave frequencies between 500 and 4000 Hz. During the ASSR recordings, a bone oscillator B-71 was placed on the mastoid of the best ear. No masking was presented, both ears were unoccluded.

Stimulus parameters are shown in Table 7.1. Only four stimuli were presented simultaneously. The bone-conducted stimuli were calibrated separately in dBHL with an artificial mastoid (Brüel & Kjaer 4930) and an amplifier (Brüel & Kjaer 2610) according to the ISO 7566 norm.

For the recording of the ASSR, a sampling frequency of 1000 Hz was used. For each intensity level, 32 sweeps were recorded. ASSR recordings were started at 40 dBHL and intensity was lowered in 10-dB steps, until no significant response at any frequency could be detected. ASSR thresholds were compared to BHTs for the same modulated sinusoids. These BHTs were determined at 5-dB precision. Further details concerning the recording of the ASSRs can be found in section 2.8.

Table 7.1: Stimulus parameters

Carrier frequency (Hz)	500	1000	2000	4000
Modulation frequency (Hz)	90	94	98	102
AM percentage	100	100	100	100
FM percentage	20	20	20	20
FM phase	-90	-90	-90	-90

7.1.2 Results and discussion

The mean BHT for bone-conducted stimuli, averaged over the four carrier frequencies, was 4 ± 7 dBHL. The mean ASSR threshold was 16 ± 12 dBHL. Difference scores (ASSR – BHT) are presented in Table 7.2. Other studies have recorded ASSR thresholds for bone-conducted stimuli (Dimitrijevic et al., 2002; Lins et al., 1996; Small & Stapells, 2005). However, placement of the bone oscillator and calibration procedures vary between studies. This affects the BHTs as well as the ASSR thresholds for bone-conducted stimuli. By comparing difference scores instead of raw ASSR thresholds, these differences are ruled out. Only two out of three studies report difference scores. In these studies (Dimitrijevic et al., 2002; Lins et al., 1996), the oscillator was placed on the forehead and the ears were occluded. Results are quite similar to the results obtained in the present study. Differences are probably the result of the intrinsic variability of the ASSR thresholds. The number of subjects is small for all studies.

Table 7.2: Across-study comparison of average difference scores (ASSR – BHT) in dB.

	Number	*Carrier frequency (Hz)*			
	of subjects	*500*	*1000*	*2000*	*4000*
Present study	10	17 ± 6	8 ± 10	13 ± 7	10 ± 13
Lins et al (1996)	8	11 ± 5	14 ± 8	9 ± 8	10 ± 10
Dimitrijevic et al (2002)	11	22 ± 8	14 ± 5	5 ± 8	5 ± 10

In Table 7.3, difference scores are reported for recordings made with air-conducted, bone-conducted and sound-field stimuli. ASSR recordings were all carried out in the same test setting. The maximum number of sweeps per intensity level was 32. The air-conduction data were taken from Chapter 3.

Bone-conduction thresholds depend on the placement of the oscillator on the skull (forehead versus mastoid placement), the tension that is used to hold the oscillator in place and whether the ear canal is occluded or not. Even when all of these variables are held constant, bone-conduction thresholds are more variable from one subject to the next than air-conduction thresholds (Dimitrijevic et al., 2002). This is reflected in the overall variability of the difference scores for bone-conduction data, which is in general somewhat larger in comparison with air-conduction and sound-field data. Nevertheless, threshold estimation with the bone-conducted stimuli was similar to that with air-conducted stimuli. An independent samples *t*-test showed no difference (p=0.365) between air-conduction and bone-conduction difference scores averaged over all frequencies as reported in Table 7.3. This was also stated by Lins et al. (1996). The auditory steady-state responses would therefore be quite accurate in assessing conductive hearing losses.

The chance of electromagnetic artifacts is higher when bone-conducted stimuli are presented compared to air-conducted stimuli. High-amplitude stimulus artifact can result in energy that is aliased exactly to the modulation frequency. At an AD sampling rate of 1000 Hz, Small and Stapells (2004) found artifactual ASSRs at 50 dBHL and above for the 500-Hz carrier frequency and at 40 dBHL and above for the 1000-Hz carrier frequency. Artifactual responses were also obtained at 50 dBHL for a 2000-Hz carrier frequency, but not at lower levels. No artifactual responses were seen for the 4000-Hz carrier frequency. Artifacts can be reduced by alternating the stimulus polarity or by changing the sampling rate. Because of these artifacts, ASSRs for bone-conducted stimuli can only be used in patients with no or limited cochlear hearing loss, as the maximum output level without artifacts is very limited.

Table 7.3: Average difference scores (in dB) for normal-hearing adults, for modulated sinusoids presented through headphones (air conduction), through the bone conductor (bone conduction) and through a loudspeaker at 60 cm (sound field). Experiments were carried out in different subject groups.

	Number	*Carrier frequency (Hz)*				
	of subjects	*500*	*1000*	*2000*	*4000*	*Total*
Air conduction	20	13 ± 8	7 ± 7	9 ± 7	15 ± 8	11 ± 8
Bone conduction	10	17 ± 6	8 ± 10	13 ± 7	10 ± 13	12 ± 10
Sound field	10	16 ± 9	15 ± 7	8 ± 9	13 ± 6	13 ± 8

In the present study, the maximal intensity level was 40 dBHL. This could have caused artifactual responses for the 1000-Hz carrier frequency. However, only in one subject the ASSR threshold was 40 dBHL and could have been the result of artifacts. This is unlikely since the BHT in this case was 10 dBHL. In all other subjects, ASSRs were found at levels below 40 dBHL.

The use of bone-conduction ASSR would be very useful in infants, to distinguish conductive and sensorineural hearing losses. In very young babies, it is difficult to determine the middle ear status by otoscopy as well as by tympanometry, as the ear canals are still very tiny and flexible. Bone-conduction ASSR may be a possibility but has not been investigated in infants. There are several practical limitations. First, bone-conduction thresholds should be assessed in addition to air-conduction thresholds and can only be assessed for one ear at a time. This means extra test time is needed. For a more general use of bone-conduction ASSRs, the efficiency will first have to be increased considerably. Second, if the baby is tested in natural sleep, it will not be easy to keep the bone oscillator in place on the baby's head, with the appropriate tension, without waking it. Third, attention would have to be paid to the complexities of clinical bone-conduction testing to determine optimum placement of the transducer, appropriate levels of masking and compensation factors for the occlusion effect (Lins et al., 1996).

7.2 Experiment 2: Sound-field stimulation

Analogous to the previous study, ASSRs are investigated in response to stimuli presented through a loudspeaker in sound field. This application could be useful to define ASSR thresholds with hearing aids, or ‘aided’ thresholds, since the use of headphones in combination with hearing aids is inappropriate.

7.2.1 Materials and methods

The viability of defining ASSR thresholds in sound field was investigated in another group of 10 normal-hearing adults. The average age of this subject group was 21 ± 1 years. Hearing thresholds for pure tones were better than 20 dBHL for octave frequencies between 500 and 4000 Hz. A loudspeaker Yamaha MS101 II was placed at 60 cm of the middle of the head of the subject. Only the best ear was tested. The contralateral ear was masked with white noise through an ER3-A insert earphone. Sounds were calibrated in dBSPL, using a Sound Level Meter (Brüel & Kjaer 2260). Stimulus and recording parameters are similar to those described in section 7.1.1.

7.2.2 Results and discussion

The mean BHT for sound-field testing, averaged over the four carrier frequencies, was 4 ± 6 dBSPL. The ASSR threshold was on average 18 ± 9 dBSPL. Table 7.3 presents average difference scores (ASSR – BHT) for sound-field stimulation. We compared results to air-conduction and bone-conduction ASSR. By comparing the difference scores, calibration differences are not an issue. A one-way multivariate analysis of variance was carried out with a factor differentiating the three types of stimulation (air conduction, bone conduction and sound field) and the four dependent variables, difference scores for carrier frequencies of 500, 1000, 2000 and 4000 Hz. The hypothesis was tested that the population means for the dependent variables are equal across all types of stimulation. Wilks’ lambda is not significant (p=0.117), indicating that based on these data the means are not different. However, the number of subjects is very small and further research is needed to make definite conclusions.

Similar to the bone-conduction ASSR recordings, only one ear can be tested at a time. To assess both ears, the contralateral ear has to be masked and test duration doubles compared to dichotic recordings. Apart from that, ASSR recordings in sound field do not imply practical difficulties and are easily done.

7.3 Experiment 3: Case studies non-organic hearing loss

Aside from hearing-impaired infants and adults, ASSRs could be useful in other patient populations, such as patients with non-organic hearing loss or pseudohypoacusis. In these patients, the hearing loss is not consistent with clinical or audiological evaluation. Pseudohypoacusis covers hearing loss due to a psychogenic cause as well as conscious malingering. In the child population it is, in the majority of the cases, not possible to determine the reason why the child presents with the hearing loss. The motivation in adults is usually evading responsibility or receiving financial compensation (Pracy et al., 1996).

In case of non-organic hearing loss, routine audiological tests that rely on the patient's behavioral responses to presented stimuli, overestimate the hearing loss. Lack of consistency in audiological testing mostly arouses suspicion of non-organic hearing loss. Objective ASSR-thresholds can reveal the real hearing thresholds. A number of case studies will be presented to indicate the benefit of objective techniques in this patient group.

7.3.1 Case 1

Background
The patient was a mineworker of 59 years old. He suffered hearing loss for several years and wore hearing aids bilaterally since one year. He was referred for an assessment concerning a workers' compensation claim with regard to occupational noise-induced hearing loss. It was requested to objectify his hearing sensitivity status.

Auditory findings
The audiogram showed a bilaterally severe sensorineural hearing loss with hearing thresholds higher than 90 dBHL. Communication was rather difficult. Even with his hearing aids, speech understanding was poor. ASSR thresholds were determined. Surprisingly, a first recording at 80 dBSPL showed significant responses to all carrier frequencies, although this intensity level was below the patient's pure-tone behavioral thresholds and the patient was not relaxed. From the second recording on, the patient was asleep and noise levels were below 4 nV after 32 sweeps. Intensity was lowered, and for the left ear, thresholds were found at 50, 40, 40 and 60 dBSPL for 500, 1000, 2000 and 4000 Hz respectively. For the right ear, ASSR thresholds were 50, 40, 50 and 70 dBSPL. Since ASSR thresholds are in general higher than the behavioral hearing thresholds, the patient suffered only a mild hearing loss in the lower frequencies, to a moderate hearing loss in the high frequencies.

7.3.2 Case 2

Background

The patient was a girl of 14 years old. She was known to have a mild to moderate hearing loss with a conductive component. In the classroom, she sat on the first row and speech understanding was sufficient without hearing aids. However, now she claimed to have a decrease of her hearing, which caused problems at school. The question arose whether hearing aids were required.

Auditory findings

Tympanometry showed bilateral normal middle-ear status. Otoacoustic emissions were missing. The pure-tone audiogram showed a bilateral hearing loss of 80 dBHL, with an air-bone gap of 10 dB. Results of the speech audiometry were, however, not in agreement with the pure-tone audiogram. The 50% speech intelligibility threshold was bilaterally shifted by only 30 dB. Moreover, the Rinne test was normal. Therefore, objective tests were carried out to ensure the hearing thresholds. Click-evoked ABR thresholds were found at 50 dBpeSPL for both ears, corresponding to 10-20 dBnHL. In addition, ASSR recordings were carried out. For both ears, thresholds were found at 30, 20, 30 and 30 dBSPL for 500, 1000, 2000 and 4000 Hz respectively, corresponding to normal or at least near-normal hearing. The hearing loss appeared to be mainly of non-organic nature.

7.3.3 Case 3

Background

The patient was a 41-year-old woman who had been involved in a car accident. After the accident, she suffered from whiplash injury, but no other physical complaints. Approximately six weeks later, she complained about hearing loss at the left ear and difficulty with speech understanding in noisy environments. Within the framework of a medical expertise for the insurance, the patient was referred for oto-vestibular examination.

Auditory findings

A hearing evaluation before the accident showed normal hearing in both ears. After the accident, several audiological evaluations were carried out. Tympanometry showed normal middle-ear function. Pure-tone audiometry indicated normal hearing on the right ear and no residual hearing on the left ear. However, the patient did not respond to unmasked pure tones of high intensity presented at the left ear, which should have been heard by the right, normal ear as a result of cross hearing.

The click-evoked ABR threshold was determined for the left ear. Peak V was identifiable down to 60 dBpeSPL, corresponding to a hearing threshold at 20-30 dBnHL. ASSR recordings were carried out in order to confirm the ABR results. However, the patient was stressed, which resulted in recordings of poor quality. Noise levels were exceedingly high. Nevertheless, the ASSR results contained interesting information. A first recording at 60 dBSPL showed significant responses at all frequencies in the right ear, which is to be expected in a normal-hearing ear. At the left ear, responses to the 2000 and 4000 Hz carrier were highly significant. For the lower frequencies, responses were not significant, but p-values were below 0.200. Further recordings demonstrated significant ASSRs down to 40 dBSPL on the right ear and 50 dBSPL on the left ear, for certain frequencies. Even these noisy recordings could clearly point out that part of the hearing impairment was non-organic.

7.3.4 General findings

Suspicion that the patient has a pseudohypoacusis or non-organic hearing loss, or a non-organic component overlaid on an organic hearing impairment, is often first aroused by inconsistencies in basic audiometric findings. ABR can confirm this suspicion but does not provide frequency-specific information on the hearing sensitivity status. If patients are willing to remain quiet during extended AEP testing, the ASSR can provide estimates for several audiometric frequencies.

In this research project, we focused on the 80-Hz response since this is the best option when testing babies and young children. However, as the 80-Hz ASSR originates mainly from the brainstem, cortical damage cannot be detected. Therefore, the 40-Hz ASSR, which has cortical sources, would be a better choice to detect non-organic hearing loss in adults.

7.4 Conclusions

The auditory steady-state response has several possible applications within clinical practice. Different types of transducers can be used during ASSR recordings and ASSR thresholds can reveal non-organic hearing loss. However, further research is still needed for a well-considered use of the ASSR in different applications.

Chapter 8

General discussion and future research directions

8.1 Discussion of research results

This research project originated from the need for an objective technique to estimate frequency-specific hearing thresholds in babies. Since 1998, a general newborn hearing screening program has been implemented in Flanders. Screening is, of course, only effective if an accurate diagnosis can be made and efficient rehabilitation can be started. Babies of only a few weeks or months old that are diagnosed with a hearing loss, require amplification. Recent digital hearing aid technology can provide adjusted amplification for different frequency bands. The fitting of these hearing aids is thus based on frequency-specific hearing thresholds.

In a first phase of this study, we constructed a complete experimental set-up, to enable the recording of ASSRs. Since 2000, we use the MASTER software at the Lab. Exp. ORL. An experimental test protocol was developed, based on previously published findings and preliminary experiments with normal-hearing adults. The main aim of these first experiments was to explore the best possible ASSR thresholds, regardless of the clinical applicability of the used methods.

A second phase of the study comprised a systematic evaluation of the experimental protocol in a group of normal-hearing and hearing-impaired subjects. A lot of time was spent on achieving the best recording conditions. Attention was paid to good electrode placement and finding a subject position resulting in a low EEG noise level. The influence of test duration was explored, in order to create a clinical protocol, which would be applicable in babies. Since prolonging individual recordings from 10 to 15 min brings little improvement in predicting hearing thresholds, we decided to reduce the maximum length of the recordings to 10 min or 32 sweeps. Moreover, we chose for an intensity step-size of 10 dB instead of 5 dB because the gain in accuracy does not compensate for the additional test duration needed. Other stimulus and recording parameters were kept the same, since results were very promising. Moreover, in this study we observed a deterioration of the quality of the recordings after a long test duration, probably related to discomfort of the subjects. This was another indication to reduce test duration in further experiments.

Internationally, the interest in ASSR began to increase and ASSR recording systems were commercialized in the last years of this study. The AUDERA, a single-stimulus technique, came on the market first. The short test duration was a very attractive feature and persuaded many clinicians to purchase the device. As we were struggling with the issue of test duration, we wanted to evaluate the AUDERA and compare it with the MASTER technique we were familiar with. Test duration was 1 h for both techniques. The AUDERA and MASTER technique performed equally well in hearing-impaired subjects. In normal-hearing and moderately hearing-impaired subjects, however, the AUDERA technique failed to make accurate predictions in contrast with the MASTER technique, which showed equivalent results in normal-hearing and hearing-impaired subjects. Although the single-stimulus technique has some advantages over the multiple-stimulus technique, it is essential that a distinction can be made between normal hearing and hearing impairment. It was remarkable that the composition of the subject group appeared to have such a big influence on the results. Consequently, comparison of results between studies with different subject groups is difficult and one has to be cautious when extrapolating results of normal-hearing listeners to hearing-impaired listeners. A second advantage of the MASTER system is the higher degree of flexibility it offers during the recordings. The artifact rejection threshold can be adjusted and the recordings can be prolonged at threshold level or in case of high EEG noise levels. In contrast, the AUDERA system is restricted in use in case of high noise levels. The averaging process cannot be continued and the noise threshold level cannot be adjusted during the recordings. Nonetheless, ASSR testing should also be feasible in patients with high EEG noise levels. Therefore, we still give preference to the multiple-stimulus technique.

In the next step of this project, we aimed to evaluate several possible applications of the ASSR technique in a number of pilot studies. Results indicated that ASSRs can also be assessed with bone-conduction and sound-field stimuli. Bone-conduction ASSR would be helpful to investigate a possible conductive hearing loss, especially since it is hard to determine the middle ear status by tympanometry and otoscopy in babies. However, the occurrence of artifacts limits the maximum output level. Sound-field presentation of the stimuli could be used to assess for instance the functional gain of a hearing aid objectively (Picton et al., 1998). Apart from babies and young children, the ASSR has also proven to be useful in adults and children with non-organic hearing loss.

Concurrent with the experiments in adults, we first recorded ASSRs in infants in November 2001. We added the ASSR to the generally used test battery. In this way, we could immediately compare the ASSR thresholds with the corresponding ABR thresholds. Behavioral hearing thresholds were, after all, often only available several months later. In the first instance, a small group of 10 infants was evaluated in a ‘controlled’ test situation. The recordings were carried out under general anesthesia. This allowed us to add the ASSR to the current test battery and to record ASSRs at all intensity steps needed. Results were again promising. ASSRs were recordable in infants. Four thresholds in both ears could be determined in about 1 h, and correlations between ASSR and behavioral hearing thresholds were high.

Results of this pilot study encouraged us to start testing babies in natural sleep. Moreover, the screening at the NICU Department of UZ Leuven was initiated, which resulted in more referrals to the ENT Department for further diagnostic evaluation. In 2003 and 2004, a group of 30 babies was tested in natural sleep. The majority of this subject group was prematurely born. The ASSR was introduced in the diagnostic test battery and recordings were generally carried out during the first consult after a failed hearing screening. Since test sessions in natural sleep are limited in time, ABR was only carried out in a few cases, to double-check the ASSR thresholds. These recordings require a high degree of flexibility of the clinician. However, 83% of the recordings were successful.

Data obtained in infants in natural sleep and under anesthesia were analyzed altogether. In total, 53 infants were tested successfully. In this group, 60% of the infants had bilateral or unilateral normal hearing, and consequently did not need amplification. In this group, frequency-specific threshold estimation is less required. However, it can still be of interest to indicate small low- or high-frequency dips in the audiogram. The other 40% (n=22), were diagnosed with hearing loss. In this group, the frequency-specific hearing threshold estimates could be used to fit hearing aids, in nine infants in anticipation of a cochlear implant. Correlations with behavioral hearing thresholds are lower in infants than in adults. This is not surprising, since there is a delay between the ASSR recordings and the assessment of the behavioral hearing thresholds. Moreover, behavioral thresholds may be minimum response levels rather than hearing threshold levels. And finally, ear canal volume was not taken into account, which could cause a greater variability of the thresholds.

In addition to the comparison of ASSR and behavioral hearing thresholds, we compared ASSR recordings in normal-hearing infants and adults. The amplitudes and SNRs in infants are much smaller compared to adults. Consequently, ASSR thresholds are higher in infants. In the first few weeks after birth, we observed a significant increase in SNR. This indicates that it might be better to postpone ASSR testing until after the immediate neonatal period. However, to make testing in natural sleep possible, tests should be carried out before the baby is three months of age. Because of these differences between adult and infant ASSRs, clinical research within the infant population is essential for a general acceptance of the ASSR in clinical practice.

Results of these studies have shown that it is feasible to use the dichotic multiple-stimulus ASSR technique in clinical practice as a follow-up diagnostic after referral of the hearing screening. It provides reasonably accurate hearing threshold estimates, within a clinically realistic test duration. Though, ASSR should not be used as an isolated test. It is of high importance that the ASSR is part of a test battery and that ASSR results are interpreted, taking into account results of other audiometric tests. A combination of ABR and ASSR would be most complete. ABR could indicate the general degree of hearing loss. If this is known, the initial intensity level of the ASSR procedure could be adjusted, which could shorten test duration for ASSR. From an international point of view, Flanders has an excellent general neonatal hearing screening program. With this study, we endeavor to provide a very good diagnostic evaluation as well.

Testing adult subjects versus babies and young children

In this research project, ASSR recordings were carried out in adult subjects on the one hand, and in infants on the other hand. Both subject groups require a very different approach. Working with adult subjects has several advantages:

- ASSR thresholds can be compared with the corresponding behavioral hearing thresholds. If the average difference between both measures is known, estimates of the behavioral hearing threshold can be made based on the ASSR threshold by subtracting this average difference or by means of linear regression analysis. These norms can then be used when testing patients that cannot provide accurate behavioral responses. We always assessed behavioral hearing thresholds with the same set-up as used for the ASSR recordings. This means that the same modulated sinusoids were presented through the same transducers. In this way, difference scores are clear and not affected by calibration issues.
- When testing adult subjects, test duration is quasi unlimited. Test sessions of three hours and more are feasible. This allows an extensive testing protocol to be completed.

- Normal-hearing and hearing-impaired adult volunteers are easy to find, since there were no special requirements to fulfill.

The testing of adults is ideal to explore a technique, but the final target group for this type of measurement is the neonatal population. The testing of babies and young children with hearing loss or at risk of hearing loss requires a flexible and patient attitude of the clinician. The child's parents are mostly very concerned about the possible hearing loss and the consequences of this, and need to be reassured. This type of research implies that results are not always straightforward. Several methodological weaknesses are inherent to this type of clinical research:

- Data sets always contain 'gaps'. ASSR recordings were often incomplete because the infant slept only a limited period of time. Similarly, behavioral threshold data are often incomplete because the attention span was too short. Moreover, in a number of infants, it was not possible to obtain behavioral thresholds within the timeframe of this research project. In some infants, behavioral tests will maybe never be successful because of mental retardation.
- The infant ear canals are still very weak and the ear canal volume is very small. Headphones could collapse the ear canal and prevent sounds from reaching the eardrum. With insert earphones, the opening of the ear tip could be positioned against the wall of the ear canal, reducing the sound pressure level reaching the eardrum. Ear muffins could prevent this problem, but have the disadvantage that the maximum intensity level is limited and that calibration is difficult. Because of the tiny ear canal volume, it is difficult to predict the sound pressure level at the eardrum.
- The time delay between ASSR recordings and behavioral threshold testing has several implications. First, the hearing thresholds might have changed in the meantime because of a progressive hearing loss or a different middle ear status. Second, the ear canal volume might have altered, which affects the sound pressure level at the eardrum. Third, there is always a loss-of-follow-up. Parents may, for instance, go to another hospital, or refuse to accept the hearing loss of their child and turn down control appointments.

ASSR threshold test procedure

As we were interested in the clinical applicability of the ASSR as an objective technique to assess hearing thresholds, we always looked at the effect of certain parameters on the ASSR threshold. However, the ASSR threshold procedure is quite comprehensive. It requires long test sessions so that only a limited number of subjects can be tested. This is in contrast to many other studies, where the influence of parameters changes on the amplitude and SNR of the ASSR are investigated at one or more fixed intensity levels. However, the increase in amplitude and SNR as a function of intensity is not linear and variability is large. Therefore, it is difficult to predict the influence of these parameter changes on the process of threshold estimation.

Quality of the recordings

As ASSRs are very small potentials (only a few nV at threshold level), the noise level of the recording system and the EEG noise should be as low as possible. Important issues for low-noise recordings are, amongst others, a good amplifier, an adequate electrode position, low electrode impedances, a relaxed position of the subject, an efficient averaging procedure and optimal acoustical and electromagnetic shielding. The best environment to make ASSR recordings is a soundproof booth with Faraday cage as used in this study. However, in most clinical settings this is not available. Moreover, it is not evident to organize tests under anesthesia in such a small booth. These tests will rather take place in very versatile environments such as an operating room. Before starting clinical tests in a less ideal setting, we recommend mapping out possible influences of environmental factors on the quality of the recordings.

8.2 Future research directions

Completion of the data set

ASSR thresholds were assessed in 53 infants, but until now, behavioral threshold data are only available in 24 infants. Many infants, especially those referred from the NICU Department were still younger than 1 year at the time of final data processing. This data set should gradually be completed, in order to get a clearer view on the relation between ASSR and behavioral hearing thresholds in infants.

Improving the efficiency of ASSR recordings

In this research, we used rather basic ASSR stimulus and recording parameters. Presumably, the efficiency of the ASSR recording and the accuracy of hearing threshold estimates in babies can be considerably improved. First, different stimulus types might evoke larger responses (John et al., 2003). For instance, exponentially modulated tones evoke larger ASSR amplitudes compared to simple SAM tones (John et al., 2004). Second, the use of weighted averaging might enhance the quality of the recordings (John et al., 2001a). Third, more complex signal detection methods might result in faster and more accurate response detection. And fourth, multi-channel EEG recordings might facilitate the detection of the responses compared to single-channel recordings (Van Dun, 2005).

The multiple-stimulus technique would be more time-efficient if responses to all eight stimuli would reach significance at about the same time. However, it often happens that one or more responses do not reach significance and the maximum number of sweeps needs to be recorded. This occurs especially in sloping hearing losses. Also in flat audiogram configurations, the 500-Hz response is more difficult to obtain and thus requires a longer test duration. In the current set-up, the intensity level can be set differently for both ears by two channels of the audiometer. The four stimuli presented simultaneously to one ear, however, have the same level. Moreover, recordings for both ears begin and end at the same time. Thus even if only one response in one ear does not reach significance, the maximum number of sweeps needs to be recorded. It would be ideal to uncouple the amplification of the eight stimuli and the recording of the eight responses. This would really speed up the test procedure of multiple-stimulus ASSR.

Conductive hearing losses

During the ASSR assessments in infants, we experienced great difficulty to distinguish conductive and sensorineural hearing losses. Otitis media is one of the most common disorders in children. It can be defined as an inflammation of the middle ear and is often evidenced by the presence of fluid in the middle ear space (middle ear effusion), which compromises the traditional sound pathway to the cochlea and creates a mild to moderate degree of conductive hearing loss. This middle ear effusion is difficult to detect in neonates. Otoscopy and tympanometry are generally used to investigate the middle ear status. However, the infant tympanic membrane is difficult to visualize since the external ear canal is often collapsed and the tympanic membrane lies in a nearly horizontal plane (Northern & Downs, 1991). Moreover, in newborn infants, tympanometry with the standard 226 Hz probe tone is questionable since the sensitivity to middle ear effusion is low. High-frequency tympanometry (1 kHz) appears to be more reliable, but this technique is not yet widespread. Bone-conduction ASSR could diagnose conductive hearing loss, but no measurements in infants have been carried out, nor in hearing-impaired adults. First the artifact problem in bone-conduction measurements will have to be solved.

Real-ear-to-coupler difference

Part of the increased variability in infants can probably be explained by the difference in ear canal volume between subjects. Currently, the modulated sinusoids presented by insert earphones are calibrated using a 2-cc coupler as described in the standard ISO 389-2. However, this 2-cc volume represents an average adult ear canal volume. The ear canal volume in babies can be much smaller, which results in a higher sound pressure level at the eardrum and thus relatively lower hearing thresholds. Moreover, the ear canal volume can change considerably during the time delay between ASSR recordings and behavioral testing. Because of the increase in ear canal volume, intensity levels at the eardrum decrease. This could give the impression that hearing threshold levels increase during time. The best solution to this calibration issue would be the use of real-ear-to-coupler differences (RECDs). The RECD is the difference between the sound pressure level measured at the eardrum (the real-ear SPL or RESPL) and the sound pressure level measured in a coupler for the same signal (Munro & Salisbury, 2002). RECD measurements can be completed quickly and they allow a level-independent transformation of intensity levels expressed in dBSPL into RESPL (Scollie et al., 1998). In this way, the comparison of thresholds assessed at different moments in time will be clearer and the prediction of behavioral hearing thresholds by means of ASSR could be improved.

According to a study of Feigin et al. (1989), RECDs increase as a function of frequency, reflecting the limitations of a 2-cc coupler in predicting real ear SPL at higher frequencies. In children, ranging in age from 4 weeks to 5 years, the mean RECD for frequencies between 1000 and 3000 Hz was 9 dB. This suggests there is a greater risk of overamplification for children when the maximum output of hearing aids is determined using standard coupler measures of SPL. A systematic decrease in RECD was noted with increasing age. The intersubject variability in RECD is high and indicates the need for these measures to be carried out individually rather than using average figures (Westwood & Bamford, 1995).

ASSR and hearing aid fitting in infants

Hearing aid fitting in infants is mainly based on prescription rules that determine the appropriate gain for different frequency bands dependent on the hearing thresholds. Since behavioral hearing thresholds are difficult to obtain in young infants, thresholds can be estimated in an objective manner using ASSR. After fitting the hearing aid, the functional gain can be defined in an objective way, as the difference between hearing thresholds without (unaided) or with hearing aids (aided). In order to define aided thresholds, sounds have to be presented through a loudspeaker in a sound field or ear-specific via audio-input to the hearing aid directly. ASSR is advantageous over ABR to assess the functional gain since the continuous modulated tones are less likely to be distorted by amplification in a hearing aid or a sound-field speaker compared to transient stimuli such as clicks. Picton et al. (1998) assessed aided thresholds in hearing-impaired children and found objective thresholds near the behavioral thresholds in aided condition. However, amplification is usually non-linear, which may lead to discrepancies in the physiologic measurement of gain (Picton et al., 2003). Moreover, gain of a hearing aid can be determined with acoustic measurements in the ear canal. Nevertheless, aided ASSR measurements can particularly be useful in patients who do not have clear behavioral or physiologic responses thresholds without aids, to demonstrate that the hearing aid does cause sound to activate ASSRs at intensities where there was no response without the aid.

Assessment of supra-threshold processing

Apart from the assessment of hearing thresholds, the ASSR could have applications in the assessment of supra-threshold processes that are important for speech understanding. The ability of the brain to follow rapid changes in amplitude and frequency can be assessed by recording ASSRs to modulations in amplitude and frequency of supra-threshold tones. An objective technique to assess supra-threshold hearing would be very helpful in the investigation of the ability to understand speech in infants. A number of studies have evaluated the relation between the detectability of independent amplitude and frequency modulation (IAFM) of a carrier tone and word recognition (Dimitrijevic et al., 2001; Dimitrijevic et al., 2004; Picton et al., 2002). When the IAFM stimulus parameters were adjusted to resemble the acoustic properties of everyday speech, the number of significant IAFM responses is related to the word recognition score in normal-hearing and hearing-impaired adults. Correlation coefficients ranged from 0.65 to 0.85, dependent on subject group and frequency of stimulation (Dimitrijevic et al., 2004). Further research might lead to an objective technique, which enables the accurate prediction of word recognition scores in infants.

The ASSR may also be used to demonstrate temporal auditory acuity, or the ability of the auditory system to discriminate rapid temporal changes in the envelope of a sound (Purcell et al., 2004). Envelope cues are very important to speech intelligibility. Purcell and colleagues (2004) investigated EFRs as an objective measurement of temporal processing in the auditory nervous system. EFRs evoked by 25% amplitude-modulated white noise with a sweep of modulation frequencies from 20 to 600 Hz were significantly related to behavioral gap and modulation detection tasks.

Objective electrophysiological measures for supra-threshold processing would be very helpful in testing subjects who are unable to give reliable behavioral responses. However, for application of these techniques in clinical practice, test duration needs to be reduced considerably and the efficiency needs to increase, to enable accurate prediction of behavioral measures.

8.3 General conclusions

In this dissertation, research about the clinical applicability of recent fundamental findings is reported. At present, the hearing abilities of all infants referred to the ENT Department of UZ Leuven after a negative screening result by Kind & Gezin or by the NICU of UZ Leuven are further evaluated by means of ASSR based on this research. In children younger than 3 months, the success rate in natural sleep is 83%. Thanks to this early assessment of the audiogram, amplification can be provided sooner and in a way that is more adapted to the patients needs. The progress of the hearing status can be followed up in an optimized way.

More specifically in this thesis:

- a robust experimental set-up was built to reliably record the small auditory steady-state responses,
- the ASSR technique was evaluated in normal-hearing and hearing-impaired adults in order to develop a test protocol suitable for clinical use,
- the two internationally most applied ASSR techniques were compared,
- a large sample of babies was tested and the possibility to estimate frequency-specific hearing thresholds by means of ASSR was evaluated,
- a diagnostic follow-up program was developed for hearing-impaired children younger than 1 year, in collaboration with Kind & Gezin, the NICU and the ENT Department of UZ Leuven.

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Acronyms and Abbreviations

ABR	Auditory Brainstem Response
AD	Analogue-to-Digital
AEP	Auditory Evoked Potential
AM	Amplitude-Modulated
AMFR	Amplitude Modulation Following Response
ASSR	Auditory Steady-State Response
BHT	Behavioral Hearing Threshold
Cz	vertex
DA	Digital-to-Analogue
EEG	ElectroEncephaloGram
EFR	Envelope Following Response
e.g.	exempli gratia: for example
ENT	Ear Nose and Throat
FFR	Frequency-Following Response
FM	Frequency-Modulated
FFT	Fast Fourier Transform
HI	Hearing-Impaired
JCIH	Joint Committee on Infant Hearing
K.U.Leuven	Katholieke Universiteit Leuven
MASTER	Multiple Auditory STEady-state Responses
n	number
NH	Normal-Hearing
NICU	Neonatal Intensive Care Unit
OAE	OtoAcoustic Emission

Oz	inion
p	probability
PCA	PostConceptional Age
PTA	Pure-Tone Average
SAM	Sinusoidally Amplitude-Modulated
SNR	Signal-to-Noise Ratio
UZ Leuven	Universitaire Ziekenhuizen Leuven
VRA	Visual Reinforcement Audiometry
cc	cubic centimeter
dB	decibel
dB(A)	A-weighted decibel
dBHL	decibel hearing level
dBpeSPL	decibel peak equivalent sound pressure level
dBSL	decibel sensation level
dBSPL	decibel sound pressure level
h	hour
Hz	hertz
kHz	kilohertz
kOhm	kiloOhm
min	minute
ms	millisecond
mV	millivolt
s	second
µs	microsecond
µV	microvolt

Summary

Since 1998, hearing of all newborns in Flanders (Belgium) is screened by the Flemish public agency Kind & Gezin at 4 weeks of age. If the outcome of the screening does not indicate normal hearing, more detailed hearing assessment is required. However, standard behavioral testing is not possible, so that assessment has to rely on objective physiological techniques that are not influenced by sleep or sedation. The most commonly used objective technique to assess hearing in infants is the click-evoked auditory brainstem response (ABR). This technique, however, is restricted to the prediction of a general degree of hearing loss. In case of frequency-dependent hearing loss, the ABR could be misinterpreted. Furthermore, for general diagnostic purposes and for efficient fitting of hearing aids, it is vital to obtain hearing thresholds at different audiometric frequencies.

The last few years, the use of auditory steady-state responses (ASSRs) has been investigated as an objective technique to assess hearing thresholds at different frequencies. This technique uses continuous rather than transient stimuli and enables the recording of responses to several carrier frequencies simultaneously. In this research project, we studied the clinical application of ASSRs as a follow-up diagnostic in the neonatal population, with the purpose to reduce the consequences of hearing loss by means of an adequate rehabilitation program.

In first instance, we evaluated the ASSR technique in normal-hearing and hearing-impaired adults in order to develop a test protocol suited for testing sleeping babies at the ENT Department. High precision of the threshold estimate as well as a reasonable test duration are crucial for the clinical applicability of a technique. Therefore, we assessed the influence of an increased test duration on the precision of the hearing thresholds estimated by dichotic multiple-stimulus ASSRs. Moreover, we compared the two internationally most applied ASSR techniques, the single-stimulus and multiple-stimulus ASSR. Based on these findings in adults, we developed a clinical test protocol that enables the prediction of a four-frequency audiogram within one hour.

With this adapted test protocol, we assessed ASSRs in a large number of babies and young children. In children younger than 3 months, the success rate in natural sleep was 83%. First, we compared ASSRs recorded in normal-hearing high-risk infants younger than 3 months of age with adult ASSRs. In infants, the ASSR amplitudes were three to four times smaller than in adults. Consequently, the normal-hearing ASSR thresholds in infants were elevated. The detectability of the ASSR increased significantly during the first few weeks and months after birth. Our study also showed that the optimal age of testing was between one week and three months of corrected age. In this age group, the success rate of testing in natural sleep is high and the use of sedatives can be minimized. Second, we evaluated ASSRs in a group of infants with a wide range of hearing threshold levels and compared ASSR thresholds with ABR and behavioral hearing thresholds. In spite of the methodological difficulties inherent to this type of research in young children, the correlation between ASSR and behavioral hearing thresholds was high, and hearing thresholds can be estimated with reasonable accuracy.

The ASSR technique has several possible applications. Aside from estimating hearing thresholds with insert phones, we investigated ASSRs in response to stimuli presented through a bone oscillator and in sound field in adult subjects. Moreover, we applied the ASSR technique in patients with non-organic hearing loss.

In conclusion, research on the clinical applicability of recent fundamental findings is reported. At present, the hearing abilities of all infants, referred to the ENT Department of UZ Leuven after a negative screening result, are further evaluated by means of ASSR based on this research. Thanks to this early assessment of the audiogram, amplification can be provided sooner and in a way that is more adapted to the patients needs. Moreover, the progress of the hearing status can be followed up in an optimized way.

Samenvatting

Sinds 1998 wordt het gehoor van alle pasgeborenen gescreend door Kind & Gezin op de leeftijd van 4 weken. Als het resultaat van deze screening geen normaal gehoor aangeeft, is een uitgebreidere gehoordiagnostiek vereist. Aangezien standaard gedragsaudiometrische tests nog niet mogelijk zijn, moeten objectieve fysiologische technieken die niet beïnvloed zijn door slaap of sedatie gebruikt worden. De meest frequent toegepaste objectieve techniek om het gehoor bij jonge kinderen te bepalen is de BERA (Brainstem Evoked Response Audiometry) die gebaseerd is op klik-geëvokeerde hersenstampotentialen. Deze techniek is echter beperkt tot het voorspellen van een algemene graad van gehoorverlies. In geval van frequentie-afhankelijk gehoorverlies, zou de BERA kunnen resulteren in een foutieve diagnose. Bovendien is het voor algemene diagnostische doeleinden en voor een efficiënte aanpassing van hoortoestellen essentieel om gehoordrempels te kennen voor verschillende audiometrische frequenties.

De laatste jaren zijn *auditory steady-state responses* (ASSR) onderzocht als mogelijke objectieve techniek om de gehoordrempel te bepalen op meerdere frequenties. In plaats van transiënte stimuli gebruikt deze techniek continue stimuli. Het is bovendien mogelijk om responsen voor verschillende stimulusfrequenties tegelijkertijd op te meten. In dit onderzoeksproject hebben we de klinische toepassing van ASSR onderzocht in de neonatale populatie, als een follow-up diagnostische test. Hierdoor willen we een adequate rehabilitatie garanderen met het oog op het reduceren van de gevolgen van gehoorverlies.

In eerste instantie hebben we de ASSR-techniek geëvalueerd bij normaalhorende en slechthorende volwasssen, om zo een testprotocol te ontwikkelen dat geschikt is voor het testen van slapende baby's op de NKO-afdeling. Zowel een hoge graad van precisie van de drempelschatting als een aanvaardbare meettijd zijn cruciaal voor de klinische toepasbaarheid van een techniek. Daarom hebben we de invloed van een toenemende meettijd onderzocht op de precisie van de drempelschattingen gemaakt op basis van dichotische meervoudige ASSR's. Daarnaast hebben we de twee internationaal meest gebruikte ASSR-technieken vergeleken, namelijk de

enkelvoudige ASSR en de meervoudige ASSR. Gebaseerd op deze bevindingen bij volwassenen, hebben we een klinisch testprotocol ontwikkeld dat de schatting van een vier-frequentie audiogram mogelijk maakt binnen een meettijd van één uur.

Met dit aangepast testprotocol hebben we ASSR's opgemeten in een grote groep baby's en jonge kinderen. Bij kinderen jonger dan 3 maanden werden de tests in 83% van de gevallen succesvol uitgevoerd in natuurlijke slaap. Eerst hebben we ASSRs opgemeten bij normaalhorende hoog-risico kinderen jonger dan drie maanden en deze vergeleken met volwassen ASSR's. Bij jonge kinderen zijn de ASSR-amplitudes drie tot vier keer kleiner dan bij volwassenen. Bijgevolg zijn de normaalhorende ASSR-drempels bij jonge kinderen verhoogd. De detecteerbaarheid van de ASSR verhoogt significant tijdens de eerste weken en maanden na de geboorte. Onze studie heeft ook aangetoond dat de optimale testleeftijd tussen 1 week en 3 maanden gecorrigeerde leeftijd is. In deze leeftijdsgroep is het slaagpercentage in natuurlijke slaap hoog en kan het gebruik van slaapmiddelen vermeden worden. Vervolgens hebben we de ASSR-techniek geëvalueerd in een groep kinderen met verschillende graden van gehoorverlies. ASSR-drempels werden vergeleken met BERA en gedragsaudiometrische drempels. Ondanks de methodologische moeilijkheden die inherent zijn aan dit type van onderzoek bij jonge kinderen, is de correlatie tussen ASSR en gedragsaudiometrische drempels hoog en kunnen gehoordrempels geschat worden met een redelijke precisie.

De ASSR-techniek heeft vele mogelijke toepassingen binnen de klinische praktijk. Naast het schatten van gehoordrempels met insert phones, hebben we de mogelijkheid onderzocht om ASSR's op te meten als respons op stimuli aangeboden via een beengeleider en in een geluidsveld bij volwassen subjecten. Bovendien hebben we de ASSR-techniek toegepast bij patiënten met een psychogeen gehoorverlies.

In deze thesis wordt onderzoek over de klinische toepassing van recente fundamentele bevindingen gerapporteerd. Op dit ogenblik wordt het gehoor van alle kinderen, die verwezen werden na een negatief screeningsresultaat naar de NKO-afdeling van UZ Leuven, verder geëvalueerd aan de hand van de ASSR-techniek gebaseerd op dit onderzoek. Dankzij deze vroege bepaling van het audiogram kan sneller versterking aangeboden worden die meer aangepast is aan de noden van de patiënt. Bovendien kan het gehoorverlies opgevolgd worden op een geoptimaliseerde manier.

Short Curriculum Vitae

Heleen Luts was born in Leuven, Belgium, on May 25th 1978. She received secondary school training (Latin-Mathematics) at the Heilig-Hart Instituuut in Heverlee and graduated in 1996. In 2000, she obtained a Masters degree in Speech-Language Pathology and Audiology (Logopedie & Audiologie) with great distinction at the Katholieke Universiteit Leuven (K.U.Leuven). During her studies she received training for three months at the Audiologisch Centrum Hoensbroeck in the Netherlands. She presented a thesis entitled: ‘Comparative study of speech understanding in noise with two-microphone hearing aids’ and received the SLF-Award for best thesis Speech-Language Pathology and Audiology in The Netherlands and Flanders. In October 2000, she started a postgraduate training and became certified in Audiology. Combined with this training, she started as a Ph.D. student at the Laboratory for Experimental Otorhinolaryngology, Faculty of Medicine, of the K.U.Leuven, under supervision of Prof. Jan Wouters. Her main research interests are objective audiometry and noise reduction in hearing aids.
She lives together with Maarten Delaet and daughter June.

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