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EFFECTS OF AGE AND STIMULATION STRATEGIES ON COCHLEAR IMPLANTATION AND A CLINICALLY FEASIBLE METHOD FOR SOUND LOCALIZATION LATENCY

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EFFECTS OF AGE AND STIMULATION STRATEGIES ON COCHLEAR IMPLANTATION AND A CLINICALLY FEASIBLE METHOD FOR SOUND LOCALIZATION LATENCY

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my wife and my children

Kindness is the language which the deaf can hear and the blind can see.
Mark Twain

ABSTRACT

Treating prelingual deafness with cochlear implants paves the way for spoken language development. Previous studies have shown that providing the intervention at six to 11 months is better than at 12-17 months. However, interventions at even earlier ages have not been researched to the same extent, for example by comparing five to eight months with nine to 11 months. That is why we retrospectively assessed the surgical risks, and analyzed the longitudinal spoken language tests, of 103 children who received their first cochlear implant between five and 30 months of age. This research particularly focused on surgery before 12 months of age (Paper I). Apart from language development, we expected that early implants would provide access to the interaural time differences that are crucial for localizing low frequency sounds. We were interested to examine this in combination with novel sound processing strategies with stimulation patterns that convey the fine structure of sounds. Therefore, in addition to the retrospective analysis, we studied the relationships between stimulation strategies, lateralization of interaural time differences and horizontal sound localization in 30 children (Paper II). Then we decided to develop a method to objectively assess sound localization latency to complement localization accuracy. A method that assesses latency needed to be validated in adults with normal hearing, and in hampered conditions, so that the relationship between accuracy and latency could be clarified. In our study, the gaze patterns from the localization recordings were modelled by optimizing a sigmoid function (Paper III). Furthermore, we addressed the lack of studies on the normal development of sound localization latency of gaze responses in infancy and early childhood (Paper IV).

Our study of spoken language development showed the benefit of cochlear implantation before nine months of age, compared to nine to 11 months of age, without increased surgical risks. This finding was strongest when it came to the age at which the child’s language could be understood (Paper I). When our group of 30 subjects underwent tests for interaural time differences, 10 were able to discriminate within the range of naturally occurring differences. Interestingly, the choice of stimulation strategy was a prerequisite for lateralizing natural interaural time differences. However, no relationships between this ability to lateralize and the ability to localize low frequency sounds were found (Paper II). The localization setup meant that detailed investigations of gaze behavior could be carried out. Eight normal hearing adults demonstrated a mean sound localization latency of 280 ± 40 milliseconds (ms), with distinct prolongation with unilateral earplugging. It is interesting to observe the similarity in latency, dynamic behavior, and overlap of anatomical structures between the acoustic middle ear reflex and sound localization latency (Paper III). In addition, normal hearing infants showed diminished sound localization latency, from 1000 ms at six months of age down to 500 ms at three years of age (Paper IV). Latency in children with early cochlear implants still needs to be studied.

The findings in this thesis have important clinical implications for counseling parents and they provide valuable data to guide clinical choices about the age when cochlear implants

are provided and processor programming takes place. The fast, objective and non-invasive method of sound localization latency assessment may further enhance the clinical processes of diagnosing and monitoring interventions in children with hearing impairment.

LIST OF SCIENTIFIC PAPERS

I. Karltorp, E., Eklöf, M., Östlund, E., Asp, F., Tideholm, B., & Löfkvist, U. (2020). Cochlear implants before 9 months of age led to more natural spoken language development without increased surgical risks. Acta Paediatrica, 109(2), 332–341.

II. Eklöf, M., & Tideholm, B. (2018). The choice of stimulation strategy affects the ability to detect pure tone inter-aural time differences in children with early bilateral cochlear implantation. Acta Oto-Laryngologica, 138(6), 554–561.

III. Eklöf, M., Asp, F., & Berninger, E. (2020). Sound localization latency in normal hearing and simulated unilateral hearing loss. Hearing Research, 108011.

IV. Eklöf, M., Asp, F., & Berninger, E. The normal sound localization latency development in infants and young children. Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ILD	Interaural level differences
ITD	Interaural time differences
UHL	Unilateral hearing loss
FS	Fine structure
SLL	Sound localization latency
dB HL	Decibel hearing level
AOI	Area of interest
MAE	Mean absolute error
EI	Error index

1 INTRODUCTION: NEURAL DEVELOPMENT OF THE CENTRAL AUDITORY SYSTEM AND THE EFFECT OF DEPRIVED HEARING

According the World Health Organization, around 466 million people worldwide suffer from a hearing disability (WHO, 2020) and 34 million of these are children. It is currently estimated that 2.5 million children suffer from profound hearing loss or deafness. Only 10% of children with profound hearing loss have undergone a cochlear implantation procedure (Şahin et al., 2017). The cost-efficiency of cochlear implants depend on a number of factors, such as the optimal age at implantation and the correct fitting parameters. These are the subject of this thesis.

Before cochlear implants were available, people who were deaf or had profound hearing impairment were referred to sign language or oral training. This thesis focuses on the outcomes of cochlear implantation (Papers I and II) in terms of surgical risks, spoken language ability, lateralization by interaural differences and horizontal sound localization accuracy. In addition to accuracy, sound localization latency is considered by the development of a method that has so far been applied to adults (Paper III), young children and infants with normal hearing (Paper IV). The papers investigated the effect of age at the time of cochlear implant surgery (Paper I) and the choice of the cochlear implant sound processing strategy (Paper II). Furthermore, we validated the latency assessment by looking at the effects of plugging one ear in adults with normal hearing (Paper III) and the effect of age on sound localization latency (Paper IV).

1.1 EARLY NEURAL DEVELOPMENT

The immature brain and neural substrates of the newborn or premature child are partly organized, namely hardwired, and partly non-organized, in the case of the tabula rasa. There is support for both “nature and nurture” in the anatomy and physiology of the human neural system. The hardwired part of this development is thought to be governed by genetic predestination and decides the type and position of the neurons and guidance of their axons. Activity driven development starts when the axons reach the synapses of their neural partners. Sensory experiences cause neural pruning and changes in synapses throughout the lifespan of the individual. The acquisition of memory, skills and reactions are some of the processes that are thought to rely on these mechanisms (Hatten, 1999).

1.2 LANGUAGE

The importance of early stimulation of the infant’s plastic brain, for optimal listening and language development, has been well described, by authors like Kuhl, (2004). For example, the auditory system needs input during infancy to develop normally (Kral & Sharma, 2012). The existence of a critical period of language acquisition, due to brain development constraints, was first proposed in a book by Penfield and Roberts (1960, p. 286+). Also, evidence exist that prelingually deaf develop better written language skills with early sign language exposure rather than late (~6 years) (Mayberry & Lock, 2003). This does not imply that early sign language before surgery will fully compensate for later cochlear implantation. On the contrary, some authors, including Kos et al. (2009), have reported that the speech production and auditory perception abilities of language are not possible without early exposure to the auditory sensory input of spoken language.

Children with congenital or early onset progressive hearing loss are now identified at an earlier age, thanks to universal newborn hearing screening programs (Ching et al., 2017). It has been suggested that newborn children who suffer from hearing impairment should be screened for hearing loss before one month of age. They should be diagnosed before three months of age and then fitted with suitable hearing aids, together with supportive family-centered interventions, no later than at six months. This is often referred to as the “1-3-6” policy (Connolly et al., 2005). Children who suffer from severe to profound hearing loss from birth are functionally deaf without hearing aids. They often derive limited benefits from conventional acoustic hearing technology when it comes to developing listening and preverbal skills. Electrical stimulation is needed to reach the auditory center and support the development of the auditory system. That is why it is important to fit cochlear implants as early as possible.

At present, it is common practice to perform implant surgery during infancy in Australia and in several countries in Europe. In the USA, the Food and Drugs Administration has recently, this year 2020, changed the earliest approved age of implantation from 12 months to 9 months of age, made possible by the existing universal newborn hearing screening programs in the country. Several other countries need to implement screening programs before it is possible to provide cochlear implants in infancy. A number of previous studies have shown that children who receive cochlear implants after 12 months of age have greater problems keeping up with the pace of language development, compared to age-matched children without hearing impairment (Colletti et al., 2011; Dettman et al., 2016).

Children below one year of age with profound hearing loss have been treated with cochlear implants at the Hearing Implant Clinic, Karolinska University Hospital, Sweden, since 2002. Currently, children with profound hearing loss receive cochlear implants as early as the age of five months. However, some children with severe to profound hearing loss from birth are fitted with cochlear implants at a later stage, for different reasons. Sometimes this is because the parents delay making decisions about their infant’s treatment and, in some cases, the cochlear implant investigation team suspect that hearing aids would be more beneficial than cochlear implants in the first instance. This is similar to findings from other centers, by authors such as Fitzpatrick (2015). This situation gives us the opportunity to compare children with severe to profound congenital hearing loss who receive cochlear implants at different ages.

Systematic reviews that were conducted on cochlear implants in infancy concluded that having an implant at an earlier age led to better results in both spoken language acquisition and speech perception (Bruijnzeel et al., 2016; Lund, 2016; McKinney, 2017). However, we still needed clearer evidence about the possible additional benefits of implants below 12 months of age.

1.3 BASIC INTERAURAL ABILITIES

While enhanced spoken language development is probably the most important goal of pediatric cochlear implants, hearing from both sides will reduce the “worse ear” effect and increase the ability of spatial orientation in an auditory environment. That can be important from both a social and survival point of view.

The ability to lateralize and identify the origin of sounds is of profound significance for the survival of many species. Two ears that have a distance in between them are important for the ability to localize sound in the horizontal plane. This is because the sounds reaching the two ears will have interaural level differences (ILD) and interaural time differences (ITD), namely loudness and temporal differences.

The ILD primarily depends on the head shadow effect: firstly, on differences in the attenuating effect of the head, as sound travels from its source to reach each ear, and secondly on differences in distance. The ITD of direct sound is created by the difference between the distances from the sound source to each respective ear. ITD is particularly important as a binaural cue when the auditory system localizes and discriminates sounds in situations where the spectral cues are masked, such as in noisy environments. When speech and noise change from same ITD to a different ITD, namely when speech and noise originate from different horizontal spatial positions rather than the same horizontal position, speech and noise will be more easily separable. An adult with normal hearing can tolerate an increase in noise of more than 5 decibels with sustained speech perception when speech and noise are spatially separated (Bronkhorst & Plomp, 1988). Since the ILD is limited to middle and high frequencies, ITD is the dominant factor for localizing low frequency sounds (Wightman & Kistler, 1992), such as the fundamental frequency of a human voice.

The ILD circuitry begins with bilateral projections from bushy cells of the anteroventral cochlear nucleus to the lateral superior olive. The contralateral anteroventral cochlear nucleus projects to the medial nucleus of the trapezoid body which projects inhibitory to the lateral superior olive, while the ipsilateral anteroventral cochlear nucleus projects exhibitory directly to the lateral superior olive. This causes the lateral superior olive to respond when the sound intensity is higher in the ipsilateral ear.

The lowest level of the neural ITD circuitry is structured as bilateral projections from the bushy cells of the anteroventral cochlear nucleus to the neurons of the medial superior olive. Simultaneous input from either ear yields the largest response in the neurons of the medial superior olive. Investigations in kittens have shown similar development to the one noted in the ILD circuitry and that the ILD and ITD circuits are present at birth (Blatchley & Brugge, 1990; Reale et al., 1987). This is consistent with the fact that newborn infants have a crude ability to localize sound. However, this circuit is immature and needs auditory input to develop further. The ability to lateralize based on ITD exists in children with normal hearing. This ability was shown by van Deun et al. (2009) when children aged 4-9 years participated in several binaural tests, including ITD thresholds.

In adults, the threshold for just noticeable ITD has been thoroughly investigated by researchers, including Brughera et al. (2013). In their study, four adults with normal hearing were instructed to lateralize, based on ITD, when listening to pure tones at various frequencies. They reported that the ITD threshold decreased with increasing frequency, from 40-60 µs at 250 down to about 20 µs at 700 Hz. The lowest thresholds, 10 – 20 µs, were obtained between 700 and 1000 Hz. The ability to lateralize, based on ITD, disappeared just above 1400 Hz. These findings were attributed to the limits in phase locking, where neurons take turn to fire and create an overall firing rate that is higher than that of any individual neuron.

Litovsky et al. (2010) described the effect of deprived hearing on neural development. They studied 11 adults who received bilateral cochlear implants after their deafness was diagnosed at various ages, from prelingual and childhood-onset to adulthood-onset. These subjects were tested for interaural intensity and time differences at different positions along the electrode array. All the subjects were sensitive to ILD cues, but ITD sensitivity was only found in those with adult-onset deafness. These results suggest that the ILD circuitry is a more robust system and not deprived, to the same extent, by prolonged periods of lack of sensory input. Another explanation could be that the ILD circuitry is more hard-wired and requires less experience during development than the ITD circuitry, which would require sensory input during a critical period of time to emerge.

1.4 LOCALIZATION AND THE SPACE MAP

There is a neural topographic representation of tactile and visual space in the brain and this is referred to as a space map. The neural maps are believed to be distributed between different brain areas, such as the parietal cortex, the hippocampal formation, the primary sensory cortices and the superficial layers of superior colliculus at the brainstem level (Lee & Groh, 2014). This means that different parts of neural structures have corresponding mapping of coordinates in the three-dimensional space of our surrounding environment. For example, our limbs have a coordinate system that starts with a corresponding local reference system. As the neural signal reaches more centrally located neural networks, the positions of our limbs or external objects are translated to a more “global” coordinate system. Our ocular system also codes positions in relation to the position and direction of the eye globe, which is then translated to a craniocentric or torso-centric reference system. On the other hand, our auditory system works on the basis of coding direction and distance primarily in a craniocentric reference system, since our ears are fixed to our head (Lee & Groh, 2012).

Another dissimilarity between the visual and auditory senses are the mapping from external spatial locations to the sensory nerves. In vision, the neurons on the retina provide a two-dimensional map that corresponds to the directions from the eye to the objects that are positioned in the visual field and reflect or emit light. The processing needed to transfer this data to a three-dimensional space map is stereo processing, which uses differences in the pictures from the two eyes and then transforms these images from retino-centric to cranio-centric or other coordinate systems. On the other hand, the auditory system receives sounds from the individual's surroundings that are mixed together and differentiated on a sensorineural level along the basilar membrane, in terms of frequency rather than position in space. This means that the auditory system needs to segregate sound sources from other sounds that might overlap in frequency. It then positions them in space using interaural and spectral cues. This segregation is performed by means of spectral and temporal characteristics, such as co-modulation across frequencies, but also from similarities in binaural characteristics, namely ITD and ILD.

The receptive fields in superior colliculus depend on the input that it will receive during the critical period of development. The response of the neurons in the superior colliculus change during development. They start off as rather broad, corresponding to unspecific positions in the auditory space, and then become specific, corresponding to narrow positions in the auditory space, according to Withington-Wray et al. (1990). They raised guinea pigs in the dark, or in an omnidirectional white noise, to see what would happen to the specificity of their neurons in superior colliculus when development took place without consistent auditory or visual sensory input. The authors concluded that the space map developed pathologically and that the direction to a sound source could not be predicted from the best response in superior colliculus. This could be equated to a situation where a child is born profoundly deaf and later receives auditory input after cochlear implantation.

Directing one's gaze towards a sound source is a natural response that has high survival and communication value. Humans move their gaze (saccadic behavior) and direct it at the high-density part of their visual field (fovea) towards the area of interest. During rapid eye movement (saccades), vision is suppressed (saccadic suppression). Therefore, saccades are elicited after careful planning and thorough decision making (Carpenter & Williams, 1995), with approximately three saccades per second, each lasting 50 to 150 ms. Express saccades is the category of saccades with shortest latency elicited before 130 ms (Fischer et al., 1993) and are believed to be processed on brainstem level.

The ability to localize and lateralize is impaired in patients suffering from auditory agnosia after brain lesions (Yamada et al., 1997). This means that they cannot identify left or right directions to auditory targets, based on ITD and ILD. It appears that localization is difficult when there are lesions on the auditory cortex (Haeske-Dewick, 1996), despite the subcortical combined processing of ITD and ILD in the inferior colliculus (Chase & Young, 2006).

So, if brainstem processing were sufficient for binaural processing and target build-up in the superior colliculus, localization would be possible without an intact auditory cortex. If attention can be directed at the level of the superior colliculus, and the saccadic burst generators can be elicited by exhibitory projection from the superior colliculus, it should at least be possible to elicit express saccades towards salient auditory targets.

A popular model used to study the brain non-invasively is to study the oculomotor response to stimuli and certain taskts. By means of eye-tracking this quite spontaneous behavioral feature can be studied with high precision. A number of methods have been described and these include electro-oculography with skin electrodes (Goldring et al., 1996; Zambarbieri, 2002), inserting scleral coils (Frens & Van Opstal, 1995; Populin et al., 2002) frequently compbined with the practice of restraining the subject's head using a chin rest and head band (Frens & Van Opstal, 1995; Ten Brink et al., 2014; Zahn et al., 1978). Recent advances in eye-tracking technology has increased measurement speeds and made the process more comfortable and natural, by avoiding head restraints during saccade research (Gredebäck et al., 2009). The test setup that we used for localization used a combined head and eye-tracker, which meant that the subject's head did not need to be restrained. This made the localization process more natural and easier to perform, especially in children. The localization ability is often defined as the acuity of the responses without the quantification of the response latency. In an attempt to extract more data from this test we decided to additionally consider the latency of the responses.

According to Mosimann et al. (2004) there is a top-down control to saccades that interfere with the bottom-up processing driven autonomously by incoming visual and auditory stimulation. Both saccadic latency (Fischer et al., 1993) and accuracy (Kowler & Blaser, 1995) can be improved voluntarily. The otherwise common accuracy-latency trade-off, where a decrease in reaction time decreases accuracy, does not seem to apply to saccades (Wu et al., 2010).

The gaze reaction times that adults display towards auditory targets are known to vary from 80-100 ms (Fischer & Weber, 1993) to up to several hundred microseconds (Fischer et al., 1993). Despite large variations within individuals, the mean saccadic reaction time shows low variations between individuals. These depend on the measurement methods. Different studies have shown means that include the 280 ms found in our study (Paper III), 250 ms (Zambarbieri, 2002) and 190 (Zahn et al., 1978). The magnitude of the saccadic reaction time, and its variability, cannot be explained by conduction times, namely synaptic delays and conduction velocity. The process of reaching the decision threshold is stochastic in nature and the differences in mean latency will reflect changes in that processing time, rather than variations in the afferent or efferent conduction time and synaptic delays (Reddi & Carpenter, 2000). Findlay & Walker (1999) have suggested a model with two parallel processes: the WHEN process, which produces saccade initiation, and the WHERE process, which determines saccadic amplitude and direction. The WHEN process can, in turn, be divided into two competing processes. The first process works by upholding fixation, despite changes in the spatial position of attention or emerging, competing visual or auditory targets. The second process works by disentangling fixation and eliciting a saccade. This theoretical model is partly supported by the findings of corresponding brain structures (Munoz & Wurtz, 1995).

While profound binaural sensorineural hearing loss limits the benefits of binaural hearing to various degrees (Bernstein, 2001), unilateral hearing loss (UHL) also compromises horizontal localization ability and has detrimental effects on brain development during early childhood (Moore, 1991).

An easy and rapid measurement system for localization latency obtained by auditory saccades may provide a sensitive test for impairments of the central auditory system. Indeed, simulated unilateral hearing loss has been shown to deprive localization ability (Asp et al., 2018; Kumpik & King, 2019) and, as showed in our study, to increase latency (Paper III). Also, it is possible that the benefits of using hearing aids can be quantified by the measurement of the localization ability. Audibility in both ears, symmetry between ears and the development of binaural integration are probable prerequisites for successful localization. The assessment of localization latency might further enhance the diagnosis and evaluation of the treatment of amblyaudia, which is deprived binaural hearing due to monaural disruption during development. This is comparable to amblyopia in vision (A. B. Kaplan et al., 2016). A study of rats showed that monaural deprivation resulted in imbalanced neural development in areas of the brainstem and auditory cortex (Popescu & Polley, 2010). If monaural deprivation occurs during periods of experience-dependent plasticity, the effects will be long lasting, but not as irreversible as their visual counterpart. Wilmington et al. (1994) tested binaural abilities, including localization, in 19 patients before and after surgery to correct congenital unilateral conductive hearing losses. They concluded that basic binaural abilities, such as ITD, were nearly normalized after surgery, whereas more complex abilities, such as sound localization, did not recover, at least not immediately. Altered binaural auditory input is likely to disturb the binaural integration in the brainstem nuclei. It can potentially make the activity in the superior colliculus, which is coding for positions in auditory space, less specific or more time consuming to attain (Lee & Groh, 2014).

Studies, including Asp et al. (2012), have showed that prelingually deaf children with bilateral cochlear implants are consistently able to localize broadband sounds in the horizontal plane. This suggests that the neural response in the superior colliculus is near normal in the rate code, at least when subject to sounds with changes in ILD. Less is known regarding the normal development of saccadic response latency to auditory targets in infants and children.

1.5 NEURAL PROSTHESIS, THE COCHLEAR IMPLANT

Neural prostheses are devices that interact with the central neural system to replace a sensory, motor or cognitive function. The most commonly spread neural prosthesis is the cochlear implant system, which replaces the functions of the outer ear, the middle ear and the mechanical parts of the inner ear. The purpose is to mimic the neural pattern that a certain soundwave, primarily speech, would have caused in a healthy ear. It does this by stimulating the hearing nerve with a microelectrode. We have known that electricity can elicit sound sensations since at least the late 18th century. Until recently, this discovery had been attributed to the inventor of the galvanic cell, Alessandro Volta (1745-1827), who described hearing a sharp sound followed by a thick boiling sound when applying a 50 Volt chock between his ears. However, records have now been unearthed that show that Laura Bassi (1711-1778), the world's first female Professor, and her husband Professor Giuseppe Veratti (1707-1793) treated tinnitus, more or less successfully, with electricity as far back as 1747 (Marchese-Ragona et al., 2019).

These findings were confirmed in the 1960s by experiments on deaf adult subjects in France. It was not until the introduction of multi-channel stimulation within the cochlea that sound perception started to become intelligible to some degree. Another leap in speech understanding took place with the introduction of sequential pulsatile stimulation, because it eliminated the detrimental channel interaction between the electrodes (Wilson et al., 1991). Open speech discrimination now became possible, by going from parallel stimulation of analogue electric waves to biphasic pulse trains on one electrode at a time. Pulses delivered from an electrode where modulated by a rectified and lowpass filtered version of the sound in the corresponding frequency band. This part of a sound is called envelope, see Figure 1 for a graphical example. One drawback with this fixed rate pulsatile stimulation is that music does not sound very natural since the fine structure (FS) is discarded.

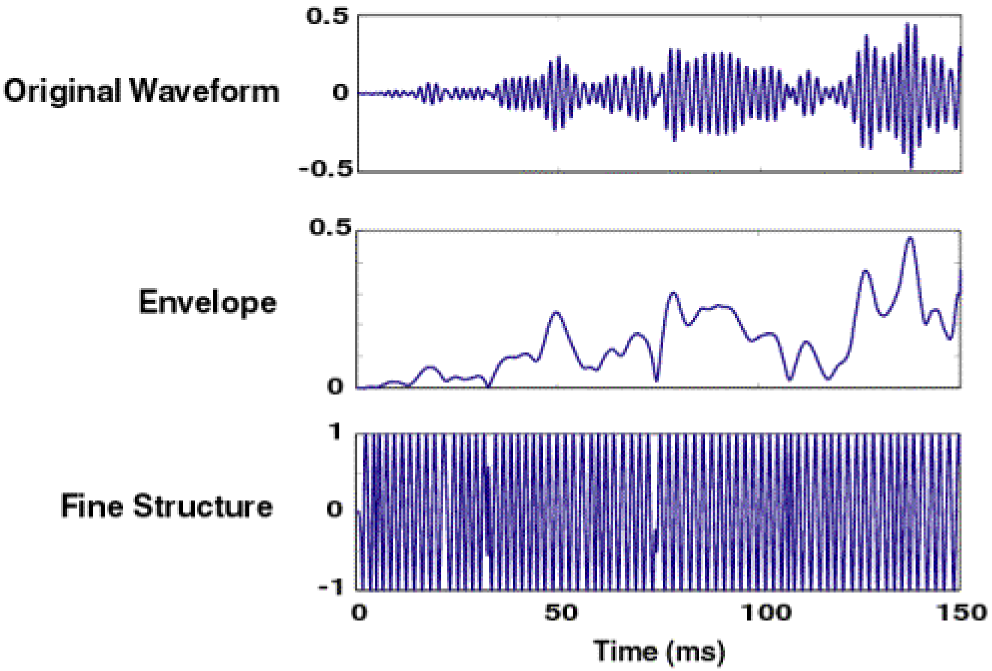

Figure 1. Decomposition of a bandpass filtered portion of a speech sound into the corresponding slowly varying envelope and the high carrier fine structure. Adopted from https://research.meei.harvard.edu/chimera/motivation.html

Efforts have however been made to provide the hearing nerve with both envelope and FS. The sound processing strategies in commercial cochlear implant processors use band pass filters on the incoming sound to separate the energy into frequency bins. Most algorithms still do not let the FS of the sound wave (the actual soundwave rhythm) affect the pulse train. Instead, they extract the energy (momentary volume) in each frequency bin with slowly varying envelope, discarding the fine structure of the wave form, for example as shown for continuous interleaved sampling sequences (CIS) in Figure 2. These non-FS, traditional strategies stimulate the hearing nerve by using an amplitude modulated pulse-train that follows the envelope (by means of rectification and lowpass filtering or the Hilbert transform) and not the actual shape of the sound wave. These include CIS strategies from Med-El and Advanced Bionics and advanced combination encoder (ACE) and MP3000 strategies from the Cochlear Corporation.

However, some novel stimulation strategies map sounds with modified electric pulse patterns. The instantaneous sound pressure is allowed to modify the stimulation pattern to follow the phase, and thus provide the FS, of the sound wave in the corresponding frequency bin. These strategies stimulate with bursts of pulses in pace with the sound wave front, the phase, of the sound. Examples include HiRes-S/P/120 from Advanced Bionics and fine structure processing (FSP), fine structure with higher rates on the four most apical electrodes, FS4, and FS4-p from Med-El (Figure 2). The p in FS4-p signifies that the rate coding can be fired in parallel on any two of the four rate-coded apical electrodes, while trying to minimize channel interaction.

The pulsatile stimulation on one or more of the electrodes situated in the most apical part of the cochlea bursts, triggered by every zero-crossing of the soundwave in the corresponding frequency bin. The actual timing of the pulses are not changed, compared to fixed envelope stimulation, but the stimulation is limited to the time following a zero-crossing and then upholds with stimulation until the next zero-crossing, as shown by FSP and FS4 in Figure 2. This is only possible when the stimulation rate is much higher than the frequency of the low-frequency zero-crossings, as in apical channels 1 or 2 with FSP and channels 1-4 with FS4. The sound processors from the above-mentioned manufacturers can be programmed with either FS strategies or non-FS strategies (Churchill et al., 2014).

Bilateral stimulation from cochlear implants by uncoordinated processors does not provide robust binaural cues due to independent automatic gain controls and unsynchronized pulse trains (Dietz, 2016). However, a sound wave passing two cochlear implant processors can preserve interaural time and level differences if stimulation is synchronized with the front of the sound wave.

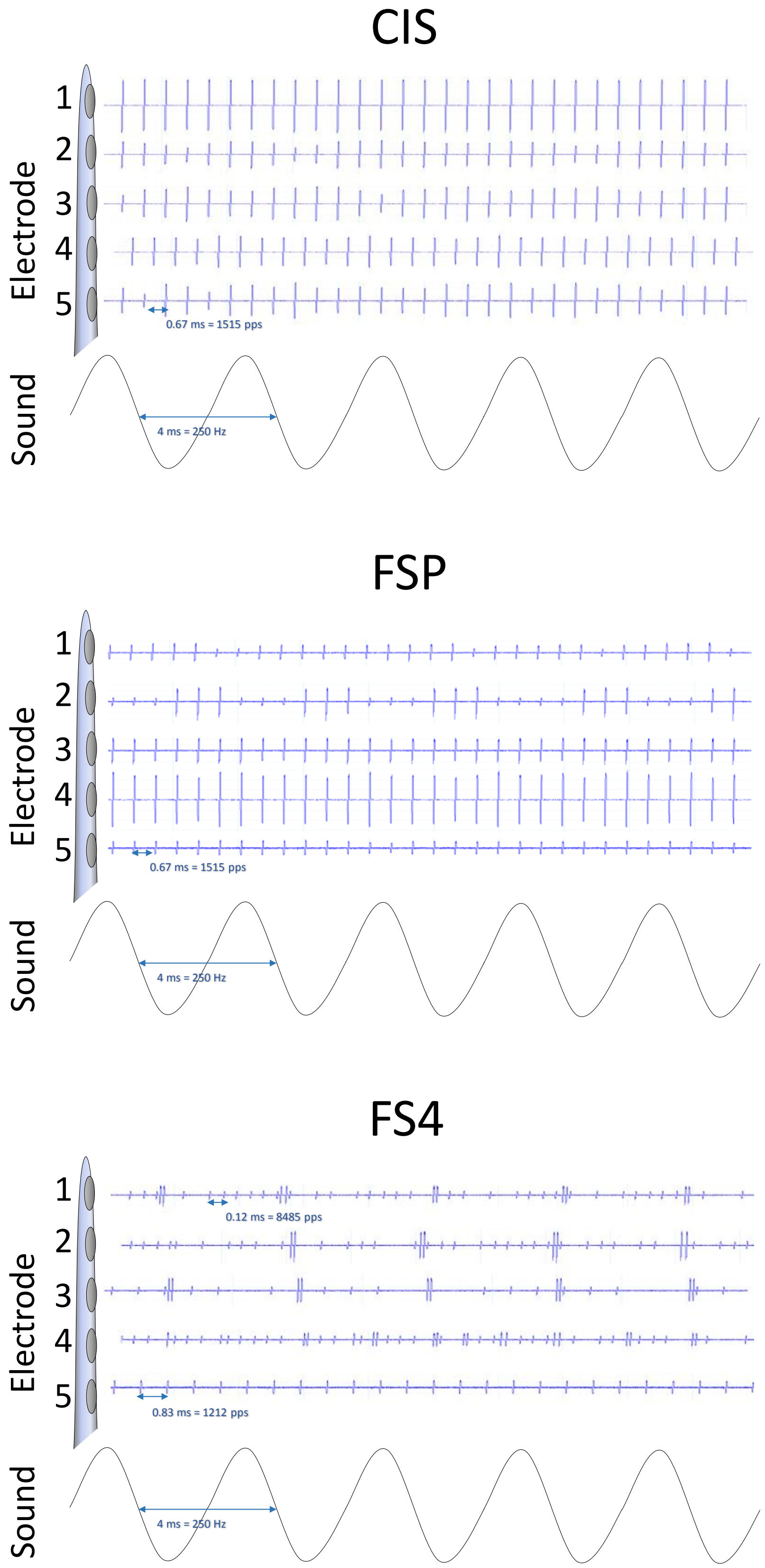

Figure 2. Three plots showing the actual electrode output (voltage) over time from the five most apical electrodes (inner part of the cochlea, corresponding to low frequency sounds). CIS = continuous interleaved sampling sequence, FSP = fine structure processing, FS4 = fine structure with a higher rate on the four most apical electrodes. PPS = pulses per second. Image source: thesis author

In aided hearing, the ILD cues are mostly preserved, even in situations where the automatic gain control of independent hearing aids or cochlear implant processors might diminish the ILD (Brown et al., 2016). However, the ability to perceive, and benefit from, ITD is more complex with aided hearing. From a physiological point of view, hearing impairment, or its consequences, might compromise the temporal accuracy of the auditory system. More often, the temporal accuracy and information is limited by the technical difficulties associated with real-time sound processing and electrical stimulation. Studies of adult subjects using research processors with direct stimulation, which bypass their clinical processors, have shown that most subjects are able to lateralize sound by ITD (Laback et al., 2015). The clinical benefit of FS strategies has been evaluated in adult samples in terms of music appreciation and speech intelligibility (Magnusson, 2011) and interaural phase differences and binaural intelligibility level difference (Zirn et al., 2016). Children growing up with cochlear implants have no previous acoustic hearing experience and they develop listening acuity solely as a result of artificial electrical stimulation. The FS strategies have been around long enough for prelingually implanted children to reach an age where participation in psychoacoustic testing is possible.

1.7 AIM

These studies focused on children with profound hearing impairments who received cochlear implantation at different ages. The aim of the studies was to develop, and use, methods to assess their neural development of basic binaural abilities, sound localization latency (SLL) and spoken language acquisition.

Hypotheses

- The age when the first first cochlear implant surgery was carried out would have an effect on spoken language development, but not on surgical risk (Paper I).
- Children suffering from prelingual deafness would be able to access ITD cues using cochlear implants (Paper II).
- The choice of sound processing strategy would have an effect on the children’s access to ITD (Paper II).
- The ability to perceive ITD would predict performance in more realistic listening situations, such as the localization of broadband or low-frequency sounds (Paper II).
- A sigmoid model would be a feasible way to assess SLL with our current set-up (Paper III).
- Simulating unilateral hearing loss by plugging one ear would affect the SLL in normal hearing adults (Paper III).
- Normal development of SLL would decrease with age (Paper IV).

1.8 THE VALUE OF THIS RESEARCH

1.8.1 Age at implantation

An important aspect of cochlear implantation research is to determine the best age for surgery, so that the child can gain the greatest benefit from the procedure. Clinical experience has shown earlier implants have led to better outcomes. Many parents of deaf children have also reported this experience. One argument against early intervention is the surgical risks associated with anesthesia at a low age. Results from spoken language tests, and the incidence of adverse surgical events, could provide evidence for the potential benefits of early implants. The societal costs, and the personal difficulties caused by less successful interventions, is high. Children who receive cochlear implants need to keep pace with their normal hearing peers as early as possible, preferably before they start elementary school, which is six years of age in Sweden. A child whose speech has developed sufficiently for them to attend a mainstream school won't have to travel to a regional school, where sign language is the main method of communication. Furthermore, the benefits of cochlear implants depend on its outcome. Cochlear implant surgery at later ages, and reduced oral communication training, have been reported to decrease the cost of quality adjusted life time (Crowson et al., 2017). The aim of the first paper was to clarify the consequences of surgery at earlier or later ages with regard to spoken language development and surgical risks.

1.8.2 Technology and stimulation

The choice of cochlear implant technology and stimulation may affect the development of spoken language. There have been developments in cochlear implant technology during the last few decades. This is due to research performed by independent researchers, as well as industrial research and development carried out by the manufacturers of cochlear implants. These research findings are the cornerstone of the further product developments that will eventually provide additional benefits for the deaf patients who receive these devices. Apart from research and development, new stimulation strategies need to be evaluated in unbiased and independent settings. The first aim is to find the best stimulation strategies for the cochlear implant devices used for individual children or adults. Before the publication of Paper II, there was no evidence about the best stimulation strategy to use in individual children and clinicians had to rely on their experience or stick to the default setting. The availability of ITD with FS strategies may enhance the experiences of children who receive cochlear implants (Paper II).

1.8.3 Sound localization ability and latency

Assessing the benefits that children with bilateral implants get from being able to localize low frequency sounds seems crucial for further development. Our novel approach was to combine a low frequency localization test with aggregated ITD outcomes. The use of eye-tracking to assess the subject's localization ability when they were in the natural situation of watching a movie, which occasionally jumped between loudspeaker/display pairs, has not been used in cochlear implant research before. For the first time, the importance that ILD plays in localization, and its correlation, could be assessed in children with cochlear implants. This contribution to our knowledge may affect future strategies for bilateral cochlear implantation and the way we fit and evaluate these devices. (Paper II)

The eye-tracking method we used for sound localization measurements allowed us to carry out detailed investigations into gaze behavior in response to a shift in sound source direction. Due to the nature of the test results, a novel model of gaze behavior was needed to measure the latency of the response. Response latencies have been researched since the late 19th century (Dixon, 1896) and visual response latency from the 1970s (Zahn et al., 1978).

Ocular responses to auditory stimuli are very natural and profound reactions, which are actually somewhat faster than the responses to visual targets. The ocular response to auditory stimuli has not been the subject of as much research to date as its visual counterpart. Perhaps it is because the response and the target belong to two different research fields, namely visual and auditory research. The latency of sound localization will provide information about the neural networks involved in a rapid and noninvasive way. This research provides the potential for both increased knowledge about the development and integrity of auditory and other neural structures, as well as clinical applications in terms of the quality of the intervention and enhanced diagnosis (Papers III and IV). The results from paper III exposed unique information about the relationship between accuracy and latency towards horizontal auditory targets. In paper IV normal data of gaze response latency was established in infants and children from 6 months to 3.4 years for the first time.

2 METHODS AND MATERIAL

2.1 COCHLEAR IMPLANT SUBJECTS (PAPERS I AND II)

Paper I looked at 193 patients who received implants from 2002-2013, before they reached 30 months of age. They were all treated by the Cochlear Implant Section at the Karolinska University Hospital Huddinge, Sweden. We know that conditions and comorbidities can increase variability in the outcomes after cochlear implant surgery and that these might be unevenly distributed across ages and distort the analysis. In order to avoid possible confounders, we applied a number of exclusion criteria (see Figure 3 for an overview):

- Patients who are deaf following meningitis exhibit considerable variations in outcomes when they receive cochlear implants. This is due to differences in the severity and extent of the bacterial infection as well as the deprivation of peripheral hearing. Furthermore, most patients who suffer from meningitis are born with normal hearing. Subjects excluded: 10.
- Severe cochlear malformation is a condition that makes it difficult to place the electrode and this can can make the electrode-nerve interface less than optimal. If a patient has a malformation, the length of the electrode can be very short or parts of the electrode can end up outside the cochlea. Subjects excluded: 12.
- Our preliminary data showed that there was usually a detrimental effect on spoken language outcomes when languages other than Swedish were used at home. Subjects excluded: 28.
- Subjects with a professional diagnosis of cognitive delay were excluded. Studies, including Birman et al (2012), have shown that deafness is accompanied by functional deficits in around 30% of the cases. Subjects excluded: 19.
- Specific language impairments were not included. Subjects excluded: 5.
- Some subjects moved to another location and were lost to consecutive follow up. Subjects excluded: 10.
- Our preliminary data also showed that when parents used sign language at home, children developed spoken language more slowly after a cochlear implant than children from homes where speech was used. Subjects excluded: 5.
- Children with late onset of hearing loss have an advantage because of their early hearing experience. Subjects excluded: 1.

We ended up excluding 90 subjects and this meant that the final cohort was 103 patients. Because the subjects that we excluded due to additional difficulties or benefits were not evenly distributed across the different ages at the time of their first implant, the possible interference with statistical outcomes was eliminated.

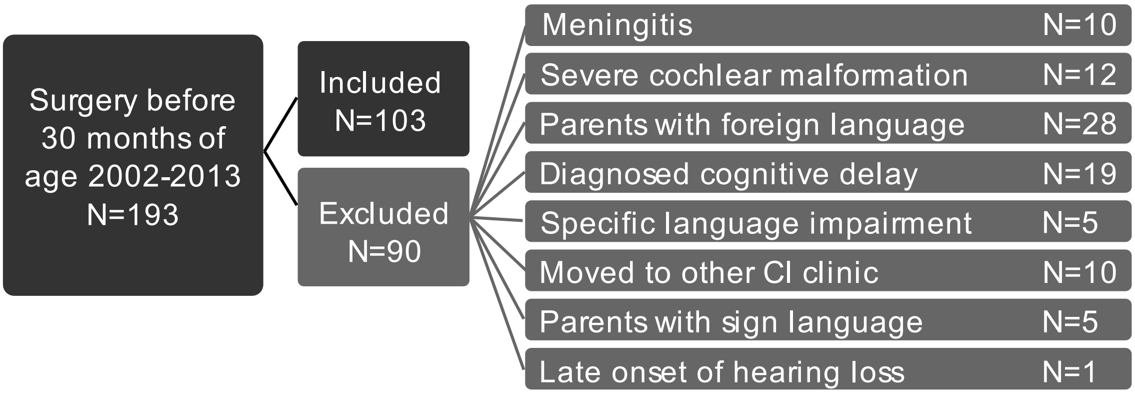

Figure 3. Inclusion and exclusion criteria for the 103 participants

All the subjects participated in a follow-up program that aimed to ensure that their spoken language development was sufficient as the main mode of communication.

The 30 subjects in Paper II were recruited from the same clinical population at the Cochlear Implant Section at Karolinska University Hospital, Huddinge, Sweden. The first nine subjects were randomly chosen for the pilot part of the study and the inclusion criteria were:

- Patients with sequential or simultaneous bilateral implantation before three years of age. This criterion was chosen to decrease variations from the confounder of age at surgery.
- Those who had achieved at least 50% of open speech discrimination of 25 monosyllabic words suitable for children. In addition, aided free field thresholds of better than 30 dB HL (warble tones at 250, 500, 1000, and 2000 Hz) seperately on both sides. These inclusion criteria assured that the implants were well-established, both in terms of use and function.

This data collection for the pilot part of the study took place during 2014. The subsequent collection was performed consecutively in 2017, when the subjects who met the above inclusion criteria attended their yearly follow up at the clinic. The children were invited to participate, and the caregivers and children provided informed, written consent and assent, respectively.

2.2 NORMAL HEARING SUBJECTS (PAPERS III AND IV)

Eight normal hearing adults (seven female) with a mean±SD age of 28 ±6 years (range 18-40) took part in the study covered by Paper III. None of them had a history of noise exposure and their pure-tone thresholds were all better than 20 dB HL in both ears at all audiometric frequencies. The maximum interaural pure-tone threshold difference was 14 dB. Before testing, the subjects underwent a middle ear investigation by otomicroscopy, tympanometry and acoustic stapedius reflex tests (probe tone 226 Hz, ipsi 0.5 to 4 kHz) with the GSI 33, (Grason-Stadler, Minnesota, USA) in both ears. The subjects all provided informed, written consent.

Apart from the test and retest in a normal hearing situation, two additional conditions of simulated acute unilateral hearing loss were induced using the EAR Classic foam ear plug (3M, Minneapolis, USA) and the Bilsom 847 NST II circum-aural hearing protector (Cole-Parmer Instrument Company Ltd, Cambridgeshire, UK). The attenuation for the two conditions were evaluated by bilateral application of the earplug and the earplug plus the hearing protector in a free field.

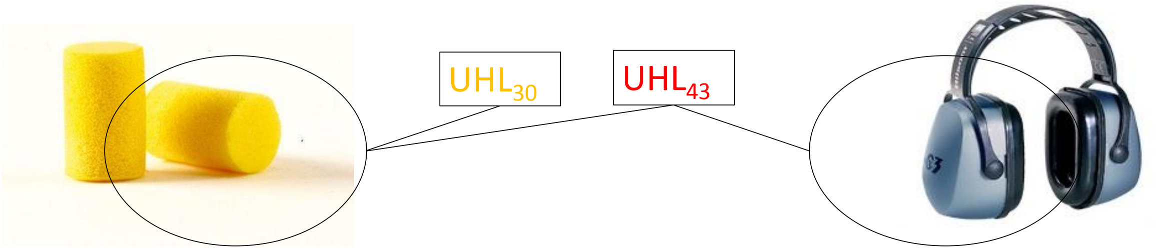

Figure 4. The simulated unilateral hearing loss conditions were obtained by using either an earplug (left) or a combination of an earplug and an ear muff (right). Image source: 3M

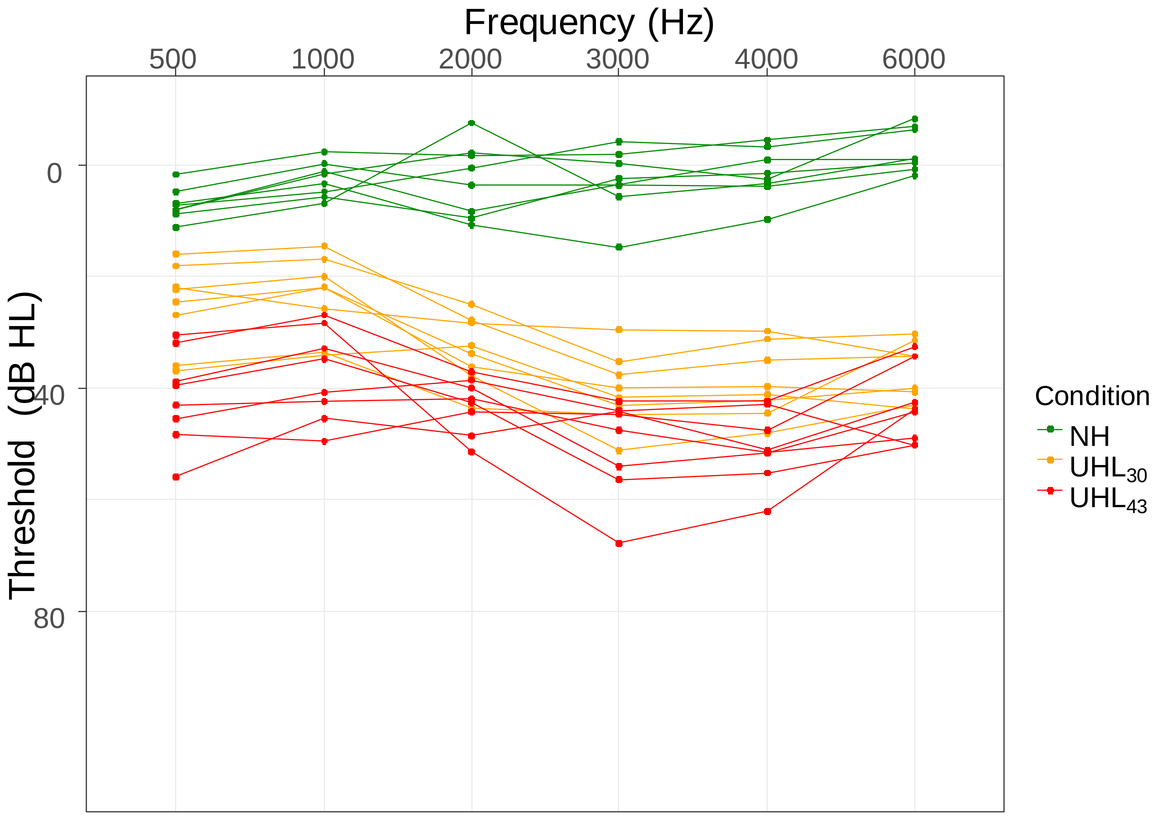

Figure 5. Free field thresholds across frequencies. Each line corresponds to one of eight subjects and three conditions: Normal hearing, simulated unilateral hearing loss with average attenuation at 30 dB TMV and 43 dB TMV respectively. Image source: thesis author

The children with normal hearing who were recruited to the study covered by Paper IV were all born full term and passed the newborn hearing screening (otoacoustic emissions). Eighteen subjects participated with a mean±SD age of 1.28 ±0.85 years (range 0.55 – 3.42).

2.3 SPOKEN LANGUAGE TESTS (PAPER I)

The language tests were performed by two of the authors of Paper I (UL and EÖ) and three additional certified speech and language pathologists at the Hospital's Hearing Implant Centre. The tests described different language abilities over time. Language understanding was assessed by using the Reynell Developmental Language Scales, Third Revision (Edwards, 1999) before surgery, and then at six, 12, 24, 36, and 48 months after the first cochlear implant fitting. The test consisted of short audio-visual instructions of increasing difficulty. Receptive (passive) vocabulary was assessed by the Peabody Picture Vocabulary Test, Third Edition (Dunn & Dunn, 1997). This is a closed-set test where the investigator presents a word audio-visually in each trial and the subject have to choose one out of four pictures. Versions IV and V were not used, as we wanted the test to be consistent across the whole cohort. The test was administered 18 months after the first fitting and then every 12 months until the patient reached 16 years of age. Expressive (active) vocabulary was assessed using the Boston Naming Test (E. Kaplan et al., 1983) where the subject is asked to name 60 pictures. Normal data was interpolated so that we could transform the raw score to the corresponding language age (Figure 6). The subject's score was converted to the age of the corresponding norm performance, resulting in for example a "Language understanding age". This age corresponds to the age of normal hearing children that would obtain the same raw score on average.

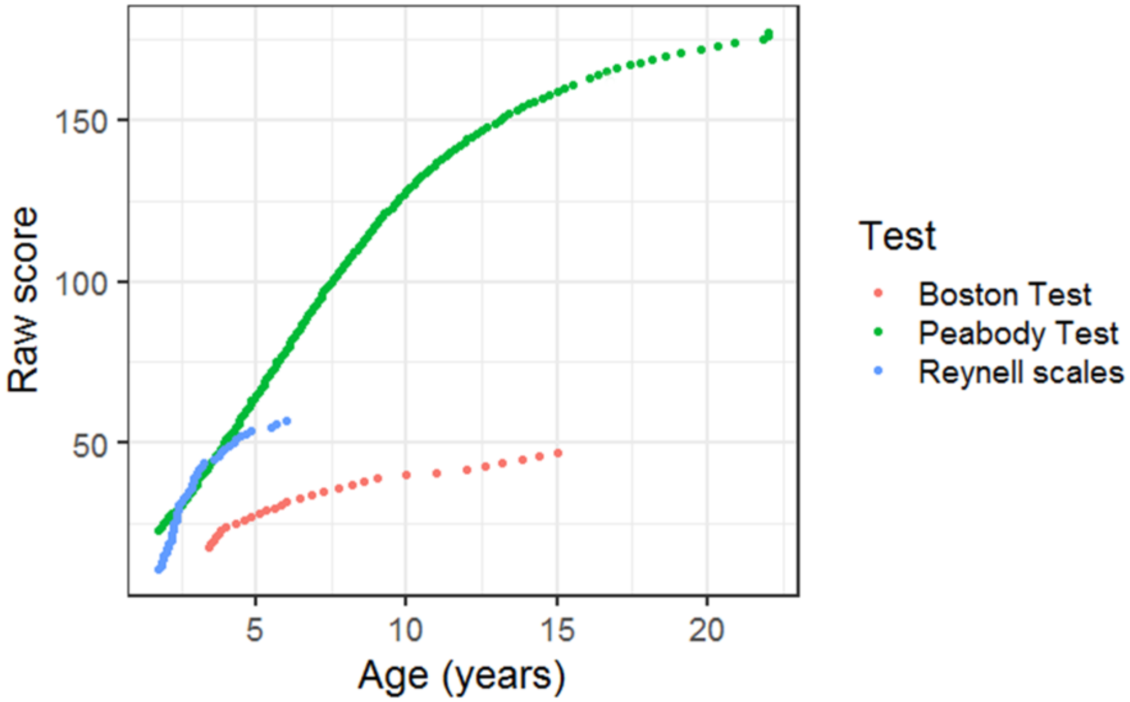

Figure 6. Age as a function of normal raw scores for the three tests. Image source: thesis author. Normal data from Edwards (1999) and the test manuals.

The first and second editions of the Speech Intelligibility Rating scales (Allen et al., 2001), were used to rate the intelligibility of the subject’s everyday speech. We did this at each follow-up visit. The outcome variable was the test age when the child’s speech was rated to be intelligible to any listener without context (level 5).

2.4 HEARING THRESHOLDS AND SPEECH PERCEPTION (PAPERS I, II AND III)

The assessment of the hearing thresholds was performed either by the modified Hughson-Westlake method, which is employed in most clinical settings around the world (American National Standards Institute ANSI S3.21-1978 R-1992). It is a Up 5 dB, Down 10 dB rule with three turning points. This method was used in papers I and II. Paper III used a modified version of the quick and reliable automated method that was first proposed by George von Békésy (1947). The subject controls the level of the tone by pressing a button as long as the tone is perceived and keeping it released when the sound is inaudible. The turning points for different frequencies are later analyzed. The modified version used in Paper II was developed and presented by Berninger, Åkesson and Leijon (2014). It followed a fixed-frequency paradigm at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz, with four turning points at each frequency. Subjects were tested in a free field with binaural symmetry in the three conditions: one normal hearing (NH), and two degrees of simulated unilateral hearing loss UHL_{30} and UHL_{43} (Figure 4 and Figure 5). Speech perception ability was assessed in Paper I by presenting a child-appropriate selection of monosyllables in quiet test, with 25 words per test (Liden, 1954).

2.5 PSYCHOACOUSTICS (PAPER II)

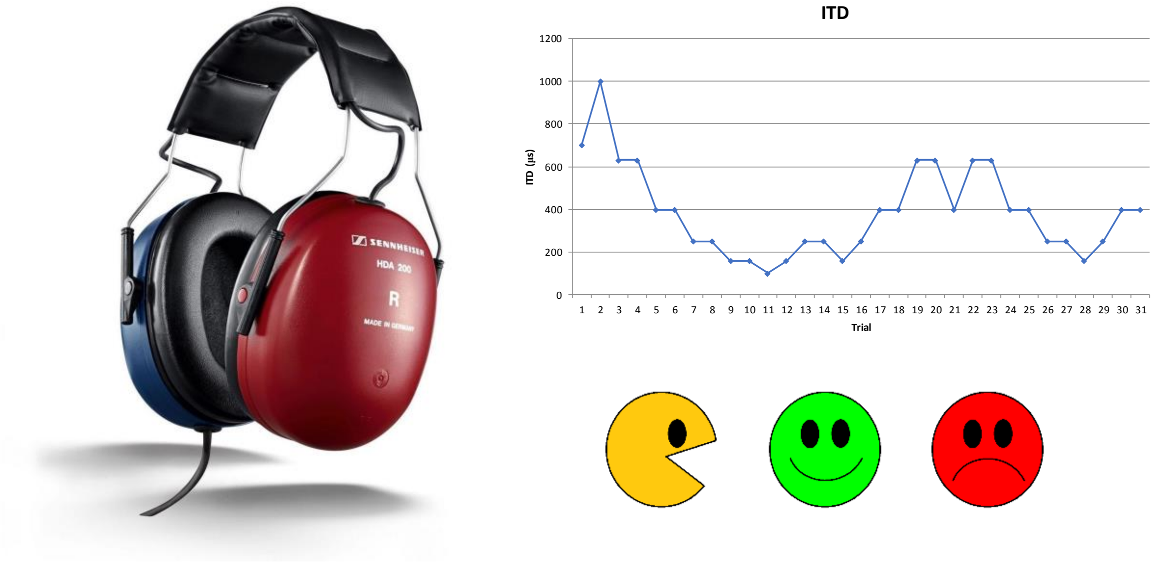

Figure 7. The HDA200 headphone from Sennheiser that were used in the psychoacoustic experiments (left). Image source: Sennheiser electronic GmbH & Co, Wedemark, Germany. The graph on the right shows a typical adaptive staircase for the interaural time difference, with the smileys underneath used to show the progress and provide feedback. The resulting threshold from the above measurement corresponded to approximately 300 µs (microseconds). Source: thesis author.

A game that was suitable for children was developed to answer the question about whether prelingually deaf children who received bilateral cochlear implants could assess ITD. The aim was to reach the threshold of discrimination of lateralized tone pairs based on only ITD or ILD. The psychophysical task of measuring the interaural time and level differences was carried out by using the transformed adaptive forced choice paradigm first proposed by Levitt (1971). This method makes the adaptive staircase a little bit more difficult to predict and allows for iteration around a threshold that is easier than a 50% chance level. Levitt described a method with a two-down and one-up rule, which means that the subject needs two consecutive correct answers before the stimulus becomes harder, but only one error for the stimulus to become easier. This method revolves around a threshold corresponding to a 70.7% chance level, an example is shown in the diagram on the right in Figure 7. An easier test is less discouraging and provides the subject with better motivation. The forced choice paradigm means that the subject has to make a choice, even if they have no clue, or not enough clues, about what choice to make. The benefit of this approach is that it avoids the inner threshold, where the subject feels unsure and wants to answer: “I don’t know” or “Play it again”. This inner threshold will vary from person to person and from time to time, but it will always be higher than the true threshold that can be reached when a subject is forced to make a guess. There are numerous ways of deciding when the staircase is finished and how to calculate the threshold. A minimum number of trials, or a minimum number of turning points, is combined with criteria on the standard deviation of the turning points to make sure that a threshold is reached. This method was chosen as it was rapid and suitable for children and a fixed number of 30 trials were used. The calculation of the threshold was defined as the mean of the last 20 presentations levels, in dB for ILD and in μs for ITD respectively. This included the presentation that would have been presented as trial number 31, to include the response from trial number 30. Before the test, the subjects listened to a short presentation on the two different stimuli that were used in each test. The first stimulus was always zero ITD and zero ILD, which corresponds to a sound coming from a position on the sagittal plane, namely perpendicular to an axis though the ears. The second stimulus had an altered interaural time or level difference, depending on the test.

2.6 LOCALIZATION SETUP (PAPERS II, III AND IV)

Figure 8. The sound localization setup consisted of 12 loudspeakers and 12 visual displays, arranged in 10-degree increments, spanning a 110-degree arc in the frontal horizontal plane. To attract the subject's gaze to the visual displays, loudspeakers and loudspeaker stands were covered in black cloth. The image above shows a screenshot from the eye-tracking software, visualizing the three-dimensional model of the 12 "areas of interest": virtual rectangles incorporating the loudspeakers and the visual display). The gaze of a participating subject, here displayed as a gaze vector (red dashed line), was detected as being directed toward the area of interest having its origin at −50 degrees azimuth. Published with permission from photographer Staffan Larsson www.medifophoto.com.

Sound localization can be measured objectively and rapidly by recording the pupil position in the eye in relation to auditory targets (Asp et al., 2016).

The setup and measurement procedure used in Papers III and IV is described in detail by Asp et al. (2016), but a short description follows. Horizontal sound localization behavior was measured in the sound field with 12 loudspeaker/display pairs placed in an audiological test room at 10-degree intervals in the frontal horizontal plane (±55 degrees azimuth), as shown in Figure 8. An ongoing auditory-visual stimulus (speech-shaped spectrum) was presented at 63 dB SPL(A) and shifted to randomized loudspeakers, with pauses in the visual stimulus, Figure 9. The visual stimulus was automatically reintroduced at the azimuth of the sounding loudspeaker after a sound only period of 1.6 seconds. The sound only period is indicated in Figure 9. Intuitively, the subject would try to find the corresponding display.

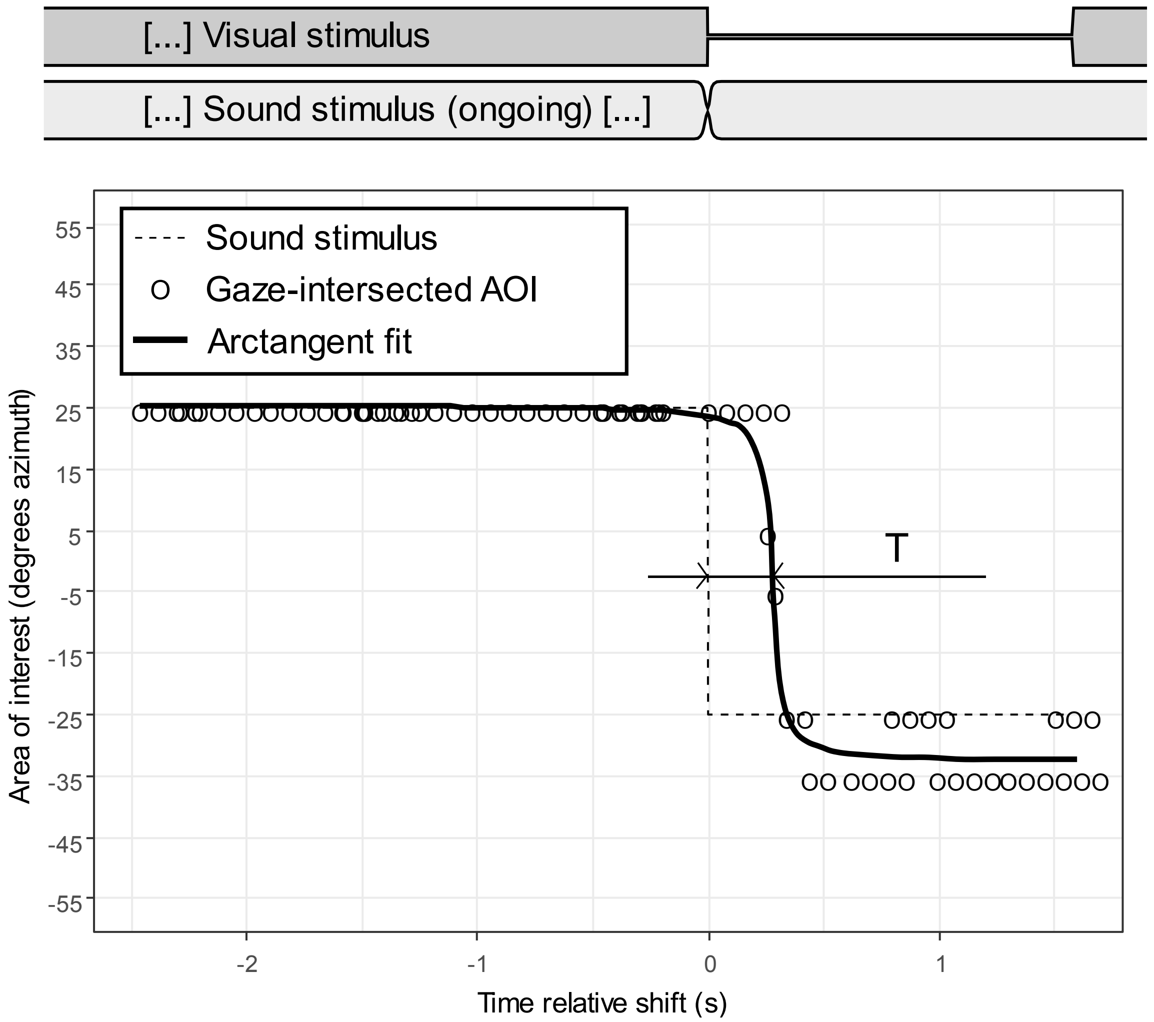

Figure 9. An example of an eye tracking recording showing the 4.1-s analysis window for an azimuthal sound shift from +25 to -25 degrees (dashed line). Samples of gaze intersected AOI are shown (open circles) together with its corresponding arctangent fit (solid line). The latency (T) in each trial was defined as the abscissa corresponding to 50% of the arctangent amplitude. Source: Eklöf, Asp & Berninger et. al., (2020). Copyright license CC-BY from Elsevier.

A corneal reflection eye tracking technique allowed acquisition of the subjects' pupil positions (gaze) relative to the rectangular areas of interest (AOI) (Gredebäck et al., 2009), which corresponded to the loudspeaker/display pairs in a three-dimensional model in the eye tracking software (Figure 8). Four infra-red cameras and three infra-red flashes collected the gaze intersection samples at a rate of 20 Hz. See Figure 9 for an example of gaze samples.

This method was able to determine sound localization accuracy from six months of age. To investigate the localization ability of children with early bilateral cochlear implants, the localization equipment was used with two different stimuli in Paper I: one broadband and one low-frequency stimulus. See Figure 10 for long-term spectra of the two stimuli.

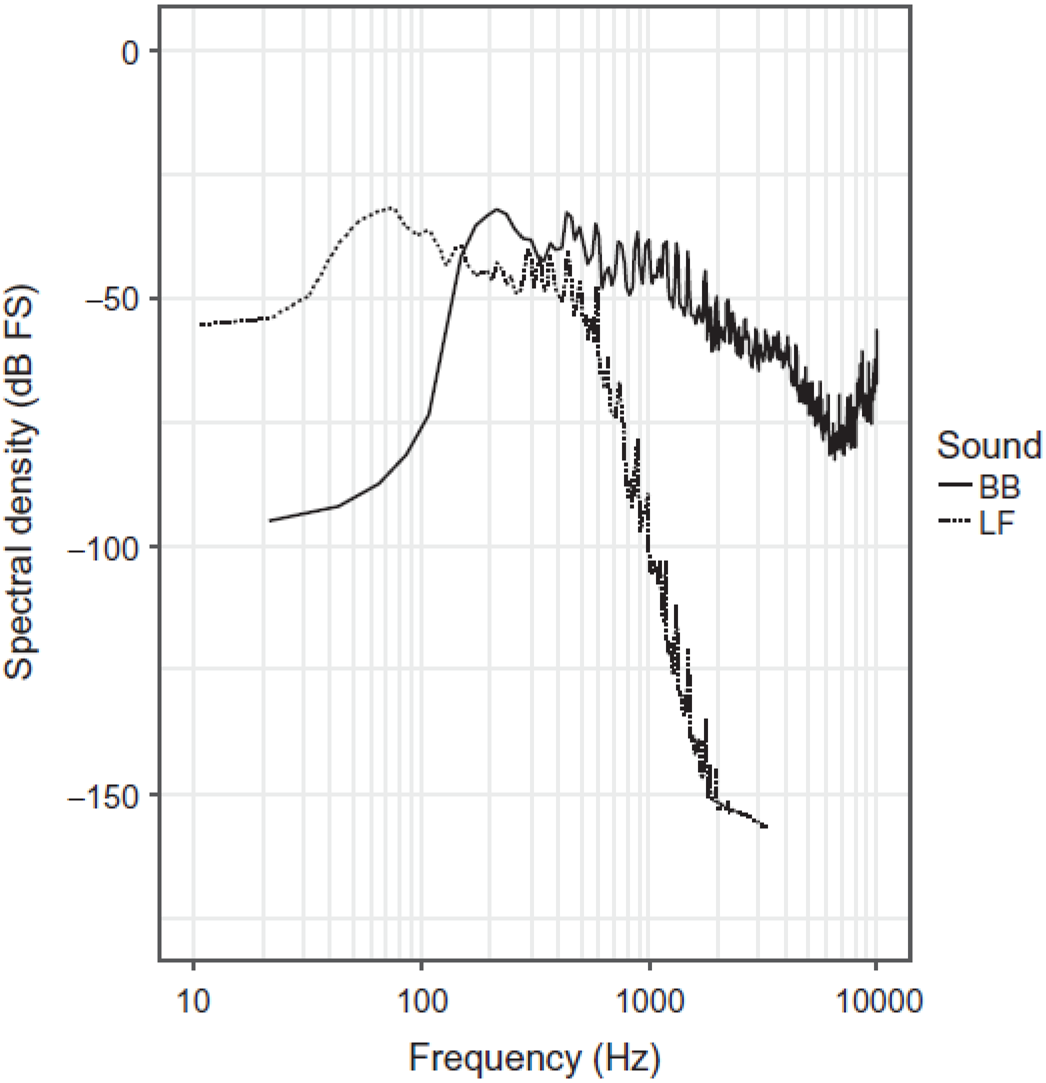

Figure 10. A spectrum of the broadband and low-frequency sounds (log-scale of frequency axis). Source: Eklöf & Tideholm (2018). Published with permission from Taylor & Francis.

The accuracy of localization can be quantified by absolute error, a measure that does not take into account the average direction or bias. The mean absolute error (MAE) is calculated by using the following formula:

Equation 1

$$MAE = \frac{\sum_{i=1}^{n} |p_i - r_i|}{n}$$

where p_i is presented and r_i is the response angular azimuth for every valid trial (i) of the number (n) of valid responses. This outcome was used in Paper II. The MAE corresponding to random performance depended on the actual combination of the presentations in every test. An alternative approach is the Error Index (EI), which has been described by various papers including Gardner & Gardner (1973), where the absolute error is normalized by all possible combinations of the responses, given the set of presentations with valid responses. The EI is calculated by using the following formula:

Equation 2

$$EI = \frac{\sum_{i=1}^{n}|p_i - r_i|}{\left(\sum_{j=1}^{n}\sum_{k=1}^{m}|p_j - q_k|\right)/n}$$

where the nominator accumulates the total absolute error between the (n) number of presentations (p_i) and corresponding valid responses (r_i) and the denominator accumulates the total error of all (m) possible responses (q_k), averaged across each of the (n) number (j) of presentations (p_j) with valid responses. This formula yields a number between zero and two, where zero corresponds to perfect localization and one corresponds to random performance. This formula was used in Papers III and IV. Given an equal distribution of the 12 possible presented sources with a corresponding valid response, the EI can be approximated by dividing the MAE by 39.7, which follows from the combination of Equations 1 and 2.

2.7 MODEL OF SACCADIC BEHAVIOR (PAPERS III AND IV)

In addition to the accuracy measured by the above described method, an estimate of the latency involved in the localization response was calculated. The previously reported eye-tracking method was used to assess sound localization accuracy from six months of age. The method is clinically feasible and only takes about three minutes to perform. An objective estimation of the latency that did not need a manual inspection was carried out.

The most suitable model had an arctangent (arcus tangent) function. This model followed the angular direction of the gaze as a function of time and four parameters were found using an optimization algorithm: the original angular gaze direction, the target gaze direction, a slope parameter and the delta time. The delta time translated the function in the horizontal axis, determining the latency (T). The algorithm minimized the root mean square error of the deviation of the fitted function and the gaze samples by using optimization.

The following formula was used to fit the samples in each trial:

Equation 3

$$a(t) = a_1 + (a_2 - a_1) * \left(\left(\frac{\pi}{2} + \arctan\left(c * (t - \mathrm{T})\right)\right)/\pi\right)$$

where a_1 and a_2 (°) are continuous variables ($-55° \leq a_{1,2} \leq +55°$) signifying the 12 gaze intersected AOI before and after the azimuthal sound shift. The slope parameter c (s^{-1}) is a combined measure of the speed and eccentricity of the trace ($0 \leq c \leq 130$), t (s) is the time and T (s) is the latency for each trial ($\mathrm{T} \geq 0$).

Since an auditory saccade takes approximately 100 ms to perform, this provided a good opportunity to collect one or two samples during the actual gaze shift.

The exclusion criterion applied in paper III was that T needed to be more than 0 and less than 1.6, which ensured that the optimization algorithm converged towards a value within the sound only period. Additional inclusion criteria were presented in the results of Paper III and applied in paper IV and these ensured that only trials with very consistent gaze data were used. The sample loss before or after the sound shift had to be less than 50%. The root mean square error of the fit had to be below 7 degrees, a threshold chosen after inspection of the histogram. In paper IV, an additional exclusion criterion was applied. If difference between the estimated gazed intersected AOI before and after shift, a_0 and a_1, was less that 10° the trial was excluded since this signified a flat response.

2.8 STATISTICAL METHODS EMPLOYED (PAPERS I, II, III, AND IV)

To investigate the differences in language development (Paper I), we developed a method to compare various tests that were carried out at different ages at the same chronological age. Yearly clinical language assessments of children implanted at different ages were compared by using linear regression and interpolation of age-equivalent scores on language tests. Figure 11 explains how this worked. This method turns a series of results from a child's assessment visits into a linear trend that can be turned into an estimated performance at a certain age. This performance can further be plotted against the age at first surgery, as seen in Figure 12 in the Results section, or evaluated by non-paired *t*-tests between surgical age groups.

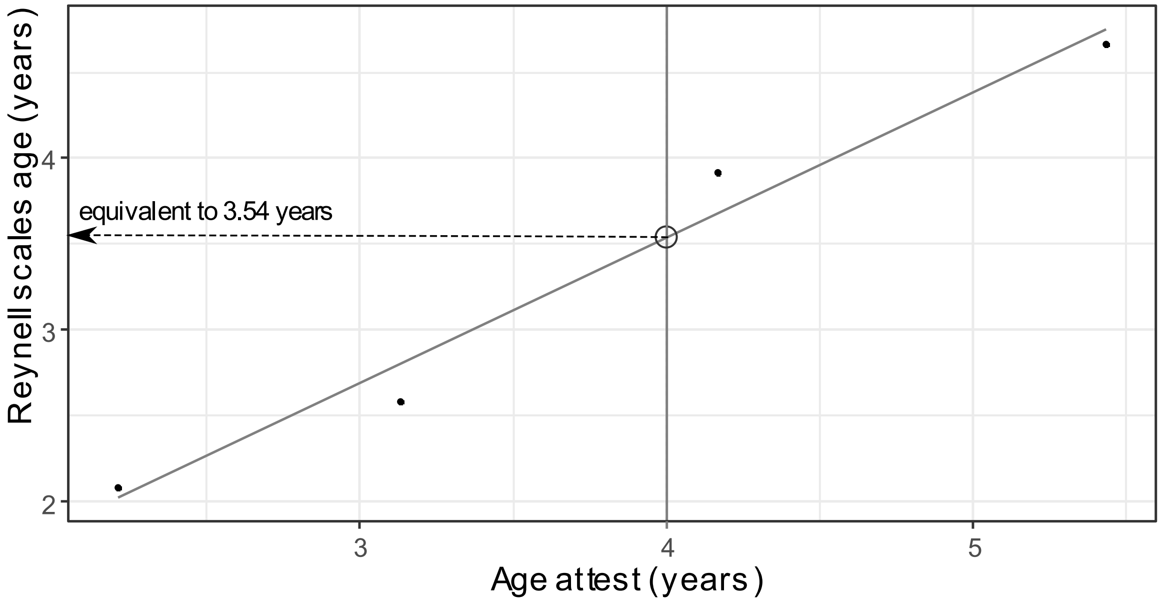

Figure 11. Example plot showing how performance at four years of age was estimated. This child was tested on four occasions between two and six years of age with the Reynell scales. The raw score was transformed to language age based on the validation of the test with children with normal hearing. The inclined line shows the linear regression line, and performance was interpolated at four years of age to correspond to 3.54 years in language development. This allowed us to compare children assessed at different ages and yielded a robust value that considered performance over time. Source: Karltorp et. al., (2020). Copyright license CC-BY-NC

A challenge with the study design of Paper III was that the same eight subjects were measured four times, which made the data points statistically dependent. Dependent samples violate one of the assumptions of regular linear regression analysis and regular analysis of variance (ANOVA). This called for a novel statistical approach that is now used across different research fields: linear mixed modelling. This approach treats individual variations separately as so-called random factors (categorical) or effects (continuous) and considers the fixed factors/effects apart from the random. Random factors allow for individual intercepts and/or slopes. There has been some debate regarding p-values and the coefficient of variance (R^2), but there are now established methods that provide robust estimates (Kuznetsova et al., 2017).

The regression analysis of latency as a function of age in Paper IV required us to transform the latency, since it deviated from the normal distribution. We used inverse transformation of latency. This is the approach suggested by Luna et al. (2008) in their investigation of saccades towards visual target.

3 RESULTS AND DISCUSSION

3.1 LANGUAGE

Passive and active vocabulary, expressive language and speech intelligibility were all found to benefit from cochlear implant surgery before one year of age, compared to surgery at a later age. We also found benefits of even earlier surgery in the children who received surgery before one year of age. At four years of age, all children implanted before one year of age met the normal hearing norm data in terms of language understanding (Figure 12A). Children implanted before nine months of age were already on track before four years of age, as shown in Figure 13 (t-test of slope and Wilcoxon signed rank test of delay compared to norm: $t = 0.29$, $p = 0.77$ and $V = 147$, $p = 0.48$ respectively). The production of speech that was intelligible to any listener without context, was also reached significantly earlier: 4.2±1.2 years if surgery was performed before nine months compared to 5.3±2.1 years if it took place at 9-11 months ($t=-2.1$, $p<0.05$).

The benefit of having surgery at an earlier age was most pronounced for speech intelligibility and partly for language understanding which were both assessed at lower test ages. For example, the Boston Naming Test, which was carried out at a median test age of eight years (data not shown), showed the benefits of earlier surgery when we compared operations carried out before and after 12 months of age. However, no significant difference in performance could be seen when surgery before nine months of age was compared to 9-11 months of age. The same was true for the Peabody picture test, which had a median test age of six years, Figure 12B. Neural development is possible by plasticity and driven by experience. The results from the development of language understanding showed that children, that lagged behind due to delayed intervention, continued to do so if the intervention was too late. Hence, the accumulated experience of language exposure during sensitive ages will determine the long-term outcome.

When the method that is used to estimate language age is based on more than one test occasion, this increases the specificity of the measure. For example, performing two tests at equal intervals before and after the age of estimation will diminish the measurement error by half, compared to one test occasion (standard deviation / $\sqrt{2}$). Theoretically, more test occasions will decrease measurement errors even more.

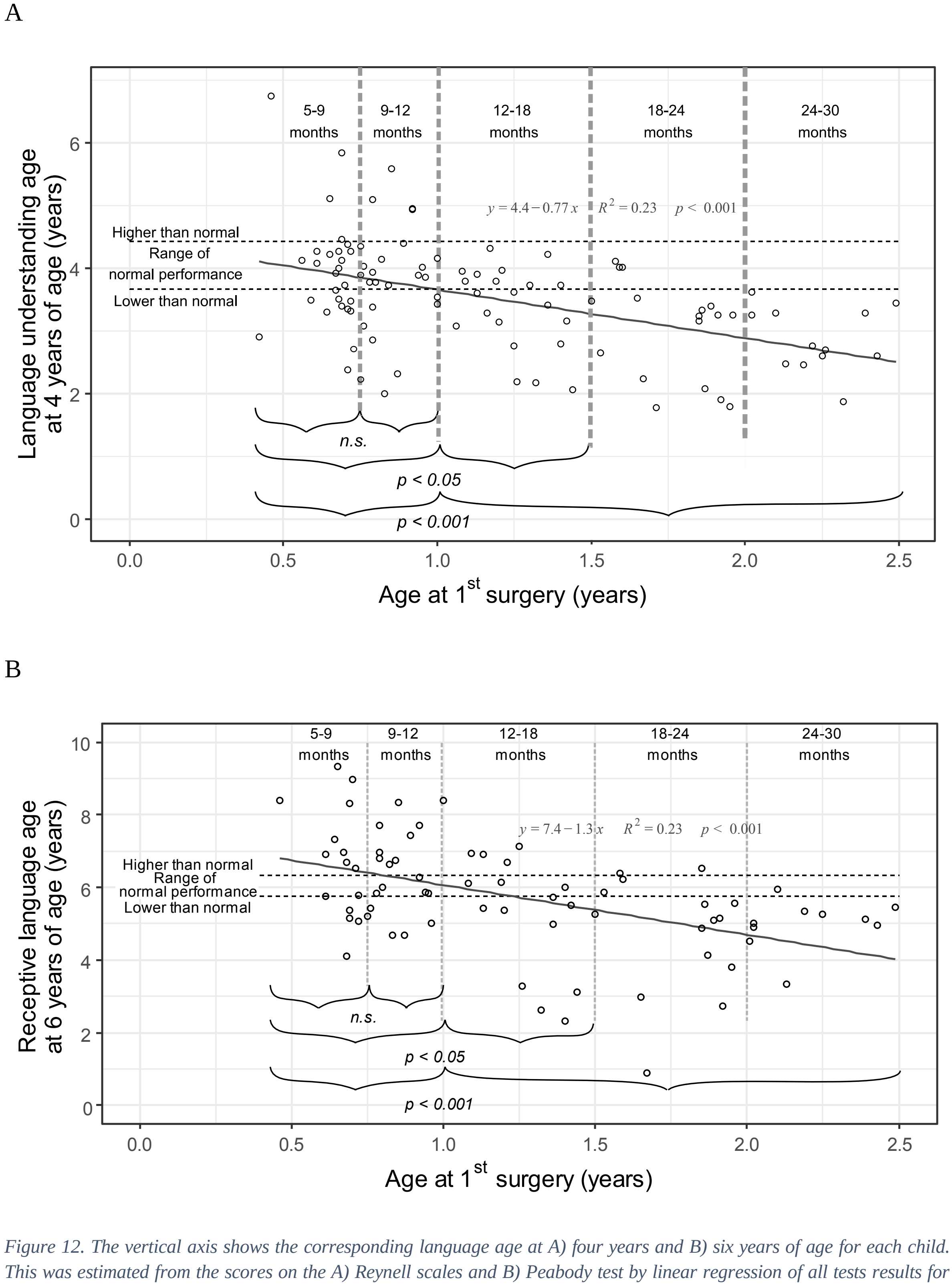

Figure 12. The vertical axis shows the corresponding language age at A) four years and B) six years of age for each child. This was estimated from the scores on the A) Reynell scales and B) Peabody test by linear regression of all tests results for each child. The raw scores were first transformed to age-equivalent norm results. The dashed horizontal lines correspond to the range of normal performance at A) four years of age (a raw score of 49 points) and B) six years of age (a raw score of 79 points). If surgery was delayed by one year, the estimated performance at four years of age dropped by nine months, according to the linear regression (inclined line). Source: Karltorp et. al. (2020). Copyright license CC-BY-NC

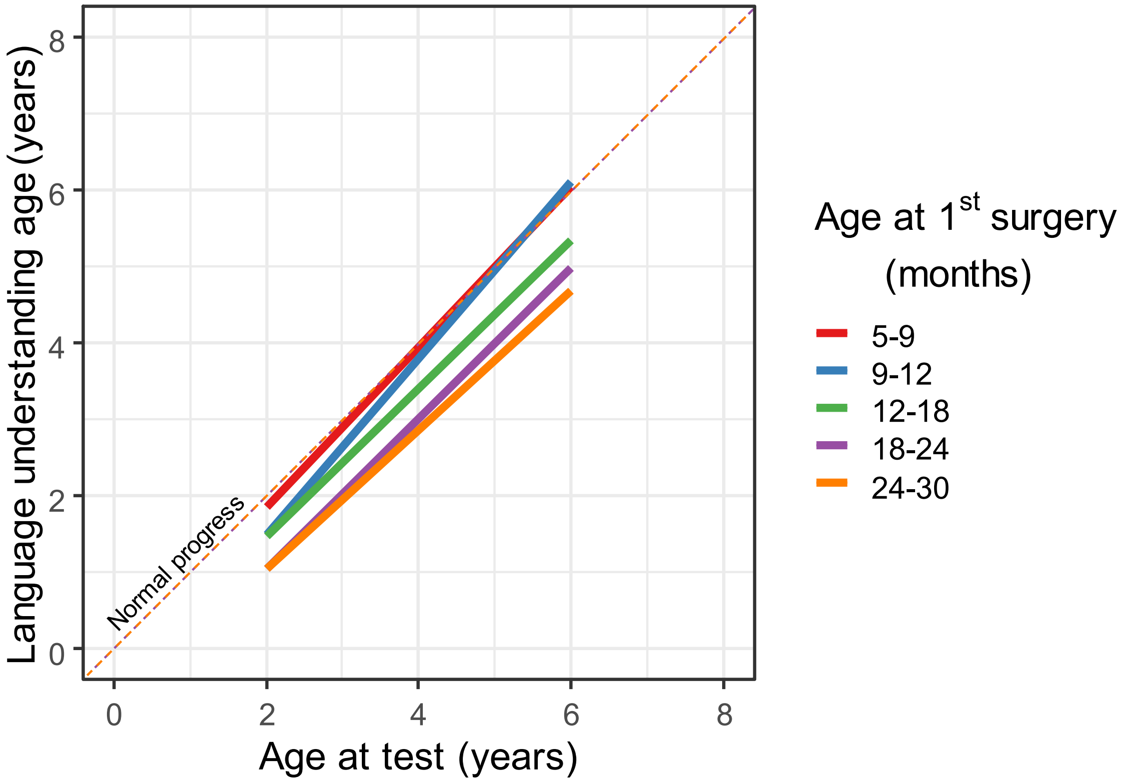

Figure 13. The lines represent mean slope and delay in each surgical age group. Means are calculated from individual regressions on language understanding, according to the Reynell scales. Source: Karltorp et al. (2020). Copyright license CC-BY-NC.

3.2 SURGICAL RISK

All adverse events during or after surgery were listed in the local quality registry as part of the regular follow up. Seroma at the implant site was the most common adverse event and was seen on six occasions in our cohort. Three events occurred in patients that had surgery before nine months of age and there was one patient in each surgical group from nine to 11 months, 12 to 17 months and 18 to 23 months. Two patients had dermatological problems: one was in the group aged 18 to 23 months and one was under nine months of age. Another patient under nine months of age had abnormal pain. Table 1.

Table 1. Complications after surgery, including some cases that occurred several years after surgery. There was no effect of the age at first surgery according to Fisher's exact test (5-11 vs 12-29 months: p=0.48, 5-8 vs 9-11 months: p=0.36)

Age at first surgery (months)	**Seroma**	**Pain**	**Skin issue**
5-8	3	1	0
9-11	1	0	0
12-17	1	0	0
18-23	1	0	1
24-29	0	0	0

3.3 BASIC INTERAURAL ABILITIES

Children who received bilateral cochlear implants showed difference in their access to interaural time. Of the 30 subjects, 20 had a sound processing strategy with theoretical access to FS information. Half of the FS strategy subjects had ITD sensitivity, but none of the non-FS subjects did (Table 2). The findings suggest that programming the device with a sound stimulation strategy, which should provide the hearing nerve with fine temporal information, should be successful, at least when it comes to single sinusoids.

The results from the rapid ITD measurements showed large variations across subjects, with a mean of 330 ±250 µs. This was worse than the results from normal hearing children reported by van Deun et al. (2009). They measured with click trains in children between eight and nine years of age and they reached a median ITD just noticeable difference of 20 and 12.5 µs respectively.

Gordon et al. (2014) presented ITD with direct electrical stimulation in children with bilateral cochlear implants and found that 80% could correctly identify ITD, but the threshold was not assessed. We made the test more realistic by using acoustic sounds administered by their clinical sound processors, rather than direct electric stimulation. This approach showed the benefit of using different stimulation strategies in a real-life setting.

The ability to detect ILD was easier to perform and possible for 29/30 of the subjects, as they were able to converge towards a threshold below10 dB, with a mean interaural difference of 2.7 ±1.7 dB. The findings are in line with previous studies on cochlear implant recipients, both in adults (Aronoff et al., 2012) and in children (Gordon et al., 2014).

Table 2. Stimulation strategy and interaural time differences.

Stimulation strategy	**ITD**	**No ITD**
CIS/ACE	0	10
FSP	4	3
FS4	6	4
FS4-p	0	3

3.4 LOCALIZATION AND THE SPACE MAP

The results presented in Paper II revealed that children with bilateral cochlear implants were able to localize a broadband stimulus with a median accuracy of 13 degrees (95% confidence interval 12-17 degrees). However, localization of the low frequency stimulus proved to be much more difficult, with a mean accuracy of 23 degrees (95% confidence interval 21 – 25 degrees). Subjects with devices that were equipped with fine-structure strategies, with or without ITD ability, did not differ when it came to the ability to localize low frequency stimuli (Figure 14).

There was a trend in the localization of the broadband stimulus and the FS and ITD subgroup (Figure 14 – left-hand box) performed somewhat better than the FS no ITD subgroup (Figure 14 – box number two from the left). The trend in the data suggests that the two subgroups with FS stimulation derived benefit from the ITD ability, whereas the non-FS group performed somewhere in between.

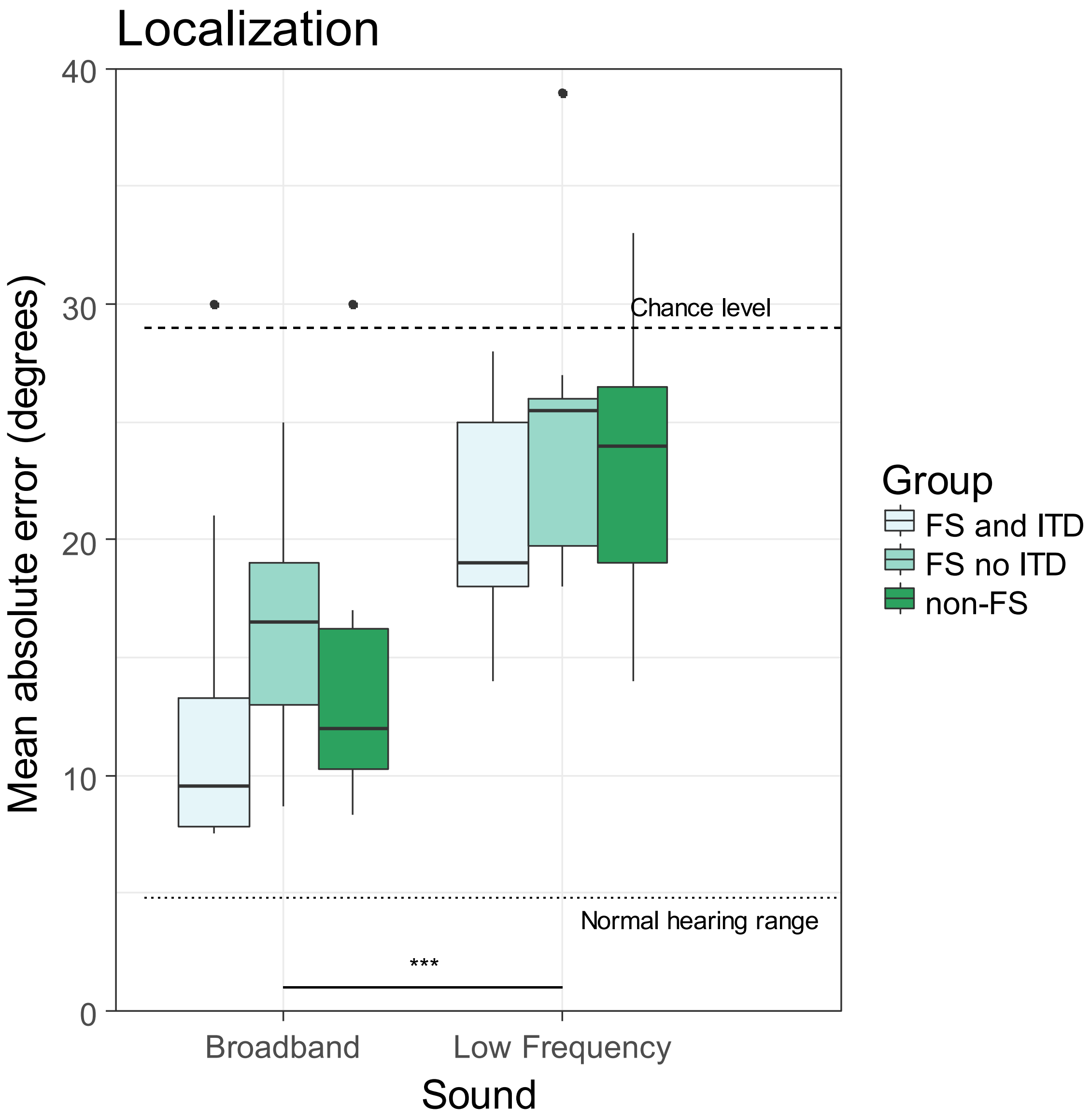

Figure 14. Boxplots of localization ability for broadband and low-pass sound grouped on FS strategy and the ability to detect interaural time differences (ITD - yes/no). Lower scores indicate better performance. The difference in performance between the broadband and the low-pass sounds was significant (V=7, p<0.001 in the 30 subjects according to the Wilcoxon paired test. This was even the case within the three groups FS and ITD (p<0.05), FS no ITD (p<0.01) and non-FS (p<0.05). Localization of low-frequency and broadband sound across the groups was not significant. Source: Eklöf & Tideholm (2018), Published with permission from Taylor & Francis.

However, the ILD threshold did correlate with the localization ability of broadband sounds (Figure 15). This correlation has previously been found in adults (Grantham et al., 2008). The result suggests that improving the ILD threshold by 1 dB will improve the mean absolute localization error by 2 degrees.

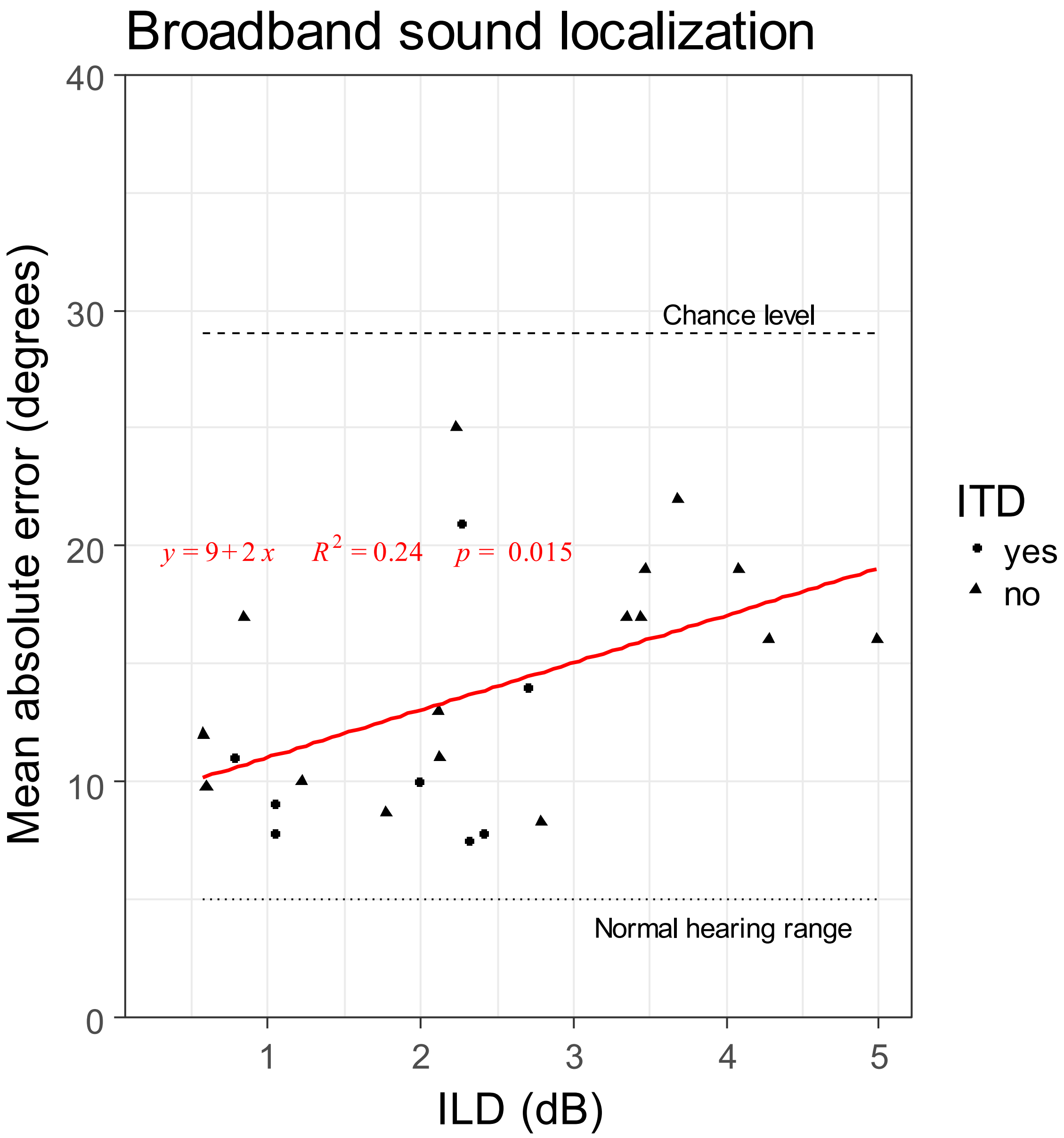

Figure 15. Lower scores indicate better performance. Correlation between localization of broadband sound and interaural level difference threshold was significant (p=0.015, with five subjects excluded as outliers). Source: Eklöf & Tideholm (2018). Published with permission from Taylor & Francis.

3.5 SOUND LOCALIZATION LATENCY

The results from Paper III demonstrate that the localization process can be modeled by applying the arctangent function to the gaze samples. The gaze responses from each azimuthal sound shift can consistently be modelled to acquire the SLL. The eight adults exhibited a SLL of 280 ms and this latency was in line with previous reports, including Ten Brink et al. (2014), Zahn et al. (1978) and Zambarbieri (2002). The simulated UHL significantly increased the SLL significantly (Linear mixed model with subject as random factor, p<0.0001, Figure 16).

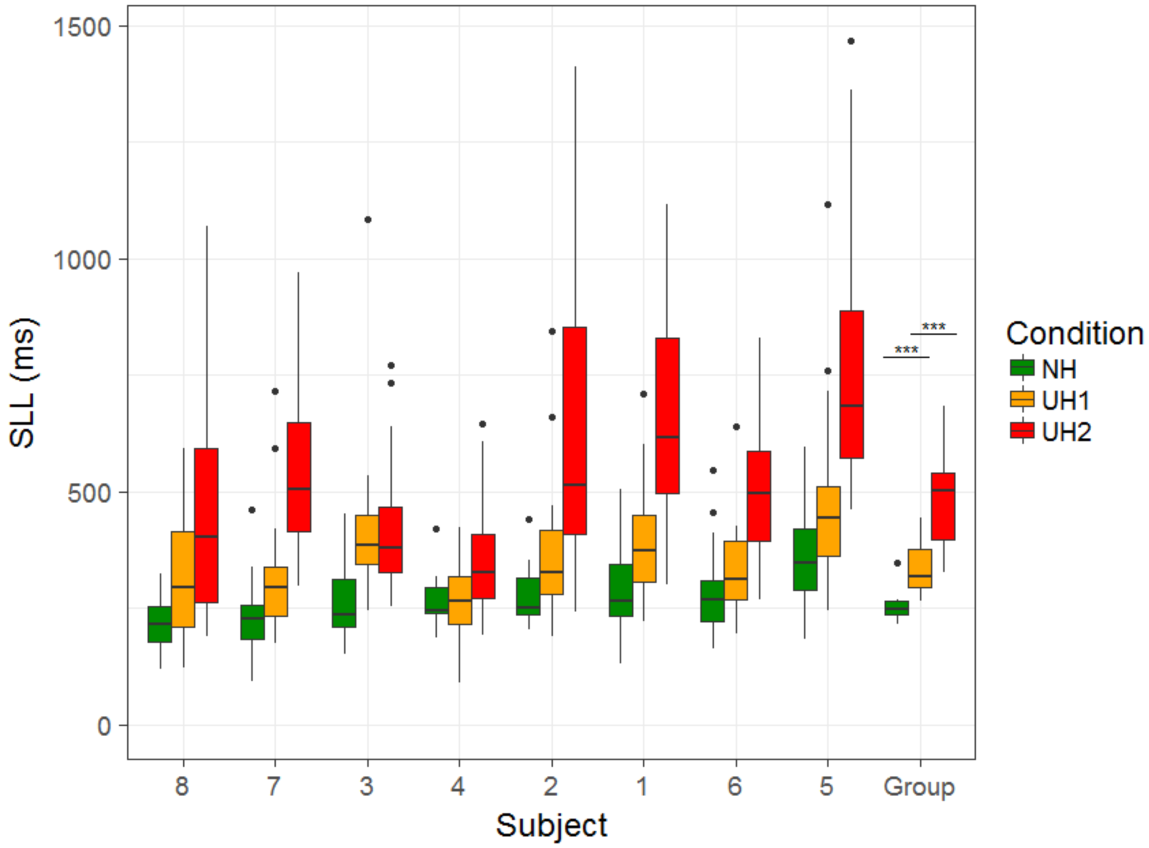

Figure 16. Individual results from up to 24 trials per subject, in ascending order by SLL in the normal hearing condition, as well as the group results that comprised eight mean measurements. The group means were significantly different between conditions (linear mixed model with subject as random factor, $p<0.0001$*).*

The SLL as a function of individual thresholds were assessed using a linear mixed model (data not shown). The threshold at 1 kHz was the strongest predictor for SLL and the increase was 7.4 ms per dB increased threshold ($p<0.0001$, linear mixed model $R^2 = 0.27$).

No effects of the accuracy on latency were found in each trial ($p=0.2$, linear mixed model). This finding suggests that there was no accuracy/latency trade-off. However, the mean latency (SLL) and the mean accuracy (Error index) did correlate across conditions (repeated measures $R^2 = 0.94$), Figure 17.

The correlations of the three repeated measures between the threshold, SLL and Error index were compared and the correlation between the SLL and Error index stood out as the significantly stronger one (William's test $p=0.02$). The increased threshold in the plugged ear had a casual effect on both the SLL and the Error index, but the stronger correlation between the two suggests that both of these were predicted by a bilateral asymmetry that was more exact than the assessment of the threshold. The increased threshold affects the latency and error to almost the same extent as indicated by the above-mentioned strong correlation ($R^2=0.94$).

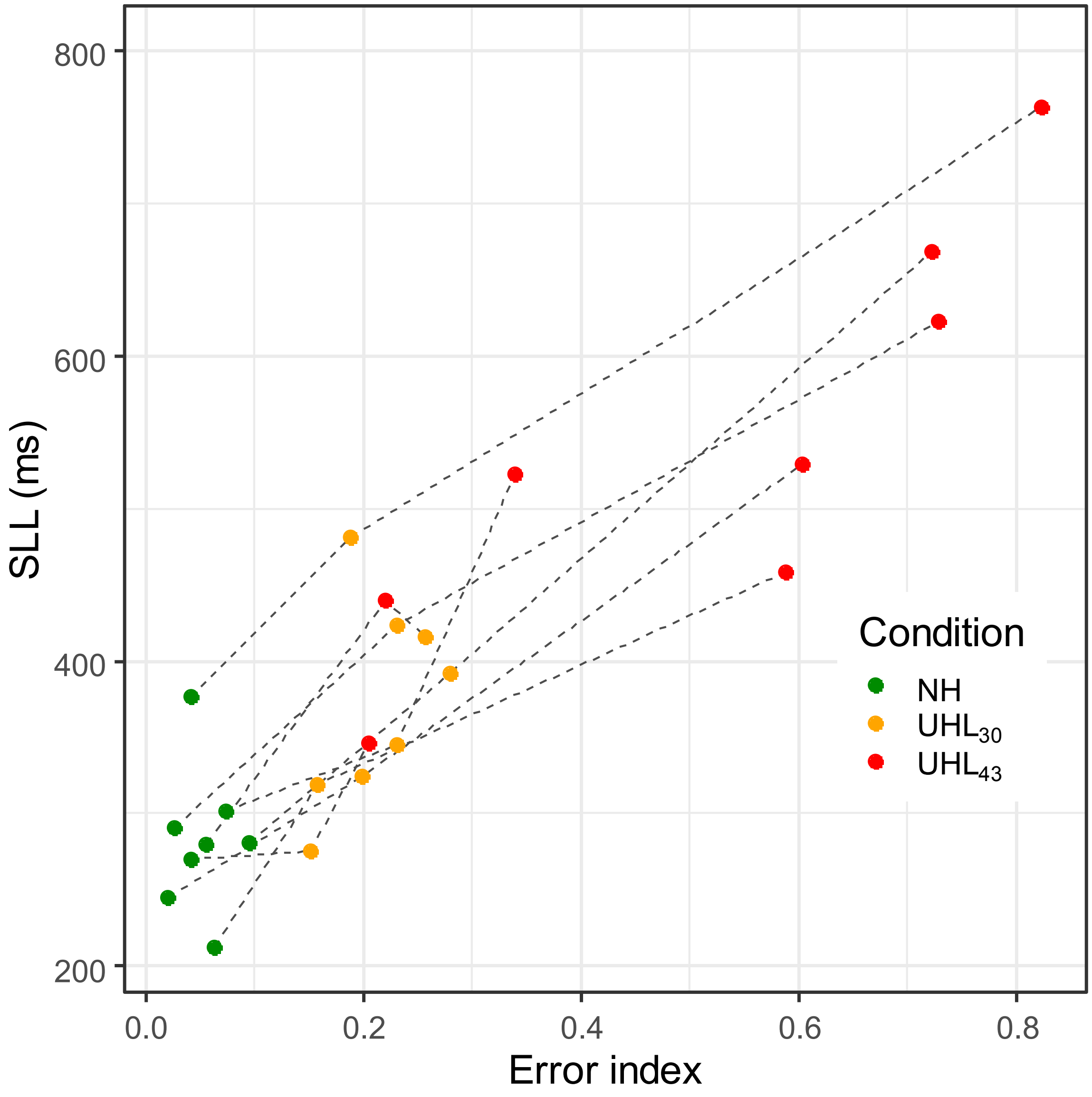

Figure 17. The relationship between sound localization latency (SLL) and sound localization accuracy (Error Index) for normal-hearing conditions (green circles), and two levels of simulated unilateral hearing loss (yellow and red circles). Dashed lines are drawn between data-points from the same subject to visualize individual patterns. Source: Eklöf, Asp and Berninger (2020). Copyright license CC-BY.

It is interesting to note that there are similarities in latency, dynamic behavior, and overlap of anatomical structures between the acoustic middle ear reflex and SLL. At reflex threshold, the latency of the acoustic middle ear reflex (500 Hz pure tone) is 240 ms, decreasing relatively rapidly to 120 ms 10 dB above threshold as can be seen presented in Fig. 1 by Borg (1982). (Borg also used the abscissa corresponding to 50% amplitude.) These dynamic characteristics correspond to latency changes of 12 ms/dB for the first 10 dB above threshold. The neural organization of the acoustic reflex response is 1) auditory afferent, 2) ventral cochlear nucleus cells with axons in trapezoid body, 3) interneurons in medial superior olive leading to 4) stapedius motoneurons of the facial motor nucleus (Borg, 1973). The corresponding neural organization for ITD and ILD is described in section 1.4 of the introduction. These similarities in latencies and dynamic behavior between the acoustic middle ear reflex and the sound localization responses, indicates that the role of the brainstem when it comes to the processing of auditory spatial information is very important.

Previous reports on simulated unilateral hearing loss, reviewed by Kumpik & King (2019), showed that localization ability deteriorated more rapidly than in the current set-up. This could be attributed to at least three differences in the stimulus and setup. The first was the length of the stimulus, which was continuous in our setup and gave the subject up to 1.6 seconds to make a decision. The second was that the sample space of the possible loudspeaker/display pairs was visible and limited to 10-degree increments. The third was that the subjects were free to move their heads and not necessarily aligned with the previous loudspeaker, which might have increased or altered the possible binaural cues.

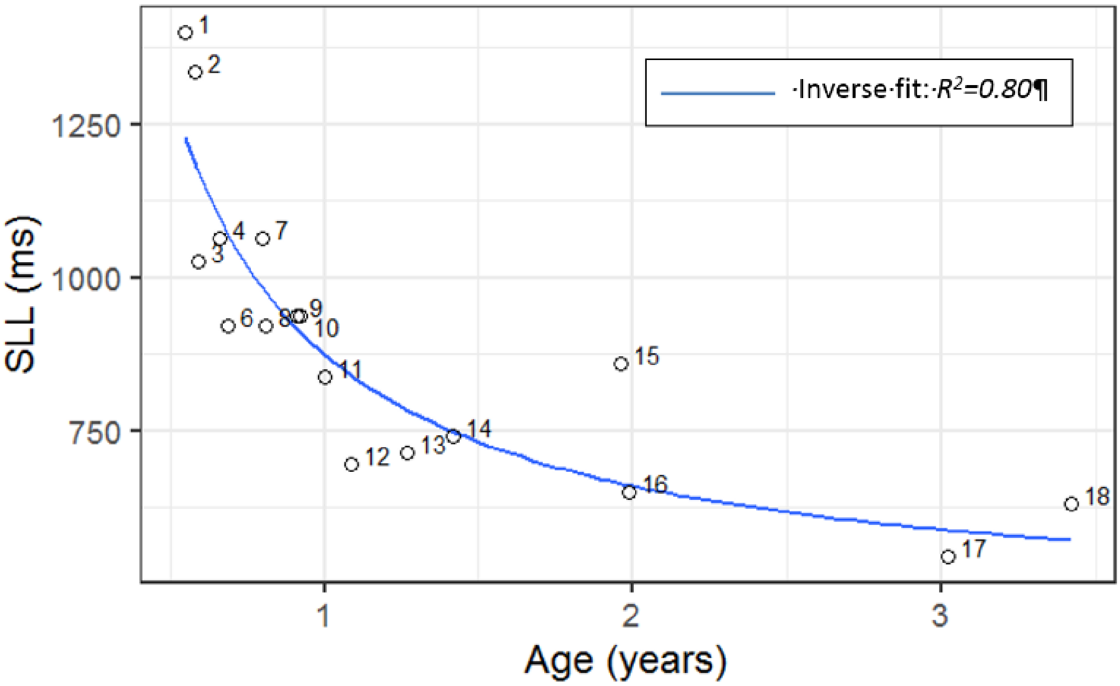

Figure 18. Sound localization latency (SLL) as a function of age for the 17 subjects where latencies could be obtained. Source: Eklöf, Asp and Berninger (2020). Copyright license CC-BY.

Then, we wanted to investigate the normal development of SLL. We therefore tested 18 normal hearing subjects, who ranged in age from 0.55 to 3.42 years. It was not possible for all the subjects to attend all 24 trials, but 15 subjects managed to attend to at least half of the trials. Furthermore, 33% of the trials passed the extended exclusion criteria described in section 2.7. An inverse regression model was applied, demonstrating a strong relationship with age ($SLL = 450 + 430/Age$, R^2=0.80, p<0.001, Figure 18),

This means that the difference between a child's SLL and the asymptote of 450 ms will decrease by half as the age doubles from about one second at nine months of age to about 600 ms at three years of age.

It has been suggested that the fastest auditory saccades are guided by processing at the level of the brainstem (Luna et al., 2008) and that the brainstem is myelinated at one years of age (Sano et al., 2007). However, the shortest latency within a test did not vary with age, but it was rather constant, at around 400 ms, throughout the age span (Table 3). This suggests that even the fastest neural pathways are still under development beyond one year of age.

The same model (inverse regression) was used to fit mean localization accuracy (i.e. EI) as a function of age, Figure 19. The model fit was high, R^2=0.74, suggesting that SLL and EI followed a similar developmental shape of the trajectory.

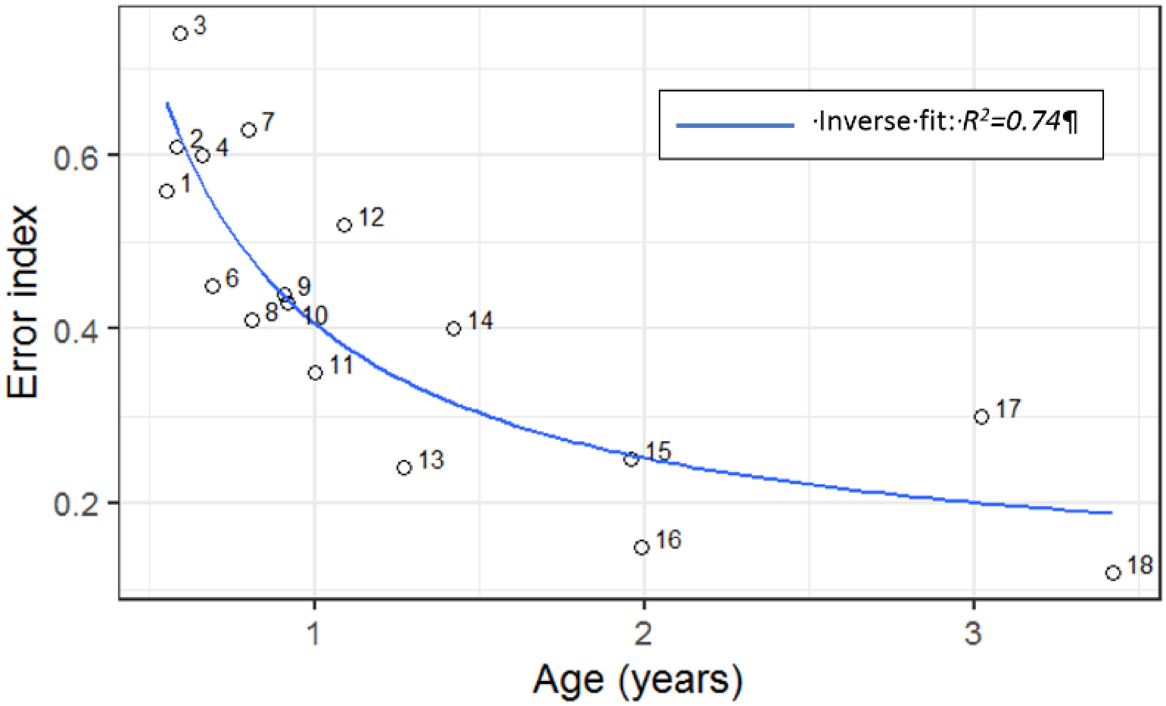

Figure 19. Sound localization accuracy (Error index) for all 18 subjects. Source: Eklöf, Asp and Berninger (2020). Copyright license CC-BY.

Given the correlation between latency and accuracy across levels of attenuation in paper III, one would assume that this would be the case with children across development. A correlation between latency and accuracy between subjects would mean that longer latency would have been related to lower accuracy and vice versa. However, there was no partial correlation between latency and accuracy and when controlling for age. This suggests that the latency and accuracy follow different trajectories and thus might have different diagnostic value.

Table 3. Results of the sound localization latency for the male (M) and female (F) patients.

Subject ID	Age (years)	SLL (ms)	Min latency (ms)	Max latency (ms)	IQR (ms)	SD (ms)	Total number of trials	Fitted Trials	EI
F1	0.55	1400	1300	1500	94	130	15	2	0.56
M2	0.58	1300	1300	1400	71	100	24	2	0.61
F3	0.59	1000	460	1500	710	460	17	6	0.74
M4	0.66	1100	620	1400	250	280	24	6	0.6
F5	0.67						8	0	0.6
M6	0.69	920	820	1000	100	140	19	2	0.45
F7	0.8	1100	440	1600	570	580	16	3	0.63
F8	0.81	920	630	1200	62	210	13	5	0.41
M9	0.91	940	690	1100	210	220	24	3	0.44
M10	0.92	940	350	1400	730	500	24	4	0.43
M11	1	840	660	1100	220	240	24	3	0.35
F12	1.09	700	410	1100	270	230	23	10	0.52
F13	1.27	710	710	710	0		9	1	0.24
F14	1.42	740	480	1100	340	240	24	7	0.4
F15	1.96	860	580	1300	390	230	24	14	0.25
F16	1.99	650	390	1400	240	230	24	23	0.15
F17	3.02	550	400	710	190	140	10	5	0.3
M18	3.42	630	480	840	130	95	24	19	0.12
Mean	**1.2**	**900**	**630**	**1200**	**270**	**250**	**19**	**6.4**	**0.43**
SD	**0.8**	**230**	**280**	**300**	**220**	**140**	**6**	**6.3**	**0.17**

Abbreviations: SLL = sound localization latency, IQR = interquartile range, SD = standard deviation.

4 ETHICAL CONSIDERATION AND METHODOLOGICAL LIMITATIONS

4.1 PAPER I

Higher levels of specificity are required in scientific papers than clinical assessments. The reasons are often few subjects, high risks of type II errors or investigator bias. Therefore, when tests of a subjective nature are performed, such as language assessments, it is necessary to cross-validate investigators to reduce measurement errors. One way of increasing specificity is by recording the test situation and letting a second investigator score the test. No cross-validation was carried out in Paper I. Due to limited resources, and the large variation known to exist in the cochlear implant population, we decided that the validity of the results would increase if we included all of the children, rather than a smaller sample, and stuck to a more rapid and less invasive routine. Furthermore, the estimations were obtained from several test occasions, which were often carried out by different investigators. In addition, we randomly assigned children who received their first surgery at different ages, or at least without systematic bias, to different investigators. This non-systematic randomization eliminated some of the investigator bias. However, multiple ratings and formal randomization would have increased the validity of the results if they had been applied.

The validation of language outcomes, by translating to a language equivalent age using norm data, could have been carried out by using normal hearing controls who were matched for confounding background parameters. The parameters that are important for language development are difficult to assess, due to the complex interaction of environmental and genetic effects. This is known as ecological development. However, individually comparing performance and age by using normal hearing controls matched on socioeconomic status, such as parental education level or income, would probably have increased the validity of the results (Shriver et al., 2017).

Furthermore, by applying the exclusion criteria described in Figure 3, the factors that could have increase variability were eliminated. Other factors could have potentially varied across the age at first surgery. These could have included the background variables of socioeconomic status and parental education, together with spoken language exposure, number of hours with active implants, oral language therapy interventions and the quality of linguistic input from families and caregivers. Controlling these parameters would have increased the validity of the results.

One possible confounder with regard to the age at surgery could have been related to their parents. The children who had early implants may have had more informed parents or parents who were pressing to have their child’s hearing issues resolved. We could have addressed this confounding factor by designing a study where deaf children who were identified at an early stage were randomized to surgery before and after nine months of age. However, few parents would agree to delay surgery for no other reason than scientific research.

A potential bias was excluding subjects with language impairment. There is a possibility that their language impairment was a consequence of deafness, as it has been shown to have a detrimental effect on language (Kos et al., 2009). However, we only excluded two out of the 103 patients on this basis, a proportion that is considered low according to a large study of a normal population (Norbury et al., 2016).

The speech perception measure that was assessed was monosyllables in a quiet environment. There was a ceiling effect in the material, meaning that children performed close to the maximum of the test. A more difficult test, with speech in a noisy environment or with competing speech sources, would have yielded a much wider range of measurements.

4.2 PAPER II

The ethical approval provided by the regional review board required that both caregivers consented to their child taking part in the study. Some subjects only had one caregiver and, in some cases, only one of the two caregivers were present at follow-up visits. In a few of these cases, we obtained the written consent of the other caregiver by mail and sometimes the consent was only obtained from the caregiver who was present. Even though the protocol was smaller than the study we sought ethical approval for, this approach did not comply with the ethical approval in some cases. It would have been better to obtain consent from both caregivers beforehand but getting addresses for separated caregivers could have been problematic. Therefore, a pragmatic decision was made to include as many subjects as possible in the material and reduce the possible confounder of selection bias.

The subjects in this study were accustomed to their processor settings, including the stimulation strategy. This was a strength of the study, but it meant that the subjects were not randomly assigned to different stimulation strategies at the initial fitting after surgery. To partly compensate for this, we could have employed a crossover design. where the subjects were tested with their current strategy, then asked to switch to another stimulation strategy for weeks or even months and then assessed again. This approach would be interesting, but we felt it would mean a too large infringement on the autonomy of the subjects.

Another limitation was the choice of stimulation frequency for the lateralization task of ITD and ILD. The choice of 250 Hz was a compromise between being high enough so that it was part of the speech spectrum, but low enough to provide temporal information for many of the clinical processors. We needed to balance the benefits and deficits. A lower frequency would have been simpler to convey to the hearing nerve, but it would have been too low to be important. For example, it would have been below the fundamental frequency of the female voice (which is around 200 Hz).

4.3 PAPERS III AND IV

Using the same stimulus for adults and children was a strength, as it meant we could make comparisons across ages. However, an adult would probably have shown more attention to a captivating movie than the children’s cartoons we used.

We did not record the visual reaction time, which is a limitation, because most of the other studies have compared these measures or used the visual reaction time as a baseline. An audiovisual version could also be added, where both auditory and visual stimuli changed to a new location simultaneously. Another alternative would have been an auditory only version, where both the visual and the auditory stimuli were turned off at least 500 ms before the move to a new location. This last protocol could have been expected to assess express saccades as well (Fischer & Weber, 1993; Shafiq et al., 1998).

We only measured gaze saccades, namely the combined effect of head and eye-ball rotations, and not the separation between the eye-ball and the head and body movements. As a result, we had no information about the nose direction at fixation before the saccade initiation. It has been shown that it is the eccentricity of the eye-ball direction relative to the target that matters for auditory response latency and that it is invariant above 15 degrees of eccentricity (Zambarbieri, 2002). The information about head and gaze movements in this test could have exposed differences in the neural networks controlling the head and eye saccades in different populations. Other studies have reported that the eye was usually activated before the neck (Goldring et al., 1996; Goossens & Opstal, 1997).

Another limitation with our setup was the fixed and discreet sample space of visible screens, which did affect the build-up of neural target representation and the saccadic response motor planning. Measurement in total darkness would have decreased the effect of the visible screens. In addition, the target loudspeaker/display pair could have been mounted on a robot arm that could be moved silently and invisibly to an arbitrary position in the horizontal plane to avoid the discreet sample space.

The quest for norm data requires normal and healthy individuals. However, the definition of normal has been the subject of a long-standing “theory of health” debate, with different approaches. One early and common approach was the biostatistical approach formulated by Boorse (1977). This approach considered that the most common state in an age and gender matched population was healthy and that the opposite, uncommon state was disease. Boorse also considered the functional state of a subject and their interaction with the environment. For example, pregnancy is not a disease despite being an uncommon state and tooth cavities are not healthy despite being common. In audiology, normal hearing controls have traditionally been found by collecting young, healthy subjects with audiometric thresholds below 20 dB HL and without any history of noise exposure (ISO 28961, 2012).

5 CONCLUSIONS

5.1 RESEARCH OBJECTIVES

- Paper 1 confirmed the first hypothesis that the age when a child received their first cochlear implantation would have an effect on their spoken language development, but not on their surgical risk. A linear regression analysis of estimated language understanding at four years, as a function of age at surgery, showed that their language understanding increased as their age at the time of surgery got lower. Furthermore, the age when they managed fully intelligible speech was one year earlier in children who received surgery before nine months of age, compared to children who had surgery at 9-11 months of age. However, the surgical risk was not associated with the age at implantation.
- Surgery performed on both ears before the age of three years provided deaf children with the ability to identify ITD and 10 of the 30 subjects were able to lateralize with just ITD cues.
- Furthermore, these 10 children belonged to a subgroup of 20 subjects who had been programmed with fine structure stimulation strategies on both ears.
- We were unable to substantitate the hypothesis that the stimulation strategy would have an effect on the ability to localize low frequency sounds. The stimulation strategy, and the associations with any ability to identify ITD, had no effect on the ability to localize low frequency sounds. However, the ILD threshold did correlate positively with the ability to localize broadband sounds.
- The results presented in Paper III show that that the localization process could be assessed by a sigmoid model. An arctangent curve was fitted to 768 trials in different conditions and the mean latency was 280 ms in the normal hearing condition.
- The simulated unilateral hearing loss conditions prolonged the latency that showed a strong correlation with a change in threshold on the attenuated side. The correlation of the localization ability and the latency, which was aggregated on a test-by-test basis across conditions and within subjects, was an almost perfect fit, with an explained variance of 94%.
- The normal development of the latency of responses towards auditory targets was further investigated in Paper IV, where an exponential decay function was fitted to the measurements. The analysis showed that the difference between infant and adult latency decreased inversively, starting from 1000 ms at six months. At two years of age it was 700 ms and at 3.5 years of age it was 500 ms. The trajectory projected that the latency would end up at 450 ms which implies that the latency will have to decrease additionally later in childhood or during adolescence to reach adult performance.

5.2 CONTRIBUTIONS TO KNOWLEDGE

Until now, the literature has lacked a thorough description of the long-term spoken language acquisition progress in a larger group of children that received cochlear implants before 12 months of age. One reason for this has been that most cochlear implant centers lack centrally coordinated follow up and data collection. The situation in Sweden is rare, because long-term regular follow-up data is available for children who receive surgery before one year of age. We were able to chart the progress made by children who received cochlear implants at different ages and this provided evidence that supported early implantation (Paper I). Based on the results from Paper I, the risk of delaying language progression by choosing to carry out the procedure at a later age, is now easier to estimate. Furthermore, the challenge of comparing children tested at different ages has been clarified by this study. We present a simple, but novel, method that allows clinicians to interpolate tests carried out on two or more occasions and estimate the child's performance level at an arbitrary age. Since this estimation was based on more than one test, the specificity of this value was higher than if a single test had been carried out (Paper I).

The next contribution to knowledge is the results from the ITD measurements in children with cochlear implants, which has only been described a couple of times in the literature (Gordon et al., 2014; Salloum et al., 2010) but never with clinical processors and stimulation strategies. We were able to test this and also found that it was necessary to have a stimulation strategy that aimed for fine structure. There has been a lack of knowledge concerning the effect of fine structure stimulation from cochlear implant devices, both from an industrial development and a clinical prescription point of view (Paper II).

The horizontal sound localization ability of children with cochlear implants have been studied extensively by a number of authors, Asp et al. (2012), Grieco-Calub & Litovsky (2010) as well as the study presented in paper II, but the corresponding response latency has not yet been considered, neither in pediatric cochlear implanted recipients or children with normal hearing. One reason is that many papers published on saccadic latency have focused on visual targets. Relatively few studies have been published that have investigated responses towards auditory targets and these include Zahn et al. (1978) and Zambarbieri (2002). Our study (Paper II), is to date, the only study to present the effect of unilateral ear-plugging on the gaze-saccadic response latency of auditory targets. One recent study analyzed the effect of unilateral cochlear implant simulation in normal hearing adults on head-saccadic responses to auditory targets (Ausili et al., 2019) and they too found a prolongation of latency. Furthermore, using the sigmoid model to assess latency was found to be a rapid and reliable approach. The application of this approach, combined with the previously developed eye-tracking method, made it possible to assess this in children from six months of age (Paper III).

The response time towards auditory targets from infancy to one year has been studied with head saccades (Muir & Hains, 2004), but less is known about latency at later ages. Our results from measurements of gaze responses in children aged six months to 3.5 years adds further insight into the maturation process of the brainstem and the higher brain areas, such as the frontal eye fields and auditory and visual primary cortices (Paper IV).

5.3 FUTURE DIRECTIONS

Providing children with cochlear implants before one year of age had a strong effect on language development at several ages, as presented in the results. However, there was no significant effect from implants before nine months of age or above the age of four years. Although we excluded children who were expected to increase the variability in the spoken language outcome, there were still many factors that contributed to the differences in the development of each individual child. Hence, a study that consider socioeconomic and other confounding factors would have been more specific when it came to assess the main effect of age at implantation. A more precise study could have predicted differences between groups of older children and teenagers by age at implantation.

In addition to early bilateral implantation, there are technical choices to be made regarding issues such as stimulation strategy. There has been very little research on the development of basic interaural abilities and localization in prelingually deaf children with cochlear implants. No knowledge is available on to what extent children using fine structure processing devices with parallel processing of the apical channels that can perceive and use ITD. Therefore, an intervention study with a group of infants randomized to two groups of stimulation strategies (FS4 and FS4-p) could be designed.

The speech perception data collected in Paper II was obtained using monosyllables in a quiet setting. Unfortunately, the performance reached a similar plateau for all implantation ages and that could have been caused by a ceiling effect. Studying speech in competing background noise would have made it possible to compare differences on a scale that did not have a ceiling. Furthermore, by introducing speech as the competing noise, the dimension of informational masking could have been assessed, which might have provided a sensitive measure of language development.

Eye-tracking was not used in the study on language development, but recent research in saccadic behavior could be used in the development of language. Lexplore (www.lexplore.se) is a Swedish company, based in Stockholm, that was formed following research at the St. Erik Eye Hospital, which is part of the Karolinska Institutet. It screens seven-year-old children for future dyslexia by analyzing their gaze behavior when they read for 45 seconds. It might be possible to assess executive function and working memory by developing a similar measurement for spoken language.

By using different auditory stimuli, as in Paper II, it is possible to assess different aspects of sound source directions. In addition to the auditory response latency, the visual response latency could be assessed for comparison purposes.

6 SAMMANFATTNING PÅ SVENSKA

Denna avhandling undersökte konsekvenserna av åldern vid vilken dövfödda barn opereras med cochleaimplantat vad avser talspråk och operationsrisker. Vidare undersöktes hur bilaterala implantat ska ställas in för att barnen ska få tillgång till temporala lokalisationsledtrådar. Slutligen utvecklades en metod för att extrahera den tid det tar för en försöksperson från att ett ljud startar till dess att blickriktningen flyttas mot uppfattad ljudkälla. Metoden använder sig av registreringar av blickriktning från en eyetracker-utrustning som framgångsrikt har mätt lokalisationsförmåga i horisontalplanet hos barn från sex månaders ålder.

Resultaten visade att operation före tolv månaders ålder hade stor betydelse för att barnet skulle hinna ikapp sina jämnåriga talspråksmässigt vid sex års ålder. Vid operation redan före nio månaders ålder var barnet ikapp ännu tidigare och till exempel kunde dessa barn uttrycka sig med ett uttal som var fullt förståeligt redan vid en genomsnittlig ålder av 4 år. Barn opererade mellan nio och tolv månader var ett år senare i detta test. Riskerna associerade med operation varierade inte med ålder vid operation.

Tester av ljud i båda öronen visade vidare att de små skillnader som uppstår när ljud kommer från en vinkel, jämfört med ljud rakt framifrån, går att upptäcka för barn med bilaterala CI. Det gällde enbart för hälften av de barn vars processorer var inställda på ett sätt som tog hänsyn till ljudets fasläge, dvs ljudvågens tidsförlopp. Inga av barnen med annan programmering klarade testet. Vid lokalisation av lågfrekvent ljud verkade dock denna förmåga inte spela någon roll.

För att djupare undersöka data från lokalisationstestet modellerades blickriktningen av en sigmoid-funktion, specifikt en arcustangent. Detta testades först hos normalhörande vuxna, utan och med olika grad av pluggning av ena örat. Det visade sig att det gick bra att använda modellen för att erhålla latensen för blickreaktionen i mer än 90% av fallen. Den genomsnittliga latensen på 280 millisekunder förlängdes med 7,4 millisekunder för varje decibel av dämpning i det pluggade örat. Dessutom visade det sig att försämrad lokalisationsförmåga och förlängd lokalisationslatens följdes i genomsnitt åt med en förklarad varians på 94% (hänsyn taget till upprepade mätningar).

Lokalisationslatensen gick att mäta även hos normalhörande spädbarn och barn från 6 månader till 3,5 år. Data från barnens tester var svårare att analysera (30% gick att modellera). Den genomsnittliga latensen per individ anpassades med en exponentiellt avtagande regression. Resultatet tyder på att skillnaden mellan barns och vuxnas lokalisationslatens minskar med 30% per år. Vid sex månaders ålder var den ungefär 1 sekund och minskade till närmare 500 millisekunder vid 3 års ålder. Den snabbaste blickreaktion som registrerades under ett test, varierade dock inte för de testade åldrarna. De var aldrig snabbare än 400 millisekunder vilket tyder på att hjärnstammen utvecklas färdigt senare under barndomen.

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