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Contralateral Suppression of Otoacoustic Emissions: Working Towards a Simple Objective Frequency Specific Test for Hearing Screening

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1. Introduction

Hearing loss affects all demographics regardless of geographical location or age. In a similar fashion to how hearing loss can isolate post-lingually deaf adults, hearing loss in the pediatric population has profound detrimental effects despite the richness of the deaf culture. A complete discussion of the adverse effects of hearing loss must include discussion of this important component of the deaf and hearing impaired population. The World Health Organization defines “disabling hearing impairment” in children under the age of 15 years as an unaided hearing threshold level in the better ear of 31 dB HL or more using pure tone averages at 0.5, 1, 2 and 4 kHz. The prevalence of childhood hearing loss is 1.2 to 1.7 cases per 1000 live births and the prevalence increases up to 6 years of age as a result of meningitis, delayed onset of genetic hearing loss, or delayed diagnosis (Kral & O'Donoghue, 2010). In the majority of cases of childhood hearing loss is congenital with a smaller proportion being progressive or acquired (A. Davis & Wood, 1992; A. Davis et al., 1997). The prevalence is greater still in developing countries because of lack of immunization, exposure to ototoxic drugs, and consanguinity (Kral & O'Donoghue, 2010). Profound hearing loss (hearing loss > 90 dB) has far-reaching, lifelong consequences in children (Kral & O'Donoghue, 2010). Andrej *et al.* report that there can be a restriction in learning and literacy as a result of the lack of development of spoken language with its impact on daily communication (Kral & O'Donoghue, 2010; Marschark & Wauters, 2008). This in turn has been shown to substantially compromise educational achievement and employment opportunity later in life (Allen, 1986; A. Davis et al., 1997; Schroeder et al., 2006; Thompson et al., 2001; Wake, Hughes, Poulakis, Collins, & Rickards, 2004a). The detrimental effects of profound hearing loss in children are summarized in Table 1. Unless children are afforded opportunities to develop language, deaf children can fall behind their hearing peers in communication, cognition, literacy and psychosocial development (Holden-Pitt & Albertorio, 1998).

Speech and language development Academic achievement Social-emotional development Childhood behavioral problems Comprised employment opportunities in later life Self-perceived health status
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*(Allen, 1986; A. Davis et al., 1997; Kral & O'Donoghue, 2010; Marschark & Wauters, 2008; Schroeder et al., 2006; Thompson et al., 2001; Wake, Hughes, Poulakis, Collins, & Rickards, 2004a)

Table 1. Detrimental Effects of Profound Hearing Loss in Childhood*

The widespread use of universal neonatal hearing screening has been established based on the growing body of evidence that early detection of hearing loss leads to early aural rehabilitation (Kennedy, McCann, Campbell, Kimm, & Thornton, 2005). Multiple studies have demonstrated the deleterious effect of bilateral hearing loss on speech and language development (Allen, 1986; A. Davis et al., 1997; Thompson et al., 2001; Wake, Hughes, Poulakis, Collins, & Rickards, 2004b). However if caught early, the effects of hearing loss are somewhat mitigated. Yoshinaga-Itano *et al.* reported on the ability of early detection of hearing loss to improve language development as measured by standardized testing (Yoshinaga-Itano, Sedey, Coulter, & Mehl, 1998; Yoshinaga-Itano, 2003). Children enrolled into language programs at earlier ages have improved vocabulary and verbal reasoning skills on standardized tests at 5 years of age (Moeller, 2000). Opponents to Universal screening cite the great cost of such widespread screening as well as efficacy in earlier years. From a pragmatic, fiduciary perspective, a cost-effectiveness study has shown that as a result of special education needs, failure to detect severe-to-profound hearing loss can cost the educational system approximately \$38 000 - 240 000 (USD) per child over their educational lifetime (Mohr et al., 2000). It would seem then that detecting these children would offset a significant amount of the cost. Furthermore, in areas that have adapted a Universal Newborn Hearing protocol, detection of congenital hearing loss has nearly doubled since its introduction (Choo & Meinzen-Derr, 2010).

It is clear that the early detection of hearing loss has strong developmental, psychosocial and societal implications as well. Therefore, in 2007 the American Academy of Pediatrics' Joint Committee on Infant hearing endorsed the early detection of hearing loss with an aim at early intervention to improve linguistic competence and literary development (Busa et al., 2007). They recommended that all infants should be screened prior to 1 month of age. Children identified with hearing loss by screening should have a comprehensive audiological assessment by 3 months of age. After audiological assessment, children with confirmed hearing loss should receive appropriate intervention by dedicated hearing loss health care and education professionals not later than 6 months of age. Children with risk factors for hearing loss (a summary of commonly cited risk factors can be found in Table 2.) should be followed by on-going surveillance starting at 2 months of age. Unfortunately in many centers the "lost to follow up" rates approach 40% of infants who do not pass their infant screening (Choo & Meinzen-Derr, 2010). All centers must work diligently to ensure children who fail their hearing screen are referred appropriately to maximize their potential and mitigate the lifelong effects of hearing loss. The following sections will provide an

overview of existing neonatal hearing screening tests and use of the medial olivocochlear system as a potential new screening method.

<p>Craniofacial syndromes: Crouzon disease, Klippel-Feil syndrome, and Goldenhar syndrome</p> <p>Syndromes known to be associated with sensorineural hearing loss: Branchio-oto-renal syndrome, Pendred syndrome, Wardenburg syndrome, Treacher-Collins, Stickler syndrome, Usher syndrome</p> <p>Neurodegenerative disorders: Hunter syndrome, Friedrich's ataxia, Charcot-Marie-Tooth syndrome</p> <p>Trauma</p> <p>Extracorporeal membrane oxygenation</p> <p>Chemotherapy</p> <p>Consanguinity</p> <p>Family history of hearing loss</p> <p>Neonatal hyperbilirubinemia</p> <p>Neonatal intensive care unit admission for > 5 days</p> <p>Infection and neonatal sepsis: CMV, measles, mumps, rubella, <i>H influenzae</i> type b, and childhood meningitis, toxoplasmosis, herpes, syphilis, bacterial meningitis</p> <p>Genetic mutations</p>
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*(Busa et al., 2007; Manchaiah, Zhao, Danesh, & Duprey, 2011)

Table 2. Risk factors for childhood hearing loss*

2. Existing neonatal hearing tests

The difficulty of testing young individuals using subjective methods has led to the development of hearing testing based on objective methods such as otoacoustic emissions and auditory brainstem response testing (James, 2011; Thompson et al., 2001).

2.1 Auditory evoked potentials

Measurement of auditory evoked potentials (AEP) has been possible since the 1960s. AEPs represent electrical activity occurring along the length of the auditory pathway. They are typically described by their latency from the onset of the auditory stimulus: early (0 to 15 milliseconds), middle (15 to 100 milliseconds) and late (100 to 500 milliseconds). Auditory brainstem responses (ABR) appear to be the most clinically useful early latency AEPs for detecting hearing loss in newborns and infants (Hecox 1974). Hecox *et al.* first speculated on the use of Auditory Brainstem Responses (ABR) as an objective method of assessing infant hearing in 1974 (Hecox & Galambos, 1974). Measurement of ABR makes use of the summation of action potentials from the cochlear nerve to the inferior colliculus of the midbrain in response to a click stimulus applied to the test ear. Since that time the use of ABR has become a widely accepted method to assess auditory function and hearing sensitivity. The commonly cited advantages and disadvantages of ABR are summarized in Table 3.

Screening ABR utilizes a click or tone pip stimulus presented via a headphone or a transducer inserted into the subject's ear. Click stimuli are commonly used and make use of a broad range of frequencies (1 – 6 kHz) but do not provide information about hearing in lower frequencies (Jacobson & Jacobson, 2004) . If necessary, tone pips can be used to acquire frequency specific information (Jacobson & Jacobson, 2004). The subject is prepared with three surface electrodes placed on the forehead and both mastoids or earlobes. The electrodes detect click or tone pip-induced action potentials that are generated in the cochlea. The signal is transmitted from along the cochlear nerve from the cochlear nucleus to the inferior colliculus. The amplitude of the action potential is measured in microvolts and averaged. The averaged potential is then plotted against time to create a waveform with characteristic peaks labeled I-VII (Table 4). Only waves I and II correspond to true action potentials. Waves III-VII are thought to represent post-synaptic activity in the major brainstem auditory centres. Given the necessity of electrode placement and duration of approximately 15 minutes, sedation is often required (Kral & O'Donoghue, 2010). The morphology and latency of the wave form is compared to a normal wave form and a pass or fail result is generated. The sensitivity of ABR is generally quoted as 84-100% and the specificity is 99.7% (A. Davis et al., 1997; Hall, Smith, & Popelka, 2004; Llanes & Chiong, 2004).

2.2 Otoacoustic emissions

Initially hypothesized in 1948 by the theoretical physicist Thomas Gold and later confirmed by Kemp in 1978, Otoacoustic emissions (OAE) now provide an important non-invasive method of auditory testing (Gold, 1948; Kemp, 1978b). OAEs are acoustic signals generated by the activity of the outer hair cells of the cochlea that occur during normal hearing. Control of outer hair cell activity is intimately linked with the olivocochlear pathway and will be discussed further in later sections. In brief, the mechanical energy generated by the outer hair cells propagates backward to the tympanic membrane. Movements of the tympanic membrane in turn produce acoustic signals that can be detected by an extremely sensitive microphone placed in the external ear canal. The presence of OAEs demonstrates the presence of functional outer hair cells suggesting the presence of a cochlea which forms the basis of this screening method. Testing of OAEs is simple and efficient requiring approximately 10 minutes. Sensitivity and specificity of OAE testing for hearing impairment ranges from 76.9-98% and 90% respectively (A. Davis et al., 1997; Llanes & Chiong, 2004; Thompson et al., 2001).

Different types of OAE can be detected but only some are useful in hearing testing (Saurini, Nola, & Lendvai, 2004). Spontaneous OAEs are obtained without any acoustic simulation. They are narrow band signals present in 40-70% of normal ears. Evoked OAEs are stimulated by acoustic signals and comprise a range of subtypes. Sustained frequency OAEs are obtained by continuous acoustic stimuli and are found in approximately 94% of people. Their measurement is typically complex and is not used very often. Transient OAEs are stimulated by clicks or tone bursts. Distortion Product OAEs (DPOAE) are produced in response to the simultaneous presentation of two stimuli and can be found in up to 98% of normal hearing individuals. As suggested by the name, stimuli for DPOAE consist of the combination of two stimuli that vary by frequency (f_1 and f_2) and intensity (L_1 and L_2). Varying the relationship of f_1 and f_2 and L_1 and L_2 determine the frequency response. Achieving an optimal response is usually obtained by setting L_1 equal or greater than L_2 e.g.

65 and 55 dBL SPL respectively are commonly used. Responses are usually the most robust when recorded at the frequency $2f_1-f_2$. Transient OAE testing applies a brief click to the test ear to elicit the hair cell response. As such, Transient OAE measurement lacks frequency specificity (Jacobson & Jacobson, 2004). Conversely, stimulus tones used in DPOAE testing combine frequency stimuli in a predictable way that can measure specific regions of the cochlea allowing frequency specific testing (Jacobson & Jacobson, 2004). While OAEs have been widely adapted for newborn hearing screening programs, they are still only surrogate markers for hearing. Their presence indicates normal function of the outer hair cell, middle ear and ear canal. As such, conditions such as auditory neuropathy, cochlear nerve hypoplasia or inner hair cell anomalies can be missed and may lead to delay in diagnosis and initiation of aural rehabilitation.

	Advantage	Disadvantage
Otoacoustic Emissions	<ul style="list-style-type: none"> Simple administration - minimal training required Cost-effective Results are immediately available Average screening time is less than ABR 	<ul style="list-style-type: none"> Only assesses outer hair cell function Debris or fluid in the external ear may affect results Failure rates are high during first 24 hours after birth No use in fluid filled middle ear Requires quiet environment Sensitivity - may fail to detect infants with very mild hearing loss or central auditory pathologies
Automated auditory brainstem response	<ul style="list-style-type: none"> Assess greater extent of auditory system Requires no interpretation by the screener ABR results are less affected by middle ear or external ear debris than OAEs Results are immediately available May detect neural or central auditory pathologies 	<ul style="list-style-type: none"> Requires more operator knowledge than ABR ABR may be susceptible to electrical interference Sensitivity - may fail to detect infants with very mild hearing loss Requires long period of time Cost May take longer in noisy environment Patient must be sleeping Potential for electrical and noise artifact

Table 3. Advantages and Disadvantages of Existing Hearing screening methods

Wave I	Action potential arising from afferent activity of cochlear nerve entering internal auditory canal
Wave II	Action potential arising from proximal cochlear nerve entering brainstem
Wave III	Arise from second order neurons beyond the cochlear nerve in the cochlear nucleus
Wave IV	Arise from third order neurons located in the superior olivary complex
Wave V	Multiple anatomic origins postulated in the vicinity of the inferior colliculus
Wave VI	Arise from medial geniculate body
Wave VII	Arise from medial geniculate body

Table 4. Characteristic auditory brainstem response waves

3. Auditory neuropathy spectrum disorder (ANSD)

One disorder that continuously eludes the new born hearing screen is ANSD. ANSD represents a range of hearing disorders of variable severity which present with pure tone hearing thresholds that may be low or approach normal, but underestimate the subject's perception of hearing difficulty. Included within the spectrum are inner hair cell anomalies, neuropathy of the auditory nerve, disruption of the olivocochlear response (OCR), and brainstem dysfunction that can be secondary to kernicterus (Amatuzzi et al., 2001; Berlin et al., 2005; Harrison, 1998; Hood & Berlin, 2001; Shapiro, 2003; Starr, Picton, Sininger, Hood, & Berlin, 1996; Yasunaga et al., 1999). The unifying feature of ANSD diseases are a characteristic finding of abnormal ABR waveforms in the presence of normal OAE and/or cochlear microphonic (CM). Middle ear muscle reflexes and the olivocochlear response are also absent. These findings are suggestive of persistent outer hair cell activity but lack of a normal afferent auditory pathway and as such would be missed by currently employed screening methods (Manchaiah et al., 2011). Accurate diagnosis is hampered by the lack of a simple commercially available test for OCR function but typically the diagnosis can be assumed from OAE and ABR results alone.

Etiologies of ANSD that have been identified include polyneuropathy (especially in adults), perinatal anoxia and hypoxia, and hyperbilirubinaemia, congenital brain anomalies, ototoxic drug exposure, and genetic factors. An estimated 40% of cases have an underlying genetic basis, which can be inherited in both syndromic and non-syndromic conditions (Harrison, 2001; Manchaiah et al., 2011; Nadol Jr, 2001; Starr et al., 1996).

Treatment options in ANSD include auditory verbal therapy, cued speech, hearing aids and cochlear implantation (Cone-Wesson, Rance, & Sininger, 2001; Rance & Barker, 2008a; Hood & Berlin, 2001). Prognostication and predicting treatment outcome is difficult and varies depending on origin. Some forms of neonatal ANSD can show significant spontaneous

improvement (Attias & Raveh, 2007; Rance & Barker, 2008b). As such determination of patient who will benefit from hearing aids or cochlear implantation is difficult (Raveh, Buller, Badrana, & Attias, 2007). The development of improved testing techniques that can be used to diagnose, characterize, and differentiate between the numerous diseases that make up this spectrum may allow patients to be treated earlier.

4. The olivocochlear pathway

4.1 Neuroanatomy and physiology

Cochlear function including the sensitivity and frequency tuning of the peripheral auditory system is influenced by incoming acoustic stimuli but also higher cochlear function. The olivocochlear pathway is a neural pathway which innervates cochlear outer hair cells (OHC), linking the superior olivary complex to the cochlea. Further insights into this pathway may improve our ability to screen for various forms of hearing loss such as ANSD.

The olivocochlear neural pathway is comprised of efferent neurons that travel from the superior olivary complex in the brainstem to cochlear hair cells. First described in 1946, Rasmussen (Rasmussen, 1946) traced the neural fibres from the floor of the fourth ventricle, along the inferior and superior vestibular nerves, then into the cochlear nerve in the bundle of Oort (the vestibulocochlear anastomosis). Later he confirmed passage of the pathway into the cochlea and named it the olivocochlear bundle (Rasmussen, 1953). This neural pathway, the olivocochlear efferent pathway, is now thought to play an important role in the olivocochlear reflex. There appear to be two forms of olivocochlear efferent fibres, medial olivocochlear (MOC) and lateral olivocochlear (LOC) efferents. The majority are the thin, unmyelinated fibres of the LOC system arising from the lateral superior olive and travel via the vestibular nerve to the cochlea where they innervate the auditory nerve supplying the inner hair cells (Kimura & Wersäll, 1962; Warr, 1975). While the LOC system received contributions from both sides of the brainstem, the majority of fibres innervate the ipsilateral cochlea (Guinan Jr, 2006). Thick, myelinated neurons of the MOC pathway originate in the medial part of the superior olivary complex. A portion of fibres cross the midline to the contralateral cochlea while others project to the ipsilateral cochlea both via the vestibular nerves (Guinan Jr, 2006). Within the cochlea the MOC fibres innervate the outer hair cells; this is referred to as the medial olivocochlear system (MOCS). The MOCS is innervated by ascending and descending neural pathways. Descending innervations arises from the inferior colliculus and auditory cortex (Mulders & Robertson, 2000a; Mulders & Robertson, 2000b).

Ascending innervation arises predominantly from the contralateral cochlea, by way of interneurons which cross the brainstem from cochlear nucleus to the olivary complex (Brown, Venecia, & Guinan, 2003; Morest, 1973; Ye, Machado, & Kim, 2000). The majority of MOCS fibres cross back over the midline to innervate the cochlea from which innervation is received (Azeredo et al., 1999; M. Liberman & Brown, 1986). A smaller proportion of MOCS fibers do not travel back across the brainstem and therefore innervate the cochlea on the same side. As they are stimulated by signals from the contralateral ear they provide a mechanism by which stimulation of one ear can influence the detection of acoustic signals by the other ear (Azeredo et al., 1999; Warren III & Liberman, 1989a).

4.2 Physiology of the olivocochlear pathway

Despite decades of investigation since the discovery of the olivocochlear pathway, understanding of its purpose remains somewhat speculative (Rasmussen, 1946). Proposed roles include protection against noise-induced hearing loss, enhancement of discrimination of sound in noise, or a role predominantly during development of the auditory pathway (Michey, Khalifa, Perrot, & Collet, 1997; Rajan & Johnstone, 1988; Walsh, McGee, McFadden, & Liberman, 1998).

There are a few studies of inter-cochlear interaction in humans which are consistent with MOCS functioning to reduce sensitivity of the cochlea to auditory stimuli. For example, contralateral pure tone stimulation causes a reduction of compound action potentials (Folsom & Owsley, 1987). Contralateral narrow band noise causes a 'negativation' of the summing potential response to ipsilateral tone bursts (i.e. the negative amplitude of summing potential increases) (Innitzer & Ehrenberger, 1977). There are indications that cortical function (e.g. visual or auditory attention tasks) influences olivocochlear activity via descending neural pathways (Froehlich, Collet, & Morgon, 1993; Maison, Durrant, Gallineau, Michey, & Collet, 2001).

Much more information on olivocochlear function has come from electrophysiological studies in animal models. Various investigations have supported the conclusion that MOCS activity turns down the gain of the cochlear amplifier (Siegel & Kim, 1982). The cochlear amplifier is an active process within the cochlea in which motor activity of OHCs increases sensitivity of the cochlea, by amplification of the basilar membrane motion induced by acoustic energy. With electrical stimulation of the olivocochlear bundle (OCB) in the floor of 4th ventricle, the amplitude of the compound action potential of the auditory nerve induced by auditory stimuli is reduced (Galambos, 1956; Nieder & Nieder, 1970; Wiederhold & Peake, 1966). In this way, the threshold of the auditory nerve can be increased by as much as 25dB an effect referred to as the 'level shift' (Galambos, 1956). By using focal stimulation near the cell bodies of olivocochlear fibers, it has been shown that MOCS mediates this effect (i.e., via action on OHCs), rather than LOCS (Gifford & Guinan Jr, 1987). Electrical stimulation of the OCB increases the cochlear microphonic and causes a decrease in the electrical impedance of scala media of the guinea pig (Mountain, Daniel Geisler, & Hubbard, 1980). These changes are considered to be due to hyperpolarization of outer hair cells (Art, Fettiplace, & Fuchs, 1984; Mountain et al., 1980). Thus electrical stimulation of MOCS suppresses OHC activity so dampening basilar membrane motion and reducing cochlear amplification. This has an indirect effect on IHC activity, as demonstrated by the level shift.

Contralateral acoustic stimulation (CAS) has been found to elicit similar effects to electrical stimulation of the MOCS. This was first reported by Fex, who found that CAS increased the cochlear microphonic (Fex, 1962). Recording from the round window in cats, Liberman showed that the compound action potential generated by ipsilateral tone pips was suppressed by contralateral noise or tones. Sectioning of the olivocochlear bundle in the floor of 4th ventricle or in the inferior vestibular nerve abolished this contralateral suppression effect (M. C. Liberman, 1989; Warren III & Liberman, 1989b). Such studies clearly show that the MOCS is stimulated by ascending signals from the auditory pathway.

Descending neural pathways also contribute to the MOCS. This has been shown in humans by increased MOCS activity when attention is focused on acoustic signals (Maison, Micheyl, & Collet, 2001). Animal studies have shown that electrical stimulation of the inferior colliculus increases MOCS activity (Mulders & Robertson, 2000a; Scates, Woods, & Azeredo, 1999). Axonal transport studies also suggest that MOCS neurons are innervated directly by neurons arising in the auditory cortex (Mulders & Robertson, 2000b). Though giving insight into olivocochlear activity electrophysiological studies have many limitations (Collet et al., 1990). Sectioning experiments, especially at the level of the floor of 4th ventricle, are imprecise and are not fully selective for efferents (though their effectiveness has been carefully demonstrated (M. C. Liberman, 1989; Warren III & Liberman, 1989b)). Electrical stimuli provide global stimulation, and in the floor of the 4th ventricle may simulate both crossed and uncrossed medial efferents that loop close to the midline (however, the LOCS is probably less easily stimulated this way as its fibers are unmyelinated). The main disadvantage with electrical stimulation is that it does not necessarily reflect normal cochlear input/output activity. Stimulation is often at supraphysiological levels, and provides unnatural synchronization and frequency of stimulation. Results can be confounded by stimulation artifact. Also neither sectioning nor electrical stimulation can be applied to humans, which limits extrapolation of findings from the animal models. The opportunity to study the MOCS non-invasively in animal models and humans was facilitated by the discovery of otoacoustic emissions (OAEs) (Kemp, 1978a).

The function of the LOCS is not well understood. Some groups have proposed a role in providing “binaural balance” for sound localization has been proposed (Darrow, Maison, & Liberman, 2006; Guinan Jr, 2006). Studies to confirm this hypothesis are still needed.

5. New technology

5.1 Frequency specificity in the Medial Olivocochlear System (MOCS)

It is now well established that the sensitivity and frequency tuning of the peripheral auditory system is influenced by the cochlear efferent neural pathways (Guinan Jr, 2006). Activation of the MOCS by acoustic stimulation of the contralateral ear has been shown to suppress sensitivity of the cochlea, for example by reduction in cochlear nerve action potential amplitude (Fex, 1962). It is considered that this effect is mediated by suppression of the cochlear amplifier effect of OHC activity (Siegel & Kim, 1982). It is likely that relatively specific stimulus conditions are required for efferents to play a role in hearing (M. C. Liberman, 1988), but despite intensive investigation, the nature of this role remains unclear. Further assessment of how the MOCS is activated by different stimuli should improve understanding of this issue (Maison, Micheyl, Andéol, Gallégo, & Collet, 2000).

Tonotopicity of the MOCS has been clearly demonstrated in recordings from single olivocochlear fibers in the cat and guinea pig (Brown, 1989; Cody & Johnstone, 1982; M. Liberman & Brown, 1986). In these studies, efferent neural tuning curves were derived by measuring firing rate in response to contralateral tones of different frequency, and were found to have a shape and sharpness similar to cochlear afferent tuning curves. In addition, horseradish peroxidase injection was used to reveal the projection of some fibers, and in all cases they terminated on OHCs at a cochlear position where afferent

neurons have a characteristic frequency (CF) similar to that measured in the cochlear efferent.

Frequency specificity of MOCS activity can also be detected when recording the response of inner hair cells and auditory nerve fibers to acoustic stimulation. For example in cats, the response of single cochlear afferent fibers to tone pips is suppressed by simultaneously applying tone pips to the contralateral ear. This suppression is maximal when the contralateral tone is similar to the characteristic frequency of the afferent fiber (Murata, Tanahashi, Horikawa, & Funai, 1980; Warren III & Liberman, 1989a; Warren III & Liberman, 1989b). Similarly, when recording the compound action potential induced by tone pips with a round window electrode, maximum suppression is induced by contralateral tone pips of similar frequency (M. C. Liberman, 1989).

As OAEs are generated by OHC activity, they may provide a more direct and non-invasive insight into the effect of the MOCS on its target cells than neural recordings. In human subjects, suppression of spontaneous OAEs is maximal with a CAS tone at a frequency close to the spontaneous OAE (Mott, Norton, Neely, & Bruce Warr, 1989). In addition to suppression, a frequency shift of spontaneous OAEs is caused by CAS and interestingly this is maximal with a CAS about 3/8 to 1/2 octaves below the spontaneous OAE frequency. OAEs evoked by tone pips can be suppressed by contralateral narrow band noise, suppression being maximal with CAS frequencies close to the frequency of the tone pip (Veuille, Collet, & Duclaux, 1991).

Contralateral suppression of OAEs has not been widely used to investigate MOCS frequency specificity in animal models. A systematic study in the barn owl produced frequency response functions in which DPOAE suppression was plotted as a function of CAS frequency (Manley, Taschenberger, & Oeckinghaus, 1999). This showed maximal suppression with CAS similar to primary frequencies. Extrapolation of these findings to other models is limited by the variability of DPOAE levels and the additional types of efferent fiber which are present in birds.

The purpose of the present study was to investigate the frequency specificity of the MOCS in the chinchilla. In this species there has been a report of difficulty in detecting MOCS change in response to contralateral stimulation (Azeredo et al., 1999). On the other hand, electrical stimulation of the olivocochlear bundle in the floor of the fourth ventricle elicits OAE suppression (Siegel & Kim, 1982). In our present study, the suppressive effect on DPOAEs of contralateral pure tone stimuli is investigated with real-time recording of the DPOAE.

5.1.1 Materials and methods

5.1.1.1 Animals

Ten anaesthetized adult chinchillas (*Chinchilla laniger*) weights 505 - 725 g were studied. The anesthetic regime was intra-peritoneal Ketamine 15mg/kg (Ketamine Hydrochloride U.S.P. 100mg/ml, Ayerst Laboratories, Ontario), Xylazine 2.5mg/kg (Xylazine 20mg/ml, Bayer Inc., Toronto), and Atropine 0.04mg/kg (Atropine Sulfate 0.5mg/ml, MTC Pharmaceuticals, Ontario). Recordings were started 15 minutes after induction of anesthesia. A second dose of anesthetic was given 45 minutes later (intra-peritoneal Ketamine 8mg/kg,

Xylazine 1.3mg/kg). Five animals were studied twice, typically with an interval of >4 weeks between recording sessions. Thus in total, 15 recording sessions were completed. All studies were approved by the local Animal Care Committee, following the guidelines of the Canadian Council on Animal Care.

5.1.1.2 Real time DPOAE measurement

DPOAEs were measured in real time with a Vivo 600 DPR device (Vivosonic Inc., Toronto, ON). In contrast to conventional OAE techniques which employ signal averaging to extract the signal from noise, this technique uses digital filtering and signal modeling. The continuous real-time signal is ideally suited to the detection of changes in OAE amplitude, such as those produced by contralateral stimuli (James et al., 2005). Primary frequencies were set at $f_2/f_1 = 1.22$ for values of f_2 between 1.6 and 8.0 kHz, with intensities of $L_1 = 70$ dB and $L_2 = 65$ dB. DPOAEs were measured at $2f_1 - f_2$. The OAE probe, in a conforming soft plastic cuff, was inserted into the external auditory meatus by straightening the soft tissues to allow the probe to abut the lateral aspect of the bony meatus (approximately 13mm from the tympanic membrane). Multiple recordings of up to three minutes duration were made in each session. All recordings were made in a sound-attenuating booth. The DPOAE probe was calibrated in the ear canal by the device and calibration confirmed in a 2ml coupler using an SR760 FFT Spectrum Analyzer (Stanford Research Systems, Sunnyvale, CA) and a precision CR: 511D Acoustic Calibrator (Cirrus Research plc, North Yorkshire, U.K.).

5.1.1.3 Contralateral stimulus

An intermittent pure tone stimulus was applied to the contralateral ear using an ER-2 transducer with a foam ear-insert (Etymotic Research Inc., IL). 60 different CAS frequencies were tested between 0.6 - 17 kHz. Sweep direction from high to low, or low to high frequency of contralateral stimulation was changed between sweeps to control for any gradual drift in DPOAE level that might occur during a recording period. CAS intensity was set at 50 dB SPL as a previous study had shown the threshold for a response to be around 30dB SPL while acoustic cross talk occurred at intensities of ≥ 70 dB SPL (using noise floor measures and recordings in cadaveric chinchilla). Stimulus duration was set at 0.5s with rise / fall times of 4 ms. The interval between stimuli was long enough to allow DPOAE levels to return to pre-stimulus levels (typically > 300ms longer than CAS duration).

5.1.1.4 Analysis of results

DPOAE signals were recorded in real time, and level changes occurring in synchrony with contralateral stimulation were noted. Subsequent analysis was performed on the recorded real time trace and on averaged data, using VivoAnalysis software (Vivosonic Inc., ON), based on LabVIEW 5.1 data acquisition software (National Instruments, TX). Averaging was synchronized with the start of the CAS and was used to smooth the data and remove non-synchronous or spontaneous variation in the DPOAE signal. Averaged data were used to measure the magnitude of the DPOAE response to CAS from the baseline (no contralateral stimulation condition) to maximum OAE change (i.e. at asymptotic level). Frequency response curves to indicate tuning of contralateral suppression were plotted with magnitude of suppression (dependent variable) versus frequency of CAS tone (independent variable).

5.1.2 Results

DPOAEs were successfully recorded in real time in all animals. DPOAE levels were stable for the duration of the experiments, though they tended to fall gradually around 2 - 4 dB/hr. Figures 1 through 5 demonstrate DPOAE suppression data progressing from the initial real time signal, to the averaged waveform, and finally ideal curve fitting to the contralateral frequency response function.

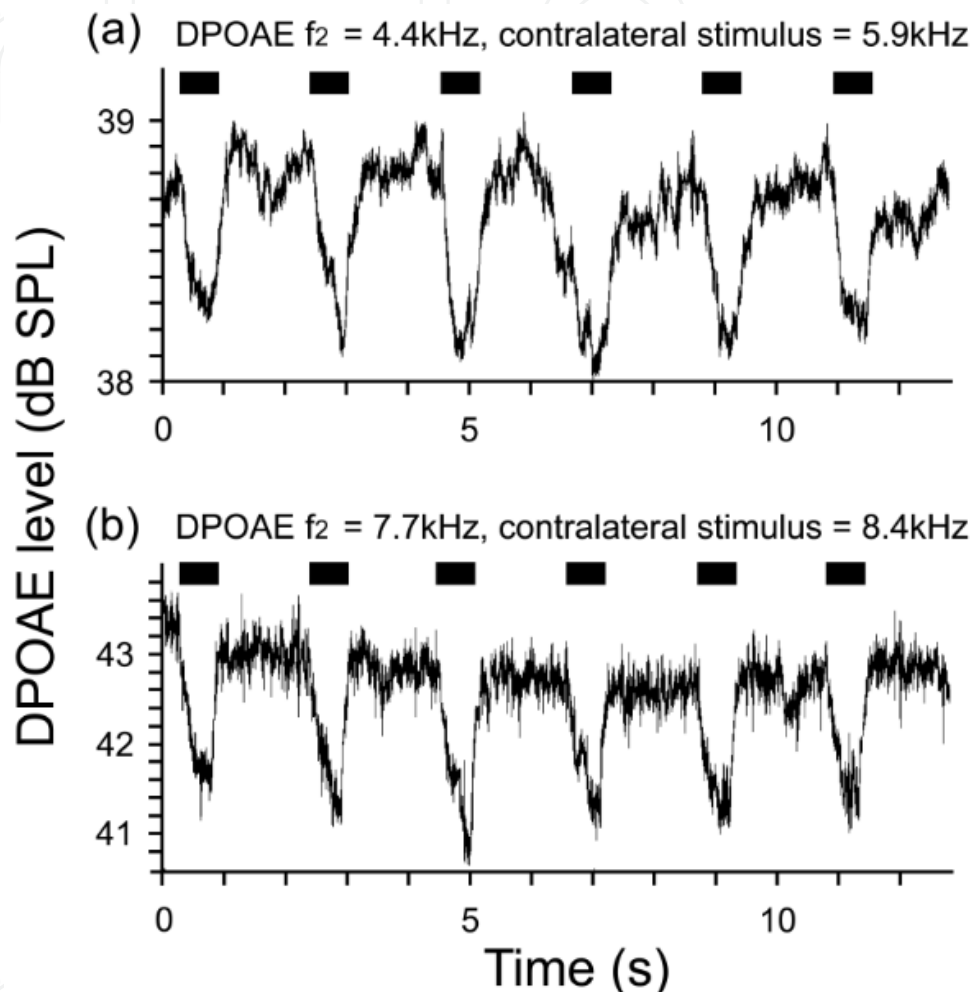


Fig. 1. Typical example of contralateral suppression of real time DPOAE signals in chinchilla: (a) DPOAE at $f_2 = 4.4$ kHz, contralateral acoustic stimulation = 5.9 kHz at 50dB SPL; (b) DPOAE at $f_2 = 7.7$ kHz, contralateral acoustic stimulation = 8.4 kHz at 50 dB SPL. (Stimulus duration = 550ms, marked by horizontal black bar).

Figure 1 shows examples of real time recordings of DPOAE suppression. Panel 1a shows variation in DPOAE level at $f_2 = 4.4$ kHz over a twelve second period during six periods of CAS at 5.9 kHz (marked by horizontal bar). Suppression of 0.5 dB from the baseline level of 38.8 dB SPL occurs with each CAS. In panel 1b, a DPOAE at $f_2 = 7.7$ kHz is suppressed by 1.2 dB by CAS of 8.4 kHz. The suppression response was sometimes smaller than the spontaneous signal variation so was not always readily visible in real-time. However, by averaging the raw real-time data in synchrony with the onset of CAS, suppression could usually be detected.

Typical examples of averaged DPOAE suppression responses are shown in figure 2. Here the DPOAE measured is at $f_2 = 4.4$ kHz, with contralateral suppression stimuli between 2.8 and 6.7 kHz. In this series, suppression is greatest (0.8 dB) with contralateral stimulations at 4.5 kHz, but is only half this value when contralateral stimulation is at 2.8 kHz or 6.7 kHz, indicating the frequency dependence of DPOAE suppression.

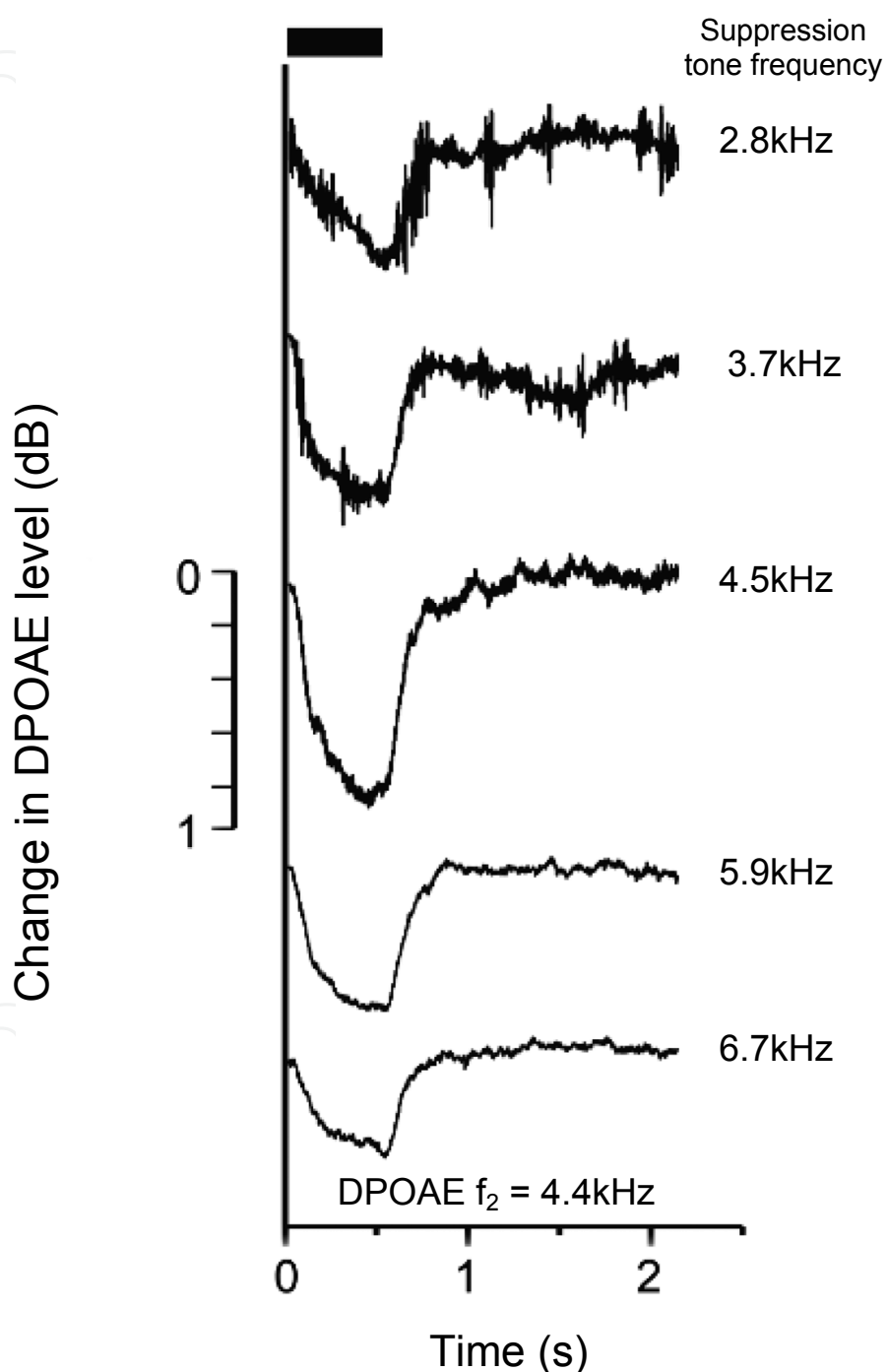


Fig. 2. Averaged DPOAE signal from 20s recording periods, synchronized with onset of contralateral stimulus. (DPOAE at $f_2 = 4.4$ kHz; contralateral acoustic stimulation at frequencies of 2.8 - 6.7 kHz (550ms duration, as black bar).

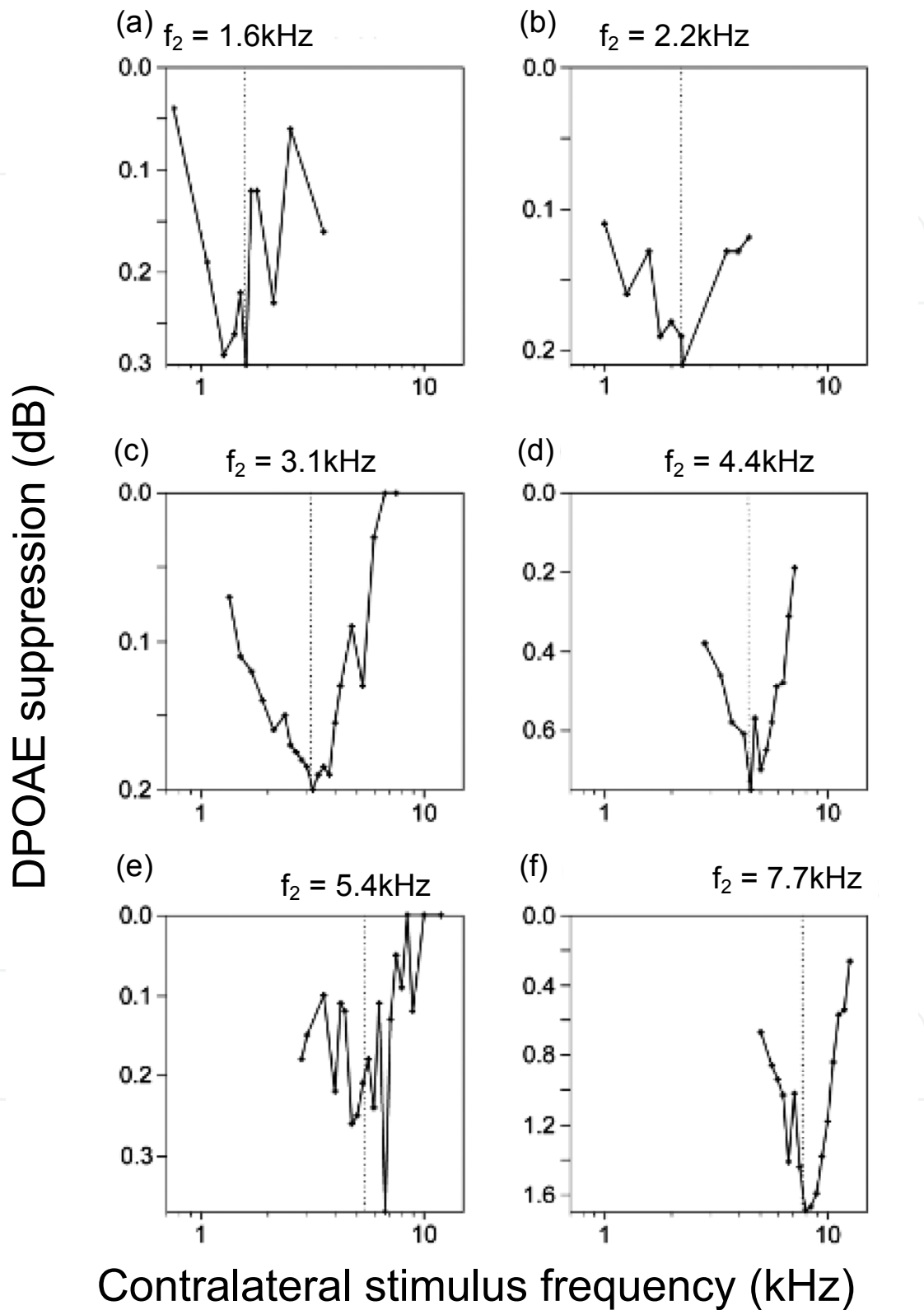


Fig. 3. DPOAE suppression plotted against contralateral stimulation frequency. Panels a - f show suppression response measured from single animal recordings at DPOAE frequencies ranging from f_2 of 1.6 kHz to 7.7 kHz.

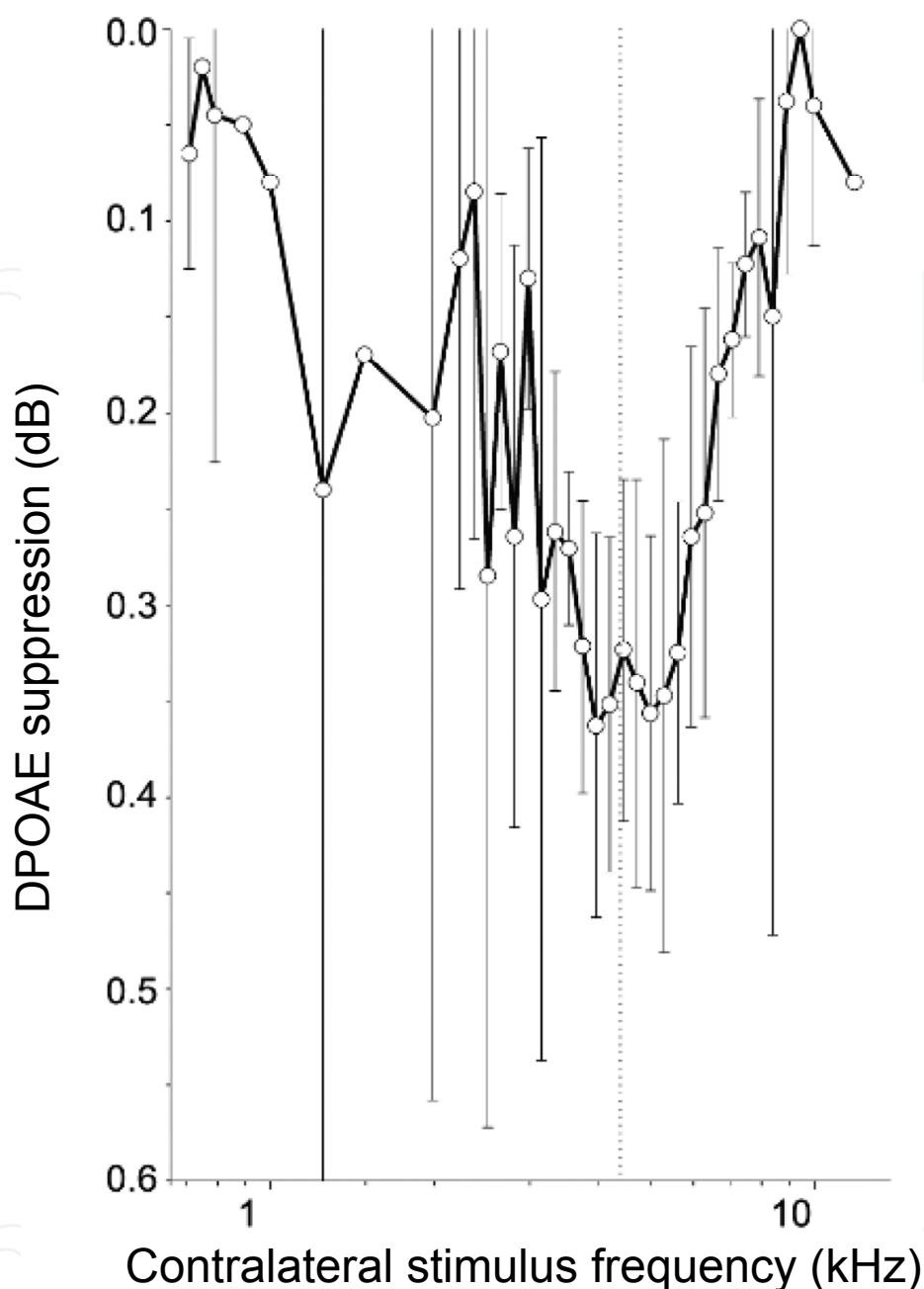


Fig. 4. Contralateral suppression frequency response curve for DPOAE of $f_2 = 4.4$ kHz (marked by vertical dotted line), derived from pooling data from 8 animals. Bars show 95% confidence intervals.

The frequency response function for $f_2 = 4.4$ kHz in figure 4 was derived from 22 recordings in eight animals. Mean suppression was plotted against CAS frequency. The large 95% confidence intervals reflect the variability of response in different experiments. However, as in figure 3, the curve peaks near the f_2 frequency (dotted line).

In figure 3, magnitude of contralateral suppression is plotted against CAS frequency for six different DPOAE frequencies. The curves peak close to the f_2 value (marked by the dotted line) but typically peak suppression magnitude occurs at a frequency slightly higher than f_2 .

In an attempt to reduce the variability of the response between recordings and to obtain finer details on the shape of the frequency response, repeated measures from CAS close to f_2 were made in successive recordings in one chinchilla. The results are shown in figure 5. Even within this single recording period in an individual animal, variability (up to 0.15dB) can be seen in successive sweeps. No repeatable notches in the curve were visible.

As illustrated in figure 5 by the continuous line, the general shape of the DPOAE suppression tuning can be characterized by fitting a regression curve to the data. In figure 6, the same regression function is plotted for four values of f_2 between 3.1 - 7.7 kHz using data combined from multiple recordings. The responses are asymmetric with a tendency to drop off more steeply at values of CAS greater than f_2 . Small suppression responses can be obtained by CAS tones more than one octave lower than the f_2 frequency.

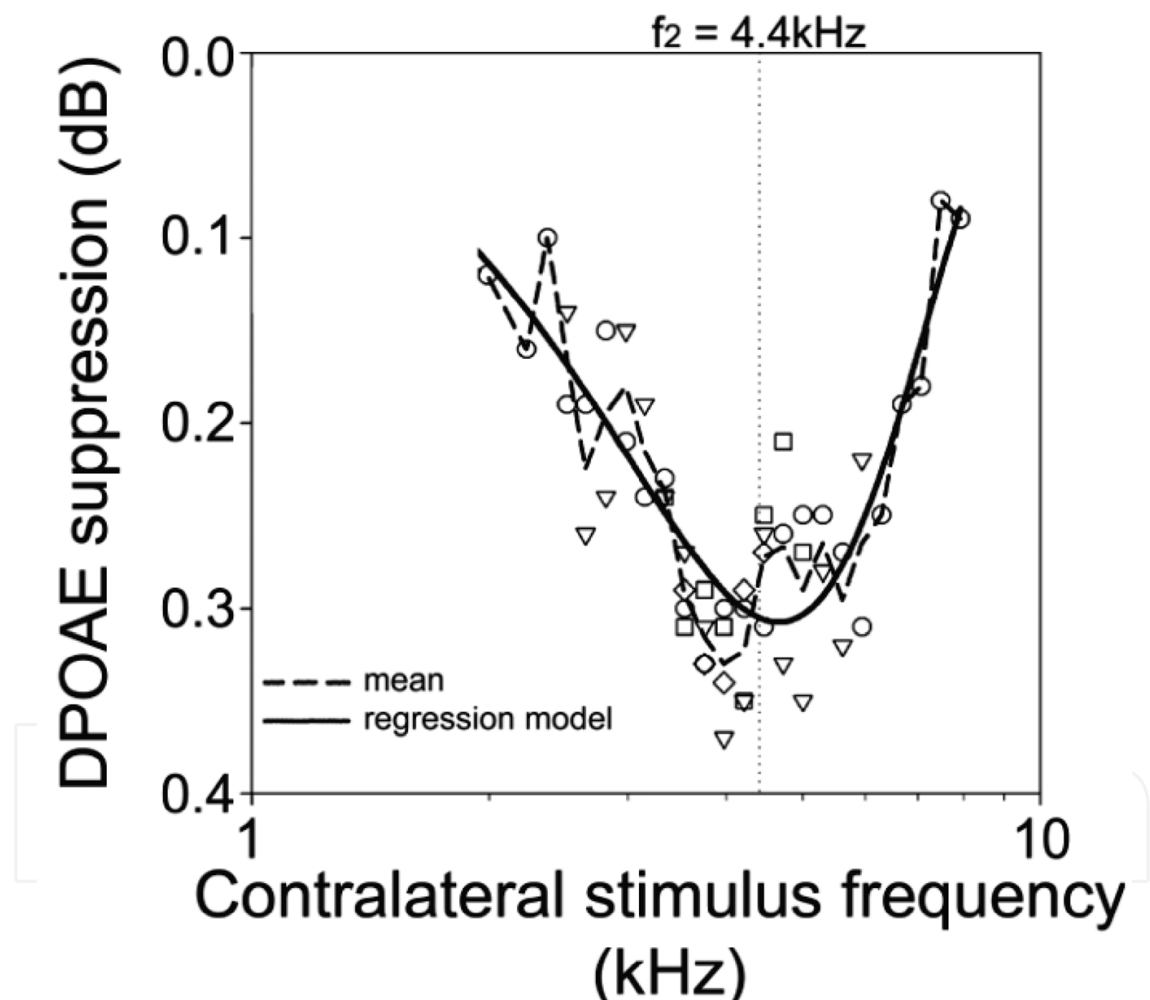


Fig. 5. Contralateral suppression frequency response curve for DPOAE of $f_2 = 4.4$ kHz derived from one subject. Dashed line is mean value. Solid line is regression curve (Weibull).

In figure 7, the suppression curves of fig. 6 are plotted on a normalized amplitude scale. The curves are broadly tuned and thus there is considerable overlap. The tuning of suppression curves for high frequency DPOAEs is narrower than at lower frequencies. The (half-

amplitude) bandwidth values for suppression curves at 3.1, 4.4, 5.4, 6.6, and 7.7 kHz (f_2) are, respectively, 1.7, 1.8, 1.4, 1.15, and 1.3 octaves.

DPOAE suppression was seen in all animals with contralateral pure tone stimulation. On rare occasions, CAS induced an increase in DPOAE level. This occurred at $f_2 = 2.2$ kHz in one chinchilla and at $f_2 = 6.6$ and 7.7 kHz in another. The maximum response occurred with a contralateral tone at or just below the frequency of f_2 . These data were excluded from analysis as they may represent a different process.

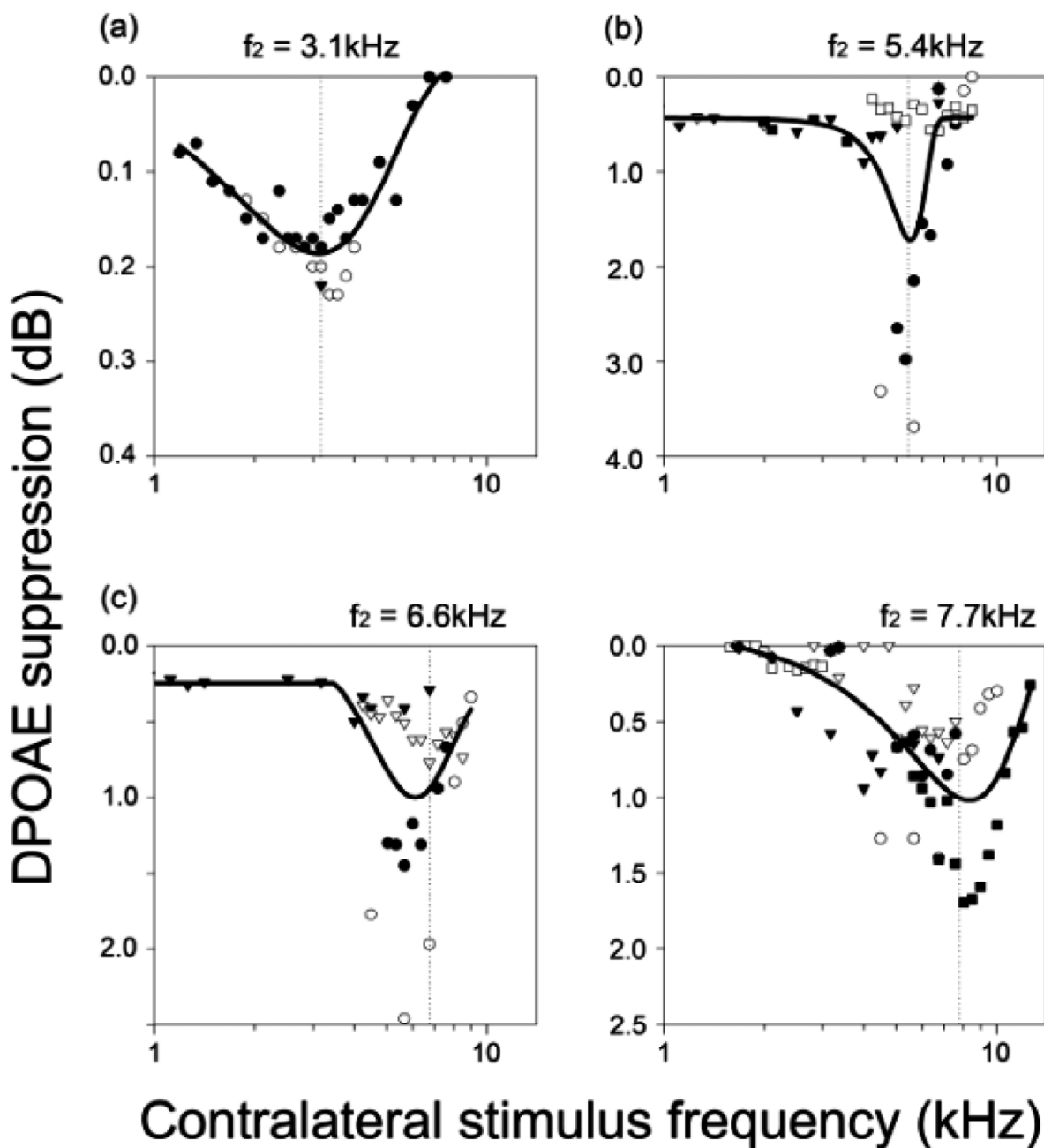


Fig. 6. Regression functions (Weibull) of DPOAE suppression frequency response curves for four values of f_2 between 3.1 and 7.7 kHz. Curves are plotted on an absolute dB suppression scale.

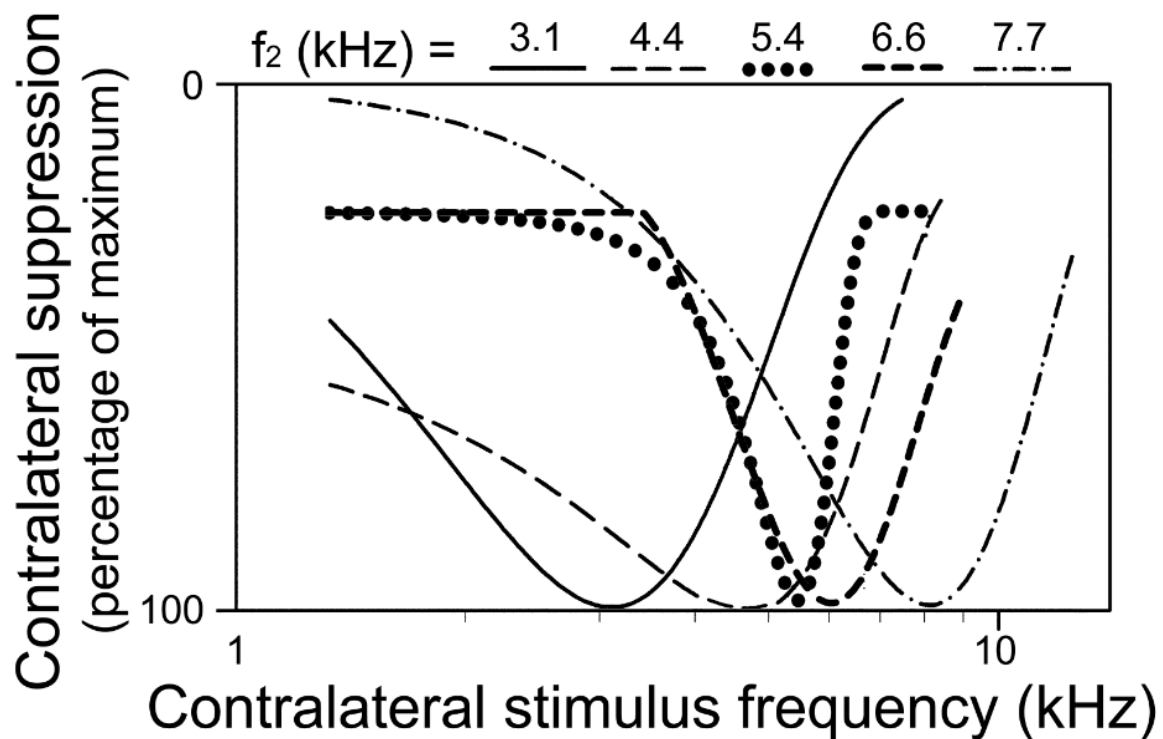


Fig. 7. DPOAE suppression frequency response curves (Weibull regressions) for f_2 values between 3.1 and 7.7 kHz, plotted on a normalized suppression scale (data from figs 4 and 6).

5.1.3 Discussion

This study demonstrates that suppression of DPOAEs by contralateral pure tones can be detected in the chinchilla with real time recording. DPOAE suppression is greatest when using contralateral stimulation tones close to primary tone f_2 . This tonotopic response is consistent with other investigations of frequency specificity in the MOCS pathway (Chery-Croze, Moulin, & Collet, 1993; Cody & Johnstone, 1982; M. C. Liberman, 1989; Murata et al., 1980; Robertson, 1984; Robertson & Gummer, 1985; Veuillet et al., 1991; Warren III & Liberman, 1989a; Warren III & Liberman, 1989b). Unlike observations in human subjects, we did not observe any dips in fine structure DPOAEs to account for differences in the magnitude of suppression at different values of f_2 or between chinchillas (Wagner, Heppelmann, Müller, Janssen, & Zenner, 2007).

Measurement of contralateral frequency tuning of MOCS fibers has revealed narrow band tuning equivalent in sharpness to cochlear afferent neurons (Brown, 1989; M. Liberman & Brown, 1986; Robertson, 1984). The final, divergent innervation pattern of MOCS fibers at the OHC level appears to degrade this cochleotopicity (or frequency tuning) by a factor of 4-5 from 0.33 octaves (the approximate bandwidth of auditory afferents) to about 1.7 octaves for $f_2 = 3.1\text{kHz}$ and 1.3 octaves for $f_2 = 7.7\text{kHz}$. The difference in tuning likely rests with the divergent OHC innervation by the MOCS fibers. Neural tracing studies in guinea pig have shown MOCS fibers innervating 15 -61 OHCs (Brown, 1989). In the cat, individual cochlear efferents contact 23 - 84 OHCs spanning 0.55-2.8mm (M. Liberman & Brown, 1986). Thus although tuning in the efferent fibers themselves appears to be as sharp as afferent tuning, the effect of individual fibers on the organ of Corti will be much less precise.

MOCS frequency tuning has been assessed in the cat by recording changes in single afferent fiber activity during CAS. Suppression of afferent firing rate is maximal with a CAS of similar frequency to the characteristic frequency of the afferent fiber (Warren III & Liberman, 1989a; Warren III & Liberman, 1989b)). Tuning of this form of contralateral suppression was asymmetric, falling off more sharply at CAS frequencies above characteristic frequency, and were much less sharp than afferent tuning. Tuning tended to be sharper at higher frequencies. These observations in the cat are consistent with the contralateral DPOAE suppression tuning reported here for the chinchilla, where bandwidths for curves at 6.6 and 7.7 kHz (f_2) are 1.15 and 1.3 octaves respectively, but are 1.7 and 1.8 octaves at 3.1 and 4.4 kHz.

As shown by others, the primary tones used to generate DPOAE stimulate the MOCS and so cause ipsilateral DPOAE suppression (Guinan, Backus, Lilaonitkul, & Aharonson, 2003; M. C. Liberman, Puria, & Guinan Jr., 1996). It can be expected that the primary tones would suppress cochlear function in the contralateral ear by MOCS activation, with the same broad frequency tuning that we have observed. Given that the magnitude of contralateral suppression of DPOAE is dependent upon intensity of the contralateral stimulus (A. James, Mount, & Harrison, 2002), a hypothetical outcome would be a notch in the frequency response curve at the primary frequencies, f_1 and f_2 . This has been observed at f_1 in the barn owl but despite thorough investigation at one frequency ($f_2 = 4.4\text{kHz}$, figure 5), we were unable to demonstrate this phenomenon in the chinchilla (Manley et al., 1999).

As in other studies, recordings were completed under anesthesia with ketamine and xylazine. This does reduce the magnitude of contralateral suppression of DPOAE and other measures of olivocochlear function but facilitates recording by providing stable recording conditions, with less behavioral noise and movement artifact (Cazals & Huang, 1996; da Costa, Erre, de Sauvage, Popelar, & Aran, 1997; Harel, Kakigi, Hirakawa, Mount, & Harrison, 1997). We have not investigated the effect of anesthesia on tuning sharpness.

As mentioned previously the exact function of the medial olivo-cochlear system remains speculative. Because of the predominantly inhibitory effect seen on outer hair cell function, improved detection of sound in noise or a protective effect have been hypothesized. Any role postulated for the contralateral suppression response should take into account the relatively slow dynamic of this reflex, being of the order of 26ms in chinchilla and 45ms in humans (James, Harrison, Pienkowski, Dajani, & Mount, 2005). The presence of a response from low intensity contralateral stimuli suggests the function of this system is less likely a protective one, but more to do with frequency tuning of the afferent neural responses via efferent effects on OHC motility. The efferent system may function as a gain control with a long time-constant, equalizing sensitivity between the ears. The optimal condition for detecting inter-aural timing or intensity differences would perhaps be when the two ears have equivalent function. In this respect, the medial contralateral efferent system may also have a role in "balancing" the ears such as to improve the accuracy of these binaural sound localization tasks.

6. Conclusions

Objective tests such as OAE and ABR are widely used in hearing screening programs and have lead to great advances in the early detection and rehabilitation of neonatal hearing

loss. However these tests do not provide a quick and easy means for assessing hearing threshold at different frequencies, indeed the presence of OAE does not even guarantee the presence of normal hearing. An objective frequency specific test of hearing ability would have widespread advantages, not just for neonatal testing but in many circumstances in all age groups.

In the present study we have demonstrated frequency specificity in contralateral suppression using a chinchilla model. The majority of studies shedding light onto the function of the MOCS have been derived from animal experiments. However, there is enough data in human studies to suggest that the human efferent system is qualitatively similar (Guinan Jr, 2006; James, 2006). We have shown previously that contralateral suppression of DPOAE can be assessed in real time in babies and adults (James et al., 2005) and can be used to test hearing very effectively in neonates (James, 2011). We have shown that this technique can distinguish between middle ear muscle reflexes and the OCR in an animal model (Wolter, Harrison, & James, 2011) and here show that it can be used to assess hearing threshold in a frequency specific manner. We envisage many clinical applications of this technique including the diagnosis and assessment of ANSD and more accurate hearing screening in neonatal and elderly populations.

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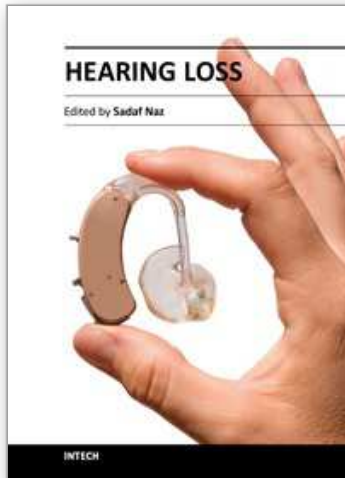
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Authored by 17 international researchers and research teams, the book provides up-to-date insights on topics in five different research areas related to normal hearing and deafness. Techniques for assessment of hearing and the appropriateness of the Mongolian gerbil as a model for age-dependent hearing loss in humans are presented. Parental attitudes to childhood deafness and role of early intervention for better treatment of hearing loss are also discussed. Comprehensive details are provided on the role of different environmental insults including injuries in causing deafness. Additionally, many genes involved in hearing loss are reviewed and the genetics of recessively inherited moderate to severe and progressive deafness is covered for the first time. The book also details established and evolving therapies for treatment of deafness.

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