Measuring and monitoring noise-induced hearing loss with otoacoustic emissions and pure-tone audiometry

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Measuring and monitoring noise-induced hearing loss with otoacoustic emissions and pure-tone audiometry

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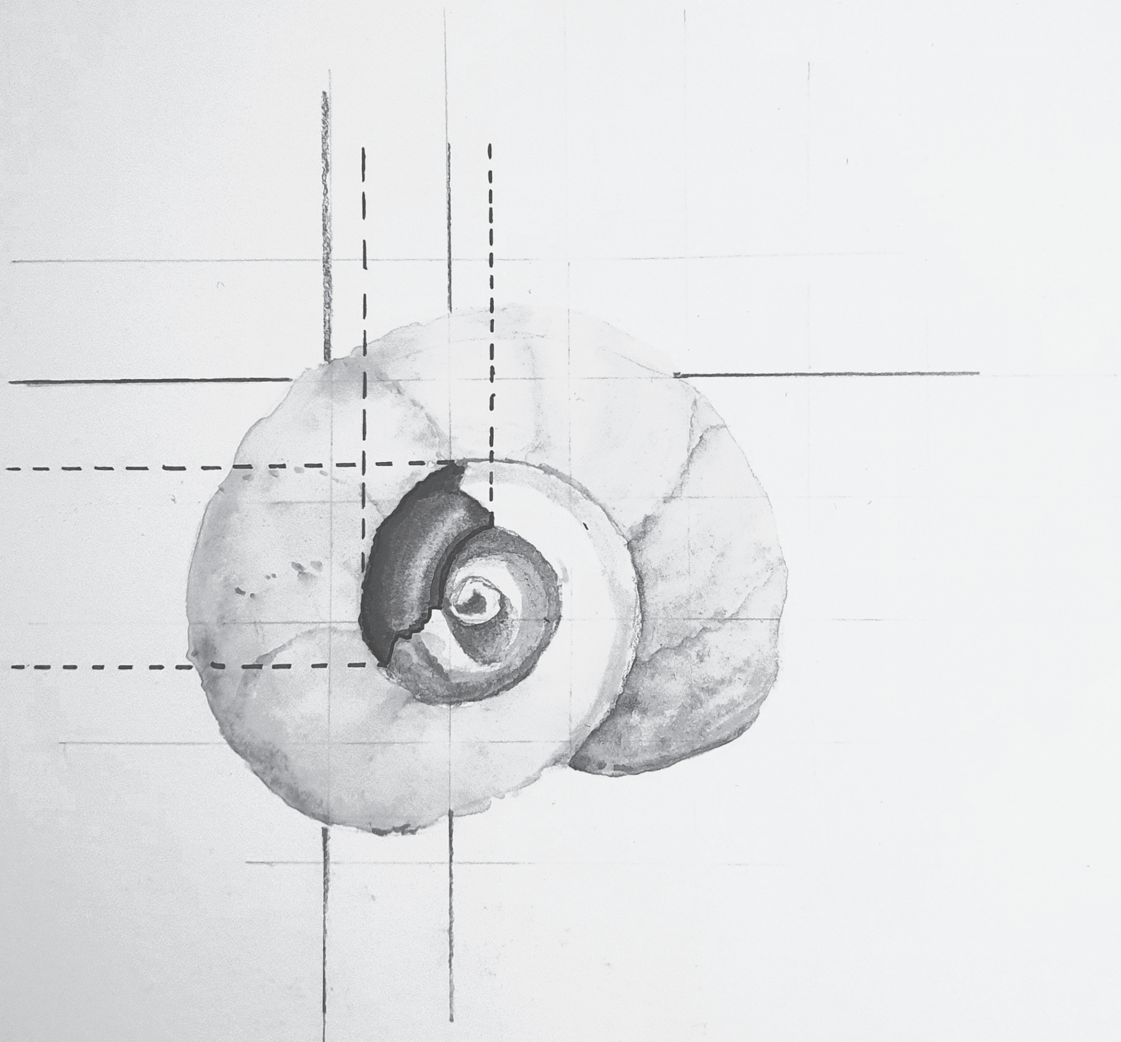


CHAPTER 1

General introduction and outline of this thesis

GENERAL INTRODUCTION

Hearing loss can impair communication with family, friends, colleagues, can impair appreciation of listening to music, and can impair the perception of everyday acoustic signals. In 2018, the World Health Organization (WHO) estimated that 466 million people worldwide suffer from some form of disabling hearing loss (WHO, 2018). Some of these people are born with hearing loss, some develop hearing loss during their life-time because of (progressive) illnesses, chronic ear infections, ototoxic medication, injuries, ageing or because of noise-exposure. The latter type of hearing damage is commonly referred to as noise-induced hearing loss (NIHL) and is, strictly speaking, preventable.

Knowledge on the relationship between prolonged noise exposure and hearing damage has been acquired since the first report on deafness in blacksmiths was published in 1830 (Fosbroke, 1830). The invention and widespread use of the steam engine, led to a new type of occupational illness called 'boilermakers' deafness (or 'ketelmakersdoofheid' in Dutch) (Barr, 1886; Bunch, 1937; Roosa, 1873; Thurston, 2013; Van Gilse, 1931). This injury or illness is considered to have played an important role in establishing the causal relationship between noise exposure and noise-induced hearing loss (Johnson, 1999). See box A for more elaborate discussion of NIHL in an historical perspective, and box B for the mechanisms of sound and the inner ear.

Nowadays, many high income countries have legislation in order to prevent occupational NIHL, and have defined limits for occupational noise exposure. Nevertheless, many people around the world either suffer from NIHL, or are at risk of losing their hearing because of occupational and/ or recreational noise exposure (WHO, 2018). An important part in the legislation is played by monitoring hearing status through periodical testing. The objective of such tests is to provide early detection of hearing loss and to prevent further damage for that particular employee and his/her co-workers (EU Directive 2003/10/EC). The focus of this thesis is the application of otoacoustic emissions (OAEs) as an alternative, promising method for monitoring hearing status in hearing conservation programs.

A: NIHL IN AN HISTORICAL PERSPECTIVE

Around 2000 years ago, several Roman scholars mentioned a relationship between the loudness of water thundering down from waterfalls in the river Nile and the loss of hearing in inhabitants of the neighboring villages (Martinez, 2014). It was Cicero (106-46 BC), the famous statesman, who first mentioned the effect of the waterfalls on hearing (Cicero, 54 BC). But more often this observation is attributed to Pliny the Elder (23-79 AD) who wrote in his Naturalis Historia (NIOSH, 1988; Thurston, 2013):

> *intravere autem et eo arma romana Divi Augusti temporibus duce p. petronio, et ipso equestris ordinis praefecto aegypti. is oppida expugnavit, quae sola invenimus quo dicemus ordine, Pselcin, Primi, Bocchin, Forum Cambusis, Attenam, Stadissim, ubi nilus praecipitans se fragore auditum accolis aufert. (Pliny, 77 AD)*
>
> *The Roman arms also penetrated into these regions in the time of the late Emperor Augustus, under the command of P. Petronius, a man of Equestrian rank, and prefect of Egypt. That general took the following cities, the only ones we now find mentioned there, in the following order; Pselcis, Primis, Abuncis, Phthuris, Cambusis, Atteva, and Stadasis, where the river Nile, as it thunders down the precipices, has quite deprived the inhabitants of the power of hearing. (Bostock & Riley, 2006)*

From this anecdotal description, it took several centuries before written reports arose on acute deafness or hearing loss after exposure to gunfire and cannon fire (McIllwain et al., 2008). The first manuscript concerning damaging effects of prolonged noise exposure on hearing was published in 1700 by an Italian doctor, Bernardino Ramazzini, who described the effects of work on health in various trades in his '*De Morbis Artificum Diatriba*' or 'Disease of workers'. The second edition was published in 1713. According to Ramazzini, the activities of coppersmiths and corn millers were known to cause hearing problems, leading eventually to deafness. On the coppersmiths he wrote:

> *'One may observe these men as they sit on the ground, usually on small mats, bent double while all day long they beat the newly mined copper, first with wooden then with iron hammers till it is as ductile as required. To begin with, the ears are injured by that perpetual din, and in fact the whole head, inevitably, so that workers of this class become hard of hearing and, if they grow old at this work, completely deaf.' (Ramazzini, 1713).*

Blacksmiths were not identified for their risk of hearing loss, but only for problems caused by exposure to heat and smoke. But in London, blacksmiths were banned from some neighborhoods from the 1400's, because of the noise and smoke and were restricted in their working hours (Thurston, 2013).

In 1830, the English doctor Fosbroke was the first to report on the relation between noise exposure and hearing loss, based on his observations in blacksmiths. He wrote that blacksmith's deafness is caused by continuous exposure to noise and stated:

> *The blacksmith's deafness is a consequence of their employment; it creeps on them gradually, in general at about 40 or 50 years of age. At first the patient is insensible of weak impressions of sound; the deafness increases with a ringing and noises in the ears. (Fosbroke, 1830)*

Noise exposure became a more prominent issue with the invention, and the improvement of the steam engine during the Industrial Revolution. In the wake of the widespread use of this engine, the amount of workers exposed to high levels sound increased. Steam engines were used in several industries, such as mining, shipping and various factories. These engines require large boilers in which the steam is generated. Boilermakers hammered rivets through steel and iron plates to connect them, leading to the so-called 'boilermakers-deafness' or in Dutch 'ketelmakersdoofheid' (Barr, 1886; Van Gilse, 1931). An English doctor, Toynbee, noted in 1860 that many workers who were situated inside the boilers became deaf (1860). This was also observed and investigated by others, such as the Scottish doctor Barr (1886) and by his American contemporary, Roosa (1873). The latter was a professor of the Ear and the Eye and published a well-known textbook in which he wrote the following:

Workmen employed in hammering large iron plates as are used in the making of boilers of steam engines are very apt to lose much of their hearing power. I am informed by the superintendents and workmen of some factories that a large proportion of the men who have long been in the horrid din of a boiler shop, become deaf. So many of these cases were found, that at one time boilermakers' deafness figured as a separate disease of the ear in the statistical reports of one of our institutions where aural diseases were treated. (Roosa, 1873)

Moreover, Roosa noted that hearing loss was also present in workers outside the boilers, but it was less severe and developed more slowly over time. Railway workers were also known to lose their hearing because of the noise of the steam locomotives and high-pitched whistles, (Gotstein & Kayser, 1881; Thurston, 2013; Zwaardemaker, 1896). Another notoriously noisy environment were textile weaving mills (McKelvie, 1933; Taylor et al., 1965). The semi-automated weaving machine with a so-called flying shuttle produced loud impact sounds when changing direction and several machines were placed together within a factory. The levels in an operating jute weaving built in 1892 ranged from 92 to 110 dB (A). This was measured in 1967 when sound level meters became available and the original looms from the 19th century were still in operation (Taylor et al., 1967).

Legislation

In 1887, members of the Dutch Parliament formed a committee to enquire about the working conditions in factories and workplaces in The Netherlands. Transcripts of conversations with employers, overseers and laborers with the members of the parliamentary committee are available (Giele, 1981). From these records it is known that boys in the age of 12-16 years old were placed inside the boilers during a full workday. They had to oppose the rivets that were banged through the steel with 'colossal hammers'. Hearing protection in the form of cotton wool in the ears was not used, and considered undesirable, because it would hinder communication with the people outside the boiler. The results from the parliamentary committee led to a nationwide outcry on the exploitation and (lack of) safety of the laborer, especially the exploitation woman and (young) children (Bijsterveld 2006; Giele, 1981). It led to the first legislation in The Netherlands concerning inspection, safety, working hours, and well-being of workers, called the 'Arbeidswet' (Goeman Borgesius, 1889). In the course of decades that followed, the legislation was extended to other sectors, and amendments were added. A similar development was seen in other countries in Europe and the United States (Bijsterveld, 2006; Glorig, 1962; Kerr et al., 2017). But it was not until 1970 that Dutch legislation explicitly contained noise exposure time limits and levels, and that codes of practice were entered in legislation on working conditions (Bijsterveld, 2006). From 2003, there is a European Directive for all member countries of the EU, aiming to protect workers from risks of hearing damage (EU Directive 2003/10/EC). This directive states the minimum requirements for protection of the workers with a priority of reduction of the exposure at the source.

Measuring hearing loss

With the expansion of noisy surroundings for workers, more and more became known of the characteristics of this type of hearing loss and its consequences for communication. Several methods were used to assess the damage: tuning forks, whispered and regular voice, whistles and ticking watches (Bunch, 1937). The well-known otologist Politzer, used the following description of noise-induced hearing loss found in coopers, boilermakers and locksmiths in his textbook 'Diseases of the Ear':

"In affection of the ear induced by the various trades, the results of the tuning forks are characteristic of a primary diseased condition of the nerve; the perception through the cranial bones is greatly diminished, and Rinné's test positive; furthermore there is a defect in the perception of the upper range of the scale, as well as for the tones of Galtons whistle" (Politzer, 1926).

This particular whistle is nowadays still known as a dog whistle. It was invented by Sir Frances Galton (1822-1911) and designed to *"conveniently ascertaining the upper limits of audible sound in different persons..."* (Galton, 1883). This device was used in the first quarter of the 20th century, alongside tuning forks but became obsolete when the first vacuum tube audiometers were introduced between 1900 and the 1930's (Dean & Bunch, 1919; Regeer & Blume, 1995; Staab, 2017). The audiometer allowed measurements of hearing sensitivity at threshold level at predetermined frequencies, enabling comparison across populations. The number of audiometric studies increased when this type of equipment became available commercially. The first comparison of audiometric studies was in a review on noise-induced hearing loss, published in 1937 in The Laryngoscope (Bunch, 1937). In the introduction, the author Bunch expressed his concerns on the increase in noise-producing machinery over the last thirty years. The study presents various papers on NIHL since the first publication by Fosbroke in 1830, and discusses the difficulty of establishing a cause-and-effect relationship between noise and hearing loss. Bunch wrote that the only way to do this is to measure hearing of employees before they enter service and at intervals during their employment and to eliminate confounding factors, but *"it seems improbable at present time that such a program will be instituted even on a small scale because of the labour and the expense involved." (Bunch 1937).* Bunch also cites a Belgian medical officer, Gilbert, who in 1922 advocated measuring hearing loss to detect it at a stage before it became profound, and who is recognized as (one of the) first to advocate periodical hearing tests (Bunch, 1937; Gilbert, 1921; Thurston, 2013).

After the second world war, in 1946, an American Committee on the Conservation of Hearing developed the first hearing conservation program consisting of: 1. The establishment of pre-employment audiograms and follow-up tests; 2. The advice for reducing noise at the source; 3. The recommendation to wear ear protectors in noisy conditions and 4. Research (Glorig, 1961). The document from the committee was revised in 1957 and at the time of writing, the author stated that there still was high reluctance to install such a hearing conservation program.

B: SOUND AND THE HUMAN INNER EAR

Sound, variation of pressure around the atmospheric pressure, enters the ear through the pinna, the outer ear. It passes through the middle ear and is transferred into mechanical motion. This transfer is performed via the tympanic membrane and connected ossicles, the malleus, incus and stapes. The footplate of the stapes is connected to the oval window, which is the entry of cochlea, the hearing part of the inner ear. Figure 1.1 shows a cross section from this snail like structure of two and a half windings (Gray, 1918).

Movement of the stapes footplate on the oval window creates a pressure wave in one of the fluid-filled compartments of the cochlea, the scala vestibule, filled with a fluid called perilymph, which is comparable to cerebrospinal fluid, and high in sodium concentration, low in potassium. The pressure wave travels upwards in the cochlea, through a small opening (helicotrema) in the top, and then downwards through another compartment, the scala tympani, also filled with perilymph. It ends with an opposite motion of another window, the round window. Between the scala tympani and the scala vestibule lies a third compartment, the scale media or cochlear duct, which is filled with a fluid high in potassium, called the endolymph. The outer wall of the cochlear duct is formed by the stria vascularis and the spiral ligament. The stria plays an important role in maintaining the endocochlear potential, i.e. the potential difference between the perilymph and the endolymph which can be considered as the battery of the cochlea.

A membrane divides the scala tympani from the scala media (basilar membrane). The movement of fluid in these two scalae creates a travelling wave along the basilar membrane. This membrane supports the organ of Corti, a very delicate structure that performs the actual sensory task of hearing. It contains the contacts with the auditory nerve fibers through the so-called inner hair cells (IHCs) which are neatly stacked in a single row along the windings of the cochlea. Opposite to the IHCs are the OHCs or outer hairs cells, which are stacked in three rows. The name of these hair cells stem from the small stereocilia, or hairs, that sprout from the cells. Another membrane rests on top of these stereocilia, the tectorial membrane. Figure 1.2 is a schematic representation of the organ of Corti in the cochlea (Gray, 1918).

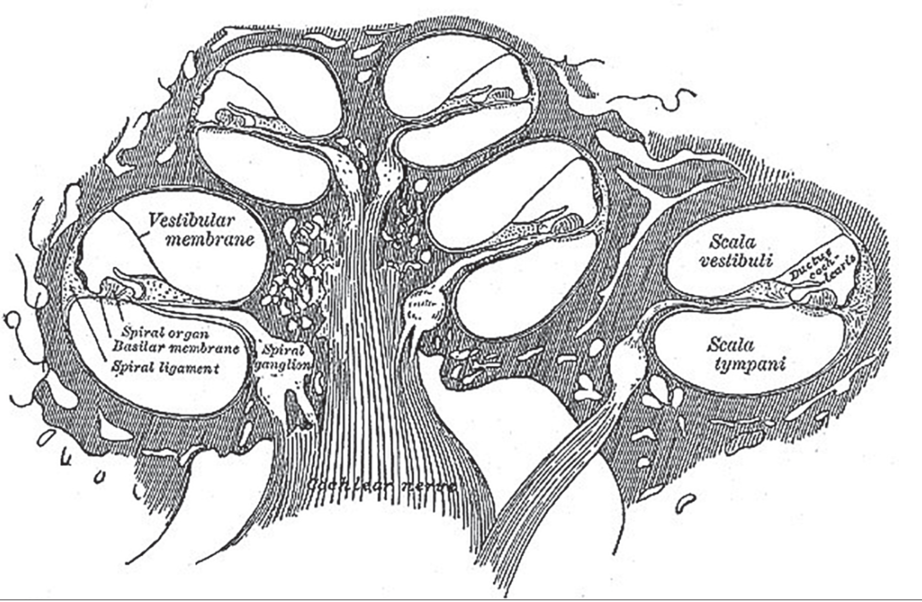


Figure 1.1: Cross section of the cochlea. The scala tympani and vestibuli are indicated. The scala media with cochlear duct lies between these scalae and is terminated by the stria vascularis which resides on the inner side of the spiral ligament. (Gray, 1918, https://commons.wikimedia.org/wiki/File:Gray928.png).

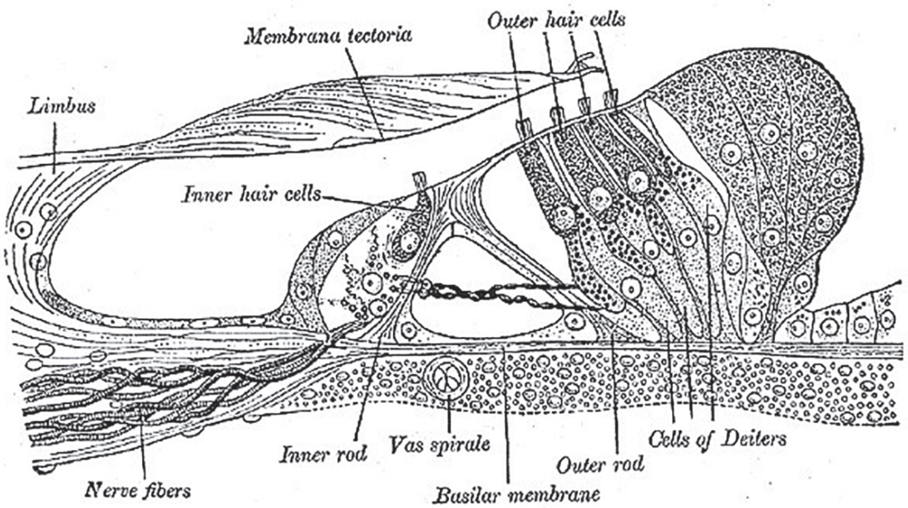


Figure 1.2: Schematic drawing of the Organ of Corti. with three rows of outer hair cells (OHCs), one row of IHCs, the supporting structures, along with the tectorial membrane and the basilar membrane. (Gray, 1918, https://commons.wikimedia.org/wiki/File:Gray931.png)

The basilar membrane acts as a passive frequency analyzer because of its mechanical properties: from base to apex it increases in width and mass, and decreases in stiffness. This results in difference resonance frequencies along the basilar membrane; cochlear tonotopy (Von Békésy, 1960). When the stapes footplate transmits pressure to fluid in the cochlea, the basilar membrane moves in a particular area that is specific to the frequency of the vibration. High frequencies cause optimal movement in the base of the cochlea, and low frequencies at the apex. This phenomenon is called cochlear tonotopy.

The movement of the fluid creates shearing forces between the basilar and tectorial membrane, which in turns causes the stereocilia of the OHCs to bend, opening ion channels near the tip of the stereocilia (Pujol et al., 2013; Purves et al., 2001). This allows positively charged potassium (K^+) ions in the endolymph to enter the cells, causing depolarization of the OHCs. As a result from the depolarization, the body of the outer hair cells contract (electromotility) which actively amplifies the initial vibration of the basilar membrane (Brownell, 1990; Plack, 2005). Next, the inner hair cell is excited, which in turn activates the synapse of the auditory nerve fiber and the message of sound (coded in frequency) is sent to the auditory cortex. The outer hair cells thus function as an active cochlear amplifier and enhance the frequency selectivity: they increase the input for the inner hair cells for low-level sounds, especially at a slightly higher frequency region than where the movement is optimal due the passive tonotopy of the cochlea (Plack, 2005).

NOISE-INDUCED HEARING LOSS

The delicate structures in the cochlea or inner ear, that were discussed in box B, enable the perception of sound. Prolonged, repeated exposure to loud sounds permanently damages these cochlear structures which in its turns results in hearing loss. An ISO-model describes the causal relationship between hearing loss as a result from exposure levels and duration in years (ISO 1999:2013). For any given level of noise exposure, the model estimates the statistical distribution of hearing loss in a population, taking into account the large variability in susceptibility for noise damage between individuals (Henderson et al., 1993).

NIHL is typically described as a bilateral, sensorineural hearing loss (symmetric loss since exposure generally is symmetric) starting with a typical ‘notch’ in the audiogram at 3, 4 or 6 kHz, with recovery at 8 kHz (Kirchner et al., 2012). With further development of hearing loss, the notch broadens to lower frequencies, see also Figure 1.3. With long-term continuous exposure to noise, the deterioration is gradual and increases most during the first 10-15 years of exposure. After that, the rate of damage decelerates with increase in threshold (Kirchner et al., 2012).

Older subjects with both age-related hearing loss (ARHL) and NIHL generally have a steeper configuration, or a 'bulging' audiogram, when compared to age-related hearing loss alone (Gates et al., 2000).

People suffering from NIHL typically complain of impaired understanding of speech, especially in noisy conditions, and can complain of tinnitus, ringing or buzzing in the ear and of less tolerance to sound (Chung & Mack, 1979; Feder et al., 2017; Kirchner et al., 2012; May, 2000; McBride & Williams, 2001; Nordman et al., 2000). These deficits can result in social isolation, depression, workplace-related injuries and accidents, and even lead to loss of income or unemployment (Girard et al., 2015; Hétu et al., 1995).

High levels of acoustic exposure can cause a hearing loss, which either recovers to its pre-exposure state, i.e. a temporary threshold shift (TTS), or not. When the hearing does not resolve, a permanent impairment remains, i.e. a permanent threshold shift (PTS). Although TTS is sometimes seen as a milder manifestation of PTS, the cellular mechanisms underlying these changes differ (Kurabi et al., 2017; Nordman et al., 2000).

Temporary damage (TTS)

Temporary damage can arise through several, additional mechanisms (Kurabi et al., 2017). Noise exposure, creating TTS in the order of ~15 dB, causes metabolic overstimulation, and a reversible reduction in the endocochlear potential through activation of ion-channels (Housley et al.,2013; Mori et al., 2009; Morton-Jones et al. 2015). More excessive noise causes the supporting cells in the organ of Corti to buckle (the inner and outer rod in Figure 1.2), which in turn uncouples the stereocilia of the OHCs from the tectorial membrane (Kimura, 1966; Nordmann et al., 2000). This uncoupling can explain temporary changes in hearing threshold levels in the order of 40 dB HL (Harding et al. 2002; Nordmann et al., 2000). When the hearing threshold recovers to the pre-exposure state, the TTS has resolved and it was long assumed that no permanent damage had occurred. Kujawa and Liberman (2009) challenge this assumption as they found that reversible threshold elevation in the order of 40 dB, may cause permanent damage to afferent nerve endings in animals.

Permanent damage (PTS)

Acute damage, or acoustical trauma, may occur as a result of a short, high intensity sound (Axelsson & Hamernik, 1987; Patuzzi et al., 1989; Savolainen & Lehtomäki, 1997). Intense sounds such as blasts or explosions can rupture the tympanic membrane or can dislocate the ossicles, thus creating a conductive hearing loss. But it can also directly damage structures through disruption of the cellular organization within the epithelium layer of the cochlea (Liberman & Beil, 1979; Patuzzi et al., 1989; Slepecky, 1986; Wong & Ryan, 2015).

However, most of the damage that is seen in NIHL is caused by noise levels that are below the threshold of instantaneous mechanical damage. Classically, this permanent type of loss has been associated with initial damage to the hair cells, followed by damage to the lateral wall and of spiral ganglion cells (Schuknecht & Gacek, 1993; Talaska & Schacht, 2007).

Chronic overexposure induces metabolic overload in the cells, which is followed by a cascade of biochemical reactions leading to either cell death or to cell repair (Henderson et al., 2006). The repair mechanism is of limited capacity, any form of moderate to severe cellular damage to structures as the outer hair cells, inner hair cells and auditory nerve fibers is permanent (Wong & Ryan, 2015). The competing mechanisms of cell death and repair are still not completely understood (Ryan et al., 2016). Damage to the hair cells of the cochlea is most recognized and in this process, reactive oxygen species (ROS) play a major role (Henderson et al., 2006; LePrell et al., 2007). These ROS, free positively charged radicals, are normally generated in the mitochondrion of the cell, but during and after overexposure to noise there is an overproduction of these ROS (Bielefeld et al., 2005). ROS have been found in cochlear tissues after damaging noise exposure (Hu et al., 2006; Shi &Nuttall, 2003; Vlajkovic et al., 2010) and remain in the cochlea up to several days after exposure (Yamane et al., 1995). Continuing presence of oxidative stress is associated with progressive cochlear injury (Liu et al., 2010). The presence of ROS can be seen as the initiator of a sequence of damaging mechanisms, such as the creation of toxic lipids, inflammation and reduced cochlear blood flow eventually leading to programmed cell death (apoptosis) or necrosis (Choung et al., 2009; Dröge, 2002; Jaumann et al., 2012; Kurabi et al., 2017; Reif et al., 2013; Yamashita et al., 2004). A reduced blood-flow caused by exposure to noise, limits the clearing of the free radicals, in a positive feedback loop creating more and more damage. Although ROS are found in the stria vascularis and supporting cells, most damage is found in the OHCs (Rask-Andersen et al., 2000; Sliwinska-Kowalska & Jedlinska, 1998; Talaska & Schacht, 2007).

Hearing damage and loss of sensitivity

Damage to outer hair cells, inner hair cells and spiral ganglion cells is associated with an increase in hearing threshold. But animal studies have failed to show any correlation between amount of OHC damage and degree of threshold increase (Chen & Fechter, 2003; Hamernik et al., 1989; 1996; Ohlemiller et al., 2000). It has been shown in chinchillas that there can be OHC loss without accompanying increase in threshold (Hamernik et al., 1996). The term 'outer hair cell redundancy' was introduced to described such and similar findings (LePage & Murray, 1993). It implies that OHCs can be damaged or lost without a measurable loss of sensitivity for soft sounds.

Recent studies have shown that damage to a large portion of IHCs can exist without affecting hearing threshold level suggesting that only a small population of working IHCs are required for the detecting of soft tonal sounds in a quiet surrounding (Lobarinas et al., 2013). Additionally, there is the earlier mentioned evidence that exposure to noise causes permanent loss of synapses between IHCs and nerve fibers, without (permanent) loss of sensitivity to soft sounds (Kujawa & Liberman, 2009; 2015; Sergeyenko et al., 2013). As a consequence the auditory nerve fibers degenerate, especially those with low spontaneous rate which are thought to be important for the suprathreshold ability to listen in noisy conditions (Furman et al., 2013). This phenomenon is called 'hidden hearing loss' since the remaining synaptic damage hides behind normal hearing threshold levels (Liberman & Kujawa, 2017; Schaette & McAlpine, 2011). Although there is histological evidence in animals, there is no clinical and reliable test for this type of loss in humans (Plack et al., 2016). Such findings imply that noise damages several structures in the inner ear, simultaneously or sequentially and that the damage is not necessarily expressed in terms of loss of sensitivity to soft sounds, i.e. hearing thresholds levels (Fernandez et al., 2020; Liberman & Kujawa, 2017).

Current regulations for the prevention of NIHL /hearing conservation

Since 2003 there is a directive for all countries in the European Union to reduce occupational noise exposure that provides occupational exposure limits (OELs) in terms of maximum duration of exposure for various noise levels (European Directive 2003/10/EC). All levels are referred to in terms of an eight-hour-equivalent, $L_{A,ex,8h}$ with an exchange rate of 3 dB (A). The exchange rate determines the exposure-duration relationship: higher exposure requires shorter durations and vice versa. The allowed exposure time should be halved for every 3 dB (A) increase in sound level.

The directive places priority on minimizing the risk of hearing loss for employees by preventing high noise levels and long duration of exposures. This is ideally achieved through a hierarchy of actions, starting with noise-control measures such as silencing equipment (shielding, noise absorption), proper maintenance, and instructions on correct usage (Sorgdrager et al., 2007). Next, organizational measures are used to reduce duration and intensity for workers. If these measures cannot prevent the risk, or if they are not reasonably feasible, the employer must provide individual hearing protection devices (HPDs). The employer is obliged to assess or measure the noise levels to which workers are exposed. The limit for the exposure is set at 87 dB (A), taking into account the attenuation provided by personal hearing protection devices. Additionally, two types of action levels are defined to undertake actions to reduce the noise exposure. A lower exposure action value is set at 80 dB (A). When this value is exceeded, employees should receive information on the risk of exposure to noise, should be offered access to periodical hearing testing (audiometry), and individual hearing protectors should be made available. An upper exposure action value is set at 85 dB (A). For exposures exceeding this upper value, the EU places the responsibility on the employer to ensure that the hearing protection is not only provided but also being used.

Prevalence of NIHL

Despite the presence of occupational exposure limits and requirements to reduce the noise levels, NIHL is still an occupational disease in many high income countries, with estimations ranging from 7-21% of all cases of hearing loss (Dobie et al., 2008; Nelson et al., 2005). The exact prevalence between countries is difficult to compare because different definitions of NIHL are in use (Rabinowitz, 2012). Lie et al. recently performed a literature review and concluded that people working in ship building, construction or other forms of industry, in agriculture and in the military are most at risk of occupational hearing loss (Lie et al., 2016).

For The Netherlands, Leensen et al. (2011) have analyzed the hearing of a population of ca. 27.000 construction workers measured from 2005 to 2006, and found that the hearing threshold levels of these workers are worse than would be expected based on age alone. Hearing damage is the third-most reported work –related injury in The Netherlands in 2018. But it should be noted that the incidence has decreased the last five years because there is no more systematic reporting of NIHL in the construction industry (Van der Molen et al., 2019). The damage occurs despite the availability and use of hearing protection devices. The noise damage is mostly related to the duration in exposure, leading to moderate or severe hearing loss at the age of retirement.

For low or middle income countries, legislation concerning occupational noise exposure limits and working hours is often not present or maintained, leading to higher incidences of hearing loss(Fuente & Hickson, 2011; Nelson et al., 2005; Robinson et al., 2015; Smith, 1998). Studies from the textile industry, sugar cane industry, mining, wood, or steel working in countries as Thailand, Vietnam, South Africa, Ghana, Guatemala, and Tanzania show high noise levels, long working hours and associated high prevalence of hearing loss (Abraham et al., 2019; Kitcher et al., 2019; Nguyen et al., 1998; Nyarubeli et al., 2018; Osibogun et al., 2000; Robinson et al., 2015; Strauss et al., 2014; Stumpf et al., 2020; Thepaksorn et al., 2019).

NIHL and recreational noise

The literature on noise exposure and NIHL has been dominated by occupational noise exposure. But recent years have shown that concern is rising about leisure activities causing hearing damage, with an accompanying increase in publications dealing with leisure noise exposure (Carter et al., 2014; Degeest et al., 2017; Jiang et al., 2015; Neitzel & Fligor, 2019; SCENHIR, 2008). The WHO performed a review on hearing loss caused by recreational exposure to loud sounds in 2015 (WHO, 2015). For middle and high income countries, the authors estimated that around 40% of teenagers and young adults aged between 12 and 35 are exposed to sound levels that could damage their hearing. The high exposures are encountered in venues such as bars, discotheques, cinemas, concerts, sporting events and nightclubs. Hobbies such as shooting and riding motorbikes are activities that are known to be accompanied by a risk of NIHL. Furthermore, the authors from the WHO report estimated that nearly 50% of these youngsters use personal audio devices (PAS) such as smartphones etc. at levels that are potentially harmful for their ears.

Because this is also a concern in The Netherlands, the Dutch Ministry of Health, Welfare and Sport, requested advice from the National Institute for Public Health and the Environment (RIVM) on maximum noise levels at the above-mentioned locations (Gommer et al., 2018). In answer to this request, Dutch experts in the field of acoustics and (prevention of) hearing loss, have made recommendations on maximum noise levels per age group. In their report, it is stated that adhering to these levels does not guarantee that nobody will develop hearing loss. Individual susceptibility, individual listening behavior and total exposure to noise levels may vary across individuals. The report therefore also advices people attending public venues where loud music and/or noise is present to take active steps in reducing their risk of hearing loss. The overall exposure can be reduced by increasing the distance from the sound sources, by using hearing protection devices (HPDs) such as earplugs, or by taking breaks during the exposure. Similar advices for individuals are given the 2018 Music Induced Hearing Loss statement from the National Hearing Conservation Association (NHCA) in the US (Fligor et al., 2018).

Measurements on NIHL

A key and obligatory component in a hearing-loss-prevention program is the measurement of hearing status (European Directive 2003/10/EC; Kirchner et al. 2012; OSHA, 2002). The importance of periodical hearing testing was already expressed in 1921 by a Belgian medical officer (Gilbert, 1921) and in 1946 by the American Committee on the Conservation of Hearing (Glorig, 1961). The goal of hearing measurement is to detect hearing loss as soon as possible to prevent further progression and inform both employee and employer of the damage (European Directive 2003/10/EC; Kirchner et al., 2012).

This also allows identification of possible susceptible subjects and of areas where intervention is possible or required. Single measurement can be performed to assess the current status of an employee's hearing. Consecutive measurement allow monitoring of the development of hearing loss. Measurement of groups of employees provides insight how well the hearing conservation program is working at that worksite.

Pure-tone audiometry (PTA)

Hearing loss is traditionally assessed by pure-tone audiometry and is expressed in terms of hearing sensitivity. This method is explicitly mentioned in the EU Directive, and considered the gold standard in measurement and determination of NIHL (Cameron & McBain, 2019; Frederiksson et al., 2016; May, 2000). At each particular frequency, the minimum audible sound pressure level (hearing threshold level) is acquired according to a procedure described in ISO standard 8253-1 (2010). This standard describes how the stimuli should be presented, i.e. when the examiner should increase or decrease the stimulus level depending on the patients' response, and describes when a reliable threshold is determined. Clinical audiometry is usually performed with a (final) 5 dB step size, but smaller more accurate step sizes can be used as well. Pure-tone audiometry requires active cooperation from the patient.

In order to ease comparison between different subjects, the audiometric 'zero' has been determined (ISO 7029:2017). At each frequency, usually between 125

Hz and 8000 Hz, hearing threshold level is plotted in units of decibel hearing level (dB HL), with higher numbers reflecting worse hearing thresholds. The graph representing this method is called the audiogram (Figure 1.3). It tests the detection threshold per frequency and thus the entire auditory pathway and requires active cooperation of the subject. TTS and PTS are expressed in the audiogram in the same way.

A problem that may arise with such a behavioral test is the test-reliability caused by factors such as both patients' and examiners' attention and experience, measurement environment and equipment. Automated procedures are often found in occupational settings. It was found that test-retest reliability in such situation was worse than in diagnostic and clinical settings, and that thresholds in the latter settings were on average 5 dB better (Dobie, 1983). Furthermore, the variability in hearing surveys in less than optimal measurement conditions was found to be larger than in clinical settings (Schlauch & Carney, 2012). This prevents small changes in hearing threshold to be detected and distinguished from measurement variability.

Although PTA is the gold standard for detection and diagnosis of NIHL, there are some disadvantages besides the above-mentioned variability. As discussed previously, real structural damage might be 'hidden' behind a normal pure-tone threshold. Furthermore, an increased hearing threshold level represents the loss of sensitivity for soft sounds, but it does not reflect problems encountered in real-life. Subjects with beginning NIHL notice a diminished capacity of understanding speech in noisy surroundings. This makes speech-in-noise testing both an interesting alternative for pure-tone audiometry, and an addition to describe functional effects of hearing damage.

Otoacoustic emissions (OAEs) are another tool that could be of interest in measuring NIHL since they reflect outer hair cell activity (Kemp, 1978; 2007) and can be assessed objectively. This can be an advantage over both audiometry and speech-in-noise testing, since these tests require active cooperation from the subject. In case of a subject feigning hearing loss for medicolegal purposes, or in case of a difficult to test subject, an objective test would be very useful.

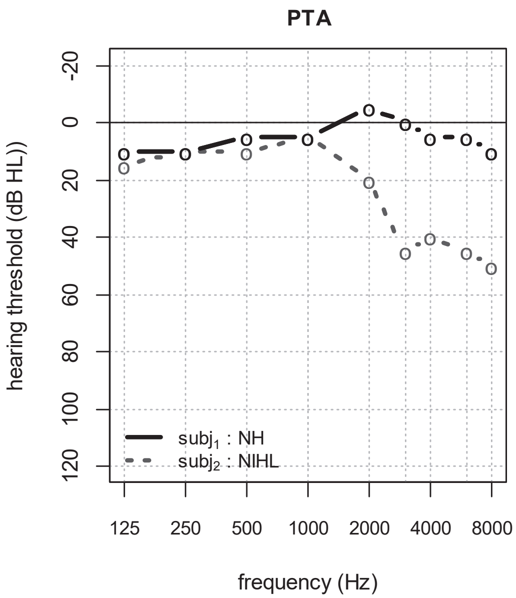


Figure 1.3: Typical audiogram for a (female) subject with normal hearing (NH, $subj_1$) and a (male) subject with noise-induced hearing loss (NIHL, $subj_2$). The solid black line represents hearing threshold for the normal hearing subject and dotted grey line represents hearing threshold for NIHL. The lower frequencies have similar hearing thresholds, but hearing thresholds for the subject with NIHL are elevated in the higher frequencies, especially in the area around 4000 Hz.

Speech-in-noise testing

Speech-in-noise tests are functional and are measured at levels above hearing threshold level (suprathreshold), thus making them less sensitive for noisy background conditions. In many countries some form of internet-based hearing screening test using speech-in-noise is available. For The Netherlands, there are several types of tests available, of which the Earcheck and Occupational Earcheck have been modified to be more sensitive for high-frequency hearing loss as seen in NIHL (Leensen & Dreschler, 2013; Sheikh Rashid et al., 2017). These improved tests are promising in terms of applicability at home and are more representative for the functional problems people experience, but they still require cooperation of the subject. Furthermore, the applicability in longitudinal monitoring has not been investigated yet.

Otoacoustic emissions

Otoacoustic emissions (OAEs) are very soft sounds originating from the positive feedback system of the outer hair cells (OHCs). These OHCs amplify the initial vibration of the basilar membrane caused by sound. Some of the thus created vibrational energy travels back to the middle ear, and back through the tympanic membrane. It can be recorded in the external ear canal when it is closed off with a probe in which sensitive microphones are placed. (Kemp, 2007). OAEs can be considered as a by-product of good working cochlea and are used extensively in newborn hearing screening programs (Prieve, 2007). The presence of robust emissions is an indication of a normal functioning cochlear amplifier. Absent or reduced emissions can be caused by a cochlear loss or by poor transmission through the middle ear. Humans with healthy ears generally have measurable emissions (Kapadia & Lutman, 1997) while (noise) impaired ears have lower or absent emissions (Attias et al., 1995; Avan et al., 1996; Gorga et al., 1993; Gorga et al., 2007).

Otoacoustic emissions can be spontaneous (SOAE) or can be evoked by sound stimulation. In clinical practice, it is common to distinguish them according to the sound source that elicits the emission, i.e. click-evoked OAEs (CEOAEs), or transient evoked OAEs (TEOAEs), stimulus frequency OAEs (SFOAEs) or distortion product OAEs (DPOAEs). There are fundamentally different mechanisms underlying the generation of emissions (See box C), which can be considered as reflection source emissions, distortion-source emissions or a combination of both (Shera & Guinan, 1999; Shera, 2004). The most commonly used forms of OAEs in clinical settings are the TEOAE and DPOAE.

C: OTOACOUSTIC EMISSIONS

Generation of OAEs

For all types of OAE there is energy travelling in the reverse direction, i.e. from the cochlea to the outer ear. Such reverse waves can be caused by reflection of energy somewhere along the basilar membrane or can be caused by nonlinearity, distortion, in the displacement of outer hair cell bundles. Across the basilar membrane, random perturbations or irregularities in the organization of OHCs can be found. They cause reflection of the travelling wave. Examples of the reflection type of emissions are low-level SFOAEs and TEOAEs. The spontaneous OAEs are caused by standing waves through internal reflections. A hypothetically mechanical smooth cochlea would not exhibit reflection source emissions.

DPOAEs are generated through another mechanism (Shera & Guinan, 1999; Shera, 2004). There is non-linearity in the relation between the OHC-displacement as function of the force. The non-linearity creates distortion sources and forms new combination tones that are mathematical combinations of two primary tones f_1 and f_2, such as $2f_1$-f_2, $3f_1$-$2f_2$, $2f_2$-f_1. The intermodulation distortion product, $2f_1$-f_2 is the strongest and is most recorded in practice.

Higher level stimuli create a combination of both types which can be determined by looking at the phase-dependency of the outcome (Shera & Abdala, 2012). In clinical practice, the magnitude or amplitude of the emission is the outcome measure, either in terms of absolute emission level, or relative to the noise level (signal-to-noise ratio, SNR). Fine structure or phase information is often not included in measurements used in clinical practice.

Clinical settings for measuring TEOAE and DPOAE

The stimulus of the 'common' transient evoked OAE (TEOAE) is a train of short (80 ms) biphasic, broadband or flat spectrum clicks at 84 dB peak equivalent SPL. The clicks can be presented in the linear mode, or in the non-linear mode with three consecutive clicks in one polarity and one click with three times the amplitude in reversed polarity, thus canceling out linear artefacts. The response of the cochlea is recorded a few milliseconds later and this procedure is repeated, often in the range of 100-300 times, depending on the strength and reliability of the emission. The average response of all repetitions is recorded as an overall response level, and often filtered into octave bands between 1 and 4 kHz. Noise levels are recorded simultaneously, which allows computation of the signal-to-noise ratios (SNR) for each recording. Recordings with high SNR, have a high response and/or low background noise. Lower SNRs can be found in situations with good recordings but noisy measurement conditions, but also in damaged ears that are measured in proper measurements conditions.

Distortion product OAEs are measured as a response of the cochlea to two distinct primary tones at frequency f_1 and f_2, and with levels of L_1 and L_2. The frequency ratio (f_2/f_1) can be varied, but most often $f_2/f_1 = 1.2$ is used. Similarly, L_1 and L_2 can be varied. A paradigm that is often seen is L_1=65 dB SPL, L_2=55 dB SPL but other combinations of primary levels are found as well.

The two primary tones create new tones as products of the distortion, at the frequency of the combinations of f_1 and f_2, and most prominently at $2f_1$-f_2. Research has shown that for the above-mentioned ratio of $f_2/f_1 = 1.2$, and with L_2 lower than L_1, the response stems mostly from the region in the cochlea corresponding to f_2 (Lonsbury-Martin et al., 1991; Lonsbury-Martin & Martin, 2007).

OAEs can be plotted as emission level as function of frequency: the frequency band when the overall response of the TEOAE is filtered into ½ octave frequency bands. For the DPOAE the overall response is usually plotted as function of f_2 (DP-gram). Another application is the input-output curve where the frequency is kept constant and the levels of the primaries are varied.

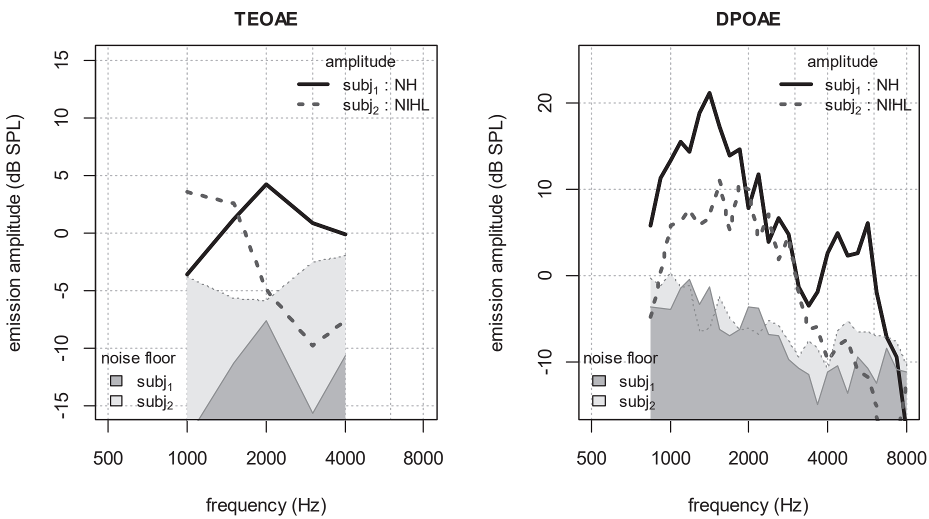


Figure 1.4: Example of TEOAE (left) and DPOAE (right) measurements for 2 subjects. Grey areas represent the noise floor present during the measurement. The solid black line represents emission amplitudes for a (female) normal hearing subject (NH, subj$_1$) and dotted grey line represents emission amplitudes for a (male) subject with noise-induced hearing loss (NIHL, subj$_2$). Emissions are present and above the noise floor for the lower frequencies, while they drop below noise floor in the higher frequencies for the subject with NIHL.

OAES AND NIHL

Since OAEs reflect the functionality of the outer hair cells, it seems a very suitable method to measure (early) effects of noise on hearing. Cross-sectional studies on subjects with hearing thresholds within normal limits have shown that emissions are lower in a noise-exposed group when compared with emissions from a non-exposed group (Lapsley Miller & Marshall, 2007). This led to the hypothesis that OAEs are capable of detecting small effects on outer-hair cells before these effects can be measured as an increase in hearing threshold level, the so-called outer hair cell redundancy (Lapsley Miller & Marshall, 2007; LePage & Murray, 1993). Any test that would detect signs of NIHL as early as possible is of interest in hearing conservation, since that would allow necessary interventions at an early stage and limit further damage.

Although cross-sectional studies can provide information on the effects of noise exposure for a group of subjects, such studies cannot provide answer in how prolonged noise exposure affects otoacoustic emissions in time. Longitudinal designs are required to investigate how well OAEs can be used to track changes in hearing over time and to monitor individuals exposed to noise.

Every measurement whatsoever, consists of some form of random, and/or systematic variation. For audiometry, measurements conditions and subject cooperation influence the accuracy of the measurement, but the same can be said for the dB step size in which thresholds are determined. For OAEs, the background conditions, middle-ear transmission and probe-fit in the ear canal can cause variability between measurements. When following the development of hearing damage in individuals, an important question is how an actual change in hearing can be distinguished from a change caused by measurement variability. In occupational practice, there are various definitions for significant audiometric shifts (see Table 4-III) but there are no such definitions for OAEs.

Although OAEs have a widespread use in neonatal hearing screening, their use in occupational, longitudinal settings is limited. Practical issues need to be investigated when subjects are monitored longitudinally for years, such as the measurability of OAEs in subjects with pre-existent hearing loss, the dependence on the noise-level of background conditions during measurements, effects of ageing and the above-mentioned definitions of shifts in PTA and OAE.

In this context, the role of otoacoustic emissions (in the form of TEOAEs and DPOAEs) in measuring and monitoring NIHL in the field of hearing conservation is investigated in this thesis and compared with pure-tone audiometry (PTA).

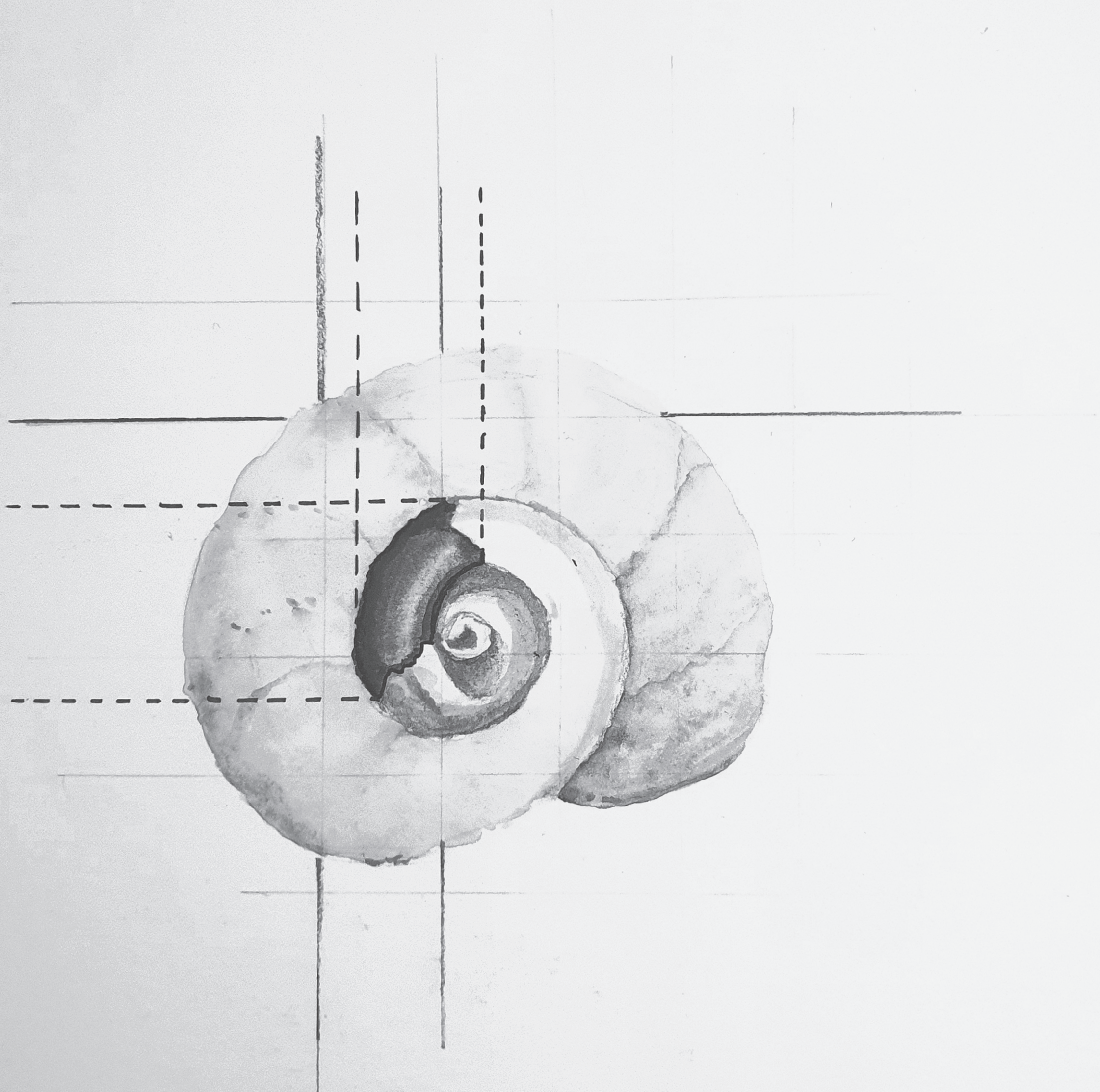
OUTLINE OF THIS THESIS

Aim of this thesis is to contribute on the role of otoacoustic emissions (OAEs) in measuring and monitoring noise-induced hearing loss (NIHL). Studies are performed in the field of occupational noise exposure (**Chapter 2,3,4**) and recreational noise exposure (**Chapter 5 and 6**).

The general applicability and boundary conditions for monitoring NIHL with OAEs are investigated in **Chapter 2**. The relationship between changes in OAE and audiometry at an individual level are discussed in **Chapter 3**. During these analyses, advanced understanding evolved that it is incorrect to claim any potential of 'early' detection based on cross-sectional studies. The few longitudinal studies that were published, used different settings and paradigms and were equivocal in their conclusion. This led to a review of peer-reviewed literature on longitudinal monitoring NIHL with OAE and audiometry (**Chapter 4**). The studies entered in the review are all conducted in occupational settings, with no control and exact knowledge of the noise exposure that the ears had to endure.

To overcome these confounding factors, a strictly controlled experiment was set up. **Chapter 4** and **5** investigate controlled noise exposure caused by dance (house) music. Recreational sources of noise exposure have been given much attention in recent years and the term Music Induced Hearing Loss (MIHL) is used to indicate this form of NIHL. In order to prevent (temporary) hearing damage , attendees of clubs, festivals or concerts are given the advice to take a break during the exposure. **Chapter 5** investigates the effect of the break (presence or absence) on hearing sensitivity as expressed in audiometric thresholds, measured in a small step size. For ethical reasons, the levels in this experiment are lower than encountered during real-life dance music festivals because the levels have to be safe for the ears of the test subjects. Nevertheless, this setting provides a unique opportunity to compare OAEs and PTA in their potential for detecting small temporary changes on hearing, especially since PTA is measured in a smaller step size than in common clinical practice (**Chapter 6**).

Many methodological issues were identified that need to be addressed when comparing different methods such as audiometry and OAE. These issues will be discussed in the final chapter of this thesis



CHAPTER 2

Otoacoustic emissions in a hearing conservation program: General applicability in longitudinal monitoring and the relation to changes in pure-tone thresholds

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Wouter A. Dreschler

International Journal of Audiology, 2010 Jun;49(6):410-9.

ABSTRACT

The hearing status of workers (N=233) in a printing office was assessed twice within seventeen months by pure-tone audiometry and otoacoustic emissions (OAEs).

One of the questions was how a quality criterion of OAE measurements based on a minimum signal-to-noise-ratio (SNR) would affect the applicability on the entire population. Secondly, effects of noise exposure were investigated in overall changes in audiogram and OAE measurements.

For TEOAEs (Transient Evoked OAEs) in the frequency band of 4 kHz, only 55% of the data points meet the SNR-inclusion criterion. For DPOAEs (Distortion Product OAEs) around 6 kHz approximately 80% of the data points satisfy the criterion. Thus OAEs have a limited applicability for monitoring the hearing status of this entire population.

Audiometry shows significant deteriorations at 6 and 8 kHz. TEOAEs show a significant decline at all frequency bands (1-4 kHz), DPOAEs between 4 and 8 kHz and less pronounced between 1 and 2 kHz. On group level, OAEs show a decline in a larger frequency region than the audiogram, suggesting an increased sensitivity of OAEs compared to audiometry.

INTRODUCTION

Since the discovery of the otoacoustic emissions (OAEs) and their relationship with the outer-hair cell motility, much research focussed on the possibilities of detecting noise-induced hearing loss (NIHL) by means of OAEs. In occupational medicine the common way to monitor hearing status is by the pure-tone audiogram, a subjective method depending on the behavioural response of the test subjects. OAEs have the advantage of being objective and in addition it has been suggested that OAEs are more sensitive to early signs of NIHL and can be measured with a higher precision. A detailed review (up to 2006) is written by Lapsley-Miller et al. (2007).

Noise exposure is known to cause inner ear damage, both in humans and in animals, starting with damage to the outer hair cells. Animal studies have shown conflicting results concerning the quantitative (cor)relation between a decrease in OAE-amplitudes and histopathological damage to outer hair cells (Canlon et al., 1993; Hamernik et al., 1996; Le Calvez et al., 1998; Hamernik & Qiu, 2000; and Harding et al., 2002). Most authors do agree that a certain degree of outer hair cell damage is reflected in OAE-amplitude but research has been inconclusive in quantifying this relation.

In humans, OAEs are known to reduce with hearing loss and several studies have led to the conclusion that OAEs might be more sensitive in detecting NIHL at an early stage (so-called preclinical damage). Hamernik et al. (1989; 1996) have shown that outer hair cell damage may occur without corresponding damage to hearing thresholds.

Investigation of standard deviations by Hall & Lutman (1999), showed a smaller standard deviation in test-retest measurements for OAEs than for audiometry. This argument induced several authors to search for evidence that OAEs would be more capable in detecting subtle changes in cochlear function.

This evidence is mainly based on the observation that groups of noise exposed subjects with audiometric thresholds within normal limits have lower OAEs than groups of non-exposed subjects with hearing thresholds within the same limits (see for example Attias et al., 1995; 2001; LePage et al., 1998; Desai et al., 1999; Balatsouras, 2004; Hamdan et al., 2008). Even though there are ample studies based on similar group designs, the validity of the conclusions derived from these studies is limited. Sisto et al. (2007) emphasize that the definition of normal hearing by hearing thresholds ≤ 20 dB HL still allows the audiometric thresholds between noise-exposed and non-exposed groups to be different. By using a more strict definition of normal hearing, they conclude that a composite OAE parameter is capable to detect very mild hearing losses (10-20 dB HL). This seems in correspondence with Dorn et al. (1998) who have shown a decrease in OAE-amplitude with hearing threshold even for people with hearing thresholds between -5 and 20 dB HL.

Lapsley-Miller et al. (2006) suggest that low-level or absent OAEs could be indicative for NIHL susceptibility. Their results are based on longitudinal study of individuals enrolled in a navy hearing conservation program. Shupak et al. (2007) followed changes in a longitudinal design too: they conclude that (broadband) TEOAEs are more suitable for detecting subclinical changes than (narrowband) DPOAEs. They do not recommend screening for changes with TEOAEs because of a high false-positive rate. In contrast, Duvdevany et al. (2007) concluded that the wideband TEOAE level could serve as a predictive tool for individual vulnerability to noise exposure. Recently, Job et al. (2009) have reported about follow-up measurements for pilots. They show that for subjects with all audiometric thresholds at 10 dB HL or better, initial DPOAE status was predictive for an increase in audiometric threshold at the follow-up measurement. Marshall et al. (2009) have done a study on impulse sounds recently. They have shown that low-level otoacoustic emissions can indicate an increased risk of future hearing.

However, the amount of longitudinal studies remains limited. The vast majority of evidence towards a better sensitivity of OAEs compared to pure-tone audiometry is based on cross-sectional studies. Despite the lack of scientific consensus on the validity of replacing regular audiometry by OAEs in occupational health settings, in some Health and Safety Departments in industrial settings in The Netherlands, the screening by conventional audiometry has been replaced by measuring otoacoustic emissions. The rationale for this replacement is the above mentioned possibility of OAEs being more sensitive to early stages of NIHL than audiometry. In case of a deterioration of OAE-levels pure-tone audiometry is used to confirm hearing loss.

This research has been initiated in order to investigate whether monitoring NIHL by OAEs is applicable for a general group of employees, currently employed in a noisy environment. The first research question concerns the general applicability. OAEs decline with age and hearing loss and in such a generalised population age may vary from 18 to 65 years. Hearing loss may vary correspondingly in such a group. Persons with a pre-existing hearing loss tend to have lower emission when starting in a hearing conservation program. It can be expected that limited hearing ability also places limitations on the range of frequencies where OAEs are measurable. This may limit the range of frequencies where OAEs can be used for monitoring or, vice versa, may limit the amount of people for whom OAEs are reliable enough to use for monitoring.

The second research objective is to study the changes in pure-tone thresholds and otoacoustic emissions during a period of 17 months of occupational noise exposure. We hypothesized that the mean hearing threshold and the emission amplitude, especially in the higher frequencies, would decrease as a combined effect of ageing and noise exposure. Will OAEs and audiometry show similar patterns in the development of hearing loss, caused either by age (age-related hearing loss ARHL) or by noise (NIHL)?

This study aimed at exploring boundary conditions in which the use of OAEs might have a contributing role in a general hearing conservation program. Analyses of the group data are used to answer questions about the frequency most suitable for monitoring purposes and the quality demands for optimal application of OAEs in industrial settings.

As mentioned previously, the number of longitudinal studies is limited. A next step will be to examine the data for two purposes: to classify and detect individual changes and to study the possibility of screening for individual susceptibility. These factors will both be addressed in a future paper.

METHODS

Participants

Measurements were performed on 320 employees of a newspaper printing office (median age 42 years, range 23-60 years old, years of employment median 18, range 0-46 years, 4 women and 316 men). First tests took place within the framework of a periodical hearing screening program and were performed during three weeks in December 2004. The follow-up measurements took place after seventeen months. Only a few (15) participants dropped out during this period due to retirement or job rotation.

The included professions can be classified in six main categories: bench workers (5%), employees working at the layout department (7%), printing department (48%), inking depot (3%) or at the expedition (19%), electricians (7%) and miscellaneous (11%).

Since 2003, there is a European Directive (2003/10/EC) within the EU-legislation that provides upper and lower action values for noise exposure for workers. It states that when noise exposure exceeds the lower action value of 80 dB (A), the employer must make individual hearing protection available for workers. When the noise exposure equals or exceeds the upper action value of 85 dB (A), individual hearing protection must be used. The directive places the correct use and verification of hearing protection devices under the responsibility of the employer. For the majority of workers in the printing office, the dose lies between these action values.

Limitation of noise exposure is achieved by shielding noise sources and providing employees with individual hearing protection devices such as otoplastics, disposable foam plugs and earmuffs. In the questionnaire, 80% of the subjects answered that they frequently used some kind of hearing protection. At the same time, only 30% of the subjects indicated a consistent use of protection in the situations that it was required. The remaining 70% admitted that they omitted the use of protection on a more or less regular basis.

Description of tests

OAE tests and pure-tone audiometry were conducted by different hearing conservation technicians or audiologists that were blinded from the results of the other test. Pure-tone audiograms were obtained at 0.5, 1, 2, 3, 4, 6, 8 kHz with an automated Hughson-Westlake procedure on an Audioscan Essilor audiometer with accompanying Beyer Dynamic DT48 headphones. For hearing thresholds larger than 15 dB HL at 0.5 or 1 kHz a Rinne tuning fork test (f=512 Hz) was performed to disclose possible conductive components in the hearing loss. In case of a negative Rinne, participants were referred for further investigation and excluded from the analysis.

Preceding the otoacoustic emission procedure, ears were visually examined. In case of obstruction, participants were asked to have their ears cleaned and the tests were rescheduled. Otoacoustic measurements were conducted, starting with TEOAE measurements and followed by DPOAE measurements.

OAEs were measured with a conventional ILO288 Echoport system (Otodynamics Ltd England) using a DPOAE- probe. The system was calibrated daily. Taking more averages could increase SNR for subjects with low emissions, but it would also increase measurement time. For reasons of uniformity, the emphasis was placed on feasibility and not on individual optimization of the response. Therefore a fixed amount of averages were taken with the noise-rejection level held constant. The TEOAEs were measured in the 'standard' nonlinear mode with a test stimulus of 80 dB (peSPL) until 280 low-noise averages were obtained. A probe-fit procedure was performed to create an optimally flat spectrum in the response. The overall response and overall noise-spectrum were recorded and filtered in the frequency bands of 1, 1.5, 2, 3, and 4 kHz.

For the DPOAEs, the stimulus levels of the two probe tones, f_1 and f_2 were L_1=75 dB SPL and L_2=70 dB SPL and the ratio between the probe tones was $f_2/f_1 = 1.22$. DPOAEs were measured at $^1/_8$ octave frequencies with f_2 ranging from 841 to 8000 Hz. A total amount of 27 frequencies was tested. Recording was stopped after three runs across frequency. This relatively high stimulus level was chosen to minimize the effect of background noise. Lower level stimuli are suggested to be more sensitive in detecting hearing loss (Gorga et al, 2007). In the follow-up measurement the measurement protocol was extended to incorporate lower stimulus levels: f_1 and f_2 were presented at ¼ octave intervals at L_1=65 dB SPL and L_2=55 dB SPL. Since these measurements are available for the second year only, they are not reported here in detail.

General procedure

Participants filled out a questionnaire before entering the measurement procedure. The questions concerned hearing status, hearing problems, otologic history, medication, recent exposure, and the use of hearing protective devices. When necessary, these results were used for counseling by the industrial medical officer.

Effort was put in avoiding TTS but it could not be ruled out completely because of rotating working schedules. Subjects were asked to wait in a relatively quiet environment to fill-out the last part in the questionnaire concerning recent exposure and recent drug use. These questions can be used as a rough estimate of recent noise exposure.

The total measurement time was approximately 50 minutes. All testing took place in a conference room in a relatively quiet part of the building. Background noise consisted of sounds from the underlying work floor and noise from departing distribution trucks.

Audiometry was performed in an Eckel AB-2000 sound-attenuating booth (according to ISO 8253-1 (1989)), placed in a large room with carpet. Otoacoustic emissions were also measured in a similar sound booth within the same room. The equipment and experimenter were placed on the outside with only the OAE-probe cable entering the booth, thus prohibiting a fully sealed door.

The same room was used in the follow-up measurements but to minimize waiting time for the employees, two OAE-systems were used separately, both placed in their own booth in the large room. The second OAE measurements took longer because of an extended measurement protocol and were therefore performed with a small ventilator in the booth. Noise levels with ventilation comply with ANSI standards (www.audiologyrooms.com).

For 60 participants the measurements were performed twice on separate days in order to derive a measure for the short-term test-retest variation. The period of time between these subsequent measurements ranged from 2 days to 2 weeks. These results will be used in future analysis where the focus will be on classifying individual changes.

Data inclusion

Of the original 320 participants, 15 were discarded because of (partially) conductive hearing losses established by the Rinne tuning fork test, 13 because of incomplete audiograms (more than one threshold missing) or incomplete datasets for one ear. The four female participants were excluded from further analysis to avoid gender effects. This yields a total number of 288 participants. Of this particular group, 233 (and thus 466 ears) were present (with complete data) for the second measurement. The presented results concern this subgroup.

In the overall analysis all data from this subgroup of 233 persons is included. For the analysis on the OAE-results an inclusion criterion was used. This criterion is based on the signal-to-noise ratio (SNR) and thus directly related to the quality of the recording. The SNR depends on the status of the cochlea, the signal, and on the measurement conditions, represented by the noise level present during the recording. Ears with different cochlear status can have the same SNR.

For TEOAE, an emission is considered to be present if the amplitude was greater than 0 dB SNR relative to the noise level in the accompanying frequency band. Similarly, for DPOAE, an emission was considered to be present when the amplitude was higher than the upper estimate of the noise level (i.e. ≥ 0 dB SNR relative to two standard deviations above the average level of the noise-floor). Some authors, for example Shupak et al. (2007) and Bhagat & Davis (2008), demanded a higher SNR at the baseline measurement, i.e. 3 or 6 dB above the estimated level of the noise-floor.

Single data points, not subjects were discarded when they did not meet the SNR-criterion. Please note that this criterion introduces a selection bias since subjects with more missing data due to low emission levels and thus low SNRs may have more noise-induced or age-induced hearing losses. An ear with a low SNR may be included in year 1 but if a deterioration in emission level occurs (or a change in background conditions), this ear would be discarded. When looking at the development of hearing loss, the ears that drop in SNR due to a decrease in emission amplitude are of interest. Lapsley-Miller et al. (2004; 2006) describe a method to take such in ears into account. Their method of noise-floor substitution has been adopted here. The follow-up OAE level is substituted with the corresponding noise-level when the second year SNR is below zero. The substitution enables the inclusion of those ears whose emissions were good at the start but whose emissions deteriorated at or below noise-level. It introduces a possible negative bias in finding more deteriorations than improvements while underestimating the actual size of the change.

Statistical techniques

Statistical analysis was performed on a personal computer with R software ((C) R Foundation, from http://www.r-project.org.

Although the distribution of hearing levels is skewed by definition, we considered the distributions of *changes* in audiometric thresholds, otoacoustic emissions, and their derived measures to be normal. Paired comparisons were done with Students *t*-tests, multiple *t*-tests for outcomes at different frequencies were adjusted with a Bonferroni-correction. The main results have been verified with non-parametric statistics as well, showing similar findings.

The participants were divided into subgroups according to the hearing thresholds and audiometric configuration. The idea of this categorization is to compare the development of hearing damage for different starting points in hearing status.

It would also provide insight whether the otoacoustic emission measurements are applicable to persons with a known hearing loss or not. Analysis of variance was carried out to detect differences between subgroups and when necessary post-hoc analysis was performed with Tukey's HSD test.

The classification used here is based on the average audiogram of both years in order to avoid incorrect conclusions caused by regression to the mean (Bland & Altman, 1994). This procedure minimizes the effect of statistical fluctuations in hearing thresholds. For reasons of security, we verified that similar analyses with the categorization based on either initial or final audiogram, lead to comparable results.

Five groups and a rest group (RE) were defined: normal hearing (NH), subnormal hearing (SN), mild notch (MN), profound notch (PN), and sloping audiogram (SL). The better hearing groups are similar to those described by Jansen et al. (2008).

Normal hearing is defined as having every threshold at 15 dB HL or better. As mentioned previously, even within such a normal hearing group, there can be variations in hearing status (Mills et al., 2007) and correspondingly in OAE-levels. According to Dorn et al. (1998), having thresholds of 15 or 20 dB HL is an indication of modest cochlear dysfunction.

The mild notch group has a small elevation in hearing threshold at 3, 4 or 6 kHz when compared to the average of 0.5, 1, and 2 kHz and the better threshold of 6 and 8 kHz. The profound notch has a larger elevation with respect to the same reference points. Finally, the sloping audiogram usually shows similar thresholds at 3 and 4 kHz, but does not show improvement at the higher frequencies. See Table 2-1 for an exact formulation of the criteria.

RESULTS

Inter-ear dependencies

For pure-tone audiometry, TEOAEs and DPOAEs we examined whether the changes between left and right ears were significantly different from each other. Multiple paired *t*-tests (with Bonferroni-correction) were conducted on the changes to determine whether a combined description would suffice or whether the changes should be described per ear. Results were considered significant for $p<0.01$.

Table 2-I: The classification uses a variable $T_{notch,max}$, which is defined as the maximum hearing threshold at either 3, 4, or 6 kHz. For typical noise notches this is the deepest point of the audiogram. Notches are determined with respect to recovery at 6 or 8 kHz and to elevated thresholds with respect to the average low-frequency hearing ($PTA_{0.5,1,2}$).

Group	Description	Criteria
NH	Normal Hearing	Every threshold ≤ 15 dB HL $\forall f : T_f \leq 15$
MN	Mild Notch	$PTA_{0.5,1,2} + 15 \leq T_{notch,\max} \leq PTA_{0.5,1,2} + 20$ $T_{notch,\max} \geq T_8 + 10 \cup T_{dip,\max} \geq T_6 + 10$
PN	Profound Notch	$T_{notch,\max} \geq PTA_{0.5,1,2} + 25$ $T_{notch,\max} \geq T_8 + 10 \cup T_{notch,\max} \geq T_6 + 10$
SN	Subnormal hearing	Not NH, MN, PN $\forall f : T_f \leq 30$
SL	Sloping	$T_8 \geq T_{notch,\max} + 5$ $T_{notch,\max} \geq PTA_{0.5,1,2} + 5$
RE	Rest	-

There were only a few significant differences; at one pure-tone audiometric frequency and at one TEOAE frequency band. In pure-tone audiometry, left ears showed more improvement at 500 Hz than right ears (2.2 dB HL, p=0.00077, *t*=4.0266, d.f.=226). For TEOAE-changes, left ears showed significantly less deterioration than right ears at 1000 Hz (-1.6 dB SPL, p=0.00065, *t*=-3.47, d.f.=184). There were no systematic left/right differences in DPOAE-changes.

Because of the limited amount of significant differences we choose to describe the changes in for all ears and not split the data in left and right ears. The results are presented for 466 ears.

Inclusion criterion

The effect of the inclusion criterion of the otoacoustic emissions on the number of valid data points was examined per OAE-method and per frequency. The criterion (SNR ≥ 0) affected the number of included data points per frequency severely. In Figure 2.1 the percentage of included data points is presented for each audiometric subgroup as well as for the total group.

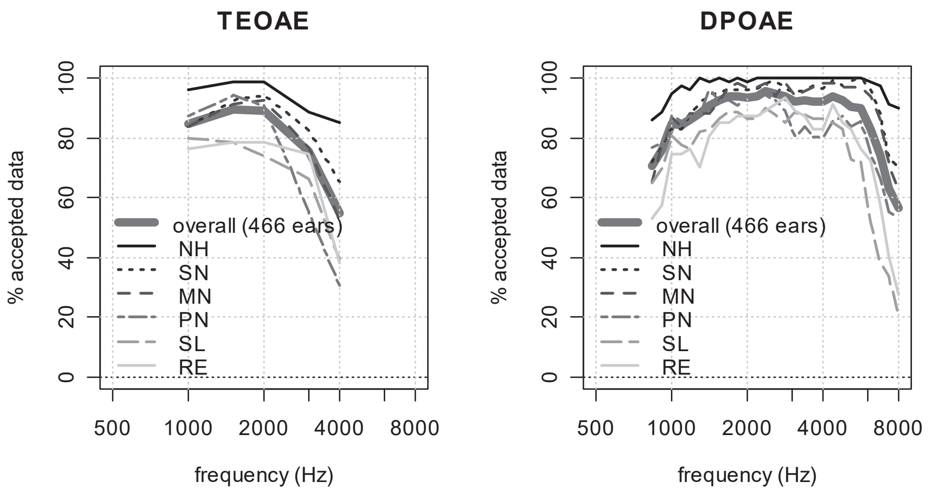

Figure 2.1: Percentage included data points per group. The total amount (relative to the original 466 ears) is indicated by the bold grey line. The NH-group has the lowest amount of missing data points, at some frequencies all ears are included. The ears with a pre-existent hearing loss tend to have more missing points.

Overall there is a large percentage of discarded data points. 90% of 'good' data points seems to be the maximum for both TEOAEs and DPOAEs (approximately 420 out of 466 ears). In all subgroups the percentage of reliable data points drops slightly for frequencies below 1500 Hz and more rapidly for frequencies above 2 kHz (TEOAE) or 4 kHz (DPOAE). In the lower frequency region background noise had a larger influence on the number of excluded data points than in the higher frequency region (with a maximum contribution to the amount of exclusions of 28% at 1000 Hz for TEOAEs). For the higher frequencies relatively low emission levels were the most common reasons of exclusion (high noise levels only had a relative contribution of 9-17% to the amount of exclusions). High noise levels were more or less homogeneously distributed over the audiometric groups.

The group labelled as normal hearing has the highest percentage of included data points. Second best is the group categorized as subnormal hearing, then the mild notch group etc. The general trend is that the percentage of discarded data rises with the degree of hearing loss. This trend is most pronounced but not limited to the highest frequencies. These findings imply that the relative contribution of 'good' ears is much larger than that of the 'bad' ears in the average values calculated for the OAE results.

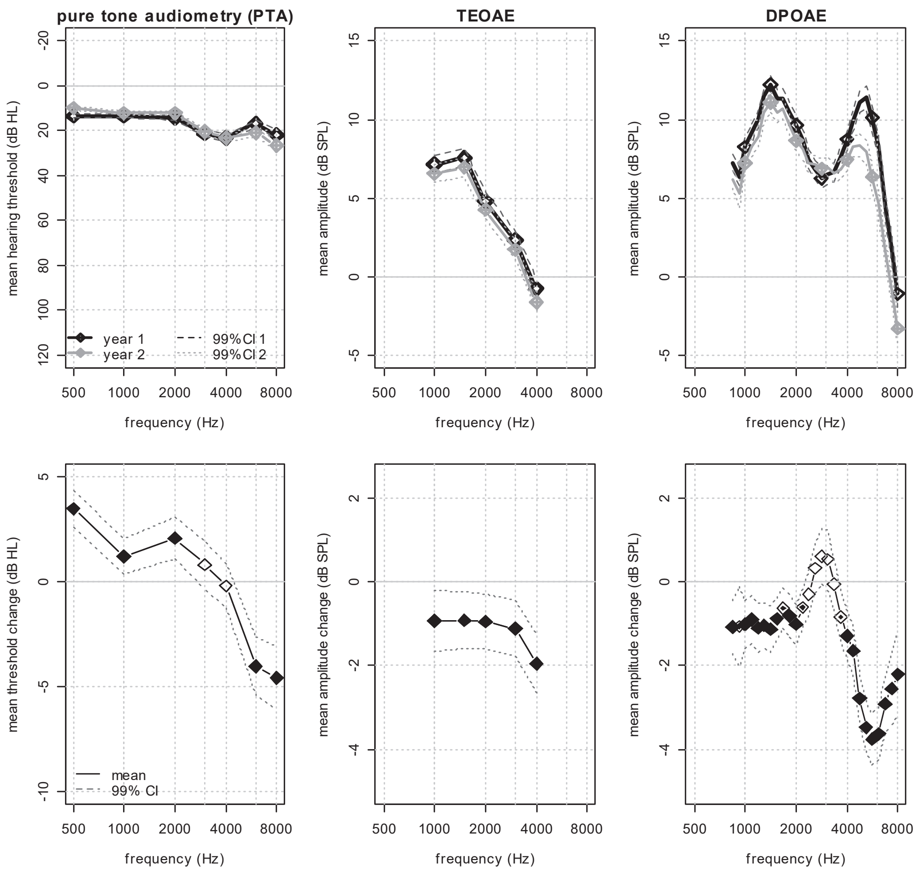

Figure 2.2: Average results of the three measurement methods of both years. Left: Pure tone audiometry (PTA), middle: TEOAE, right: DPOAEs. Results for year 1 and year 2 are distinguished. The average differences between year 1 and year 2 and their 99% confidence intervals as a function of frequency are plotted in the lower panels. A closed diamond ◆ indicates a significant change ($p<0.01$) in a paired t-test at that particular frequency, corrected for multiple comparisons (Bonferroni-correction). The dot-filled diamonds ◈ are significant but without Bonferroni-correction. A change smaller than zero corresponds to a deterioration in hearing between measurement 1 and 2, a change larger than zero (positive) corresponds to an improvement in the measurement and no change corresponds to a stable situation.

Overall analysis

In the upper row of panels of Figure 2.2 the average (group) results of the first measurement are compared with the results from the second measurement (after 17 months) for pure-tone thresholds, TEOAE levels, and DPOAE levels (for the left, middle, and right panels, respectively). The amount of contributing ears depends on the frequency, as can be seen in Figure 2.1. The bottom row of panels shows the mean differences (changes in hearing) and the corresponding 99% confidence intervals. For the differences in pure-tone thresholds, the thresholds of the second test (follow-up) are subtracted from the thresholds of the first test (baseline). In case of the otoacoustic emissions, the results of the baseline are subtracted from the results of the follow-up. This procedure enables a uniform approach in considering the changes: a negative change corresponds to deterioration (increase in hearing threshold and decrease in OAE-amplitude); a positive change indicates an improvement (decrease in hearing threshold and increase in OAE-amplitude).

Outcomes from both measurements are examined with paired *t*-tests. The mean changes and corresponding 99% confidence interval are presented in the bottom row of panels in Figure 2.2. The results ($p<0.01$ after Bonferroni correction) can be summarised as follows:

Changes in audiometry

For audiometry, results were considered significant for $p<0.01/7$. In the low frequencies a significant improvement of 3.5 dB at 500Hz ($p=4\cdot10^{-22}$, t=10.2, d.f.=459) and of 1.2 dB at 1 kHz ($p=3\cdot10^{-4}$, t=3.64, d.f.=465) in average hearing threshold can be seen. The thresholds for the highest frequencies (6 and 8 kHz) have deteriorated. At 6 kHz the mean deterioration is 4.0 dB HL ($p=4\cdot10^{-13}$, t=-7.47, d.f.=465) and at 8 kHz 4.3 dB ($p=4\cdot10^{-14}$, t=-7.82, d.f.=456). A low frequency improvement might be attributed to acoustical circumstances, probably due to the presence of more background noise during the first measurement. The results in the high-frequency area might be attributed to deterioration due to aging, noise exposure, or an interaction of these factors. It should be noted that there is no overall effect at 3 and 4 kHz, the frequencies that are often regarded as most sensitive for NIHL. However, at 6 and 8 kHz a significant deterioration was found.

Changes in TEOAE

The average results showed an overall deterioration for all the frequency components and were considered significant for $p<0.01/5$. The deteriorations vary from -0.92 to -1.11 dB SPL between 1 and 3 kHz and reach a maximum of -2.0 dB SPL at 4 kHz ($p=4{\cdot}10^{-12}$, $t=-7.27$, d.f.=255). As can be seen in Figure 2.1, approximately only 55% of data points can be used for analysis in this frequency band.. This means that the observed effect is caused by the ears with relatively 'good' emissions.

Changes in DPOAE

For DPOAEs there were two frequency regions where a significant ($p<0.01/27$) decrease in OAE-amplitude occurs. The third column of panels in Figure 2.2 shows a distinct deterioration in 4-8 kHz area, with a maximal effect of -3.8 dB SPL ($p=3{\cdot}10^{-44}$, $t=-15.8$, d.f.=419) at $f_2=5657$ Hz. In the first 'bump' of the DPOAE-spectrum, between 1-2 kHz, there is a smaller, but significant deterioration in mean amplitude between the baseline and follow-up with a local maximum of -1.13 dB SPL ($p=2{\cdot}10^{-7}$, $t=-5.29$, d.f.=423) at $f_2=1414$ Hz.

Similarly to the TEOAE results, the inclusion criterion reduces the amount of valid data especially in the higher frequencies. The deterioration is based on 70% of the total amount of ears.

Correlations between test results

There were only a few significant correlations ($p<0.01$) between the changes in the pure-tone thresholds and the changes in OAE-parameters after 17 months, but they were all relatively low (no correlation larger than 0.2 at any frequency combination). The maximum Pearson correlation coefficient was found between the change in pure-tone threshold at 6 kHz and DPOAE-frequency of 7336 Hz and amounted to $R=-0.16$ ($p<0.001$).

Also, there were some significant ($p<0.01$) correlations between changes in DPOAEs and changes in TEOAEs but these correlations were also relatively weak (none larger than 0.3 at any frequency combination). The highest correlation coefficient was found between the TEOAE change in the frequency band around 1 kHz and the DPOAE at 1297 Hz ($R=0.26$, $p=1.57\ 10^{-8}$). Despite these relatively low correlations there was a general pattern discernible: the low frequency area of the DPOAEs showed a small but systematic correlation with changes in the lowest frequency band (1 kHz) of the TEOAEs. For DPOAEs at higher frequencies until 6 kHz, the higher TEOAE bands showed weak correlations as well.

Table 2-II: The six audiogram groups, the mean age in years, the total number of ears (N) in each group. The total number of ears adds up to 466, corresponding to 233 different subjects. For the OAE measurements these numbers are generally smaller depending on frequency due to the inclusion-criterion.

Group	Description	Age (stdev) yrs	N
NH	Normal Hearing	36 (5)	80
SN	Subnormal hearing	40 (8)	125
MN	Mild Notch	44 (9)	69
PN	Profound Notch	45 (8)	56
SL	Sloping	46 (8)	89
RE	Rest	42 (9)	47

Subgroup analysis: audiometric configuration

In order to take into account the initial hearing status each individual ear was categorized according to his audiometric configuration, averaged between baseline and follow-up. The groups were labeled as normal hearing (NH), subnormal hearing (SN), mild notch (MN), profound notch (PN), sloping (SL), and a rest group (RE).

The exact numbers of ears and age distribution are tabulated in Table 2-II and the average audiometric configurations per subgroup can be seen in Figure 2.3. The corresponding mean emission levels of the first and second measurements per subgroup are shown in separate panels. Error bars are omitted to enhance visual inspection. The group sizes are quite different. As a consequence missing data will affect smaller groups more than larger groups.

Results for the subgroups demonstrate more or less similar trends when compared to the overall results of Figure 2.2.

Changes in audiometry

For each frequency analysis of variance (ANOVA) was conducted on the change in pure-tone thresholds with audiometric configuration as independent variable. Subjects were included based on the same SNR-criterion (i.e. SNR $\geq$ 0) as mentioned in the previous analysis. There was no significant main effect, thus no difference between different subgroups for the change in pure-tone hearing threshold.

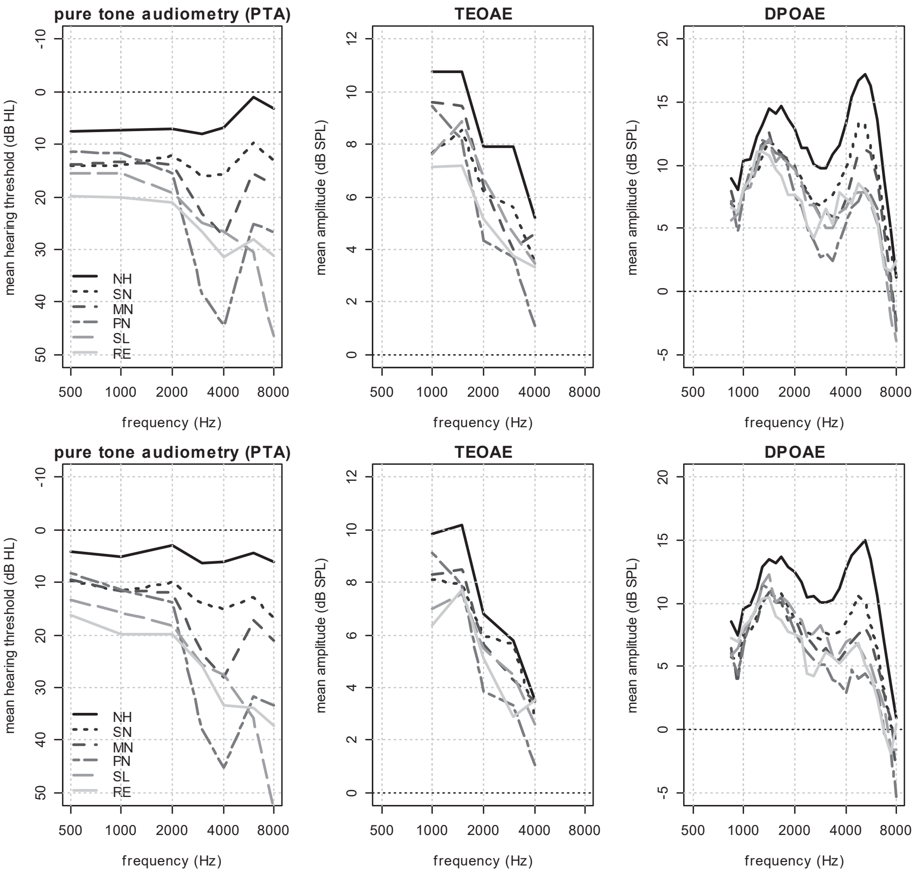

Figure 2.3: Average hearing thresholds (left), TEOAE-amplitude (middle) and DPOAE-amplitude (right) for measurement 1 (upper panels) and measurement two (bottom panels). The ears are divided into categories based on their audiometric configuration.[1]

Changes in TEOAE

Visual inspection of Figure 2.3 shows the largest deterioration in TEOAE amplitude for the normal hearing group (NH), especially at 3 kHz. However, analysis of variance did not show any main effects of change in TEOAE with audiometric group as independent variable.

1 *This figure is different from the version in the published paper. Here, the original measurements for both years are presented where the paper only shows the difference between both measurements.*

Changes in DPOAE

Only five DPOAE frequencies showed a main effect with the audiometric configuration as the independent variable for p=0.05. These results were not significant for p=0.01. Although there were some main effects, post-hoc tests (Tukey-HSD) showed two significant differences in change in emission level between the groups. At 4 kHz, the group with the profound notch (PN), showed a larger deterioration than the group with the sloping audiogram (SL). Similarly, at 8000 Hz, the SL-group showed a larger deterioration than the group defined as subnormal hearing (SN).

DISCUSSION

General applicability in monitoring

The first question mentioned in the introduction is whether OAEs can be used in monitoring NIHL in a setting such as a newspaper printing office. Demanding a minimum quality of the recording in the form of an inclusion criterion of SNR ≥ 0, reduced the amount of valid data points drastically. For both TEOAE and DPOAE the maximum percentage of accepted data was close to 90% and reduces to approximately 50% in the highest frequencies. Unfortunately, this happened to be the area where NIHL is expected to be most prominent. Nevertheless, we observed a significant deterioration in the TEOAE measurements in all frequency bands. The maximum effect occurred at 4 kHz, even despite the fact that this was the frequency band with the smallest amount of accepted data points (contribution of approximately 50%). Similarly, DPOAEs showed the largest deteriorations around 6 kHz where approximately 80% of the data is included. The noise-floor substitution might have underestimated the size of the change in emission level when the second year emission dropped far below the noise-floor. The effect is probably small, since the amount of substitutions is only 5% averaged over frequency, increasing from 7% at 5187 Hz to a maximum of 12% at 8000 Hz.

The relatively high levels for the DPOAE primaries were chosen to obtain as high SNR's as possible; the majority of studies in this field is conducted with lower stimulus levels. Examination of the amount of valid data points from the extra measurements in year 2 showed that lowering the primary levels to 65-55 dB SPL reduces the amount of valid points drastically. Whereas for the higher level primaries 90% is included in the region between 4 and 6 kHz, lowering the primaries reduces the percentage of points with a large enough SNR to 60-70%. At 8 kHz the percentage reduces from 50% to 20%.

Some studies used a higher SNR in the inclusion criterion (Shupak et al. 2007; and Bhagat & Davis 2008). This would reduce the amount of valid measurements even more. Requiring a SNR ≥ 6 dB decreases valid TEOAE data points with about 20% across frequency. For the 4 kHz band, only 20% of the data points would be accepted. For DPOAEs the overall reduction is 10-20 % across frequency which leads to about 35% of valid data points at 8 kHz. Choosing such a relatively high-quality starting point limits the application of OAEs in an industrial setting like this, because it reduces the amount of subjects for whom OAEs are a suitable monitoring tool. On the other hand, using a less stringent inclusion criterion, would create a risk of subjects 'dropping out' in the early years of the conservation protocol in case of a progression of the hearing loss due to age and/or noise exposure.

The conclusions concerning development of hearing damage are based on the ears with present emissions both at baseline and at follow-up. This does not mean that the worse ears do not decline! It is just that the method itself is not capable of following changes in emissions below 0 dB SNR or below follow-up noise level. Pure-tone audiometry remains the preferred method of testing in such cases. An alternative could be monitoring at lower frequencies, i.e. between 1 and 2 kHz, since the SNR is generally higher in that region (see Figure 2.1). Also in this area a significant but smaller, deterioration was observed. The change in this frequency region has only very limited correlation with the change in the high-frequency region. However, future research and more longitudinal monitoring has to indicate which DPOAE parameters are the most relevant for detection and monitoring of NIHL. In the data of this study both the changes in high-frequency DPOAEs and in the lower frequencies are not significantly correlated with changes in the pure-tone audiogram at an individual level. So the high-frequency DPOAEs are not necessarily more related to changes in audiometry than changes in low-frequency DPOAEs.

The classification by audiometric configuration did not reveal a difference in the rate of change in pure-tone threshold or OAE-amplitude between ears with different audiograms. Hearing loss as defined by audiometric configuration has more influence on the amount of exclusions than on the size of the change itself. The classification is rather arbitrary although the chosen rules follow a similar approach as the criteria for noise-notches described by Coles et al. (2000), Dobie (2005). The cut-off point for normal hearing was set by 15 dB HL. According to Dorn et al. (1998), even within this group the DPOAE level decreases monotonically with threshold. Here, our focus was placed on difference in change, not in difference in amplitude between groups. Even so, we are aware that the chosen criteria are not a sufficient requirement for a homogeneous (with respect to OAE-level) group. Stricter criteria may affect the conclusions concerning the differences between the groups.

Small middle ear problems may affect the test-retest variability and were not detected by the screening procedure with the tuning fork. It is known that tympanometric pressure is of influence on the amplitude of OAEs (Marshall et al., 1997). A more complete protocol would incorporate tympanometry. In case of a deviation from normal peak immitance the test should be rescheduled. This could increase the amount of valid data points for both test results and could reduce the test-retest variability.

So, when applying otoacoustic emissions in a regular noise-exposed population, pre-existing hearing loss limits the range of measurable emissions for monitoring purposes. Maybe the answer lies in defining a pre-exposure starting point with enough room for deterioration, i.e. large enough emissions and good SNR at several adjacent frequencies. For a more general application in industrial healthcare, a well-defined limit in allowable hearing loss might be welcome. Including frequencies where half of the population does not have reliable emissions does not seem a good choice. On the other hand, the main effects that we have observed occur in the same high frequency bands. When looking at the most pronounced changes on group level, the 4-8 kHz range for DPOAEs seems the most useful area for following individuals.

A choice seems unavoidable: if one aims at using OAEs for a general population, the higher frequencies should be discarded. If one aims at finding optimal parameters for monitoring, the emphasis should be placed on this same high-frequency region and only subjects with a good starting point should be included in a monitoring program using OAEs.

It is important to note that the SNR-inclusion served as a selection bias for both OAE-types: the observed deteriorations in emission level occur in ears that started with measurable emissions. Nevertheless, the categorization by audiometric configuration did not reveal clear-cut evidence that the ‘better’ ears deteriorate faster than ears already suffering from (subnormal) hearing loss. This implies that OAEs can be used in monitoring as long as they are measurable have enough ‘room’ to decline. Besides monitoring purposes, OAEs can have other applications. Screening for susceptibility is currently being investigated, for example by Lapsley-Miller et al. (2006) or Job et al. (2009). Another application is objectively documenting inner-ear status in cases where aggravating is suspected.

Patterns in development of hearing loss

The second aim of this study was to investigate the patterns in development of hearing loss in audiometry and OAEs. As hypothesized, mean hearing threshold increased and emissions amplitude decreased. In the pure-tone audiogram an improvement was found in the low-frequency area. It seems unlikely that hearing status would improve over 17 months. Further analysis indicated that the background conditions (i.e. the sealing of the audiometric booth) are the most likely cause for this change.

The overall hearing deterioration in the audiogram occurs at 6 and 8 kHz, at a higher frequency than the typical 'noise notch' area. In a recent study Job et al. (2009) examined hearing changes for pilots with a follow-up period of 3 years. They found significant changes in the audiogram starting at 3 kHz. Similarly to this study, the maximum effect occurred at 8 kHz, not at the typical noise notch frequencies. However, they did not determine hearing thresholds at 6 kHz.

The deterioration of high-frequency thresholds can be a combined effect of noise exposure and ageing. In order to incorporate 'natural ageing', a rough correction factor was applied to the change in hearing status at 6 kHz for each ear. This factor was based on the ISO 7029 (2000). This model provides a median, or any other percentile, hearing threshold for any age at any frequency. When it reads median, it can be replaced by any chosen percentile for a similar approach.

Subtracting medians of subsequent years provides a rough estimate of median change in hearing threshold due to ageing. Since the interval between these two measurements consists of 17 months, a linear interpolation was used to estimate median hearing change only after 17 months for every subject in the study group. After subtracting this value from the actual observed change for each individual, an estimate remains that can be ascribed to other, non-ageing factors. When applying this 'natural ageing' factor based on either median or 10^{th} percentile, the change is still significantly different from zero ($p<0.001$). This suggests that the observed effect is caused by more than ageing and thus noise exposure is the most likely cause.

Transient evoked otoacoustic emissions show a general significant decline in amplitude but the observed effect is maximal at 4 kHz. Since this is the highest frequency band it is difficult to make a parallel between typical ageing and noise frequencies. It is known that emissions generally decline with age and more in higher frequencies than in the lower region (Engdahl, 2002; Satoh et al., 1998). This argument applies to the distortion product otoacoustic emissions as well (Dorn et al., 1998).

Whether a decrease in OAE response in the elderly occurs without accompanying hearing loss or whether the decline in OAEs arises from the same mechanisms as the increased pure-tone hearing thresholds is under discussion. Recently, Uchida et al. (2008) concluded that the effect of age on DPOAEs in normal-hearing elderly subjects presents itself independently from peripheral hearing loss measured by audiometry. These conclusions correspond to those of Dorn et al. (1998). Others have found no age effect when controlling for hearing thresholds (Cilento et al., 2002).

There are no (ISO-) models to use as an estimate of natural ageing for OAEs. However, the observed average effect of approximately 3 dB after 17 months seems large compared to the maximal decline of 5 dB/decade at 6 kHz mentioned by Engdahl (2002). DPOAEs showed a significant decline between 4 and 8 kHz, the most pronounced effect is around 6 kHz, similarly to the audiometric results.

The results are expressed in terms of one of the primary tones of the stimulus, f_2. Lonsbury-Martin and Martin (2007) suggest that for higher levels primaries such as used here, the generation site of the distortion product is more near the geometric mean frequency Öf_1f_2. This shift in frequency does not alter the general conclusions: instead of a frequency range from 841 to 8000 Hz, the range would be from 768 to 7303 Hz. The maximal deterioration would then occur at 5164 Hz, instead of at 5657 Hz. Expressing the results in terms of the geometric mean would thus shift every frequency towards the lower side of the spectrum. This would place the maximal effect a little closer to the frequencies typical for NIHL.

Generally speaking, the period of 17 months of noise exposure showed in all methods a larger deterioration in hearing than would be expected by ageing alone. OAEs show a reduction in emission amplitude in a broader frequency range than pure-tone audiometry. This could be interpreted as an indication for pre-clinical outer hair cell damage that is not (yet) visible in the audiogram in that particular frequency range. The authors believe that it is too soon to take a strong stand in this matter. It would be very interesting to follow this population in a long-term follow-up to see if and when the low frequency area will be affected and if the decline in OAEs will continue at the same pace.

CONCLUSIONS

OAEs can only be used as a monitoring tool for a subset of the population investigated in this study. The use of an inclusion criterion based on the signal-to-noise ratio of the emission results in a large amount of subjects for whom the emission in the high-frequency area cannot be tracked in time. This means that pure-tone audiometry is indispensable when there is a pre-existing hearing loss and/or when the OAEs at start are too low. Occupational Health Officers should be made aware of this limitation before OAEs are considered as a replacement for conventional audiometry in hearing conservation programs. Monitoring is only possible when there is room for deterioration!

The different outcome measures (pure-tone thresholds, TEOAEs and DPOAEs) all show a high frequency deterioration after seventeen months of noise exposure in a newspaper printing office. Remarkably, the changes do not occur exclusively in the most critical frequency area for the detection of NIHL (around 4 kHz) but –for pure-tone thresholds- in the higher frequencies. An age-correction at 6 kHz reveals that the observed effect is very likely to be caused by noise exposure.

The deteriorations in OAEs take place in a broader frequency range than the increase in pure-tone threshold for audiometry. TEOAEs show a decline in all frequency bands, with a maximum at 4 kHz. DPOAEs show the maximal effect around 6 kHz. Additionally, the DPOAEs show a smaller change in the lower frequency area between 1-2 kHz.

OAEs show a decline in a larger frequency region than the audiogram, suggesting an increased sensitivity of OAEs on group level compared to audiometry. This could be interpreted as an indication for preclinical damage. Monitoring the development of hearing and emission loss on an individual level will be studied in future work.

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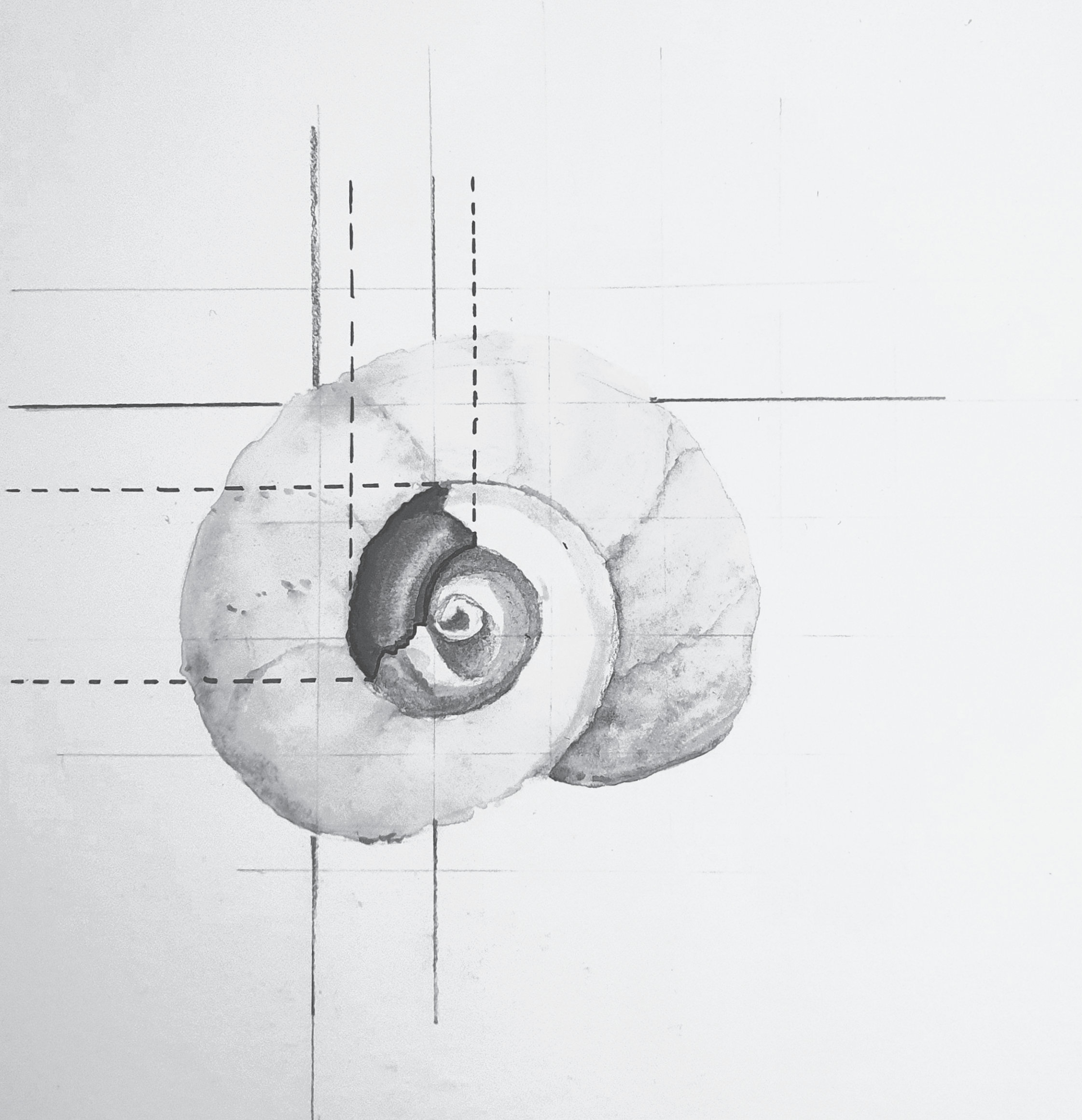

CHAPTER 3

Overall versus individual changes for otoacoustic emissions and audiometry in a noise-exposed cohort

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ABSTRACT

Objective: For a noise-exposed group of workers, group-averaged and individual changes were compared for pure-tone audiometry, transient-evoked otoacoustic emissions (TEOAEs), and distortion product otoacoustic emissions (DPOAEs) in order to see if they exhibit the same pattern in time.

Design: Baseline and 17-months follow-up hearing status was examined with pure-tone audiometry, TEOAEs, and DPOAEs.

Study sample: 233 Noise-exposed employees were measured while 60 subjects from this group contributed to test-retest reliability measures.

Results: Group-averaged changes and individual shifts followed similar patterns: decreases for audiometry at 6-8 kHz and DPOAE at 1.5 kHz and enhancements for DPOAE at 3 kHz. TEOAEs showed an overall deterioration while both individual deteriorations and enhancements were larger than chance. DPOAE at 6 kHz showed the largest group-averaged change, while the number of individual shifts was not significant. There were no clear relations between changes in audiometry and changes in OAE.

Conclusion: Significant individual OAE changes do not necessarily follow the same pattern as the group-averaged results. This limits the applicability of OAE testing for the monitoring of individual subjects. Furthermore, hearing deterioration might manifest itself in a local enhancement of otoacoustic emissions and not only in the form of decreases in amplitude.

INTRODUCTION

Noise-induced hearing loss (NIHL) affects the outer hair cells before damaging the inner hair cells and other structures in the cochlea. Since otoacoustic emissions (OAEs) are related to the functionality of the outer hair cells, it is not surprising that the impact of NIHL on OAEs have been investigated ever since the discovery of otoacoustic emissions by David Kemp in 1977.

Several studies have shown that groups of noise-exposed subjects with audiograms that are within normal limits have lower emission levels than groups of non-exposed subjects with audiograms within the same normal limits, (see for example Attias et al., 1995; 2001; Attias and Bresloff, 1996, LePage and Murray, 1998; Desai et al., 1999; Balatsouras, 2004; Hamdan et al., 2008).

Many authors discuss the potential value of OAEs in detecting so-called preclinical damage, i.e. damage in the cochlea that is not yet measurable or detectable in the regular pure-tone audiogram. Lapsley Miller and Marshall (2007) have written a detailed review (up to 2006) on the sensitivity of OAEs in detecting early stages of noise-induced hearing loss. This review concluded that OAEs show a great promise in detecting preclinical damage and susceptibility to NIHL but they also emphasize that there is much to discover about optimal OAE-parameters and mechanisms underlying the possibility that OAEs might change before the audiogram. They call for more large-scale, longitudinal studies. Despite this optimistic view on the sensitivity for preclinical damage, other investigators indicate that the above-mentioned group comparisons cannot be regarded as sufficient evidence for enhanced sensitivity. One of the weaknesses of these comparisons lies within the definition of normal hearing when all thresholds are better than 25 dB HL or 20 dB HL. As Sisto et al. (2007) emphasize, defining normal hearing using only a cut-off value (of 20 dB HL in most cases) allows room for a difference in hearing thresholds between the noise-exposed and the control groups. This is confirmed by Dorn et al. (1998) who found that OAE-amplitudes decrease monotonically for normal hearing subjects with hearing thresholds increasing from -5 to 20 dB HL.

Another shortcoming in these group studies is that they are cross-sectional. The amount of longitudinal studies examining the effects of noise exposure on changes in emission amplitude is limited.

Lapsley Miller et al. (2006) followed changes in emissions and in audiometric thresholds for recruits enrolled in a navy hearing conservation program, and found that low-level or absent OAEs could serve as an indicator for NIHL susceptibility. Shupak et al. (2007) concluded that TEOAEs are more suitable for detecting subclinical changes than DPOAEs although a high false-positive rate kept them from recommending screening for changes with TEAOEs . This is in contrast to the conclusion of the study on combat-soldiers who were followed for two years by Duvdevany and Furst (2007). They stated that TEOAE level could serve as a predictive tool for individual vulnerability to noise exposure. Job et al. (2009) followed a group of pilots with all audiometric thresholds at 10 dB HL or better at baseline and concluded that initial DPOAE status predicts an increase in audiometric threshold at the follow-up measurement (three years later). Marshall et al. (2009) have investigated the long-term effects for impulse sounds and showed that low-level otoacoustic emissions can indicate an increased risk of future hearing loss. Although these studies have their longitudinal approach in common, the studies by Shupak et al. (2007), Duvdevany and Furst (2007), Job et al. (2009) and Helleman et al. (2010) look at group-averaged changes while Marshall et al. (2009) and Lapsley Miller et al. (2006) describe both group changes and individual threshold and emissions shifts.

The group-averaged results of this dataset have been described in the above-mentioned study by Helleman et al. (2010). Both TEOAEs and DPOAEs showed significant effects in a larger frequency region than audiometry did. Audiometric thresholds showed an increase at 6 and 8 kHz, not at 4 kHz. This change was larger than would be expected by age alone. A more detailed description of this age-correction can be found in Helleman et al. (2010). The broader effect in OAE could be interpreted as an enhanced sensitivity of OAE versus audiometry when looking at the effects of noise exposure on the entire cohort. It doesn't necessarily imply that the same statement can be made for individual cases. This paper aims to explicitly investigate whether significant changes for individuals follow the same pattern as the group-averaged results.

In order to do this, an individual classification of change was constructed. The classification led to a dichotomous outcome variable to separate significant changes from no change. The change itself can be further divided into a deterioration or an improvement, depending on the sign of the difference. The averaged results are similar to the averaged change of the entire cohort under investigation as mentioned in the previous study, albeit after a slightly different inclusion procedure.

Although both types of outcome variables should produce similar results, there are to two possible scenarios: the individual changes follow the same pattern as the averaged result or they do not. In the first scenario, the individuals exhibiting significant changes explain the observed overall effect. This will support the hypothesis that OAEs have an enhanced sensitivity relative to audiometry, because those effects reported for a group of subjects are also present for individuals. However, when the patterns are not congruent, the potentially higher sensitivity for the effects of noise might be present at a group level but cannot be utilized to follow individuals over time. The comparison of different types of outcome parameters could thus provide insight into the applicability of the potentially enhanced sensitivity of OAEs in a hearing conservation programs for groups of subjects and/or for individuals.

The classification with a dichotomous variable to identify significant individual changes requires a method that determines when a change is significantly different from a random variation. In order to avoid that random variations are interpreted as real effects, information about test-retest reliability is necessary. This helps in determining correct identification of real changes in hearing status, either pathological or physiological, from changes due to variations and measurement error. Test-retest reliability also provides information on the minimal amplitude above the noise level that is required for identification of a significant decrease in amplitude.

In examining otoacoustic emissions much emphasis has been placed on good test-retest reliability. Some of these findings are obtained without probe-replacement. Obviously this is not the case for longitudinal monitoring for noise-induced hearing loss or ototoxicity with months or years between subsequent measurements. ASHA (American Speech-Language Hearing Association) has developed guidelines for ototoxicity when a change in audiogram is considered to be significant (i.e. ≥ 20 dB at one frequency or ≥ 10 dB at adjacent frequencies) (1994). Similarly, OSHA (Occupational Safety and Health Administration) and NIOSH (National Institute for Occupational Safety and Health) have developed audiometric criteria for labelling a significant threshold shift in monitoring noise-induced hearing loss. OSHA states: 'A standard threshold shift is a change in hearing threshold relative to the baseline audiogram of an average of 10 dB or more at 2000, 3000, and 4000 Hz in either ear' (OSHA). NIOSH defines a significant threshold shift as a 15 dB change, relative to the baseline audiogram, at any of the frequencies 0.5, 1.0, 2.0, 3.0, 4.0, or 6.0 kHz, (after retest) (NIOSH). Such consensus statements are not available for OAEs.

This study focuses on monitoring of noise-induced hearing loss and was set up to 1) determine a measure for individual significant changes for audiometry and otoacoustic emissions 2) compare these to other studies and 3) to compare the patterns of these individual changes with group-averaged results.

METHODS

Participants

Average changes in hearing status of a group of 233 male employees of a newspaper printing office have been described previously by Helleman et al. (2010). First tests took place within the framework of a periodical hearing screening program (in 2004) and the follow-up measurements took place after seventeen months (2006). Originally there were 320 subjects who were measured in the first test round. However, omitting cases with incomplete or erroneous data, missing follow-up measurement or the possible presence of a conductive hearing loss yielded the final number of 233 subjects.

This cohort consisted of several professions working at different departments (electricians (7%), bench workers (5%), layout department (7%), printing department (48%), inking depot (3%), expedition (19%), and miscellaneous (11%)) and the median age of this group was 42 years (range 23-60) whereas the median years of employment was 18 year (range 0-46). For the majority of workers, the exposure in $L_{A,eq}$ is between 80-85 dB (A). Limitation of noise exposure is achieved by shielding noise sources and by providing employees with individual hearing protective devices (HPDs). A questionnaire showed that 80% of the employees used HPDs regularly but only 30% indicated a consistent use.

Description of tests

OAE tests and pure-tone audiometry were conducted by hearing conservation technicians or audiologists that were blinded for the other results. Audiograms were obtained at 0.5, 1, 2, 3, 4, 6, 8 kHz with an automated Hughson-Westlake procedure on an Audioscan Essilor audiometer with Beyer Dynamic DT48 headphones. A Rinne tuning fork test (f=512 Hz) was performed when hearing thresholds at 0.5 or 1 kHz were larger than 15 dB to disclose possible conductive components. In case of a negative Rinne, participants were referred for further investigation and excluded from further analysis.

Ears were visually examined before the procedure of measuring OAEs. In case of obstruction, participants were asked to have their ears cleaned and the tests were rescheduled. Otoacoustic measurements were conducted, starting with TEOAE measurements and followed by DPOAE measurements. All measurements were performed on both ears.

OAEs were measured with a conventional ILO288 Echoport system (Otodynamics Ltd England) using a DPOAE- probe. The system was calibrated daily. A fixed amount of averages was taken with the noise-rejection level held constant. The TEOAEs were measured in the 'standard' nonlinear mode with a test stimulus of 80 peSPL until 280 low-noise averages were obtained. The response spectrum was visually judged by the examiner and the probe was adjusted when this seemed necessary to secure an optimally flat spectrum in the response. The overall response and overall noise-spectrum were recorded and filtered in the frequency bands of 1, 1.5, 2, 3, and 4 kHz.

For the DPOAEs, the stimulus levels of the two probe tones, f_1 and f_2 were L_1=75 dB SPL and L_2=70 dB SPL and the ratio between the probe tones was $f_2/f_1 = 1.22$. Several studies show that lower-level stimuli are more sensitive in detecting hearing loss (see for a summary Gorga et al. 2007). This relatively high stimulus level was chosen to minimize the effect of background noise. DPOAEs were measured at $^1/_8$ octave frequencies with f_2 ranging from 841 to 8000 Hz. A total amount of 27 frequencies was tested. Recording was stopped after three runs across frequency.

General procedure

Participants completed a questionnaire before entering the measurement procedure. The questions concerned hearing status, hearing problems, otologic history, medication, recent noise exposure, and the use of hearing protective devices. When necessary, these results were used for counseling by the industrial medical officer.

Effort was put in avoiding temporary threshold shifts (TTS) by aiming for a minimal noise-free period of two hours but it could not be ruled out completely because of rotating working schedules. Subjects were asked to wait in a relatively quiet environment to fill-out the last part in the questionnaire concerning recent noise exposure and recent drug use. These questions can be used as a rough estimate of recent noise exposure.

The total measurement time was approximately 50 minutes. All testing took place in a conference room in a relatively quiet part of the building. Background noise consisted of sounds from the underlying work floor and noise from departing distribution trucks.

Audiometry was performed in an Eckel AB-2000 sound-attenuating booth (according to ISO 8253-1 (1989)), placed in a large room with carpet. Otoacoustic emissions were also measured in a similar sound booth within the same room. The equipment and experimenter were placed on the outside with only the OAE-probe cable entering the booth, thus prohibiting a completely sealed door.

An almost identical setup was used in the follow-up measurements but to minimize waiting time for the employees, two OAE-systems were used separately, both placed in their own booth in the large room.

For a random sample of 60 participants the measurements were performed twice on separate days in order to derive a measure for the short-term test-retest variation. The period of time between these subsequent measurements ranged from 2 days to 2 weeks. Some subjects were measured twice in the initial measurements, some during the follow-up measurement. This study uses test-retest measurements of the population under investigation, not from an external reference group or laboratory conditions. This approach was chosen to derive test-retest variability for a noise-exposed cohort in the most realistic settings and boundary conditions of this specific hearing conservation program.

Data inclusion

The overall analysis includes data of 233 persons and thus 466 ears. Some ears exhibit emissions that are below noise level. This can be caused by a low emission, a high noise level or both. The signal-to-noise ratio (SNR) reflects the quality of the recording. The SNR depends on the status of the cochlea, the signal, and on the measurement conditions, represented by the noise level present during the recording. Ears with different cochlear status can have the same SNR.

For TEOAE, an emission is considered to be present if the amplitude was greater than 0 dB SNR relative to the noise level in the corresponding frequency band. Similarly, for DPOAE, an emission was considered to be present when the amplitude was higher than the upper estimate of the noise level (i.e. ≥ 0 dB SNR relative to two standard deviations above the average level of the noise-floor as derived by the ILO-equipment). Single data points, not subjects were discarded when they did not meet the SNR-criterion. Please note that this criterion introduces a selection bias since subjects with more missing data due to low emission levels and thus low SNRs may have more noise-induced or age-related hearing losses. An ear with a low SNR may be included in year 1 but if deterioration in emission level occurs (or a change in background conditions), this ear would be discarded.

When looking at the development of hearing loss, all ears that drop in SNR due to a decrease in emission amplitude are of interest. Lapsley-Miller et al. (2004; 2006) describe a method to take such ears into account by substituting emissions below the noise level by the noise level itself (noise level substitution). If the follow-up OAE level is absent (SNR below zero), the OAE-level is substituted with the corresponding noise-level if the follow-up noise-level is lower than the initial OAE. This substitution enables the inclusion of those ears whose emissions were good at the start but whose emissions deteriorated below noise-level. It introduces a possible negative bias in finding more deteriorations than improvements while underestimating the actual size of the change. Helleman et al. (2010) and Keppler et al. (2010) also use this noise level substitution. Reuter et al. (2007) studied different rejection criteria and come to the conclusion that only ears that are below noise level in both measurements should be discarded, without doing the noise level substitution. They found that in laboratory settings repeatable emissions below noise level could be obtained. Since the emissions in this study were not obtained in laboratory settings, it was considered safer to be conservative and use the noise level as an estimate of to the observed effect. This means that more data are included with the possibility of a bias towards underestimation of the actual change.

In this paper, a more extensive approach to this noise level substitution is chosen: the noise level substitution has been performed in both directions to consider changes in both directions thus enabling the potential use of more data and avoiding the negative bias. This implies that decreases in OAE *below* the noise level can be estimated but also that improvements that *rise* above the noise level are taken into the account. This means that only ears that are below noise level in both measurements are rejected. This approach resembles the advice given by Reuter et al. (2007) to only reject data that are below noise level both before and after noise exposure. In accordance with their approach, all analyses were also performed on all the raw data (without any inclusion criterion). This way we verified that the conclusions for the changes in TEOAE and DPOAE were not influenced by the method of inclusion (not published).

Data analysis

Outcome parameters

The outcomes are first presented in their raw form, i.e. for the single frequencies that were measured. For the more thorough individual analysis the measurements were combined into half-octave band averages (for audiometry the average of 6-8 kHz, for DPOAEs the average around 1.5, 3 and 6 kHz) or the overall broadband response (for the TEOAEs). These frequency areas were chosen based on the areas where the main group effects were visible. This reduces the amount of output parameters drastically from 39 (7 thresholds+5 TEOAE frequencies +27 DPOAE frequencies) to 5.

Individual analysis: significant emission or threshold shifts

In order to determine an area in which a change in either method can be seen as a significant change, the standard error of measurement (*SEM* or SE_{meas}) was calculated. This measure quantifies the precision of individual outcomes on a test (Weir, 2005) and combines a standard deviation (SD) of test and retest and some kind of reliability coefficient (*r*). The reliability of a test refers to the consistency of a measurement.

$$SEM = SD\sqrt{1 - r} \tag{3. 1}$$

This method was first described by Ghiselli (1964) and for OAE measurements used by several authors such as Beattie et al. (2003), Ng and McPerson (2005), and by Lapsley-Miller et al. (2006). They used the Pearson product-moment correlation coefficient as the measure for reliability *r*. Keppler et al. (2010) used the two-way random average measures intraclass correlation coefficient (ICC) for consistency as the measure for reliability. When there is no systematic difference between test and retest, different types of ICC are similar and *r* is closely approximated by the Pearson correlation coefficient (Weir 2005). Wagner et al. (2008) and Stuart et al. (2009) use Cronbach's alpha as the measure for reliability in the formula for the *SEM*.

Beattie et al. (2003) and Lapsley-Miller et al. (2006) used pooled standard deviations of test and retest whereas others such as Keppler et al. (2010) used overall standard deviations. These differences should not be large when there is no systematic difference between test and retest. This study used the pooled standard deviation and the Pearson correlation coefficient.

Similarly to Beattie et al. (2003) and Keppler et al. (2010) a difference is considered significant (95% interval, 0.05 level) when it exceeds the confidence interval of change (CIC):

$$CIC = 1.96\sqrt{2}\,SEM \qquad (3.2)$$

In this study, the standard error of measurement is based on test-retest measurements of 60 participants and thus 120 ears, measured with the same equipment in the same test conditions, and is determined for all audiometric frequencies and all parameters in the OAE measurements. Only emissions exceeding 0 dB SNR for both test and retest are taken into account for determination of *SEM*. Some differences between test-and retest were very large and could be classified as erroneous measurements. In order to discard these errors objectively, a robust outlier detection rule was used, based on the median outlier deviation (MAD). A data point with a MAD-score of 3.5 was considered as an error as recommended by Davies and Gather (1993).

This results in a criterion for labelling a change as significant. For each individual the baseline situation was subtracted from the follow-up measurement. Only when the change exceeded the previously determined criterion the change was labelled as a significant threshold shift (STS) for audiometry and as a significant emission shift (SES) for otoacoustic emissions. For reasons of consistency the deteriorations are labelled as a STS^- or a SES^-, indicating increased audiometric thresholds and reduced OAE-levels, respectively. Likewise, the improvements are labelled as STS^+ and SES^+, indicating reduced audiometric thresholds and increased OAE-levels, respectively. This method is adopted from Lapsley-Miller et al. (2004), but as mentioned previously, the test-retest values were obtained from a sample of subjects within the population under investigation.

By definition of the 95% confidence interval of change, it would be expected to observe both 2.5% improvements and 2.5% deteriorations per frequency, just by chance. The count of the amount of individual changes in both directions can be compared with expected count to see if the observed count varies much from chance alone. Furthermore, the null hypothesis that the observed proportion (p_{obs}) is equal to the expected (p_{exp}) can be tested with the statistic z (Altman 1995, p 231):

$$z = \frac{p_{obs} - p_{\exp}}{SE(p_{obs})} = \frac{p_{obs} - p_{\exp}}{\sqrt{\dfrac{p_{\exp}(1 - p_{\exp})}{n}}} \tag{3. 3}$$

The standard error of the observed proportion ($SE(p_{obs})$) is equal to the standard error of the expected proportion under the null hypothesis. The z-value corresponds to a p-value in a normal distribution.

RESULTS

Standard error of measurement

The standard error of measurement (*SEM*) was determined based on test-retest measurements of 60 subjects, and 120 ears. The results for single frequencies and combined frequencies are plotted in Figure 3.1A, the numerical values of the average results are summarized in Table 3-I. The standard error of measurement for pure-tone audiometry is around 5 dB up to 3 kHz and higher for the highest frequencies. Averaging the frequencies around 6 and 8 kHz reduces the standard error of measurement to 5.0 dB HL.

TEOAEs show a relative constant *SEM* (i.e. 1.5 dB SPL) across frequency (range 1.1-1.8 dB SPL) which is similar to the *SEM* of the overall response (Figure 3.1B). DPOAEs show a more or less constant *SEM* up to 3 kHz (2.2-3.2 dB SPL) after which the standard error of measurement increases to maximum 4.8 dB SPL at 6727 Hz (Figure 3.1C). Averaging the results in half-octave bands (i.e. 4 adjacent frequencies) does not reduce the *SEM*. The values of the *SEM* are 2.5, 2.8, 4.5 dB SPL for 1.5, 3 and 6 kHz respectively.

Individual changes and group effects

Individual significant changes are identified and compared to group-averaged changes. The outcome parameter is the percentage of ears that show a significant change in hearing. For audiometry, the significant thresholds shifts (STS's) are counted, for OAEs the significant emissions shifts (SESs) are counted. Both the percentage of significant changes and the difference between deteriorations and improvement against the average group change are plotted in Figure 3.2 for pure-tone audiometry (A), TEOAEs (B) and DPOAEs (C).

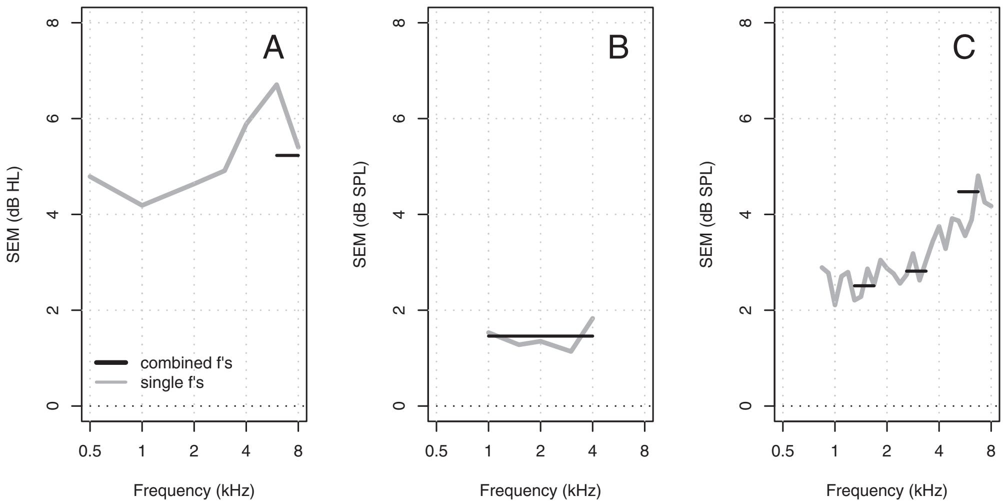

Figure 3.1: The standard error of measurement (SE_{meas} or *SEM*) as a function of frequency for single frequencies and combination of frequencies for pure-tone audiometry (A), TEOAE (B) and DPOAE (C) (½ octave band for PTA and DPOAE and for the overall response for the TEOAE).

Table 3-I: The standard error of measurement (*SEM*) for the different methods. N_{ears} stands for the amount of test-retest measurements from the original 60 subjects, 120 ears that were taken into account.

Measure	*SEM* (dB)	Range for single f	CIC_{95} (dB)	N_{ears} (%)
PTA_{6-8}	5.2	5.4 - 6.7	14.5	111 (93)
$TE_{overall}$	1.5	1.1 - 1.8	4.0	111 (93)
$DP_{1.5}$	2.5	2.2 - 2.9	7.0	109 (91)
DP_3	2.8	2.6 - 3.2	7.8	108 (90)
DP_6	4.5	3.6 - 4.8	12.4	94 (78)

Figure 3.2A shows that for audiometry the percentage STS^+ or STS^- is less than 10% for all frequencies up to 4 kHz. Only at 6 and 8 kHz, the percentage of STS^- exceeds 10% with a maximum of 20% at 8 kHz. The differences between significant deteriorations and improvement follow the average group results (see Figure 3.2A, lower panel). The average group results were tested for significance with paired *t*-tests, p-values were adjusted for multiple comparisons with Bonferroni correction. On group level there was a significant improvement in the low frequencies (0.5-2 kHz), and a significant deterioration at 6 and 8 kHz.

TEOAEs show for all frequency bands -except at 4 kHz- between 10 and 20 % significant deteriorations and improvements (see Figure 3.2B, upper panel). At 4 kHz there are less than 10 % significant changes in either direction. Overall there are more deteriorations (SES^-) than improvements (STS^+) and this pattern is in agreement with the average results where there is an overall trend of deterioration (see Figure 3.2B, lower panel). This deterioration is not significant for any of the frequency bands.

In Figure 3.2C the results for DPOAEs are presented: for all frequencies –except for the mid-f region- the percentage of significant changes is less than 10%. More specifically, for all regions except around 1.5, 3 and 6 kHz, the percentage of STS^+ or SES^- is less than 5%. In the 1.5 and 6 kHz region, there are more SES^- than SES^+ and around 3 kHz there are more SES^+ than SES^-. This pattern is also visible in the average group results in the lower panel of Figure 3.2C. The average improvement around 3 kHz is small, but significant and in the same order of magnitude as the deterioration around 1.5 kHz. The average deterioration around 6 kHz is much larger although the amount of significant changes is comparable to the other frequencies.

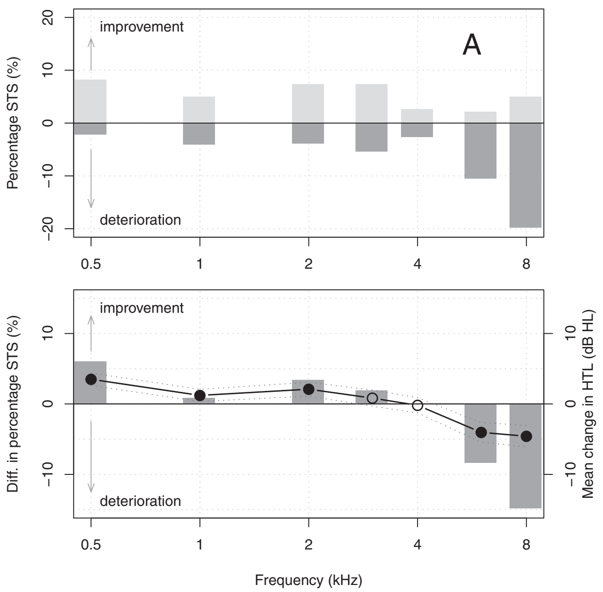

Figure 3.2A: Upper panel: The bars represent the percentage of significant threshold shifts (STS) as a function of frequency. Lower panel: The bars represent the difference in percentage STS+ and STS- per frequency (left axis), the points and lines represent the mean group results and the dotted lines represent the 99% confidence interval (right axis). Filled points are significantly different (p<0.01) from zero (no change).

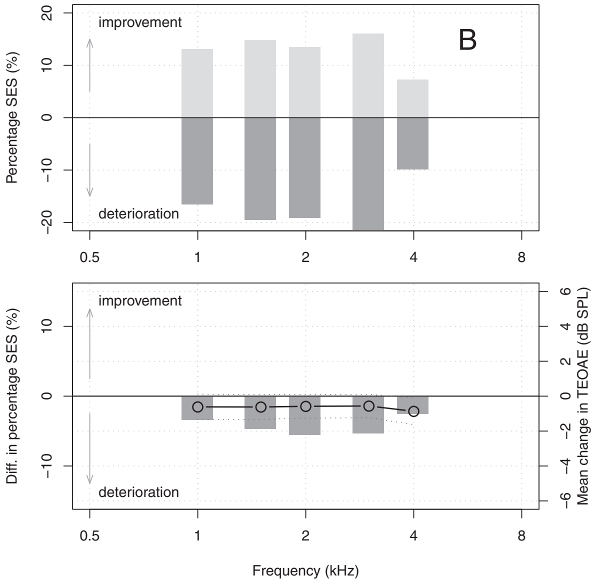

Figure 3.2B: Upper panel: The bars represent the percentage of significant emission shifts (SES) as a function of frequency for TEOAEs. Lower panel: Difference in percentage SES+ and SES- per frequency (left axis), mean group results are presented by the points and lines, 99% confidence intervals by the dotted lines (right axis).

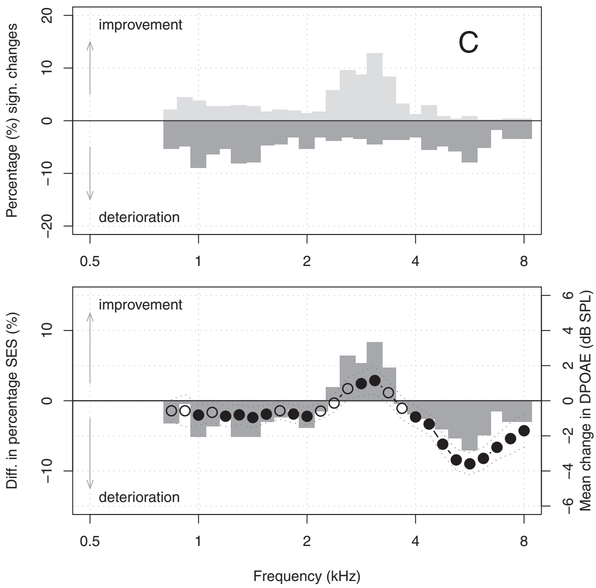

Figure 3.2C: Idem for DPOAEs, filled points are significantly different (p<0.01) from zero (no change).

Table 3-II: Observed incidence of STSs or SESs per measure. N valid represents the number of contributing ears per measure. P-values were computed according to formula (3.2) and are tabulated for $p < 0.05$. N.S. stands for not significant.

Measure	PTA_{6-8}	TE_{ov}	$DP_{1.5}$	DP_3	DP_6
N valid (ears)	466	450	454	466	441
STS^-/SES^- (deterioration)	64 p<<<0,0001	62 p<<<0,0001	20 p=0.0102	11 N.S.	13 N.S.
Expected (2.5%)	2.5% (11.7)	2.5% (11.3)	2.5% (11. 4)	2.5% (12)	2.5% (11.3)
STS^+/SES^+ (enhancement)	11 N.S.	47 <<<0,0001	9 N.S.	41 p<<<0,0001	1 p=0,00194
Expected (2.5%)	2.5% (11.7)	2.5% (11.3)	2.5% (11.4)	2.5% (12)	2.5% (11.3)

Incidence of observed changes

The incidence of STS and SES in both directions (improvements and deteriorations) is tabulated in Table 3-II. The observed incidence was compared to the expected incidence of 2.5% for both improvements and deteriorations with Formula 3.2. The incidence of deteriorations for audiometry (PTA_{6-8}), TE-overall response (TE_{ov}) and DP around 1.5 kHz ($DP_{1.5}$) is higher than the expected chance level of 2.5%. The incidence of improvements for TE-overall response and the DP response around 3 kHz (DP_3) is also significantly higher than would be expected. Labeling these increases in emission amplitude as improvement suggests that hearing status actually improves which is unlikely after seventeen months of noise exposure. Until it is clear whether these changes are actual improvements in *hearing status* these increases of amplitude will further be described as enhancements in emission amplitude.

Another way of visualizing the difference between average group results and individual changes is presented in the scatterplot of Figure 3.3A**.** The DPOAE-amplitude around 3 kHz for measurement 1 is plotted against the amplitude of measurement 2. There is small group effect of an enhancement and a large amount of SES^+.

Although the amount of deteriorations around 6 kHz (DP_6) is not different from what would be expected, there are significantly less improvements than would be expected by chance. Again, the differences between average group results around 6 kHz and individual changes are presented graphically in the scatterplot of Figure 3.3B. This graph clearly shows that there is a significant group deterioration whereas the amount of SES^- (13) does not differ significantly from the expected amount (11.3).

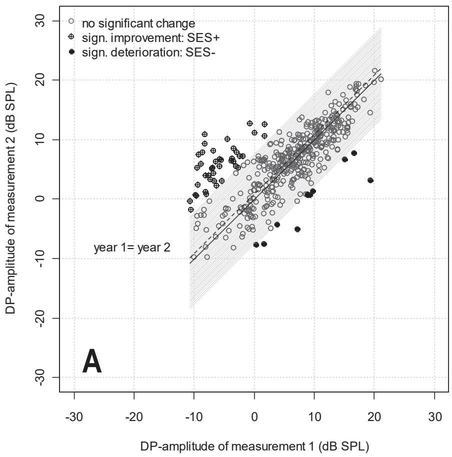

Figure 3.3A: Scatterplot of DPOAE emission amplitude of measurement 1 versus measurement 2 for 3 kHz (left panel). **B**: Idem for DPOAE emission amplitude for 6 kHz (right panel). The grey area represents the confidence interval of change (CIC) so all open circles (○) correspond to a non-significant change. There are 41 SES+ (⊕) at 3 kHz and 1 at 6 kHz, and there are 11 SES- (●) for both 3 and 6 kHz. The mean enhancement/deterioration is expressed by the dashed line.

Combining audiometry and OAEs

The relation between changes in audiometry and changes in otoacoustic emissions is investigated for those outcome parameters that exhibit significant changes larger than chance. Changes in hearing thresholds are thus divided into either a significant threshold deterioration (STS^-) or no significant threshold deterioration ('No STS^-'). For the TEOAE there are three possibilities: a significant enhancement (SES^+), no significant change (NC), or a significant deterioration (SES^-). This is because both the incidences of the enhancements and decreases are larger than chance. Only 1.5 kHz (deterioration) and 3 kHz (enhancement) exhibit incidences larger than chance for the DPOAE. This results in a two-way distinction of either a SES^- or 'No SES^-' at 1.5 kHz and SES^+ or 'No SES^+' at 3 kHz respectively. The counts of all possible combinations are presented in Table 3-III. Figure 3.4 illustrates how these counts are constructed by plotting the change in overall TEOAE amplitude (SES^-, NC, or SES^+) versus the change in hearing threshold at 6-8 kHz (STS^- or 'No STS^-').

In the total group of 390 cases without a STS^- 39 cases have a significant emission decrement (SES^-) and 58 significant emission increments (SES^+) while the majority (293) does not show a change is emission level (NC). A significant threshold deterioration is found in 60 cases, but in only 11 cases this is accompanied by significant emission shifts (8 SES$^+$ and 3 SES$^-$ respectively). So the majority of cases with a STS$^-$, i.e. 49, does not exhibit an accompanying SES (in either direction).

Table 3-III: Combination (counts) of cases with a significant threshold deterioration at 6-8 kHz (STS$^-$) with significant emission shifts (SES$^+$ or SES$^-$) for the overall TEOAE and for DPOAE levels at 1.5 kHz and 3 kHz.

Measure	TE_{ov}				$DP_{1.5}$			DP_3		
	SES$^+$	*NC*	*SES$^+$*	*total*	*No SES$^-$*	*SES$^-$*	*total*	*No SES$^+$*	*SES$^+$*	*total*
STS$^-$	3	49	8	60	58	2	60	54	10	64
No STS$^-$	58	293	39	390	376	18	394	371	31	402
total	61	342	47	450	434	20	454	425	41	466

Similar to the TEOAE, the counts for the DPOAE at 1.5 (SES$^-$) and 3 kHz (SES$^+$) are considered and compared to the occurrence of either a significant threshold deterioration (STS-) or no significant deterioration ('No STS$^-$'). At 1.5 kHz, the incidence for individual deteriorations is larger than chance (total of 20 SES$^-$ versus 434 of 'No SES$^-$'). The amount of STS$^-$ cases is 60 versus 'No STS$^-$' 394. From the 20 SES$^-$ cases, only 2 exhibit an accompanying STS$^-$ while there are 18 cases that can be labeled as 'No STS$^-$'. The amount of 'No STS$^-$' and corresponding 'No SES$^-$' is the largest: 376 versus 58 cases that show a STS$^-$ without SES$^-$. At 3 kHz the distinction is made between SES$^+$ and 'No SES$^+$'. For the total of 41 cases with a SES$^+$, 10 also have a STS$^-$ at 6-8 kHz, versus 31 without a STS$^-$. There are 54 cases with a STS$^-$ but without a SES$^+$. Again, the majority of cases show 'No STS$^-$' and 'No SES$^+$' (371).

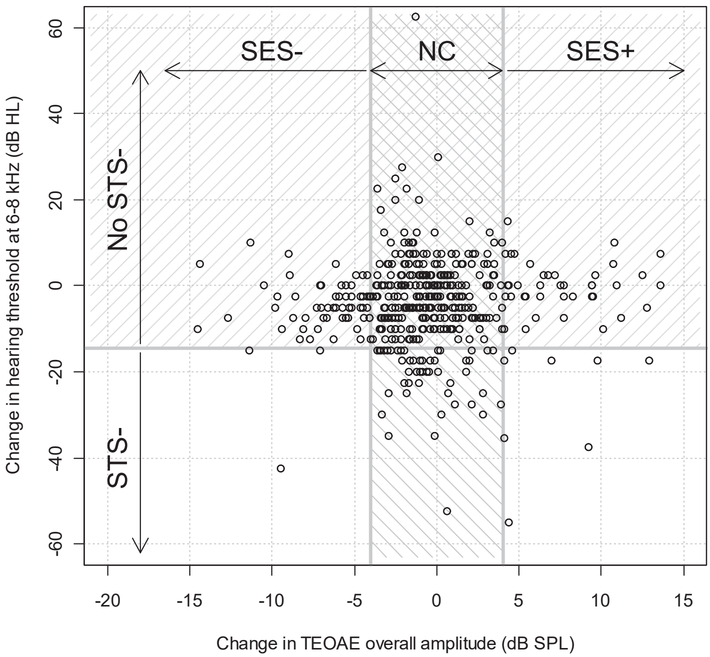

Figure 3.4: Scatterplot of change in TEOAE overall amplitude (horizontal) versus change in hearing threshold level at 6-8 kHz (vertical). The 95% confidence intervals are presented by the grey lines. There is a distinction between 'No STS^{-}' and 'STS^{-}' and for the occurrence of either an enhancement (SES^{+}) or deterioration (SES^{-}) in TEOAE amplitude versus no change ('NC'). The counts are tabulated in Table 3-III.

DISCUSSION

Standard error of measurement

For each measurement method single frequency *SEM*s were calculated. For pure-tone audiometry, averaging the thresholds over two frequencies ½ octave apart (i.e. 6 and 8 kHz), reduced the standard error of measurement when compared to those derived for the single frequencies. The overall response of the TEOAE yielded a comparable *SEM* as those for the single frequencies. For the DPOAE measurements averaging over ½ octave band (four frequencies) did not reduce the *SEM* much either. This implies that for OAEs the underlying measurement errors are not independent for measurements at neighboring frequencies.

Standard errors of measurement for OAEs have been reported elsewhere, but different methods have been applied to derive the *SEM* in various studies. There are several options for the measure for reliability from formula (1) (i.e. Pearsons rho, Cronbachs alpha or the intraclass correlation coefficient). Because OAE reliability depends on the measurement paradigm and equipment, Lapsley-Miller et al. (2006) warn not to generalize the results to other settings. Keeping this advice in mind, it seems plausible to be cautious when comparing our results and the values found in other studies. Combination of datasets and measurement paradigms could stimulate the process to reach consensus on the method to determine the *SEM* and how to classify changes in monitoring purposes.

The reported value for the standard error of measurement (*SEM*) for audiometry is 5.2 dB. For TEOAE-overall the corresponding value is 1.5 dB, which is similar to single frequency values reported by Marshall et al. (2009), ranging from 1.3 to 2.0 dB SPL, and from Lapsley-Miller et al. (2006), that range from 1.1 to 2.5 dB SPL. However, for DPOAEs the *SEM* values obtained (range 2.5-4.5 dB) are generally higher than those reported in other studies. The standard errors of measurement for DPOAEs from Marshall et al. (2009) range from 2.0 to 2.9 dB SPL, and from Lapsley-Miller et al. (2006) from 1.5 to 2.0 dB SPL. These values are comparable to other studies such as by Franklin et al. (1992), Beattie and Bleech (2000), Lapsley-Miller et al. (2004) and Seixas et al. (2005). In all those studies lower level stimuli were used and a non-exposed control group was used whereas in this study, the test-retest values were derived from participants in the hearing conservation program.

Given the fact that only the *SEM*s for DPOAEs in this study were higher than in other studies, possible explanations were considered. First, the effect of the presentation levels of the primary tones was investigated. In this study DPOAE-primaries were set at 75-70 dB SPL whereas they were 65-45 dB SPL in the studies by Marshall et al. (2009) and Lapsley-Miller et al. (2004; 2006). Franklin et al. (1992) found that varying the primary tone level from 55 dB SPL to 75 dB SPL had little influence on test performance. This could imply that the differences between previous results and ones reported here are caused by the use of the internal control group, i.e. a group where pre-existent hearing loss might be present.

The study by Keppler et al. (2010) is one of the few who have used both the higher stimulus levels of 75-65 dB SPL and the lower levels of 65-55 dB SPL. They report very low *SEM* values (range from 0.71 to 1.6 dB) for both presentation levels in a very homogeneous group of young, otologically normal subjects. In that study, they used the intraclass correlation coefficient (ICC) instead of the Pearson correlation coefficient and an overall standard deviation instead of a pooled standard deviation. Their ICC is very high (> 0.95) which could explain the small *SEM* when looking the expression of formula (1). Other studies report much lower values for the reliability measure and this would lead automatically to higher *SEM*s.

Sockalinham et al. (2007) report the two-way fixed ICC in a study for test-retest reliability in children. Their ICCs range from 0.64 to 0.85. Ng and McPherson (2005) have used primary levels of 70 dB SPL and report a correlation of 0.81 between test and retest, resulting in *SEM*-values ranging from 1.11 to 3.45 dB. Stuart et al. (2009) have explicitly investigated low-level DPOAEs (i.e. L_2 ranging from 30-45 dB SPL) and report reliability measures in the form of Cronbachs alpha higher than 0.85 in 87% of the investigated cases. Above-mentioned reliability coefficients are in the same order of magnitude as the correlation coefficient from this study, except for the very high ICCs reported by Keppler et al. (2010).

Next, the effect of the required signal-to-noise ratio on the *SEM* was considered. Beattie et al. (2003) found no influence of the SNR because 'our DPOAEs were sufficiently high in comparison to the background noise that the noise had no effect on the signal in the DPOAE- bin'. The reported *SEM*-values range from 2.0 to 3.5 dB SPL when requiring an SNR of 6 dB. Wagner et al. (2008) studied short-term variability of DPOAEs and only found minor differences in repeatability for SNRs ranging from 6 to 35 dB. They consider a minimum SNR of 6 dB to be a reasonable recommendation for a clinical measurement paradigm. All these investigations showed minor influence of SNR at high signal-to-noise ratio. Keppler et al. (2010) made a distinction between signal-to-noise-ratios of < 12 dB and ≥ 12 dB and found much lower ICCs and thus higher *SEM*s for the lower SNRs (ICC ranging from 0.19-0.98 versus 0.89-0.96 respectively). This study included cases with an SNR ≥ 0, similar to studies reported by Lapsley-Miller et al. (2004; 2006). It is not unlikely that the test-retest values obtained from a noise-exposed subgroup (this study) suffer more from background noise than those from a control group (Lapsley-Miller et al. 2004; 2006). When requiring an SNR of 6 dB for the test- restest data, the *SEM* is reduced by approximately 1 dB on average (range 0-2.5 dB SPL in the frequency range from 1-6 kHz) at the cost of roughly a double amount of exclusions. This illustrates that effects from noise on the OAE- results at the lower SNRs cannot completely be discarded.

In short, the values for the *SEM*s in this study are comparable to other studies, especially for audiometry and TEOAEs. The values for DPOAEs are slightly higher than the majority of other studies but they are in the same order of magnitude. Possible explanations could be the inclusion criterion (SNR) for the test-retest measurements and the use of a noise-exposed group to use in the test-retest measurements. Such a group is probably much more heterogeneous than a non-noise exposed control group and would have lower emissions. On the other hand this group seems appropriate because of the similarity with the population of interest.

Individual changes and overall effects

At first glance, the group-averaged results and the combined individual results follow similar patterns for all three types of measurements. At frequencies where there is a significant deteriorative group effect there is also a difference in the amount of significant individual deteriorations versus improvements. The difference between deteriorations and improvements or the absolute amount of changes is not always significantly different from chance.

This is the case for the DPOAE around 6 kHz where the incidence of SES^- is not significantly different from the incidence that would be expected by chance alone, even though this frequency shows the largest effect on group level. In fact, the largest deviation from the expected individual changes in OAEs occurs around 3 kHz and encompasses an increase in emission strength but at this frequency the averaged group effect is much smaller than at 6 kHz.

So at 3 kHz the individual significant shifts are in congruence with the group-averaged results while at 6 kHz this is not the case. At 6 kHz the amount of significant individual shifts is not statistically different from chance. So the relatively large effect of a group-averaged decrease in emission level is caused by a lot of individual ears with contributions that –by themselves- are not distinguishable from measurement variation.

Combination of individual changes

The results presented in Figure 3.4 and Table 3-III show that 1) there is no clear pattern (correlation) between individual changes in TEOAE and audiometry and thus 2) there is no clear pattern between the occurrence of the combination of a SES and a STS. All combinations are present. This was also found by Lapsley-Miller et al. (2006) in their study of sailors exposed where they found 'no compelling relationship between changes in audiometric changes and changes in OAEs'. A more detailed statistical analysis did not give evidence for changes in OAEs to coincide or occur simultaneously with changes in audiometry. They noted a high amount of cases with a permanent threshold shift (PTS) that had absent or low-level emissions. For the dataset in this study there are a lot of cases with absent emissions, especially at 6 kHz (see for more details Helleman et al. (2010)). From the total of 64 cases with a STS-, there were 5 with missing data around 6 kHz, versus 20 with missing data that exhibited no STS-. The odds ratio (*OR*) for people who have an missing data in the average DPOAE at 6 kHz for the occurrence of a threshold shift at 6/8 kHz is larger than 1 (*OR*=1.62), when compared to people who do not have a missing data but the result is not significant (*CI* [0.59 4.48]).

The occurrence for a SES^{+} without a STS_{-} could be considered as a sign for potential enhancement. But then the question arises how cases of a STS_{-} without a SES_{+} should be considered? Would that imply potentially enhanced sensitivity for audiometry over OAEs? Or are these cases not suitable for monitoring with OAEs anymore? In the situation where both results are in congruence, there are very few counts of corresponding significant changes in both methods. Of all possible combinations, the highest agreement is –obviously- in those cases where there is no significant individual change in both OAE and audiometry! This is the case for 293 ears when looking at TEOAE in both directions and STS_{-}, for 376 ears with DPOAE at 1.5 kHz, and for 371 ears at 3 kHz. It is important to note that this is not due to a shortcoming of either one of the methods since it is expected that the largest amount of ears would not exhibit an individual shift.

Increase in emission strength

The observed increase in emission strength at 3 kHz was unexpected and required further investigation. First, it should be noted that all ears contributed to the analyses in this dataset. Second, the enhancement was both present in the raw data (not published) and after a different type of noise level substitution (Helleman et al. 2010). That approach introduced a bias towards finding more deteriorations because only drops below noise level from the first measurement to the next were substituted. So although unexpected, this implies that the enhancement is a 'real' enhancement and is not caused by the inclusion criterion used.

Ears with no measurable emissions at 6 kHz are more likely to present with an enhancement of OAE-amplitude around 3 kHz. The association in occurrence of an enhancement in DPOAE at 3 kHz and an occurrence of a significant threshold shift in the audiogram was investigated by means of the diagnostic odds ratio. For this analysis, the thresholds shifts are considered the golden standard for hearing deterioration and the enhancements are hypothesized to represent damage of the auditory system. The odds ratio (*OR*) for people who have an enhancement at 3 kHz for the occurrence of a threshold shift at 6/8 kHz is 2.2 (*CI* [1.03 4.78]) when compared to people who do not have an enhancement at 3 kHz.

Investigation of the audiograms of this population (see Helleman et al. (2010) for the classification) shows that especially ears that have a profound noise-notch or have a sloping audiogram show this enhancement. These groups also contain most ears that have no measurable emissions at 6 kHz. The individual significant enhancements occur in the left part of Figure 3A which corresponds to relative low levels for the initial measurements. For the SES^+ cases, after the increase in emission amplitude, the emission remains smaller than for a lot of cases with higher emissions for both initial and follow-up measurement.

These findings suggest that naming these significant emissions shifts as improvements would be incorrect. Enhancement seems a more suitable and neutral term since the observed increases in amplitude show an association with the occurrence of a threshold deterioration, which in its turn can be considered as a manifestation of noise induced hearing loss. This enhancement in DPOAEs has been reported in others studies examining both animals and humans, after noise exposure, administration of salicylate or ototoxic drugs. Kakigi et al. (1998) administered ototoxic drugs to chinchillas and found increases in emissions amplitude in the frequency region *below* the damaged area. They suggest that when a cochlear lesion progresses apically in the case of ototoxicity there is often a transient increase in DPOAE-amplitude. In a study with guinea pigs after administration of salicylate Huang et al. (2005) suggest that this ‘paradoxical enhancement’ could be a result from cochlear hypersensitivity. They also suggest that it might be the cause of tinnitus generation around the ‘audiometric edge’. Guinea pigs also showed a long-term enhancement in the middle frequencies of DPOAE measurements after prolonged noise exposure in the study by Mei et al. (2009) where the authors also propose the possibility of enhancements as signs of tinnitus generation. In this study, no evidence regarding to tinnitus or increase in tinnitus was found in answers from the questionnaire, for subjects showing this enhancement. Nevertheless, these studies underline that similar apparently contradictory enhancements have been found in other types of hearing damage.

Shupak et al. (2007) found enhancements in humans after noise exposure in both TEOAEs and DPOAEs, although only in a minority of cases. For left ears they found a significant difference between the change in baseline and first follow-up and the change between first and second follow-up. The change between baseline and first follow-up was in the form of a small enhancement (i.e. 0.08 dB SPL). The frequency area where this effect occurred was between 3.8 and 6.0 kHz. They only included cases with an SNR ≥ 6 dB and the authors did not report whether the enhancement itself was significant. They mention the possibility of overcompensation of the outer hair cells by reduced activity of the medial olivocochlear system.

The enhancement effects in this study are much larger. An explanation could be that only ears with pre-existing hearing loss show this enhancement and those ears might not have been included in analyses where a high initial SNR was used for inclusion as in the study by Shupak et al. (2007). In a study on the effects of MP3 exposure on OAEs, Bhagat et al. (2008) also report some enhancement in synchronized spontaneous otoacoustic emissions (SSOAEs). They report that depending on the frequency 35-50% of their subjects showed an increase in emission amplitude, although the overall group effect was a reduction in emission amplitude. The inclusion criterion in that study was set at SNR ≥ 3 dB.

CONCLUSION

The use of the standard error of measurement (*SEM*) enables the classification of individual changes to be significant or not. The size of the *SEM*s is comparable or slightly higher than reported by other studies despite differences in measurement paradigm.

Many studies on OAEs and NIHL are based on group results. This study compares individual changes and group-averaged effects. It shows that the individual changes do not always follow the same pattern as the overall results. Although OAEs might have an enhanced sensitivity for changes due to noise exposure for groups of individuals, this study shows that in the individual case this increased sensitivity is not found on an individual basis. Moreover, the congruence between individual changes of audiometry and OAEs is limited and only present when both measures exhibit no change.

At 6 kHz where the group effect is the largest, the criterion for of significant change is too large to reliably detect the smaller changes that occur on group level. In other words, there are many subjects with consistent but insignificant changes that fall within the 95% confidence interval, but who do contribute to the significant average group effect. Nevertheless, at some frequencies the amount of individual changes is significantly larger than would be expected by chance alone. For future studies it is interesting to reach a consensus regarding correct derivation of the standard error of measurement because this would simplify the application of OAEs in monitoring applications and would enable comparison of different studies.

A remarkable finding of this study is that in the DPOAE-results at 3 kHz significantly more individual enhancements were found than would be expected by chance alone. This is the area where there are measurable emissions left *and* an area that lies next to the 'classical' noise-notch area around 4 kHz. It seems that some cases with pre-existent hearing loss present with an enhancement in emission amplitude. It would be interesting to investigate this effect further in follow-up studies. From this finding it can be concluded that changes rather than deteriorations in OAEs should be the scope.

More longitudinal studies are required to investigate if any of the effects that are observed here can be reproduced and if they have some kind of predictive value.

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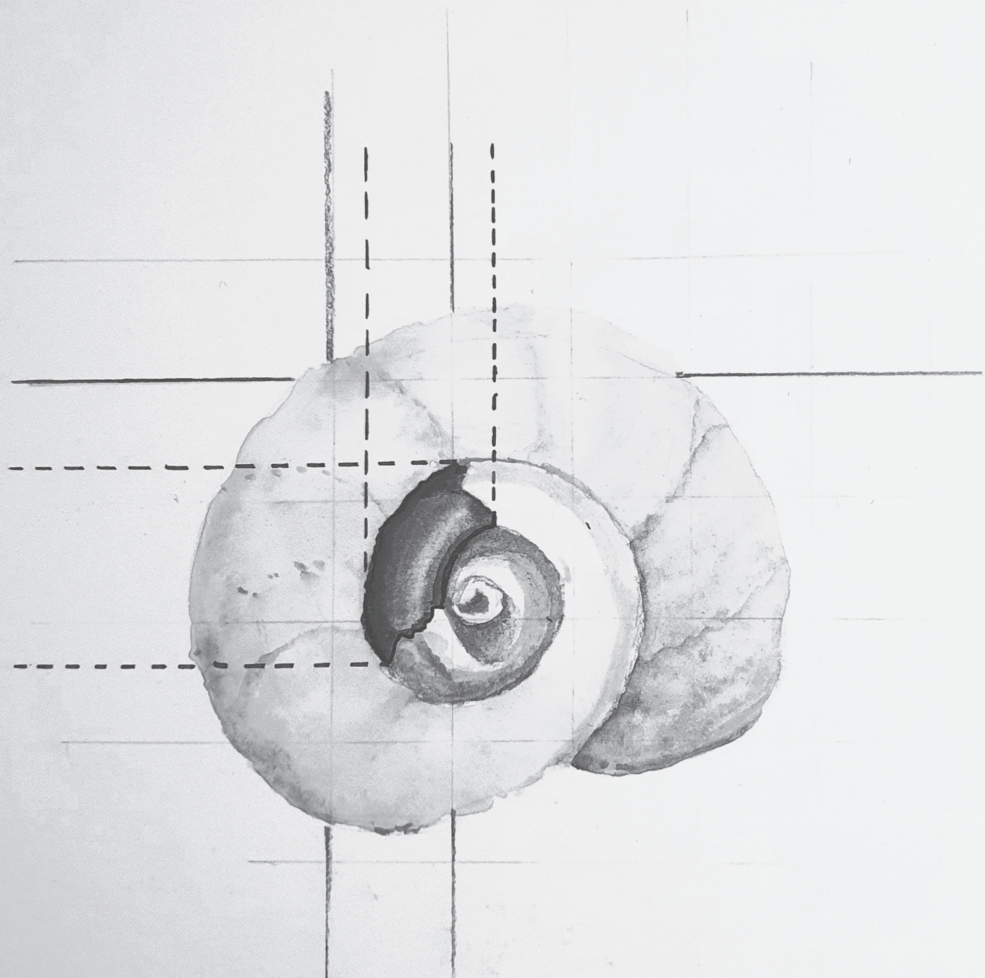

CHAPTER 4

Otoacoustic emissions versus audiometry in monitoring hearing loss after long-term noise exposure- a systematic review

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ABSTRACT

Objective: The objective of this systematic review was to compare otoacoustic emissions (OAE) with audiometry in their effectiveness to monitor effects of long-term noise exposure on hearing.

Methods: We conducted a systematic search of MEDLINE, Embase and the non-MEDLINE subset of PubMed up to March 2016 to identify longitudinal studies on effects of noise exposure on hearing as determined by both audiometry and OAE.

Results: This review comprised 13 articles, with 30–350 subjects in the longitudinal analysis. A meta-analysis could not be performed because the studies were very heterogeneous in terms of measurement paradigms, follow-up time, age of included subjects, inclusion of data points, outcome parameters and method of analysis. Overall there seemed to be small changes in both audiometry and OAE over time. Individual shifts were detected by both methods but a congruent pattern could not be observed. Some studies found that initial abnormal or low-level emissions might predict future hearing loss but at the cost of low specificity due to a high number of false positives. Other studies could not find such predictive value.

Conclusions: The reported heterogeneity in the studies calls for more uniformity in including, reporting and analyzing longitudinal data for audiometry and OAE. For the overall results, both methods showed small changes from baseline towards a deterioration in hearing. OAE could not reliably detect threshold shifts at individual level. With respect to the predictive value of OAE, the evidence was not conclusive and studies were not in agreement. The reported predictors had low specificity.

INTRODUCTION

Exposure to loud noise may cause sensorineural hearing impairment, called noise-induced hearing loss (NIHL). Occupational NIHL is a hazard for workers on construction sites, in factories, on farms but also for railway workers, musicians, miners, navy or army personnel and in many other trades (Feder et al., 2017; Kirchner et al., 2012; Leensen et al., 2011).

Shooting, riding motor-bikes or repeated exposure to loud music in nightclubs, concerts or personal music players might cause hearing loss as well (Carter et al., 2014). Prolonged, repeated exposure to loud sounds damages the delicate structures in the cochlea. Noise exposure induces metabolic and mechanical changes causing cell death and physical loss of integrity of hair cells (Henderson et al., 2006; Kurabi et al., 2017; Śliwińska-Kowalska & Jedlińska, 1998; Talaska & Schacht, 2007). The damage starts with the outer hair cells (OHC), which form the cochlear amplifier, before damaging the inner hair cells and other structures in the cochlea (Henderson et al., 2006). Functionally, the noise-induced damage results in loss of hearing sensitivity for certain frequencies, typically starting around 4 kHz, impaired understanding of speech especially in noise, and can be accompanied by decreased sound tolerance and/or ringing in the ears (tinnitus) (Chung & Mack, 1979; Feder et al., 2017; Kirchner et al., 2012; May, 2000; McBride & Williams, 2001; Nordmann et al., 2000). These functional deficits can result in social isolation, depression and more workplace-related accidents and injuries (Girard et al., 2015; Hétu et al., 1995).

With long-term continuous exposure to noise, the deterioration is gradual and increases most during the first 10–15 years of exposure (Kirchner et al., 2012). Damage may also occur acutely as a result of exposure to a short, high intensity sound (Axelsson & Hamernik, 1987). Noise exposure can cause a temporary hearing loss, ie, a temporary threshold shift (TTS), or a permanent threshold shift (PTS). Nordmann et al. suggest that the underlying mechanisms for PTS and TTS are different (2000).

Many countries worldwide have rules and regulations in order to protect employees from damaging their hearing. An example is the European Directive (2003/10/EC) that provides both exposure limit values and exposure action values with respect to daily and weekly exposures (European Parliament and the Council, 2003). It also specifies the allowed peak sound pressure level. The employer has to assess or measure the noise levels to which workers are exposed.

The exposure limit value is 87 decibels, taking into account the attenuation provided by personal hearing protection equipment. The exposure action value is fixed at 80 decibels (lower value) and 85 decibels (upper value). The risks arising from this exposure have to be minimized by choosing methods or equipment producing less exposure to noise, instructions on the correct use of the equipment, technical measures (shielding, noise absorption) or organizational measures that reduce duration and intensity. If these measures cannot prevent the risk, the employer must provide individual hearing protection devices (HPD) and provide access to periodical audiometric screening. For exposures >85 decibels, the EU places the responsibility on the employer to ensure that hearing protection is being used.

One of the main goals of hearing conservation programs is to detect hearing loss as soon as possible and halt further deterioration (Kirchner et al., 2012). A key role in such a program is measurement of hearing status, traditionally assessed by pure-tone audiometry. It tests the detection threshold per frequency and thus the entire auditory pathway and requires active cooperation of the subject. The presence or absence of a noise notch, or a “bulging” audiogram plays an important role in medicolegal cases, although notches at 6 kHz can also be found in subjects not exposed to noise (Coles et al., 2000; Lutman et al., 2016; McBride & Williams, 2001). Other methods that are used in hearing testing in occupational settings, either separately or in conjunction with audiometry, are speech-in-noise testing (Leensen & Dreschler, 2013) and the measurement of otoacoustic emissions (OAE) (Feder et al., 2017; Forshaw, 2011; Marshall et al., 2001; Sliwinska-Kowalska & Kotylo, 2001). Since OAE are related to the functionality of the OHC, it is not surprising that the relationship of NIHL and OAE has been investigated since the discovery of OAE by David Kemp (1978).

OAE are very soft sounds originating mainly from the micromechanical properties of the normal functioning OHC in the cochlea (Kemp, 1978). They can be spontaneous or evoked by sound stimulation and can be recorded in the external ear canal. Transiently evoked OAE (TEOAE) are elicited by broad band clicks and reflect the OHC’s activity throughout the length of the basilar membrane in the cochlea, stimulus-frequency OAE (SFOAE) are emitted in response a continuous tone. Distortion product OAE (DPAOE) are evoked by two simultaneously presented pure-tone stimuli and reflect the OHC’s activity at specific positions on the basilar membrane. Spontaneous OAE (SOAE) exist as well. Emissions can be classified according to the mechanism creating the emission: they can be caused by linear reflection within the cochlea (for example

SOAE or low-level SFOAE or TEOAE) of arise by non-linear distortion (DPOAE) (Shera, 2004; Shera & Guinan, 1999). Higher level stimuli create a combination of both types.

Measuring OAE does not require active cooperation from the subject and is therefore an objective tool. This is an important benefit when compared to pure-tone audiometry. A disadvantage is the dependency of middle-ear status for the transmission of the stimulus and response through the ear canal. A suboptimal transmission of sounds through the middle ear reduces the small stimulus and even weaker response of the inner ear and results in absent or low-level emissions, also in case of an intact cochlear amplifier (Zhao et al., 2000).

OAE are currently applied in neonatal hearing screening programs worldwide, but can also be used in a more diagnostic manner such as monitoring hearing status in subjects exposed to noise or to ototoxic agents (Konrad-Martin et al., 2014). Over the years, there has been much interest in a presumed role for OAE in detecting hearing loss at an earlier stage than audiometry and the hypothesized potential in predicting future hearing loss (Lapsley Miller & Marshall, 2007). Hamernik and colleagues have shown in histopathological studies that OHC damage in animals can occur without an increase in hearing thresholds (1989). Such findings have led to the term OHC-redundancy, implying that loss of OHC does not directly lead to loss of detection sensitivity. Several cross-sectional studies found differences in emission levels between noise-exposed and non-exposed subjects while the audiometric thresholds were within the same limits (Attias et al., 1998; 2001; Desai et al., 1999; Engdahl et al., 1996; Lapsley Miller & Marshall, 2007; Marshall et al., 2001; Xu et al., 1998). For a more detailed discussion of these studies, see the review by Lapsley Miller & Marshall (2007). Such findings led to the hypothesis that OAE might be a more sensitive test for cochlear function and that they might be able to detect so-called preclinical damage.

There are two aspects that should be taken into account before this can be concluded from these studies. First, as emphasized by Sisto and co-authors (2007), there could be a difference between two groups of subjects in audiometric thresholds even when they are both within normal limits depending on the definition (usually ≤25 or 20 dB HL). In their study, Sisto et al. found OAE to be capable of detecting even mild hearing losses (10–20 dB HL). The second limitation is that differences on group level as detected by cross-sectional studies cannot always be regarded as signs of future hearing loss. For an actual predictive value, longitudinal studies are required. This is the same when the goal is to identify subjects that are more vulnerable than others.

In the abovementioned review from 2007, Lapsley Miller and Marshall called for more large-scale longitudinal studies and emphasized that more knowledge was required about optimal OAE parameters. From our own knowledge in this field, it was felt that the results and conclusions from the few longitudinal studies since then have not shown consistent results.

The lack of consistency among these studies was the basis for this review, which aims to provide a comparison between different longitudinal studies on OAE and audiometry on behalf of policy-makers, audiologists and occupational hygienists. Its focus is the role of OAE in monitoring NIHL after long-term exposure compared to audiometry by investigating and structuring available data in a well-defined, reproducible and systematic manner. We compared the setup, methodology, and quality of different studies, before we analyzed the outcomes on group-averaged data and on a subject level (individual shifts). The focus of this systematic review was on the possibility of (i) replacing audiometry by OAE in hearing conservation programs and (ii) early detection in the form of a predictive value or identification of vulnerability. We sought for agreement between studies with respect to these issues and possible overarching trends.

METHODS

Protocol and registration

This review was prospectively registered in the Prospero database under number PROSPERO 2015:CRD42015027111 and reported according to MOOSE guidelines (Stroup et al., 2000).

Literature search

A medical librarian (JL) performed a comprehensive search in OVID MEDLINE, OVID Embase and the non-MEDLINE subset of PubMed from inception to 14 March 2016 to identify studies on the use of OAE to monitor NIHL. The search included both free text and controlled terms (i.e, MesH in MEDLINE) for OAE and NIHL or activities known to be related to NIHL (certain occupations and leisure activities). No language or other restrictions were applied. The entire MEDLINE search strategy is shown in Appendix A. On completion, citations identified in each database were imported into EndNote and de-duplicated. Forward and backward snowballing of the identified relevant papers was applied and the search was adapted in case of additional relevant studies. Corresponding authors were contacted via email if their studies could not be obtained otherwise.

Eligibility criteria

Original studies were included in which subjects were exposed to noise (continuous or impulse) and hearing status was assessed on more than one occasion (longitudinal or repeated measures approach) with both audiometry and evoked OAE (TEOAE and/or DPOAE). Studies on animals, infants or neonates were excluded. Studies on OAE and audiometry with noise *and* another intervention (ototoxicity or preventive strategy as in antioxidants) were excluded except when there was a control group with noise as the sole intervention.

Selected articles

Two authors (HH and HE) independently screened titles and abstract of all included studies. When disagreement occurred whether or not to exclude a paper in this stage, consensus was reached through discussion or by consultation of a third reviewer (WD). The same two authors independently examined the full-text articles, again with consensus through discussion and/or subsequent consultation of the third reviewer. Screening was conducted with support of Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). After full-text screening only studies reporting on long-term (weeks/years) exposure and permanent effects on hearing were included.

Quality assessment

A modified Downs & Black checklist (Downs & Black, 1998) was used to assess quality, including reporting, external and internal validity, risk of bias. The checklist originally consists of 27 items with a maximum count of 32 points. For this review, questions that were not relevant or applicable were omitted and other items were adjusted slightly, with more attention on the reporting of confounders and appropriate statistical tests (multiple comparisons with ears and frequencies).

The adapted checklist (see Appendix B) consisted of 14 items with a total count of maximum 16 points. Items 1–3, 5–7, 11, 16, 17, 20, and 26 were incorporated from the original list with an explicit question relevant for this topic. Items 4, 9 and 18 were modified. If no explicit hypothesis was given, the objective(s) of the study had to be clear. Confounders that we felt needed to be addressed, were age, middle ear status, previous and recent noise exposure, and use of hearing protection. Reporting on these items in a sufficient manner would yield two points, whereas partial or unclear reporting on these items yielded one point. Any attempt to address variation in the published data was rewarded with one point. Standard errors (SE) of the mean were considered sufficient, although standard deviations (SD) or confidence intervals (CI) are preferred from a statistical point of view (displaying actual spread or estimated effect size).

The final item on the reporting section deals with test statistics. It was required to have a full description of test statistics, degrees of freedom, and *p*-value. The original Downs & Black checklist only requires the *p*-value to be given explicitly. External validity was assessed with the question whether the participating subjects were representative of the entire population from which they were recruited. Four items dealt with internal validity, with a maximum of five points. The final question concerned selection bias: were losses to follow-up taken into account? This question was made more explicit by asking whether the amount of excluded data points was reported if inclusion was based on a certain signal-to-noise ratio (SNR) criterion.

The first two authors independently assessed quality and, when the scores on separate items were different, a consensus score was reached through discussion. Studies were not excluded based on the outcome but the overall quality assessment was used in the narrative comparison of the included studies.[2]

Summary measures and synthesis of the data

A narrative approach was used to qualitatively compare studies in descriptive characteristics (population, exposure, age, gender, etc.), aim, methodology, outcome and conclusion. The principal (quantitative) outcome measures were hearing threshold levels and emission amplitude and the change from baseline values for these measures. Both the vulnerability assessment and individual analyses were discussed in a narrative manner.

2 *Articles written by two of the four authors of this review (HH and WD) were scored in a similar matter by the first two authors (HH and HE) of this review. It was felt that it would be of more value to address these articles in a similar and reproducible manner, than to omit assessing these articles.*

A simplified approach allowed comparison of the size of change from baseline across different longitudinal studies by ignoring possible effects of initial hearing status or the inclusion criterion applied and by averaging changes across frequencies. This approach was chosen because of anticipated difficulties in combining numerical outcomes from different studies, but we realize that this provides only a first-order approximation. Although the typical noise-notch occurs around 4 kHz, we expected some studies to look at broader frequency ranges than at 4 kHz only. In order to take this specific region into account and to be able to compare across studies, the changes between 2 and 8 kHz were averaged (i.e., one octave above and one octave below the noise-notch area). This allowed comparison across studies with different frequency regions, possibly at the cost of underestimating the maximal effect. Besides the reported frequencies, there could be differences in the way thresholds were derived (manually or automatically) and the step size or test resolution chosen (usually 5 dB).

For OAE, the measurement paradigm may differ across studies, e.g., with respect to the use of SNR or emission amplitude as outcome measure, the level of stimuli, the frequency resolution, single or average measures, and exclusion criteria applied. For DPOAE, the reported emission levels (not SNR) between 2 and 8 kHz was averaged into one single measure, regardless of the chosen inclusion SNR criterion. Similarly, for TEOAE the response in the 4 kHz region was used in this analysis. The actual emission amplitude is a direct measure of cochlear function whereas SNR also reflects measurements conditions.

RESULTS

Study selection

The search identified 657 references. The PRISMA flowchart (Moher et al., 2015) summarizing the data collection process, number of records in each step and reasons for exclusion is presented in Figure 4.1. Based on full-text, 120 articles were assessed and 105 studies dealing with short-term (hours/days) and temporary effects on hearing were excluded. Only 15 studies described effects of prolonged noise exposure on hearing, and 2 of these long-term studies were excluded.

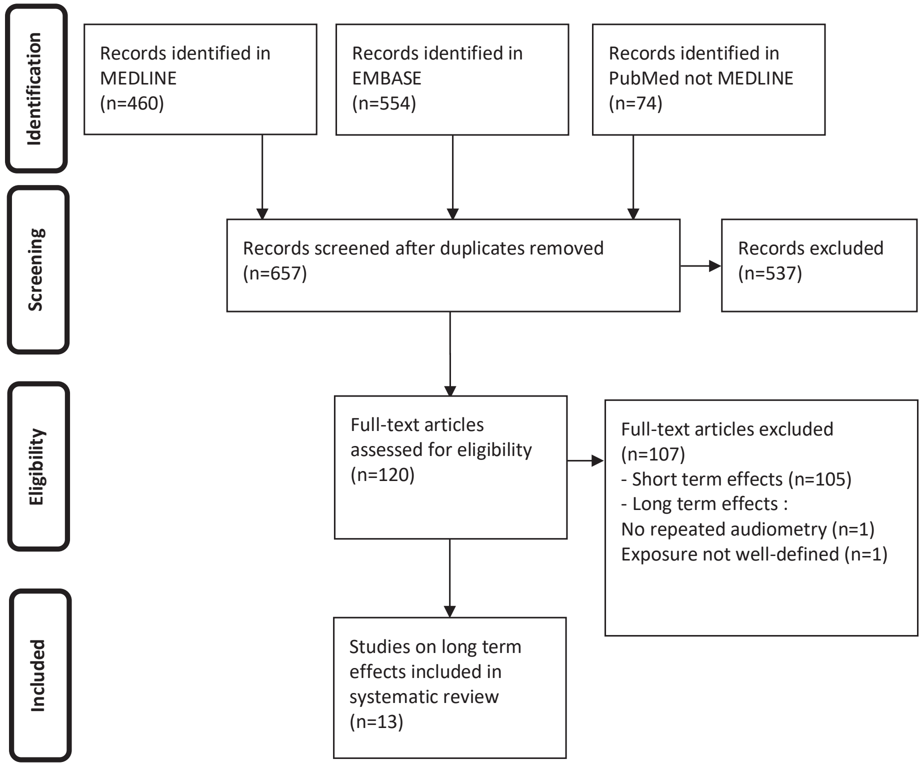


Figure 4.1: Flow diagram of the conducted search (based on the PRISMA 2009 Flow Diagram)

Study characteristics

General description

All 13 eligible studies reported changes in hearing status of subjects occupationally exposed to noise. They described 11 unique populations. Both Seixas and Helleman and their co-authors (Helleman et al., 2010; Helleman & Dreschler, 2012; Seixas et al., 2005, 2012) reported on (more or less) the same population in two different manuscripts. Seixas and his co-authors presented data on the same population but with a different follow-up time (three versus ten years) and these papers were analyzed separately. Helleman and co-authors reported on the same group, with the same follow-up but with a different approach in the analysis (individual versus group results) and these papers were considered as one study with respect to the outcomes. There was considerable variation in methodological and other properties of included studies. This made it difficult to describe overarching trends.

Table 4-1 addresses the major descriptives of the included studies. Three studies dealt with impulse noise (Duvdevany & Furst, 2007; Konopka et al., 2005; Marshall et al., 2009), but the majority assessed the effects of prolonged, continuous noise exposure (Helleman et al., 2010; Helleman & Dreschler, 2012; Job et al., 2009; Lapsley Miller et al., 2004, 2006; Moukos et al., 2014; Murray et al., 1998; Seixas et al., 2005, 2012; Shupak et al., 2007). Changes in hearing status of professionals were reported for both OAE (TEOAE and/or DPOAE) and pure-tone audiometric thresholds.

All studies were observational and had no control over the noise exposure, with six studies having a non-exposed group serving as control group. Some studies only report group-averaged results, while others perform an analysis on a particular subgroup or perform analyses on individual changes in OAE and audiometry. Six studies explicitly test the hypothesis whether (a form of) OAE are suited to predict individual susceptibility and look at the predictive value (Duvdevany & Furst, 2007; Lapsley Miller et al., 2006; Marshall et al., 2009; Murray et al., 1998; Shupak et al., 2007). See Table 4-I for more details.

The age ranges of the subjects included differed between studies from a narrow range (18–20 years) on young army recruits to a broad range (19–61 years) for other studies. A smaller age range with no previous noise exposure form a relatively homogenous group in initial hearing status. Older subjects with a known history of noise exposure might enter the studies with a pre-existing hearing loss.

Some studies initially report a few hundred subjects but the numbers in Table 4-I are the actual amount of subjects contributing to the longitudinal analysis and these numbers are generally much smaller. There were studies combining the results for left and right ears, studies using ear as factor in analyses and studies presenting changes for left and right ears separately whilst performing other analyses on the ears combined. In order to combine this for all included studies, left and right ears were combined in the first order, overall analysis presented in this review. Thus, the number of ears measured at baseline and at one of the follow-up measurements ranged from 56–518 and the number of subjects ranged from 30–350.

Table 4-I: General description of the included studies. Unless otherwise stated, the reported numbers correspond to numbers in the study group (exposed subjects) not for the control group or the baseline group. Follow-up time is the time between the first and last measurement used for group analysis. Please note that the number of subjects does not provide complete information because in some studies subjects with incomplete datasets were excluded, while ears or single data points were excluded in others. [OAE=otoacoustic emissions; DPOAE=distortion product OAE; TEOAE=transiently evoked OAE; G=group analysis, I=individual analysis, PV=predictive value or vulnerability analysis, B= Baseline, M=male, F=female, yrs=years, wks=weeks, mos=months, SOAE=Spontaneous OAE; LE=low exposure, HE=high exposure, I/O=input-output curve.]

		Study aim	**Study population**	**Analysis (G/I/ PV)**	**Subjects (N) per analysis (Male/Female)**				**Age at baseline (yrs)**				**Follow-up time**	**Control group**	**OAE type**
					B	*G*	*I*	*PV*	*Range*	*Median*	*Mean*	*SD*			
A	*Duvdevany & Furst (2007)*	Characterization of changes in audiograms and TEOAE over time, and investigation of predictive value ear vulnerability	Combat soldiers	G PV	84 (M)	30 (M)	-	30 (M)	-	-	18	-	2 yrs	No	TE
B	*Konopka et al. (2005)*	Comparison of the sensitivity of TEOAEs with standard and extended audiometry in early evaluation of acoustic trauma.	Soldiers	G	92 (M)	92 (M)	-	-	-	-	19	-	1 yr	Yes	TE
C	*Marshall et al. (2009)*	Investigation of vulnerability based on low-level or absent OAEs in future hearing loss after impulse noise exposure	Marine recruits	G I PV	401[a] (M)	60 (M)	285 (M)	285 (M)	17.4–28.1	19.2	-	-	3 wks	Yes	TE DP

Table 4-I: Continued.

		Study aim	Study population	Analysis (G/I/ PV)	Subjects (N) per analysis (Male/Female)				Age at baseline (yrs)				Follow-up time	Control group	OAE type
					B	*G*	*I*	*PV*	*Range*	*Median*	*Mean*	*SD*			
D	*Helleman & Dreschler (2012)*	Comparison of group-averaged and individual changes for audiometry, TEOAEs, DPOAEs in order to see if they exhibit the same pattern in time.	Workers in printing office	I	320 (316M 4F[b])	-	233 (M)	-	23-60	42	-	-	17 mos	No	TE DP
E	*Helleman et al. (2010)*	Exploring boundary conditions in which the use of OAEs might have a contributing role in a general hearing conservation program.	Workers in printing office	G	320 (316M 4F[b])	233 (M)	-	-	23-60	42	-	-	17 mos	No	TE DP
F	*Job et al. (2009)*	Investigation of vulnerability for future hearing loss with initial DPOAE.	Pilots	G PV	521 (M/F[c])	350 (M/F[c])	-	160 (M/F[c])	20-40[d]	-	-	-	3 yrs	No	DP IaDP
G	*Lapsley Miller et al. (2006)*	Assess changes in audiometric threshold and OAEs in sailors after 6 months of hazardous noise exposure on an aircraft carrier.	Sailors	G I PV	338 (303M 35F)	75 (67M 8F)	338 (303M 35F)	-	18-46[d]	M: 22 F: 21	-	-	9 mos	Yes	TE DP

Table 4-I: Continued.

		Study aim	Study population	Analysis (G/I/ PV)	Subjects (N) per analysis (Male/Female)				Age at baseline (yrs)				Follow-up time	Control group	OAE type
					B	*G*	*I*	*PV*	*Range*	*Median*	*Mean*	*SD*			
H	*Lapsley Miller et al. (2004)*	Investigation of OAEs in a hearing conservation program to find if, when and how OAEs change with hearing thresholds.	Navy personnel	G I	474 [e] (M/F[c])	69 (57M 12F)	69 (57M 12F)	-	14-49[a]	-	F:24.5 M:25.8	F:5.1 M:5.9	1 yr[f]	Yes	TE DP SOAE
I	*Moukos et al. (2014)*	Comparison of initial and the final audiological evaluation in a long follow-up with conventional audiometry and DPOAE.	Workers tobacco company	G I	76 (58M 14F[g])	34 (29M 5F)	34 (29M 5F)	-	32–54	-	43.7	6.9	9 yrs	Yes	DP
J	*Murray et al. (1998)*	Investigation if OAE testing gives earlier warning of potential hearing loss than PTA.	Musicians	G I PV	119 (61M 58F)	74 M/F[c])	74 (M/F[c])	74 (M/F[c])	19-61[a]	-	-	-	5 yrs	No	TE Repro
K	*Seixas et al. (2012)*	Characterization of the effects of noise exposure including intermittent and peaky exposure, on hearing damage as assessed by PTA and OAEs.	Construction Apprentices	G	372[h] (M/F[c])	258 (229M 29F)	-	-	-	-	27.6	6.6	10 yrs	Yes	DP

Table 4-I: Continued.

		Study aim	Study population	Analysis (G/I/ PV)	Subjects (N) per analysis (Male/Female)				Age at baseline (yrs)				Follow-up time	Control group	OAE type
					B	*G*	*I*	*PV*	*Range*	*Median*	*Mean*	*SD*			
L	*Seixas et al. (2005)*	Evaluation of the relations between noise exposure related changes over time for a range of frequencies and DPOAE primary intensities	New construction workers	G	372 (M/F[c])	268 (240M 28F)	-	-	-	-	27.2 (LE) 27.8 (HE)	6.7 (LE) 6.8 (HE)	3 yrs	Yes	DP I/O
M	*Shupak et al. (2007)*	Comparison of changes in TEOAEs, and DPOAEs with audiometric thresholds during the first 2 years of occupational noise exposure	Ship engine room recruits	G PV	135 (M)	42 (M)	-	42 (M)	18-20[d]	-	-	-	2 yrs	Yes	TE DP

[a] This number includes the control group; [b] Female participants were excluded to avoid gender effects; [c] Number male/female not mentioned; [d] Age only reported for baseline group; [e] This number is for the study group; [f] Time between measurements in individual analysis may >1 year; [g] Number of male/female given after excluding four subjects; [h] This number is not mentioned in the article, but copied from the original study by the same authors.

Most studies report a baseline measurement and one follow-up although there were also studies that measured hearing status repeatedly during the duration of the study, ranging from six months for impulse noise to ten years for continuous noise (Duvdevany & Furst, 2007; Lapsley Miller et al., 2004; Seixas et al., 2012). The period between baseline and final measurement ranged from several weeks in the case of high-level impulsive noise to ten years in the case of exposure to more continuous industrial noise. There could be large – and unknown – differences in the actual sound levels to which subjects were exposed. These differences could be caused by the following confounders: nature and level of the noise sources, duration between initial and final measurement and the use and quality of hearing protective devices.

Quality assessment

Risk of bias was assessed for all studies included. The range of items met on the modified Downs & Black scale was 9–14 with a mean of 11.8 (SD 1.3). See Appendix B for a more detailed explanation of the scored items and the questions written in full. The scored items per study are found in Appendix C.

In the reporting section (items 1–8, 9 points maximum), the scores of the individual articles ranged from 5–9, (mean 7.13, SD 1.30). The objectives are reported in Table 4-1. One study did not mention clear goals, aims or hypotheses (Marshall et al., 2009). It was deduced from the results and similar studies by the same authors. Four studies mentioned their outcome measures for the first time in the results section of their article while they were not described in the introduction or methods (Lapsley Miller et al., 2004; Moukos et al., 2014; Murray et al., 1998; Shupak et al., 2007). Two did not clearly mention the noise exposure in terms of (estimated) levels and/ or durations (Helleman et al., 2010; Helleman & Dreschler, 2012). Six studies obtained two points for describing the confounders (Lapsley Miller et al., 2004, 2006; Marshall et al., 2009; Seixas et al., 2005, 2012; Shupak et al., 2007), seven studies partially addressed confounders, and obtained one point (Duvdevany & Furst, 2007; Helleman et al., 2010; Helleman & Dreschler, 2012; Job et al., 2009; Konopka et al., 2005; Moukos et al., 2014; Murray et al., 1998).

With respect to reporting on variability in the data, studies have used SE, SD and/ or CI with different *p*values to report their data. This did not allow for a comparison. Two studies did not address the variability in the data (Job et al., 2009; Konopka et al., 2005). Eight studies fulfilled the criterion for reporting the statistics appropriately (Duvdevany & Furst, 2007; Helleman et al., 2010; Helleman & Dreschler, 2012; Lapsley Miller et al., 2004, 2006; Marshall et al., 2009; Shupak et al., 2007).

Table 4-II: Set-up parameters for pure-tone audiometry (PTA) and otoacoustic emissions (OAE). All studies were conducted with frequency ratio of f_2/f_1=1.2. [Stim int = stimulus, intensity stab=stability, oct=octave, SNR=signal-to-noise-ratio, NFS=noise floor substitution, L=linear, NL=non-linear, L_1=level of first primary, L_2=level of second primary. NM=not mentioned; DPOAE=distortion product OAE; TEOAE=transiently evoked OAE] .

Test parameters		**PTA**	**TEOAE**					**DPOAE**			
		Freq range (kHz)	*Inclusion*	*Freq range, (kHz)*	*Stim int (dB peSPL)*	*Mode*	*No of avg*	*Inclusion*	*Freq range f_2 (kHz)*	*Freq res (total)*	*L_1/ L_2 (dB SPL)*
A	*Duvdevany & Furst (2007)*	0.25, 0.5, 1, 2, 3, 4, 6, 8	N.M.	overall	84	NL	260	-	-	-	-
B	*Konopka et al. (2005*	0.25-12	SNR≥0	1-5 (1 kHz)	80	NL	260	-	-	-	-
J	*Murray et al. (1998)*	0.5, 1, 1.5, 2, 3, 4, 6, 8	stab ≥80%	overall/ wave repro	80	NL	260	-	-	-	-
CD	*Helleman et al. (2010;2012)*	0.5, 1, 2, 3, 4, 6, 8	SNR≥0 NFS	1-4 (1/2 oct)	80	NL	280	SNR≥0[a] NFS	0.8-8.0	1/8 oct (27)	75/70
G	*Lapsley Miller et al. (2006)*	0.5, 1, 2, 3, 4, 6	SNR≥0 NFS	0.7-4 (1/2 oct)	74	NL	260	SNR≥0[a] NFS	1.8-4.5	1/6 oct (9)	57/ 45, 59/ 50, 61/ 55, and 65/45
H	*Lapsley Miller et al. (2004)*	0.5, 1, 2, 3, 4, 6, 8	SNR≥0 NFS	0.7-4 (1/2 oct)	L: 80, 74, 68, 62 NL: 80, 74	L NL[b]	540	SNR≥0[a]	1.0-8.0	31 freq spaced evenly in log2 steps	70/60, 65/55, 65/45, 60/50, 60/40, 55/45, and 55/35

4

Table 4-II: Continued.

Test parameters		PTA	TEOAE					DPOAE			
		Freq range (kHz)	*Inclusion*	*Freq range, (kHz)*	*Stim int (dB peSPL)*	*Mode*	*No of avg*	*Inclusion*	*Freq range f_2 (kHz)*	*Freq res (total)*	*L_1/ L_2 (dB SPL)*
C	*Marshall et al. (2009)*	0.5, 1, 2, 3, 4, 6	SNR≥0 NFS	0.7-4 (1/2 oct)	74	NL	260	SNR≥0[a] NFS	1.8 -4.5	1/6 oct (9)	57/ 45, 59/ 50, 61/ 55, and 65/45
M	*Shupak et al. (2007)*	0.5, 1, 2, 3, 4, 6, 8	SNR≥6[d]	1-4 (1/2 oct)	80	N.M.	256	SNR≥6[d]	0.9 - 12.0	1/3 oct (12)	65/55
F	*Job et al. (2009)*	0.25, 0.5, 1, 2, 3, 4, 8	-	-	-	-	-	SNR≥2	0.6-8.9	1/8 oct (32)	65/55
I	*Moukos et al. (2014)*	0.25, 0.5, 1, 2, 3, 4, 6, 8	-	-	-	-	-	SNR≥0[a] NFS	1.0-6.0	1/2 oct (7)	65/55
K	*Seixas et al. (2012)*	0.5, 1, 2, 3, 4, 6, 8	-	-	-	-	-	No criterion[c]	2.0-8.0	1/2 oct (5)	65/55
L	*Seixas et al. (2005)*	0.5, 1, 2, 3, 4, 6, 8	-	-	-	-	-	No criterion	1,0-10.0	21 log spaced f2 freq	65/55

[a] relative to 2 standard deviations of the noise floor estimate, [b] NL mode not analyzed, [c] only in sub analysis SNR≥6, [d] for the baseline measurement only

Although the source from which subjects were drawn was usually quite clear (e.g., soldiers, construction workers etc.), only two studies were explicit about the way subjects within this group were recruited (Lapsley Miller et al., 2004; Seixas et al., 2005). The range for the scores on the internal validity (four items) was 3–5.

Six studies reported explicitly how the complexity of left and right ears and the repeated nature of frequencies were taken into account, resulting in two points for question 12 (Duvdevany & Furst, 2007; Helleman et al., 2010; Helleman & Dreschler, 2012; Konopka et al., 2005; Lapsley Miller et al., 2004; Moukos et al., 2014). Six studies did not report on the loss to follow-up (Duvdevany & Furst, 2007; Konopka et al., 2005; Lapsley Miller et al., 2004; Moukos et al., 2014; Seixas et al., 2012; Shupak et al., 2007).

Test characteristics

Table 4-II provides information on the characteristics of the stimuli and measurement protocols for the audiometry and OAE measurements. It can be seen that there are differences in frequency span, resolution and properties of the OAE-stimuli such as the used stimulation level.

An important difference between studies is the required SNR for an emission [either transiently evoked (TE) or distortion product (DP)] to be entered into the study. Only the study by Duvdevany & Furst (2007) did not mention whether or not data points, ears or subjects, were excluded based on SNR. Seixas and co-authors explicitly mentioned that they did not impose an inclusion criterion (Seixas et al., 2005, 2012). In contrast, Shupak et al. (2007) only included data points with an SNR ≥6 and Job et al. (2009) required SNR ≥ 2. The other studies required SNR≥0 for an emission at a certain frequency to be entered in the data set (Helleman et al., 2010; Helleman & Dreschler, 2012; Konopka et al., 2005; Lapsley Miller et al., 2006; Marshall et al., 2009). With one exception, so-called noise floor substitution was applied in these studies (Helleman et al., 2010; Helleman & Dreschler, 2012; Lapsley Miller et al., 2004, 2006; Marshall et al., 2009). This approach allows more data to be used when initially present emissions drop below the noise floor in follow-up measurements. Such substitution possibly underestimated the actual effects, see for a more detailed description one of above-mentioned original studies (Helleman et al., 2010; Helleman & Dreschler, 2012; Lapsley Miller et al., 2004, 2006; Marshall et al., 2009).

Outcomes

The results were first analyzed for the group-averaged data and compared with the control groups if available. The second step was to look at individual shifts in audiometry and OAE. The third step focused on the possibility of predicting a shift in threshold from OAE-parameters or the possibility of identifying vulnerable subjects. Finally, the general conclusions on the use and role for OAE from the studies were compared.

Outcomes: comparison of group changes.

Seven studies reported significant changes in audiometry and OAE (TE and/or DP) over time (Duvdevany & Furst, 2007; Helleman et al., 2010; Helleman & Dreschler, 2012; Job et al., 2009; Lapsley Miller et al., 2004; Moukos et al., 2014; Seixas et al., 2012; Shupak et al., 2007). The study on the musicians did not find any significant effect on either audiometry or TEOAE (Murray et al., 1998). The three remaining studies did not observe a significant change from baseline for audiometric thresholds but did find a significant change for both TEOAE and DPOAE (Lapsley Miller et al., 2006; Marshall et al., 2009) and for DPOAE alone (Seixas et al., 2005). For these studies, the frequency range for the TEOAE-effects was 1–3 kHz or 1–4 kHz and the effect size approximately 1 dB SPL (Lapsley Miller et al., 2006; Marshall et al., 2009). For the DPOAE, an effect size of 1.5 dB SPL was found at 2–4 kHz (Lapsley Miller et al., 2006) and an effect size of 0.8 dB SPL at 2.5–3.6kHz (Marshall et al., 2009).

Seixas and co-authors found small but significant decrements (0.5 dB SPL) per year for a group of young construction apprentices, with a significant difference in response over time compared to controls in the 3–4 kHz region (Seixas et al., 2005). In the follow-up study by the same group, the construction workers were measured after ten years and both audiometry and DPOAE were significantly deteriorated (Seixas et al., 2012). The long-term changes were very small for both workers and controls and showed a similar time course. But in the region <6 kHz for audiometry and ≥3 kHz for DPOAE, the changes for the construction workers were larger than for the controls. It was computed that per 10 dBA increase in exposure level, the hearing thresholds increased with 2–3 dB HL and the DPOAE with 1 dB SPL during these ten years.

In the nine year follow-up of Moukos et al. (2014), the changes in audiometry took place between 4–6 kHz, while the largest effects in DPOAE were found between 3–5 kHz. This was the same DPOAE region as in the study with pilots where the audiometric changes took place at and >3 kHz (Job et al., 2009). Shupak et al. (2007) found significant DPOAE changes in the 4–6 kHz region that were accompanied by TEOAE changes between 2–4 kHz and audiometric changes between 4–6 kHz.

Both TEOAE and audiometry changed significantly in two studies on soldiers exposed to impulse noise, but there were differences in the frequency region where the effects took place: Duvdevany & Furst (2007) observed a decrease in wideband TEOAE at a group level accompanied by threshold increases at 1 kHz and higher frequencies but without a significant correlation for individual changes. Hearing thresholds of the soldiers in the study by Konopka et al. increased in the extended high-frequency range (≥10 kHz) parallel to a decrease in TEOAE level at 2–4 kHz, while these effects were not significant in the control group (Konopka et al., 2005). Helleman et al. (Helleman et al., 2010) and Lapsley Miller et al. (Lapsley Miller et al., 2004) both observed that TEOAE showed a small decrease and in a broader frequency range than audiometry and DPOAE but this effect was either not significant or also occurred in the control group. Helleman et al. (2010) found significant changes for audiometry in the 6–8 kHz region, and for 1–2 kHz and 4–6 kHz in DPOAE. They also reported an increase in emission strength around 3 kHz for the DPOAE. Lapsley Miller et al. (2004) found a significant change of 2.0 dB HL in audiometric thresholds around 3–4 kHz, accompanied by an overall decrease in DPAOE-emission level of 2.3 dB SPL between 1–3 kHz.

Figure 4.2 is a simplified representation of the above-mentioned changes. The group-averaged changes (shifts) from baseline threshold were compared with the changes (shifts) from baseline emissions level with extra information regarding duration of exposure and the number of contributing ears.

Some concordance in the effects in OAE and audiometry can be seen. With one exception, all hearing thresholds increase and emission levels are generally lower in the follow-up measurement (Lapsley Miller et al., 2006). Both effects imply a deterioration in hearing, which can be expected in a noise-exposed, ageing population. However, the effects are rather small, amounting to 1–2 dB in audiometry up to three years and 4–9 dB HL for longer durations.

Moukos et al. (2014) report the largest average change in audiometry from baseline with almost 10 dB HL after nine years in the tobacco industry versus almost 5 dB HL in the ten year study by Seixas et al. (2012). In contrast, the changes in DPOAE were larger for the younger construction workers in the study from Seixas and colleagues when compared with the tobacco workers from Moukos et al. Age, initial hearing status, compliance with the use of hearing protection devices and exposure levels might have affected the size of the observed changes in hearing. Changes in TEAOE have been followed for at most three years, amounting to a maximum shift from baseline of 2 dB SPL in the highest frequency band. DPOAE in the same time frame shift on average 2 dB SPL and up to 4–5 dB SPL for longer durations of exposure.

Outcomes: Individual shifts.

Six studies investigated individual shifts in audiometry and OAE. Four of these looked at both TEOAE and DPOAE (Helleman & Dreschler, 2012; Lapsley Miller et al., 2004, 2006; Marshall et al., 2009), one only at DPOAE (Moukos et al., 2014) and one at TEOAE (Murray et al., 1998). The first step in such an approach is to determine which change in audiometric thresholds and emission level qualifies as a real shift, the second step is to compare the number of threshold shifts with emission shifts and look for agreement. All different approaches and numerical values to define a significant shift are expressed in Table 4-III.

The continuous data of change in emission amplitude or change in hearing threshold level is transferred in a dichotomous "yes" or "no", discarding information on the spread of the data. Such a fence criterion can be obtained by adopting established criteria from literature or standards, creating a new criterion, or using a statistical criterion based on test–retest measurements. The majority of studies used the term significant threshold shift (STS) or significant emission shift (SES) and these terms were adopted in this review.

Table 4-III shows that the significant shifts range from 5–25 dB HL for audiometry, 3.2–7.6 dB SPL for the TEOAE and from 4.6–12.4 dB SPL for the DPOAE. It should be noted that some studies have used an average of several frequencies where others use a shift at a single frequency. We refer to the original papers for more details on the used criterion, as the underlying frequencies and the reasons behind each choice.

The next step is to compare the number of shifts in audiometry (STS) with shifts in OAE (SES) and look at congruency between cases. The first general observation, regardless of the chosen criterion was that the number of significant shifts was low when compared to the total number of ears. This implies that for the majority of ears, the difference from baseline was not large enough to qualify as a significant individual shift, even though most group results were significant.

Significant shifts may occur in both directions, but the main focus was on worsening of hearing sensitivity and thus on decrease of emission amplitude and increase in hearing threshold level.

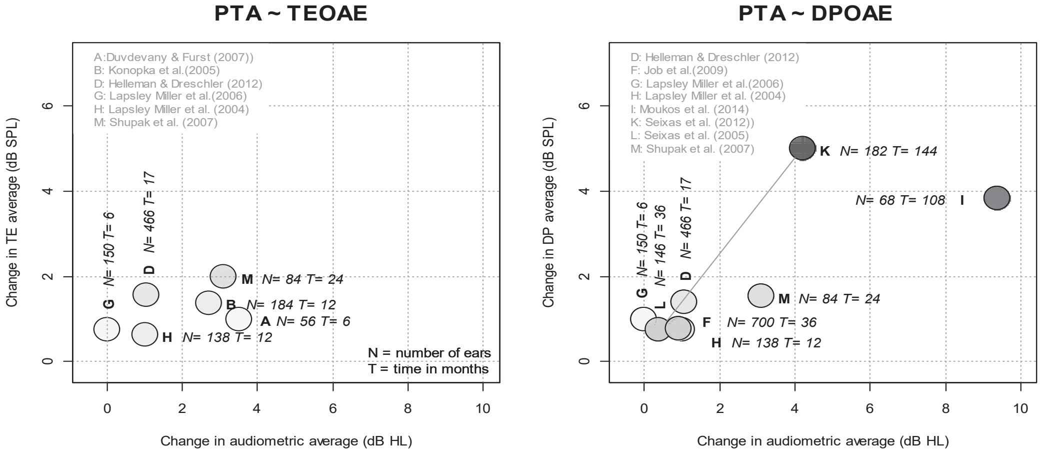


Figure 4.2: Shift in audiometry (dB HL) versus shift in emission level (dB SPL) for TEOAE in the 4 kHz band (left) and for the high frequency averaged DPOAE (right). Please note the ranges of the axes. The color of the circles corresponds to the duration, with darker colors representing longer durations. The dashed line represents the two studies by Seixas and colleagues going from 3 years follow-up (L) to 10 years (K).

The majority of studies reported the number of ears, not the number of subjects having significant shifts. Everything here is reported in number of ears, discarding information on left versus right ears. Based on the studies that mentioned both subjects and number of ears, there seemed to be more unilateral than bilateral shifts. Some studies reported the actual number of ears, others in percentages of the total valid data or percentage of ears with repeated measurements[3].

Table 4-IV shows the number of significant shifts for audiometry, TEOAE and DPOAE per study. The percentage of permanent STS ears (worsening of hearing threshold levels) ranged from 4.4–43% with differences in the reported frequency region. The minimal amount of shifts was 4.4% (N_{STS}=18) at the average of 2.3 and 4 kHz (Lapsley Miller et al., 2006), increasing to 7.4% at combinations between 2–4 kHz (N_{STS}=42) (Marshall et al., 2009), 8.7% at combinations between 2–6

3 *It was not always straightforward to deduce the numbers from percentages and vice versa, caused by the vagueness of the exact number of ears in that particular computation.*

kHz (N_{STS}=12) (Lapsley Miller et al., 2004), 9.5% at 6 kHz (N_{STS}=14) (Murray et al., 1998), 13.7 % (N_{STS}=64) at the average of 6 and 8 kHz (Helleman & Dreschler, 2012)and finally to the maximum percentage of shifts of 43% at both 4 and 8 kHz ($N_{STS=}$29) (Moukos et al., 2014). The latter amount deviates strongly from the other studies, while the used criterion is in the range of the others. The group-averaged threshold and emission shift of this study were also much larger than other studies and significantly larger than in the control group. Factors that could have played a role in this difference are the longer duration and the potential presence of temporary threshold shifts. The workers were measured during a workday, but after a noise-free period of at least one hour. Such an effect could have been also present in the baseline measurement making it impossible to estimate the effect. This argumentation is also valid for the study by Helleman and co-authors where the measurements were performed in a similar manner (2010; 2012).

A more valid approach to separate temporary from permanent shifts is to confirm the STS by remeasuring the audiogram after at least a few noise-free days as was done by several other authors (Lapsley Miller et al., 2004, 2006; Marshall et al., 2009). Although audiometric shifts in the opposite directions (decrease in hearing threshold level) were mentioned to occur incidentally, they were not investigated any further.

The total number of SES could be obtained in five of the above-mentioned studies, three on both TEOAE and DPOAE (Helleman & Dreschler, 2012; Lapsley Miller et al., 2006; Marshall et al., 2009), one on TEOAE only (Murray et al., 1998), and one on DPOAE only (Moukos et al., 2014). One study only mentioned the occurrence of SES in case of an STS (Lapsley Miller et al., 2004). The numbers are given in Table 4-IV. In case of the significant emission shifts (decrease) for TEOAE, the range was 6.8–14%. The minimal amount of shifts was 6.8% ($N_{SES,TE}$=10) (Murray et al., 1998), increasing to 8.6% ($N_{SES,TE}$=49) (Marshall et al., 2009), 12% ($N_{SES,TE}$=41) (Lapsley Miller et al., 2006) and is maximal at 14% ($N_{SES,TE}$=62) (Helleman & Dreschler, 2012). Two studies also observed significant increases in TEOAE-emission level, with 10% ($N_{SES,TE+}$=47) (Helleman & Dreschler, 2012) and 24% ($N_{SES,TE+}$=35) significant shifts (Murray et al., 1998). In another study, some increases in emission level were seen in the 18 STS cases, but they were considered improvements and therefore not investigated any further (Lapsley Miller et al., 2006).

For the DPOAE, the percentage of significant emission shifts ranged from 4–52% for decreasing emission levels. The minimal amount of shifts was 4% at 1.5 kHz ($N_{SES,DP}$=20) (Helleman & Dreschler, 2012), increasing to 7.7% between 2.5 and 4 kHz ($N_{SES,DP}$=44) (Marshall et al., 2009), 12% at 2.5 kHz($N_{SES,DP}$=41) (Lapsley Miller et al., 2006) and the largest number of shifts amounted to 52% at 5 kHz ($N_{SES,DP}$=34) (Moukos et al., 2014). Again significant increases in emission level were found: 9% shifts for the DPOAE level at 3 kHz ($N_{SES+,DP}$=41) (Helleman & Dreschler, 2012). In other studies, significant individual increases in DPOAE were mentioned but not investigated because they were considered as random error (Moukos et al., 2014) or as improvements and only mentioned for STS ears (Lapsley Miller et al., 2006).

For the majority of studies, the numbers of significant shifts and percentages with respect to the total number of ears were small. A possible explanation for low numbers of shifts can be found in emission data that were excluded based on a SNR criterion. Cases with emission levels dropping below this criterion would be excluded, leading to an underestimation of the actual number. This consideration was put forward by several authors and the previously mentioned noise floor substitution can partially resolve this (Helleman et al., 2010; Helleman & Dreschler, 2012; Lapsley Miller et al., 2004, 2006; Marshall et al., 2009). But still, there might be cases were the substitution could not be applied since the emissions were low in both measurements. Such cases were not entered in the analysis and recorded as missing data.

Overall there were only a few cases that had both a STS and a SES. The final column of Table 4-IV expresses the maximal agreement in the number of ears having both a shift in audiometry and OAE. The percentages of agreement are relatively small, ranging from 1–19% of the total number of ears. The study from Lapsley Miller et al. (2004) only reported the number of SES cases for the 12 ears (N_{STS}=12) that also had an STS. Several studies mentioned that no association with SES and STS status was found, with all combinations occurring (Helleman & Dreschler, 2012; Marshall et al., 2009; Moukos et al., 2014; Murray et al., 1998). This was emphasized by two studies providing a scatterplot of change in TEOAE amplitude (Helleman & Dreschler, 2012) or TEOAE wave reproducibility (waverepro) (Murray et al., 1998) versus audiometric changes. These graphs showed the lack of agreement in SES and STS and the spread of the data[4].

4 *Counting the cases in the scatterplot lead to other numbers than were reported in the text, the numbers from the discussion in the text are adopted here.*

Table 4-III Significant threshold shifts (STS) and significant emissions shift (SES), their size and origin. [PTA=pure-tone audiometry; DPOAE=distortion product otoacoustic emissions; TEOAE=transiently evoked otoacoustic emissions; NM=not mentioned; CI=confidence interval; SEM=standard error of measurement, ΔSEM=standard error of measurement of the difference].

Significant shift		**PTA: STS**		**TEOAE: SES**		**DPOAE: SES**	
		Size (dB HL)	*Rationale*	*Size (dB SPL)*	*Rationale*	*Size (dB SPL)*	*Rationale*
C	*Helleman & Dreschler (2012)*	>14.5	Δ*SEM*; 95% CI 60 subj (111 ears, test-retest)	4.0	Δ*SEM*; 95% CI; 60 subj (111 ears, test-retest)	7.0-12.4[a]	Δ*SEM*; 95% CI;60 subj (94-109 ears , test-retest)
G	*Lapsley Miller et al. (2006)*	> 8.3-25[a]	Δ*SEM*; 98% CI; 28 subj (56 ears, control)	3.2-7.5[a]	Δ*SEM*; 98% CI; 28 subj (35-46 ears, control)	4.6-8.5[a]	Δ*SEM*; 98% CI; 28 subj (33-43 ears, control)
H	*Lapsley Miller et al. (2004)*	>8.3-25[a]	Avg+3* *SEM;* 53 subj (106 ears, control)	3.5-7.6[a]	Avg+3**SEM;* 53 subj (83-103 ears, control)	5.0-7.2[a]	Avg+3* *SEM*; 53 subj (93-106 ears, control)
C	*Marshall et al. (2009)*	>8.3-15[a]	Δ*SEM*; 98% CI; 32 subj (64 ears, control)	4.0-6.1[a]	Δ*SEM*; 98% CI; 32 subj (36-54 ears, control)	6.0-8.7[a]	Δ*SEM*; 98% CI; 32 subj (36-54 ears, control)
I	*Moukos et al. (2014)*	≥ 15	NIOSH (1998)	-	-	5.8-12.4[a]	Avg+3* *SEM*; 33 subj (58-65 ears , control)
J	*Murray et al. (1998)*	≥ 15	Aust./NZS1269 (1998)	wave repro >28%	From unpublished study	-	-
A	*Duvdevany & Furst (2007*	≥ 10	N.M	-	-	-	-
F	*Job et al. (2009)*	> 5	All freq ≤ 10dB HL change to at least one freq ≥ 15	-	-	-	-
M	*Shupak et al. (2007)*	≥ 10	N.M.	-	-	-	-

[a] Frequency dependent.

Table 4-IV: Numbers of significant threshold shifts (STS) and significant emissions shift (SES) in number of ears and percentage, percentage of maximal agreement between STS and SES cases. - Indicates a decrease in emission level, + indicates an increase in emission. If not explicitly stated otherwise, the numbers in the table correspond to a decrease in emission level.

Significant shift		PTA:STS		TEOAE: SES		DPOAE: SES		Agreement STS/SES_{TE}		Agreement STS/SES_{DP}	
		N (ears)	%	*N (ears)*	%	*N(ears)*	%	*N(ears)*	%	*N(ears)*	%
D	*Helleman & Dreschler (2012)*	64	13.7	SES^- 62 SES^+ 47	14 10	SES^- 20 SES^+ 41	SES^- 4.4 SES^+ 9	SES^- 3 SES^+ 8		SES^- 2 SES^+ 10[a]	0.4 2.1[a]
G	*Lapsley Miller et al. (2006)*	18	4.4	41	12	41	12	-[b]	-[b]	-[b]	-[b]
H	*Lapsley Miller et al. (2004)*	12	8.7	-[c]	-[c]	-[c]	-[c]	4	2.9[d]	2	1.5[d]
C	*Marshall et al. (2009)*	42	7.4	49	8.6	42[e]	7,4[e]	12	2.1	7[e]	1.2[e]
I	*Moukos et al. (2014)*	29	43	-	-	34	52	-	-	13	19.6
J	*Murray et al. (1998)*	14	9.5	SES^- 10 SES^+ 35	6.8 24	-	-	1 -[f]	0.6 -[f]	-	-

[a] For the combination of STS and SES^+ at 3kHz, SES^- at 1.5 kHz, [b] unknown number/ percentage: only mentioned that 31% of STS ears had SES_{TE} either increase or decline, and 50% had SES_{DP} for any of the measured frequencies, either increase or decline, [c] total number of SESs not reported, only reported for ears with a permanent STS, [d] percentage was not given in original text with different number of ears per analyses, computed for this table based on percentage STSs column, [e] for another DP setting N_{SES} = 44 with an accompanying 6 STS/SES cases, [f] Number of ears with SES^+ and STS not mentioned in original text.

4

To summarize these findings: despite differences in criteria and frequency region, the actual numbers exhibiting shifts in both OAE and audiometry were very small, calling for caution and reluctance in the interpretation of the results. This was also emphasized by Marshall and co-authors (2009). From the two papers providing a scatterplot, it can be seen that the number of ears exhibiting a shift might alter with a different fence criterion. These graphs also show the evident lack of a relationship between changes in OAE and audiometry both on a continuous scale and when classified as SES and STS. The scatterplots also show that there were increases in emission level and decreases in hearing threshold level. When explicitly mentioned (Helleman & Dreschler, 2012; Murray et al., 1998), these changes in OAE were in the same order of magnitude, but nevertheless they were regarded as random variation or as outliers in other studies (Lapsley Miller et al., 2006; Moukos et al., 2014).

Outcomes: predictive value and vulnerability

Six studies investigated a possible role for OAE in predicting future hearing loss as measured in audiometry. Table 4-III expresses the size of change in audiometric threshold that was classified as a shift. Five approaches were based on low or absent initial OAE levels predicting a change in audiometric threshold. This could be done retrospectively (possible vulnerability) or prospectively (predictive value).

Another approach was chosen by Duvdevany & Furst (2007). They tested ear vulnerability retrospectively among soldiers with TEOAE. The group, all initial hearing thresholds ≤20 dB HL, was split into two subgroups: having threshold changes at any frequency ≤5 dB (no hearing loss, NHL) or ≥10 dB (slight hearing loss SHL). The authors found that the SHL group had less variation in TEOAE values in time and could relate this to having "medium" emission strength. This led the authors to conclude that subjects having normal audiograms in combination with either relatively strong or low emission strength had more "tough ears" than ears having medium emission strength.

Murray and co-authors looked if TEOAE results are able to provide a warning for potential hearing loss in an earlier phase than pure-tone audiometry (1998). They predefined a target group (based on another control group) with hearing levels within normal limits (<25 dB HL) and with low-level emission, defined as an initial waverepro <35%. There was no evidence for this parameter to be of predictive value since there were about as many cases exhibiting shifts in audiometry without changes in waverepro or without low initial waverepro. They concluded that further investigation was required.

Lapsley Miller et al. noted that in the 16–18 ears exhibiting STS, there was a relatively high amount of OAE data either missing or already low at baseline (2006). They looked further into this matter by examining positive predictive values of absent or low-level emissions as a predictor for the occurrence of an STS, and found that for ears with lower emissions, there was an increased risk for developing PTS of 17–20% with TEOAE, 14–17% for DPOAE. They concluded that OAE might be a diagnostic predictor for NIHL, showing damage to the inner ear before hearing loss is present in the audiogram (Lapsley Miller et al., 2006).

In the next study by this group, it was investigated whether low level or absent emissions increased the chance of developing a STS for subjects exposed to impulse noise (Marshall et al., 2009). Per type of OAE there were 17–21 ears with a STS compared with 217–263 ears without. If both ears from one subject were measured, the worst ear (hypothetically the most susceptible) was chosen for the computation of the likelihood ratios. The increased risk compared to the baseline risk of getting a STS maximized to nine fold depending on the condition. The authors concluded that OAE are predictive of incipient NIHL but, in view of the small numbers in the study, the results are indicative only (Marshall et al., 2009).

This was in contrast to the conclusions by Shupak et al. who reported that lower (minus 2 SD below average) initial OAE are inappropriate for predicting future elevations in pure-tone thresholds (Shupak et al., 2007). When they used another, absolute criterion on the same data [i.e. adopted from Prieve et al. (1993) and defined as signal repeatability <50%, or SNR <3 dB, or absolute emission level <5 dB SPL] OAE could label ears as either resilient or vulnerable. But this came at the cost of a high false-positive rate and thus questions the practicality of such a tool (Shupak et al., 2007).

Job et al. (2009) agreed with the group of Lapsley Miller et al., when they tried to identify vulnerable ears by creating an index of abnormality (the so-called IaDPOAE). Their goal was to predict ears shifting from normal hearing (≤10 dB HL) to having an increased threshold (>25 dB HL). The index was based on normative data from a control group, with a high abnormality corresponding to a low DPOAE amplitude. They concluded that ears with an index of abnormality ≥15% had larger odds of changing from the normal hearing group to the group having one threshold >25 dB HL. They found a significant but low (0.27) correlation between initial IaDPOAE and final hearing thresholds. These findings led them to conclude that DPOAE could be a biomarker of vulnerability with continuing noise exposure (Job et al., 2009).

Finally, although not explicitly set out to investigate any predictive value, Helleman & Dreschler (2012) tried to verify these findings by looking at the absence of emissions in the STS ears but the odds ratio was not significant (i.e. 5 ears missing OAE-data with a STS, versus 20 missing OAE data without a STS).

DISCUSSION

Strengths and weaknesses

As far as the authors know, this systematic review is the first attempt to systematically combine results from several observational studies on longitudinal changes in hearing as measured with OAE and audiometry. Only long-term effects on emission amplitudes were investigated and compared, whereas short-term effects and (contralateral) acoustical suppression were not examined. A separate review could be conducted on studies investigating short-term effects; more than hundred studies were found and could be examined further at full-text level. When also looking at (contralateral) acoustic suppression of OAE, even more studies are available for analysis.

In the current situation, the heterogeneity in the long-term studies did not allow for a meta-analysis to compare changes or compare statements on enhanced probabilities. The first order attempt to combine changes in audiometry and OAE could be done by a simplification of the actual data. Frequency information, initial hearing status and for example hearing at time-points between baseline and final measurement were omitted. The constructed graph illustrates that the group-averaged changes were only small for all individual studies.

Potential biases in the review process

Some of the included studies aimed to explore the relationship between OAE and audiometry whereas others explicitly set out to investigate a form of predictive value. Publication bias is a risk in any field in the hypothesis-generation stage, especially when the a-priori possibility that the hypothesis is true, is small and/or the statistical power is low (Ioannidis, 2005). Many relationships that were found are based on small numbers and would require further investigation in larger studies to be confirmed.

Another point for discussion is the inclusion of two articles by two of the authors from this review (i.e, HH and WD). Because of the limited amount of studies available, it was felt that omitting these studies would be less favorable than a potentially less objective assessment of the quality of own work. No studies were excluded based on the quality and the group-averaged result from these studies lies amidst the cluster of other studies, so no bias was expected.

Justification for exclusion

A limitation in this study is the exclusion of some papers that could not be obtained. This amount was minimized by several attempts to contact the corresponding author through email and ResearchGate. Nevertheless, there were three longitudinal studies in Polish by the same author that were not available. For two of these, details in the abstract were identical to a paper by the same author that was included (Konopka et al., 2005). Consequently, no bias from omitting these papers was expected. The third unavailable Polish paper by the same author, concerned effect of jet engine noise on technical staff, impulse noise for soldiers and a control group (Konopka et al., 2014). The conclusion from the abstract mentions that there were more changes in TEOAE after one year than in audiometry. These effects could not be assessed numerically and therefore could not be combined with the results in other studies. Conference papers or grey data were not explicitly searched for in this review.

Assessment of quality of included studies

The quality as assessed by the Black & Downs checklist differed across studies but no studies were excluded based on this assessment. There were considerable differences in the domains of reporting data and analysis of repeated measurements. But comparison of raw data was considered to be important despite quality issues in the above-mentioned items. In retrospect, more stringent quality criteria for reporting and analyzing could have been applied to allow for more differentiation in the quality between the studies. As long as no studies were excluded based on quality, this would not have changed the overall conclusions but it might have given more weight to higher quality studies.

Consideration of alternative explanations for observed results

All studies were observational studies without control and exact knowledge over the actual noise exposure in terms of level, duration and the use of hearing protective devices. The prediction of a future threshold shift does not depend solely on initial hearing status, the (unknown) exposure is the actual cause for the damage that occurs. This makes it difficult to distinguish between ears that are inherently more sensitive and ears that have just been exposed more between measurements (by higher noise levels, longer duration of exposure or inconsistent use of hearing protection).

Generalization of the conclusions

The overarching conclusions of this review are that the studies are very different and heterogeneous in many aspect, and that the overall change in both methods are relatively small for the time frame that hearing was followed. Besides, all studies agreed that all combinations between emission shifts and threshold shifts occur, ie, shifts in emission without accompanying shift in audiometry, shifts in audiometry without accompanying shift in OAE, shifts in both (always lowest count) and finally, no shifts in both methods. In the studies included, the largest agreement was for the ears showing no shifts. Individual changes in both methods had no or very low correlations. So generally speaking, OAE and audiometry failed to identify the same subjects exhibiting significant shifts.

Hearing threshold level as measured in the pure-tone audiogram still is the reference standard. For the low number of threshold shifts that occurred, OAE could not be used to reliably detect a change in audiometry when based on a baseline test and one follow-up measurement. It cannot be ruled out that with a higher prevalence of shifts, OAE could be more able to identify them, for example after exposure to higher noise levels for a longer time. Whether an emission shift precedes the occurrence of a threshold shift could not be answered based on the studies included in this review. This question can only be answered by studies with at least three measurements available for analysis.

Several papers reported that lower or absent emissions indicated a higher risk for future threshold shifts (Job et al., 2009; Lapsley Miller et al., 2004; Marshall et al., 2009; Shupak et al., 2007). Different statistical parameters have been used to express this increased probability. Methods using the odds ratio, positive predictive values and likelihood ratios were based on the presence of a shift in a certain group versus another group. The chosen criteria for size and definition of a shift have a large impact on these statistics and thus on the proposed relationships. There were also many cases with low-level or absent emissions that did not exhibit audiometric shifts, thus creating many false positives.

Besides this dependency of the sensitivity for the chosen criteria and the false positives, some studies also presented other outcomes: Murray et al. (1998) did not find evidence for a predictive value, and Duvdevany & Furst (2007) reported that having either high or low TEOAE at baseline was an indicator for resilient ears. The latter reported that the ears with “medium” strength emissions were more at risk and that resilient ears could also be ears that had lower emissions at the start. So there was no consensus on the hypothesis that the ears with lower emissions at the start are more sensitive to noise-induced audiometric shifts.

Recommendation for further research

It would have been desirable if this review could end with clear, unequivocal recommendations for future research. The heterogeneity mentioned earlier does unfortunately not allow for such statements. The first goal should be to reduce the differences in setup between studies and resolve some methodological issues. General consensus in the field is needed concerning stimulus parameters and measurement paradigms. A simple recommendation is the use of tympanometry to avoid changes caused by middle-ear pathology. Care should be taken to avoid TTS by introducing a suitably long noise-free period between latest exposure and measurements. Another recommendation is to use the emission strength and not signal-to-noise ratio when working with emissions. The signal-to-noise ratio is a useful measure of quality but the outcome itself is dependent upon measurement conditions whereas the emission amplitude itself reflects properties of the cochlea.

Next, we recommend more complete reports of raw data to allow the reader to make an assessment of the data for him or herself. We call for a more uniform approach in reporting emission and audiometric data by presenting the raw data with a measure of spread, i.e. standard deviation per frequency in a graph or table. Noise levels should be included as well to allow the reader to assess the measurement conditions. Correct statistics should take into account (some of) the dependency between frequencies and ears. Another example of required information is data on the exclusions: how many data points/ ears / subjects have been omitted for emissions, and for audiometry? How does this potentially affect the conclusions?

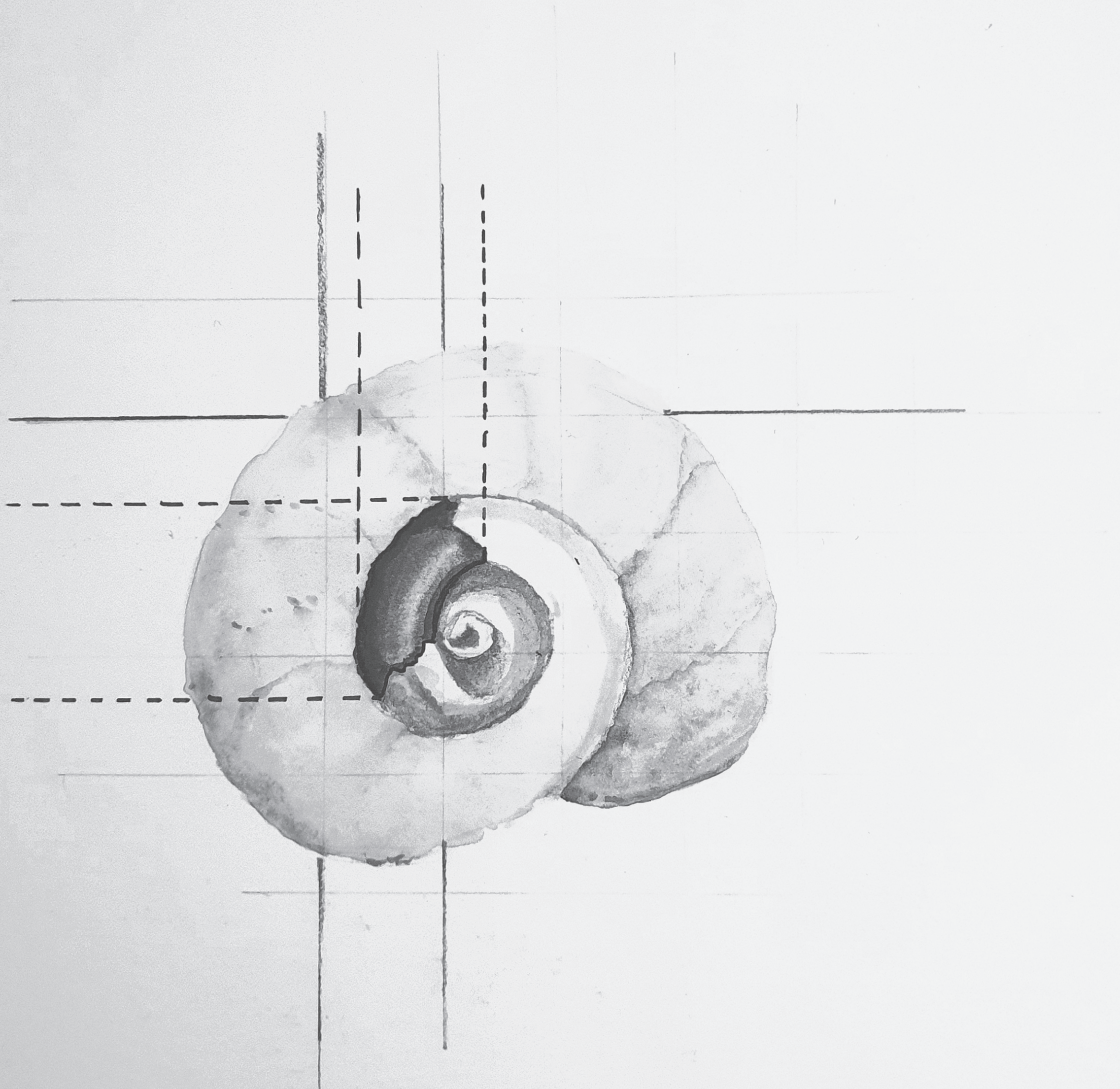
It is clear that several approaches were used to define an individual shift. When the underlying data is not presented, the effect of the size of the criterion cannot be assessed by the reader. Scatterplots may provide information on a continuous scale, whilst fence criteria are dichotomous. Agreement on the details how to define a shift, analysis for the effect the chosen fence, analysis on a continuous scale or a simple, uniformly accepted definition of a shift could also allow better comparison between studies and the prevalence of shifts that occur.

Concluding remarks

The studies were very heterogeneous making it impossible to perform a meta-analysis on the available data. There were several factors responsible for this heterogeneity such as the studied populations in terms of number of subjects, age, initial hearing status, and noise exposure (level and duration). Properties of the OAE formed another factor responsible for differences between the studies (for example level of primaries, method of including emissions). Quality assessment by the Black & Downs checklist made it clear that there were differences in reporting style, clearness of the applied statistical methods, missing data and subgroup analyses. With respect to the analysis of the data, there was a large variation in the applied statistical methods and the definitions used for individual shifts used for subgroup analyses.

The first-order attempt used in this study to pool the data required overlooking many sources of confounders and differences between the results of the individual studies. When looking at the overall results, both audiometry and OAE showed small changes from baseline towards a deterioration in hearing. There were many methodological complications in the definition of individual shifts. Nevertheless, it is safe to state there was no clear congruent behavior in the combined occurrence of audiometric and otoacoustic shifts in any of the studies. Therefore, the results of this study support the conclusions of several authors that the main contribution of OAE is in addition to pure-tone audiometry rather than instead of.

When low numbers of ears with threshold shifts were investigated more closely, some studies suggested that specific abnormal OAE-properties possibly indicated a higher risk for future hearing loss. But the underlying statistical methods are sensitive for the criteria chosen and there was no agreement on whether `abnormal´ emission were low-level, absent or abnormally high. These discrepancies imply that there is neither consensus nor clear evidence that OAE are able to predict future noise-induced threshold shifts. It would be interesting to compare all the data from the studies from this review and analyze the effect of the reported criteria. This could give more insight if generalization of the conclusions is possible, especially with respect to the role of OAE as being predictive, being an inherent biomarker for noise-induced hearing loss or just a symptom of it.



CHAPTER 5

Short-term music-induced hearing loss after sound exposure to discotheque music: the effectiveness of a break in reducing temporary threshold shift

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ABSTRACT

Objective: To investigate the effect of a break in music exposure on temporary threshold shifts.

Design: A cross-over design where subjects exposed to dance music for either two hours consecutively or exposed to two hours of dance music, with a one-hour break in between. Outcome measure was the change in hearing threshold, measured in 1-dB steps at different timepoints after ending the music.

Sample: 18 Normal hearing subjects participated in this study.

Results: Changes in pure-tone threshold were observed in both conditions and were similar, regardless of the break. Threshold shifts could be averaged for 1, 2, and 4 kHz. The shift immediately after ending of the music was 1.7 dB for right ears, and 3.4 dB for left ears. The difference between left and right ears was significant. One hour after the exposure, right ears were recovered to baseline conditions whereas left ears showed a small but clinically irrelevant remaining shift of approximately 1 dB.

Conclusions: The advice to use chill-out zones is still valid, because this helps to reduce the duration to the exposure. This study does not provide evidence that a rest period gives an additional reduction of temporary threshold shifts.

INTRODUCTION

There is a growing awareness of the possibility of developing non-occupational noise-induced hearing loss after music exposure. In many countries there are campaigns to explain the risks involving exposure to leisure noise. Both exposure caused by personal music players (PMP) and caused by the high levels encountered at concerts or in night clubs have received a lot of attention in the recent years.

According to Smith et al. (2000) and Serra et al. (2005) average noise levels at night clubs and dance clubs have been measured to be in the range of 100 dB (A) or higher. With estimated attendance times of several hours per week (Serra et al. 2005, Jokitulppo & Bjork 2002) these doses can be considered to be harmful. Gunderson et al. (1997) found that levels around 90 dB (A) are typically encountered in the bar areas in night clubs with amplified music. Kelly et al. (2012) measured the noise exposure of employees in Irish nightclubs and found that the $L_{ex,8h}$ for an averaged nightclub employee was 92 dB (A). For disc-jockeys for example, the average exposure level was found to be 96.1 dB (A) in a study by Bray et al. (2004). This was the typical average level extrapolated to an eight hour work-session. The level for a typical set with an average duration of 113 minutes was 103.2 dB (A). For employees in a nightclub Gunderson et al. (1997) measured levels from 94.9 dB (A) to 106.7 dB (A). Potier et al (2009) measured equivalent sound levels in DJ's mixing booths and found values ranging from 92.3 to 102.1 dB (A) measured at 20 cm distance from the head. They measured one minute samples at different stages during a techno-set. Even the levels encountered in chill-out zones can potentially damage hearing. In 2004, the UK-based Royal National Institute for the Deaf (RNID , now Action on Hearing Loss) reported an average level of 92.3 dB (A) in chill-out areas in clubs in several British cities ('A Noise Hangover?', RNID, 2004).

A recent study by Beach et al. (2013) found that about 14% of young Australians (18-35 yrs old) are at risk of hearing damage from noise exposure by nightclubs, pubs/ bars, fitness classes, sports events, and concerts/ live music venues. They emphasize that clubs are a major source of high noise exposure for youngsters. This is also noted by other studies (Smith et al. 2000, Jokitulppo & Bjork 2002; Vogel et al. 2010). Beach et al. (2013) conclude that 'The time has come for nightclubs to display warnings about noise levels, and ensure free or low-cost earplugs available for employees and patrons'.

Such an initiative was started in 2011 in the Netherlands: there was a collaboration of clubs and music venues, called “Oorveilig” (i.e. “Ear Safe”) that aims to protect the hearing of its visitors by abiding a set of rules. This initiative is supported by the Nationale Hoorstichting (National Hearing Foundation) by facilitating education and equipment to keep the sound exposure within predetermined limits. One of the requirements is to create a zone where ‘ears can get some rest’, without specifying a permissible sound-pressure-level. Similar recommendations to use the chill-out zones and take regular breaks from the loudest areas are given in the UK in the campaign “Loud Music” (http://www.actiononhearingloss.org.uk/loud-music/5-ways-to-protect-your-hearing.aspx).

Vogel et al. (2009) report that experts on music-induced hearing loss in adolescents considered such chill-out zones as a relevant and important measure to reduce music exposure at a group level.

In February 2014 the above-mentioned initiative was implemented as an official agreement between the State Secretary for Health, Welfare and Sport and the organisation for the Dutch entertainment and music event industry. This agreement consists of three measures to ensure that visitors and employees can attend music venues safely and to raise awareness for the risk of developing Noise-Induced Hearing Loss (NIHL). There is an agreement about the limitation of the level at which the music is played, measurement of that level, and the availability of hearing protection devices. Employers are still legally bound by the EU directive for the protection of their employees at such events. (A preliminary text can be found at http://www.vnpf.nl/media/files/definitieve-versie-convenant.pdf).

Noise exposure is described most precisely by the actual sound pressure level reaching the eardrum. Occupational noise exposure in Europe is described in terms of the A-weighted free-field related sound pressure level normalized to eight hours: $L_{Aeq,8h}$ (Directive 200/10/EC, 2003). In Europe, Canada, and Australia, the limit for $L_{Aeq,8h}$ is set at 85 dB. This higher action level is to ensure that for daily averages of 85 dB (A) the employee is obliged to use some kind of hearing protective device and that the employer is obliged to ensure/ enforce the use of hearing protection. It should be noted that these limits do not guarantee that nobody will develop hearing loss. The amount of people that might develop noise-induced hearing loss even regarding the safety limits is at an economically ‘acceptable’ level. By defining hearing impairment as an average hearing threshold level at 1,2,3, and 4 kHz of 25 dB or more, ISO predicts 6%, NIOSH 8% as the excess risk for workers exposed to an daily average dose of 85 dB (A) in a working life of forty years (NIOSH, 1998; Prince et al. 1997).

In most countries, the exchange rate is based on the equal energy principle, i.e. a doubling in exposure time is accompanied by a 3 dB increase in dose. Or, vice versa, each 3dB increase in sound exposure, the time exposed must be cut in half in order to deliver equal sound energy to the ear. So 88 dB (A) is 'allowed' for 4 hours and 91 dB (A) for 2 hours and 100 dB (A) for only 15 minutes.

There are no such rules or directives for voluntary visitors to clubs and music venues but the workplace limits can serve as a guideline when looking at leisure noise exposure. But it should be noted that guidelines such as the above mentioned EU Directive aim at minimization of permanent thresholds shifts for workers exposed for days, weeks, and years in a row. The frequency at which young people expose themselves to leisure noise varies very much from once a month to almost daily. Williams et al. (2010) converted (A-weighted) incidental leisure noise exposures to a yearly dose that would be acceptable in an occupational setting. The Allowable Year Exposure (AYE) is about 220 Pa^2h. They concluded that 14.1 % of 18-35 year olds acquired more than one year's AYE by their leisure noise activities. Hearing status was not investigated in this population.

5

Noise exposure puts the hearing system under strain. This can cause a temporary deterioration in hearing or a temporary threshold shift (TTS). Prolonged exposure to high noise levels permanently changes hearing sensitivity, causing permanent threshold shift (PTS). It depends on the intensity and duration of the exposure whether TTS or PTS (or both) will develop. PTS develops gradually over time by irreversible damage to the sensitive structures in the organ of Corti. But immediate PTS may occur after very high exposure levels. The levels that are encountered in a typical club can induce both types of threshold shifts.

It is not clear what the effect of taking a break in the music is on the development of immediate TTS or gradual PTS. The equal energy principle would predict that the cumulative dose determines the strain that the ear has suffered. Strasser et al (2003) found that the equal energy principle was applicable to industrial noise exposure. They compared the effects of industrial noise of two hours of 91 dB (A) with one hour of 94 dB (A) and found that TTS and recovery patterns were similar. The observed TTS was smaller when the sound consisted of classical music, for the same exposure level and duration (91 dB (A) for two hours). Qiu et al. (2013) conclude that the equal energy hypothesis is valid for different exposure when they do not differ too much with respect to the time-pattern of the spectral behavior. They investigated the effect of kurtosis and breaks for equal energy exposures on chinchillas. The duration of the exposure was five days for continuous exposure and nineteen days for interrupted exposures.

It is only possible to study effects of a break in humans in a controlled environment when the limits are considered safe. A restriction should be placed here, based on recent findings by Kujawa & Liberman (2006; 2009), and Lin et al. (2011). In experiments with mice, they showed that exposures leading to TTS might cause *permanent* damage of the synapses while the threshold recovered to normal. The (high) exposure levels that were studied, resulted in TTS of approximately 40 dB. Le Prell et al. (2012) noted that *'The TTS threshold below which there is no lasting synaptic change is not known, and should there be any new evidence which suggests that even a small TTS that rapidly recovers is harmful, studies such as these would not be possible.'*

This manuscript investigates if there is a measurable TTS after two hours of noise exposure at 91 dB (A) and if there is an effect of the break in the noise exposure. Or in other words: is there evidence suggesting that it makes a difference for your ears to have a noise-free period (break) between two hours of noise exposure?

METHODS

Subjects

Inclusion was based on an informed consent and an audiometric screening on normal hearing. Subjects underwent hearing screening with regular pure-tone audiometry (Decos Audiology 2010.1) and tympanometry (Titan, Interacoustics). The screening tests were performed in a sound proof booth at the ENT-Audiology department of the Academic Medical Centre (AMC).

Subjects were included with hearing thresholds at 15 dB HL or better (at 0.5, 1, 2, 3, 4, 6 and 8 kHz) and peak tympanometric pressure between -100 and +100 daPa. They listened to a short sample of the exposure stimulus and were asked if they wanted to enter the study.

A total of 37 adolescents showed interest in this study. From these subjects, ten choose not to participate because they found it too time consuming or ended the communication. Five subjects found the music too loud and four subjects did not meet the inclusion criterion for the audiometric thresholds. This resulted in 18 young adults (14 female, 4 male) who participated (mean age =21.4 yrs, sd= 1.6 yrs).

The experimental procedures were explained to each subject and they signed an informed consent form. The study protocol was approved by the AMC Medical Ethical Committee.

EXPERIMENTAL DESIGN

A cross-over design was chosen to account for inter-individual differences. There were two different experimental paradigms: A and B. Both paradigms contain two hours of music presented at 91 dB (A) output from the headphone. In paradigm A the music is played during two hours consecutively, in B there is a pause of an hour between the two exposure moments. Paradigms A and B were measured on separate (but not consecutive) days, in a randomized order. More details are given in Figure 5.1. Subjects were randomly assigned to start with paradigm A or B (so either AB or BA).

Baseline measurements took place at T_0, after which subject in condition A had to wait one hour before the exposure started. In condition B the exposure started immediately after the baseline measurement and continued for one hour. Figure 5.1 depicts this as blocks of 20 minutes. During the break, three measurement were performed (at T_1,T_2 and T_3 respectively) after which the music exposure continued for the final hour. After two hours of exposure measurements T_4, T_5 and T_6 took place. They were the same for condition A and B.

All measurements started with right ears, then left ears. But because otoacoustic emissions (transient and distortion product) were measured before audiometry took place, audiometry commenced at least 5 minutes after the end of the exposure. Otoacoustic emissions are discussed in another paper.

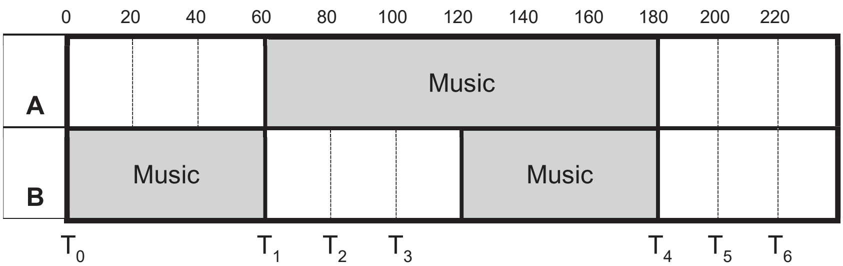

Figure 5.1: Schematic representation of the experimental paradigm.
Music exposure is indicated by the grey areas, T represents a timepoint where audiometric thresholds were determined. T_0 is the baseline measurement; T_1, T_2 and T_3 are only present in condition B whereas T_4, T_5, and T_6 are present in both conditions.

Stimulus

The music sample consisted of songs from the dance CD 'Housequake volume 2' by Roog & Erick E (2008, www.housequake.nl). This CD consists of 17 dance tracks, mixed into each other, thus creating an almost continuous exposure. To create an hour of music, the first 13 tracks were chosen and a small repetitive part (of ~2 min) in the final track was inserted between the ending of the original repetitive part and the end of the original sample. Music was presented to both ears through headphones (Sennheiser HDA200) to reduce intersubject variability caused by subjects' movements through the audiometric room. The outputs for the left and right headphone were identical. The system was calibrated with a Brüel & Kjær Artificial Ear (Type 4153) and a Brüel & Kjær sound level meter (2260 Investigator). The music was played with Cool Edit 2000 through a RME Fire Face 800 soundcard. All settings were checked daily with an artificial ear.

Audiometric evaluation

Pure-tone audiometric thresholds were obtained using an Interacoustics AC40 audiometer with Sennheiser HDA200 headphones. An automated procedure from the audiometer (Békésy tracking, 1 dB step size, 6 reversals, pulsed tone) was used to obtain precise air conduction thresholds (in dB HL) at 0.5, 1, 2, 3, 4, 6, and 8 kHz. The tests were performed in a sound-isolated booth at the ENT-/audiological department of the Academic Medical Centre (AMC).

Statistical analysis

All data were analyzed using R (R Development Core Team, 2012) by using linear mixed effects models with a restricted maximum likelihood estimator (REML) from the R packages *nlme* (Pinheiro, Bates et al. 2012) and multiple linear comparisons with Tukey contrasts from the *multcomp* package (Hothorn, Bretz et al. 2008). Estimated p-values were considered significant at the a= 0.05 level.

First, the baseline audiograms were compared to see if there were differences between the experimental conditions or the order in which the paradigms were conducted. Baseline conditions were compared in a linear mixed model with frequency, ear, and condition (A and B) as fixed factor. Second, the order in which the paradigms were conducted (AB versus BA) was examined. The change in hearing threshold was investigated with frequency, ear, condition (A or B), and time (T_4, T_5, T_6) as fixed variables. For both models, ears were nested within time, condition, and subjects, respectively. This means that the data from one subject is grouped hierarchically from subject to condition, measuring moment (time) and finally ear. To reduce the amount of parameters and measurement variation, it was verified which frequencies could be combined.

Manual inspection of the individual results showed some very large and unexpected differences (both improvements and deteriorations) in threshold around 20 dB. These data points were considered unreliable and objectively marked when they exceeded the median absolute deviation (MAD) more than 3.5 times (Davies and Gather 1993)) based on the largest effect (at time T_4). This amounts to 15.6 dB HL. These data points (one improvement and three deteriorations) were removed from the final analysis.

RESULTS

Effects in pure-tone audiogram

The average audiometric thresholds per frequency are plotted for each point of time, from baseline at T_0 to the end of the experiment at T_6 in Figure 5.2. By subtracting the hearing threshold levels from the initial baseline measurement, a change in hearing threshold was obtained for each moment after baseline (i.e. T_1-T_6). The group-averaged changes with respect to the baseline condition are plotted in Figure 5.3. The standard errors of the mean of the baseline measurement per frequency, condition and ear are indicated by the grey area.

The baseline audiograms did not exhibit a difference between experimental paradigms or ears. But it can be seen that the thresholds at 0.5 and 6 kHz are higher than the other frequencies and that 3 kHz is on average better than the other frequencies. Similarly (not plotted), there was no difference between the first baseline audiogram and the second. Statistical analysis confirmed that there are no significant differences between ears, condition or order, only for frequency (the threshold at 500 Hz and all other thresholds except at 6 kHz)

The next step was to investigate the effect of the exposure paradigm on changes in hearing thresholds, see Figure 5.3. Inspection of the graphs show that at moment 4 (T_4) there was an average change in threshold from baseline (T_0). This effect is visible for both ears, in both conditions, and for all frequencies. It seems more pronounced in the frequency ≤ 4 kHz than in the higher region (6 and 8 kHz). The average change in threshold between baseline and immediately after ending the music (T_4) was the order of magnitude of 2.5 dB.

The change from baseline at T_5 and T_6 represented the recovery process. There seems to be a difference between right and left ears: right ears seem to recover faster than left ears in these exposure conditions. Looking at the graphs for the rights ears show that at T_6 thresholds were comparable to baseline conditions, the change from baseline was near zero. But there was a remaining shift of 1 dB for left ears.

The results of the statistical analysis are presented in Table 5-1. Effects were considered significant for $p < 0.05$. In agreement with the visual inspection of Figures 5.2 and 5.3, there are no significant differences between condition A and B. The systematic shift ranges from 2.3 dB to 3.2 dB but are not different between the frequencies. The effect for ear contributed significantly to the model ($p < 0.0001$). Left ears have a systematically larger threshold shift of 0.95 dB than right ears. Table 5-1 presents the exact values per factor and their confidence intervals.

As expected, the time of measurement was a significant factor ($F[6,1199]=13.26$, $p< 0.0001$). For left ears the average shift at T_5 was 1.16 dB (*95% CI* [1.7 0.62]) smaller than the shift at T_4. At T_6 the average shift was 1.27 dB (*95% CI* [1.8 0.72]) smaller than at T_4. Multiple linear comparisons clearly indicated that the threshold shift at T_4 differed significantly from the change at T_5 and T_6, while there was no significant difference between T_5 and T_6. The remaining average shift for right ears was not different from zero, which implied that average hearing has returned to normal at the end of the experiment. This was not yet the case for left ears.

Combining frequencies

Because of the relatively consistent behaviour for different frequencies, a simplified model was built, using the average shift at 1, 2 and 4 kHz. This average is an often used average in audiology, also known as the high Fletcher index. It expresses hearing loss with an emphasis on the higher frequencies which are known to be sensitive to noise-induced hearing loss. Combining frequencies into one number reduced random measurement error and simplified the analysis and the discussion of the results. Since there was no difference in condition, the results were combined to increase power. The same nesting structure as in the original model was used.

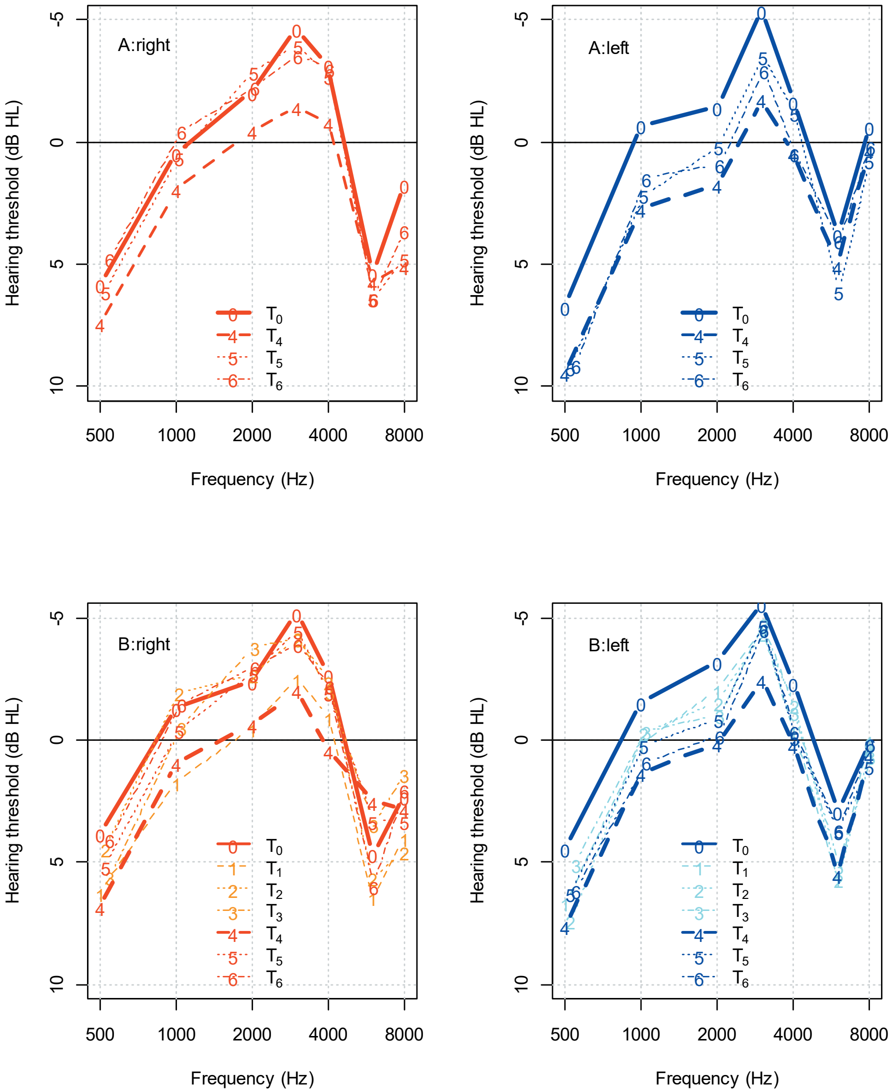

Figure 5.2: Average hearing thresholds for right and left ears. Different measurement moments (T_0 to T_6) are indicated with different linetypes. Solid lines represent the baseline audiogram. The upper panels show experimental condition A (no break during the exposure). The lower panels show experimental condition B (with break). Error bars or other measures of spread are omitted to enhance the visibility of the temporal pattern. Please note that the y-axis is limited to 10 dB HL.

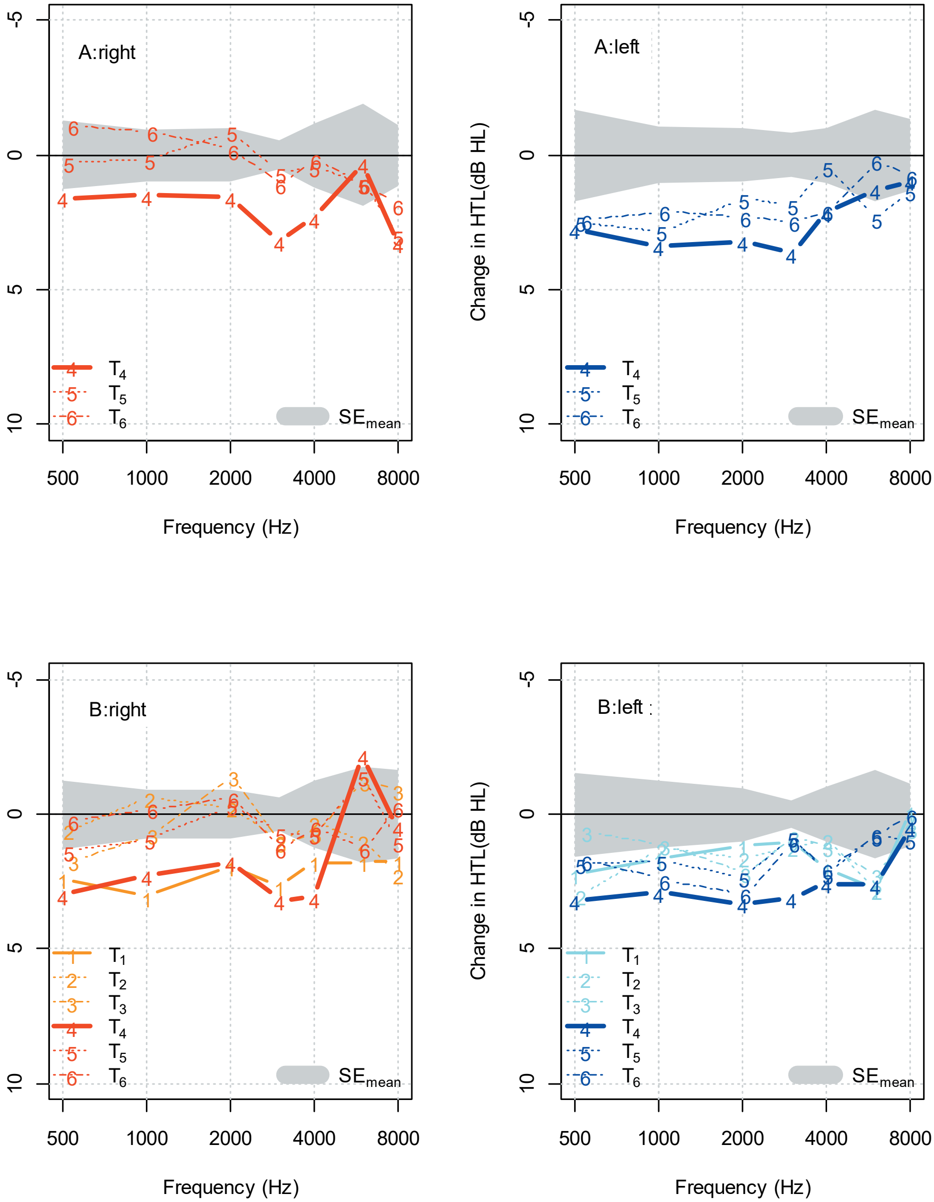

Figure 5.3: Average *change from baseline* in hearing thresholds for right and left ears. The changes at different moments (T_1 to T_6) are indicated with different line types. The upper panels show experimental condition A (no break during the exposure). The lower panels show experimental condition B (with break). The grey area represents the standard errors of the mean of the baseline measurement (per frequency, condition and ear), other measures of variation are omitted.

Table 5-I: Results from the statistical analysis for the threshold shift as a function of ear, condition, time and frequency. Estimates are given for the shift at T_4 for left ears, in condition A and at a particular frequency. The estimated correction terms to compute the shift for right ears, condition B or different moment (i.e. T_5, T_6) are presented too.

Factor	*Estimate*	*95% Confidence interval*	
Frequency: 500 Hz	2.89	1.97	3.81
Frequency: 1000 Hz	2.94	2.02	3.86
Frequency: 2000 Hz	2.65	1.73	3.57
Frequency: 3000 Hz	3.21	2.28	4.14
Frequency: 4000 Hz	2.99	2.07	3.91
Frequency: 6000 Hz	2.34	1.42	3.27
Frequency: 8000 Hz	2.27	1.34	3.20
Ear Right	-0.95	-1.36	-0.54
Condition B	*-0.23*	*-1.17*	*0.70*
Time5	-1.16	-1.70	-0.62
Time6	-1.27	-1.81	-0.72

Ear ($F[1,103]=35.13$, $p < 0.0001$) and time ($F[2,66]=13.34$, p< 0.00 01) contributed significantly to the model while condition (break) did not affect the size of the observed shifts. Left ears exhibited an average threshold shift of 3.4 dB (*95% CI* [2.64 4.14]) immediately after the music exposure. The shift reduced to 1.8 dB (*95% CI* [1.07 2.57]) and 1.9 dB (*95% CI* [1.12 2.65]) at respectively T_5 and T_6. The average shift for right ears was smaller than for left ears, the difference was 1.7 dB (*95% CI* [1.11 2.22]). This means that for right ears at T_5 and T_6 the remaining threshold shifts were not statistically different from zero. Multiple comparisons (Tukey HSD) showed that the threshold shift at T_4 was different from T_5 and T_6, while T_5 and T_6 did not differ from each other.

Audiometric thresholds were determined in the break of condition B to investigate if there would be a shift after only one hour of exposure (i.e. T_1) and if so, if it would be different from the shift at the end of the exposure (T_4). Similar to the previous models, ear ($F[1,105]=13.22$, $p < 0.001$) and time ($F[5,83]=3.49$, $p= 0.0066$) contributed significantly to the model. Immediately after one hour of music (T_1), there was a 2.52 dB HL threshold shift for the left ears (*95% CI* [1.52 3.51]), for right ears the effect was 1.17 dB HL smaller. Similar to the full model, this ear difference was significant (*95% CI* [0.053 1.80]). At the subsequent times (T_2 and T_3) the shift reduced to 1.46 dB HL (*95% CI* [0.44 2.47]) and 1.36 dB HL (*95% CI* [0.7 2.36]) at T_2 and T_3 respectively. For this model the threshold shift at

T_4, T_5 and T_6 amounted to 2.52 (*95% CI* [2.25 4.23]), 1.46 (*95% CI* [0.77 2.79]), 1.36 dB HL (*95% CI* [0.68 2.71]) respectively. The confidence intervals show that all threshold shifts were different from zero for the left ears.

With respect to the differences between one and two hours of music exposure, the comparisons of interest were the difference in threshold shift between T_1 and T_4 and the difference in recovery between T_3 and T_6. These differences were examined with multiple linear comparisons. The shift after two hours was on average 0.72 dB larger than after one hour, but the difference was not significant (*95% CI* [-0.51 1.95]). Similarly, the remaining shift at T_6 was 0.33 dB larger than the remaining shift at T_3 but, again, this difference was not significant (*95% CI* [-0.92 1.58]).

DISCUSSION

For the exposure levels in this experiment there is neither a difference in the size of the TTS nor in the pattern of recovery of TTS between both experimental conditions. This means that one hour of rest does not affect the size of the observed TTS at the end of the exposure. We will discuss the observed effects first, followed by the implications of this study.

Observed effects

The shift immediately after ending of the music was 1.7 dB for right ears, and 3.4 dB for left ears. The effect is observed in a broader frequency region than solely around 4 - 6 kHz, the region where the noise- notch typically occurs. Consequently, the temporary threshold shifts found in this study can be described by averaging adjacent audiometric frequencies (i.e. 1, 2, and 4 kHz) without loss of generality. This is in agreement with the observations from Derebery et al. (2012) who assessed threshold shifts after attending a music concert for three hours and found that the maximum TTS was not limited to 4 kHz and that they could average threshold shifts at 2, 3, and 4 kHz. They found an average shift of 6.3 (right ears) to 6.5 dB (left ears), ranging from no change for some subjects to shifts of 15 dB for others. Whether observed differences between right and left were investigated, is not reported. The measured average sound level during the three hours of the concert was 98,6 dB (A). At higher exposure levels in discotheques, larger effects of TTS were found by Müller et al. (2010). After music exposure with average levels of 102 dB (A) for a duration of three hours, they found significant worsening of pure-tone thresholds by more than 10 dB in 15 ears (8 left versus 7 right). Both level and duration are considerably higher than the levels used in this experiment. Howgate and Plack (2011) investigated cochlear changes in one ear after recreational noise for subjects with regular recreational exposure. They measured sound level values ranging from 90-103 dB (A) averaging to 99 dB (A). This caused substantial TTS, which was maximal around 4-6 kHz and had a value of 10 dB one hour after ending the exposure.

In this study, left ears show more threshold shift than right ears and did not fully recover to baseline condition one hour after cessation of the music. The remaining effect in the left ear is 1 dB on average and although significant, it is not considered to be clinically significant for an individual. However, the data show a significant asymmetry (1.7 dB) between both ears that cannot be attributed to the test order: right ears were measured prior to left ears for all subjects and measurements. If some recovery has taken place between the measurements, this will favour the thresholds for the left ears. This means that the 'real' change from baseline if left and right would have been measured simultaneously is equal or even larger than the differences found.

Le Prell et al. (2012) found no left-ear differences in their experiment where 33 subjects were exposed to 94, 98, and 100 dB (A). They found the largest TTS at 2-6 kHz. Ears with the best pre-exposure baseline audiogram showed the largest TTS. The right-left differences are not explicitly investigated in some studies (Derebery et al. (2012), Müller et al. (2010)) whereas in other studies the effect of ear was investigated in a statistical model. For the 18 subjects in this study there was a significant ear effect. It is of interest to investigate whether this effect will manifest itself also in the analysis of the otoacoustic emission data (future work in this area is in progress).

Implications

The use of chill-out zones is still effective, because it reduces exposure to noise for a certain percentage of time. But besides that, this study does not provide evidence that there is an extra protective effect due to a recovery period in the chill-out zone. Clubs and other venues should make sure that the levels in those zones are sufficiently low, i.e. well below 90 dB (A). Although after 100 dB (A) a level of 91 dB (A) may be perceived as 'chilling out', hearing can still be damaged!

It is complicated to compare the results of different studies because exposure levels, conditions, and effect sizes are different. In this study we used a laboratory approach. This facilitates a very strict control of the experimental parameters, but as a consequence the exposure levels are maximized by ethical restrictions that have to be obeyed in an experimental setup. Compared to the observations described in the Introduction, the levels from this experiment are in the lower range from the levels that can be encountered when visiting real nightclubs or musical venues. This raises the question how representative these relatively low levels in this experiment are and whether the results presented can be extrapolated to other exposure levels or types of music. This can only be done with a limited degree of accuracy. But an important finding is that - even at the relatively low exposure levels used compared to real-life exposure – the exposure leads to small but significant temporary threshold shifts. Since real-life dance music exposure produces much higher levels, the risk for TTS can only be limited if this is translated into shorter allowable durations than the 2 hours used in this study.

These comparisons indicate that - although the levels used in this setup are relatively low when compared to real-life leisure noise activities - they are applicable in a number of other situations as well (leisure noise with hearing protection, quieter activities such as an acoustical performance or by employees at work in the music industry).

CONCLUSIONS

In strictly controlled conditions of music exposure, there was no difference in the observed TTS with or without a break for relatively low levels of noise exposures. The advice to use chill-out zones is still valid, because this helps to reduce the duration to the exposure. This study does not provide evidence that there is an extra protective effect due to a recovery period in the chill-out zone.

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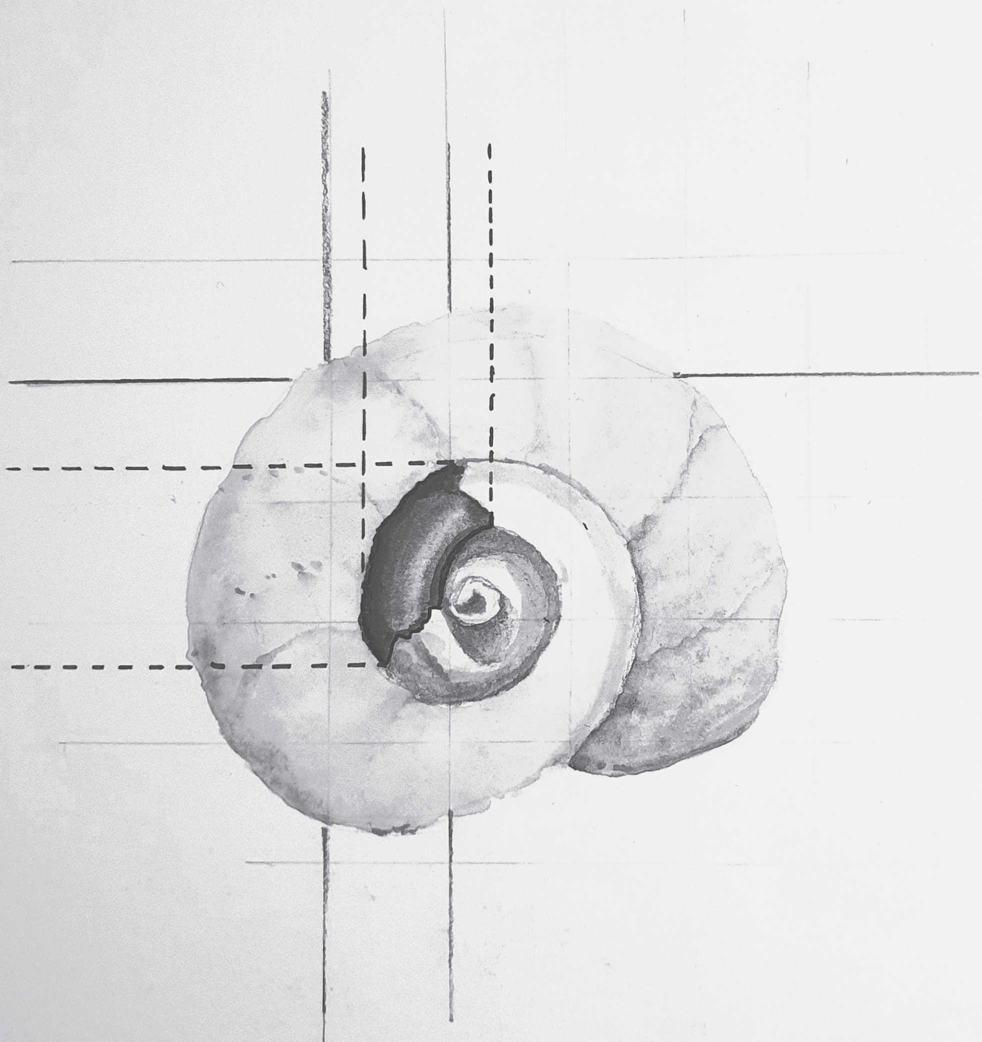

CHAPTER 6

Comparison of temporary changes in hearing threshold levels and otoacoustic emission levels after short term exposure to dance music

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(To be) Submitted to the International Journal of Audiology

ABSTRACT

Objective: Comparison of temporary changes in hearing thresholds and otoacoustic emission after dance music exposure.

Design: Changes in PTA and OAE at pre-determined timepoints were compared in a cross-over design consisting of two hours of music, either consecutively or with a break.

Sample: 18 Normal hearing subjects.

Results: Changes from baseline were on average 2.50 dB for PTA, 0.61 dB for TEOAE and 1.04 dB for DPOAE, were similar for presence or absence of a break, and exhibited a similar time-pattern. PTA and OAE returned to near baseline condition within one hour after exposure. There was no relationship between individual changes in PTA and TEOAE, a very limited relationship between changes in PTA and DPOAE. The overall number of significant individual shifts was low and shifts did not reproduce.

Conclusions: PTA, TEOAE and DPOAE exhibited a similar pattern in time after noise exposure. Overall effects were small. The data shows that the sensitivity of audiometry measured in 1 dB step size is comparable to OAEs in detecting significant individual shifts. There is a lack of reproducibility in all three methods and a lack of agreement *between* the methods. The data does not support an increased sensitivity of OAEs.

INTRODUCTION

In 2015, the World Health Organization (WHO) estimated that around 40% of teenagers and young adults aged between 12 and 35 in middle- and high- income countries could risk their hearing by exposing themselves to sound levels that are potentially damaging (WHO, 2015). These levels can be encountered in venues such as bars, discotheques, cinemas, concerts, sporting events and nightclubs (WHO, 2015). Furthermore, the WHO stated that nearly 50% of these teenagers and young adults are exposed to unsafe sound levels from the use of smartphones and other personal audio devices. For employees of bars, clubs, concerts etc., the maximal exposure levels are regulated, for example by the European Directive 2003/10/EC, in which exposure limit values and action values are stated in order to protect the hearing of workers exposed to noise (2003). But such limitations do not exist for visitors attending the above-mentioned venues voluntarily. In the "make-listening-safe" campaign from the WHO, several actions are proposed to prevent the development of hearing loss caused by leisure noise exposure. These actions are aimed at limiting the time spent in noisy activities and at minimizing the level of exposure by moving away from sources of loud sounds (speakers). Visitors going to discotheques, nightclubs, concerts, bars, sporting events and other noisy places are advised to take short listening breaks to help reduce the overall duration of noise exposure, and/ or use earplugs to reduce the exposure level.

The effect of the recommended breaks on temporary shifts in hearing threshold levels have been investigated in a prior paper by Helleman and Dreschler (2015). A clear, but small, temporary pure-tone threshold shift (TTS) was observed after two hours of dance music, but there was no difference in in the size of the overall shift in hearing threshold between two conditions: one with and one without a break of one hour. Pure-tone thresholds were measured with a stepsize of 1 dB. This enables the detection of smaller effects of noise exposure when compared with regular audiometry which is most commonly measured in 5 dB steps. Some studies suggested that pure-tone audiometry (PTA) is not suitable to detect small, temporary changes in hearing after noise exposure and claim that otoacoustic emission are more sensitive (Attias & Bresloff, 1996; Bhagat & Davis, 2008; Keppler et al., 2010). The presence of significant changes in OAEs accompanied by an absence of significant changes in audiometry has led to that conclusion. One explanation is based on animal studies where it has been shown that (permanent) damage in the outer hair cells, reflected by the emission level, can be present with normal, or near normal audiometric thresholds (Hamernik et al., 1996). This is called outer-hair-cell-redundancy, implying that not every hair cell is required to function normally in order to have normal threshold (LePage & Murray, 1993). An alternative or additional explanation is discussed by Keppler et al. (2010) amongst others. The stepsize of 5 dB in clinical measurements of the audiometric threshold causes a large test-retest variability and obscures effect sizes smaller than that variability.

From the TTS study by Helleman and Dreschler (2015), there is additional, unpublished otoacoustic emission (OAE) data available. This dataset forms a chance to compare small, temporary effects of noise exposure on both OAE and 1 dB step-size audiometry, at group level and for individual ears. A recent review on longitudinal and permanent changes in PTA and OAE showed that there was no concordance between them (Helleman et al., 2018). However, in the studies included in the review, typically lasting months to years, there was no control over the actual exposure level that subjects were exposed to. Although this TTS-experiment was designed to investigate the effect of a break, it can provide insight in whether concordance in changes is present in a well-controlled exposure paradigm. We hypothesized that the more precise determination of threshold and homogenous exposure for all subjects would create better agreement between average changes in hearing thresholds and emission levels and possibly between individual shifts.This paper investigates the relationship between changes in audiometry and OAE in a controlled, short-term experiment, using the same audiometric data as in Helleman and Dreschler (2015). Questions of interest are: **1.** Do OAEs exhibit a similar pattern as pure-tone thresholds after dance music exposure with respects to temporary damage, recovery, and the effect of a break? **2.** Are individual ears affected by the exposure, and if so, is there individual agreement on changes in audiometry and OAEs? 3. Are OAEs equally or even more sensitive to a temporary hearing threshold shift than audiometry, when measured in smaller stepsizes (i.e. 1 dB) instead of the regular clinical stepsize of 5 dB?

METHODS

Subjects

The subjects have been previously reported by Helleman and Dreschler (2015). In short, inclusion was based on an informed consent and an audiometric screening on normal hearing (15 dB HL or better) and peak tympanometric pressure between -100 and +100 daPa. Subjects listened to a short sample of the exposure stimulus and were asked if they wanted to enter the study. Eighteen young adults

(14 female, 4 male) participated in this study (mean age =21.4 yrs, sd= 1.6 yrs). The experimental procedures were explained to each subject and an informed consent form was signed. The study protocol was approved by the AMC Medical Ethical Committee.

Experimental Design

The cross-over design has first been described by Helleman and Dreschler (2015) and has two different experimental conditions. They both contain a total of two hours of music presented via headphones at an output level of 91 dB (A). In condition A the music is played continuously during two hours, in condition B there is a pause of one hour between two equal exposure moments of one hour. Figure 6.1 depicts the experimental design in blocks of 20 minutes. All subjects participated in both conditions, and were randomly assigned to start with paradigm A or B (so either AB or BA). Paradigms A and B were measured on separate (but not consecutive) days.

During the break, three measurement were performed (at T_1,T_2 and T_3 respectively) after which the music exposure continued for the final hour. Measurements T_4, T_5 and T_6 took place after cessation of the two hours music exposure.

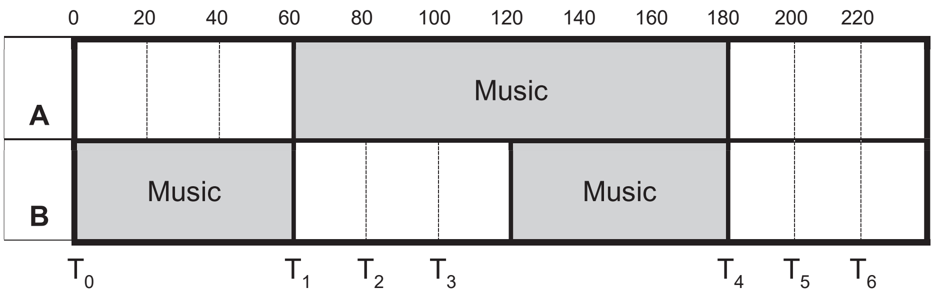

Figure 6.1: Schematic representation of the experimental paradigm. The shaded areas correspond to the music exposure, the white areas to the break and measurements. T represents a timepoint (moment) where measurements were performed. T_0 is the baseline measurement; Measurements at T_1, T_2 and T_3 are only performed in condition B whereas measurements at T_4, T_5, and T_6 are performed in both conditions.

All measurements started with right ears, then left ears. A fixed order was used, starting with right ear TEOAE, then DPOAE, left ear TEOAE, DPOAE, right ear audiometry, and finally left ear audiometry. The total duration of a full set of measurements was about 13 minutes.

Stimulus

The house music sample consisted of songs from the dance CD 'Housequake volume 2' by Roog & Erick E (2008). This CD consists of 17 dance tracks, mixed to create an almost continuous exposure. More details can be found in the previous paper by Helleman and Dreschler (2015). Music was presented to both ears identically through headphones (Sennheiser HDA200). The system was calibrated with a Brüel & Kjær Artificial Ear (Type 4153) and a Brüel & Kjær sound level meter (2260 Investigator). The music was played with Cool Edit 2000 through a RME Fire Face 800 soundcard.

Audiometric evaluation

Pure-tone audiometric thresholds (PTA) were obtained using an Interacoustics AC40 audiometer with Sennheiser HDA200 headphones. An automated procedure from the audiometer (Békésy tracking, 1 dB stepsize, 6 reversals, pulsed tone) was used to obtain high-precision air conduction thresholds (in dB HL) at 0.5, 1, 2, 3, 4, 6, and 8 kHz. The tests were performed in a sound-isolated booth at the ENT-Audiology department of the Amsterdam UMC, University of Amsterdam. The audiometric thresholds per frequency were presented and analyzed in the previous paper (Helleman & Dreschler, 2015). In de present study, the pure-tone average threshold of 1, 2, and 4 kHz is used.

Otoacoustic emissions

OAEs were measured using Otodynamics ILO v6. Transient Evoked OAEs (TEOAE) were evoked using a 86 dBpeSPL click stimulus (280 clicks) in the non-linear mode. Distortion Product OAEs (DPOAE) were evoked with pairs of pure tones recorded at $2f_1 - f_2$ (with amplitude L_1=65 dB SPL, L_2=55 dB SPL, 2 points per octave, f_2/f_1 frequency ratio 1.22). The tests were performed in a sound proof booth at the ENT-/audiological department of the Amsterdam UMC, University of Amsterdam. The outcome parameters that were analysed were the overall response level of the TEOAE and the averaged DPOAE emission level at 1000, 1189, 1414, 1682, 2000, 2378, 2828, 3364, and 4000 Hz. These levels were chosen for direct comparison with the PTA-data after verification that effects were not limited to high frequencies only. It has also been shown that averaging over a wider frequency range reduces the effect of minima or maxima in the DP-fine structure, resulting in better agreement between PTA and DPOAE levels (Engdahl & Kemp, 1996; Sisto et al., 2007).

Data clearing and exclusion

Despite efforts for optimal probe placement in the ear canal, some OAE-recordings were unreliable in terms of low signal-to-noise ratio and/ or low reproducibility for the TEOAE-measurement, or low signal-to-noise ratio for the DPOAE-measurement. Overall response levels of TEOAE were included when the whole wave reproducibility was >=60% (leading to the exclusion of 6 data points). The DPOAE recordings were first averaged, and then included when the averaged SNR was >=0 (leading to the exclusion of 10 data points). There were no exclusions for OAEs in the baseline condition (T_0, see Figure 6.1).

A decrease in emission level below the noise floor could imply a negative effect of noise exposure on hearing but in all cases of exclusion it was clear that the noise level increased and/or that this effect took place at a timepoint in the recovery phase.

Four outliers were removed from the audiometric data. They were presumably caused by incorrect responses to the automated procedure and were classified based on the median absolute deviation (MAD) (Davies & Gather, 1993). See the original paper by Helleman and Dreschler (2015) for more details.

One subject was excluded from the entire analysis because of unreliable OAE measurements for TEOAE and DPOAE at all timepoints (high noise levels, low reproducibility).

Statistical analysis

Group-averaged data

Averaged hearing thresholds and emission levels were analysed with the program R (R Development Core Team, 2018) by using linear mixed effects models with a restricted maximum likelihood estimator (REML) from the R packages *nlme* (Pinheiro, Bates et al., 2012) and multiple linear comparisons with Tukey contrasts from the *multcomp* package (Hothorn, Bretz et al., 2008). Estimated p-values were considered significant at the a= 0.05 level, thus 95% confidence intervals (*CI*) are given. The analysis itself was performed in a similar manner as was done in the previous manuscript regarding the PTA threshold shifts (Helleman and Dreschler, 2015). But here, instead of shifts, absolute threshold data and emissions levels were analysed because emission levels are more easy to interpret than emission shifts. Condition, ear, and timepoint were entered as fixed effects and random effects were intercepts for ears within subjects[5]. Inspection of residual plots were used to check for deviations from normality and for homoscedasticity. An interaction term between timepoint and condition can be used to assess the difference in change of hearing threshold level, or emission level, between the condition with and without the break. In the PTA-data from the previous paper, an interaction between ear and time in the recovery phase after the exposure was observed. This was investigated for TEOAE and DPOAE as well. The order of baseline measurements was checked for signs of a learning effect (audiometry only) and for residual damage caused by the first exposure session.

Individual changes

Scatterplots will be used to visually asses patterns in individual shifts and to assess association between changes in audiometry and OAEs. Individual changes from baseline are expressed as significant shifts when they exceed the so-called 95% confidence interval of change (CIC_{95}) or smallest detectable difference (SDD). This interval is based on the standard error of measurement, SE_{meas} or *SEM*, and quantifies the precision of individual outcomes on a test (Weir, 2005). It has been used to classify significant shifts in OAE-measurements by several authors (Beattie & Bleach, 2000; Beattie et al., 2003; Helleman & Dreschler, 2010; Keppler et al., 2010; Lapsley-Miller et al., 2006; Ng & McPerson, 2005; Stuart et al., 2009; Wagner et al., 2008).

The *SEM* was computed with test-retest measurements according to the formula by Ghiselli (1964): $SEM=SD_{ov}\sqrt{(1-r)}$ In this study the overall standard deviation SD_{ov} for baseline A and B, and the Pearson product moment correlation coefficient (*r*) between condition A and B were used. Since we are discussing the difference between two measures and a 95% confidence interval, the *SEM* is multiplied by two factors and can be computed as $CIC_{95}= 1.96\sqrt{2}\,SEM$.

RESULTS

Group averaged results

Averaged hearing thresholds and emission levels are plotted in Figure 6.2 for both left and right ears and for each measurement point, starting with T_0 until the

5 *In the primary paper on the effects of a break on TTS, a more elaborate random structure was used with ears nested in time, condition and subject. Such model did not converge for the OAE-data. In order to describe PTA and OAE in a comparable manner, the same structure was chosen for random and fixed effects for all methods. The results were very similar for the PTA data.*

end of the experiment at T_6. Condition A (no break) and condition B (break) are plotted separately. Please note that the range of the y-axis for hearing threshold is very small when compared to a regular audiogram. With respect to the initial baseline measurements: there are no statistical differences between ears starting with condition A followed by B (AB) and vice versa (BA) for all three methods (audiometry, TEOAE and DPOAE). But there was a significant difference in initial baseline between condition A and B for audiometry ($F[1,33]= 8.71$, $p=0.0058$). Baseline hearing thresholds in condition B were on average 0.99 dB HL better than in condition A (*CI* [0.31 1.67]).

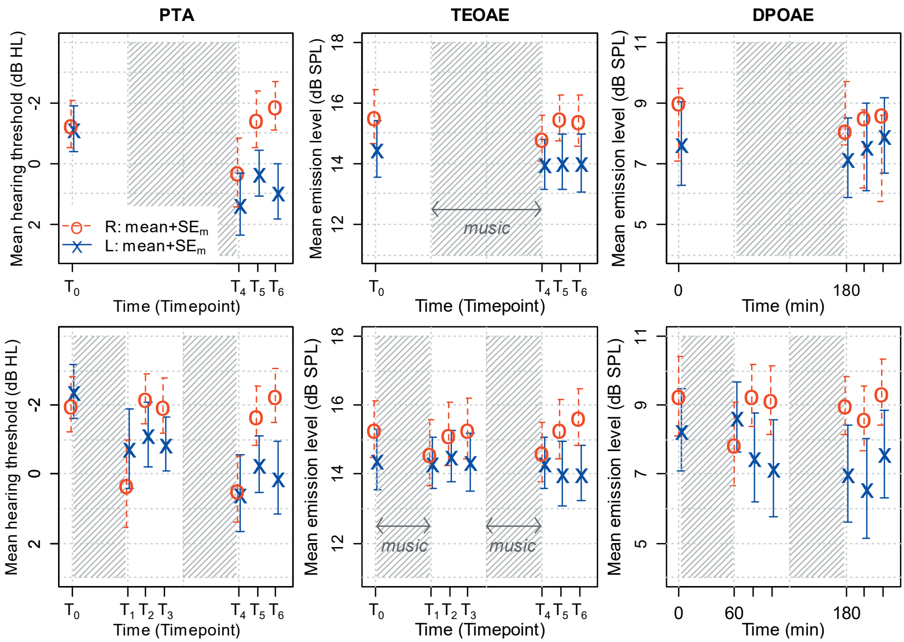

Figure 6.2: Mean audiometric thresholds (first column), TEOAE-response level (second column), and DPOAE emissions level (third column) for both condition A (first row) and B (second row). The shaded areas correspond to the music exposure. The x-axis is the time axis expressed in either timepoints (T_0 to T_6) or the corresponding time in minutes (in the DPOAE graphs). Means and standard errors of the mean (SE_{mean}) are plotted for both left (x) and right ears (o). The orientation of the vertical axis is chosen so that lower points correspond with poorer results.

Closer inspection of the graphs shows that there was a small effect of worsening of hearing (i.e. increase in threshold, decrease in emission level for both TEOAE and DPOAE) after exposure. This can be observed in both conditions and for both ears, although overall right ears seem to have better values across the measures. For audiometry we have reported that there was a significant interaction between ears and time (Helleman & Dreschler 2015), i.e. left ears exhibited a slower recovery (larger remaining shift) at T_5 and T_6 than right ears. This effect was not statistically significant for the TEOAE and DPOAE models. The interaction between timepoint and condition was not significant for any of the methods (audiometry, TEOAE, DPOAE) implying a comparable shift in threshold or emission at T_4 in condition A and T_4 in condition B. For all three methods the model had condition, ear and time as fixed factors and no interaction terms.

Audiometry

The statistical effects for the pure-tone audiometry were insensitive to the differences in number of subjects, nesting structure and use of thresholds instead of shifts and the effects were similar to those mentioned in the previous paper (Helleman and Dreschler, 2015). Time ($F[3, 230]= 20.71$, $p<.0001$) and condition ($F[1,230]= 9.71$, $p=0.0021$) were both significant factors. The effect of condition can be interpreted as a linear effect of 0.70 dB better thresholds in condition B than A (*CI* [0.26 1.15]). This is very similar to the observed difference in baseline condition (0.99 dB). Hearing threshold level at baseline was -0.81 dB HL (*CI* [-2.33 0.71]). The exposure caused an increase in threshold, or an average shift, of 2.50 dB HL at T_4 (*CI* [1.87 3.12]) resulting in an average threshold of 1.69 dB HL. The shift is reduced at T_5 to 0.93 dB HL (*CI* [0.31 1.56]) and at T_6 to 1.05 dB HL (*CI* [0.42 1.68]). There was a trend that right ears had overall better hearing thresholds but this was not significant (estimate of 1.12 dB HL (*CI* [-2.28 0.04]). Multiple comparisons (Tukey HSD) showed that the threshold shift at T_4 differed significantly from the change at T_5 and T_6, while there was no significant difference between T_5 and T_6. Also, in this model, the threshold shift at T_5 and T_6 remained statistically different from the threshold at baseline. The left panel of Figure 6.3 shows the estimated threshold differences between measurement moments.

TEOAE

For the overall TEOAE-response, condition and ear do not contribute to the model; only the factor time is required to describe the effects of noise exposure ($F[3,228]= 7.85$, $p= 0.0001$). Overall TEOAE response at baseline is 14,42 dB SPL (*CI* [12.78 16.05]), reducing with an average of 0.61 dB at T_4 (*CI* [0.87 0.34]), an average of 0.47 dB at T_5 (*CI* [0.74 0.20]) and 0.21 dB at T_6 (*CI* [0.48 -0.06]). Multiple comparisons (Tukey HSD) show that the observed decreases in TEOAE at T_4 and T_5 are significant relative to baseline, but the emission level at T_6 does not differ from baseline. Emission levels at T_4 and T_5 do not differ from each other, neither did T_5 and T_6, but emission levels at T_4 and T_6 are significantly different from each other. These differences are visualized in the middle panel of Figure 6.3.

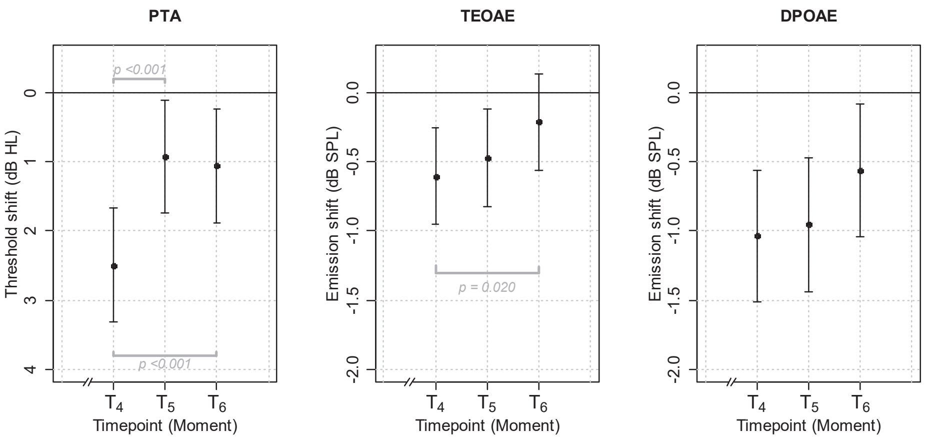

Figure 6.3: Results from multiple comparisons (Tukey HSD) between timepoints with respect to the change from baseline, for both left and right ears. The differences from baseline are plotted so that the values on y-axis represent a threshold or emission *shift*. Estimated shifts and 95% confidence intervals are plotted for T_4-T_0, T_5-T_0 and T_6-T_0. The other significant differences are indicated by horizontal grey lines. For PTA, TEOAE and DPOAE it is clear that the largest change from baseline is observed at T_4 and that there is recovery to (nearly) baseline condition.

DPOAE

The results for the averaged DPOAE are shown in the right-hand panel of Figure 6.3, and very similar to the results for the TEOAE: For the averaged DPOAE -response, condition and ear do not contribute to the model but the factor time contributes significantly ($F[3,224]= 12.91$, $p< 0.0001$). Overall DPOAE-response at baseline is 7.98 dB SPL (*CI* [5.56 10.40]), reducing with an average of 1.04 dB at T_4 (*CI* [0.67 1.40]), an average of 0.95 dB at T_5 (*CI* [0.58 1.32]) and 0.56 dB at T_6 (*CI* [0.19 0.93]). Multiple comparisons (Tukey HSD) show that the observed decreases in emission at T_4, T_5 and T_6 are significant relative to baseline. Emission levels at T_4, T_5 and T_6, however, do not differ significantly from each other. From the Figure 6.3 (right-hand panel), it can be seen that the recovery is clearly taking place although not yet reaching baseline emission level.

Comparison within the break condition

Separate models for condition B only, allow comparisons of timepoints within condition B (i.e T_1 versus T_4, T_2 versus T_5 and T_3 versus T_6). Although the PTA threshold shift, TEOAE shift and DPOAE shift at T_1 are all significantly different from zero, they are not different from the corresponding observed shifts at T_4. The corresponding recovery measurements (i.e. T_2 versus T_5 and T_3 versus T_6) also do not differ statistically from each other.

INDIVIDUAL RESULTS

Table 6-I indicates the fence, or the sizes of shift that can be classified as significant and the underlying parameters that were used to construct the CIC_{95}. Table 6-I shows that the correlations between test and retest (for baseline conditions) are high, yielding small CICs (indicated by narrow grey areas in the graph).

Table 6-I: Values for the overall standard deviation (SD_{ov}), Pearson product moment correlation (r) coefficients for the baseline measurements in condition A and B for all three methods and number of contributing subjects. These results in the standard error of measurement (SEM) and thus in a confidence interval of change (CIC_{95}).

Method	SD_{ov}	r	SEM	CIC_{95}	N_{ear}
PTA	3.12	0.803	1.39	3.84	34
TEOAE	3.51	0.968	0.630	1.74	34
DPOAE	4.90	0.964	0.930	2.58	34

Figure 6.4 shows the behaviour of individual ears in scatterplots for PTA, TEOAE and DPOAE separated by ear. The grey area indicates the CIC_{95}. Points that fall outside this area are considered significant threshold shifts (STS for PTA) or significant emission shifts (SES for TEOAE and DPOAE). A threshold shift of 3.84 dB HL or more, a TEOAE emission shift of 1.73 dB SPL or more, and DPAOE shift of 2.58 dB SPL or more were considered significant. Changes that are smaller fall within the grey area and cannot be labelled as significant at an individual level. Since there are two measurements (condition A and condition B) for each subject and for each ear, an observation can be made on the reproducibility of the occurring changes. Contributions for the same subjects are connected with lines. The shorter the line, the more agreement. In more specifically: the closer the points are together on the x-axis, the more agreement there is in the baseline situation, the closer together on the y-axis the more agreement on the threshold or emission level at T_4.

The first observation that can be made from the scatterplots in Figure 6.4, is that most points fall below the unity line, but within the "no significant change" area. This observation is valid for PTA, TEOAE and DPOAE. There is spread in the size of individual changes from baseline and in the individual reproducibility.

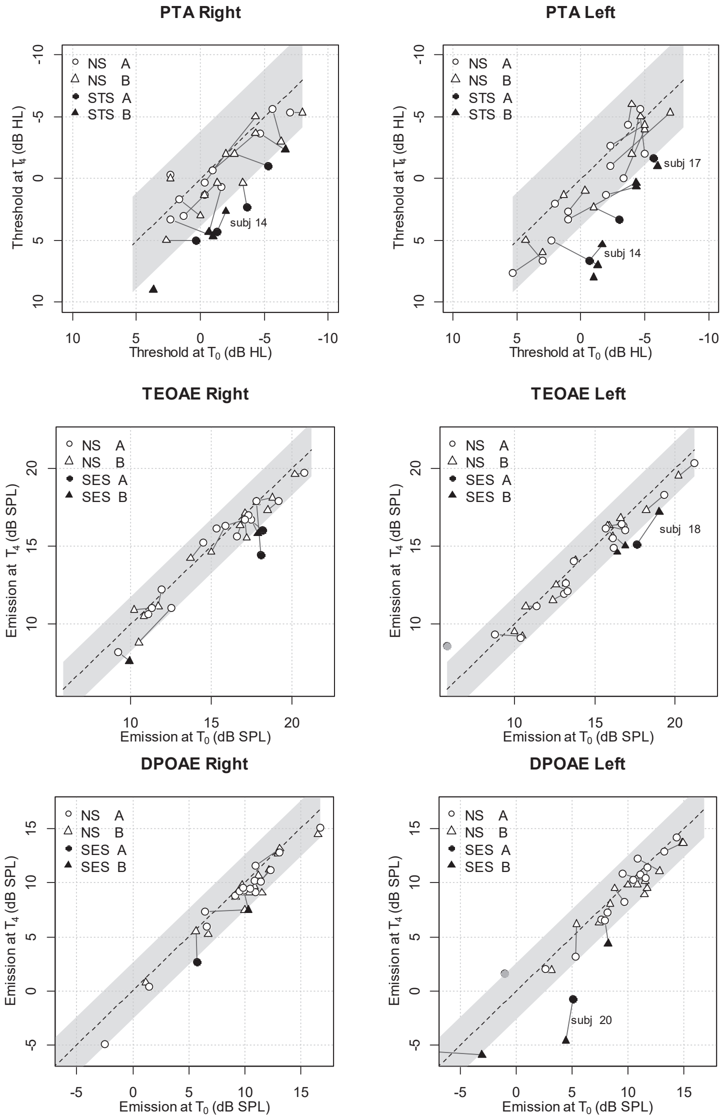

Figure 6.4: Scatterplots of baseline condition, T_0, on the x-axis, and threshold or emission level at T_4 on the y-axis. The unity line, dashed, indicates perfect agreement between the threshold at T_0 and T_4. Audiometry is plotted in the first row, TEOAE in the second, DPOAE in the third row. Please note the difference in range on the axes. Left and right ears are plotted in separate graphs. Contributions from the same subject are connected with lines with o indicating condition A, and Δ indicating condition B. The shaded area indicates the area of the CIC_{95} in which the change cannot be labelled as a significant shift. Data points below this band can be labelled as significant shifts in the direction of worsening of hearing, indicated by filled symbols. In two cases an increase in emission level after exposure was found, indicated by the grey filled symbols (1 case in TEOAE and DPOAE). Subjects that have significant shifts in both condition A and B are explicitly labelled by their study reference number.

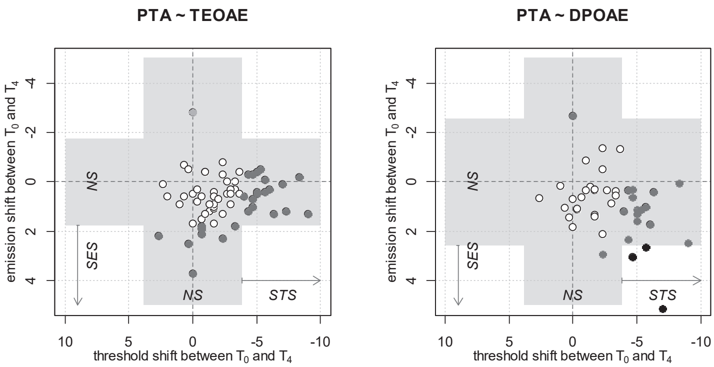

Figure 6.5: Scatterplots between changes in audiometry (x-axis) and TEOAE-amplitude (y-axis) in the left graph, and changes in audiometry (x-axis) and DPOAE-amplitude (y-axis) on the right. Left and right ears are both plotted as individual data points and only cases in condition A are plotted. The grey areas indicate changes that are not significant (NS). Changes that fall outside these areas are either a significant threshold shift (STS) or a significant emissions shift (SES) or both. Grey filled circles ● represent cases with either a SES or a STS, black filled circles ● are cases with both a STS and a SES. Arrows indicate the direction of worsening of hearing (increase in threshold and decrease in emission amplitude).

There are some significant individual threshold and emissions shifts, but there are only few subjects that have a reproducible shift in both conditions (both filled symbols). From the graphs, it can be verified that there are more significant shifts in audiometry (STS) than in emissions (SES).

The relationship between the changes in audiometry and changes in OAE is evaluated by plotting individual shifts in PTA against shifts in TEOAE or against shifts in DPOAE (Figure 6.5). Contributions from left and right ears are plotted in one graph. Visual inspection shows no clear relationship between changes in PTA and OAE. Changes in DPOAE and PTA seem to occur more simultaneously than changes between PTA and TEOAE. This is confirmed by the Pearson product-moment correlation coefficient, that assesses the numerical relationship between changes in PTA and TEOAE, and in PTA and DPOAE. There is no significant correlation between change in PTA and change in TEAOE ($p>0.05$). There is a significant, moderate, negative relationship between change in PTA and DPOAE ($r= -0.43$, *CI* [-0.61 -0.21], $t = -3.77$, $df = 64$, $p = 0.00036$). Increases in hearing threshold level are accompanied by a decrease in DP emission level. There were 3 cases that exhibited individual significant shifts in both DPOAE and PTA, albeit in either condition A or B, while there are no cases exhibiting significant shifts in both TEOAE and PTA.

When combining the contributions from left and right ears in the two conditions, the total number of ears is 68. Out of this total, there are 18 significant PTA shifts, with 12 ears exhibiting a STS in either condition A *or* B and 3 ears in both A *and* B. For TEOAE, the total number of significant shifts is 8, with 6 ears exhibiting a SES in A *or* B, and 1 in A *and* B. There are also 6 SESs for the DPOAE, of which only 1 SES in both conditions.

DISCUSSION

This study investigates whether there is congruent behaviour of precisely measured pure-tone thresholds, and otoacoustic emissions after controlled exposure to dance music, with a focus the behaviour of individual ears. This experiment was designed to assess the effect of a break on threshold and emission shifts.

The exposure limits (91 dB (A)) are considered to be safe when compared with occupational regulations but are on the lower end of those encountered when going clubbing (Bray et al. ,2004; Müller et al., 2010), or when attending concerts, festivals or sporting venues (Derebery et al., 2012; Neitzel & Fligor, 2019; Ramakers et al., 2016; WHO, 2015). On such occasions, attendance is typical in the range of several hours and sound pressure levels of approximately 100-110 dB (A) can be encountered. The findings from this study cannot easily be extrapolated to situations with other exposure conditions and/ or other designs but they are discussed in comparison with other studies.

Main findings

Listening to two hours of dance music at 91 dB (A) causes temporary hearing damage which is comparable for the condition with and without a break during the exposure. The presence or absence of a break does not affect the size of peripheral damage and the recovery process as measured with PTA (Helleman and Dreschler, 2015), TEOAE and DPOAE, at least for levels and durations comparable to this design. There are small but significant changes in both PTA thresholds and OAE levels. Therefore PTA and OAE show congruent behaviour for detecting small effects of temporary hearing damage at group level.

Although the recovery is not yet complete, threshold and emission shifts at T_6 have recovered within 1 dB from baseline level (Figure 6.3). From a clinical point of view, the remaining shifts, and thus the state of peripheral hearing at T_6, cannot be distinguished from the pre-exposure state.

Plots of individual shifts from baseline for PTA, TEOAE and DPOAE show that the overall mean change comes from the contribution of the majority of ears (Figure 6.4). There are only a few changes that can be labelled as significant shifts for specific individuals. Comparison of changes in PTA with changes in OAE shows that there is no clear congruency at an individual level between PTA and TEOAE. There are no simultaneous significant shifts in PTA (STS) and TEOAE (SES) (Figure 6.5), and there is no significant correlation between the PTA and TEOAE shifts. In contrast, the PTA-DPOAE relationship suggests a weak relationship in the expected direction; i.e. an increase in hearing threshold accompanied by a decrease in emission level. However, there is only a poor correlation between changes in DPOAE and PTA, and there are only few cases that exhibit both a significant threshold increase (STS) and a DP-emission level decrease (SES). But even without these extremes there seems to be a trend of more congruency between DPOAE and PTA, than between TEOAE and PTA (Figure 6.5).

In this study, there are more STSs in PTA overall, than there are SESs in either TEOAE or DPOAE. This finding does not support an increased sensitivity of OAEs in detecting early individual damage. But it should be noted that for all three methods, the total number of significant shifts and the reproducibility of these shifts is low. Ideally, a repeated, identical design on two occasions and a larger power is required to quantify how well individual shifts reproduce. The current findings are limited in number of ears, in amount of damage and thus in number of significant shifts. Limitations, caused by the lack of reproducibility and sensitivity for the chosen fence, do not allow further, in-depth analysis of the occurrence of SESs and STSs.

Higher exposure levels or longer durations than are used in this design are not allowed for ethical reasons. However, this would probably have created more damage and might thus show more agreement between OAE and PTA. Nevertheless, this study illustrates that for PTA measured in 1 dB step size, the behavior of PTA thresholds and OAE levels are comparable and that small, temporary damage can be distinguished from baseline measurements by both methods

Comparison with other studies

The use of the averaged data from the 1-4 kHz range as measure for PTA, TEOAE and DPOAE is based on the observation that there was a change in this broad frequency range for all three methods. This is also reported in some other studies on temporary hearing damage. Bhagat and Davis reported a similar broadband behaviour of changes in DPOAE in the 20 ears of their study, as a result of well-controlled noise exposure caused by MP3-players at 85 dB(C) for 30 minutes (2008). They observed an average increase in hearing threshold from 0 to 1 dB HL between 0.25 and 8 kHz using a 'standard clinical procedure', but these changes were not significant. The significance of the changes in DPOAE and absence of significance in PTA, led the authors to suggest that changes in OAE preceded changes in PTA. This hypothesis cannot be confirmed based on the results of the present study. There was no data displaying or discussing the relation in changes between PTA and DPOAE.

Keppler and colleagues also performed a study on the effects of noise-exposure caused by MP3-players on 21 ears, investigating different gain settings and type of headphones (earbuds or supra-aural) (Keppler et al., 2010). Equivalent 1h exposure levels varied from 72 dB (A) at 50% gain setting to 103 dB (A) at 100%. They found no main effects for changes on group level for PTA, except at 0.25 kHz, and for the DPOAE. When only looking at the data measured with supra-aural headphones, there was a significant increase in threshold at 2 kHz of 1.78 dB HL. They also reported an overall significant decrease in TEOAE-level at 2 kHz of 0.47 and 0.7 dB SPL depending on the type of headphones (supra-aural or earbuds). When comparing the reported size of changes in PTA from the two above-mentioned studies, it seems that the audiometry using 1 dB steps as applied in the present study is better suited for proving such small deteriorations in thresholds to be significant, suggesting a comparable sensitivity for PTA and OAE.

The similar behaviour is illustrated as well by a study from Kumar et al., where 14 subjects (28 ears) were exposed to white noise at 90 dB SPL for 2 minutes (2013). Audiometry was measured with a 2 dB step size. There were significant changes for PTA between 1 and 8 kHz, ranging from 2.3 to 5.8 dB, for TEOAE between 1.5 and 4 kHz, ranging from 0.9 to 2.6 dB, and for the overall response level of 0.9 dB. There was a very weak correlation (0.18-0.24) between changes in TEOAE and PTA.

Exposure paradigms in real-life situations are generally higher than in controlled studies. But also after higher exposure levels, the effect is also not limited solely at 4kHz. For example, Derebery et al. measured thresholds and OAEs in 29 ears of teenagers attending a pop-concert (2012). They found changes in PTA thresholds between 1 and 4 kHz, and also in DPOAE-levels but did not report on individual correlations of these changes. The mean PTA, averaged at 2,3 and 4khz, increased with 6.5 and 6.3 dB HL for left and right, respectively. The mean overall DPOAE amplitude decreased with 1.4 dB SPL. Exposure during the concert was recorded in the area where subjects were sitting, but the levels were not controlled. The average level during the 3-hour concert was 98.5 dB (A). A similar exposure was reported by Ramakers et al., who monitored a group of attendees with (N=26) and without earplugs (N=25) at a festival (2016). For the non-earplug group, they reported a mean time- averaged exposure level 100 dB (A) for a duration of 4,5 hours. This led to significant changes in hearing thresholds in the region of 3 and 4 kHz, on average 6.8 and 8.3 dB for left and right ears, respectively. DPOAEs showed significant changes in the region between 2 and 6 kHz, with an average of 2.2 dB in the region between 2-8 kHz. Individual changes or relation between methods were not discussed. Müller et al. (2010) measured young subjects (N =15 ears) attending a discotheque for the duration of three hours with an average level of 102 dB (A). Subjects were allowed to move freely in the discotheque. Both PTA and DPOAE showed significant changes of 14 dB for PTA and 13 dB for DPOAE. They also delved into the relationship between changes in OAE and PTA and report that most subject exhibited congruent changes in PTA and DPOAE, but that there were also divergent cases. On group level, no correlations between changes were found. They discuss whether the occurrence of a large temporary shift is in fact an illustration of a protective effect through reduction of the cochlear gain. Not only attendees at such activities expose their ears to high levels of sound; Santos et al. measured average sound levels during typical sets in a DJ booth and found levels ranging between 93 and 110 dB (A) (2007). They measured PTA, TEOAE and DPOAE for 30 DJs before and after their work. PTA shifts were significant between 0.5 and 8 kHz, ranging from 5.3 to 8.9 dB. TEOAE signal-to-noise ratios decreased significantly between 2 and 4kHz, ranging from 3.0 to 4.9 dB, DPOAE-levels decreased significantly at the most frequencies between 2 and 4kHz, but exact values of shifts were not reported.

Limitations

Reproducibility in changes

As discussed previously, the occurrence of significant shifts (STS and SES) does not reproduce well in both conditions. PTA requires the focused cooperation of subject, and full attention to the delivered stimulus. For OAE, probe placement in the ear canal and calibration errors could have caused undesired variation between measurements. When several measurements are available, averaging reduces this variation. Marshall and Heller used two baseline measurements on two different days as normalized baseline for measuring changes in PTA and TEOAE after half-octave band noise exposure (1998). The scatterplots of Figure

6.4 indicate that the use of averaged data would have reduced the number of significant shifts. Some of the current STSs would not be significant anymore although some others, now borderline, would become significant.

In contrast, small variations in both horizontal and vertical directions imply a stable baseline, and a stable, reproducible shift. The PTA data of subject 14 illustrates that averaging would not have affected these shifts. He or she has relatively reproducible shifts in both conditions, for both left and right ear without a large influence of baseline variation. Other examples of low variation can be found around the unity line in both conditions, maybe suggesting less susceptible ears.

STS/ SES criterion

The exact numbers of STSs and SESs are affected by the size of the fence criterion, but the fence used will not affect the underlying (lack of) relationship between changes in PTA and OAE. A different definition of the confidence interval of change, *CIC*, can be visualised by sliding the borders of the grey areas in the scatterplots. Choices in derivation of the *CIC* affect the size of the fence: another fence criterion would result in a different number of SESs and STSs, The fence that is derived in this study for the OAEs, is in the same order of magnitude as is found in the study by Keppler et al. where subjects listened to a MP3-player at different gain settings (2010). They presented criteria for significant emission shifts in TEOAE and DPOAE ranging from 1.6-3.2 dB SPL for ½ octave frequency bands. In that study, a threshold change was considered significant when exceeding 10 dB HL. There are several other studies on temporary effects of noise exposure on hearing were TTS is also defined as a threshold of shift equal or greater than 10 dB HL at single or combination of frequencies (Derebery et al., 2015; Ramakers et al., 2016; Santos et al., 2007). Since there are no averaged PTA shifts larger than 10 dB in this study, applying such an a priori criterion would have failed to detect any STSs at all.

A review of longitudinal studies has shown that the criteria to define a SES or STS range from 5-25 dB for PTA, from 3.2-7.6 dB for TEOAE and from 5.0-12.4 dB for DPOAE, depending on the underlying computation and or the combination of frequencies included (Helleman et al., 2018). The values presented in Table 6-I are smaller. The ears in this study are younger, and have no prolonged, continuous history of noise exposure which makes their emissions more robust and stable. This could lead to higher reproducibility of the emission levels and thus to a smaller fence. For the PTA, the smaller step size partially explains the smaller value of 3.8 dB HL. Another factor that contributed to the smaller sizes of the criteria, is the averaging across a wide frequency range.

Dependency of the data

The generalisation of the results is hampered by the fact that the data underlying the scatterplots and correlation stems from only 18 subject with each four contributions (left and right ears in two conditions) while they are treated independently. This could have overestimated the relation between PTA and OAE. Despite this dependency, there is no correlation between TEOAE and PTA. When the data points from the two conditions are analysed separately, the observations remain the same. There is no agreement between PTA and TEOAE. The PTA and DPOAE correlation remains significant and is in the same order of magnitude as from the initial analysis. This separate analysis supports the finding of the small but significant correlation between PTA and DPOAE for the group-averaged data whilst also showing the lack of reproducibility in detecting significant individual shifts in two separate occasions. As mentioned previously, the five individual cases exhibiting both STS and SES (DP) do not reproduce in both conditions.

Order of measurement

The fixed order of measurement after the noise exposure (right TEOAE, DPOAE, left TEOAE, DPOAE, right PTA, left PTA), could systematically affect the observed magnitude of changes in hearing. Measurements take place during different stages of the recovery process and this confounds a direct comparison between timepoints of both methods. The above-mentioned study by Marshall and Heller have shown that –after 10 minutes exposure to narrow band noise- the temporary threshold shift and temporary emissions shift resolve rapidly in the first 10-15 minutes after ending the exposure (Marshall & Heller, 1998). They measured continuously, alternating between PTA and OAE at a single frequency. Such a procedure provides more information on the dynamics of the first hour of recovery after temporary changes in hearing. This study also follows the recovery during the first hour, but with only three measurements, after lower exposure and thus less damage. It cannot be ruled out that some of the damage resolves between measuring the first OAE and (the last) PTA at T_4 or that more recovery has taken place when the final PTA is measured at T_6 when compared with OAE at that moment. In other words: there might be an underestimation of the maximal thresholds shift at T_4 when compared with OAEs and vice versa, an underestimation of the recovery as measured with OAEs at T_6.

Hidden hearing loss

Animal studies have provided evidence that peripheral temporary damage might be accompanied by permanent synaptic damage (Kujawa & Liberman, 2009; Liberman et al., 2016; Lobarinas et al., 2017). Despite recovery of peripheral hearing as expressed with pure-tone thresholds and OAEs, the exposure may have caused permanent damage to the synapses and/or hearing in noise (Fernandez et al., 2020; Kujawa & Liberman, 2009, Lobarinas et al. 2017). By design, and by the lack of criteria for measuring this 'hidden hearing loss' in humans (Fernandez et al, 2020; Liberman et al., 2016, Schaette & McAlpine, 2011), this study cannot answer the question whether such permanent synaptic damage has occurred. When compared to the above-mentioned animal studies, noise level and duration from this experiment are lower, the measured damage is much smaller, making it seem unlikely that permanent neuronal damage has occurred. This is supported by suggestions from Lobarinas et al. (2017) that neuronal damage is more probable after exposure causing larger TTS, i.e. TTS in the order of 30 dB measured after 24 hours.

CONCLUSION

Audiometric thresholds, TEOAE-level and DPOAE-levels exhibited a similar pattern in time after carefully controlled exposure to dance music for continuous exposure and exposure with a break in between. The overall effects were small but this study illustrates that temporary hearing loss does occur in 'safe' conditions.

For individual changes, there was no relationship between PTA and TEOAE, and a very limited relationship between changes in PTA and DPOAE. The overall number of significant individual shifts was too low, and without reproducibility on both occasions, to base any conclusion on the number of STSs compared to SESs. This data does not support the hypothesis that OAEs are generally more sensitive at detecting significant individual shifts after 'low' exposure to dance music but it does show that high-precision PTA measured in small steps is capable of detecting similar patterns as OAEs. Increasing the exposure level would probably result in more damage, and more variation between subjects and might thus show more agreement between individual changes in PTA and OAE.

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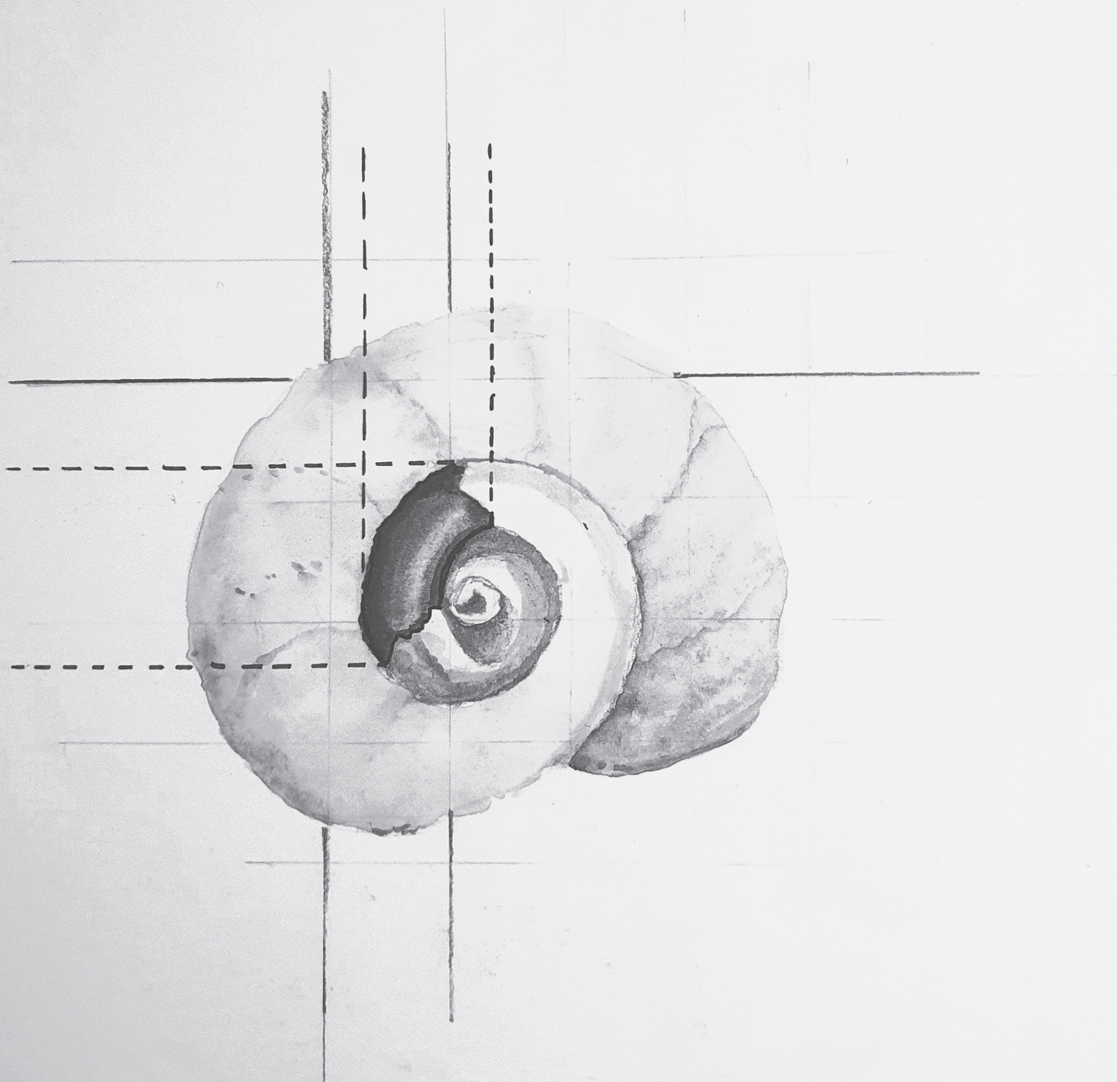


CHAPTER 7

General Discussion

GENERAL DISCUSSION

Despite knowledge that prolonged noise exposure can lead to hearing loss, and despite the presence of preventive regulations, noise-induced hearing loss (NIHL) is a worldwide problem. Hearing damage in workers exposed to occupational noise still occurs in high income countries where exposure limits exist, and where hearing conservation programs are in place. The burden of NIHL is considered to be even higher in low- and middle income countries where there is lack of regulations and/or its enforcement (Fuente & Hickson, 2011; Nelson et al., 2005; Shaikh, 1999).

Reduction of the total exposition can be achieved through lowering exposure levels at the source (for example through shielding of machinery, absorption, lowering sound levels at concerts), reducing the levels at the eardrum (individual hearing protection), or reducing the duration of the exposure. Although there is a hierarchy of control measures, the most often applied approach to reduce noise exposure is the use of hearing protection devices (Morata & Meinke, 2016). A recent Cochrane systematic review investigated various interventions to reduce occupational NIHL. It showed that there are only a few randomized studies dealing with these interventions. This results in only limited high-quality evidence that control measures can prevent hearing loss (Tikka et al., 2017). Overall, the review showed that there is (low-quality) evidence that stricter legislation results in lowering of the noise levels at the workplace, and that proper (better) use of hearing protection devices (HPDs) reduces the risk of hearing loss. Furthermore, there was insufficient data to find an independent protective effect of individual components of hearing loss prevention programs, such as periodically performed audiometric tests and education of employees. The authors warn against interpreting the absence of evidence as absence of effectiveness and call for more high-quality studies in this domain.

With this warning in mind, it is still felt that periodically testing of hearing function is an important component of hearing conservation programs. The rationale of this frequent testing is to allow early detection of NIHL, to raise awareness, and identify those subjects that are most at risk. That might be people who have a genetic vulnerability to noise damage or who exhibit risky listening/ working behavior by exposing themselves to (unnecessary) high noise levels (Carlsson et al., 2005; Ding et al., 2018). Merely identifying these subjects is not enough, the subsequent steps are to inform the individual subject about the damage, and look for methods to reduce the exposure to avoid further damage.

For occupational settings, this can be achieved through the previously mentioned hierarchy of control measures, the last resort of which is the choice of alternative employment (European Parliament and the Council, 2003). But in recreational settings, the subjects expose themselves voluntarily to potentially damaging noise levels by visiting night clubs, attending concerts and prolonged listening to personal audio devices (Carter et al., 2014; World Health Organization, 2015).

The “make listening safe” campaign from the WHO was launched in 2015 and is focused on reducing – preventable- NIHL caused by recreational exposure to loud sounds (https://www.who.int/activities/making-listening-safe). It is also aimed at raising awareness on the risks of NIHL and on safe listening practices for (young) individuals. The campaign stresses the need for safe listening to policy-makers and the WHO is investigating existing regulations in entertainment venues in collaboration with other partners.

Measurement of hearing status

The current standard for determination of hearing damage is pure-tone audiometry, PTA. One of the problems of this test is that – as stated by Marshall and Lapsley Miller - “ the measure of success is also the measure of failure”, by which they mean that as soon as a hearing loss is found and recorded, the ears are already irreversibly damaged (Marshall & Lapsley Miller, 2007). They call for a test that allows earlier identification of hearing loss and suggest that otoacoustic emissions (OAEs) might be capable of such early detection.

Another alternative for hearing testing can be found in speech-in-noise testing. There are some online applications where people can measure their own hearing status. Such tests are less affected by background noise conditions, can be self-administered and can create awareness (Leensen et al., 2011; Sheikh Rashid et al., 2017). However, most work on these applications is done in cross-sectional settings, not on measuring the development of (temporary) hearing damage in an individual over time.

This thesis was initiated by the question whether OAEs are capable of detecting hearing damage at an earlier stage than PTA as was claimed by several other authors (Attias et al., 1998, 2001; Desai et al., 1999; Engdahl et al., 1996; Lapsley Miller & Marshall, 2007; Marshall et al., 2001; Xu et al., 1998). It stems from a hypothesis that there can be damage to outer hair cells, thus reducing OAE-amplitude, that does not yet affect the detection of soft sounds, i.e. the pure-tone threshold. Many of these studies were based on a cross-sectional design. The questions whether changes in OAEs precede changes in PTA, or whether low-level emissions are predictors of future hearing loss, require repeated measurements in longitudinal studies, combined with a clear definition of the change that is of interest.

Aim of this thesis was to contribute in clarifying the role of OAEs in measuring and monitoring NIHL. Therefore, the first step was to look at OAE and PTA in a monitoring approach, thus a study with more than one measurement in an occupational setting. The results discussed in **Chapters 2** and **3**, consist of a baseline measurement and only one follow-up measurement after seventeen months. When looking at predictive values or individual susceptibility, more measurements would be required. But nevertheless, the results from **Chapters 2** and **3** led to some more refined questions regarding how change can be measured. An important methodological issue that was encountered was the question when a change from baseline can be considered to be significant and when it is considered to be a measurement variation. And – given a robust definition of a significant shift- is it possible to predict a threshold shift from a change or shift in OAE-amplitude? These aspects have been investigated in our own data in **Chapters 2** and **3** and are held against the methods and results from studies by other authors, collected and evaluated in a systematic review in **Chapter 4** of this thesis.

In addition, a study into the short-term effects after carefully controlled noise exposure was conducted in a recreational setting. This experiment was designed to investigate the effects of a break during dance music exposure on temporary hearing damage, which is discussed in **Chapter 5**. Hearing damage was measured with both OAEs and PTA, with the latter measured in a smaller step size (i.e. 1 dB). The applied method of determination of individual shifts was again applied to compare shifts in OAE and PTA in **Chapter 6**.

The studies of the long-term effects (**Chapters 2** and **3**) and the studies of the short-term effects (**Chapters 5** and **6**) are very different in nature in terms of subjects, initial hearing, exposure, etc. Nevertheless, when comparing the observations from these studies there are several key points that can be distilled and deserve to be discussed. They can be disentangled in terms of observations and findings (see below), and in terms of methodological issues regarding the measurements and regarding determination of significant individual shifts.

Observations and findings

The general observation of the individual studies reported in this thesis are that both PTA and OAE showed signs of damage either permanently or temporarily, on group level. Overall, the hearing thresholds increased after noise exposure, and emission levels decreased for both the short-term, controlled, dance music experiment (Chapters 5 and 6) and the long-term study on the employees in the newspaper printing office (Chapters 2 and 3).

Comparison of PTA and OAE

One of the purposes of monitoring is looking at individual subjects, or individual ears. One of questions of interest is how well changes in PTA are represented in changes in OAE. This can be investigated visually by plotting individual changes in PTA against changes in either TEOAE or DPOAE, and can be quantified by product moment correlation coefficients.

There were no significant correlations between individual changes in OAEs and PTA for both the long-term industrial setting discussed in Chapter 3 and the short term, controlled dance music experiment discussed in Chapter 6. There was one exception: a very weak correlation was found between the changes in PTA and DPOAE emission level in the dance music experiment. For the long-term study (Chapter 3), there was a large amount of missing data, and no control over the exposure, and PTA was measured in an automated procedure with a 5 dB step size. This was also the case for the majority of studies by other authors that were discussed in the review (Chapter 4). No significant correlations were found between changes in both methods.

The controlled experiment with the dance music (in Chapter 6), also failed to show clear correspondence between individual changes in PTA and TEOAE despite the higher accuracy (i.e. 1 dB step size) with which the audiometry was performed. It is clear though that both techniques show a small but significant, temporary overall deterioration in hearing at group level. The scatterplots of Figure 6.4 illustrate that 1-dB-step PTA, TEOAE and DPOAE perform very similar when looking at individual changes. There is variability present in all three methods, but most ears show a small worsening of hearing without exhibiting many significant individual shifts. These graphs suggest a similar performance for PTA measured in smaller steps compared with TEOAE and DPOAE. A 5 dB step size would not have been able to illustrate the behavior of damage in the paradigm studied.

Timing and order of the measurements could have influenced some of the effects that are reported, but the scatterplot (Figure 6.5) illustrated the lack of agreement between changes in PTA and TEOAE for individual cases for the paradigm studied. The situation is slightly different for the relationship between changes in DPOAE and PTA: There seemed to be a very weak relationship between changes in both methods (r = -0.42). This correlation was obtained when contributions from left and right ears were combined from both condition with and without the break (A *and* B). The correlation remained significant and in the same order of magnitude when contributions from paradigm A and paradigm B were separated.

An important finding from this chapter is that temporary damage can occur at levels that are generally considered 'safe'. A break – in the situation studied here- did not reduce the overall damage neither in PTA nor in OAE-measures. For higher sound levels and longer durations, which are more representative for real life attendance of concerts or festivals, leisure noise activities might lead to more damage, maybe even to permanent damage. More damage will be reflected in larger changes in both PTA and OAE, and might also lead to more agreement between individual shifts in PTA and in OAE.

Enhancements of OAEs

An unexpected finding in the results from the studies on the employees of the newspaper, was an overall mean increase in emission level that could not easily be explained. At first glance, such an enhancement might be interpreted as an improvement in hearing which is unlikely considering the continuation of the damaging noise exposure. Enhancement of OAE-levels has also been reported in animal studies on noise exposure, and was also found in US Veterans who underwent treatment with ototoxic drugs (Huang et al., 2005; Kakigi et al., 1998; Konrad-Martin et al., 2014; Mei et al., 2009).

Chapter 3 showed that the number of individual positive significant emission shifts (SESs), was larger than chance. Further analysis showed that most of these significant shifts occurred in ears that already had substantial damage as seen in the audiogram in the high frequency region. Most cases that exhibited such a positive SES, came from the groups with worst hearing at 4 kHz, i.e. the group labelled as having a profound notch (threshold at 4 kHz ~45 dB HL on average) or as having a sloping configuration (threshold at 4 kHz ~35 dB HL on average) (Figure 2.3).

Closer inspection of the scatterplot (Figure 3.3A) suggested that ears with low emission levels around 3 kHz, had a higher occurrence of significant enhancements, i.e. positive SESs. And finally, for ears exhibiting positive SESs, odds were significantly higher that this occurred simultaneously with a STS at 6-8 kHz. These enhancements are mentioned occasionally in some studies included in the review of Chapter 4, but were either not investigated any further or discarded as random errors (Lapsley Miller et al., 2006; Moukos et al., 2014). It would have been very interesting to examine the enhancements in these studies further, and to verify the findings from Chapter 3, (the significant association of enhancements in DPOAE-level around 3 kHz with a worsening of PTA in a higher frequency region).

In the short term study (Chapters 5 and 6) there were no signs of this enhancement. DPOAE contribution were averaged between 1 and 4 kHz, but only after verification that the observed effects were comparable across this range. The observations in other studies and in animal studies both suggest that this effect is more likely to be a manifestation of permanent damage.

Differences between TEOAE and DPOAE

This thesis has consistently discussed observations in TEOAE and DPOAE in parallel. Although their generating mechanism is different, the clinical behavior on group level is very similar for TEOAEs and DPOAEs throughout this thesis. Generally speaking, there was a lack of agreement between individual cases. However, in the two occasions where there was some (very limited) agreement (i.e. the 3 kHz enhancement from Chapters 2 and 3, and the overall change in DPOAE from Chapter 6) it occurred between DPOAE and PTA rather than between TEOAE and PTA.

Methodology

Effects of noise: Reduction of background noise levels

OAE recordings consist of an (estimated) emission level and an (estimated) noise level. Low frequency noise is most dominant, and is often caused by inadequate sealing of the probe in the ear canal, breathing noise of the subjects, and internal noise of the equipment. Reduction of noise levels would improve the SNR and could extend the applicability of OAEs in the region near the noise floor (Lapsley Miller & Marshall, 2007). Optimal boundary conditions for (repeated) OAE-measurements can be achieved through better ear tip seal (through custom made earmolds for measurements), and/or the use of noise reduction algorithms (Nadon et al., 2015).

Effects of noise: Inclusion based on the signal-to-noise ratio (SNR)
As was stated in the review of Chapter 4, it is recommended to use the emission amplitude as outcome measure, and not the signal to noise ratio (SNR). The emission amplitude reflects properties of the cochlea, whilst the SNR is a composite measure that conveniently reflects two aspects that are important in the interpretation of OAEs, i.e. the emission level and the noise floor. High emission levels and high noise floors may result in the same SNR as a case with lower emission levels measured in less noisy conditions. When SNR is used as outcome measure, these two situations cannot be distinguished from each other. The studies in this thesis, and some of those included in the review use the SNR as a measure of quality of the recording and as an inclusion criterion, not as an indirect measure for emission strength.

Such inclusion criterion is applied on the data of the newspaper printing office that is discussed in Chapters 2 and 3. It shows that there is only a low number of emission levels that are at, or above the noise floor (SNR ≥ 0). Some studies have used higher SNR-values before emission were considered present, whilst others claim that no such restrictions should be used when looking at OAE-data (Reuter et al., 2007). For the newspaper employees, this led to an inclusion of approximately 90% of the TEOAE measurements at 2 kHz, steadily declining to 60% at 4 kHz. For the DPOAEs at baseline, the average number of valid measurements was 90% in the region between 1.5 and 6khz, reducing to 60% at 8 kHz. For the controlled experiment with dance music exposure (Chapters 5 and 6), emissions were also considered to be present for SNR ≥ 0. There were only 10 DPOAE single data points (~2.5% of the total recordings) that were excluded in the dance music experiment because of the higher emission amplitudes usually present in young adults. There were no exclusions in the baseline conditions.

However, two differences should be mentioned that could have influenced the SNR of the recordings. The first concerns the level of the primary tones that were used to elicit the DPOAE, which will later be discussed in more detail. The second difference is that the emissions in the controlled experiment (Chapter 6) were averaged across a broader frequency span. This could improve the SNR and thus result in a lower number of exclusions, but raw data from the controlled experiment of Chapter 6 can illustrate that this effect is probably limited. Investigation of the SNRs for single frequencies, showed that the number of exclusions was much lower in the controlled dance music experiment than in the newspaper printing office. Immediately after the music ended, at T_4, there were only 0-3 % of the data points with SNR<0 (i.e. 0-2 ears) between 3 and 6 kHz. The higher emissions levels in itself are the cause for higher SNRs and more included data points, not the averaging.

Effects of noise: Noise Floor Substitution (NFS)

Noise floor substitution is a method that allows the above-mentioned observations to be included in an analysis while they would have been omitted otherwise (Lapsley Miller et al., 2004). It allows an estimation of the minimal actual change when initially good emissions drop below noise floor in subsequent measurements and are considered to be absent. Low-level or absent emissions are substituted with the noise floor level, provided that the noise floor is lower than the emission level of the initial measurement. Such an approach allows the contribution of more data points but might underestimate the actual effect size. Additionally, it creates a bias towards finding deteriorations because only cases that drop *below* noise floor are substituted.

Noise floor substitution was applied in the mean group results discussed in Chapter 2. Since the substitution scheme is only applied to cases where there is a possible deterioration, it is labelled 1-way NFS here.

Chapter 3 used noise floor substitution in two directions (2-way NFS): not only emissions that *drop* below the noise floor of the *second* measurements but also emissions that *rise* above the noise floor from the *first* measurement are taken into consideration. The 2-way NFS does not create a bias towards decreases only. Now, only data points that were below noise level on both occasions were omitted. At first glance, there is little difference between the overall mean changes visualized in Figure 2.1 and 3.2. This simple change in inclusion does not affect the outcomes severely, but is does affect which overall group mean effects are considered as significant. It can be seen from Figures 2. 1 and 3.2 that overall TEOAE-emission decreases, but after also including data points that rise *above* noise floor, the overall mean change is reduced and the change is no longer significant. In contrast, after altering the one-way noise floor substitution into two ways, the observed enhancement around 3 kHz is now considered significant.

Illustration of SNR-inclusion and NFS

In order to illustrate how these inclusion schemes might affect the outcomes, part of the data from Figure 2.2 is reproduced below in Figure 7.1. It represents the mean TEOAE-amplitude and mean DPOAE-amplitude of the newspaper printing office (Chapter 2) with various inclusion criteria. Figure 7.1 illustrates how the amplitude of the emission is affected by exclusion of contributions with

SNR < 0, and by the application of noise floor substitution (NFS). The new figure represents three inclusion schemes: **A**. raw data (no SNR requirement, no NFS), **B**. SNR ≥ 0 **C.** SNR ≥ 0 & 1-way NFS (as originally presented in Chapter 2). The results look very similar but there are differences in overall amplitude. The raw data lead to the lowest emission amplitude (A), followed by the data after SNR and 1-way NFS (C). The data that are most severely restricted by the SNR criterion (B), result in the highest mean emission level. In parallel: the number of accepted data was highest for the raw data (no exclusions), then for the situation with NFS and lowest (most exclusions) for the SNR only criterion.

The percentages of accepted data for both the SNR only, and the 1-way NFS scheme are presented in Figure 7.2. It shows that the patterns are comparable across frequency but that there are approximately 10% more inclusions when data points that drop below the noise floor in the second measurement (1-way NFS) are taken into account.

Levels of DPOAE primaries

The stimulus levels chosen in the study in the subjects of Chapters 2 and 3 (i.e. L_1=75, L_2=70 dB SPL) were chosen to elicit responses above the possibly noisy environment of a printing office. For the controlled experiment with the dance music, lower stimulus levels were used (i.e. L_1=65, L_2=55 dB SPL). Lower stimulus levels generally result in lower overall emission levels, which in its turn could hypothetically have led to the exclusion of more data points. For normal hearing ears this effect is expected to be less than for ears with hearing loss.

This can be illustrated with the extra set of measurements that was mentioned in Chapter 2 where DPOAE-measurements were performed at L_1=65, L_2=55 dB SPL. With the same SNR requirement (SNR ≥ 0) the amount of data points was even further reduced to 60-70% between 4 and 6 kHz. As a consequence, a large amount of data points did not contribute to the overall analysis, while there might have been cases that initially had good emissions but dropped below noise floor in the follow-up measurements.

Emissions generated by lower level primaries are often considered to be better suited for detecting hearing loss (Avan & Bonfils, 1993; Gorga et al., 2007). It might be that with the chosen (higher) level of primaries in Chapters 2 and 3, the emission levels reflect a more passive part of the cochlea (Whitehead et al., 1992). Although low level primaries thus create a more sensitive test, the higher levels are more specific, i.e. when an emission is absent, one is even more sure that there is some form of hearing loss. This was the case for the workers in newspaper printing office reported in Chapters 2 and 3, where there were a lot of absent emissions in the high frequency region (unaffected by background noise) despite the higher level of the primaries

Upper limit of measurability

OAEs are generally considered to be byproducts of outer hair cell activity. They are absent when OHC damage is substantial. This places an upper limit on the measurability, caused by the compressive function of the OHCs which 'ends' around hearing thresholds levels of 60 dB HL. This limit has been confirmed by data from a large study by Gorga et al. (1997) and is unaffected by choice of SNR inclusion.

While the damaging noise exposure continues, OHCs in the lower frequency regions will be affected, resulting in changes in emission levels. In the region where OHC damage is maximal, additional exposure may lead to damage in IHCs and/or other structures. For subjects that already have substantial hearing loss, follow-up with audiometry is warranted since it can be expected that their emissions will not decrease any further because of the above-mentioned limit (floor effect). Whether the upper boundary should be set at thresholds exceeding 40, 50 or 60 dB HL is open for debate, but this limitation should be considered in occupational settings when there is a large chance of pre-existent hearing loss, e.g. in an older population of employees.

Individual shifts

Methodology of determination of individual shifts

Chapter 4 compared various studies in the field of monitoring NIHL with OAEs. There is large variety between various studies in the methods used to report individual significant shifts in both PTA and OAE. The lack of agreement when to consider individual changes as significant hinders comparison across studies: some used a statistical computation while others used a pre-defined amount of change, see Table II in Chapter 4. The review showed that there is agreement between several studies on using the standard error of measurement (*SEM*) to construct a confidence interval of change (*CIC*) to classify whether an observed shift is significant. This results in an exact values for a significant threshold shift (STS) in case of PTA, or for significant emissions shifts (SES) in case of TOAEs and DPOAEs.

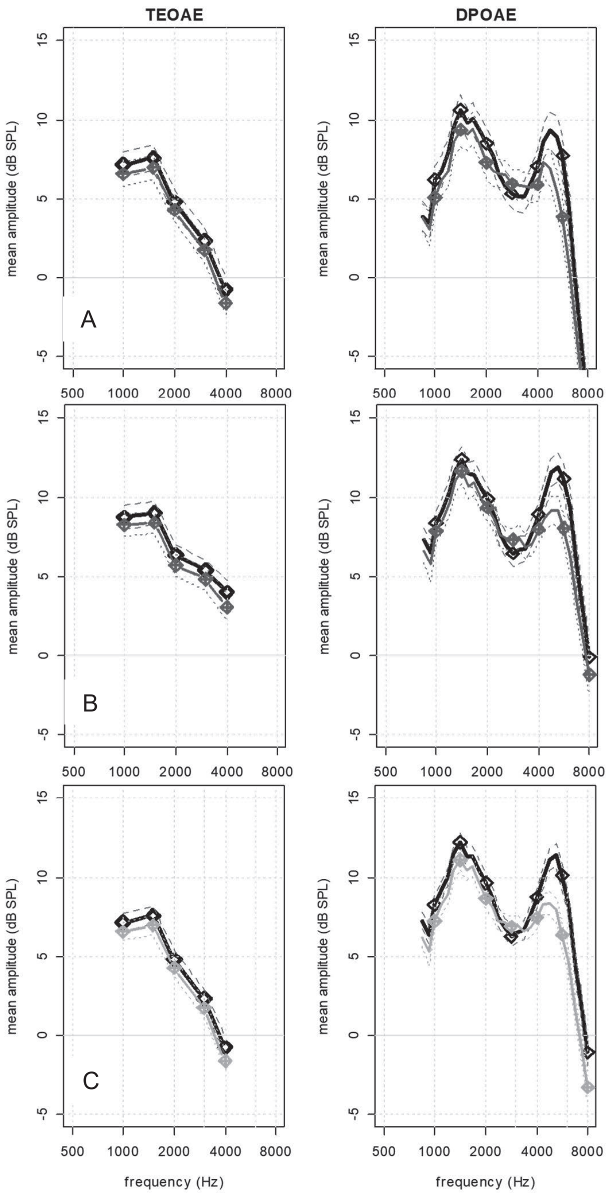


Figure 7.1: The effects of SNR and 1-way NFS inclusion on the overall TEOAE-level and the DPOAE level. Data for measurement 1 and 2 are plotted. **A**(Top panels): Raw data, no SNR no NFS: TE ranges from +7 dB SPL to -1.5 dB SPL, DP from 10 dB SPL to far below -5 dB SPL. **B** (Middle panels): SNR ≥ 0: emission amplitudes are higher, TE ranges from +9 dB SPL to +3.5 dB SPL, DP from +12.5 to -1 dB SPL. **C** (Bottom panels): SNR ≥ 0 & 1-way NFS as presented in Figure 2.2: emission amplitudes are between A and B, TE ranges from +7 dB SPL to -1.5 dB SPL, DP from +12 to -2.5 dB SPL

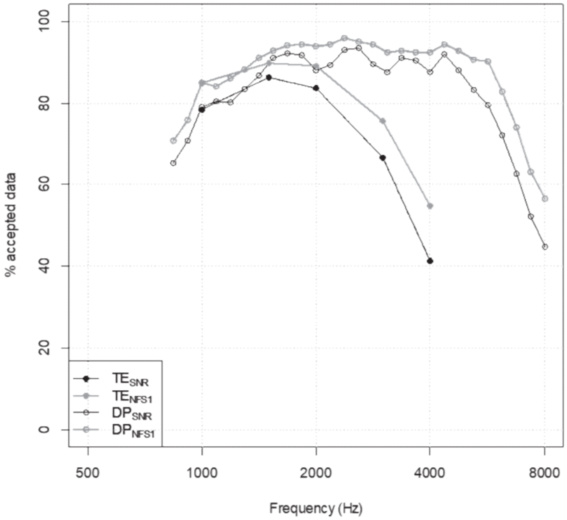


Figure 7.2: Percentage of accepted data after inclusion based on SNR ≥ 0 (black lines), and after noise floor substitution (NFS1) (grey lines). The percentages for both TEOAE (filled symbols) and DPOAE (open symbols) are plotted. Although the inclusion criterion affects the percentage of accepted data at all frequencies, the effect is more pronounced in the higher frequencies.

Effects of fence criteria

Reduction of measurement variability reduces the *SEM* and subsequently the *CIC*. Furthermore, the choice of the confidence interval (e.g. 95% or 90%) also determines the *CIC*. A lower *CIC* would result in more shifts being labelled as a STS or SES. Merely counting number of STSs or SESs transforms a continuous outcome in a dichotomous outcome, thereby discarding much information. The scatterplots in Chapter 3 show that most ears show individual reductions of emission levels and increases in hearing threshold levels within the boundaries of the *CIC*, without being significant at group level. These plots illustrate the effect of the fence on the numbers of significant individual shifts while maintaining information about the distribution of the observed changes. This method is also applied to individual short term effects of dance music exposure in Chapter 6. A similar pattern was found: the observed changes fall mostly below the unity line but within the boundaries of the *CIC* caused by measurement variation. The cross-over design shows that there are only a few ears that exhibit significant shifts in a consistent way on both occasions.

Computation of the SEM

The method of constructing the *SEM* was first described by Ghiselli et al. (1964) and has been used in several studies on OAEs (Beattie et al., 2003; Beattie &

Bleech, 2000; Keppler et al., 2010; Lapsley Miller et al., 2006; Ng & Mcpherson, 2005; Stuart et al., 2009; Wagner et al., 2008). But there are some underlying differences in the actual computation of the *SEM*, as discussed in more detail in Chapter 3. These stem from a different choice for the reliability parameter *r*, such as Pearson's moment correlation *r*, Cohens's kappa, *k*, or the intraclass correlation coefficient (*ICC*) in its various forms (Weir, 2005). Although the effects of these different choices seem marginal at first glance, the resulting differences in *CIC* are enlarged through the multiplication of the factor *1-r* (3.1), with the z-score corresponding to the chosen confidence interval (3.2). All *SEM*s from the studies in this thesis (except those by other authors in the review of Chapter 4) are derived with Pearson's moment correlation and all *CIC*'s are derived for a 95% confidence interval (i.e. z-score of 1.96, CIC_{95}). Explicitly stating the components of the *SEM* and the limits chosen (e.g. 90%, 95%, or 98%) is advised as a prerequisite to allow comparison across studies since the current practice is that everybody is using their own (convenient) criteria.

Effects of averaging

Another factor that hinders comparison across studies is caused by averaging across a certain frequency range. The data from Chapter 6 have been averaged across a rather broad frequency span (i.e. 1-4 kHz) to reduce outcome parameters after assessing that the effect was comparable across this range. The data from Chapter 3 were averaged across a smaller range.

In order to compare the *SEM*s from both datasets, Figure 3.1 is recreated in Figure 7.3 with the addition of the data from Chapter 6 (dance-music experiment). The ½ octave bands *SEM*s around 1.5 and 3 kHz for DPOAE were added for illustration as well, although these were computed based on 4 points per octave (thus averaging over 2 single frequencies) whereas those from *SEM*s for Chapter 3 were based on 8 points per octave (averaging over 4 single frequencies).

The *SEMs* for single frequencies can directly be compared between the two data sets. This shows smaller (better) *SEM*s for the single frequency measurements for PTA, TEOAE and DPOAE in the controlled experiment of Chapter 6. It also shows that averaging –generally speaking- reduces measurement variability when compared to single frequencies, thereby lowering the *SEM*.

Effects of 1 dB stepsize on the SEM for PTA

The dance-music experiment, described in Chapters 5 and 6, showed that smaller steps in audiometry reduced the test-retest variability for PTA and thus reduced the *SEM* from 5.2 dB HL to 1.4 dB HL. Consequently, any change larger than 3.8 dB HL was considered significant in this experiment. This is much lower than the results measured in 5 dB steps (Chapters 2 and 3) where a change was considered significant when it exceeded 14.5 dB HL.

Figure 7.3 shows that between 1 and 4 kHz, the *SEM* for PTA is lower than between 6 and 8 kHz for both datasets. Averaging in that frequency region for the data from Chapter 3 would also have reduced variability and thus smaller changes to be labelled as significant. But although averaging is part of the explanation, the single frequency *SEMs* of Figure 7.3 show that the step size of 1 dB severely reduces measurement variation allowing for a more accurate determination of the threshold.

Nevertheless, despite the lower CIC_{95} in the controlled experiment of Chapters 5 and 6, the number of cases that exhibited an STS was too low to warrant any in-depth analysis on comparison of STSs and SESs.

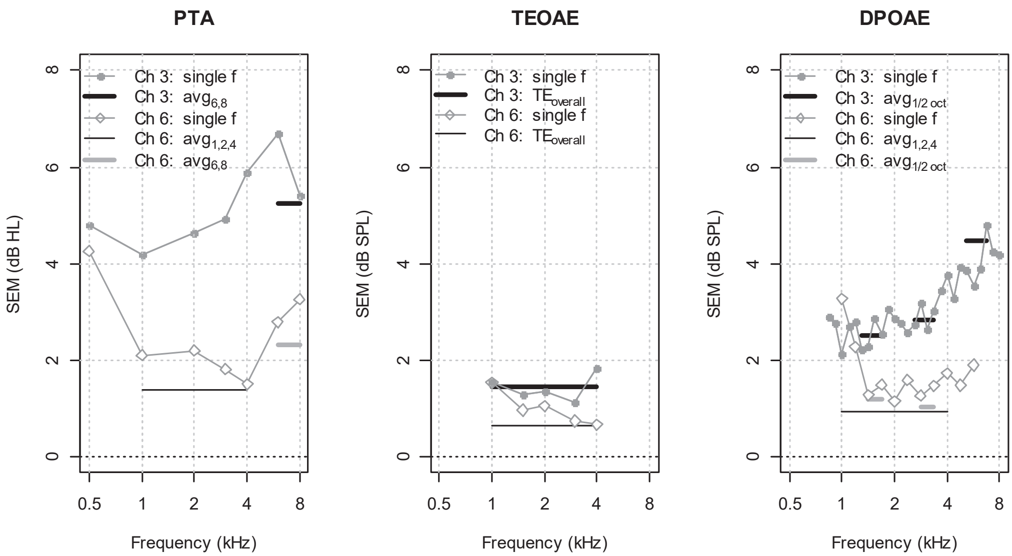


Figure 7.3: *SEM*s for pure-tone audiometry (left), TEOAE (middle) and DPOAE (right) recreated from Chapter 3 (newspaper printing office) for both single frequencies (·) and for combinations of frequencies (thick solid line). *SEM*s from Chapter 6 (dance music experiment) are added, both for the single frequencies (◊) and for the used average of 1,2 and 4 kHz (thin solid line line), and for ½ octave bands (grey line).

Effects of SNR on the SEM

Marshall and Lapsley Miller et al. (2006) recommend that every group under investigation requires its own norm data, in order to derive its own test-retest variability based on specific measurements conditions. In contrast to that opinion, Reavis et al. (2015) have asked the question whether it is possible to define a common standard in DPOAE measurements that tells when a change is considered suspicious enough to warrant further investigation through repeating the measurements and/or adding diagnostic tests (i.e. audiometry). They reported a meta-analyses of repeated measures in OAE data for optimization of a monitoring program in ototoxicity and retrieved data from 10 individual DPOAE studies who reported test-retest data, including data from the study in Chapters 2 and 3. Instead of looking at test-retest data at a combination of frequencies, they requested and included the original data at single frequencies. Reavis and colleagues assumed that more precise test-retest standards can be obtained by combining the values from different studies, regardless whether they stem from research done in the field of ototoxicity, NIHL or OAE-methodology.

The - valid- rationale behind such meta-analysis is that all individual studies are subject to sampling variation and that combining them would give a better predictor of the actual *SEM*. But this rationale is in contrast with the choice made in the review from Chapter 4. There it was explicitly chosen *not* to perform meta-analysis because of the heterogeneity of the underlying data sets. Does the heterogeneity, for example caused by different inclusion criteria, affect the *SEM*? It has already been illustrated how an SNR-based criterion affects absolute emission levels as seen in the longitudinal analysis (Chapters 2 and 3), but does it also affect short-term test-retest reliability?

The *SEMs* in OAEs for the young, normal hearing subjects in Chapters 5 and 6 were lower (better) than for the older noise-exposed employees in the newspaper printing office of Chapters 2 and 3. Note that the inclusion criterion (SNR ≥ 0 dB) and underlying statistics (see below) were identical in both groups of subjects. For the overall TEOAE, the *SEM* of the normal hearing subjects of Chapters 5 and 6 was 0.63 dB SPL versus 1.5 dB SPL in the older noise exposed subjects of Chapters 2 and 3. For the averaged DPOAE emission level between 1 and 4 kHz, the *SEM* of the normal hearing subjects of Chapters 5 and 6 was 0.93 dB SPL, versus 2.5-4.5 dB SPL for the averaged DPOAE emission level around 1.5, 3 and 6 kHz (Figure 7.3).

The broader region of averaging is only a partial explanation for the lower *SEM*s found in the dance music experiment of Chapter 6. The single frequency *SEMs* of Figure 7.3 are also much lower than those from the elder subjects suggesting that the higher quality of emissions in the youngsters reduces measurement variability. Thorson et al. (Thorson et al., 2012) reported that small emission levels in subjects with some hearing loss were more variable over time than emissions with larger amplitudes. Results from other studies with younger subjects and higher SNR requirements also resulted in lower *SEM*s. Keppler et al. (2010), for example, reported very low *SEM*s in young people, ranging from 0.7 to 1.6 dB SPL for SNR ≥ 0 dB, and from 0.7 to 1.3 dB SPL when SNR ≥ 12 dB was required(L_1=65, L_2=65 dB SPL). But the computation of these *SEM*-values were based on a slightly different choice for the reliability parameter. Therefore, one should be careful to directly compare the thus obtained *SEM*-values from the ones reported in Chapter 6.

The SNR-requirements that were used in the above-mentioned meta-analysis from Reavis et al. (2015) ranged from 0 to 3, 6, 10 and to 12 dB SNR. The *SEM*s from all 10 included studies ranged from 0.57 to 3.9 dB SPL and were computed at 1, 2, 4 and 6 kHz. When compared with the other studies, the contributions obtained from Chapters 2 and 3 were in the higher region/ the highest, with studies with SNR ≥ 0 dB generally having higher *SEMs* than studies with stricter inclusions. The requirement of SNR ≥ 6 dB is often seen as inclusion criterion in OAE-studies (Beattie et al., 2003; Bhagat & Davis, 2008; Kumar et al., 2013; Shupak et al., 2007; Wagner et al., 2008). This value stems from the early days in OAE testing, when studies showed that requiring an SNR of 6 dB allows a false positive rate of 0.05, i.e. falsely labelling an emission as present when it is not (Kimberley et al., 1997). According to Wagner et al. (2008) there is little effect of the SNR on the reliability, as expressed by the *SEM*, as long as the SNR is 6 dB or higher.

When the criterion of 6 dB is applied to the test-retest data of the employees in the printing office of Chapter 3, lower *SEM* values were obtained. They were on average 1 dB lower/ better than those for the original dataset(with SNR ≥ 0 dB) despite the doubling of the number of exclusions. Consequently, the CIC_{95} was reduced with approximately 2.8 dB. This computation illustrates that lower emissions have larger variability (as expressed in higher *SEM*s) and thus require larger changes to become significant. The accuracy in detecting significant changes is higher in a population with ears having higher emissions. This effect of the SNR on repeatability should somehow be taken into consideration when pooling data from different studies, or when applying general standards on different populations.

Recommendations in reporting

Comparisons between the results from other studies and those from this thesis are hindered by some methodological differences. These differences have been mentioned in the review and the effects on the outcomes are more thoroughly assessed in this general discussion. For future studies, and possible meta-analysis of data there are some recommendations that can be made with regard to presentation of the data. Access to raw data and measures of spread allows assessment of choices made in averaging, SNR-inclusion, dependency between ears, and fence criteria. Raw data can be visualized in graphs or tables and placed in an (online) appendix.

It is a matter of speculation but if all studies included in the review in Chapter 4 had presented their raw data, maybe the enhancements in DP -amplitudes would have not been considered erroneous or paradoxical.

Added value/ general conclusion

What can we learn from this work and from the combination of studies presented in this thesis? The question why we measure hearing is of relevance in the determination of the added value of OAEs, when compared with PTA. What do we want to know?

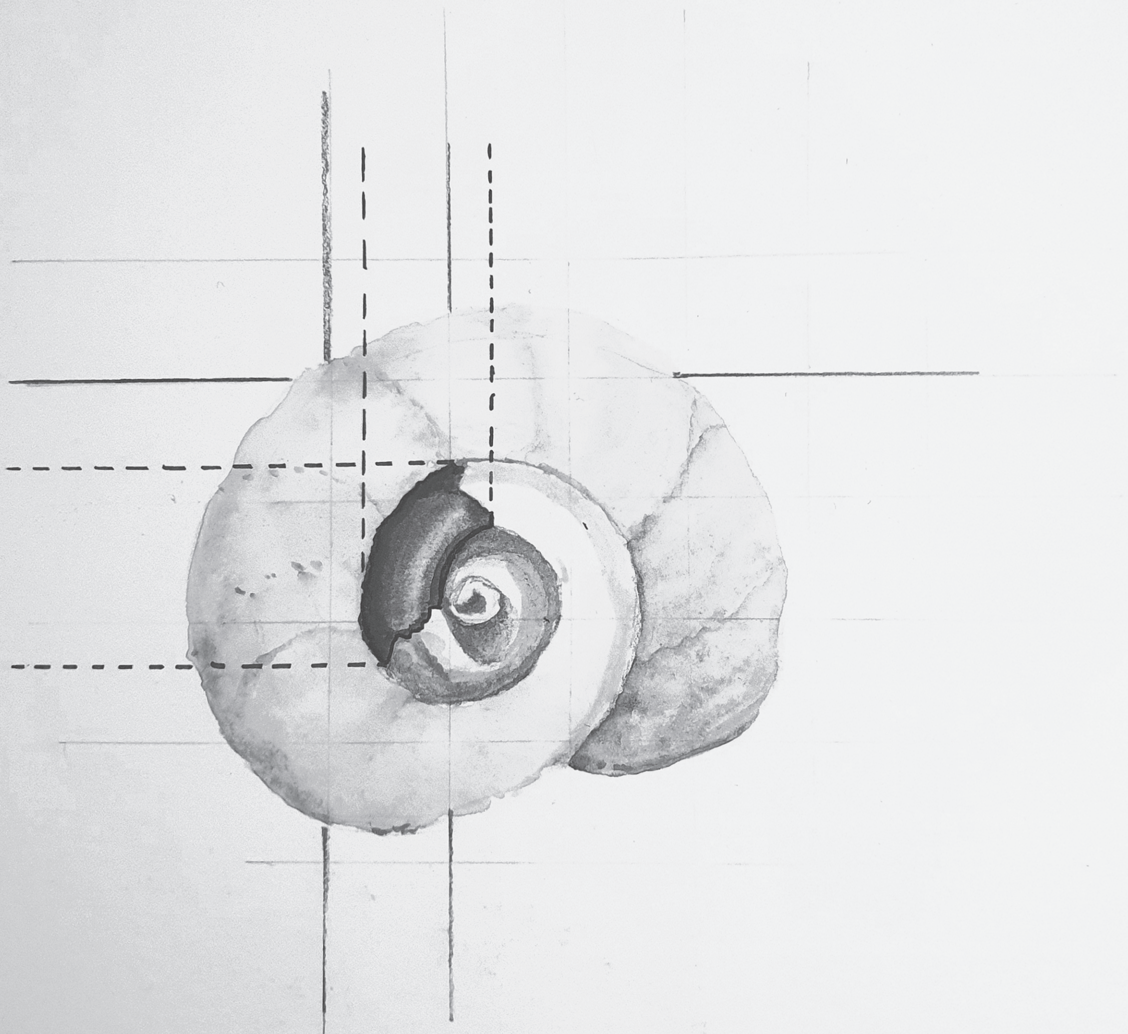
When looking for early detection, the studies in this thesis are not optimally suited for predictive analyses. That would require a longer follow-up and more measurements. Chapters 2 and 3 have stepped away from cross sectional studies discussing the merit of OAEs and have collected data in a longitudinal approach. Unfortunately, we only had two measurements to compare changes. But the review in this thesis (Chapter 4) has shown that the existing data regarding predictive values in longitudinal settings is scarce, and very heterogeneous in setup. The discrepancies in the underlying studies implied that there was no clear evidence that OAEs are able to predict future noise-induced hearing damage in an earlier phase than PTA.

Both OAEs and PTA show signs of damage after exposure to noise, especially when looking at results at group level. But the study from Chapter 3, as well as other studies included in the review of Chapter 4, and the cross-over design in the controlled experiment of Chapter 6, have shown that significant OAE shifts cannot reliably detect significant shifts in hearing tresholds. When the goal is to assess hearing threshold levels and/ or hearing threshold shifts, for example for medicolegal purposes, pure-tone audiometry is still required. OAEs cannot replace the audiogram in that respect. They can be used in parallel, or for specific purposes.

Measurement of PTA in small steps makes both methods (in OAE-settings considered here) equally sensitive for small, short-term temporary effects of hearing damage, presumably only peripheral damage. This makes them both suitable to inform subjects exposed to noise about the effects of exposure habits and the use of hearing protective devices (HPDs) on their hearing. The objectiveness of OAEs may be considered as an advantage in assessing the effects of HPDs during a workday. Such procedures can also be used to investigate the effect of other control measures of a hearing conservation program. By assessing a group-averaged emission shift before and after shielding of certain equipment, the effect of the control measure can be assessed. This is line with the recommendation of the Cochrane group to have a better evaluation of engineering solutions (Tikka et al., 2017). When this approach is used for elderly employees with pre-existing NIHL, OAEs have the disadvantage that the emissions can be absent in part of the population. If their contribution is included into the analysis of the overall effect, these ears will exhibit no change (absent remains absent). When the better ears show signs of temporary damage, the effect will be averaged across the group. This could results in an underestimation of the actual damage that is occurring and overestimation of the effectiveness of the control measure.

Therefore, application of OAEs should probably be limited to for those subjects with good emissions at the start, i.e. young, relatively good hearing subjects. They have higher emissions and subsequently less measurement variation than subjects that already suffer from outer hair cell damage. Despite technical improvements that might reduce the noise floor, better ears both have more room for decline and require less change to warrant further investigation. Another argument for monitoring with OAEs for young, relatively good hearing subjects comes from predictions of the ISO-1999 model that noise-induced hearing loss develops most during the first years of occupational exposure (ISO 1990).

In conclusion, OAEs in occupational settings should not be recommended as a replacement for PTA. They can be considered as an addition to the current practice depending on the specific goals of the audiological evaluation and on the population under investigation. When OAEs are added as an evaluation tool, it is important to carefully consider the quality of the measurements and also the chosen statistical method, since they both can substantially affect the outcomes.



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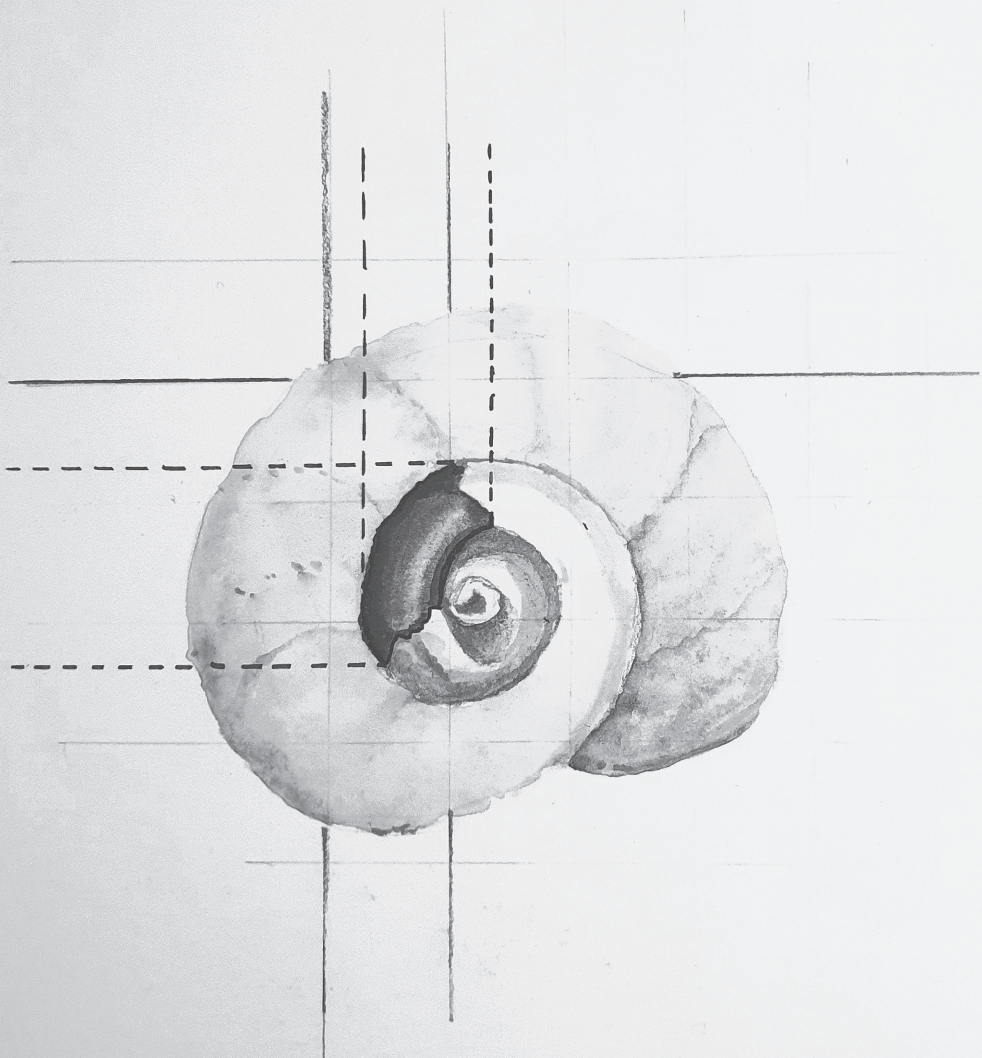
LIST OF ABBREVIATIONS

ARHL	Age-related Hearing Loss
CI	Confidence Interval
CIC	Confidence Interval of Change
dB	decibel
dB (A)	decibel A-weighted
dB HL	decibel Hearing Level
dB SPL	decibel Sound Pressure Level
DPOAE(s)	Distortion Product Otoacoustic Emission(s)
EOAE(s)	Evoked Otoacoustic Emission(s)
(k)Hz	(kilo) Hertz
HPD	Hearing Protection Device
ICC	Intraclass Correlation Coefficient
IHC	Inner Hair Cell
ISO	International Organization for Standardization
MN	Mild Notch
NFS	Noise Floor Substitution
NH	Normal Hearing
NIHL	Noise-Induced Hearing Loss
MIHL	Music-Induced Hearing Loss
OAE(s)	Otoacoustic Emission(s)
OHC(s)	Outer Hair Cell(s)
PN	Profound Notch
PTA[1]	Pure-Tone Audiometry
PTS	Permanent Threshold Shift
RE	Rest
SD	Standard Deviation
SEM(s)[2]	Standard Error of Measurement
SE_{meas}	Standard Error of Measurement
SE_{mean}	Standard Error of the Mean
SES(s)	Significant Emission Shift
SL	Sloping
SN	Subnormal (hearing)
SNR	Signal-to-Noise Ratio
STS(s)	Significant Threshold Shift
TEOAE(s)	Transient Evoked Otoacoustic Emission(s)
TTS	Temporary Threshold Shift

[1] *not to be confused with Pure Tone Average*
[2] *not to be confused with Standard Error of the Mean*



SUMMARY & SAMENVATTING

SUMMARY

Noise-induced hearing loss (NIHL) is a global problem, and is most often caused by prolonged occupational exposure to loud sounds in various industries. But leisure activities such as listening to loud music or riding a motor bike can be damaging as well. Knowledge on the relation between noise exposure and hearing damage has accumulated in the wake of the widespread use of the steam engine in the Industrial Revolution. **Chapter 1** is a general introduction on noise induced hearing loss, described from a historical point of view. It provides information on the mechanisms of hearing damage, especially on how outer hair cells are affected by noise exposure. Since otoacoustic emissions (OAEs) are generated by the activity of the outer hair cells, they are of potential interest for monitoring the development of hearing loss in noise exposed subjects. This thesis discussed the potential use of OAEs in monitoring hearing damage caused by noise, and discussed the comparison with pure-tone audiometry (PTA).

Chapters 2 and **3** discussed hearing in a longitudinal setting in noise exposed workers in a newspaper printing office. **Chapter 2** explored the applicability of OAE-measurements in an occupational setting. It showed that for many noise exposed subjects with a long-term history of exposure, and according hearing loss, OAEs could not reliably be measured. For the high frequencies, i.e. at 4 kHz and above, the emission level dropped below the noise floor while the hearing threshold continued to worsen in that region. OAEs are often considered to be present when they exceed the noise floor with a certain amount (signal-to-noise ratio, SNR). With a criterion of SNR ≥ 0, the number of included data points reaches a maximum of 90% for both TEOAE and DPOAE in the region around 2 kHz, reducing for both lower and higher frequencies. For the TEOAE around 4 kHz, the percentage of valid data points is approximately as low as 50%. For the DPOAE at 6 kHz the percentage is 80%, and at 8 kHz the percentage is only 60%.

Chapter 3 looked at the same subjects as in **Chapter 2** but focused on differentiation of (random) changes from significant shifts and showed that overall, both PTA and OAE show significant worsening of hearing over time. Exploration of the relation of individual changes within each subject showed that there was no congruency between changes in PTA and changes in OAE. Most ears contributed a little in the overall effect of significant worsening of hearing. But almost all individual changes were too small to be labelled as significant shifts, both for PTA and OAE. The occurrence of significant individual shifts was

very low, and near chance level. An interesting finding from the study presented in **Chapters 2 and 3** was that at group level, the DP-emission level in the mid frequency region *increased* significantly, implying an enhancement of OAEs instead of the expected reduction. This phenomenon occurred more often in ears where emissions in the higher frequencies were missing, with a substantial hearing loss in this region.

The review in **Chapter 4** compared the above-mentioned results with similar studies on longitudinal changes in OAEs and PTA caused by occupational exposure. An obvious limitation in many studies, including the study discussed in **Chapters 2** and **3**, is that they consist of only 2 measurements. This makes them suited to discuss the changes in hearing over time and compare OAE and PTA in that respect. But in order to discuss the potential to predict future hearing loss, more measurements and a generally longer follow-up are required. The studies included in the review were very heterogeneous in manner of reporting, statistical techniques to determine significant shifts, number and age of subjects, required SNR, and stimulus parameters of the emissions, thereby hindering straightforward comparisons between studies. But the lack of agreement between changes in OAE and PTA, and the lack of simultaneous occurrences of significant PTA and OAEs shifts was clear from all studies.

Leisure noise activities may cause hearing damage as well, either temporary or permanent. This thesis has shown in **Chapters 5** and **6** that temporary damage occurs after music exposure at levels lower than encountered in real life clubbing or concert situations. Both small-step PTA and OAE were capable of detecting these small changes at group level, caused by listening to dance music during two hours, either consecutively or with a break in between. Both techniques showed that there was no difference for the total temporary damage with or without the presence of a break. Both PTA and OAE can be used to demonstrate temporary and small effects of noise on hearing. The cross-over design showed that the occurrence of individual significant shifts was not reproducible within ears. Furthermore, there was no congruency between individual changes in PTA and OAE.

The long-term study of the newspaper printing office and the short-term study on controlled dance music exposure, were very different in nature in terms of subjects, initial hearing, exposure, etc. But despite these differences there are important findings based on the combination of the results. Individual significant shifts in OAEs could not reliably detect individual significant shifts in hearing threshold. At group level, both methods were capable of detecting small changes, especially when PTA was measured in a smaller step size. Additionally, for young and normal hearing subjects the accuracy in which an individual change in OAE can be labelled as significant is higher than for elderly, noise-exposed subjects. This argument implies that when OAEs are considered for monitoring NIHL, OAEs are more suitable in young subjects with relatively good hearing as a starting point in the early stages of NIHL.

In conclusion, OAEs in occupational settings should not be recommended as a replacement for PTA. OAEs can be considered as an addition to the current practice depending on the specific goals of the audiological evaluation and on the population under investigation.

SAMENVATTING

Gehoorverlies door lawaai expositie (ofwel Noise Induced Hearing Loss: NIHL) is een wereldwijd probleem en wordt meestal veroorzaakt door langdurige, beroepsmatige blootstelling aan harde geluiden. Ook activiteiten in de vrije tijd kunnen schadelijk zijn, denk hierbij aan luisteren naar luide muziek of motorrijden. De kennis over de relatie tussen blootstelling aan lawaai en gehoorschade heeft zich sterk ontwikkeld in de periode na de opkomst en wijdverbreide gebruik van de stoommachine in de industriële revolutie.

Hoofdstuk 1 is een algemene inleiding over lawaaischade, beschreven vanuit een historisch oogpunt. Het geeft informatie over de mechanismen van gehoorbeschadiging, en vooral over hoe de buitenste haarcellen worden beïnvloed door blootstelling aan lawaai. Aangezien otoakoestische emissies (OAE's) worden gegenereerd door de activiteit van de buitenste haarcellen, zijn ze van potentieel belang voor het volgen van de ontwikkeling van gehoorverlies bij personen die aan lawaai zijn blootgesteld. Dit proefschrift besprak het mogelijke gebruik van OAE's in het monitoren van lawaaischade aan het gehoor, in vergelijking met reguliere audiometrie (pure-tone audiometry: PTA).

In **hoofdstukken 2** en **3** werd het gehoor besproken van werknemers die blootgesteld worden aan lawaai in een krantendrukkerij, waarbij het ging om een herhaalde metingen en dus een longitudinale setting. **Hoofdstuk 2** onderzocht de toepasbaarheid van OAE-metingen in een de bedrijfsgezondheidzorg, door vergelijking van uitkomsten in TEOAEs (Transient Evoked Otoacoustic Emissions) en DPOAEs (Distortion Product Emissions) met reguliere audiometrie. Het toonde aan dat OAE's niet betrouwbaar gemeten konden worden bij mensen met reeds bestaand gehoorverlies ten gevolge van langdurige lawaai-expositie. Voor de hoge frequenties, d.w.z. bij 4 kHz en hoger, daalde het emissieniveau onder de ruisvloer terwijl de gehoordrempel in dat gebied verder verslechterde. OAE's worden als aanwezig bestempeld wanneer de emissie een bepaalde, exacte verhouding heeft ten opzichte van de ruisvloer (signaal-ruisverhouding, SNR). Met een criterium van SNR ≥ 0 bereikt het aantal geïncludeerde datapunten een maximum van 90% voor zowel TEOAE, als DPOAE in de regio rond 2 kHz. Dit percentage neemt af voor zowel lagere als hogere frequenties. Voor de TEOAE rond 4 kHz bedraagt het percentage geïncludeerde datapunten hooguit 50%. Voor de DPOAE bij 6 kHz is het percentage 80% en bij 8 kHz is het percentage slechts 60%.

S

Hoofdstuk 3 bekeek dezelfde proefpersonen als in Hoofdstuk 2, maar richtte zich op het onderscheiden van willekeurige ten opzichte van significante veranderingen. Het toonde voor het groepsgemiddelde een significante verslechtering van het gehoor in de tijd aan. Onderzoek naar de relatie van individuele veranderingen binnen een proefpersoon toonde aan dat er geen duidelijke overeenkomst was tussen veranderingen in PTA en veranderingen in OAE. Aan de algehele significante verslechtering van het gehoor droegen de meeste oren in beperkte mate bij. Maar bijna al deze individuele veranderingen waren te klein om zelf als significante verandering te worden aangeduid, zowel voor PTA als voor OAE. De hoeveelheid significante verandering was erg laag en op kans niveau.

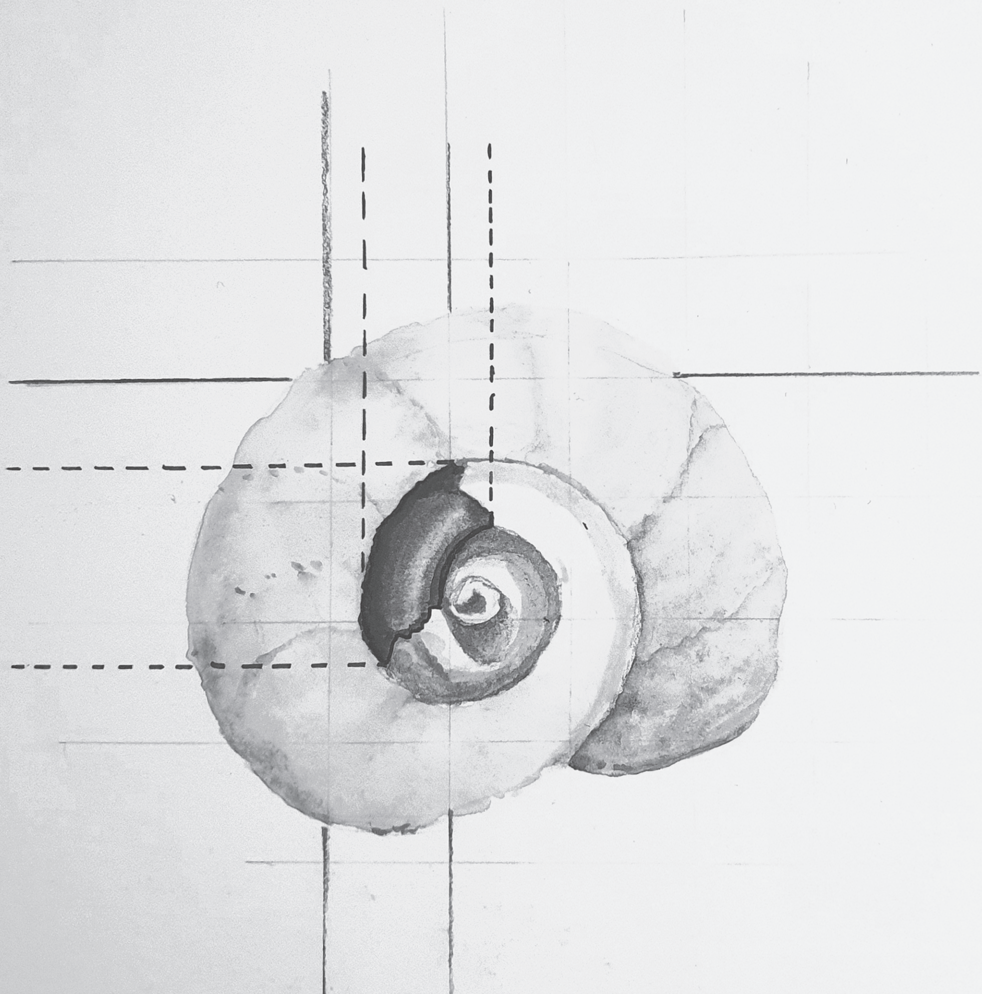
Een interessante nevenbevinding van de studie gepresenteerd in de hoofdstukken 2 en 3 was dat het DP-emissieniveau voor het groepsgemiddelde in het middenfrequentiegebied significant steeg. Dit lijkt een verbetering van OAE's te suggereren in plaats van de verwachte vermindering. Dit fenomeen leek vaker voor te komen in oren waar emissies in de hogere frequenties ontbraken, en zou daarmee juist een teken van verslechtering kunnen zijn.

In het literatuuronderzoek in **hoofdstuk 4** werden de bovengenoemde resultaten vergeleken met vergelijkbare studies naar longitudinale veranderingen in OAE's en PTA door beroepsmatige blootstelling aan lawaai. Een voor de hand liggende beperking in veel onderzoeken, waaronder de studie die in de hoofdstukken 2 en 3 wordt besproken, is dat deze uit slechts twee metingen bestaan. Dit maakt hen geschikt om de veranderingen in het gehoor in de tijd te bespreken en OAE's en PTA in dat opzicht te vergelijken. Maar wanneer het gaat om de mogelijkheid van het kunnen voorspellen van toekomstig gehoorverlies, zijn meer metingen en langere follow-up vereist. De onderzoeken opgenomen in het review, waren zeer heterogeen, Het gaat hierbij om verschillen in statistische technieken om significante verschuivingen vast te stellen, aantal en leeftijd van proefpersonen, vereiste SNR's en stimulusparameters van de emissies. Deze heterogeniteit belemmerde rechtstreekse vergelijkingen tussen studies. Desondanks kwam in alle studies het gebrek aan overeenstemming tussen veranderingen in OAE en PTA en het ontbreken van gelijktijdige optredende significante PTA- en OAE-verschuivingen duidelijk naar voren.

Lawaaischade, tijdelijk of permanent, kan ook optreden na activeiten in de vrije tijd. **Hoofdstukken 5** en **6** van dit proefschrift toonden aan dat tijdelijke schade optreedt na blootstelling aan muziek op een niveau dat lager is dan in echte club- of concertsituaties. De expositie bestond uit het luisteren naar dansmuziek gedurende twee uur, hetzij opeenvolgend, hetzij met een pauze ertussen. Zowel PTA, gemeten in kleine stapgrootte, als OAE's waren in staat om deze kleine veranderingen op groepsniveau te detecteren. Beide technieken lieten zien dat er geen verschil was voor de totale tijdelijke schade met of zonder de aanwezigheid van een pauze. Zowel PTA als OAE kunnen worden gebruikt om tijdelijke en kleine effecten van hard geluid op het gehoor aan te tonen. Het cross-over ontwerp toonde aan dat het optreden van individuele significante verschuivingen binnen de oren van één proefpersoon niet reproduceerbaar was. Bovendien was er geen overeenstemming tussen individuele veranderingen in PTA en OAE.

Het lange termijn onderzoek van de krantendrukkerij en het korte termijn onderzoek naar gecontroleerde blootstelling aan dansmuziek liepen uiteen wat betreft proefpersonen, gehoor, blootstelling enz. Maar ondanks deze verschillen zijn er belangrijke bevindingen op basis van de combinatie van de resultaten. Individuele significante verschuivingen in OAE's konden individuele significante verschuivingen in gehoordrempel niet betrouwbaar vaststellen. Op groepsniveau waren beide methoden in staat om kleine veranderingen aan te tonen, vooral wanneer PTA in een kleinere stapgrootte werd gemeten. Daarbij is voor jonge en normaal horende proefpersonen de nauwkeurigheid waarmee een individuele verandering in OAE als significant kan worden aangemerkt, hoger dan voor oudere, aan lawaai blootgestelde proefpersonen. Dit impliceert dat als OAE's worden overwogen voor het monitoren van lawaaischade, ze geschikter zijn bij jonge proefpersonen met een relatief goed gehoor als uitgangspunt.

Kortom, OAE's zouden niet moeten worden aanbevolen als vervanging voor PTA in de bedrijfsgezondheidszorg. Wel kunnen ze worden beschouwd als een aanvulling op de huidige praktijk, afhankelijk van de specifieke doelen van de audiologische evaluatie en van de onderzochte populatie.



DANKWOORD

DANKWOORD

Het heeft even geduurd… Een duurloop, of is het beter te vergelijken met een lange zeiltocht? Er zijn momenten dat je lekker opschiet maar ook momenten dat je niet verder kunt. Wind tegen, storm of averij. Soms moet je je koers wijzigen, kan je niet uitvaren, lig je verwaaid in een haven of moet je omdraaien. Daarna moet je weer alle moed bijeen rapen om voort te gaan en kost het moeite om weer vooruit te komen. Maar ook als het windstil is schiet de tocht niet op. Bij deze wil ik eenieder bedanken die mij onderweg heeft aangemoedigd.

Wouter, dank voor je geduld en in het af en toe accepteren dat ik ergens voor anker lag. Het is intussen al lang geleden dat ik bij het AMC kwam voor mijn wetenschappelijk onderzoek. Binnen een paar maanden liepen we rond bij de drukpersen van de Telegraaf. Dat project heeft me uiteindelijk naar Amsterdam gebracht, waar ik mijn opleiding tot klinisch fysicus - audioloog heb afgerond. Bedankt voor alle inhoudelijke overleggen, leermomenten en ook interesse in mijn persoonlijke leven. Dank voor je rol als opleider en promotor. Ik hoop dat jouw afscheidssymposium de vorm kan krijgen zoals je dat verdient, en wens je veel geluk in deze nieuwe fase van je leven.

Dank Patrick, voor je ‘Het is wat het is’ en jouw rustige rol op de achtergrond en als extra sparringspartner in de eindfase van dit traject. Laten we de koffie op vrijdagmiddag er af en toe in houden!

Veel dank aan de leden van promotiecommissie voor het kritisch doorlezen en beoordelen van dit proefschrift.

Monique, ik wist al tijden dat *als* ik hier zou geraken, ik jou graag aan mijn zijde zou willen hebben. Dank voor je vriendschap, de gezelligheid en goede inhoudelijke discussies op het AMC. Ik koester hele goede herinneringen aan Orlando en Las Vegas, en zal niet gauw vergeten dat je zowaar boos heb gezien! Ook de laatste jaren kon ik even op je terugvallen voor muziektips (variatie op Eddie!), en advies op afstand, ‘kill your darlings’.

En dan de andere preventisten: Noortje en Marya. Jullie paden hebben elkaar niet gekruist, maar desondanks wil ik jullie allebei bedanken voor de samenwerking, het sparren over werk en over al die andere zaken die de revue passeerden. Miranda, jij hoort hier ook tussen! We startten samen bij De Telegraaf. Dank voor je feilloze organisatie bij dit project en later bij de musici. Ik hoop je nog vaak in Abcoude tegen te komen en even bij te praten. Hilde, eigenlijk hoor jij ook bij preventie. Zonder jou was dit boekje niet geweest wat het nu is, want zonder jouw doorzettingsvermogen had ik het review niet voor elkaar kunnen krijgen. Leuk dat we elkaar in het werkveld nog regelmatig zullen treffen!

Aan al mijn (oud) AMC collega's: heerlijk om zo warm welkom te worden geheten als ik weer even aan het werk was op het oude nest. Ik weet alleen niet of die gezelligheid de productiviteit nou echt ten goede kwam. Ik heb goede herinneringen aan al die donderdagochtenden met het research-overleg. Als ik iedereen op moet noemen, vergeet ik ongetwijfeld de nodige namen, maar in het bijzonder nog dank voor Rolph, Thamar, Maaike en Maaike, Tim en Sabine voor de samenwerking, collegialiteit, luisterende oren, broodnodige koffie, en afleiding. Marjolein, bedankt voor al je werk rondom het pauze-experiment.

Voor mijn Friese oud-collega's ook een speciaal woordje: dank jullie wel voor het warme welkom in Leeuwarden en daarmee mijn start in de audiologie.

Lieve collega's van het UMC Utrecht, Alex, Jojanneke, Jeanet, Inge en alle andere fijne collega's uit het AZU en WKZ: jullie betrokkenheid heeft me veel steun gegeven in de afronding van dit project. Ik kijk ernaar uit nieuwe (wetenschappelijke) projecten op te pakken. Zullen we dan toch die research bespreking zoals we die in het AMC hadden invoeren Koen? Jelmer, succes met jouw zeiltocht! Bert, intussen geen collega meer, maar ik ben nog steeds blij met de kans die je me gaf om nog een paar jaar van jouw expertise te kunnen leren. Last but not least, Ralf, het is zo goed samenwerken, te sparren, dingen aan elkaar over te kunnen laten en over van alles te kunnen praten. Ik vind het heel fijn dat ook jij naast mij wil staan op deze dag.

Maar ook naast het werk zijn er zovelen die mij in de loop van de tijd hebben vergezeld, en/of een hart onder de riem hebben gestoken. Dames A, voor de noodzakelijke afleiding en vriendschap naast het werk en gezin. Dank voor al jullie betrokkenheid en voor de gezelligheid in en om het veld! Esther en Marjolein, jullie nog een extra bedankje voor de koffie en peptalks na onze hardlooprondjes. Verder nog een woordje van dank voor Annet, voor je luisterend oor en aanmoediging.

Liief IJskoud, uit het oog is niet uit het hart. Jullie vriendschap door de jaren heen betekent veel. En Minke, jouw vriendschap al helemaal; van klas- naar club- en huisgenootje. Het begon echt met ons project over zonnepanelen, op het dak van de school. Ik kijk ernaar uit dat jullie weer in Nederland gaan wonen!

Sytske, hoe fijn is het dat we onze vriendschap altijd weer op kunnen pakken waar we gebleven waren? Ik vind het fantastisch dat jij zo enthousiast werd om een illustratie voor de voorkant te maken. Dank voor de prachtige tekening.

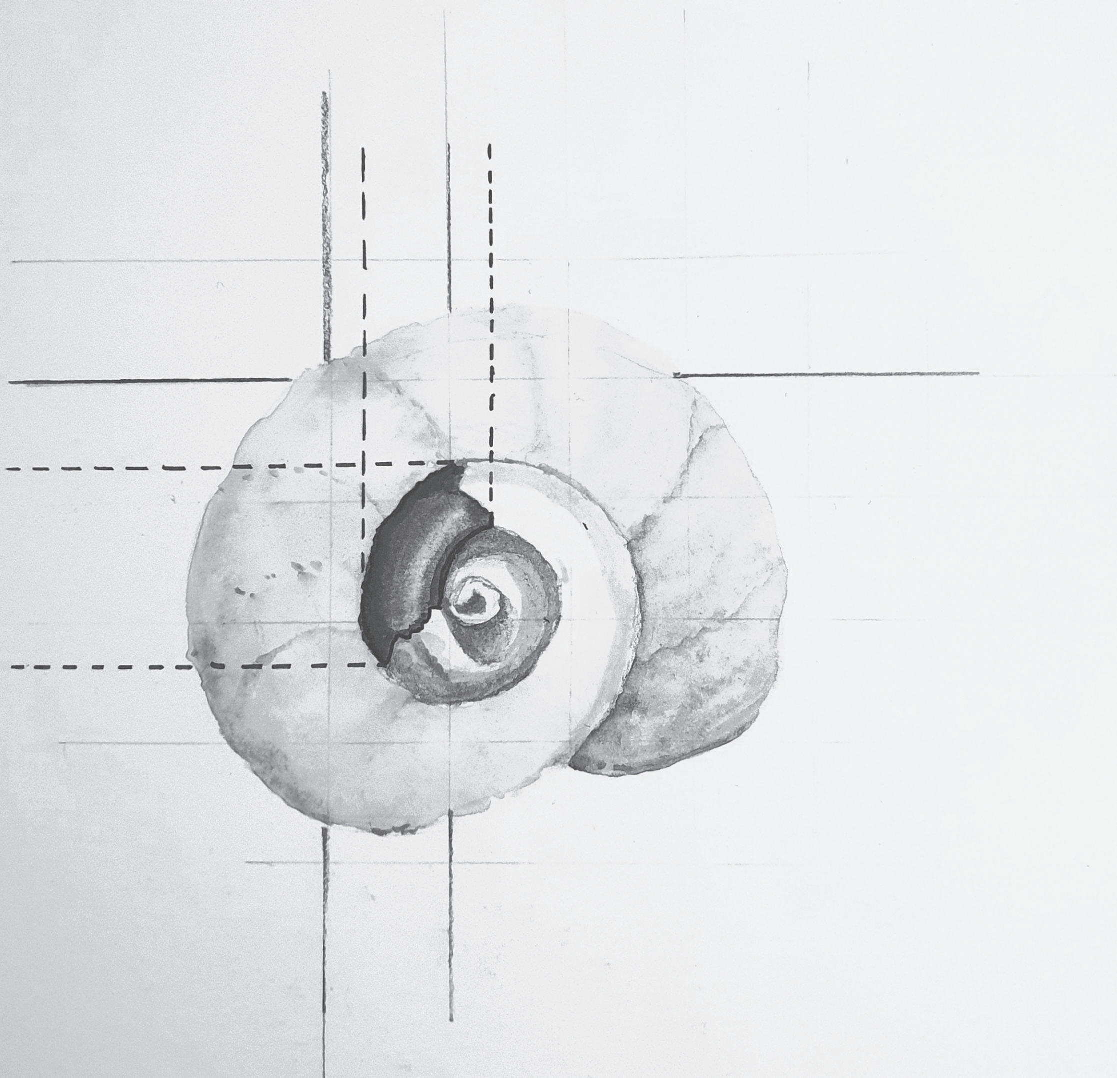
Mijn (schoon)familie: Tjerk, fantastisch dat je mijn proefschrift nog hebt kunnen lezen en dat we erover hebben kunnen praten. Nancy en Wim, jullie aandacht en belangstelling voor mijn onderzoek en natuurlijk ook de oppas vrijdagen hebben mij enorm gesteund. Govert en Kristina, en Aafke, ik ben blij dat ik jullie 'erbij' heb gekregen. Hajo, lieve grote broer, weinig woorden zijn nodig: ik weet dat je er bent als ik je nodig heb!

Mama, dit boekje draag ik op aan papa en aan jou. Jij bent een voorbeeld voor het doorgaan en keuzes moeten maken in moeilijke tijden. Je hebt zelf een vergelijkbaar traject moeten stopzetten toen papa voor het eerst - en niet voor het laatst- ziek werd. Je hebt me altijd aangemoedigd door te gaan. Papa, als jij er nog was geweest, had ik dit eerder af kunnen ronden. Jouw stem in mijn achterhoofd helpt me bij het navigeren.

'Is je boekje dan nu af?' Ja, lieve Meike en Saar, het is af. Het feest houden we tegoed in deze rare tijden. Ik vind het zo bijzonder dat jullie er echt bij kunnen zijn. Jullie zorgzaamheid voor mij, nieuwsgierigheid in de wereld, eerlijkheid en vooral jullie knuffels betekenen immens veel voor me.

En tenslotte, mijn lief, Sandor. Ik kan niet onder woorden brengen wat je voor me betekent. Jouw geduld, en steun zijn zo groot en onvoorwaardelijk geweest, niet alleen in dit proefschrift maar ook in alle andere zaken in mijn leven.

D



CV & PHD PORTFOLIO

CURRICULUM VITAE

Hiske Helleman was born on May 17th 1978 in The Hague. After graduation in 1996 from the Haags Montessori Lyceum (gymnasium), she studied Applied Physics at Delft University of Technology. Her Masters' thesis was done in the Laboratory of Acoustical Imaging and Sound Control. Subsequently, she obtained a position as Medical Physicist – Audiologist in training at the Audiological Centre Leeuwarden. In 2007 she transferred to the Academic Medical Centre (now Amsterdam UMC) in order to combine the further training for audiologist with scientific research projects in the department of Clinical and Experimental Audiology. She contributed on various projects concerning occupational hearing loss for 'Expertise centrum Gehoor en Arbeid' and took part in the group 'Prevention of Hearing Loss' with the work on OAEs and monitoring of NIHL.

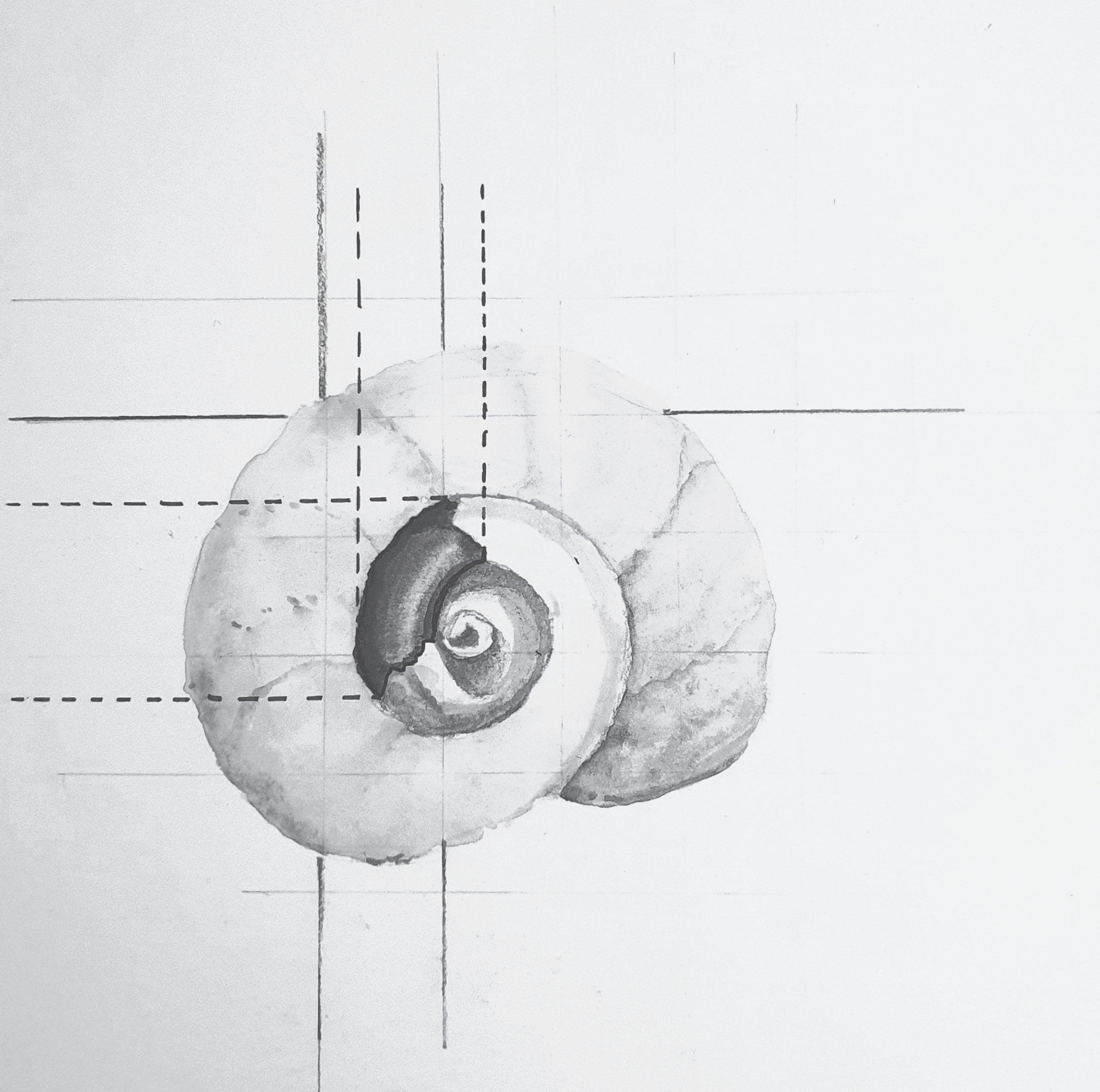
Since 2015, she has been working in the Audiological Centre of the UMC Utrecht as a Medical Physicist – Audiologist, while continuing with the research on OAEs and NIHL under supervision of professor dr. ir. Dreschler, leading to this thesis.

PHD PORTFOLIO

Name PhD student:	ir. H.W. Helleman	
PhD period:	2009-2020	
Name PhD supervisor:	Prof. dr. ir. W.A. Dreschler	
PhD training	**Year**	**ECTS**
Courses		
Time management	2012	0.3
BROK (‘Basiscursus Regelgeving Klinisch Onderzoek’)	2013	1.5
Teach the teacher	2015	0.5
BROK Recertification	2016-2020	0.5
Seminars, workshops and master classes		
‘International Expert Symposium on the usefulness of Otoacoustic Emissions (OAE) Testing in Occupational Health Surveillance’, (HSE), Manchester UK	2011	0.5
PACT-day (Platform for Audiological Clinical Testing	2013	0.2
Weekly audiology research meetings AMC	2009-2015	5
Biannual meeting Nederlandse Vereniging voor Audiologie	2009-2020	1
Annual ENT scientific research day	2012-2015	0.3
Annual KKAU meetings	2009-2020	1
Annual NVKF meetings	2009-2020	1
Monthly ENT research meetings UMC Utrecht	2015-2020	0.2
Workshop Insights in Influence, UMC	2018	0.1
Presentations		
National Hearing Conservation Associaton, Orlando, USA	2010	1
International expert symposium HSE, Manchester, UK	2011	1
ENT scientific research day	2013	0.3
National Hearing Conservation Associaton, Las Vegas, USA	2014	1
‘Multidisziplinarität in Der Audiologie’, DGA-NVA, Bochum Ge	2015	1
Pento symposium ‘Gehoor geven aan…’	2016	0.3
NVA presentation on review monitoring NIHL with OAE	2018	0.3
KKAU presentation on monitoring ototoxicity in children	2017	0.2
(Inter)national conferences		
NHCA Orlando	2010	
Objective Measures Amsterdam	2012	
NHCA Las Vegas	2014	

DGA Bochum	2015	
Teaching		
Guest Lecturer 'Sound and Hearing' for General Military Physicians, Netherlands School of Public and Occupational Health (NSPOH), (bi) annual	2010-2013	1
Bi-montly lecture for medical students on audiology	2010-2015	0.3
Supervising audiologist in training in scientific research	2015-2017	0.3
Contribution on OAEs in course Objective measures for audiologist in training, UMC Utrecht	2019	0.2

Publications
Peer reviewed
Noise induced hearing loss and other hearing complaints among musicians of symphony orchestras. *Jansen EJ, Helleman HW, Dreschler WA, de Laat JA.* Int Arch Occup Environ Health. 2009 Jan;82(2):153-64.
Otoacoustic emissions in a hearing conservation program: general applicability in longitudinal monitoring and the relation to changes in pure-tone thresholds. *Helleman HW, Jansen EJ, Dreschler WA.* Int J Audiol. 2010 Jun;49(6):410-9.
Overall versus individual changes for otoacoustic emissions and audiometry in a noise-exposed cohort. *Helleman HW, Dreschler WA.* Int J Audiol. 2012 May;51(5):362-72.
Short-term music-induced hearing loss after sound exposure to discotheque music: the effectiveness of a break in reducing temporary threshold shift. *Helleman HW, Dreschler WA.* Int J Audiol. 2015 Feb;54 Suppl 1:S46-52.
The long-term results of speech perception in elderly cochlear implant users. *Jolink C, Helleman HW, van Spronsen E, Ebbens FA, Ravesloot MJ, Dreschler WA.* Cochlear Implants Int. 2016 May;17(3):146-50.
Otoacoustic emissions versus audiometry in monitoring hearing loss after long-term noise exposure - a systematic review. *Helleman HW, Eising H, Limpens J, Dreschler WA.* Scand J Work Environ Health. 2018 Nov 1;44(6):585-600.
Other
De toepasbaarheid van otoakoestische emissies als screenings- en monitoringsinstrument voor lawaaischade in de bouwnijverheid. (Report, 2011) *Leensen MCJ, Helleman HW, Jansen EJM, Dreschler WA.* Intravenous aminoglycosides in cystic fibrosis (CF) Patients, early detection of ototoxic, drug induced hearing loss: Developing a new protocol. (Poster, 2019) *De Kiviet, AC, Van Oirschot, MMM, van der Ent, CK., Helleman, HW, Boerboorm, RA* *UMC Utrecht*



APPENDICES

APPENDIX A: SEARCH STRATEGY FOR MEDLINE

Search Strategy: 2016-03-14

#	Searches	Results
1	Otoacoustic Emissions, Spontaneous/	3342
2	(otoacoustic* or oto-acoustic* or otoacustic* or otoemission* or oto-emission*).tw,kf.	4643
3	((OAE or OAEs or EOAE* or EOE or EOEs or SOAE* or SSOAEs or SSOAEs or DPOAE* or IaDPOAE* or TEOAE* or TAOE* or TOAE* or CEOAE* or VSOAE*) not ((older adult* adj2 epilep*) or EOsinoph* Esophag* or "Ontology of Adverse Event*" or Electro-Orientat* Effect* or East of England*)).tw,kw.	3451
4	(distortion product* or transient-evoked or click-evoked).tw,kf.	3642
5	**or/1-4 [OAE]**	**6182**
6	(animals/ not humans/) or (rat or rats or rabbit* or mice or mous* or murine or sheep or ovine or ewe or ewes or dog or dogs or canine or cat or cats or feline or baboon* or monkey* or primates or chinchilla*).ti.	4412599
7	**5 not 6 [OAE human]**	**4738**
8	Hearing Loss, Noise-Induced/	6407
9	noise, occupational/	2857
10	music/ or mp3-player/ or radio/	13576
11	leisure activities/ or recreation/ or dancing/ or basketball/ or boxing/ or football/ or soccer/	25701
12	military personnel/ or military medicine/ or blast injuries/ or firearms/	59488
13	engineering/ or industry/ or manufacturing industry/ or construction Industry/ or mining/ or fisheries/	46027
14	noise, transportation/ or exp transportation/ or automobile driving/	72405
15	dental clinics/ or dental high-speed equipment/ or dentists/	19661
16	snoring/	3480
17	(environmental exposure/ or occupational exposure/ or occupational medicine/ or occupational diseases/ or occupational health/) and (noise/ or nois*.ti.)	3820
18	noise & health.jn.	507
19	(hearing adj2 (loss* or impair* or damag* or harm* or deterio* or chang* or disabil* or ability or disorder* or d?sfunct*) adj6 (nois* or music or musician*)).tw,kf.	3386
20	(NIHL or ONIHL or HSPIHL).tw,kf.	520

#	Searches	Results
21	(nois* adj3 (group* or populat* or contracting or pollut* or hindranc* or nuisanc* or induc* or etiol* or aetiol* or expos* or overexpos* or dosimetr* or dose* or damag* or trauma* or harm* or injur* or hazard* or susceptibl* or profession* or occupation* or industr* or work* or high intensit* or acute or chronic or long-term or longterm or short-term or shortterm or sudden* or loud or impulsive or impact or firing or recreat* or leisur* or traffic)).tw,kf.	13427
22	((impulse or continuous*) adj1 nois*).tw,kf.	819
23	((hearing conservation adj (program* or test*)) or HCP or HCPs).tw,kf.	3106
24	(music* adj3 (loud* or devic* or digital or amplified or band* or instrument* or expos* or overexp* or induced or listen* or recreat* or leisur* or professional* or amateur* or work* or people)).tw,kf.	3364
25	((portable or personal) adj3 (music or player* or audio or listening or stereo*)).tw,kf.	345
26	((stereo or music or audio) adj3 player*).tw,kf.	121
27	(PLD or PLDs or PM-system* or PMs or MP3 or MP-3 or ipod* or i-pod*).tw,kf.	8963
28	((max* or loud* or high or level or listen* or music* or sound* or nois* or devic* or control) adj3 volum*).tw,kf.	27985
29	(musician* or (band*1 adj2 (member* or marching or brass or amateur* or professional* or perform* or rehears*)) or singer* or choir* or opera or operas or concert* or postconcert* or orchestr* or symphon* or popconcert* or pop or rock or jazz* or heavy metal or bar or bars or trumpet* or percussion* or violin* or danc* or disco or discos or disco-s or discothe* or house music* or dj or djs or d-j or disc jockey* or aerobics).tw,kf.	120083
30	(spectator* or ((recreation* or soccer or PSL or sport* or football* or basketball) adj3 (match* or event* or game*)) or vuvuzela*).tw,kf.	3210
31	(snoring and snorer*).tw,kf.	658
32	((high or loud) adj sound*).tw,kf.	620
33	(acoustic adj (shock* or nois*)).tw,kf.	423
34	(occupat* adj3 (hearing loss* or hearing impair*)).tw,kf.	404
35	(hunting or hunters or police* or militar* or battalion* or soldier* or air force or aircrew or infantr* or ((marine or army or mil) adj3 (personn* or officer* or staff or recruit* or corps or men or people or worker*)) or marines or navy or airbas* or bomb* or blast or blasts or shoot* or fire or firearm* or firing noise* or firework* or ((small or combat or service*) adj2 arm*) or artillery or weapon* or gunfir* or gunshot* or shotgun* or gun or guns or rifle* or pistol* or kalashnikov* or missile*).tw,kf.	191795

#	Searches	Results
36	(aviation or airport* or flight* or pilots or aircrew* or air crew* or jet plane* or jet fighter* or aircraft* or air craft* or airplan* or air plan* or aeroplan* or warplane* or helicopter* or ship or ships or fishing or fisherm#n* or fishery or fisheries or railroad* or railway* or locomotive* or roads or car driver* or automobile*).tw,kf.	90787
37	((nois* or ship* or jet or boat* or vessel* or person* or work* or employ* or profession* or driver* or room*) adj6 engin*).tw,kf.	5315
38	(industri* adj3 (work* or setting or hearing loss* or hearing impair* or expos* or recording*)).tw,kf.	5613
39	((construction or maintenance or drilling) adj3 (work* or apprentric* or industr* or trade*)).tw,kf.	4347
40	(((factory or factories or plant or plants or industr*) adj3 (stamping or metal*)) or metalwork* or metal-work* or metalproduct* or metal-product*).tw,kf.	4860
41	(dentist* or dental clinic*).tw,kf.	65307
42	((teacher* or class room* or classroom*) and nois*).mp.	375
43	**or/8-42 [NIHL]**	**687116**
44	**43 and 7**	**460**

APPENDIX B: MODIFIED DOWNS AND BLACK CHECKLIST

Adopted from Downs and Black (1998).

No.	*BD nr*	*Subject*	*Score*
Reporting			
1	1	Is the hypothesis/aim/objective of the study clearly described?	1= yes 0= no
2	2	Are the main outcomes to be measured clearly described in the introduction or methods section? If the main outcomes are first mentioned in the results section, the question should be answered no. *ALL primary outcomes should be described for YES*	1= yes 0= no
3	3	Are the characteristics of the patients and population included in the study clearly described? Inclusion and/or exclusion criteria should be given. *At least age, gender and type of group should be described for YES.*	1= yes 0= no
4	4 MOD	Are the interventions of interest clearly described? *Is noise described in terms of (estimated) level and duration of exposure?*	1= yes 0= no
5	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided. *For YES: age, previous noise exposure, use of hearing protection and middle ear status should be described*	2= yes 1= partially 0= no
6	6	Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.	1= yes 0= no
7	7	Does the study provide estimates of the (random) variability in the data for the main outcomes? In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. *For YES an attempt should be made to describe variation in the data.*	1= yes 0= no
8	9 MOD	*Are test statistics* (t, F, U, *etc.*), *correlation or regression coefficient (Pearson's* r, *Spearman's rho, etc.), or measure of effect size (eta-squared, partial-eta-squared, omega-squared, etc.) provided?* *Was:* Have actual probability values been reported (e.g. rather 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.01	1= yes 0= no

No.	*BD nr*	*Subject*	*Score*
external validity			
9	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected.	1= yes 0= no 0= unable to determine
internal validity – bias			
10	16	If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer YES.	1= yes 0= no
11	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients? Where follow-up was the same or similar for all study patients the answer should be YES. Studies where differences in follow-up are ignored should be answered no.	1= yes 0= no 0= unable to determine
12	18 MOD	Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but there is no evidence of bias, answer should be yes. Is distribution of data (normal or not) is not described it should be assumed that the estimates used were appropriate and the question should be answered with YES. *Corrections for repeated measures (time/ frequency/ear) or reporting how these multiple comparisons are dealt with is YES*	2= yes 1= partially 0= no
13	20	Were the main outcome measures used accurate (valid and reliable)? For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, question should be YES. *If SNR/waverepro is used without any reference to noise floors = NO*	1= yes 0= no

No.	*BD nr*	*Subject*	*Score*
internal validity - selection bias			
14	26	Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported = no *If data inclusion criteria are used (e.g. based on SNR) and amount of excluded data points Is not reported = no*	1= yes 0= no
Total score			Min:0 Max:16

APPENDIX C: RESULTS FROM THE DOWNS AND BLACK CHECKLIST PER STUDY

The score is determined as 1=Yes, 0=No or Unable To Determine, except for item 5 and 12 where 2=Yes. 1=partially, 0=No.

		Duvdevany & Furst (2007)	*Helleman & Dreschler (2012)*	*Helleman et al. (2010)*	*Job et al. (2009)*	*Konopka et al. (2005)*	*Lapsley Miller et al. (2006)*	*Lapsley Miller et al. (2004)*	*Marshall et al. (2009)*	*Moukos et al. (2014)*	*Murray et al. (1998)*	*Seixas et al. (2012)*	*Seixas et al. (2005)*	*Shupak et al. (2007)*
	Reporting													
1	Is hypothesis clear?	1	1	1	1	1	1	1	0	1	1	1	1	1
2	Main outcomes in the introduction or methods?	1	1	1	1	1	0	0	0	0	1	1	1	1
3	Are inclusion and/ or exclusion criteria population clear?	1	1	1	0	0	1	1	1	1	1	1	1	1
4	Is interventions (noise) clearly described?	1	0	0	1	1	1	1	1	1	1	1	1	1
5	Principal confounders mentioned?	1	1	1	1	1	2	2	2	1	1	2	2	2
6	Can the main findings be checked by reader?	1	1	1	1	1	1	1	0	1	1	1	1	1
7	Is variation in outcome data described?	1	1	1	0	0	1	1	1	1	1	1	1	1
8	Are test statistics, corr or regr coeff or measure of effect size provided?	1	1	1	0	0	1	1	1	1	0	0	0	1
	External validity													
9	Is identification of source population and selection clear?	0	0	0	0	0	0	0	1	0	0	0	1	0
	Internal validity – bias													
10	No "data dredging"? Not planned analyses clearly indicated?	0	1	1	1	1	1	0	1	1	1	1	1	1

		Duvdevany & Furst (2007)	*Helleman & Dreschler (2012)*	*Helleman et al. (2010)*	*Job et al. (2009)*	*Konopka et al. (2005)*	*Lapsley Miller et al. (2006)*	*Lapsley Miller et al. (2004)*	*Marshall et al. (2009)*	*Moukos et al. (2014)*	*Murray et al. (1998)*	*Seixas et al. (2012)*	*Seixas et al. (2005)*	*Shupak et al. (2007)*
11	Adjustements for different lengths of follow-up?	1	1	1	1	1	1	1	1	1	1	1	1	1
12	Are statistical tests used appropriate? Description of multiple comparisons?	2	2	2	1	2	1	2	1	2	1	1	1	1
13	Were the main outcome measures used accurate (SNR)?	1	1	1	1	0	1	1	1	0	0	1	1	0
	Internal validity - selection bias													
14	Loss to follow-up reported? Excluded data points (SNR-inclusion) reported?	0	1	1	1	0	1	0	1	0	1	0	1	0
Total score		***12***	***13***	***13***	***10***	***9***	***13***	***12***	***12***	***11***	***10***	***12***	***14***	***12***