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Cerebral lateralization of language in deaf children and adults with cochlear implant (CI): a neurofunctional study with transcranial doppler ultrasound (fTCD)

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ABSTRACT

Severe to profound sensorineural hearing loss (SNHL) is a pathological condition, that affects about 1-3/1000 newborns, but as shown by several studies on humans and animals, can be considered a scientific opportunity for understanding the role of auditory stimuli in neuroplasticity. In the late decades the advent of Cochlear Implantation (CI) has also permitted further investigation on how stimuli restoration can affect neuroplasticity in previously deprived subjects.

This issue has been studied in terms of timing of restoration (age of implantation) and side of stimulation (afferented ear), and effects on auditory perception and language development in the case of humans.

Within this theoretical frame, the present study focuses on language lateralization, measured through functional Transcranial Doppler ultrasonography (fTCD), a non invasive technique, that quantifies a Lateralization Index (LI) detecting blood flow during language performance.

At this aim, 3 different groups of subjects were evaluated by fTCD:

(i) 36 children with prelingual profound bilateral SNHL with monolateral CI (and 24 control subjects with normal hearing); they were also evaluated in language achievement (PPVT, TCGB, Inpe high and low frequencies, GASS and language composite score);

(ii) 11 children with profound congenital unilateral hearing loss (UHL) (and 11 control subjects with normal hearing bilaterally); they were evaluated on verbal and non verbal development (PPVT, TROG2, IQ, PRI, WMI, PSI, VCI, VMI);

(iii) 6 adults with preverbal profound bilateral SNHL, evaluated before and after CI.

The results show that (i) left dominance is maintained, even if bilateral representation for language appears more frequent in children with monolateral CI; children with right ear implanted or left LI show better language performance.

(ii) left activation was confirmed in children with right UHL while it was not confirmed in those with left UHL. Performance on verbal test were significantly better in children with right hearing.

(iii) No significant changes LI were observed in adults, after implantation.

On the basis of the present study neuroplasticity of auditory and language circuits appears to be a complex phenomenon in which some biological constraints for left dominance for language are confirmed, but other factors, such as age of reafferentation, and side of afference can play roles, that have still to be clearly understood. Furthermore the present study brings some support to the right ear advantage hypothesis and this should be taken into account while choosing the ear to be

implanted, in the case of unilateral CI. From this point of view the right implant could be considered the first choice in monolateral or sequenced implantation. fTDC for LI evaluation can be considered in the case of late diagnosed deafness before implantation.

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1. **INTRODUCTION**

One of the central issues of developmental neuroscience is the understanding of how highly specialized functions, such as language, are biologically constrained and to which extent they depend on and can be modified by environmental inputs.

The study of brain language in congenital deaf children whose auditory afferents have been restored with cochlear implant (CI) offers a privileged window of observation to study the brain plasticity mechanisms and a unique opportunity to understand the development of the auditory system.

In the case of congenital deafness, there is some evidence from animal and human studies that early auditory deprivation leads to an atypical organization of the auditory nervous system (Gilley et al., 2008; Kral & Sharma, 2012). Profound congenital deafness may also alter the pattern of cerebral asymmetry for language, which has seen to favor the left hemisphere, early in life in typically developing infants with normal hearing (Dehaene-Lambertz et al., 2006). Alterations of neural connections have been reported together with functional impairment and immaturity of the auditory cortex, as well as cross-modal recruitment of some auditory areas in order to perform non-auditory functions, with an overall reorganization of cognitive functions, due to the absence of auditory input. The deficit in synaptic plasticity (involving cortical development and cross-modal recruitment) is interpreted as being the cause of the well-known difficulties in language skills, evidenced in congenitally hearing-impaired children, with late cochlear implantation (Kral & Sharma, 2012).

The results of earlier studies aimed at determining whether deaf children develop the same pattern of hemispheric asymmetry for language as hearing children (Kelly & Tomlinson-Keusey, 1981) revealed an inverse laterality pattern in the two groups. In fact, in a visual half-field presentation task of words or letters, deaf subjects showed a left visual field advantage (suggestive of right hemisphere dominance for linguistic stimuli), whereas hearing subjects showed a right visual field advantage (indicative of a left hemisphere dominance). In a study by Marcotte and Morere (1990) cerebral lateralization for speech in right-handed normal hearing and deaf adolescents was assessed by using a dual-task paradigm. Subjects with normal hearing at birth and deafness acquired after 3 years of age displayed left hemispheric dominance for speech production, whereas children with both congenital and early acquired deafness (onset 6-36 months) showed an atypical cerebral representation. These results support the hypothesis that exposure to adequate environmental stimulation during a critical developmental period may be necessary to activate left hemispheric dominance for speech. However, according to D'Hondt and Leybaert (2003), hemifield paradigm studies do not provide clear empirical evidence of left hemisphere advantage for written words by deaf children, because lateralization effects may vary in relation to the semantic or phonological nature of the task.

In the last twenty years, with the advent of cochlear implants (CI), deaf children have been able to benefit from the critical sensory inputs that are necessary to develop a 'listening brain'. Restoration of auditory input through monaural cochlear implantation in children who were born profoundly deaf offers a unique opportunity for investigating the role of stimulus-dependent mechanisms in the asymmetrical organization of neurofunctional circuitries sub-serving language and the variables that influence these processes, such as CI side, age at implantation and language experience before CI.

However, there is wide variation in individual outcomes following cochlear implantation, and some CI recipients never develop usable speech and oral language skills. The causes of this enormous variation in outcomes have only been partly understood so far. The variables most strongly associated with language outcomes are age at implantation and mode of communication during rehabilitation.

Language development of patients with severe to profound hearing-loss and CI bearers is characterized by extreme individual variability. It has been shown that early CI allows language development to follow dynamics that are comparable to those of normal hearing subjects, and that it generally allows for suitable cortical maturation, with the development of speech perception and of oral language acquisition. The optimal time to perform CI is within the second year of life, which represents the end of the critical period for language development, when the central auditory pathways show the greatest plasticity in response to auditory stimulation (Kral & Sharma, 2012). This period seems to coincide with events that contribute to the crossmodal reorganization of the temporal cortical areas devoted to language (Kral, 2007).

If the neural networks normally dedicated to the processing of acoustic-linguistic stimuli are reorganized so as to adopt a non-reversible functional specialization, the auditory function after implantation will be limited to the functional properties of the subset of regions that have been spared from the reorganization and are therefore prone to the processing of auditory stimuli (Lee et al., 2007).

If the spared regions are limited to the primary auditory areas, the understanding of language is likely to be compromised since the essential steps for language development will be lost. Conversely, if the regions available are large, language development has a better chance to develop (Lee et al., 2007).

As reported by several authors (Hugdahl, 2005; Kimura, 1967; Langers at al., 2005; Woldorff et al., 1999), although both auditory cortices receive sensory input from both ears in the normal hearing population, they are excited most strongly by stimulation of the contralateral ear. In the case of deaf children with unilateral auditory reafferentation, the question on the effects of right- or left-sided CI on hemispheric dominance for language has never been clearly settled.

Numerous studies report that the duration of hearing loss is believed to be the most important variable for determining the linguistic results of implanted subjects; however, some cases show that other factors are called into question, for example the environmental factors (Lee et al., 2007).

Since cortical plasticity varies dramatically from one individual to the other, the individual level of cortical reorganization can efficiently predict the linguistic results of the CI bearer (Lee et al., 2001). For the very fact that cortical reorganization plays such an important role in determining language development of cochlear implanted subjects, it is extremely interesting to be able to evaluate the hemispheric lateralization of language functions after implantation.

Direct measures of cerebral language lateralization by means of classical non-invasive methods, such as the dichotic listening paradigm and functional Magnetic Resonance Imaging (fMRI) are not feasible in deaf subjects with CI: for the former, since most patients are monaurally fitted with CI, and for the latter, because high MRI magnetic fields (P1.5 T) may interfere with the magnetic components of the implant. In the past decade neuroimaging with Near Infrared Spectroscopy (NIRS) has shown to be a potential complement to the above objective techniques, but application in deaf subjects with CI has just started (Sevy et al., 2010). Some indirect evidence on cerebral language lateralization of implanted subjects has been provided by Gilley et al. (2008), who used high density EEG recordings to estimate generators of the P1 response.

In recent years, functional transcranial Doppler ultrasound (fTCD) has been proposed as a reliable alternative method for measuring cerebral lateralization during speech in both adults and children. This technique assesses cerebral lateralization by comparing changes in mean blood flow velocity in the middle cerebral arteries (MCAs) during domain-specific tasks. fTCD has shown to be highly correlated with classic measures of hemispheric lateralization such as the Wada test (Knechtet al., 1998) and fMRI (Deppe et al., 2000; Somers et al., 2011). fTCD has good temporal resolution and provides continuous information about event-related changes in cerebral blood flow associated with functional cortical activation (Deppe et al., 2000); it is non-invasive and is particularly suitable for children (Bishop et al., 2009; Haag et al., 2010). Furthermore, Bishop et al. (2009) have created an fTCD animation description task designed to be particularly engaging for children. This paradigm has shown good split-half reliability in children and in adults, and a highly significant correlation with other fTCD tasks, such as word generation and picture description tasks.

In developmental manipulations of the symmetry of auditory input, as occurs with unilateral deafness (Langers et al., 2005; Burton et al., 2012; Kral et al., 2013a, 2013b) or asymmetric moderate hearing loss (King et al., 2001; Popescu & Polley, 2010), the hemispheres can be differentiated according to the anatomical relationship to the (better) hearing ear. Plastic reorganizations are often reported in the hemisphere contralateral to the hearing ear. However, the ipsilateral cortex also receives asymmetric input and is likely to participate in behavioral consequences of unilateral hearing.

The primary auditory cortex contains mainly binaural neurons - neurons responsive to stimulation of only one ear are virtually absent (Zhang et al., 2004).

Stimulation of one ear most frequently leads to excitation in the neurons of the contralateral cortex but may cause excitation or inhibition in the ipsilateral cortex (Imig & Adrián, 1977). Contralateral "dominance" is the consequence of the cortical representation of the contralateral acoustic hemifield.

Recently, the effects of unilateral deafness (UHL, unilateral hearing loss) have attracted clinical interest owing to the predominantly monaural therapy of prelingual deafness with one cochlear implant (Graham et al., 2009; Gordon et al., 2013) and the relatively high incidence of unilateral deafness (Eiserman et al., 2008; Watkin & Baldwin, 2012). Unilateral deafness is now considered an indication for cochlear implantation of the deaf ear, but so far, mainly in cases of postlingual deafness due to tinnitus in the deaf ear (Vermeire et al., 2008; Buechner et al., 2010; Firszt et al., 2012). The effects of congenital, or early onset unilateral hearing loss are less well explored.

Children using one CI have similar hearing problems as children with UHL, and both groups have difficulties in listening to speech in noise (Beijen et al, 2008; Gordon & Papsin, 2009) and localized sound (Litovsky et al, 2006).

In an attempt to study plasticity in terms of laterality for language in the case of unilateral acoustic afference we have extended the experimental sample by including subjects with UHL since birth. In patients with bilateral hearing loss, we have evaluated whether hemispheric dominance for language varies in relation to CI side, in terms of fTCD activation contra- or ipsilateral to the ear implanted, or in subjects with UHL in relation to the side of profound unilateral hearing loss.

We also checked whether language performances were correlated with the hearing afferent side, with the time of acoustic reafferentation with CI and with hemispheric language lateralization indices that is measured by fTCD.

From a theoretical point of view, the study of cerebral language organization in deaf children after acoustic reafferentation and in children with UHL could provide insights into the plasticity of the auditory system and the neural substrates underlying language processing.
From a clinical point of view, fTCD may prove to be a valuable technique in assessing cerebral language processing in deaf children with CI, and could help clinical teams in CI management by providing clearer indications on the modes of intervention also in case of monolateral deafness.
Evaluation of hemispheric dominance for language also in adults with severe to profound prelingual hearing loss, before and after CI, may offer the opportunity to test whether auditory inputs produce changes in lateralization, proving that, although to a lesser extent, brain plasticity is still active.

2. AUDITORY SYSTEM AND HEARING LOSS

2.1. Anatomy and function of the inner ear

The inner ear is a sensory organ responsible for the senses of hearing (cochlea), balance (vestibule) and detection of acceleration in vertebrates (semicircular canals).

The cochlea is a bony tube, coiled around a central axis, the modiolus, thereby forming a spiral of two and a half turns in humans. The tube has a total length of 30 mm, its internal diameter tapers from 2 mm at the window level, to about 1 mm at the apical end. The overall size of the coiled cochlea also decreases from the basal turn to the apical one. The cochlea is divided by the anterior membranous labyrinth into three compartments or scalae: the scala vestibuli, scala tympani and scala media (Figure 1).

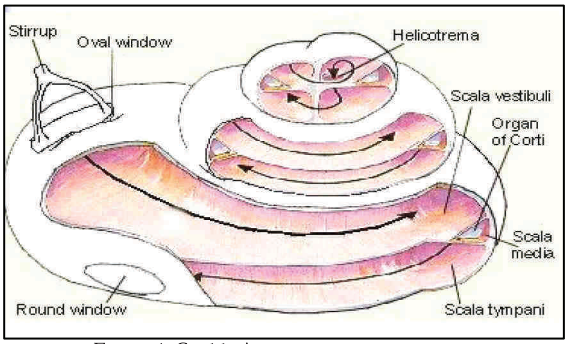

Figure 1: Cochlea's anatomy.

The scala media is bounded by the osseus spiral lamina projecting from the modiolus and prolonged externally by the basilar membrane, by the Reissner's membrane and by the lateral wall. Its cross-section is thus approximately triangular. The basilar membrane, extending from the spiral lamina to the spiral ligament, supports the organ of Corti (Figure 2) containing the sensory cells. The lateral wall is lined by the spiral ligament and the heavily vascularized stria vascularis.

The scala vestibuli is above the scala media bounded by the Reissner's membrane. The oval window, closed by the stapes footplate and annular ligament, opens into the vestibule, connected to the scala vestibuli by the fenestra vestibuli. Therefore, stapes movements directly result in pressure variations in scala vestibuli.

The scala tympani is below the scala media, bounded by the basilar membrane. The round window opens into the scala tympani at the beginning of the basal turn. It is separated from the gaseous middle ear cavity by the round window membrane. On the apical side of the cochlea, since the scala media is shorter than the cochlear tube, a small opening called helicotrema connects the scala vestibuli and tympani (Figure 2).

The scala media is filled with a few microlitres of endolymph, formed by the stria vascularis, which has a high K+ concentration of about 150 mM and a low Na + concentration (1 mM). Owing to the function of the stria vascularis, a large positive endocochlear potential can be measured in the cochlea: 80-90 mV.The scalae vestibuli and tympani contain perilymph , an extracellular-like fluid with a low K+ concentration (4 mM) and a high Na+ concentration (140 mM). As these two scalae are connected through the helicotrema, there is little difference between their ionic contents. Resting potential in perilymph is 0 mV.

The organ of Corti, first described thoroughly by Alfonso Corti in 1851, rests on the basilar membrane and osseus spiral lamina (Figure 2). The basilar membrane is made up of fibres embedded in extracellular amorphous substance. Two zones are separated, the pars tecta or arcuate zone extending from the spiral lamina, and the pars pectinata or pectinate zone reaching the spiral ligament. The structure of the basilar membrane is responsible for the passive resonant properties of the cochlea. The mechanical properties of the basilar membrane, and particularly its stiffness, vary gradually from base to apex and, as a result, its resonance frequency decreases while the distance from the round window increases, with a rate of about one octave every 3 mm. This progressive decrease is mainly due to two geometrical factors: in a basoapical direction, the width of the membrane from the osseus spiral lamina to the spiral ligament increases from about 0.12 mm at the base to about 0.5 mm at the apex, while its thickness decreases by a similar amount.

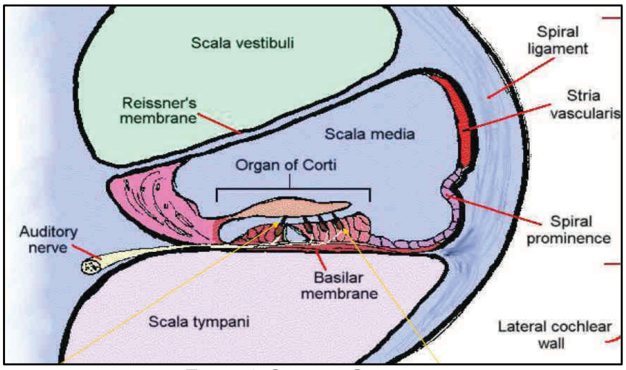

Figure 2: Organ of Corti.

The major components of the organ of Corti are the inner and outer hair cells (Figure 3), resting on the basilar membrane, surrounded by supporting cells (Deiter's cell, pillar cells, Hensen cells and Claudius cells). The tops of sensory cells bathe in endolymph and are covered by a flap of gelatinous substance called the tectorial membrane(Figure 3). The apical parts of the inner and outer hair cells and the supporting cells form the reticular lamina. Its cell junctions are thight, and thus, the reticular lamina acts as an ionic barrier between the endolymph and the perilymph. Conversely, perilymph can diffuse through the basilar membrane. Thus a perilymph-like fluid bathes the cell bodies of sensory and support cells.

Aligned with the length of the cochlea from base to apex, one row of inner hair cells and about three parallel rows of outer hair cells can be found. The overall number of inner hair cells is around 3500 in humans, whereas about 12000 outer hair cells are found. Both types of cells have apical stereocilia bundles. Rather than being true cilia made of tubulin, the stereocilia are microvilli, made of actine filaments inserted into the cuticular plate. They vary in height, particularly those of outer hair cells, as a function of distance to the oval window. Tip and lateral links connect neighbouring stereocilia. They are aligned in about four V- or W- shaped rows, with the tallest stereocilia being on the outer, lateral wall side of the cells. In mammals, the tallest stereocilia of the outer hair cells are strongly embedded in the tectorial membrane, whereas the stereocilia of inner hair cells do not seem to touch the tectorial membrane. Instead, their tips are very close to to Hensen's stria, forming a groove along the lower surface of the tectorial membrane.

Sound stimuli have their origin in the surrounding environment and are transmitted to the inner ear through the external and middle ear. Specialized structures convert sound waves from the external air to the liquids of the inner ear permitting a mechanical vibration of the endolymphatic fluid, which results in the stimulation of the auditory hair-cells and the generation of electrical activity. These messages are transmitted as action potentials by the auditory nerve fibers towards more central parts of the brain (Figure 3).

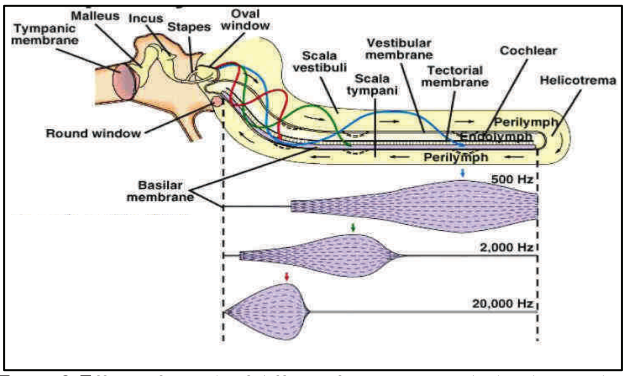

Figure 3: Effects of sounds of different frequencies on the basilar membrane.

Owing to the piston-like action of the stapes footplate in the oval window, a differential pressure occurs between the scala vestibuli and tympani. It is thought that Reissner's membrane fully transmits pressure waves from the scala tympani to the scala media and thus the differential pressure is actually applied on the two sides of the basilar membrane and induces vibrations at the level of the organ of Corti. Stereocilia bundles are deflected by two different mechanisms: shearing for the outer hair cells due to the movement of the tectorial membrane relative to the reticular lamina, and the movements of subtectorial endolymph acting on inner hair cells stereocilia through viscous forces. Deflection of stereocilia by sound waves alternately opens and closes ion channels, presumably at or near the tip links. These tip links are therefore believed to be of great functional importance (Pickles et al., 1984).

As a result of the strong electrochemical gradient existing between endolymph (+80 mV) and intracellular space (-40 to -70 mV), K+ ions flows into the sensory cells and induce a decrease in the membrane potential. This depolarization determine a release of glutamate by the inner hair cells activating the afferent nerve fibers. Outer hair cells exhibit electromotility contributing to shaping the mechanical excitation of inner hair cells (Figure 4).

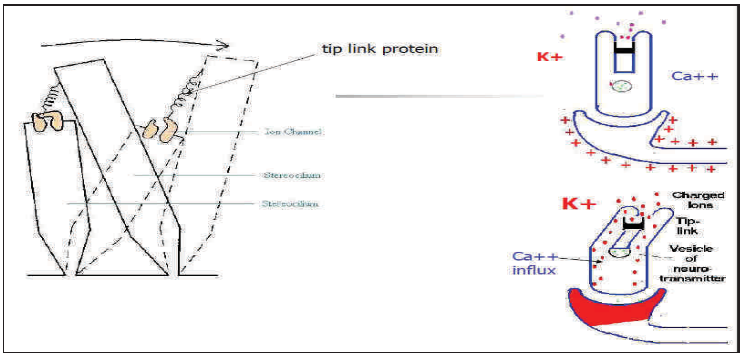

Figure 4: Deflection of stereocilia by sound waves alternately opens and closes ion channels, presumably at or near the tip links.

Hair-cells are innervated by sensory neurons that project towards the auditory nuclei in the brainstem. The spiral ganglion contains about 25000 cell bodies of afferent auditory nerve fibers. Their dendrites come from the base of the hair cells, through small holes distribuited along the osseus spiral lamina (Figure 5). About 95% come from inner hair cells and are called type I neurones. These neurons have a large diameter and are covered with a myelin sheath, enabling fast conduction of action potentials towards the first relay, in the cochlear nucleus. Inner hair cells have a diverging innervation, about 10 type I fibers, or more, connect to one inner hair cell. The remaining 5% of nerve fibers innervate outer hair cells. Outer hair cells are divergently innervated by type II neurons. Their role are completely unknown to date.

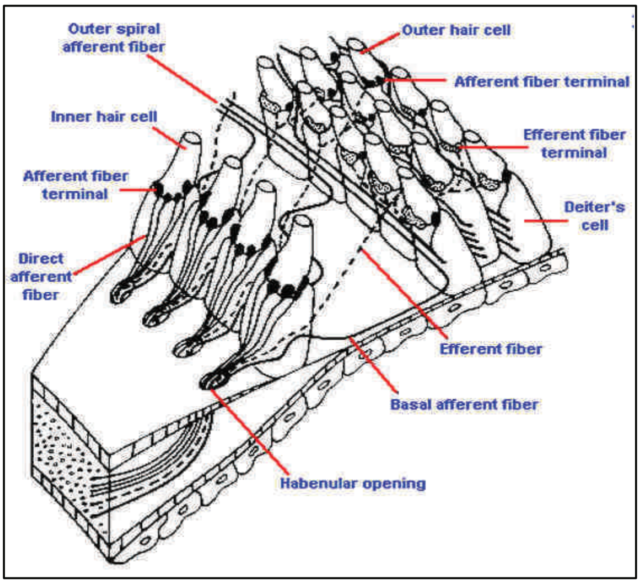

Figure 5: Hair-cells are innervated by sensory neurons that project towards the auditory nuclei in the brainstem

The auditory-nerve contains about 2000 efferent fibers, originating from the superior olivary complexes on both sides of the brainstem. Two neural bundles reach the cochlear area, one from the medial superior olive synapses with the base of outer hair cells, whereas another comes from the lateral olivary complex and projects on the afferent dendrites coming from inner hair cells. The medial olivocochlear neurones have large, almost cholinergic, synapses with the outer hair cells, and presumably modulate their motility. The lateral olivocochlear neurons involve more complex neurotransmission. They probably regulate the function of type I afferent neurons and may also play a role when these neurons are damaged (Luxon et al., 2003).

Sound-wave frequency discrimination is based on the position of the hair-cells along the longitudinal cochlear axis, which is correlated with the position of the sensory neurons in the cochlear ganglion. This tonotopical order is conserved in the central auditory nuclei, where sensory neurons project, reproducing the hair-cell order in the cochlea (Figure 6). Thus, in addition to cell diversification, spatial patterning is an essential requirement for the correct function of the inner ear.

In most cases, when a patient has a severe-profound hearing loss he will have lost most of the hair cells in the inner ear. These people benefit from the multiple-channel CI.

The central auditory pathway is composed of a number of nuclei and complex pathways that ascend within the brainstem (Fig. 6). The pathways are even for experts, terribly complex and the details of the various connections are, for our purposes, not important. The pathway into the brain begins with auditory nerve fibers that project from the cochlea into the brain where they first make synaptic connections with other neurons in the cochlear nucleus (Fig. 6). The cochlear nucleus is the first synaptic station of the auditory system in the brain. The neurons from the cochlear nuclei on both sides of the brain send their axons deep into the brain stem and make synaptic connections in a region of the medulla called the superior olivary complex. Since the superior olivary neurons receive information from both cochlear nuclei, they can be excited (or inhibited) by sounds delivered to either ear. Neurons receiving information from both ears are called binaural neurons. The comparison of information from the two ears is important for determining the location of a sound in space, as we will discuss in the following chapters. Thus, the first place that information from the two ears converges upon common neurons in the auditory pathway is in the superior olivary complex in the medulla. This is considerably different from the visual system, where information from the two eyes is first combined in the visual cortex. The axons from the superior olive are then sent to the inferior colliculus in the auditory midbrain. The outputs of the inferior colliculus are sent to the medial geniculate body, the auditory thalamus and counterpart of the lateral geniculate body in the visual system. The projections of the medial geniculate are then sent to the auditory cortex in the temporal lobe.
Although the auditory cortex has a number of subdivisions, a broad distinction can be made between a primary area and peripheral, or belt, areas. The primary auditory cortex (A1) has a topographical map of the cochlea, just as the primary visual cortex (V1) and the primary somatic sensory cortex (S1) have topographical maps of their respective sensory epithelia. Unlike the visual and somatic sensory systems, however, the cochlea has already decomposed the acoustical stimulus so that it is arrayed tonotopically along the length of the basilar membrane. Thus, A1 is said to comprise a tonotopic map, as do most of the ascending auditory structures between the cochlea and the cortex. Orthogonal to the frequency axis of the tonotopic map is a striped arrangement of binaural properties. The neurons in one stripe are excited by both ears (and are

therefore called EE cells), while the neurons in the next stripe are excited by one ear and inhibited by the other ear (EI cells). The EE and EI stripes alternate, an arrangement that is reminiscent of the ocular dominance columns in V1. The sorts of sensory processing that occur in the other divisions of the auditory cortex are not well understood, but they are likely to be important to higher-order processing of natural sounds, including those used for communication. It appears that some areas are specialized for processing combinations of frequencies, while others are specialized for processing modulations of amplitude or frequency.

Sounds that are especially important for intraspecific communication often have a highly ordered temporal structure. In humans, the best example of such time-varying signals is speech, where different phonetic sequences are perceived as distinct syllables and words. Behavioral studies in cats and monkeys show that the auditory cortex is especially important for processing temporal sequences of sound. If the auditory cortex is ablated in these animals, they lose the ability to discriminate between two complex sounds that have the same frequency components but which differ in temporal sequence. Thus, without the auditory cortex, monkeys cannot discriminate one conspecific communication sound from another. Studies of human patients with bilateral damage to the auditory cortex also reveal severe problems in processing the temporal order of sounds. It seems likely, therefore, that specific regions of the human auditory cortex are specialized for processing elementary speech sounds, as well as other temporally complex acoustical signals, such as music. Indeed, Wernicke's area, which is critical to the comprehension of human language, lies within the secondary auditory area.

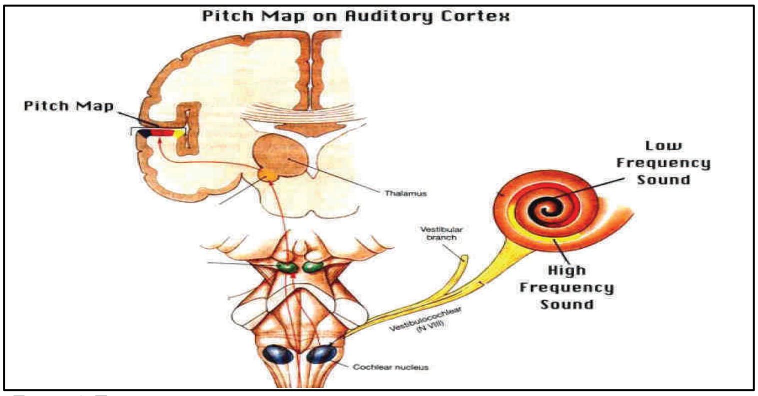

Figure 6: Tonotopical order is preserved from cochlea to the central auditory nuclei.

2.2 Bilateral sensorineural hearing loss

- Epidemiology of bilateral sensorineural hearing loss

Permanent hearing impairment (PHI) is the most common sensory defect in childhood. The incidence of congenital severe to profound hearing loss is about 1-3/1.000 newborns in industrialized countries. Its prevalence can double by age of school entry and can increase by 3 to 10 times in at-risk pediatric populations or in poor countries (Kral, 2013; Smith et al., 2005). The prevalence for severe to profound deafness is about 59 cases per 100,000 children.(Davis et al., 1997) About one in 1,000 children is severely or profoundly deaf at three years old. This rises to two in 1,000 children aged 9 -16 (Fortnum et al., 2001).

Of a total of 1,000 births a child is suffering from profound deafness and of 300 born one has a hearing loss of varying degrees (Fortnum et al., 2002).

Hearing loss is a common disabilities generally associated with increasing age, with significant social and psychological implications. Its frequency varies from 0,2% under 5 years of age to over 40% in persons older than 75 years. In Italy it has been recently estimated that there are about 8 millions of people with hearing loss of varying degree.

Approximately 12% to 17% of American adults (roughly 40 million people) report some degree of hearing loss (Statistics by the National Institute on Deafness and Other Communication Disorders, 2010, http://www.nidcd.nih.gov/health/statistics/Pages/quick.aspx) and this number can be expected to increase as a result of increased life expectancy.

In the UK around 3% of those over 50 and 8% of those over 70 have severe to profound hearing loss. people with severe to profound hearing loss make up around 8% of the adult deaf population (Royal National Institute for the Deaf. Information and resources. 2006 URL:http://www.mid.org.uk/information_resources/).

This number is likely to rise with the increasingly elderly population. In those over 60 years old the prevalence of hearing impairment is higher in men than women, 55% and 45% for all degrees of deafness (Abutan et al., 1993).

Hearing loss is often associated with other health problems; Fortnum and colleagues found 27% of children who were deaf had additional disabilities. In total, 7581 disabilities were reported in 4709 children (Fortnum et al., 2002). However, this may be an underestimate as ‘no disability’ and ‘missing data’ responses were not distinguished.

Additionally 45% of severely or profoundly deaf people under 60 years old have other disabilities - usually physical, this rises to 77% of those over 60 years (Royal National Institute for the Deaf. Information and resources. 2006 URL:http://www.mid.org.uk/information_resources/).

- **Etiology of hearing loss**

The etiology of hearing loss can be classified according to its nature as sensorineural hearing loss (SNHL), conductive hearing loss (CHL) or mixed hearing loss (MHL). Congenital hearing loss could be genetic or non genetic (acquired), syndromic or non-syndromic. Hearing loss can be classified according to the severity into mild (26-40 dB HL), moderate (41-70 dB HL), severe (71-90 dB HL) and profound (more than 90 dB HL).

The prevalence of hearing disorders combined with the lack of recovery makes the treatment of SNHL a major challenge in the area of otology and audiology. In most cases of SNHL, the primary pathology is the loss of mechanosensory hair cells located within the organ of Corti. The survival and/or death of a hair cell can be influenced by exposure to a variety of factors, including loud sounds, environmental toxins and ototoxic drugs. Aging, genetic background, and mutations in "deafness" genes also contribute to hair cell death. In mammals hair cells are only generated during a relatively brief period in embryogenesis. In the mature organ of Corti, once a hair cell dies, it is not replaced. Instead, the loss of a hair cell leads to rapid changes in the morphology of surrounding cells to seal the opening in the reticular lamina that results from the loss of a hair cell (Lenoir et al., 1999; Raphael, 2002).

Genetic factors are believed to be responsable for about half of the cases of congenitally deafened children (Alzahrani et al., 2015). The mode of inheritance is divided approximately as follows: autosomal recessive 75%, autosomal dominant 10 to 20%, X-linked 2 to 3%, mitochondrial inheritance represents less than 1%. Two-thirds of SNHL are non-syndromic where the only finding is SNHL with or without vestibular dysfunction, the remaining syndromic one-third presents with other physical anomalies. Mutated genes involved in the syndromic SNHL are essential for cochlear normal physiology as well as other body tissues, while gene mutations in the non-syndromic SNHL affect only the auditory system. Loci on the mutated genes are labelled as DFN (DeaFNess) followed by (A) for dominant inheritance, (B) for recessive inheritance and nothing for X-linked inheritance. A number indicating the sequential order of locus identification and mapping follows each prefix.

The majority of non-syndromic SNHL has an autosomal recessive inheritance pattern (75%) (Rehm, 2005). Generally children born with severe to profound SNHL affecting all frequencies. The genes involved are: connexins 26 (Cx 26, 79%) e 30 (Cx 30, 20%) (the connexions are a member of gap junction proteins involved in the potassium homeostasis in the cochlea), pendrin, that is an ion transporter found in cochlea and thyroid gland, otoferlin protein is encoded by the

OTOF gene (DFNB9), mutation of this gene will lead to auditory neuropathy/auditory disynchrony.

The autosomal dominant inheritance pattern tends to be less severe than the recessive form, affecting mainly the high frequencies. The genes involved are: cochlin that is the most abundant protein in the cochlea, it is encoded by COCH gene (DFNA9), affected individual have late onset progressive SNHL associated with vestibular impairment, X-linked less frequent, mitochondrial non syndromic less than 1%; walframin is located in the endoplasmic reticulum of the inner ear, it is characterized by low frequency progressive SNHL.

The X-linked inheritance pattern is less frequent than the previous ones, the POU3F4 gene is the most popular X-linked non-syndromic SNHL gene.

Mitochondrial inheritance is the least common of the non-syndromic genetic SNHL (less than 1%).

The genetic syndromic SNHL are autosomal recessive: Usher, Pendred, Jervell and Lange-Nielsen; autosomal dominant: Branchial oto-renal, Stickler, Waanderburg; X-linked Alport; Mitochondrial MELAS; MERF, Kearns-Sayre, Maternally inherited diabetes.

The acquired prenatal causes of SNHL are TORCH infection (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus and congenital syphilis) and teratogenic substances (thalidomide, aminoglycosides, chloroquine antibiotherapy during pregnancy, fetal alcoholic syndrome is also associated in about 27% with SNHL).

The Cytomegalovirus (CMV) infection is the most common cause of non genetic SNHL. The over all incidence in newborn is estimated to be about 0,64%, the route of transmission is either transplacental, perinatal by aspiration of cervicovaginal secretions or by breast-feeding. Only 10% approximately are symptomatic at birth (low birth weight, microcephaly, seizure disorders, jaundice and cerebral palsy) while the remain 90% do not show any signs of congenital infections although 10 to 20% of them might develop late onset neurological deficits. SNHL varies from mild to profound, uni o bilateral and prelingual or progressive postlingual.

The risk factors of acquired perinatal SNHL include: neonatal jaundice, anoxia, prolonged neonatal intensive care unit (NICU), prematurity and low birth weight.

The acquired postnatal causes of SNHL are: bacterial meningitis (35%) and ototoxicity (aminoglycosides, cisplatin).

SNHL in adult population is commonly caused by an age-related hearing loss: presbyacusis (Abutan et al., 1993). Presbyacusis is a complex disorder, influenced by genetic, environmental/lifestyle and stochastic factors. Approximately, 13 % of those over age 65 show advanced signs of presbyacusis. By the middle of 21st century, the number of people with hearing impairment will have increased by 80%, partly due to an aging population and partly to the increase of social, military, and industrial noise (Lee et al., 2005).

According to Rosenhall et al. (1993), presbyacusis is a biologic phenomenon of which no one can escape, starting at 20-30 years of age, and becoming socially bothersome when the person reaches 40-50 years. Early diagnosis and intervention in presbyacusis are paramount in order to provide the elderly with a good life quality.

Even though every individual shows a steady decline in hearing ability with ageing, there is a large variation in age of onset, severity of hearing loss and progression of disease, which results in a wide spectrum of pure-tone threshold patterns and word discrimination scores. Presbyacusis has always been considered to be an incurable and an unpreventable disorder, thought to be part of the natural process of ageing, but nowadays, it is recognized as a complex disorder, with both environmental and genetic factors contributing to the etiology of the disease. This is a progressive hearing loss due to the failure of hair-cell receptors in the inner ear, in which the highest frequencies are affected first. Hearing loss may also be due to noise exposure, ototoxic drugs, metabolic disorders, infections, or genetic causes (Weinstein, 1989).

The second leading causes of adult sensorineural hearing loss (SNHL) in The United States is noise-induced hearing loss. The usual presentation of noise-induced hearing loss is high frequency sloping SNHL with high-pitched tinnitus and loss of speech discrimination. For broad-spectrum industrial noise, hearing loss is greatest at 3-6 KHz. The mechanism of noise-induced hearing loss appears to be a softening, fusion and eventual loss of stereocilia in the outer hair cells of frequency specific regions of the cochlea. Acoustic trauma in the form of intense short-duration sound may cause a permanent hearing loss by tearing cochlea membranes, thereby allowing endolymph and perilymph to mix. Infectious causes of hearing loss in adults include viruses, syphilis, chronic and acute otitis media, Lyme disease, and bacterial meningitis. Viral infections are common causes of SNHL in children. In adults, herpes zoster oticus is a well known cause SNHL. Other viruses, such as human spumaretrovirus and adenovirus have been implicated in selected cases of sudden SNHL. Chronic otitis media may lead to progressive SNHL, either by tympanogenic supporative labyrinthitis, or by labyrinthine fistula. Acute otitis media may also lead to SNHL, but the etiology is unclear. Bacterial meningitis causes hearing loss in about 20% of cases, most commonly bilateral, permanent, severe to profound SNHL. Haemophilus influentia, Neisseria meningitis and Streptococcus pneumoniae are the most common in children. The hearing loss associated with bacterial meningitis occurs early in the course of the disease, and appears to be due to the penetration of bacteria and toxins along the cochlear aqueduct or internal auditory canal leading to a suppurative labyrinthitis, perineuritis, or neuritis of the eighth nerve. Thrombophlebitis or emboli of the small labyrinthine vessels and hypoxia of the neural pathways may also contribute to the hearing loss. Antibiotics may contribute to hearing loss indirectly by causing a rapid accumulation of bacterial degradation products such as endotoxins and cell wall antigens. The evoked host inflammatory response is thought to worsen destruction of normal tissue. Support for this theory comes from corticosteroid use during bacterial meningitis, which dampens the inflammatory response, and has been shown to improve post-meningitis hearing.

Ototoxic medications include antibiotics, loop diuretics, chemotherapeutic agents, and antiinflammatory medications. The cochleotoxic activity of aminoglycosides is in part due to their accumulation and prolonged half-life in perilymph, especially in patients with renal compromise. Energy-dependent incorporation of the antibiotics into hair cells occurs, and results in damage in the outer hair cells, beginning in the basilar turn. In the vestibular system, Type I hair cells are more susceptible to aminoglycosides. Gentamicin, tobramycin, and streptomycin are primarily vestibulotoxic, while kanamycin and amikacin are primarily cochleotoxic. Ototoxicity is increased with treatment greater than 10 days, preexisting hearing loss, concomitant exposure to noise, or use of other ototoxic agents. Loop diuretics such as furosimide and ethacrynic acid, as well as erythromycin and vancomycin may cause permanent ototoxicity, especially in combination with other ototoxic agents. Salicylates in high levels may cause reversible hearing loss and tinnitus. The mechanism is likely a salicylate-mediated increase in the membrane conductance of the outer hair cells. Cisplatin causes a permanent, dose-related, bilateral high frequency SNHL. As with aminoglycoside usage, high frequency audiological testing (8-14KHz) and by careful monitoring of peak of serum levels may identify early ototoxicity when using cisplatin.

SNHL caused by autoimmune disease may be associated with vertigo and facial palsy. The following autoimmune disorders may cause hearing loss: Cogan's disease, systemic lupus erythematosus, Wegener's granulomatosis, polyarteritis nodosa, relapsing polychondritis, temporal arteritis and Takayasu's disease. Histopathologic findings are quite variable. Some cases of hearing loss from autoimmune disease improve with steroids.

Hematologic disorders such as sickle cell anemia and blood viscosity disorders may lead to SNHL. Sickle cell disease likely causes thrombosis and infarction of the end vessels of the cochlea of some affected patients. Some 20% of sickle cell patients have SNHL. Similarly, blood viscosity disorders and megaloblastic anemias may induce cochlea end vessel disease.

Both otosclerosis and Paget's disease have been associated with SNHL. However, the etiology of the hearing loss is unclear. Histopathologic specimens have failed to show consistent injury to the cochlea or neural pathways.
Endocrine disorders such as diabetes mellitus, hypothyroidism and hypoparathyroidism, may be associated with hearing loss in adults. However, the etiologies of hearing loss associated with endocrine disorders are unclear, and the causal relationships have yet to be established.

- **Consequences - Language Development in Children with Hearing Loss**

Deafness implies a high risk of language learning impairment and language-based learning disabilities, since the functional development of the auditory cortex critically depends on auditory experience (Kral et al., 2005).
Sensory deprivation during periods of maximal receptiveness (known as sensitive periods) impairs the auditory system function and compromises cortical and cognitive development, thus affecting the mutual interaction of the cortical areas (Sharma et al., 2007)
As a result of decoupling the auditory system from other systems in the brain, there is a compromise of key cognitive functions, such as working memory, attention and sequence learning (Kronenberger et al., 2014).
Pre-verbal hypoacusia, which appear before the first year of life, are important for the consequences they may have on the neuropsychic development of the child. The lack of perception of the verbal stimuli, which are the receptors triggering language development, may cause not only serious delays or permanent alterations in the process of language acquisition, but also interfere with the processes of personal development and of separation-identification. The effects of hearing loss on the child’s social, cognitive and linguistic development depend on the severity of hearing loss. The severe-profound hypoacusic child is deprived of a source of solicitations and essential information for the development of its capacities of emotional regulation in extra-uterine life, the lack of which involves the risk of cascade effects on the entire neuropsychic development. Exchanges between adult and child from the first weeks of life actually include many characteristics of the suprasegmental component of adult conversation (intonation, rhythm, melody). Reduced perceptive-auditory acuity implies scarce attention to the oral model, as well as an unstable representation of the sounds, with difficulty in the decoding/encoding processes, and consequently in the delay of the stages of comprehension and language production.

In case of severe hypoacusia, defined by a hearing threshold of 71-90 dB, or profound hypoacusis, with greater hearing threshold of 90 dB, the acquisition of oral language is possible only if it is supported by adequate prothesization associated with early intensive – possibly multimedia – treatment, or by a cochlear implant system, which is all the more effective the earlier is the age in which the intervention takes place (Fortnum et al., 2002). From a psychological point of view, in the child with severe hypoacusia compared to the normal-hearing child, there is greater risk of early disorders of the relation and of the emotional regulation, on account of the impossibility to use the vocal signals of the mother, which absolve the essential function of regulating the “distant” interactions.

Children with severe to profound hearing loss must of necessity develop a high degree of autonomy; they are often children who exhibit a hyper-investment of the gestural channel and aspects of social isolation. Already during the first and second year of life differences in brain organization are established between normal- and impaired-hearing children: indeed the lack of auditory experiences can prevent the creation of a neural circuitry that is necessary to learn language through the hearing function in the same time and manner of hearing children. Language development in hearing-impaired children presents peculiar features: children with severe-to-profound hearing loss produce significantly fewer words than their normally hearing peers, so that a 6-year-old hearing-impaired child has a vocabulary similar to that of a 3-year-old hearing child, independent of the degree of hearing loss (Mayne et al., 1999). Furthermore, hearing-impaired children do not have "the" explosion of language vocabulary that characterizes the development of hearing children (Rinaldi & Caselli, 2009). At the grammar level, children with severe/profound hearing loss can have a proper grammatical structure in the very early stages of development, but later the distance from normal hearing children becomes more evident (Dahl et al., 2003). The factors affecting language development in hearing-impaired children are the age in which deafness is diagnosed (the children diagnosed before 6 months of age show greater language skills than those diagnosed later, regardless of the degree of deafness (Moeller, 2000), and the beginning of language rehabilitation and general cognitive abilities of each child (Mayne et al., 1999).

Other factors involved in determining the degree of language development are family environment, type of language to which children are exposed, and educational context (Pizzuto et al., 2001). A more advanced linguistic level is reached by children whose parents participate actively in their education, promote their autonomy, and are well adapted to their children's problems

In a study by Caselli and Rinaldi (2008), the authors compared hearing-impaired children with normal-hearing children in relation to chronological age and age of "auditory experience". The outcomes of the study show that children with hearing loss have a significant delay at the level both of vocabulary and of the grammar structures used, they use a lower number of expressions and fewer functors, and present weaknesses especially in free morphology compared to their peers of the same chronological age. Acquisition of the grammar structure is significantly more problematic than the acquisition of vocabulary. However, a comparison between the two groups of children with respect to the age of auditory experience does not show statistically significant differences at the level of vocabulary and basic grammar acquisition. Even the study of the gestural level and of the modes of nonverbal communication revealed no significant differences between the two groups. It follows that the age of "auditory experience" as formal exposure to language is fundamental in the evaluation of the deaf child.

2.3 Unilateral Hearing Loss (UHL)

Bone conduction hearing thresholds >30 dB in any three consecutive frequencies in the worse ear. The better ear did not have any three consecutive frequencies with hearing thresholds > 20 dB (Ghogomu et al., 2014).

The three consecutive pure tone thresholds which when averaged gave the largest value were used to define severity of hearing loss. Hearing loss was classified as mild (30–45 dB HL), moderate (46–70 dB HL), severe (71–90 dB HL), or profound (> 90 dB HL). The hearing loss was classified as high frequency if the lowest of the abnormal frequencies was > 2000 Hz, and as low frequency if the highest of the abnormal frequencies was ≤ 2000 Hz.

Severe-to-profound UHL, defined as pure tone average (PTA) of at least 70 dB hearing level (HL) in the affected ear at 500, 1000, 2000, and 4000 Hz; and normal hearing (NH) in the better hearing ear, defined as a PTA (500, 1000, 2000 Hz) of less than 20 dB HL, with a threshold at 4000 Hz less than 30 dB.

- **Epidemiology of UHL**

Prior to the implementation of Universal Newborn Hearing Screening (UNHS), Unilateral Sensorineural Hearing Loss (USNHL) often went undetected until school-age. Prior to screening, only 3% of patients were identified by age 6 months. Since onset of UNHS, this percentage increased to 42% (Ghogomu et al., 2014).

The prevalence of UHL is estimated at 1 per 1000 children at birth (Johnson, 2005), increasing with age due to delayed-onset congenital hearing loss and acquired hearing loss. While UNHS leads to early detection of many cases of USNHL, there was a significant (60%) proportion of patients who do not have detectable USNHL at birth.

Given the high sensitivity of hearing screening, and the fact that the results of 97% of the post-UNHS newborn hearing screens were known, it suggests that patients who passed their hearing

screens and were later found to have hearing loss may have simply developed the hearing loss later. The exact time of onset of the majority (91%) of these patients is unknown due to the absence of obvious triggering events. In this group of patients, at least 39% were missed by caregivers and primary care physicians and were not detected until school age screening was performed. This finding underscores the continued importance of parents and physicians in detection of USNHL in the post-UNHS era. It also suggests a role for pre-school age (2–4 years) hearing screening to allow for intervention prior to school age.
Implementation of UNHS was associated with a significant decrease in the age of detection of USNHL (Ghogomu et al., 2014).
Furthermore, approximately 10% of children born with UHL eventually develop bilateral hearing loss (BHL) (Declau et al., 2008; Uwiera et al., 2009).

- **Etiology of UHL**

The incidence of temporal bone anomalies in congenital UHL is high compared with congenital BHL. High-resolution computed tomography (CT) and Magnetic Resonance Imaging (MRI) allow to detect abnormalities including: including enlarged vestibular aqueduct (EVA), cochlear nerve aplasia or hypoplasia, small internal auditory canal (IAC), cochlear or labyrinthine dysplasia, enlarged cochlear aqueduct (ECA), Mondini deformity, cochlear and vestibular malformations, and common cavity malformation, temporal bone fractures. Among children with severe to profound UHL, the prevalence of cochlear nerve aplasia or hypoplasia approaches 50% (Clemmens et al., 2013; Nakano et al., 2013).
Hereditary etiology if an immediate family member had a diagnosis of SNHL or if genetic testing was abnormal (genetic mutations in Connexin 26/30 and Pendred SLC26A4 genes), also if these mutations tend to be associated with bilateral rather than unilateral SNHL. Other syndromic causes of childhood hearing loss may initially present, or simply be associated with, a unilateral loss, for example, branchio-otorenal syndrome and Waardenburg syndrome.
Other important causes of sensorineural UHL include congenital cytomegalovirus (CMV) infections, meningitis, and trauma. Although children with symptomatic congenital CMV infection are more likely to have BHL, children with asymptomatic CMV infection are more likely to have UHL (Goderis et al., 2014)
Temporal bone trauma is a common cause of acquired postlingual UHL.
Important causes of conductive UHL include unilateral aural atresia, cholesteatoma, chronic otitis media, otosclerosis, ossicular discontinuity, and congenital ossicular malformations.

There are some ‘risk factors’: Neonatal Intensive Care Unit (NICU) stay, prematurity (<37 weeks), ototoxic medications, jaundice requiring treatment, confirmed autoimmune disease, encephalopathy, brain infarcts, hydrocephalus, and syndromes associated with hearing loss.

- **Consequences of UHL**

Historically, UHL was considered to have few, if any, adverse functional consequences on children. However, since the early 1980s, many studies have been done showing the adverse effects of UHL on speech and language development, behavior, and academic achievement (Culbertson & Gilbert, 1986; Bess et al., 1998; Bovo et al., 1988; Brookhouser et al., 1991; Dancer et al., 1995; Lieu, 2004; Lieu et al., 2010).

The audiological disability resulting from lack of binaural hearing can be summarized as difficulty picking out a desired signal in the midst of background noise and trouble with identifying the source of a signal in 2- or 3-dimensional space.

Children with hearing loss in general are known to experience increased fatigue from the extra cognitive effort expended to detect, decode, process, and comprehend speech (Bess & Hornsby, 2014; Kuppler et al., 2013).

They also experience more difficulty with learning new words and multitasking, which can result in possible negative results in school settings (McFadden & Pittman, 2008). In addition, infants and young children require a greater signal to noise ratio than adults to comprehend speech sounds in the presence of masking noise (Nozza et al., 1988). Thus, young children with UHL may experience more difficulty with speech in noise than adults with UHL and certainly more difficulty than their normal-hearing peers. Children with UHL often struggle with receptive listening due to background noise and difficulty with sound localization.

Many studies have documented delays in speech and language in children with UHL since the reports from the 1980s and 1990s. USNHL has also adverse consequences on speech and language development (Lieu, 2004) and is often not present or detectable at birth (Ghogomu et al., 2014).

There are limited data regarding the effects of UHL on speech-language development in preschool children but more in elementary school children.

Kiese-Himmel (2002) reported that among the 31 children with UHL in her study, the average age of first word spoken was not delayed (mean 12.7 months, range 10–33 months), but the average of first 2-word phrase spoken was delayed (mean 23.5 months, range 18–48 months). Compared with children with normal hearing, fifty-eight 4- to 6-year-old children with UHL had significantly delayed language in Sweden.

Among school-aged children, a series of controlled studies have documented a robust, negative effect of UHL on speech-language scores. A recent study of Lieu (Lieu, 2015) , compared with 74 normal-hearing siblings, 74 children with UHL were found to have significantly poorer scores on the Oral and Written Language Scales. Verbal intelligence quotient (IQ) scores were also lower among the children with UHL.

The academic and developmental difficulties faced by children with UHL are reflected by the gap in speech-language scores that exists between them and children with normal hearing (NH) (Lieu et al., 2010).

Bess and Tharpe (1984) were the first to report a negative consequence of UHL in children, showing that 35 % of children with UHL failed at least one grade as compared with 3.5 % for the school district overall. Their findings were corroborated by other investigators who found 22% to 24% rates of failing at least 1 grade compared with district-wide averages of 2% to 3% (Tillman et al.,1963; Bovo et al., 1988). In addition, 12% to 41% of children with UHL were noted to receive additional educational assistance, and a high rate had educational or behavioral problems (20%–59%) (Brookhouser et al., 1991).

Very little is known about how academic or developmental delays demonstrated in children with UHL translate into adolescence. Fischer and Lieu (2014) demonstrated that adolescents with UHL have worse overall and expressive language scores than controls with normal hearing and had significantly lower Full scale (Verbal) and Performance IQ.

These findings suggest that UHL in adolescents is associated with a negative effect on standardized language scores and IQ. They also demonstrate that the developmental gap between children with UHL and children with NH does not resolve as the children progress into adolescence and may even widen as the children grow older. Therefore, these results strongly encourage implementation of early intervention for children with UHL to prevent speech-language delays. More studies in adolescents are warranted to evaluate educational outcomes.

Although speech-language scores and IQ do not directly translate to school performance, the secondary measures of repeated grades in school, teacher's report of school-related behavioral problems, and specification of individualized education plans (IEPs) or Section accommodations for hearing disability at school demonstrated trends for increased incidence in adolescents with UHL, similar to what has been found in other studies of younger children with UHL (Bess & Tharpe, 1984; Brookhouser et al., 1991; Oyler et al., 1988).

Concerns about the potential effect of UHL on cognition began to appear as children with UHL were reported to have lower IQ scores, usually among children with profound or right-sided UHL (Niedzielski et al., 2006; Purcell et al., 2016; Bess & Tharpe, 1984; Hartvig et al., 1989).

Several studies have found lower scores on standardized cognitive tests in children with UHL compared with children with normal hearing (Lieu et al., 2012; Lieu et al., 2013; Fisher & Lieu, 2014).

For many years, it has been acknowledged that adults with acquired UHL experience significant social and emotional decrements in quality of life (QOL) because UHL disrupts their ability to interact with others.54,55 Qualitative reports of how UHL affects QOL include social interactions (ie, one-on-one preferred to group interactions) and difficulty with conversations (eg, pretending to hear what was said, concentrating really hard to understand, or misunderstanding words) (Borton et al., 2010). Studies have shown that children and adolescents with UHL report their own hearing-related QOL to be significantly poorer than children and adolescents with normal hearing (Rachakonda et al., 2014; Umansky et al., 2011).

3.COCHLEAR IMPLANT

Cochlear implantation (CI) is a viable option for providing access to auditory stimulation in severe-to-profound hearing loss/impairment of cochlear origin. it has been demonstrated that CI is safe and effective for deaf children (Forli et al., 2011). Several observational studies have shown that early auditory intervention with a CI and prompt enrollment in a (re)habilitation and education program enable hearing impaired children to gain good quality access to auditory stimulation, achieve age-appropriate spoken language levels and eventually provide opportunities for normal social and academic development (Russel et al., 2013; Kral, 2013).

3.1 Indication for Cochlear Implant in children

The national and international literature and the principal international guidelines on the procedure consider as universally accepted the usefulness/effectiveness of unilateral cochlear implantation in severely-profoundly deaf children.

The IC is indicated in children with bilateral congenital deafness or acquired severe-profound entities with limited benefit prosthetic. The average hearing loss at 500-1000-2000 Hz frequency must be equal to or greater than 90 dB HL. The assessment of the threshold involves the use of subjective and objective methods, repeated in multiple sessions in order to obtain repeatable and reliable data. This criterion is essential in children with neuro-motor, cognitive or behavioral disabilities associated.

At present, although there is no consensus about how narrowly the critical window of time for optimal auditory development is defined, there is a growing body of evidence that supports implantation before 12 months of age and early activation after CI. Concerns are related to very early CI, because of the delayed maturation of auditory pathways, especially in preterm neonates, which could lead to an incorrect CI indication.

Nevertheless, some of the evidence suggests that the sensitive period may extend to about 3 years of age. It must be considered that the younger children are, the more difficult it is to test their hearing and to determine benefit from wearing a hearing aid or from CI.

A decision to implant may result in irreversible loss of whatever natural hearing is still present, but delaying that decision beyond the critical window of auditory development results in less than optimal ability to develop speech and language skills.

Early CI in children enables not only the development of the verbal communications, but also improves social skills, having broader consequences on the individual's life person (Chang et al., 2015).

The final judgment on the benefit to be formulated after a reasonable period of adaptation to amplification, not less than 3-6 months, especially in the case of first prosthesis. Exceptions are post-meningitis deafness with neuroradiological signs of ossification labyrinthine. The benefit assessment is performed with survey instruments age-appropriate, easy to administer and replicable. They include the observation structured, behavioral tests, objective tests, parental questionnaires. These allow you to accurately estimate the auditory-perceptual skills, the young patient's language and communication. The multimodal assessment of the child is used to minimize the possibility of error due to the impact that non-auditory factors such as attention, psychomotor profile, cognitive and linguistic maturity level can have on the results of the investigation.

The most controversial issues for which international consensus is lacking are: post-CI outcomes linked to precocity of CI; bilateral (simultaneous/sequential) CI vs. unilateral CI and vs. bimodal stimulation; benefits derived from CI in deaf children with associated disabilities.

With regard to the outcomes after implantation linked to precocity of intervention, there are few studies comparing post-CI outcomes in children implanted within the first year of life with those of children implanted in the second year. The selected studies suggest that children implanted within the first year of life present hearing and communicative outcomes that are better than those of children implanted after 12 months of age. Concerning children implanted after the first year of life, all studies confirm an advantage with respect to implant precocity, and many document an advantage in children who received cochlear implants under 18 months of age compared to those implanted at a later stage.

With regard to bilateral CI, the studies demonstrate that compared to unilateral CI, bilateral CI offers advantages in terms of hearing in noise, sound localization and during hearing in a silent environment. There is, however, a wide range of variability. The studies also document the advantages after sequential bilateral CI. In these cases, a short interval between interventions, precocity of the first CI and precocity of the second CI are considered positive prognostic factors.

In deaf children with associated disabilities, the studies analyzed evidence that the CI procedure is also suitable for children with disabilities associated with deafness, and that even these children may benefit from the procedure, even if these may be slower and inferior to those in children with isolated deafness, especially in terms of high communicative and perceptive skills.

3.2 Indication for Cochlear Implant in adults

It is considered as universally accepted the usefulness/effectiveness of unilateral cochlear implantation in severely/profoundly adult patients.

CI indications in adults are variable in the different countries. With regard to hearing threshold levels, the international guidelines indicate different levels of hearing over which CI is indicated. Some guidelines refer to the pure tone audiometry between 0.5-1-2 KHz (PTA) while others refer to the mean threshold between 2 and 4 KHz (UK Cochlear Implant Study Group. 2004).

In adult patients, according to the Food and Drug Administration (FDA), CI is indicated with a PTA>70 dB, while according to Belgian guidelines with a PTA>85 dB associated to auditory brainstem responses (ABR) threshold ≥ 90 dB HL. The British Cochlear Implant Group (BCIG) considers CI appropriate for adult patients with thresholds between 2 and 4 KHz >90dB. Italian guidelines admit CI in adult patients with a PTA >75 dB (Quaranta et al., 2009).

Concerning hearing aid training and rehabilitative results with traditional hearing aids before implantation, Italian and British guidelines consider CI appropriate in cases with open set speech recognition score of < 50%, the FDA in cases with open set speech recognition score < 60% and Belgian guidelines in cases with open set speech recognition score < 30%.

In a recent review made by Berrettini et al. (2011a) CI was considered an appropriate procedure for adult patients with bilateral severe to profound hearing loss (mean threshold between 0.5-1-2 KHz > 75 dB HL), with open-set speech recognition score ≤ 50% in the best aided condition without lip-reading. In selected cases CI would be indicated if open-set speech recognition score is ≤ 50% in the best aided condition without lip-reading with background noise signal to noise ratio +10.

CI is admitted in selected cases with better residual hearing at low and middle frequencies and hearing threshold between 2 and 4 KHz ≥ 90 dB, with an open-set speech recognition score ≤ 50% in the best aided condition without lip-reading.

According to the only two systematic reviews on the clinical effectiveness of unilateral CI, published in the literature to our knowledge (NICE, 2011; Bond et al., 2009) there is consistent evidence that a monolateral CI is a safe, reliable and effective strategy for adults with severe to profound sensorineural deafness.

There are controversial issues for which international consensus is still lacking: monolateral CI in advanced-age adult patients; bilateral (simultaneous/sequential) CI vs. unilateral CI and vs. bimodal stimulation; benefits derived from the monolateral CI procedure in adult patients with prelingual deafness.

With regard to CI in elderly patients, some studies document an improvement of the quality of life (Orabi et al., 2006) and perceptive abilities (Chatelin et al., 2004) after CI, even if the benefits were found to be inferior in patients over 70 years at the time of surgery. Thus, from the results of a recent review (Berrettini et al., 2011b), advanced age is not a contraindication for the CI procedure.

With respect to unilateral CI, bilateral CI offers advantages in hearing in noise, in sound localization and less during hearing in a silent environment (Mosnier et al., 2009; Laszig et al., 2004).

However, high interindividual variability is reported in terms of benefits from the second implant. With regard to CI in prelingually deaf adults, some studies document benefits deriving from the CI procedure in terms of improvement of perceptive abilities and in the quality of life after CI, as well as subjectively perceived benefits (Santarelli et al., 2008; Chee et al., 2004). However, there is high interindividual variability (Klop et al., 2007).

3.3 Cochlear implant characteristics

The multiple-channel CI restores useful hearing in severely-profoundly deaf people. It bypasses the malfunctioning inner ear and provides information to the auditory centers in the brain through electrical stimulation of the auditory nerves. It has enabled tens of thousands of severely profoundly deaf people in over 70 countries to communicate in a hearing world. The prototype speech processor and implant were then developed industrially by Cochlear Pty. Limited and trialed internationally for the US Food and Drug Administration (FDA). In 1985, it was the first multiple-channel CI to be approved by the FDA as safe and effective for postlingually deaf adults. In 1990, it was the first implant to be approved by the FDA as safe and effective for children from two to eighteen years of age.

The CI is now demonstrated to be more cost-effective than a hearing aid in severe-profound SNHL in adult and infant patients (Turchetti et al., 2011a; Turchetti et al., 2011b). Furthermore, the costs to achieve a Quality Adjusted Life Year (QALY) show it to be comparable to a coronary angioplasty and an implantable defibrillator.

CI consists of an external microphone and speech processor (Figure 7a), and an implanted receiver–stimulator and electrode array (Figure 8). The microphone is usually directional, and placed above the ear to select the sounds coming from the front, and this is especially important in conversation under noisy conditions. The voltage output from the microphone passes to a speech processor worn behind the ear (in adults-Figure 7a) or attached to a belt (body worn version for children-Figure 7b). The speech processor filters the speech waveform into frequency bands, and the output voltage of each filter is then modified to lie within the dynamic range required for electrically stimulating each electrode in the inner ear.

Figure 7(a-b): External component of the cochlear implant for adults (a) and children (b).

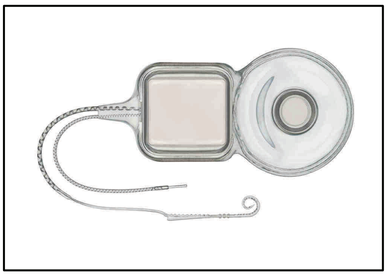

Figure 8: Internal component of the cochlear implant for adults.

A stream of data for the current level and electrode to represent the speech frequency bands at each instant in time, together with power to operate the device, are transmitted by radio waves via a circular aerial through the intact skin to the receiver–stimulator (Figure 9).

The receiver–stimulator is implanted in the mastoid bone and decodes the signal and produces a pattern of electrical stimulus currents in a bundle of electrodes, inserted around the scala tympani of the basal turn of the cochlea. These electrodes excite the auditory nerve fibers and subsequently the higher brain centers, where they are perceived as speech and environmental sounds.

One of the most important characteristics of CI is the intracochlear array. Current CI devices have from 12 to 22 electrodes in intracochlear array, that could be straight or perimodiolar.

Perimodiolar electrodes are designed to coil during or after insertion to occupy a position closer to the modiolar wall of the cochlea, where the spiral ganglion cells reside. These electrodes require a different insertion technique than the straight ones, and specialized insertion tools have been created to facilitate insertions. The potential advantages of perimodiolar electrodes include: (1) more selective stimulation of spiral ganglion cell subpopulations; (2) less current required for each stimulus, thereby reducing the power consumption; and (3) less damage to the cochlear elements. These potential advantages may translate into better speech understanding using newer processing strategies, longer battery life and preservation of residual hearing.

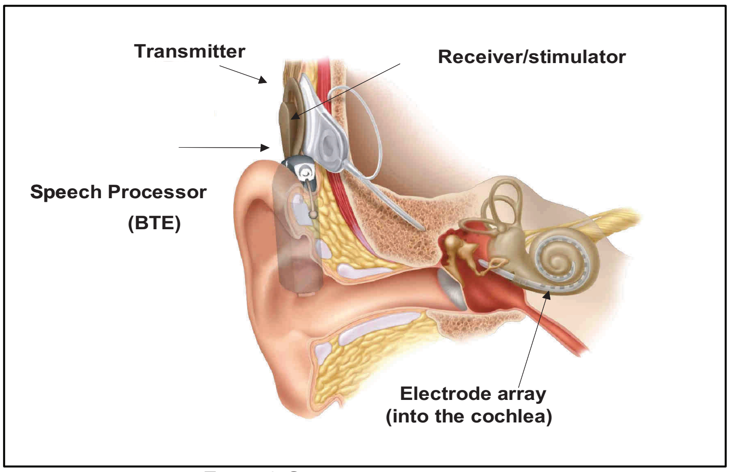

Figure 9: Cochlear implant in section

4. AUDITORY DEPRIVATION AND NEUROPLASTICITY

The development of the central nervous system is characterized by early additive and subtractive events. Additive events consist in the formation of neurons and in neuronal migration, a phenomenon that seems to be almost complete already at the twenty-fifth week of gestation. The newborn's brain has more neurons now than it will ever have in its life, but the volume of the brain is four times smaller than the adult's, and dendritic arborization and axonal growth will support its volumetric increase. This hypothesis is supported by synaptic density studies showing different successive stages. During the first year of life there is an increase in the density of dendritic synapses, coinciding with the process of synaptogenesis; subsequently, between the ages of 2 and 4, there is a synaptic density peak called "synaptic explosion". This is followed by a subsequent slow density decline, by synaptic pruning, which reduces the number of synapses by 50% during adolescence with respect to the peak of the first years of life (Huttenlocher & Dabholkar, 1997). This process supports the phenomena of plasticity (Johnston, 2009). The function of a specific brain region appears to be largely influenced by peripheral sensory stimuli and by the stimulation it receives from the connected cortical areas. The experiential stimulus probably determines many of the circuits that are established in that area. The hierarchical development of the synaptic connections in the human cerebral cortex supports the hypothesis that synaptogenesis and synaptic elimination are associated with the function, which implies that cortical development is influenced by the environment. The selection of the neural connections is established by the frequent activation of those nervous paths that are maintained, while the paths not regularly used are lost. It has been reported in the literature (Fallon et al., 2008), that genetic predisposition is sufficient to generate, even in the absence of auditory experience, a rudimentary auditory system able to provide the spatiotemporal references necessary to the perception of language once the sensory signal has been restored, as occurs after cochlear implant operation. According to Fallon et al. (2008), the auditory stimuli play a key role in the modulation of the structural organization of the central auditory system and these plasticity features contribute to the success of many implantation interventions.

The plastic capacity of the cortical and subcortical structures is considered maximum in a period defined as critical and ending within the first 2-4 years of development (Sharma et al., 2002a). It is believed that the changes induced by experience during this period may change the mechanisms responsible for the sensory processes.

Neuronal plasticity is a fundamental and characterizing process of the development of the central nervous system that can be defined, in the case of hearing impaired children, as the set of active or dynamic modifications of the neuronal properties resulting from an altered peripheral stimulus (Fallon et al. , 2008).

It is important to note that not all the changes in responsiveness and neuronal organization are necessarily of a plastic nature; some may in fact be described as passive consequences of an altered auditory stimulus. Many changes are brought about by the absence of the sensory stimulus and they precede the restoration of the stimulation occurring thanks to the cochlear implant. The studies carried out by Fallon et al. (2008) on the encephalon of deaf cats showed that the changes induced by an absent auditory stimulus include a significant reduction in the spiral ganglion neurons, demyelination of the soma and, to some extent, of the central processes of residual neurons as well as the reduction of the spontaneous activity of the auditory pathway neurons. Furthermore, after the damage of the ciliated cells, the dendritic processes of the spiral ganglion cells undergo extensive degeneration. Most of these changes occur in the downstream portion of the auditory pathways of the cortex and involve input stimuli and organization of such stimuli in the cortex. A study by Teoh and collaborators shows that the auditory system undergoes degeneration if it does not receive sensory stimuli (Teoh et al., 2004). Prolonged deafness determines changes in the ultrastructural organization of the parts of the brain dedicated to hearing; the histological changes include a reduction in the density of the synaptic vescicles, a reduction of the terminal branches, a widening of the synaptic range; the physiological changes include effects adverse to synchronization of the excitation of the post-synaptic potential, and also an increase in the response threshold of the cochlear nucleus. These anatomical and physiological changes have proven to be partially reversible if the nerve is not stimulated again. The development and organization of the sensory pathways are therefore dependent on sensory experience. Sensory deprivation, as occurs in deafness, hinders normal growth and the formation of early connections that are necessary for the typical development of the auditory system.

4.1 Plasticity and cortical reorganization in children with implanted cochlear devices

Many authors have studied the development and limits of plasticity of the auditory pathways and of the auditory cortex by recording cortical auditory evoked potentials. Evoked potentials (EP) are electrical responses to sensory stimuli recorded with electrodes positioned on the scalp. The EPs can be classified according to the site generating the electric field according to whether the responses are coming from the cortical areas or from the intermediate nuclei. From a clinical point of view the most important auditory EPs are those of short latency (within 10 msec) relative to the response of the nerve nuclei present in the brainstem (ABR, Auditory Brainstem Responses). Five waves, ranging from I to 5 and with significant latency, can be distinguished.

The cortical EPs are mainly used in the field of research; in particular, in children the latency of the first positive peak, P1, is considered a biomarker of the maturation of the cortical auditory areas, as demonstrated by Sharma et al. (2007). P1 is a wave characterized by robust positivity and it presents a latency of 100-300 ms in children. The latency of P1 varies according to age and for this reason it is considered a maturation index of the auditory cortex (Sharma et al., 2002a). Evidence obtained from intracranial recordings suggests that the neural P1 wave generator is the thalamic-cortical projection to the auditory cortex (Eggermont & Ponton, 2002; Kral, 2007). Since the auditory stimulus reaches the auditory cortex in less than 20-30 ms after stimulation, it is reasonable to assume that the early components of the response of the cortical acoustic EPs evoked, such as P1 and N1, which have a higher latency in children, reflect second-order cortical processing of the auditory stimulus; such stimulus includes the input coming from the feedback between the primary auditory area and the associative areas. Cortical acoustic evoked potentials (CAEPs) and P1 latency were measured by Sharma and colleagues in deaf children with cochlear implant received at different ages, in order to examine the limits of plasticity of the central auditory system. Dorman et al. (2007) examined P1 latency in 245 deaf children with implant and reported that children receiving cochlear implant before 3 years 6 months of age have a P1 latency equal to their peers, while those receiving implant after 7 years of age show an anomalous latency of the cortical response. Wave morphology is also considered a measure of development that can be studied after the recovery of auditory stimulation. In early implanted children wave morphology presents features that are similar to those of normal hearing subjects, while it shows anomalies in late implanted children and is characterized by a polyphasic form or by low amplitude (Sharma et al., 2009).

Both in children implanted before 3 years and 6 months, and in those implanted after 7 years of age, the authors found a change in P1 latency of 35% in the first month of cochlear implant activation; instead, the children implanted after 3 years and 6 months showed a subsequent reduction of the maturation process, which instead continued in the group of children receiving cochlear implant before that age. According to the authors, the initial change of latency can be related to synaptic processes as long-term potentials, while the change that continues to be present in the early implanted children can be related to the rearrangement of the synaptic structures.

In their studies Sharma et al. (2002b) argue that the central auditory system is highly plastic in early childhood for a significant period of 3 years and 6 months. Although there is likely to be more than one sensitive period in the central auditory system, the duration of the sensitive period identified by Sharma and collaborators coincides with numerous changes in the structural development of the auditory cortex. During the first 2-4 years of life there is a massive reorganization of the dendritic trees (Moore, 2004). Eggermont and Ponton (2003) longitudinally studied the maturation of the P1 - N1 complex in two deaf children with cochlear implant. They found that the auditory system has a critical period of development that ends approximately between 3 and 6 years and whose growth is highly dependent on the auditory sensory stimulus. Auditory stimulation obtained with cochlear implant induces early signs of development of the system, with P1 latency appropriate to the hearing age (sound exposure time). In these subjects the decline of P1 wave latency stops 6-8 years after implant, and the N1 wave does not change over time, nor does it ever develop. Therefore, the authors report that the highest growth is reached in a relatively short time and in any case remains inferior to the growth experienced by normal hearing children. These results indicate that the final maturation of the auditory pathways depends on the duration of the deafness preceding chronic stimulation with cochlear implant.

In these last years there has been a constant reduction in the age of implant; however, the real benefits of very early implantation (before 12 months of life) are not yet completely clear, as also highlighted by the recent review by Peterson and collaborators, who report the conclusions of more recent studies (Peterson et al., 2010).

The review shows that the most important and significant factor for language development is the age in which the subjects are implanted.

Some studies show that children implanted in the first year of life have better auditory and especially comunicative-language results than those implanted after 12 months of age (even compared to the second year of life), allowing in some cases completely typical language development (Forli et al., 2016). Nonetheless the numerosity of samples is usually small, some of the studies do not show statistical significance and long-term results; the influence of the duration of use, rather than the earliness of CI, especially on the linguistic results is not reported.

Additional factors were investigated, such as the residual pre-prosthetic implant measured as PTA (pure tone threshold), which resulted predictive of language outcome in the work by Holt and Svirsky (2008). This study evidences that language development in cochlear implanted children also seems to depend on the language skills investigated. The authors, who assess the effects of early age implant (<12 months) on language outcomes, show development trends for different linguistic components. They found that while the sensitive period for the acquisition of receptive and expressive language seems to end at the age 2-3 years and 6 months, for abilities such as word recognition the sensitive period seems more prolonged, up to 4 years and even more. Different instead are the results obtained by Teoh et al. (2004) for patients with late implant. According to this study, the critical period may extend for some abilities, such as word recognition, until 12 years of age; however, almost all the patients who received cochlear implant after 12 years of age are rarely able to recognize words in open set. According to the authors of the review the differences among these results depends on the measures taken into consideration to determine the outcome measures. This line also fits into the study conducted by Harrison et al. (2005) on a large number is congenital deaf children who received an implant between 1 and 15 years of age. According to the authors, the results show that there is not a critical period after which the implant is no longer useful, but they confirm that children receiving early CI will gain the greatest benefit. The authors do not find a rigidly fixed period and claim that every behavioral response is the result of multiple neuronal and cognitive mechanisms, each of which has its own period of development which is different from the others. The overlap of these periods, alongside a complex integration of the different parts of the system, show how unlikely it is for a single critical period to exist. Furthermore, it is easier to identify a critical period when the acoustic-perceptual components rather than the linguistic and behavioral components are investigated. The sensitive period for the development of language as documented by studies using the cortical evoked potentials is not perfectly concordant with the period that emerges from behavioral studies. This difference can be due to the characteristics of the studies: indeed the electrophysiological studies with cortical evoked potentials use very simple stimuli (the syllable /ba/), which activate specific parts of the auditory system. Behavioral and linguistic studies are instead dependent on the perception of words and on the integration of words in meaningful sentences. This task is more complex and underlies different variables that involve the auditory and linguistic system as a whole.

4.2 Crossmodal plasticity

The human cerebral cortex is able to address some levels of crossmodal reorganization by means of a sensory mode, when another sensory mode presents a deficit (Lee et al., 2001). Restored afference of the auditory stimuli to a cortex that has undergone a process of reorganization as a result of deafness probably implies the possibility of functional access only to those areas still available after the period of auditory deprivation. The time in which the reorganization and degeneration of the sensory pathways have acted is likely to limit the success of the cochlear implant, since the auditory cortex has organized itself according to different sensory afferents, generally visual.

Conversely, early restoration of the auditory signals seems to suggest typical cortical development (Lee et al., 2007). Evidence in support of this hypothesis is offered by the study of Gilley et al. (2008), performed with the cortical EPs in three groups of children: children with normal hearing, deaf children with cochlear implant received before 4 years of age, and deaf children with cochlear implant received after 7 years of age. The authors used a high-density electroencephalographic recording to identify the source of generation of the P1 wave response in the three groups of children, after they had listened to a syllable. This study presents a particularly interesting result: implanted children show an activation exclusively in the contralateral ear to the one with cochlear implant. Gilley et al. (2008) suggest that, in the children they studied, the bilateral auditory pathways are not sufficiently developed during auditory deprivation. In such case, the results obtained could support the hypothesis of cortical doubling of the auditory pathways which, according to Kral (2007), occurs during the period of auditory deprivation.

Gilley et al. (2008) attributed the differences concerning the generation site of the P1 wave in the three groups of children to different degrees of cortical reorganization following periods of different acoustic deprivation. None of the 30 children receiving implant after 7 years of age showed the source of the signal to be localized in areas associated with the auditory cortex, but a parietotemporal location contralateral to the side of the implant. Some authors found that in the case of prelingual deaf children crossmodal visual-aural cross plasticity is a factor that limits language development. Lee et al. (2007) investigated the level of brain metabolism at rest with PET in 33 children before implantation, and then compared the metabolic level with the results obtained from linguistic tests performed 3 years after implantation. The results obtained showed that the hypometabolism at rest of the auditory cortex (Brodmann's Area 41, 42) is predictive for a better perception of language after cochlear implantation. According to the authors, the grade of temporal hypometabolism correlates positively with the linguistic results following the implant, so as to make this a possible prognostic factor. Lee et al. (2007) suggested that the failure of the hypometabolism of the auditory cortex at rest, reported by PET in subjects over 8 years of age, reflected a recovery from the hypometabolic state induced by auditory deprivation; such recovery seemed to be caused by the use of the temporal regions by different cognitive processes and this, according to the authors, was predictive of a lower susceptibility to recovery of the hearing function and therefore of worse linguistic results (Lee et al., 2007). The authors also reported an increased activity of the left dorsolateral prefrontal cortex before implantation, associated with good language receptive results at three years after implantation. Low linguistic outcome was instead associated with higher glucose activity in the right posterior superior temporal sulcus and in the right Heschl's gyrus (Lee et al., 2007).

4.3 Hypothesis of cortical dissociation

By studying congenital deaf cats Kral (2007) formulated the hypothesis that cortical dissociation between primary and associative areas would be the mechanism responsible for the end of the sensitive period for auditory development. As a matter of fact, electrical stimulation of the acoustic nerve after the end of the sensitive period causes a delay in the activation of the supragranular cortical layers and an almost complete absence of long-latency signal in the infragranular layers of the primary auditory cortex.

According to the author, the almost complete absence of stimulation effects in layers IV and III suggests an incomplete development of the inhibitory synapses and an altered flow of information from layer IV to the supragranular layers. These layers of the primary auditory cortex receive the projections of the associative cortical areas sending long-term feedback to the subcortical areas. The lack of activity in the infragranular layers may be interpreted as a functional dissociation of the primary areas from the high-grade associative areas.

In the absence of an auditory experience the activity of the infragranular layers of the cortex would be largely compromised and the projections for the associative areas would not develop appropriately, resulting in weakened feedback and in a dissociation between the secondary associative areas and the primary areas, with a lack of "top-down" modulation (Kral, 2007).

This would make the secondary areas available for other sensory modalities and therefore the processing of auditory stimuli would be difficult after the end of the sensitive period (Kral, 2007).

Sharma et al. (2009) and Gilley et al. (2008) tried to check whether a similar mechanism might be responsible for the end of the critical period also in human beings.

The results obtained by Gilley et al. (2008) in the study with high density electroencephalogram (EEG) cited above are consistent with the hypothesis of cortical dissociation formulated by Kral (2007). This cortical dissociation would allow the secondary areas to be reorganized by other sensory modes.

Recent studies performed by various authors, including Sharma et al. (2007), provide clear evidence of an activation of high-level auditory associative areas for visual and somatosensory stimuli, suggesting the presence of a cross-modal reorganization in these areas.

According to Sharma et al. (2009), a further element in support of this hypothesis is obtained from the study through the cortical EPs recorded in deaf children. The confirmation of polyphasic waves in deaf adults and in some deaf child who have not received cochlear implant might be the result of a central auditory system developed abnormally and/or of a reorganization secondary to the period of auditory deprivation.

In conclusion, as claimed by Teoh et al. (2004), the most important limiting factor for auditory development in subjects receiving cochlear implant after 7 years of age and in adults, seems to be the reorganization of the auditory cortex, which is somehow "occupied" by non auditory-verbal sensory processing.

Therefore, children should receive hearing aids as soon as possible, and oral rehabilitation only after prosthesis and cochlear implant activation.

5. LANGUAGE FUNCTION - Lateralization of language as a paradigm for the study of nervous plasticity

5.1 Lateralization of the language function

Language is a lateralized function which in most right-handed and in many left-handed subjects results to be controlled by the left hemisphere (Cabeza & Nyberg, 2000; Knecht et al., 2000; Lidzba et al., 2006; Price, 2000). This functional asymmetry seems to be anatomically related to a larger left temporal planum (Steinmetz et al., 1989). Although women were thought to show different patterns for the hemispheric dominance of language (Shaywitz et al., 1995), a recent meta-analysis has failed to find any differences between men and women in the lateralization of language (Sommer et al., 2004). The idea that language has a neural correlate, and that it is located in the left hemisphere was formulated by Paul Broca in the mid-nineteenth and has been confirmed by one and a half centuries of experiments conducted on individuals who have become aphasic after damage to the left hemisphere.

The concept of localization, in the strict sense of the expression supported by Broca, has been replaced with that of a large network that looks at language in its different phonological and semantic components, and in terms of lexical retrieval, verbal memory and articulatory processing. While in the adult brain evidence of the existence of a neural network dedicated to the language is robust, it is still largely debated whether the neural structures dedicated to language and to their localization are present from birth, and, in particular, how they develop during the long period of language learning. The perception of language is dependent on the primary auditory cortex, located in Heschl's gyrus at the bottom of the lateral groove. The primary auditory perception depends on the bilateral auditory cortices (Belin et al., 1999), and speech perception uses the bilateral temporal lobes, although with a predominance of the left hemisphere (Hickok & Poeppel, 2000) .

In order to determine which cerebral regions support language processing from birth, Dehaene-Lambertz et al. (2002) used functional magnetic resonance to study the cerebral activity evoked by a female voice reading a book first and then by a manipulated recording obtained by rewinding the medium in 3-month-old children, both in wakefulness and during sleep. The results of this study indicated that the infantile cerebral cortex is already structured in various functional districts and from the earliest months of life, and that the areas activated by the listening extensively involved the temporal lobe of the left hemisphere. A significant hemispheric asymmetry was observed, caused by a greater activation of the left than of the right temporal planum. Furthermore, there was also an unexpected activation of the Broca area, since verbal production at this age is limited to brief vocalizations; actually, the more specifically pre-linguistic expressions start a few months later with canonical lulling. However, the study of language development in children with early brain injury, which involves the language areas of the brain, shows that the consequences on language are milder than those observed in adults after comparable lesions (Chilosi et al., 2005) . The positive prognosis for language development in children is generally attributed to the highest degree of plasticity of the brain in the early years of life, which allows intra-hemispheric compensation or a reorganization of the language function in the hemisphere contralateral to the lesion. On the basis of the evidence that children undergoing left hemispherectomy develop language with no clinically evident alterations, Lenneberg et al. (1967) hypothesized the concept of hemispherical equipotentiality according to which, at birth, the two cerebral hemispheres are equipotential for language. According to the author, the specialization of the left hemisphere for language increases until puberty alongside a reduction of plasticity potential. One of the first observations of Broca was that the left prefrontal cortex is very important for the production of language (Broca, 1861). The focal lesions of the Broca area in adults led to an incapacity of language production, with the perception and understanding of language that remained intact (Damasio & Geschwind, 1984). Motor control of speech consists of two networks: a preparatory loop including cortical structures (supplementary motor area, prefrontal dorsolateral cortex including the Broca area), and cerebellar structures (upper cerebellum); while the executive loop comprises cortical structures (motor cortex), subcortical structures (thalamus, putamen/pale, caudate), and cerebellar (inferior cerebellum) (Riecker et al., 2005). The silent production of words leads to an activation of the same areas, although with lower activation of left brain dominance (Friedman et al., 1998; Riecker et al., 2000). Today, a predisposition of the left hemisphere to the analysis of input language, alongside the potential of the right hemisphere to take on linguistic tasks, are not considered antithetical but an expression of adaptability of the nervous system to learn and to develop alternative neuro-functional organizations in case of early lesions of the left hemisphere.

5.2 Mechanisms of hemispheric lateralization

Hemispheric specialization is traditionally explained in terms of structural and functional asymmetry between the homotopic regions of the two cerebral hemispheres (Stephan et al., 2007). The existence of hemispheric differences in the structure of the connections, especially in the language areas, is clearly demonstrated both in the fetal and in the adult brain (Galuske et al., 2000). Hemispheric lateralization concerning the language functions was demonstrated very early (Broca, 1861; Wernicke, 1874), and led to intensive research on brain dominance. These studies allowed to assign traits to the two hemispheres that could be observed: the left analytical hemisphere and the right emotional hemisphere (Paredes & Hepburn, 1976). In an extensive review of the literature, Bradshaw and Nettleton (1981) concluded that the left hemisphere is dedicated to the analysis of time-dependent sequences and of verbal processes, while the right hemisphere may fulfil the functions that the left hemisphere is unable to perform. The functional asymmetry of the hemispheres was assigned to a structural difference that was influenced by genetics and by environmental factors during development (Geschwind & Galaburda, 1985).

Recent approaches investigate the causes and the functional principles of hemispheric specialization in terms of asymmetric connections within the different cortical areas of the hemisphere and between the two hemispheres. This could lead to the end of the asymmetry of the brain structure with regard to cellular architecture and macroscopic features (Stephan et al., 2007).

The study by Bokde et al. (2001) investigates the hypothesis according to which the left anterior inferior frontal gyrus (aIFG) is involved in the semantic analysis of the words, while the left posterior inferior frontal gyrus (pIFG) plays a role in the phonological of the words. This study, conducted with fMRI, showed that the left posterior frontal gyrus (pIFG) is functionally connected to the temporal areas of the left hemisphere for the phonological analysis of words, pseudowords, and strings of letters, but not for false characters. Instead, the left inferior anterior frontal gyrus (aIFG) showed a significant functional connection with the left temporal areas only for the presentation of real words and therefore of the only words with semantic content. The interesting aspect of these outcomes is that in both cases the observed connections occurred entirely within the left hemisphere.

In addition to the intra-hemispheric connections, the inter-hemispheric connections also contribute to producing cerebral asymmetry. The main concepts describing the inter-hemispheric connections are three: the concepts of information transfer, of inter-hemispheric inhibition, and of hemispherical recruitment. The first concept claims that sensory information must be transferred from the non-dominant to the dominant hemisphere in order to ensure efficient processes in the specialized hemisphere. The second concept states the existence of inhibitory connections between the two hemispheres, while the third concept establishes that the stimuli received by the dominant hemisphere are also distributed to the non-dominant hemisphere for processing, and that the results return to the dominant, in order to overcome the costs of information transfer through the callosum corpus (Stephan et al., 2007).

Many questions concerning brain lateralization are still unknown. In particular, it remains unclear which aspects of language and non-verbal abilities are lateralized, whether there are disadvantages associated with atypical patterns of brain lateralization and whether lateralization undergoes a development with age (Bishop et al., 2010).

Furthermore, to date, very little is known about the mechanisms determining the different hemispheric localization of verbal and nonverbal functions (Whitehouse & Bishop, 2009). The hypothesis of depending predispositions claims that functional asymmetry is determined by a model of obligatory organization in which the location of the language and visuospatial functions are connected causally, more precisely that a function is located on one hemisphere because the contralateral hemisphere has already been taken over by the other.

According to this hypothesis, the homotopy areas of the two hemispheres - like the adjacent areas in the same hemisphere - inhibit each other, so that when the region of a hemisphere is inhibited, the adjacent area in the same hemisphere is activated and produces the inhibition of the corresponding region of the contralateral hemisphere (Whitehouse & Bishop, 2009).

In contrast with the first scenario, there is a second hypothesis, of the so-called independent predispositions, which claims that the division of the tasks is a statistical rather than a causal phenomenon. According to this hypothesis, hemispherical specialization may be produced by independent factors of the genetic, biological and environmental type, or by their combination.

Whitehouse and Bishop (2009) conducted a study in which they used Functional Transcranial Doppler ultrasonography fTCD to understand whether the different hemispheric localization of the verbal and visuospatial abilities was conditioned by a dependent or independent predisposition. The results of the study are in favor of the second hypothesis, showing that there is a predisposition for language to be represented in the left hemisphere and for spatial memory to be represented in the right hemisphere, but these phenomena result to be clearly independent.

6. AIMS OF THIS STUDY

The aims of the study were multifold:

- to investigate the effects of early severe bilateral acoustic deprivation and subsequent reafferentation with CI on patterns of hemispheric dominance for language, in comparison with healthy peers (study 1: 36 children with bilateral profound hearing loss fitted with CI and 24 normal controls matched for chronological age, sex and handedness)
- to investigate the effects of congenital profound unilateral hearing loss on patterns of hemispheric dominance for language in comparison with healthy peers (study 2: 11 children and 11 controls matched for chronological age)
- to evaluate whether hemispheric dominance for language varies in relation to CI side, in terms of fTCD activation contra-or ipsilateral to the ear implanted , or in relation to the side of profound unilateral hearing loss
- to check language outcome in children fitted with CI and in children with UHL in relation with the hearing afferent and the hemispheric activation side
- to assess hemispheric dominance for language in adults with severe to profound prelingual hearing loss, before and after CI, (study 3: 6 adults), to test whether after long lasting non optimal acoustic afferentation, brain plasticity is still active.

7. MATERIALS AND METHODS

7.1 Patients *Study 1*

Children with congenital profound bilateral hearing loss fitted with CI

The experimental sample consisted of 36 subjects, 26 children fitted with right CI and 10 children fitted with left CI, and 24 controls matched for chronological age, sex and handedness.

This study follows a previous research project funded by the Fondazione Mariani (Grant R-10-82 a AM C.) 2010-2011, in which fTCD has been applied on a sample of children with typical development, on subjects with bilateral sensorineural hearing loss who underwent cochlear implant and in a group of children with early left hemisphere brain lesions.

Children with CIs were recruited from a wider sample of patients referred to the Otorhinolaryngology, Audiology and Phoniatrics Unit of Pisa University Hospital, between April 2012 and May 2016.

The characteristics of the sample are summarized in Table 1.

The main criteria for inclusion were: profound preverbal sensory-neural hearing loss; no signs of brain damage or major malformations of the cochlea associated with deafness no signs of either neurological or psychiatric disorders associated with deafness and normal non-verbal IQ at Leiter International Performance Scale-Revised; exposition to only oral Italian language and auditory-verbal language training after implantation; full insertion of CI, The length of CI use was set at 24 months (or more) post-cochlear implant activation. The presence of additional neurological and psychiatric disorders was excluded by clinical and instrumental evaluation (including cerebral MRI performed before CI implantation). Moreover, only children who showed lexical and grammar skills sufficient to carry out the fTCD narrative task participated in the study.

Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

Clinical and audiological evaluation

Before receiving CI the experimental sample underwent a full clinical and audiological evaluation, that includes:

- General history and investigation of the etiology of deafness, age at diagnosis, time of Hearing Aid
- Otoscopy and Otomicroscopy
- ABR - Auditory Brainstem Responses
- EOAE - Evocated Otoacustic Emissions
- Tonal behavioral audiometry in free field with/without hearing aid

- Impedance analysis
- Logopedic assessment of both auditory-perceptual and linguistic communicative skills, differentiated according to the age of the child and the language level reached;
- High-resolution imaging: Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) (Petrous - inner ear CT and brain MRI with contrast medium)

After cochlear implant, side and age at implantation were recorded and all patients were submitted to:

- Behavioral tone audiometry in free field only with the cochlear implant, or with cochlear implant and hearing aids in the monoimplanted ear (patients using bimodal stimulation)
- Cognitive assessment, using the non-verbal Leiter-R performance scale. The Leiter-R consists of two standardized tests, but the study used only the first test, Visualization and Reasoning (VR), which consists of 10 subtests that measure non-verbal cognitive abilities related to visualization, spatial skills and reasoning.
- Evaluation of the perceptual and linguistic communication level achieved:
  - Tests of auditory skills (with cochlear implant) by evaluating recognition rate of disyllabic words and phrases, and understanding of sentences. The tests are performed in quiet and noise, with signal-to-noise ratio (S/R) +10. The number of tests used varies according to the child's age and to the level of language development.
  - Communicative-linguistic assessment with the following Italian standardized tests of both lexical and grammatical comprehension and production.
- For the evaluation of receptive vocabulary, children were administered the Italian version of the L.M. Peabody Picture Vocabulary Test by Lloyd M. Dunn and Leota M. Dunn (1997). The test consists of 180 items (with 5 pre-training tasks in increased order of difficulty9. For each item the subject examined is shown a series of 4 illustrations in black and white. The task is to select the image that represents the stimulus word.

The Peabody Picture Vocabulary Test - PPVT has been standardized in Italian by Stella et al. (2000); normative data is referred to the age range between 2 and 11 years.

- Grammar comprehension was measured by the Test of Comprehension of Grammar for Children (TCGB), Chilosi and Cipriani (1995). This multiple-choice test assesses the child's ability to understand 6 different, orally presented, grammatical structures.

The test, which in its full version includes 76 items, requires the selection of a stimulus sentence by choosing 1 out of 4 options. The aim of this tool is to assess the comprehension of different grammar structures (locative, dative, active affirmative, inflectional, active negative, passive and relative). During the test the stimulus sentence can be repeated in the case of a first erroneous answer. The score assigned to the answers varies from 0.5 (autonomous correction following the first repetition of the ITEM) to 1.5 (permanence of the error after the first repetition). The test has been standardized in Italian children aged between 3.6 and 8 years of age.

- Expressive vocabulary was assessed by means of the INPE one word picture vocabulary test (Brizzolara, 1989). In this test subjects are asked to name the figures contained in the tables consisting of four elements.

The test comprises two lists of words of high and low frequency of use, from which two partial scores are derived. In our protocol we used both lists for the subjects between 3.4 and 10.6 years of age, but only the list of low frequency words for older subjects. The final score is an error score. Denomination errors are classified in 5 categories: phonological errors (the subject pronounces the words incorrectly by either substituting or omitting phonemes); semantic errors (the word produced belongs to the same semantic category of the stimulus word); perceptual errors (wrong perception of the item); circumlocutions (the subject does not name the object but describes its features or its use); no answers.

- Morpho-syntactic production was evaluated with two different tests based on the age of the child: the test of repetition of sentences with clitic pronouns and the test of repetition of complex sentences. The test of repetition of sentences with clitic pronoun was standardized over a population of children aged between 3 and 6 years (Cipriani et al., 1993). The test of repetition of complex sentences, addressed to older children, has not yet been standardized. Both tests consist in the repetition of a stimulus sentence administered by the examiner in an audiovisual mode and with no graphic support. The test of repetition of sentences with clitic pronouns includes 30 six-word sentences, containing a total of 24 clitics, 44 articles and 10 prepositions. The raw score (number of sentences repeated without any error) is compared to the average and reference standard deviation. The test of repetition of complex sentences, formed by 13 sentences of different syntactic complexity, has no reference values, and therefore allows to obtain only a raw score.

- Expressive grammar was evaluated on spontaneous language samples and classified according to a six level rating system GASS (grid of analysis of spontaneous speech).

In order to estimate the overall level of linguistic proficiency of participants, a composite score was calculated by assigning each language test, one or two points for a z-score respectively lower or higher than -1.5; total scores ranged from 4 to 8 (8 being the maximum score).

The subjects, regularly evaluated during the audiological follow-up for cochlear implant fitting procedures, underwent to fTCD when we felt they could perform the linguistic task, on the basis of chronological age and language level achieved.

The mean chronological age of the experimental sample at the time of clinical and audiological evaluation and of fTCD was 8.2 years (SD 3.7 y, range 3.5-17.7).

Twenty-six children received a right CI (at a mean age of 2.7 y, SD 2.04 y, range 1.1-10.4) and ten were provided with a left ear implant (at a mean age of 4.5 y, SD 2.8 y range 3.2-8). The difference between age at implantation of the two groups was statistically significant ($t = 2.1$, $p = 0.04$).

The mean length of CI use (hearing age) was 4.7 years (SD 2.8 y, range 2–9.3 y). Hearing age of right-ear (M 4.43 y, SD 2.59) and left-ear implanted children (M 5.4 y, SD 3.37) did not differ statistically ($t=0.92$, $df=34$, $p=0.36$).

At the time of fTCD and clinical evaluation the mean chronological age of right CIs was 7.5 y (SD 3.5) and 9.8 y for left ones (SD 3.7 y) and did not significantly differ ($t=1.73$, $df=34$, $p=0.09$).

Before cochlear implant, the hearing threshold in free field without hearing aids corresponded to a mean PTA (Pure Tone Audiometry) of 101 dB; hearing threshold in free field with hearing aids was 58 dB, and after CI the hearing threshold in free field was 33 dB (with cochlear implant activated).

Subject N.	Gender	Handedness	Age at behavioral and fTCD testing (years)	Hearing loss etiology	Hearing loss characteristics	PTA in free field without hearing aids (dB)	Age at first hearing aids fitting (months)	PTA in free field with hearing aid (dB)	Age at CI (years)	Ear implanted	Hearing age (years)	Bimodal Stimulation	PTA in free field with CI (dB)
1	F	Right	3,7	Unknown	stable	100	5	65	1,8	Right	1,95	yes	25
2	M	Right	4,7	Prematurity	stable	60	10	40	2,2	Right	2,51	no	
3	F	Right	5,0	Unknown	stable	95	8	50	1,5	Right	3,52	no	45
4	F	Right	5,4	CMV	progressive	95	14	80	1,4	Right	3,95		35
5	F	Right	5,6	Cx26 hetero	stable	110	6	60	1,8	Right	3,86	no	30
6	F	Right	5,7	Cx26 homo	stable	120	12	75	1,7	Right	4,01	yes	25
7	F	Right	5,6	Unknown	stable	115	10	75	1,3	Right	4,28	no	35
8	M	Right	7,5	Unknown	stable	100	16	60	3,0	Right	4,50	yes	30
9	M	Right	9,9	Cx 26 homoz	progressive	105	18	50	2,6	Right	7,36	no	25
10	M	Right	10,7	Cx 26 homoz	stable	110	12	65	2,3	Right	8,42	no	35
11	M	Right	10,7	Cx 26 homoz	stable	105	12	60	2,3	Right	8,42	no	30
12	M	Right	13,7	S. Jervell-Lange	progressive	100	18	45	3,5	Right	10,20	no	50
13	F	Right	13,5	Cx 26-30 hetero	progressive	110	36	55	5,0	Right	8,48	no	35
14	F	Right	5,6	Unknown	stable	80	12	45	3,8	Left	1,87	no	35
15	F	Right	9,7	Cr 6p25.3	progressive	120	30	55	3,8	Left	5,82	no	35
16	M	Right	9,7	Prematurity	progressive	85	9	57	8,0	Left	1,69	yes	30
17	F	Right	10,5	CMV	progressive	120	9	70	3,2	Left	7,35	no	30
18	M	Right	11,3	Unknown	stable	110	9	80	3,0	Left	8,29		40
19	F	Right	8,8	Prematurity	stable	100	9	55	4,0	Left	4,81	yes	40
20	M	Right	12,9	Cx26 hetero	progressive	90	25	59	8,0	Left	4,87	no	30
21	M	Right	3,5	Unknown	stable	90	4	53	1,5	Right	1,97	no	30
22	M	Left	7,4	Unknown	stable	100	10	60	1,4	Right	5,96	no	30
23	F	Right	6,9	Unknown	stable	110	48	50	4,0	Right	2,92	yes	22
24	M	Right	3,8	Cx26 homo	stable	120	19	45	1,8	Right	1,92	yes	28
25	F	Right	17,7	Unknown	stable	120	24	65	5,0	Left	12,69	no	20
26	M	Left	5,9	Cx26 hetero	stable	100	6	69	1,2	Right	4,69	yes	38
27	F	Left	7,8	Cx26 hetero	stable	95	48	43	4,5	Left	3,32	yes	30
28	F	Right	6,6	Unknown	progressive	95	17	60	1,8	Right	4,8	yes	35
29	M	Right	9	Unknown	stable	100	6	65	3,0	Right	6,0	yes	30
30	F	Right	3,8	Unknown	stable	95	6	45	3,9	Right	0,1	yes	40
31	M	Left	5,60	Unknown	stable	95	5	70	1,50	Right	4,10	no	50
32	F	Right	4,0	Cx26 homo	stable	85	4	65	1,1	Right	2,83	yes	45
33	F	Right	10,2	Unknown	progressive	105	24	55	6,2	Right	4,00	yes	35
34	F	Right	10,5	Cx26 hetero	stable	110	8	50	10,4	Right	0,10	yes	40
35	M	Right	17,00	Unknown	stable	110	48	65	4,5	Right	13	no	25
36	M	Right	3,3	Cx 26	stable	100	6	70	18,0	Left	2,58	yes	35

*Table 1.*Etiological and audiological features and handedness of children with CI.
Legend: PTA=Pure Tone Audiometry; dB Decibel; CI Cochlear Implant; fTCD Functional Transcranial Doppler.

7.2 Patients *Study 2*

Children with severe-profound unilateral hearing loss (UHL)

The experimental sample consisted of 11 children, with a mean chronological age at the time of clinical and audiological evaluation and at the time of fTCD evaluation of 8.5 years (SD 3.4, range 3,5-14), and 11 normal controls matched for chronological age.

Six children with severe-profound hearing loss in the right ear from birth and five children in the left ear.

The main criteria for inclusion of children with unilateral hearing loss were: severe-profound unilateral congenital hearing loss; a normal hearing ear; no signs of brain damage; no signs of either neurological or psychiatric disorders associated with deafness and normal non-verbal IQ at Leiter International Performance Scale-Revised.

The experimental sample underwent clinical and audiological evaluation, that included:

- General history and investigation of the etiology of deafness
- Otoscopy and Otomicroscopy
- ABR - Auditory Brainstem Responses
- EOAE - Evokated Otoacustic Emissions
- Tonal behavioral audiometry in free field or with headphones, according to age and collaboration;
- Impedance analysis
- High-resolutions imaging: Petrous - inner ear and brain Magnetic Resonance Imaging (MRI) with contrast medium, and CT of the petrous bone in selected cases.
- Cognitive and behavioral assessment: WISC-IV scale (verbal and nonverbal intelligence) (Wechsler, 2003), Visuo-Motor Integration abilities (Beery, 1997), Check Behavior Check-List (CBCL) for identifying behavioral problems (Achenbach, 2003), CORSI test of visuo-spatial short-term memory (Corsi, 1972).
- Logopedic rating of both auditory-perceptual skills and linguistic communicative development, differentiated according to the child's age and the language level reached.

Subjects were assessed by taking into account receptive lexical and morphosyntactic aspects of language and perceptive abilities. Language tests included the Peabody Picture Vocabulary test (Italian standardization) (Stella et al, 2000) and the Italian version of TROG-2 (Test for Reception of Grammar, Version 2, by Bishop, 2009).

The TROG-2 is a morphosyntactic comprehension test, administered from four years until adulthood. It allows to assess the understanding of grammar contrasts such as by suffixes, function words and word order. The test consists of 80 items and is divided into several subtests, each composed by 4 items and referred to specific grammar contrasts. The subtests are organized

according to increasing order of difficulty and the test is interrupted when five consecutive subtests are failed.
Perceptive abilities were evaluated by the administration of lists of words and expressions for which the identification percentage was noted. The verbal material was taken from the "Common Evaluation Protocol of the Results in Rehabilitation Audiometry" (Burdo et al., 1994). The test involves the administration of lists of disyllabic words and lists of meaningful expressions. Patients are presented 20 disyllabic words and 10 phonetically balanced expressions. The number of words correctly repeated for each expression are recorded next to each expression, in order to calculate "word scoring" on a percentage basis. Assessment can be performed in silence or with noise. The in-noise test is performed similarly, with the addition of a cocktail party-like noise sent with an S/N ratio +5 dB, the source of which is placed at a distance of one meter behind the patient. As indicated in the Protocol, the S/R report can be modified according to the clinical needs. In our evaluation protocol the in-noise test of auditory abilities was performed by an S/R ratio of + 10dB. A narrow-band noise intensity equal to 60 dB was supplied by an audiometer positioned at a distance of 1 meter behind the patient. The verbal material was proposed by a speech therapist positioned in front of the patient (1 meter) with a voice intensity equal to 70dB (Quaranta et al 1996, Santarelli et al. 2008).

As in study 1, in order to estimate the overall level of linguistic proficiency of participants, a composite score was calculated by assigning each language test, one or two points for a z-score respectively lower or higher than -1.5; total scores ranged from 4 to 8 (8 being the maximum score).

Subject N.	Gender	Handedness	Age at behavioral and Doppler testing (years)	Etiology Hearing Loss	Hearing loss development	Side Hearing Loss
1	M	Right	6,3	CMV	stabile	Right
2	F	Right	11	Unknown	stabile	Left
3	F	Right	5,5	Ear malformation	stabile	Right
4	F	Right	5	Ear malformation	stabile	Right
5	M	Right	9	Unknown	stabile	Right
6	M	Right	6,3	Ear malformation	stabile	Left
7	M	Left	8	Cochlear nerve agenesis	stabile	Right
8	F	Right	12	Unknown	stabile	Right
9	M	Right	12,5	Staphylococcal infection	stabile	Left
10	M	Right	14	Pneumococcal infection	stabile	Left
11	F	Right	3,5	Unknown	stabile	Left

Table 2. Etiological and audiological features of the study sample children with UHL.

The mean chronological age of right sided hearing impairment at the time of clinical and audiological evaluation and of fTCD evaluation was 7.6 years (SD 2.6 y) and of left sided hearing impairment was 9.4 (SD 4.4y).

From an etiological point of view (see table 2), 4 children had an unknown etiology; in 1 case hearing loss was due to CMV infection, in 1 case there was a mutation in 35delG load the Connexin 26 gene (GJB2) heterozygous associated with cochleo-vestibular dysplasia and ectasia of the duct and the endolymphatic sac; 2 cases presented with ear malformations (large vestibular aqueduct associated with incomplete partition type II and common cavities); 1 case had a cochlear nerve agenesis; 1 case suffered from staphylococcal infection during delivery and 1 case from pneumococcal infection.

7.3 Patients *Study 3*

Prelingually deafened adults fitted with CI

The experimental sample consisted of 6 adults with prelingual, long-term deafness, who received a cochlear implant. Originally 7 patients were included in the study, but one did not produce enough useable epochs with fTCD.

The main criteria for inclusion at the pre-implantation evaluation were: profound preverbal sensory-neural hearing loss; no signs of brain damage or major malformations of the cochlea associated with deafness; no signs of either neurological or psychiatric disorders associated with deafness; use of hearing aids and auditory-verbal language training before implantation; full insertion of CI and length of CI use set at 24 months (or more) post cochlear implant activation.

As reported for pediatric patients, also the experimental sample of adults underwent clinical and audiological evaluation before undergoing CI. It included:

- General history and investigation of the etiology of deafness, age at diagnosis, time of prosthesisation and prosthetic results, assessment of the candidate's current amplification and history of hearing aid use.
- Otoscopy and Otomicroscopy
- ABR - Auditory Brainstem Responses
- EOAE Evokated Otoacustic Emissions
- Tonal and vocal audiometry in headphones
- Tonal and vocal audiometry in free field with/without hearing aids;
- Impedance analysis
- Test of auditory skills, by evaluating the recognition rate of disyllabic words and phrases and understanding of sentences. The test was performed in quiet and noise, with signal-to-noise ratio (S/R) +10.
- High-resolution imaging: Petrous - inner ear and brain Magnetic Resonance Imaging (MRI) with contrast medium and Computerized Tomography (CT)

After cochlear implant, all patients underwent:

- Tone audiometry in free field with only cochlear implant or cochlear implant and hearing aids (patients using bimodal stimulation)
- Assessment of the perceptual and linguistic communication level achieved by evaluating the recognition rate of disyllabic words and phrases, and understanding of sentences. The test was performed in quiet and noise, with signal-to-noise ratio (S/R) +10.

Language communication skills were considered normal given the educational level attained, without specific facilities (patients 1-3 and 5 university degree; patients 4 and 6 high school graduation)

Subject N.	Gender	Handedness	Hearing loss etiology	Hearing loss development	PTA in headohones without hearing aid (dB)	Age at the first hearing aids fitting (months)	PTA in free field with hearing aid (dB)	Age at CI (years)	Ear implanted	Bimodal Stimulation	PTA in free field with CI (dB)
					right I left						
1	W	Right	Genetic	progressive	96 I 100	24	50	21	Right	no	25
2	M	Right	Unknown	progressive	>120	11	70	28	Right	no	25
3	M	Right	Antibiotics	progressive	120 I 110	60	40	48	Right	yes	30
4	M	Right	Unknown	progressive	90 I 95	40	39	59	Left	yes	30
5	M	Right	Antibiotics	progressive	100 I 97	48	45	46	Left	no	35
6	W	Right	Unknown	progressive	100 I 110	20	50	22	Left	no	25

Table 3. Etiological and audiological features of the adult sample. Legend: PTA=Pure Tone Audiometry; dB Decibel; CI Cochlear Implant.

	Before CI			After CI	
Subject N.	Recognition rate of words (%)	Recognition rate of phrares (%)		Recognition rate of words (%)	Recognition rate of phrares (%)
1	25	0		70	50
2	0	0		75	60
3	10	0		90	80
4	10	0		70	40
5	0	0		60	0
6	50	0		100	90

Table 4. Recognition rate of disyllabic words and phrases before and after CI

7.4 Functional Transcranial Doppler ultrasonography (fTCD)

All the participants in the three studies underwent fTCD to measure hemispheric activation during a language task, so to obtain a language lateralization index (LI).

For the measurement of cerebral dominance, intra-operative brain mapping (Rutten et al., 2002; Roux et al., 2003) and the intra-carotid amobarbital procedure (IAP) (Wellmer et al., 2008) remain the golden standards. However, due to their invasiveness these procedures are restricted to patients undergoing neurosurgery. For many years, the only way of reliably assessing cerebral lateralization for speech in individuals was the Wada technique, an invasive method in which function of one cerebral hemisphere was transiently disrupted by administration of sodium amytal via a carotid artery (Wada & Rasmussen, 1960). This method has been widely used in presurgical assessment of patients with epilepsy, to establish which hemisphere is dominant for language, but is not feasible for studies with non-clinical samples. Functional magnetic resonance imaging (fMRI) is starting to replace the Wada technique in clinical assessment, but is too expensive for routine use in research studies (Pelletier et al., 2007).

The rapidly increasing body of literature on language lateralization that emerged over the last 15 years therefore largely stems from the application of non-invasive functional imaging techniques to measure language lateralization.

Functional transcranial Doppler has been applied less frequently for the measurement of LIs, despite the high correlation with the golden standard intra-carotid amobarbital test (Knake et al., 2003; Knecht et al., 1998; Rihs et al., 1999). FTCD allows for the determination of cerebral dominance by measuring changes in cerebral blood flow velocity (CBFV) in the right and left middle cerebral arteries (MCAs) during rest and during a word generation task (Deppe et al., 2004). The MCAs provide blood to a large region covering the lateral cortices of the brain, including the frontal, temporal, and parietal language areas (van der Zwan et al., 1993). During a language task, language areas of the dominant hemisphere will be more active than the contralateral areas, inducing an asymmetrical increase in CBFV in the MCAs. The difference in task related increase in CBFV between the left and right MCA can be used as a measure for cerebral dominance (Deppe et al., 2004). Degree and direction of cerebral dominance can be expressed by calculating a LI that describes the relative difference in increased cerebral blood flow between both hemispheres in subjects performing a language task. Functional transcranial Doppler has some major advantages over scanner based neuroimaging techniques: the technique is much cheaper, more comfortable for the subject, non-invasive, easily applicable and its mobility allows measurements outside hospital or research institute settings for investigations of larger groups in the population (Chilosi et al., 2014).

Furthermore classical non-invasive methods such as the dichotic listening paradigm and functional Magnetic Resonance Imaging (fMRI) are not feasible in deaf subjects with CI: for the former, since most patients are monaurally fitted with CI, and for the latter, because high MRI magnetic fields (P1.5 T) may interfere with the magnetic components of the implant.

This method uses ultrasound to measure event-related changes in blood flow in the middle cerebral arteries (MCA). A breakthrough in the use of fTCD for this purpose came from the work of Deppe and colleagues, who devised analytic methods that took into account both the activity from the heart rate cycle, and any differences in overall blood flow between left and right sides, using an analysis package, 'Average' (Deppe et al., 1997). Prior to this, measurements of blood flow in left and right MCAs tended to be too noisy to give reliable results. However, with these more sophisticated techniques, it was possible to detect perfusion asymmetries between the two MCAs of around 1%, and to show reliable left hemisphere activation for speech-based tasks in typical adults.

The method gives high correlations with both the Wada technique (Knecht et al., 1998) and fMRI measures of cerebral lateralization (Deppe et al., 2000; Somers et al., 2011)

Schematic of a TCD measurement

The blood flow velocity in the basal cerebral arteries can be measured by transcranial Doppler ultrasonography. Fig. 10 illustrates how an ultrasound probe is adjusted for the acquisition of the blood flow velocity in the middle cerebral artery. The velocity measurement is based on the Doppler effect.

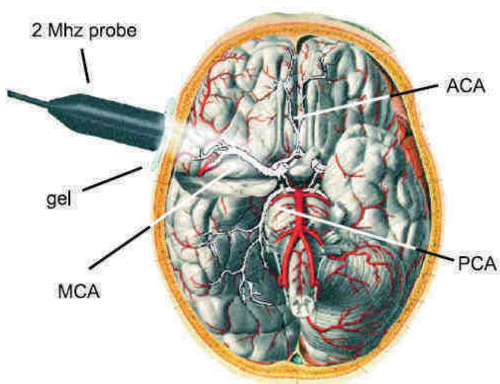

Figure 10. Measurement of the CBFV in the middle cerebral artery (MCA) by TCD. The anterior and posterior cerebral arteries can be insonated by TCD as well. Legend: MCA middle cerebral artery, ACA anterior cerebral artery, PCA posterior cerebral artery

Apparatus

Bilateral blood flow velocity in middle cerebral arteries (MCAs) was measured simultaneously by a commercially available Doppler ultrasonography device (DWL Multidop T2: manufacturer, DWL Elektronische Systeme, Singen, Germany), using two 2-MHz transducer probes mounted on a flexible headset. For the experimental presentation and stimulus design, Presentation software (Neurobehavioral System) was used. Visual stimuli (videoclips) were presented on a standard 15' Dell laptop, which sent parallel port marker pulses to the Multidop system to signal the start of each epoch.

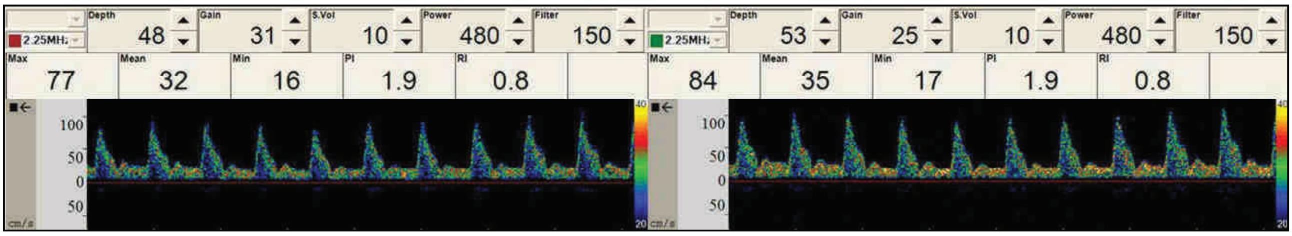

Figure 11. Doppler sonographic diagrams of MCA. The ordinate represents the different Doppler frequency. The abscissa reflects a time of about 10s. Legend: MCA middle cerebral artery

Data recording

Cerebral blood flow velocity (CBFV) in the MCAs was recorded bilaterally during the whole experiment. Insonation techniques including correct identification and depth adjustment have been published elsewhere (Ringelstein et al., 1990). For the identification of the beginning of each trial (''epochs''), a marker signal was generated by the animation presentation software and recorded simultaneously with the CBFV signals.

fTCD Language paradigm

Language lateralization was assessed by the animation description task (Freeze Foot Story), developed by Bishop et al. (2009), which includes 30 twelve-second silent videoclips. All the original animated .avi files were kindly provided to us by Professor Bishop and were sequenced into a single movie, run by ''Presentation Program''.

As described by the Authors (Bishop et al., 2009), during each videoclip the child was asked to silently observe a 12-s cartoon, and then, cued by an acoustic signal and a visual question mark, to describe for 10 s what he/she had seen; each trial ended with an 8-s silent rest period. The 12 s during which the participant watches the videoclip constitute the baseline period, whereas the 10-s description time is considered the activation period. The whole experiment had a duration of about 30 min for each subject.

The Multidop system records the activation and baseline times. The mean velocity of blood flow during the activation period is then compared to that of the baseline.

In order to familiarize the participants with the experimental fTCD task, each child took part in a training session consisting of an animated movie representing a part of the complete story (5 of the original videoclips). The observation and description times were the same as in the fTCD condition, that is 12 and 10 s, respectively. Children were usually accompanied by a parent who sat behind them.

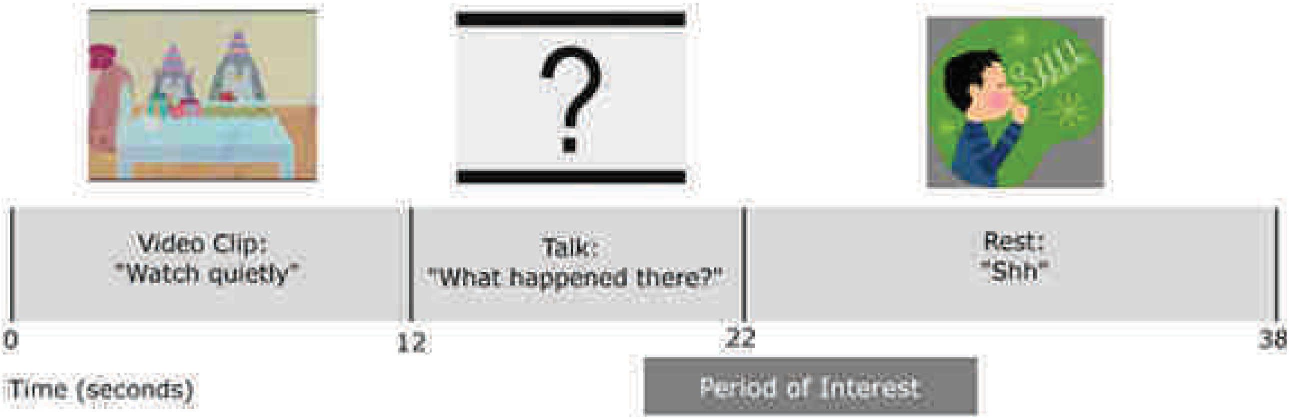

Figure 12. Schematic outline of experimental trial in children

For adults with good literacy, we used the Rhyme generation task with written stimuli, which was created based on the one used for the acquisition of fMRI, validated on a group of Italian regular readers (Pecini et al., 2008). Participants were instructed to read a two-syllable word and silently find a new word rhyming with it, to avoid motion artifacts. A total of 25 stimuli were presented, at a frequency of 0.25 Hz (1/4 sec), 6 words for block (image 13). It is followed by a rest period of 20 seconds, during which the patient is asked to close eyes. A beep identifies the end of the rest period and the restart of the task. The paradigm, constituted by 25 cycles of duration of 44 seconds each, takes about 20 minutes.

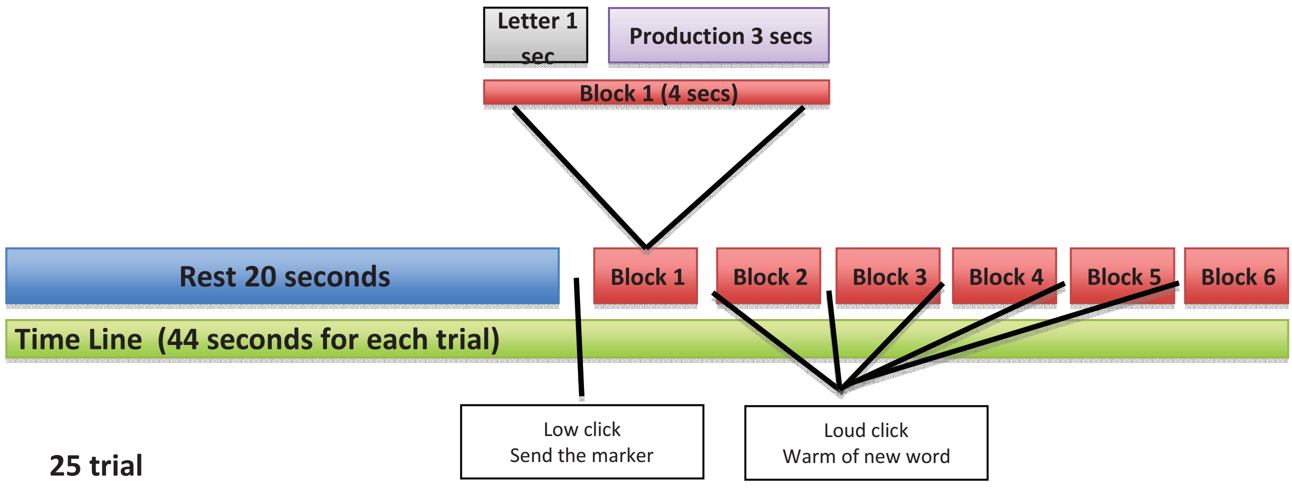

Figure 13. Schematic outline of experimental trial in adults

Data analysis

The fTCD data were analyzed with the Average software (Deppe et al., 1997). CBFV data was segmented into epochs related to marker signals, and averaged.

Epochs containing CBFV values outside the range of 60–140% of the mean were excluded as measurement artifacts. Transformation to relative units was performed using the following formula:

$$dV = 100 \frac{V(t) - V_{pre.mean}}{V_{pre.mean}}$$

where V(t) is the CBFV over time and Vpre.mean is the mean velocity during the 12-s precueing interval.

As a measure for the quantification of the perfusion differences between the left and right hemisphere, the fTCD lateralization index (LI) was calculated with the formula:

$$\mathrm{LI} = \frac{1}{t_{\mathrm{int}}} \int_{t_{\max} - 0.5t_{\mathrm{int}}}^{t_{\max} + 0.5t_{\mathrm{int}}} \Delta V(t)\mathrm{d}t$$

where DVi(t) = dVi(t)left _ dVi(t)right is the difference between the relative velocity changes of the left and right MCAs. The time point tmax represents the latency of the absolute maximum of DV(t) with in the activation intervals (4–10 s); as the integration interval, a time period of tint = 2 s was chosen. The Li quantifies the average difference of relative CBFV changes in the activation period in comparison to baseline in percent. A positive value corresponds to greater left than right hemisphere activation indicating left hemisphere asymmetry for language, while a negative value indicates right hemisphere lateralization. The LI standard error of the mean (SEM) represents the variability between the laterality indexes over the accepted epochs, thus, a lower SEM of the lateralization index accounts for higher performance continuity and higher quality of the Doppler signal throughout the investigation.

Following Knecht et al. (1998) hemispheric dominance was classified as left or right when mean LI deviated more than two standard errors from 0, for lower LI deviation values lateralization was considered uncertain or bilateral.

The internal consistency of LI measures was tested by split-half and odd–even Pearson's product moment correlation coefficients.

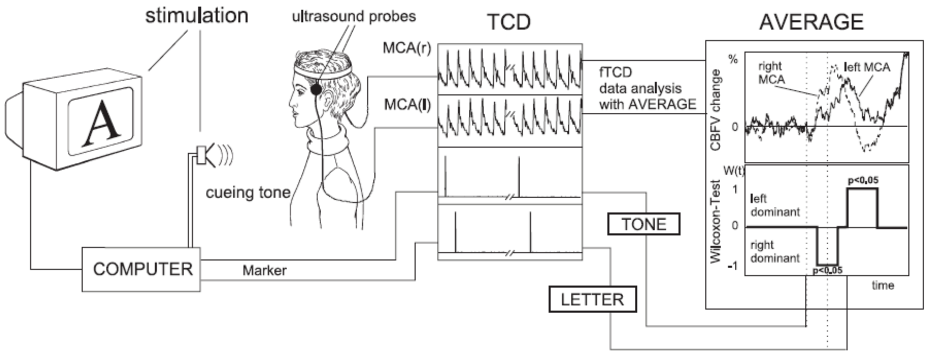

Figure 14. Setup for the determination of the hemispheric dominance of speech (from Deppe et al, 1997)

8. STATISTICAL ANALYSES

For metric measures, such as LI, groups were compared by the use of T-test for independent samples or ANOVA and Levène test for testing variability. T-test for dependent samples was used to compare 24 CI subjects with 24 paired controls subjects.

For ordinal measures, such as language Composite scores, non parametric (Mann Whitney) analyses were used to compare groups. Non-parametric ANCOVA (analysis of covariance) was used to isolate single effects if covariance was detected. Pearson's and Spearman's correlation coefficients were computed respectively for metric and ordinal measures.

Multivariate modeling (stepwise regression) with language outcome as dependent variable and age of CI and CI side as independent variables was used to isolate effect of single variables.

For comparison between frequencies within groups, Fisher test was used if contingency tables were 2x2 and Chi2 for larger contingency tables.

Statistical tests were considered as significant if relative p was lower than 0,05. All analyses were carried out using IBM SPSS Statistics, version 20.0.

9. RESULTS

9.1 *Study 1*

Children with congenital severe to profound bilateral hearing loss fitted with CI

9.1.1 - Language Lateralization Indices

The mean laterality index (LI) of patients with CI was 2.03 (SD 4.06), indicative of a prevalent left hemisphere activation during the language task. Mean laterality indices in controls and patients with CI did not differ significantly (t= 0.03, p=0.9).

If side of implantation was considered, mean LI values of right-ear implanted children differed significantly from 0 (M 2.7, SD 3.9; (t=3,2, df=25, p=0,03), whereas left-ear implanted children showed more inconsistent results and the mean LI did not differ significantly from 0 (M 0.27, SD 0.8; t=0,44, df=9, p=0,67).

Though age at implantation differed between children with right and left-ear CI, the effect of side on LI was statistically significant, when adjusted for age at implantation (ANCOVA, p = 0.008).

On a categorical level, 53% (19/36) of subjects showed a positive LI, indicative of left hemisphere dominance (LH), 17% (6/36) had right hemisphere dominance (RH) and 31% (11/36) were uncertain. The distribution in control subjects (75% left, 17% right and 8% uncertain) are similar to that reported in the literature for typically developing children (Bishop et al., 2009; Haag et al., 2010; Lohmann et al., 2005).

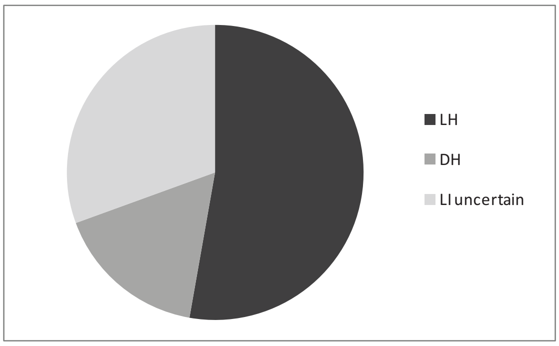

Figure 15. Distribution of hemispheric dominance in sample study.

Legend: LH=Left Hemisphere Activation; RH= Right Hemisphere Activation; LI=Lateralization Index

When taking into consideration direction (positive or negative values), and not magnitude of LIs, 27/36 (75%) had a positive LI and 9/36 (25%) a negative LI.

Comparison between age at implantation of deaf subjects with negative and positive LIs did not reveal any statistically significant difference (Mann-Whitney U=42.5, p=0.46).

Hemispheric activation was contralateral to the side of the implanted ear (LH with right ear CI, and RH with left ear CI) in 17/36 children (47,3%), and ipsilateral (RH with right-ear CI and LH with left-ear CI) in 8/36 children (22,3).

By taking into consideration direction (positive or negative values), the frequency of activation was controlateral in 25/36 children (69,5%), and ipsilateral in 11/36 children (30,6%).

Furthermore, the frequency of controlateral activation was significantly higher in right- than in left-ear implanted children (Chi square = 5.029, df = 1, p = 0.02).

About 53,8% (14/26) of right-ear implanted children presented with contralateral activation in the left hemisphere, 34,6% (9/26) were uncertain and 11,5% (3/26) activated the ipsilateral right hemisphere. In the case of left-ear implantation, 30% of children activated the controlateral right hemisphere, 50% showed left hemisphere activation (ipsilateral to the implanted ear) and 20% presented an uncertain activation.

When considering direction (positive or negative values), and not magnitude of LIs, 80,7% (21/26) of right-ear implanted children presented a positive LI and 19,2% (5/26) negative LI. In children with left ear CI, 60% (6/10) had positive LI and 40% (4/10) negative LI.

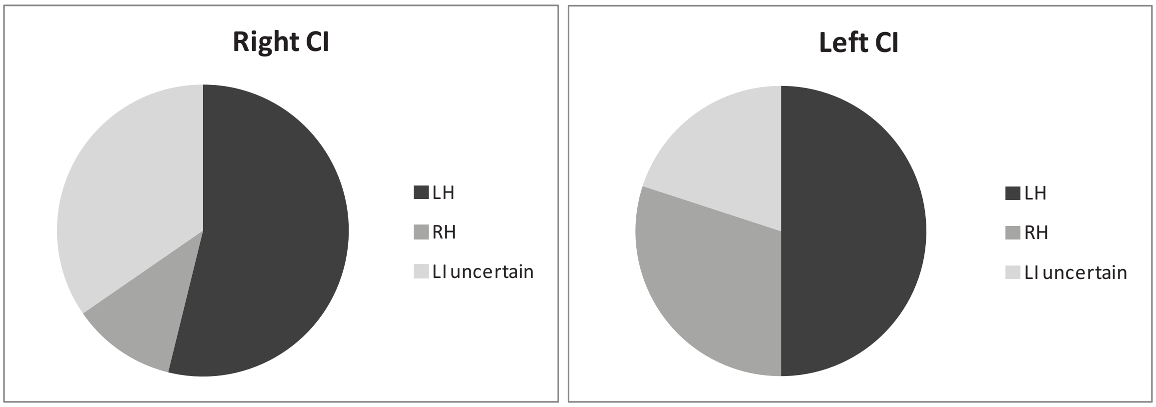

Figure 16a-16b. Distribution of hemispheric dominance in right- and left- ear implanted children.
Legend: LH=Left Hemisphere Activation; RH= Right Hemisphere Activation; LI=Lateralization Index

LI in Early and Late implanted subjects

In order to evaluate the effect of age at implantation, we divided the patients in an "early" and a "late" implanted group (before and after 4 years of age).

The first group, included 26 children (13 females and 13 males), with a mean chronological age of 6.9 years at the time of evaluation and a mean age at implantation of 2.2 y, (SD 0.9, range 1.1-3.9 y).

The second group included 10 children (7 females and 3 males), with a mean chronological age of 11.5 years, who received CI after 4 years (mean age at implantation of 6.6 y, DS 2.2, range 4-10.4 y).

In the "early" group, the side of CI was right in 21 subjects and left in 5, and the distribution of lateralization indices was 46% left, 13% right and 38 % bilateral.

In particular, in the case of right CI left lateralization occurred in 57%, right in 38% and bilateral in 4%. In the case of left CI left hemispheric lateralization occurred in 20%, right in 60% and bilateral in 20%.

Finally, approximately 57.7% of patients in the "early" group presented with hemispheric activation contralateral to the implanted side.

In the "late" group, the side of CI was right in 5 patients and left in 5. The distribution of lateralization indices was 70% left, 20% right and 10% bilateral.

In particular, 40% of subjects with right CI had left, 40% right and 20% bilateral activation.

All patients with left CI had left hemispheric lateralization.

Finally, about 30% of patients in the "late" group presented with a hemispheric activation contralateral to the implanted side.

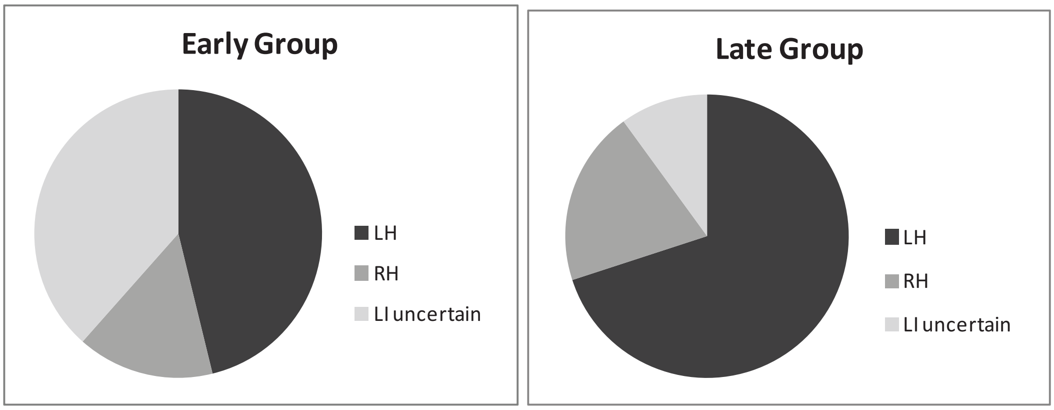

Figure 17a-17b. Distribution of hemispheric dominance in early and late group.

Legend: LH=Left Hemisphere Activation; RH= Right Hemisphere Activation; LI=Lateralization Index

Activation of the contralateral right hemisphere in the presence of left-ear CI occurred in 4 out of 5 subjects of the early group, whereas all the children of the late group who received a left-ear CI showed an ipsilateral activation of the left hemisphere.

9.1.2 - *Linguistic Outcome*

Evaluation of language outcome confirmed that CI participants with both left and right hemisphere activation performed significantly lower than controls ($U = 96$, $p < 0.01$).

The language composite score varied from 4 to 8 , with a mean score of 5.7 (SD 1.6).

Figure 9 shows the distribution of composite scores by number of subjects.

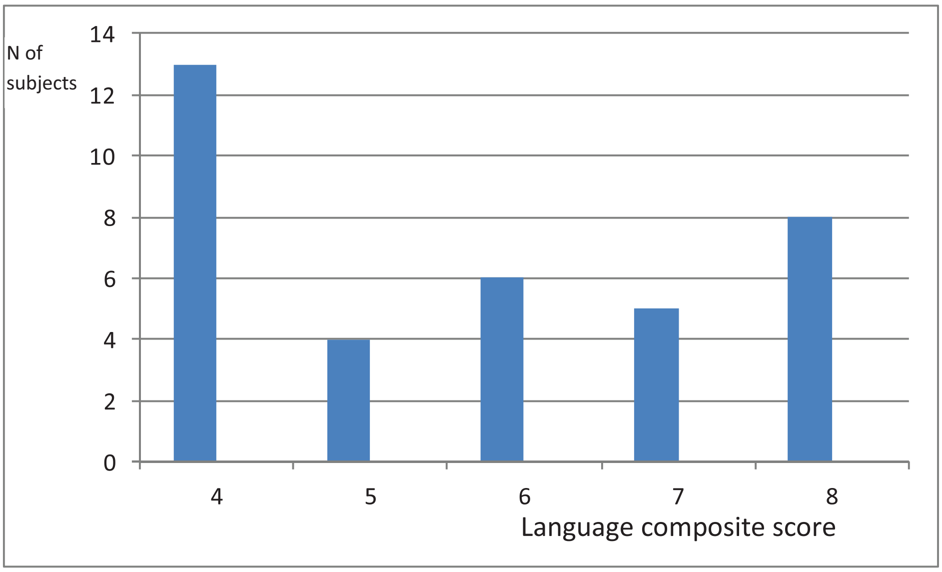

Figure 18. Distribution of language composite scores in the sample

The composite scores of implanted children with left hemisphere activation was higher (M 6,10, SD1,16, range 4–8) compared to right hemisphere activation (M 4,6, sd 1, Range 4–8), but the difference was not statistically significant (Mann Whitney U=105, p=0.5).

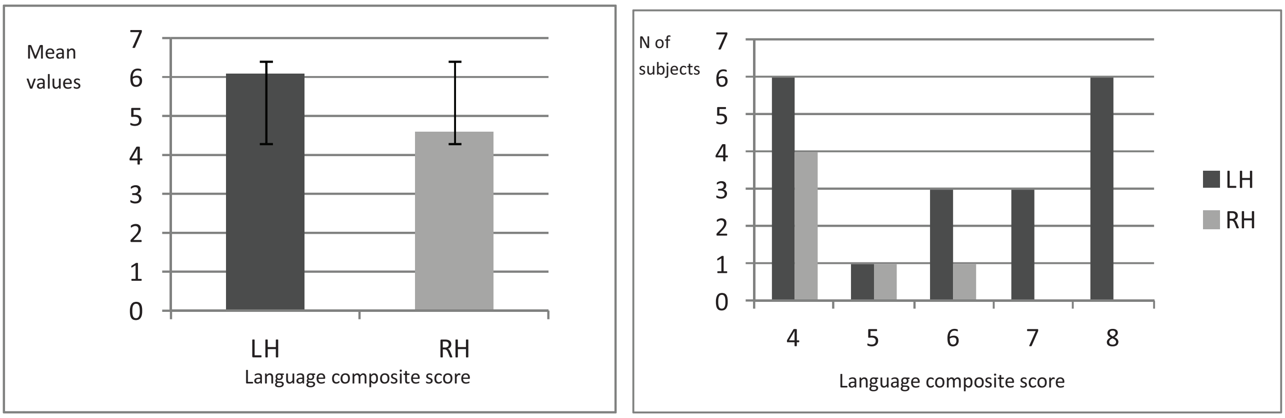

*Figure 19a-19b.*ean values and distribution of language composite scores in left and right hemisphere activation.
Legend: LH=Left Hemisphere Activation; RH= Right Hemisphere Activation; LI=Lateralization Index. Bars represent SD.

However, as shown in figure 19b, differently from subjects with left hemisphere activation, none of subjects with right hemisphere activation attained the maximum composite score.

Therefore, we compared subjects scoring 4-5 with those scoring 7-8, and we found a statistically significant difference between the two groups (Fisher test p=0.03).

With regard to CI side, language composite scores varied in relation to <u>side of implantation</u> (right CI: M 6.19, SD 1.62; left CI: M 4.7, SD 0.94) for a significantly lower language performance in left- compared to right-ear implanted subjects (Mann Whitney U=67, p=0.026).

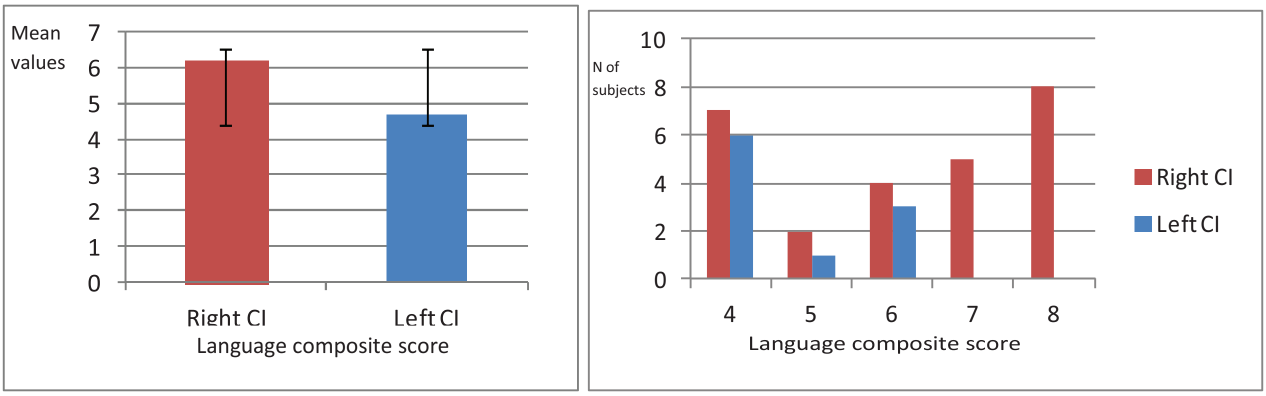

Figure 20a-20b. Mean values and distribution of language composite scores in right- and left- ear implanted children.
Legend: LH=Left Hemisphere Activation; RH= Right Hemisphere Activation; LI=Lateralization Index. Bars represent SD.

Taking into consideration language performance on each single test, statistically significant differences were found in relation to side of implantation only in receptive vocabulary (PPVT score) for better performances of right- compared to left-ear implanted children (Mann Whitney U=68, p=0.038).

	Right CI	Left CI
	mean (SD)	mean (SD)
PPVT (*standard score*)	76.1 (21.4)	58.6 (29.4)
TCGB (*z-score*)	-2.5 (3.2)	-4.6 (4.6)
INPE high frequency (*z-score*)	-0.8 (2.4)	-1.46 (1.5)
INPE low frequency (*z-score*)	-1.4 (2.1)	-2.2 (0.9)
LCS (raw score)	6.1 (1.6)	4.7 (9.4)
GASS (*level*)	4.2 (0.1)	4.1 (0.8)

Table 5. Language scores of each test. Legend: Ppvt= Peabody Picture Vocabulary; Tcgb= Test of Comprehension of Grammar for children; Inpe= One Word Picture Vocabulary; LCS= Language composite score; GASS= Grid for the Analysis of Spontaneous Speech.

Language composite scores varied also in relation to <u>age at implantation,</u> with a statistically significant inverse correlation between age at implantation and language scores (Spearman's rho = -0.33, p = 0.05).

Moreover, early (M 6.1, 1.6 SD) implanted children scored significantly higher than late (M 4.7, 1.05 SD) implanted ones (t=2.1, p=0.017) and had a quite better grammar comprehension, the difference between TCGB scores approaching statistical significance (t =1.8, p 0.071).

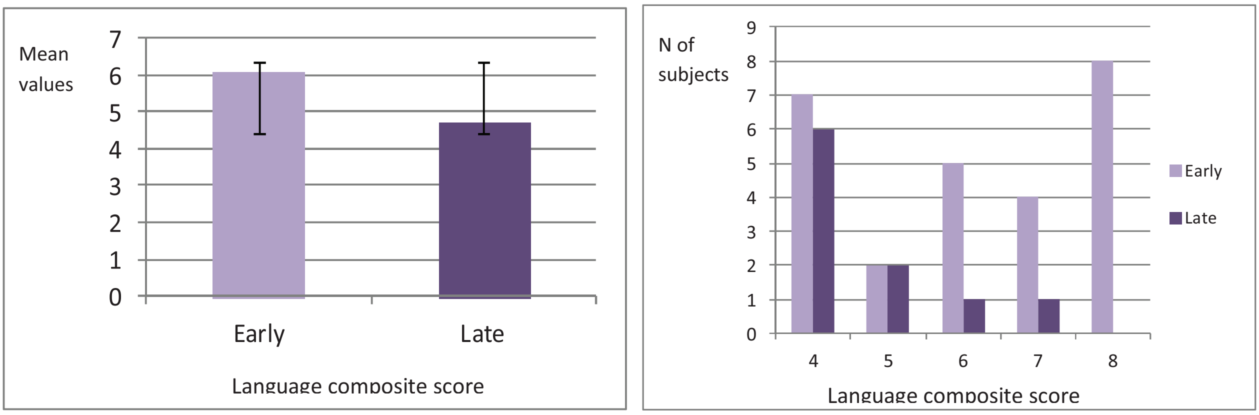

Figure 21a-21b. Mean values and distribution of language composite scores by number of subjects in the early and late group. Bars represent SD.

The number of children with low language scores (4-5) and those with high score (7-8) was significantly different in the two groups (Fisher test p=0.02), for a better performance in the early group.

EARLY GROUP:	**Right CI** mean (SD)	**Left CI** mean (SD)	LATE GROUP:	**Right CI** mean (SD)	**Left CI** mean (SD)
PPVT *(standard score)*	74.7 (22.2)	66.8 (30.9)	PPVT *(standard score)*	86 (13.5)	50.4 (28.8)
TCGB *(z-score)*	-1.8 (3.4)	-2.8 (4.1)	TCGB *(z-score)*	-2.9 (2.4)	-6.7 (4.7)
INPE high frequency *(z-score)*	0.7 (2.5)	-0.5 (0.5)	INPE high frequency *(z-score)*	-1.7 (1.4)	-3 (1.7)
INPE low frequency *(z-score)*	-1.3 (2.2)	-2.1 (0.3)	INPE low frequency *(z-score)*	-1.9 (1.8)	-2.8 (1.3)
LCS (raw score)	6.2 (1.7)	5 (1)	LCS (raw score)	5 (1.2)	4.4 (0.9)
GASS *(level)*	4.3 (1.1)	4.4 (0.9)	GASS *(level)*	4 (0.7)	3.9 (0.7)

Table 6a-6b. Language scores of each test in early and late group. Legend: Ppvt= Peabody Picture Vocabulary; Tcgb= Test of Comprehension of Grammar for children; Inpe= One Word Picture Vocabulary; LCS= Language composite score; GASS= Grid for the Analysis of Spontaneous Speech.

In the "early" group, the performance of left ear implanted children was lower than that of right implanted ones, even if it did not reach significance.

In the "late" group, there was a significant difference in receptive vocabulary (PPVT score) between right and left ear implanted children (t=2.35, p=0.05), with the advantage of the first ones.

By performing a linear regression analysis with language outcome as dependent variable and age at CI and CI side as independent variables, CI side showed higher statistical significance (F=6.2, p=0.017) than age in the regression model (F=5.8, p=0.021) and in step-wise model only side of CI remain as significant factor on composite language outcome.

The effect of side of CI on language composite score was still significant also when ANCOVA was computed with age at CI as covariate.

	LCS	PPVT	TCGB	INPE high frequency	INPE low frequency	GASS
1	8	94	1,2	4	1,4	5
2	8	81	-0,28	-0,35	0,6	5
3	8	74	0,2	1,42	-0,97	5
4	4	66	-2,33	-1,73	-2,8	2,5
5	6	68	-0,6	-0,17	-2,8	5
6	7	60	-0,87	0,2	0,02	5
7	8	77	0,09	1	-0,7	5
8	8	80	0	0,79	-0,92	5
9	5	55	-1,84	-0,36	-2,26	5
10	4	46	-9,1	-1,03	-1,96	4
11	4	31	-7	-4,9	-4,72	3,5
12	6	119	0,94	0,17	-1,82	5
13	4	44	-4,94	-0,39	-2,57	5
14	6	94	0	--	-1,7	5
15	5	100	-3,17	--	-1,68	4
16	4	66	--	-0,96	-2	4
17	6	72	0,87	--	0,8	5
18	4	52	-6,56	-2,45	-2,54	5
19	8	96	0,5	1,04	0,06	5
20	8	116	0,5	0,63	0,25	5
21	7	115	-2,68	1,69	3,6	5
22	4	50	-6	-6	-6	2
23	4	40	-10	-2,37	-0,79	4
24	8	100	1,81	2,23	0,85	5
25	4	26,47	-10	-3	--	3
26	4	100	-8,6	-5	--	3
27	4	35	-10	-1,7	-3	4
28	6	74	-1,29	-1,87	-2	5
29	4	50	-3	-1,8	-3	3,5
30	7	75	0,5	0,6	0,7	5
31	4	35	-6	-6	-6	2
32	7	70	0,13	1,53	-2,31	5
33	5	73	-2,5	-1,15	-2,8	4
34	4	--	-6	-3,16	-4,7	3
35	7	85	0	0	0	5
36	6	70	0,5	-1	--	3

Table 7. Communicative-language assessment of CI sample. Legend: Ppvt= Peabody Picture Vocabulary; Tcgb= Test of comprehension of Grammar for children; Inpe= One Word Picture Vocabulary; LCS= Language composite score; GASS= Grid for the Analysis of Spontaneous Speech.

Subject N.	Ear implanted	LI value	SD	LI side
1	Right	3,34	1,35	Left
2	Right	3,03	1,44	Left
3	Right	-0,84	0,61	Uncertain
4	Right	2,75	0,88	Left
5	Right	-4,06	0,72	Right
6	Right	1,18	0,63	Uncertain
7	Right	1,35	0,89	Left
8	Right	3,43	1,28	Left
9	Right	11,08	1,57	Left
10	Right	4,55	0,59	Left
11	Right	2,29	0,82	Left
12	Right	13,00	0,92	Left
13	Right	2,06	1,20	Left
14	Left	0,49	0,71	Uncertain
15	Left	-6,48	0,51	Right
16	Left	4,56	0,77	Left
17	Left	-3,54	0,84	Right
18	Left	-3,07	0,79	Right
19	Left	2,52	1,20	Left
20	Left	5,61	2,89	Left
21	Right	-2,11	2,47	Uncertain
22	Right	4,97	2,95	Uncertain
23	Right	-4,30	0,70	Right
24	Right	4,83	2,22	Uncertain
25	Left	2,46	0,58	Left
26	Right	5,01	0,85	Left
27	Left	2,88	0,37	Left
28	Right	2,30	0,96	Uncertain
29	Right	1,16	0,74	Uncertain
30	Right	3,20	0,55	Left
31	Right	1,07	0,70	Uncertain
32	Right	7,18	0,58	Left
33	Right	2,13	0,70	Uncertain
34	Right	-2,91	0,81	Right
35	Right	4,71	1,28	Left
36	Left	-2,66	2.39	Uncertain

Table 8. LI value of the CI sample. Legend: LI=Lateralization Index

9.2 *Study 2*

Children with severe to profound unilateral hearing loss (UHL)

9.2.1 -Language Lateralization Indices

At the time of fTCD and clinical evaluation the mean chronological age of the experimental sample was 8.4 (SD 3.4) and of the controls was 8.5 y (SD 3.4 y) and did not significantly differ (t=0.069, p=0.9).

Mean laterality indices in patients with UHL was 1.1 (SD 4.1) and in controls 2.1 (SD 2.3), indicative of a prevalent left hemispheric activation during the language task but the difference between the two groups wasn't statistically significant (t=0.7, p=0.5).

LI variability in the experimental and control group appeared comparable (Levene's test F 3.5 SD 0.073.).

With regard to the side of hearing loss, children with right UHL had a mean LI value of 2.43 (SD 2.5) , while in subjects with left UHL it was -0.31 (SD 3.38).

On a categorical level, 54,5% (6/11) of children with UHL showed a positive LI, indicative of left hemispheric dominance (LH), 36,4% (4/11) had right hemispheric dominance (RH) and 9% (1/11) were uncertain.

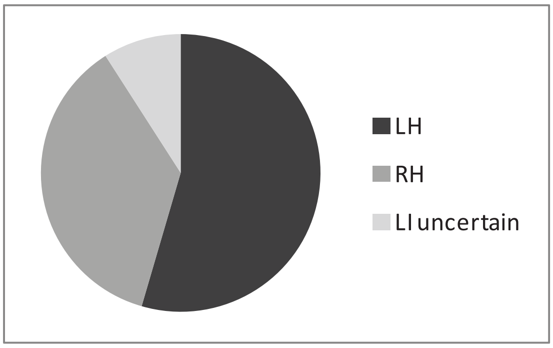

Figure 22. Distribution of hemispheric dominance in patients with UHL.
Legend: LH=Left Hemisphere Activation; RH= Right Hemisphere Activation; LI=Lateralization Index

Hemispheric activation was controlateral to the ear with normal hearing threshold in 4/11 (36.4%), ipsilateral in 6/11 (54,5%) children, and uncertain in one.

With regard to LI direction, we didn't found any statistically significant difference between patients and controls in distribution of LIs (Pearson Chi square 2.3). However, 4/11 children with UHL, but only 1/11 of controls showed right hemisphere lateralization.

The distribution of LIs in subjects with right UHL was 66.7% (4/6) left and 33.3% (2/6) right.

The distribution of LIs in subjects with left UHL was 40% (2/5) left, 40% (2/5) right, and 20% (1/5) uncertain.

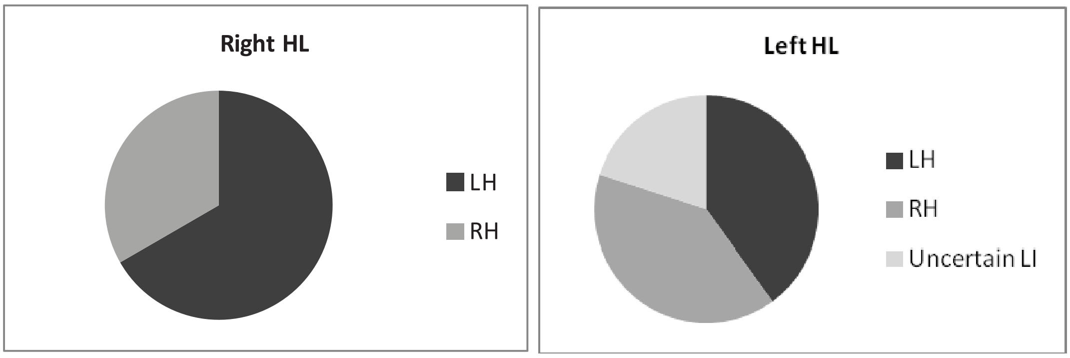

Figure 23a-23b. Distribution of hemispheric dominance in right- and left- unilateral hearing loss.
Legend: HL= Hearing Loss; LH=Left Hemisphere Activation; RH= Right Hemisphere Activation; LI=Lateralization Index

9.2.2 -Linguistic and Cognitive Outcome

Evaluation of language outcome revealed that subjects with UHL performed significantly lower than normal controls (t test t=2.09, df 20, p=0.049).

Within UHL subjects, the composite score of children with left hemisphere activation was higher (M 7.5, sd 0.8, range 7–8) than the composite score of patients with right hemisphere activation (M 6.5, sd 1.9, **r**ange 4–8), but the difference wasn't statistically significant (t=1.16, df 8, p = 0.27).

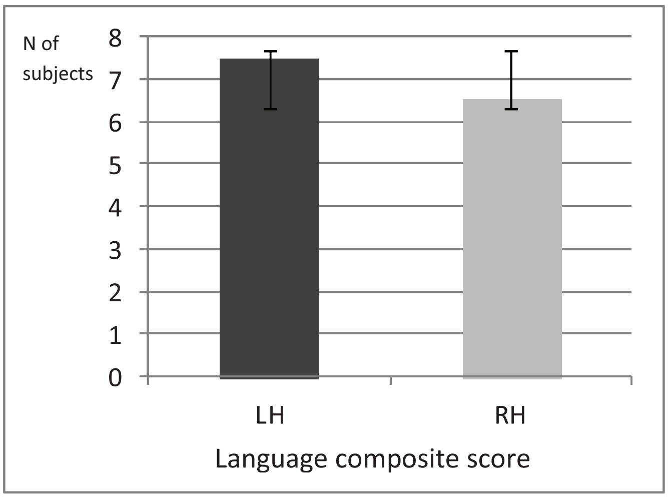

Figure 24. Mean language composite score in subjects with left and right hemisphere activation.
Legend: LH=Left Hemisphere Activation; RH= Right Hemisphere Activation; LI=Lateralization Index. Bars represent SD.

For what concerns cognitive performances in UHL subjects, no statistically significant differences were found between subjects with left and right LI hemisphere activation, either when computing mean values for each cognitive test or when comparing absolute frequencies of subjects obtaining a standard score less or more than 90 in each single test.

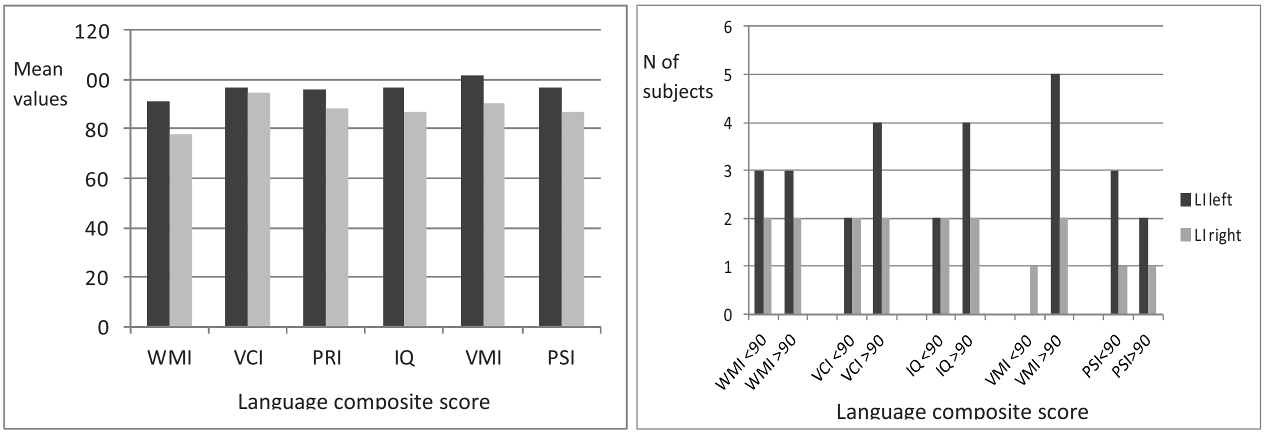

Figure 25a-25b. Mean values and distribution of test in subjects with left and right hemispheric dominance.
Legend: IQ=Intelligence Quotient; PRI=Perceptual reasoning Index; WMI=Working Memory Index; PSI=Processing Speed Index; VCI=Verbal Comprehension Index; VMI= Visual Motor Integration; LI=Lateralization Index.

Furthermore language composite scores varied in relation to side of hearing loss (right ear: M 6.5, SD 1.51; left ear: M 8, SD 0.0) for a significantly lower language performance in right - compared to - left hearing loss subjects (U=5, p = 0.034).

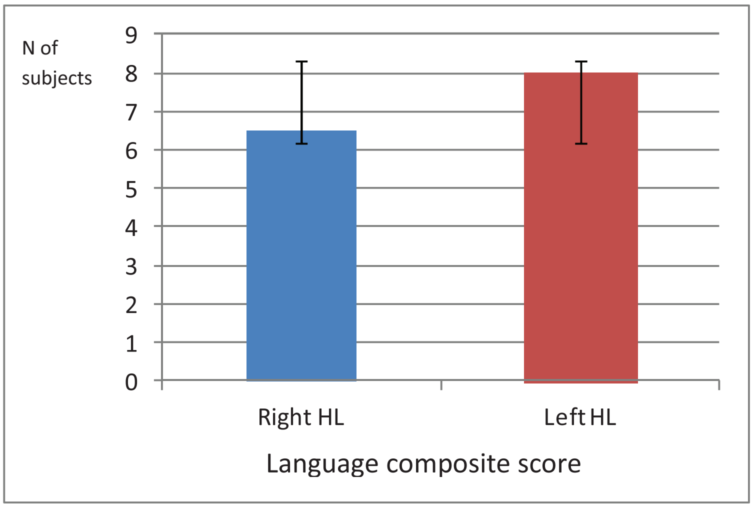

Figure 26. Mean language composite score in subjects wit left and right hearing loss (HL). Bars represent SD.

Subjects with right UHL scored lower than left UHL in each single test of cognitive abilities (table 9), but the differences were statistically significant only for WMI (t=-3.2 p=0.0094) and IQ (t=-2.8 p= 0.021).

This data was confirmed also taking into consideration the absolute frequency of right and left UHL subjects obtaining a standard score more or less than 90 on each test. Left UHL subjects showed more frequently than right UHL scores above 90 for WMI (χ^2=7.6, p=0.0057), IQ (χ^2=5.23, p=0.02) and VCI (χ^2=5.23, p=0.02), but, interestingly, not for non verbal tests such as VMI (χ^2 = 0.917, p=0.33), PSI (χ^2=2.3, p=0.12) and PRI (χ^2 =2.101, p=0.07).

	Right HL	Left HL
	mean (SD)	mean (SD)
WMI	75.67 (17.6)	103 (6)
VCI	89.17 (21.8)	108.2 (12.8)
PRI	89.67 (17.6)	102.4 (11.9)
IQ	83.5 (17.8)	108.8 (9.5)
VMI	92.17 (17.4)	107.8 (7.6)
PSI	93.4 (20.4)	105.67 (16.7)

Table 9. Legend: IQ=Intelligence Quotient; PRI=Perceptual reasoning Index; WMI=Working Memory Index; PSI=Processing Speed Index; VCI=Verbal Comprehension Index; VMI= Visual Motor Integration; LI=Lateralization Index.

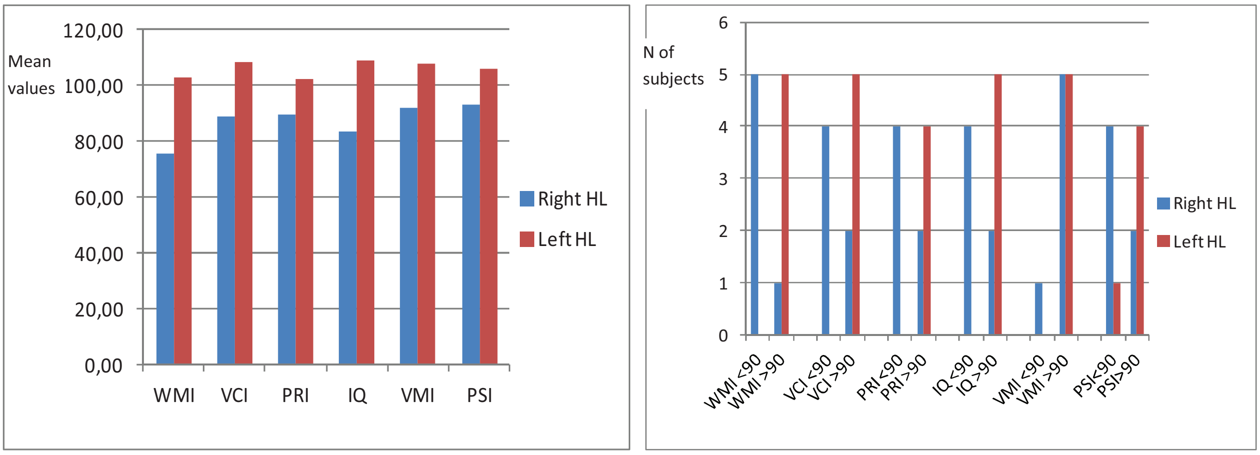

Figure 27a-27b. Mean values and distribution of test scores in subjects with left and right hearing loss
Legend: IQ=Intelligence Quotient; PRI=Perceptual reasoning Index; WMI=Working Memory Index; PSI=Processing Speed Index; VCI=Verbal Comprehension Index; VMI= Visual Motor Integration; LI=Lateralization Index.

Finally, the language composite score was significantly correlated with verbal subtests of cognitive evaluation, in particularly WMI (Spearman's rho = 0.9, p<0.01) and VCI (Spearman's rho = 0.7, p=0.015).

Subject N.	Side Hearing Loss	PPVT standard score	LCS	IQ total	PRI	WMI	PSI	VCI	VMI	LI value	SD	LI side
1	Right	94	7	87	111	82	85	80	96	8,69	0,9	Left
2	Left		8	119	122	112	126	102	118	1,29	1,4	Uncertain
3	Right	74	6	75		65		75		-2,86	2	Right
4	Right		6	77	76	73	126	66	101	1,95	0,3	Left
5	Right	118	8	110	111	85	103	122	117	6,32	0,8	Left
6	Left	103	8	96	93	106	85	102	98	1,68	0,7	Left
7	Right	115	8	94	85	100	85	110	96	2,56	0,8	Left
8	Right	57	4	58	69	49	68	82	59	-2,1	0,8	Right
9	Left	120	8	115	100	100		115		3,32	1,2	Left
10	Left	100	8	100	104	97	106	94	110	-3,89	1,1	Right
11	Left	--	8	114	93	100		128	103	-3,97	1	Right

Table 10. Language and cognitive assessment of children with UHL and LI value and side. Legend: Ppvt= Peabody Picture Vocabulary; TROG= Test for Reception of Gramma-Version 2; LCS= Language composite score; IQ=Intelligence Quotient; PRI=Perceptual reasoning Index; WMI=Working Memory Index; PSI=Processing Speed Index; VCI=Verbal Comprehension Index; VMI= Visual Motor Integration; LI=Lateralization Index; na= not available; ne= not evaluable.

It's interesting to remark that the effect of side of acoustic afference on language composite score was maintained when UHL and CI subjects were grouped together (right ear CI and left UHL: M 6.48 SD 1.6; left ear CI and right UHL: M 5.37 SD 1.45), with a difference between right and left ear afference that approached statistical significance (U =178, p =0.078).

In contrast, the effect of side of hemispheric activation (LI) on language composite score was not significant (U=186, p=0.38).

9.3 *Study 3*

Prelingually deaf adults fitted with CI

Testing was performed preoperatively and annually after implantation.

	Before CI				After CI		
	LI value	SD	LI side	Ear implanted	LI value	SD	LI side
1	2,23	0,88	Left	Right	1,97	0,73	Left
2	-5,69	3,02	Uncertain	Right	-3,35	1,98	Uncertain
3	2,41	0,78	Left	Right	--	--	--
4	4,76	1,79	Left	Left	2,6	0,54	Left
5	3,1	1,16	Left	Left	2,28	0,53	Left
6	3,08	0,87	Left	Left	2,15	0,67	Left

Table 11. LI value before and after CI of the sample study. Legend: LI=Lateralization Index; CI=Cochlear Implant.

Preoperatively, five adult of six patients presented with left hemisphere lateralization and one with an uncertain lateralization.

fTCD evaluation performed before CI, showed that among adults with right CI (3/6) one had left, one had right and one an uncertain lateralization. Patients with left CI (3/6), all showed a left hemispheric lateralization. Therefore, fTCD performed 12 months after CI, indicated no change of lateralization in 5 subjects and in one case the recorded epochs were not sufficient to compute LI for technical reasons.

10. DISCUSSION

10.1 *Study 1*

The current study addresses the question of how hemispheric asymmetry for language develops in children with profound sensorineural hearing loss, who receive monoaural cochlear implantation by using functional transcranial Doppler ultrasound (fTCD).

Mean LIs of deaf patients and controls were comparable in terms of prevalent left hemisphere activation during speech that approached values reported in literature for normal-hearing children (Bishop et al., 2009; Haag et al., 2010; Lohmann et al., 2005). However, in our experimental sample there was a greater representation of subjects with uncertain LI compared to the data reported in literature for typically developing children. This difference seems to be even more evident in the early compared to the later implanted group, although no statistical significance was reached. This data suggest that early reafferentation facilitates the expression of vicariant plastic phenomena, with greater possibility of shifting linguistic dominance and therefore, partly avoiding the genetic constraints of left hemispheric dominance. However, the issue appears to be more complex, because early implanted children were also assessed at a lower chronological age. As a matter of fact, a qualitative analysis of the characteristics of the subjects showed that there was a greater representation of patients with inferior chronological age at the time of evaluation. Moreover age of evaluation was significantly different ($t=2.4$, $p=0.02$) between subjects showing clear laterality, right or left (LH - RH: M 9.9, SD 3.9, $n = 25$), and those showing uncertain laterality (M 6.07 SD 2.1, $n= 11$). This might suggest that LI measurement may be influenced by the age at which the test is performed; this could occur because children of different ages use different cognitive strategies to perform the same task, or because lateralization is a process that increases at a certain age. Few studies are indeed relative to children with young age at the evaluation (Haag et al., 2010; Bishop et al., 2009) and this issue might not have been yet clarified.

A third option, also resulting from the few studies of lateralization using this technique, is that lateralization has different gradients according to the task used (Badcock et al., 2012; Haag et al., 2010; Stroobant et al., 2009; Bishop et al., 2009). Indeed, Bishop et al (2009) found a significant correlation among LIs from different tasks (Word Generation, Picture Description and Animation Description). This is not surprising, given the different linguistic and cognitive operations involved in the tasks. Different regions in the MCA territory will be implicated in each task, and the extent of cerebral lateralization is likely to show task-specific variations. Because of the poor spatial resolution of fTCD it is not worth investigating such effects, although the findings could be used to generate predictions about individual differences in task-specific laterality that could be investigated using fMRI. Preliminary data of this type were also found in our sample through the use of another paradigm of rhyme generation.

Another variable taken into account was the side of CI and its effects on lateralization.

Language activation was contralateral to the side of the implanted ear in 69.5% of our participants, in accordance with the normal hearing population, in which auditory signals from one ear reach both auditory cortices, but contralateral projections are stronger and more preponderant than ipsilateral ones (Hugdahl, 2005; Langers et al., 2005). However, in our sample the proportion of patients with prevalent activation of the contralateral pathway varied in relation to the side of the implanted ear. Almost 80.7% of right-, but only 60% of left-ear implanted children showed normal left-hemispheric activation; thus, 40% of left-ear implanted children atypically activated the right hemisphere. Thus, most deaf children in our group keep the inborn i.e. biologically constrained left-hemispheric language preference (Bishop, 2013). However, activation of the contralateral right hemisphere in the presence of left-ear CI occurred in those (4 out of 10) subjects implanted within 4 years of age, whereas children who received a left-ear CI at a much later age showed ipsilateral activation of the left hemisphere.

These findings suggest that unilateral reafferentation of the left ear may induce reorganization of language functions in the right hemisphere if it occurs early in life. According to this hypothesis the transfer of language functions to the right hemisphere may be the effect of cerebral plasticity analogously to what occurs in children with early left focal brain lesions (Chilosi et al., 2005; Guzzetta et al., 2008; Staudt et al., 2001).

Considering the whole sample, hemispheric dominance for language appeared to be influenced by both age and side of implantation, even if covariance analysis showed a preminent effect of the CI side on age of implantation.

Looking at language outcome, all deaf children showed a rather satisfactory language development after CI and acquired lexical and grammar skills sufficient to carry out the fTCD narrative task.

However, implanted children’s linguistic proficiency was, on average, significantly lower in comparison to their hearing peers.

Interestingly, with regard to the LI effects on language outcome, language scores significantly differed between children with left and right LI. Nonetheless, a better and significantly higher language efficiency in subjects with predominant activation of the left hemisphere, an expected result on the basis of the literature, was no found. This finding might be partly related to the high presence of subjects with uncertain lateralization, or to other factors that are known to affect language development, such as residual hearing (Giuntini et al., 2016), rehabilitation methods and hearing aid fitting (Bastanza et al, 2016; Bubbico et al., 2007), which may have influenced the effect of LI on language efficiency.

The last important result was that the side of implantation was significantly related to language outcome, with the right side favoring language efficiency (Henkin et al., 2014). In particular, this effect was evidenced by the language composite score and also by the test of lexical comprehension (PPVT), a test acknowledged for its validity and psychometric reliability (Hoffman et al., 2012; Rice et al., 2006) .

These outcomes also appeared to be confirmed by the second study and seem to support the REA (right ear advantage) hypothesis, which will be discussed later.

Our experimental sample, although not balanced between left and right CI subjects on the basis of age, imposed multivariate analyses which, however, confirmed the validity of the association between side of CI and language efficiency regardless of age.

Moreover, it was confirmed that the age at CI is a determining factor and, therefore, there is a correlation between CI age and language efficiency. Language composite score varied in relation to age at implantation, with a statistically significant inverse correlation between age at implantation and language outcomes (Spearman's rho = -0.33, $p = 0.05$).

10.2 *Study 2*

Patients who are deaf on one side from birth can provide unique information about the organization of lateralized functions. The effects of congenital or early onset unilateral hearing loss are less explored.

Language acquisition was assumed to proceed normally in children with unilateral hearing loss (UHL) since they have one functioning ear. However, it is known that children with UHL score poorly on speech-language tests and have higher rates of educational problems compared to normal hearing (NH) peers. Furthermore, UHL has been associated with decreased performance on other domains, such as hearing in noise, sound localization, general academic performance, verbal IQ, self-esteem and exhaustion (Kuppler et al., 2013; Lieu et al., 2013; Vila & Lieu, 2015), even though patients do not always suffer from their hearing loss in daily life activities.

Even in congenitally UHL, where there is no variability of auditory exposure time, in our opinion the results indicate that children with the right auditory afference (left hearing loss) do better than the right deafened children (who have left auditory afference).

The study of the language function in our sample of children with UHL seems to find evidence of the right-ear advantage (REA) hypothesis. We have found that the composite language score was significantly lower in right, compared to left hearing loss subjects.

According to the REA hypothesis (Jensen et al., 1989), unilateral left ear deafness would have less detrimental effects on cognitive performance than unilateral right ear deafness, because, in the former case, the contralateral connections to the language dominant hemisphere are still intact. Proposed by Kimura (1963), the dichotic listening paradigm held that the right ear was preferred for listening to speech, owing to the predominant representation of a right ear stimulus in the left cerebral hemisphere, where language typically lateralizes (Kimura, 1963).

According to the REA, children with left UHL should enjoy a speech-language advantage and children with right UHL should have greater difficulties with language skills, but the evidence is currently inconclusive (Hartvig et al., 1989; Niedzielski et al., 2006; Lieu et al., 2010). Older studies pointed to a higher rate of grade failures and worse verbal test performance in children with right UHL (Bess and Tharpe, 1984; Hartvig et al., 1989; Niedzielski et al., 2006). However, a large case-control study (Lieu et al., 2010) did not find any right or left ear differences on cognitive achievement, nor language outcomes, contrary to prior studies which underlined differences between children with right and left UHL. However, the degree of hearing loss is an important factor for composite scores of oral language expression, and this large sample study (109 cases) included children with UHL of any degree, from mild to profound (PTA > 30 dbHL in the affected ear). The negative findings could be explained by the fact that mild and moderate hearing loss may not impact as importantly as profound deafness.

Whether the "right ear advantage" (REA) exists for speech perception is still controversial (Hugdahl, 2011). Although children with UHL performed worse on expressive speech-language tests, it is less clear that the side of hearing impairment influences cognitive abilities.

Previously, Niedzielski et al (2006) observed that children with right sided hearing loss had a limited range of concepts, lower capability of learning verbal material and logical reasoning, abstract thinking and classifying. Left sided hearing loss caused deterioration of intellectual abilities within non verbal intelligence.

In our study we have found that only the language related performance is significantly (WMI - working memory index- p=0.0094 and IQ -intelligence quotient- p= 0.021) lower in right compared to left hearing loss subjects. However, there is no difference for the non verbal test (VMI - visual motor integration, PSI - processing speed index - and PRI - perceptual reasoning index).

The language outcome is significantly worse in children with right with respect to left unilateral hearing loss. This may depend on the fact that the left hemisphere, more predisposed to process language, if deafferented from an early phase, could be not optimally sustained by compensatory reorganization mechanisms at intra or inter-hemispheric level.

The lack of optimal condition (right auditory afference, contralateral to the left hemisphere that is important for language) seems to affect language outcome, independent from reorganization.

Subjects with right hearing impairment with right lateralization exploit the connections to the healthy ear. Instead, the subjects who organize language on the left, use the paths ipsilateral to the healthy ear. In both cases some cognitive performances (WMI, IQ) appear to be disadvantaged from this condition.

A recent study (Rachakonda et al., 2014) found diffusion tensor imaging (DTI) differences between right and left UH: increased FAs (fractional anisotropy, a DTI parameter) for right UHL in the left lateral lemniscus and the subcortical white matter of the left Heschl's gyrus.

However, the small sample size and the sample of children with both acquired and congenital hearing loss, may have influenced the results; therefore, the authors conclude that these negative findings do not preclude the existence of such differences.

Instead, several DTI regions showed differential strengths in correlation with language and verbal IQ outcomes in UHL and normal hearing subjects. These discordances suggest that the brain of children with UHL undergo reorganization in the white matter, to help compensating the lack of typical peripheral auditory stimuli to the controlateral hemisphere.

Other authors (Schmithorst, 2014), by using fMRI in children with UHL, found that subjects with right severe-to-profound UHL displayed smaller activation in a region encompassing the right inferior temporal, middle temporal, and middle occipital gyrus, evidencing differences due to monaural hearing in cross-modal modulation of the visual processing pathway. They displayed increased activation in the left posterior superior temporal gyrus as well as reduced deactivation of the anterior and posterior region of the default mode network (DMN).

These results show altered neurophysiology in children with UHL for cross-modal modulation and also a deficiency in deactivation of the DMN during audio-visual tasks. The outcomes strongly suggest that one good ear is insufficient to promote the development of the normal cognitive function. This physiological signature may underlie the poor academic and behavioral outcomes associated with UHL.

In our study, mean LIs of patients were similar in terms of a prevalent left hemisphere activation during speech, which approached the values reported in literature for normal-hearing children (Bishop et al., 2009; Haag et al., 2010; Lohmann et al., 2005).

Language activation was contralateral to the intact ear in 36.4% of our participants, and ipsilateral in 54.4%. These data differ from the normal hearing population, in which auditory signals from one ear reach both auditory cortices, but controlateral projections are stronger and more preponderant than ipsilateral ones (Hugdahl, 2005; Langers et al., 2005). These data also differ from the results of study 1 regarding children fitted with monolateral CI. Although the sample size is low, these data are unexpected, especially language lateralization in children with left hearing loss.

To date, we are unable to provide a univocal interpretation of the data and even the existing hypotheses in literature are contradictory.

Various studies have shown a reorganization of the auditory and language pathways in patients with UHL, with bilateral activation patterns, indicating a functional reorganization of auditory pathways.

Some studies claimed that patients with unilateral hearing loss show more activity in the ipsilateral hemisphere upon hearing stimuli in the intact ear, suggesting some type of plasticity in brain functioning (Burton et al., 2012). These authors studied subjects that performed an fMRI odd-ball task in which they had to press a button when hearing a deviant stimulus. In normal hearing participants, the contralateral is stimulated more than the ipsilateral hemisphere when auditory stimuli are presented unilaterally, in line with the typical dominance of crossed over uncrossed projections. In patients with unilateral hearing loss, however, the ipsilateral projections seem to gain importance.

Similarly Kral et al (2013), by investigating congenitally deaf cats with local field potentials (LFPs), reported that animals with early-onset unilateral hearing loss, the ipsilateral hemisphere responded more strongly to stimulation of the hearing ear. This suggests a specific adaptation process at the hemisphere ipsilateral to the hearing ear, involving specific (down-regulated inhibitory) mechanisms not found in the contralateral hemisphere.

Other authors argue that congenital unilateral deafness may lead to over-excitation of the contralateral pathway. Gordon et al. (2013) argued that congenitally deaf children receive better after bilateral cochlear implants, because a unilateral implant may cause permanent reorganization of the brain. They presented evidence, from an EEG study measuring the cortical activity during tone listening that unilateral implants may overactivate the contralateral hemisphere due to the lack of inhibition from the deaf ear. Therefore, whereas later acquired unilateral deafness seems to result in strengthening the ipsilateral pathway (Burton et al., 2012), congenital absence of auditory input may lead to an excessive stimulation of the auditory pathway contralateral to the hearing ear.

Our results are more in line with the observation that ipsilateral connections of the spared ear become stronger, so that the functioning ear activates both hemispheres (Burton et al., 2012; Hine et al., 2008). Indeed, the subjects with right hearing loss maintained a prevalent left hemispheric activation (66.7%). A recent study (Van der Haegen et al., 2015) show that a lack of sensory auditory input on the right side, which is strongly connected to the contralateral left hemisphere, does not necessarily lead to atypical lateralization of speech perception, speech production and reading. The authors tested seven participants with congenital right ear deafness on three fMRI language paradigms (word generation, sentence perception, and word reading) which are known to show clear left hemisphere asymmetries. The results showed a clear left hemisphere dominance for the three tasks in all patients. Congenital unilateral right-sided deafness hence does not systematically lead to a reorganization of higher-order auditory processing in terms of laterality in the temporal lobes. This goes against Gordon et al. (2013)'s claim, according to which unique input from the left ear would lead to overactivation of the right hemisphere auditory cortex. It should be noted that their study included children with congenital bilateral hearing loss, instead of unilateral deaf adults.

It remains to be understood the hemisphere lateralization of left UHL, whose percentages (left 40%, right 40% and uncertain 20%) appear unexpected and difficult to be integrated with what has been said up to now. Other factors such as genetic constraints are likely to overrule the role of sensory input in the development of (a)typical language lateralization. The origins of hemispheric specialization have been indeed attributed to several influences such as genetic, evolutionary, developmental and environmental factors (Bishop, 2013; Hervé et al., 2013).

10.3 *Study 3*

The plasticity of brain circuitries subserving auditory and verbal functions decreases with age (Fryauf-Bertschy et al., 1997), therefore implantation in prelingually deafened adults is a controversial issue (Green et al., 2005).

Worldwide literature (Fitzpatrick et al., 2004; Green et al., 2005; Kos et al., 2009) and clinical practice have shown that cochlear implantation in prelingually deafened adult patients does not improve speech intelligibility, nor does it affect articulation or language skills. However, it brings about notable changes in hearing, it broadens the range of frequencies perceived so patients are mostly satisfied with the benefits of cochlear implantation.

To this regard, while until the mid 1990s prelingually deafened adult patients were considered poor CI candidates, because improvement in speech perception seemed to be limited, several recent studies have suggested that the latest implant technology has resulted in open-set speech perception abilities, although variability among individuals was great and performance lagged behind that of post-lingually deafened adults (Bosco et al. 2013; Chee et al., 2004; Kaplan et al., 2003; Klop et al., 2007; Santarelli et al., 2008).

It has to be considered that prelingually deafened adults consist of a very heterogeneous group of patients; a substantial number of individual factors, such as aetiology of deafness, age at diagnosis, rehabilitation and communication mode, language development, use of hearing aids before implantation, residual hearing, progression of hearing loss, educational experience variably affect the results after implantation (Teoh et al., 2004) . This contributes to the wide variability observed in the results. To this regard it is useful to remark that in Italy since the sixties the oralism has been the main rehabilitative choice for patients suffering with preverbal deafness. An oralist rehabilitation mode, based on the use of hearing aids and devices in combination with lip-reading when necessary, have been promoted and sign-language has been limited to selected cases and to restricted communities. As a consequence, in Italy the very majority of adult patients with preverbal deafness seeking for a CI have been using consistently hearing aids following an oralist rehabilitation mode and have developed oral language, even if with variable degrees of performance.

Controversy regarding functional reorganization in the adult brain still remains. To investigate whether neuroplasticity is present in adults with prelingual deafness, we evaluated with fTCD hemispheric dominance for language before and one year after CI.

Controversies are present in the literature concerning functional cerebral reorganization in adult subjects (Kujala et al., 2000), but studies on patients with post-lingual hearing loss submitted to CI suggest the possible existence of plasticity in the auditory cortex similar to that one observed in pre-lingual deafness.

In the mature brain, auditory deprivation reduces the neuronal activity in the primary auditory cortex and in the related areas and produces a functional reorganization over time.

Plasticity was prominent in the superior temporal and anterior cingulate gyri in the sensory deprived mature brain (Lee et al., 2003). Patients with long auditory deprivation have been shown to have worse prognosis after CI (Proops, 1999).

In brain activation studies of prelingual deafness using H2O PET (Lukaszewicz-Moszynka et al., 2014) or fMRI (Plante et al., 2015), the auditory cortex was found to be activated by the processing of visual motion and complex visual pattern changes (Bucley & Tobey, 2011; Vachon et al., 2013).

These findings demonstrate the capacity of the auditory cortex to reorganize cross-modally after auditory deprivation of the human brain.

In deaf adults fitted with cochlear implants, cross-modal recruitment (measured by event-related potentials) has been correlated with decreased performance on speech perception tasks (Sandmann et al., 2015). Thus, the degree of sensory deprivation necessary to induce cross-modal cortical plasticity remains unclear. A recent study by Campbell and Sharma (2014) provides new evidence of cross-modal reorganization in adult onset mild to moderate hearing loss. The authors recorded visual evoked potentials (VEP) using high-density electroencephalography and showed increased amplitudes of P1, N1 and P2 VEP components, decreased N1 latency, a novel P2' component and current source density reconstructions. This data would reflect a shift toward ventral stream processing, including activation of auditory temporal cortex in hearing-impaired adults. Furthermore, they observed a strong negative correlation between cross-modal re-organization (as reflected by decreased N1 latency) and speech perception in noise. This study provides the first evidence that visual cross-modal re-organization not only begins in the early stages of hearing impairment, but may also be an important factor in determining behavioral outcomes for subjects with prolonged hearing loss.

Sandmann et al. (2015) used EEG to examine the temporal dynamics of changes in the auditory cortex controlateral and ipsilateral to CI in postlingually deafened adults. They showed an improvement in auditory discrimination ability, especially in the first eight weeks of CI experience. The finding of rapid and limited cortical changes in adult CI may be of clinical relevance and can help estimate the role of plasticity for therapeutic gain.

Investigations of cerebral glucose metabolism in deaf patients by using 18F-FDG PET have provided further functional evidence of neuroplasticity (Lee et al., 2001). Cerebral glucose metabolism in the primary auditory and related cortices in individuals with prelingual deafness were shown to decrease in younger patients, but to increase as they got older, and, in fact, recovered fully or even exceeded the normal level of activation. The recovery of metabolism in older individuals was explained by plastic changes in the auditory neuronal circuitry, due to expansion of the afferent neural network by other sensory systems. Expansion was possible because of the lack of functional specialization of the auditory cortex in younger individuals, and its resultant vulnerability to other forms of sensory stimulation. This kind of plasticity was demonstrated to prevent the recovery of the designated hearing function by auditory neural substrates after cochlear implantation and rehabilitation in prelingually deaf patients (Lee et al., 2001).

Our data are not sufficient to confirm the presence of plasticity in adults and the scarcity of data does not allow to make inferences. The data are complex, not univocal, and suggest that plasticity is partly subjected to biological constraints and partly to other factors whose interactions (age, binaurality, deafness progression, previous residual hearing, afferent side) are currently unknown. Other confounding factors linked to the type of task, used cognitive strategies and language components, age-specific paradigm effects could also have a role in determining hemispheric lateralization.

11. METHODOLOGICAL CONSIDERATIONS

This study have some limitations related to the small sample size (36 children and 6 adults with CI and 11 children with UHL) and the presence of a paired control group matched 1: 1 not for all subjects. In addition, children with right CI (26) were more numerous than those with left CI (10), and the mean age at CI of the two groups differed statistically, but this is due to the fact that right implantation has been preferred for practical reasons (easier manipulation for right-handed patients).

From a methodological point of view it is also worth considering that in childhood subjects may use different cognitive strategies from adults to carry out the same task, so LI may vary according to age (paradigm-specific age effects). Moreover, it is known that different types of task (description task and linguistic narrative, word generation, rhyme generation) may give different LIs (Bishop et al., 2009; Haag et al. 2010).

The residual hearing before CI could have an important role in determining future outcome, but this variable has been scarcely considered in this study, since it could not be precisely measured in consideration of the young age of the subjects. Tonal behavioral audiometry in free field is used in this case and it does not allow differential quantification for the two ears. Another potential confounding factor could be the perceptive gain due to the application of Hearing Aid, that could not be precisely quantified in this sample for the same reason as above.

12. CLINICAL IMPLICATIONS

For children with prelingual profound bilateral deafness candidates to unilateral cochlear implant, these findings may have implications for determining which side has to be implanted. Our data suggest that the language outcome pattern observed in the unilateral deafness is similar to that of mono-cochlear implant users (Ponton & Eggermont, 2001), if the afference arrives to the right ear. All other known factors being equal (e.g., degree of hearing loss, etc.), it would seem most prudent to place the implant on the right side, thus stimulating the pathway that produces the most robust activation of the typically speech-dominant left hemisphere (Khosla et al., 2003).

Even if recent trends in otosurgery show a significant increase of bilateral CI and a decrease of the age of implantation, which does not allow the feasibility of fTCD, this method could be useful in progressive or late-onset deafness or in case of late diagnosis, in which therapeutic CI would be an option and which side to implant an important issue. Indeed in those cases in which language has already developed it could be important for choosing the side to implant, to consider which hemisphere has been committed for language processing.

Furthermore a better understanding of the compensatory strategies used in children with UHL, especially regarding cortical reorganization and neuroplasticity, could potentially be helpful in designing of the effective treatment and management strategies (Schmithorst et al., 2005).

There are no definitive evidence-based guidelines on how children with UHL should be treated. A recent study of Lieu (2015), suggests that it is recommended a collaborative/team approach, involving parents, audiologists, speech therapists, educators, pediatricians, and the child when he or she is old enough to have an opinion. Families may have strong opinions about the approach to their infant child; some parents will have observed no apparent hearing problems in their baby and are happy to observe and wait, but others want to be as aggressive as possible, enrolling in parent-infant programs and fitting the child with hearing aids. For those who prefer a wait and watch approach, observation and screening for speech-language delay is a reasonable option.

Other parents opt for early auditory rehabilitation with amplification from hearing aids (McKay et al., 2008). Although there have been no studies showing direct benefits to language outcomes, studies suggest that binaural hearing is possible with the use of hearing aids in children with UHL.

Cochlear implant is the current research and clinical frontier for children with severe to profound

UHL. Hassepass and colleagues (2013) in Germany, reported favorable outcomes of CI in 3 children, two of whom had postlingual profound UHL. Other centers around the world are conducting pilot studies in small numbers of children. One extremely important limitation to CI in this population, is the high prevalence of cochlear nerve aplasia and hypoplasia. If no cochlear nerve is identified, CI is not expected to be beneficial, and an auditory brainstem implant would have to be considered the final possible option.

Future research will be needed to confirm this hypothesis and test the consequences of a cochlear implant for language laterality in congenitally unilateral deaf patients.

13. FUTURE PERSPECTIVES

It would be desirable to extend the study of both children and adults fitted with CI with additional electrophysiological techniques, such as:

- EABR: Electric Brainstem Auditory Responses (Guenser et al., 2015)
- EMLR: Electric Middle Latency Responses (Gordon et al., 2005)
- Electrical Cortical potential (Hossain et al., 2013): - SVR: Slow Vertex Responses
  - ERP: Event Related Potential
- High Density EEG (Campbell & Sharma, 2014)

The obtained electrophysiological data could add interesting information about the organization of cortical areas devoted to auditory perception and language in deaf subjects with CI. These electrophysiological data could also provide information for better calibration, programming, rehabilitation and training of the subject implanted, especially in "difficult" cases.

Study possible correlations between electrophysiological data and auditory outcomes and language post-CI could ultimately provide useful information for prognostic purposes.

14. CONCLUSION

In conclusion, our data indicate that fTCD is a valid tool in evaluating cerebral language dominance in deaf children fitted with CI and show that, despite severe auditory deprivation, normal predisposition for language processing in the left hemisphere is generally maintained.

Neural language organization, after auditory deprivation and subsequent reafferentation, seems to follow a near-normal pattern of hemispheric dominance, but language proficiency may be non-optimal in some children. Unilateral hearing experience leads to a functionally-asymmetric brain with different neuronal reorganizations.

Taken together, our results suggest that brain organization of language functions is the result of a complex interaction between experience-dependent mechanisms and asymmetrical neurobiological constraints (Neville et al., 1998, Sharma et al., 2009). Thus, neurodevelopmental plasticity after cochlear implantation seems to be influenced by stimulus-driven experience within a time-limited sensitive period (Kral & Sharma, 2012).

From a clinical perspective, early age at implantation and right-ear CI appear to contribute to a more favorable language outcome, thanks to the convergence of an optimal sensitive period for language learning and reafferentation of the auditory route contralateral to the left hemisphere.

The choice of which ear to implant may be more problematic when CI fitting occurs later in life, because the effects of CI reafferentation on hemispheric dominance could be influenced by previous neural organization related to the longer pre-implantation hearing experience.

From a clinical point of view if all other known factors are equal (e.g., degree of hearing loss, etc.), it would seem most prudent to place the implant on the right side, thus stimulating the pathway that produces the most robust activation of the typically speech-dominant left hemisphere (Khosla et al., 2003).

Though the results of this study must be considered preliminary, they provide evidence in support of the hypothesis that, in deaf subjects, fTCD evaluation of language lateralization may represent an easy and non-invasive procedure that could be added to the standard pre-implantation assessment protocols currently in use, especially in late-onset hearing loss. Further investigation on larger samples is required to confirm our data.

Also unilateral deafness appear to result in an asymmetric functional brain, with the two hemispheres showing differential responses to the deaf and the hearing ear.

This findings provide some evidence in support of child brain developmental plasticity, because it is well known, from both animal and human studies, that absence of sensory input from birth affects normal growth and connectivity necessary to form a functional sensory system and may alter the organization of language-related neural circuitries (Gilley et al., 2008; Kral & Sharma, 2012; Peterson et al., 2010).

Future studies on language laterality of these patients may still be interesting in order to further explore alternative explanations for hemispheric language dominance (e.g. genetic influences may overrule the influence of unilateral sensory deprivation from birth), behavioral consequences of hearing loss and the organization of non-language functions in unilateral deafness.

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