FACTORS INFLUENCING

CORTICAL AUDITORY EVOKED POTENTIALS

IN COCHLEAR IMPLANTEES

Thesis submitted for the degree of

DOCTOR OF PHILOSOPHY (Ph.D.)

By

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DECLARATION CERTIFICATE BY THE CANDIDATE

I declare that the thesis entitled, "Factors influencing cortical auditory evoked potentials in cochlear implantees" submitted by me for the Degree of Doctor of Philosophy (Ph.D.),is the record of research work carried out by me during the period from January 2013 to December2015,under the guidance of Prof.Mohan Kameswaran, and the co-Guidance of Prof. R.S. Anand Kumar and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other university or other similar institution of higher learning.

Signature of the Candidate

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Place:

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Prof. R. S. Anand Kumar

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Place :

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Dr. K. Sathiya

LIST OF ABBREVIATIONS

ACE- Advanced Combination Encoders

ABR- Auditory Brainstem Response-ABR

BAEPs-Brainstem Auditory Evoked Potentials -BAEPs,

CAP-Categories of Auditory Perception

CAPD-Central Auditory Processing Disorder

CIGI-Cochlear Implant Group of India

CI-Cochlear Implant

CAEPs-Cortical Auditory Evoked Potentials

EAS-Electro Acoustic Stimulation

EEG-Electro Encephalo Gram -EEG

EABR-Evoked Auditory Brainstem Reflex

ECAP-Evoked Compound Action potential

ESRT-Evoked Stapedial Reflex Test

fMRI- Functional Magnetic Resonance Imaging

LLAEPS-Late latency Auditory evoked potentials

MERF-Madras ENT Research Foundation

MEG-Magneto Encephalo Graph

MRI-Magnetic Resonance Imaging

MLAEPs-Middle Latency Auditory Evoked potentials

LIST OF ABBREVIATIONS (CONTD)

NRT-Neural Response Telemetry

SAS-Simultaneous Analog Strategy

SPEAK -Spectral Peak

SIR-Speech Intelligibility Rating

SOC-Superior Olivary Complex

ABSTRACT

Introduction: Cortical auditory evoked potentials (CAEPs) are a non-invasive tool that can provide objective information on the functioning of the auditory pathways. In our study, we study CAEP parameters like P1 latency, amplitude and morphology as tools of measure of auditory cortical maturation after electrical stimulation following cochlear implantation and compare the values in children implanted below 3 years (yrs) of age and between 3-6 years of age. Furthermore, in our study, we also recorded Category of Auditory Perception (CAP) and Speech Intelligibility Ratio (SIR) scores for subjectively assessing post-implantation outcomes and correlated the values with CAEP parameters. The results of our study are discussed.

Materials and methods: 64 congenitally deaf children were enrolled for the study. They were divided into 2 groups (A-below 3 yrs of age & B-between 3 and 6 yrs). All implantees were followed up at 3, 6 and 12 months with CAEP parameters (P1 amplitude and latency and morphology), CAP and SIR scores were recorded. Students paired and un-paired t-tests, Pearson's correlation and Hosmerand Lemeshow Goodness of fit test were the statistical tools used.

Observation and results: CAEP latency at 3 months, group 1 showed statistically significant difference when compared with group B. At 6 months post implantation there is no statistically significant mean difference between group 1 and 2 in SIR score whereas other variables were found to be significant. However at 12 months, the P1 latency alone was comparable in both groups indicating that intensive post implantation auditory-verbal habilitation plays significant role in both groups. The correlation between CAP, SIR with P1 latency, amplitude is discussed.

Multiple logistic regression test was done to assess how well the model fitted the data. It resulted in a non significant value, which is an indication of a model that predicts the population fairly well.

Conclusion: Overall CAEP P1 latency, amplitude, CAP and SIR scores in cochlear implantees show significant improvement following implantation and values improve with increased use of the implant, thus indicating ongoing cortical maturation. The earlier the implantation, the earlier the maturation of auditory cortex and stress on intensive auditory-verbal habilitation after implantation must be appropriately explained to the care-givers / parents.

Keywords: Cortical Auditory Evoked Potential (CAEP), CAP, SIR, early implantees, late implantees.

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1. INTRODUCTION

1.1 Hearing Loss – The Indian Perspective

Among the five special senses which humans possess, the sense of hearing is considered to be the most important one, as it is crucial for the development of communication, which forms the basis of human civilization. Hearing loss at birth often remains undetected as a silent handicap until it ends up as a double tragedy, of deafness along with speech and language deprivation. 'Deaf & Dumb' individuals have a social stigma attached to them even in present day society, living within a deaf world, with no means of verbal communication and thus leading a non-productive life.

As per the WHO report of 2010 on Newborn and infant hearing screening around 0.5 to 5 per 1000 neonates and infants have congenital or early childhood onset sensorineural deafness or severe-to-profound hearing impairment. This scenario is even more pronounced in developing countries like those in the Indian subcontinent, where the problems of consanguinity and poor peri-natal care are common. India has a population of over 1 billion, of which an estimated 3 million children are affected by congenital hearing loss of varying degrees. Every year around 25,000 children are newly diagnosed with congenital severe to profound deafness across the country. The above data from the National Program for the Prevention and Control of Deafness 2006, published by Garg S et al, emphasizesthe gravity of the situation in India.[1] However, hearing loss is a truly remediable congenital handicap, remediable due to remarkable advances in biomedical engineering and surgical techniques.

1.2 Auditory Neural Prostheses

The advent of auditory neural prostheses like the cochlear implant has successfully broken the “acoustic barrier”, thus integrating children born with hearing loss into normal society, providing them with vital communication skills to lead a highly productive life. The human auditory system is unique in its organization due to the phenomenon of **tonotopicity** (place-pitch organization) which gives it the opportunity to receive and integrate external electronic circuits. [2] The cochlear implant is considered as a monumental innovation of the twentieth century, and it represents a successful attempt by man, to interface a prosthetic device with the central nervous system, thereby re-establishing a lost special sense.

1.3 Cortical auditory evoked potentials

Measurement of Cortical auditory evoked potentials (CAEPs) is a non- invasive and objective electrophysiological test that provides detailed information regarding the functioning of central auditory nervous system. The development of sensory pathways in the cortex is determined by both intrinsic and extrinsic stimulus- driven factors. Absence of sensory input as in deafness impedes the normal growth and connectivity needed to form a functional sensory system. As normal function of the sensory pathways is a necessary prerequisite for normal development of speech and language skills, children with hearing loss are at a higher risk of abnormal development of these skills.[3]

CAEPs are evoked by sound and processed in or near the auditory cortex. They are therefore referred to as Cortical Auditory Evoked Potentials. There is considerable clinical and scientific interest in CAEPs to probe threshold and

suprathreshold auditory processes because they are believed to reflect the neural detection and/or discrimination of sound.[4]

Testing CAEPs in awake, alert infants, show that these evoked potentials could be used as a metric of physiological development in the same way that Auditory Brainstem Responses (ABR) are used at the level of the brainstem. That is, the motivation was to use CAEP to understand underlying physiological processes and the neural substrates of perception.[5]Caton's experiments in 1875 on rabbits in the late 19th century has shown that acoustic stimuli can modify cortical electrical potentials and there isspontaneous waxing and waning of the electrical activity recorded from the brain of rabbits and monkeys.[6] Electroencephalography recordings also contained a component which was dependent upon acoustic stimuli was first noted in 1939 by Davis, P. A.[7]

As maximum amplitude of the CAEP potential is recorded when the electrodes are placed on the vertex, it was previously thought that the waveforms represented a nonspecific cerebral process. But, further research and developments in technology has enabled precise recordings confirming the presence and increasing the clinical applications of late latency Auditory Evoked Potentials (LLAEP).[8]

Cochlear implants bypass peripheral cochlear damage in patients with bilateral profound sensorineural hearing loss. They directly stimulate cell bodies in the spiral ganglion thus, avoiding the deleterious effects of stimulus deprivation.

Components of P1N1P2 complex - P1 is the first major component of the P1N1P2 complex, is a vertex positive voltage deflection that often occurs approximately 50ms after the onset of sound stimulus. It is usually small in

amplitude in adults but large in young children and may dominate their response.In the auditory modality the latencies of the N1 and P2 peaks are about 100 and 175 ms respectively.[9]For potentials between 20 and 60 msec, the results of the study by Wood CC et al, demonstrate the sources in primary auditory cortex on the superior temporal plant near the temporo-parietal junction whereas for potentials between 60 and 250 msec, the results demonstrate multiple sources which partially overlap in time.[10]Additional regions may contribute to this response like Hippocamous planum temporal and posterior lateral superior temporal area.[11] The latency of P1 changes during infancy and childhood. P1 is generated by auditory thalamic and cortical sources. [12]

In normal hearing newborns the mean P1 latency is approximately 300 milli seconds. Over the first 2–3 years of life there is a rapid decrease in latency (to approximately 125 ms at age 3) and then a more gradual decrease in the second decade of life. The mean P1 latency in normal hearing adults (ages 22–25 years) is approximately 60ms. Because P1 latency varies as a function of chronological age, it can be used as a biomarker to infer the maturation of the auditory pathways in infants and children. Of particular interest are infants and children with significant hearing losswho regain hearing after being fit with a cochlear implant. [12] Acentral issue in the field of pediatric cochlear implants is the optimalage range for implanting a congenitally deaf child. The prevailing wisdom is that implantation at an early age will produce better results than implantation at a relatively late age. [12]

N1 appears as a negative peak approximately 100 ms after the onset of sound stimulus. N1 latency can be larger in some cases depending on the duration and complexity of the signal used. N1 follows P1 and precedes P2 Compared to

P1, N1 is relatively large in amplitude in adults (typically 2-5 microvolts). In young children, N1 generators may be immature and therefore the response may be absent particularly if rapid stimuli are given. In another study by Ceponiene R et al, the supratemporal and the non-specific components of the N1 have protracted maturational courses, and that children's N1 is composed of differentially weighted components from those in adults. The neural sources of the N1 and the N2 appeared to be generated in different anatomical locations, their relative configurations being the same in the 9-year-old children and in adults. The P1 and N2 peaks did not show fundamental transformation with age.[13]N1 is known to have multiple generators in the primary and secondary auditory cortex and therefore described as having at least 3 components.[9]

P2 is a positive waveform that occurs approximately 180 ms after the onset of sound stimulus. It is relatively large in amplitude in adult (2-5 microvolts or more) and may be absent in children. P2 appears to have generators in multiple auditory areas including the primary auditory cortex, secondary auditory cortex and the mesencephalic reticular activating system. P2 is not as well understood as the P1 and N1 components.[4] [14]

Auditory evoked potentials are divided into early or Brainstem Auditory Evoked Potentials (BAEP), Middle Latency Auditory Evoked Potentials (MLAEP), and long latency auditory evoked potentials (LLAEP) as shown in Figure 1.1which shows the four main wave components of the long latency or cortical auditory evoked potentials.

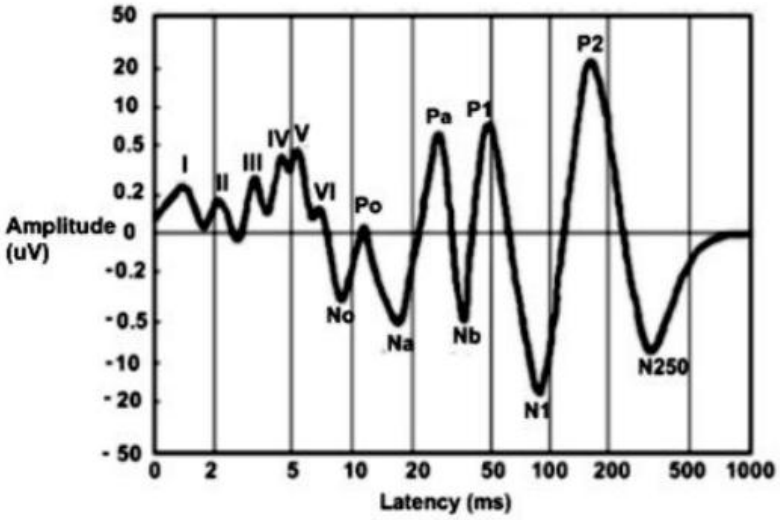


Fig: 1.1 Adapted from Picton TW Hilyard SA Krausz HI and Galambos R (1974): Human auditory evoked potentials. I. Evaluation of components. Electroencephalography and Clinical Neurophysiology, 36 (2), p 181.

1.4 Cortical decoupling

Studies in congenitally deaf cats have suggested a possible mechanism for the end of the sensitive period for auditory stimulation. When electrical stimulation is started after 4–5 months of deafness, i.e., after the end of the sensitive period for central auditory development in cats, there is a delay in the activation of supragranular layers of the cortex and a near absence of activity in the infragranular layers (layers V and VI).[15]

The near absence of outward currents in layers IV and III of congenitally deaf cats suggests incomplete development of inhibitory synapses and an alteration of information flow from layer IV to supragranular layers. The higher order auditory cortex projects back to A1 (primary auditory cortex), mainly the

infragranular layers and the infragranular layers (V and VI) in turn send long range feedback projections to the sub cortical auditory areas. The absence of activity in infragranular layers can be interpreted to suggest a functional decoupling of primary cortex from higher order auditory cortex, thus affecting feedback projections to subcortical auditory structures.[16]

The secondary auditory areas are decoupled from the primary auditory areas and are no longer able to provide important cognitive, “top-down” modulation. The end of the sensitive period the primary auditory cortex may be partially or completely disconnected (de-coupled) from surrounding higher-order cortex including language cortex. This leaves higher-order auditory cortex susceptible to recruitment from other sensory modalities.[17] This decoupling of primary and secondary auditory areas may actually make the secondary areas more available to other modalities in the process of re-organization. These mechanisms are cited as the reasons why auditory processing becomes difficult after the sensitive period. The central auditory system development thus largely depends on the pattern of neural activity at the periphery. Hearing loss, especially during early development, may negatively affect central development. Perhaps there is a critical period during which cochlear function needs to be particularly intact. Neonatal hearing disorders lead to problems in language development which becomes evident only later. Perhaps the best practical strategy is to assume the worst and make every possible effort to normalize hearing during early postnatal years. This involves early detection of hearing problems through neonatal or infant hearing screening programs and subsequent early intervention with hearing aids, cochlear implants and auditory habilitation training in the affected children.

Central auditory system development is significantly guided by cochlear activity patterns. It follows that a cochlear implant or other hearing prosthesis provided to a young infant would have a dual purpose. The device not only aids "hearing," but the augmented stimulation of the system would also have an influence on central development. There is much evidence of radical plastic change in the brains of congenitally deaf or blind subjects, where cortical areas that no longer serve one modality seem to take on some function for the remaining, dominant sense,a phenomenon termed 'cross modal plasticity'.[18] [19] [20]

In a deaf subject using sign language, some processing of visual information is carried out in the auditory cortex.[21]These are examples of brains that have developed with very unusual alterations to sensory input. Thus, the brain is a complex, wired system that, under certain circumstances, is capable of being rewired. This rewiring is often initiated by alterations in sensory input. As we learn more about the plasticity of synaptic connections and the variety of potential mechanisms that can alter the way the neurons connect and communicate, it has become clear that the brain is a constantly reorganizing system. **Plasticity** is the rule, not the exception. So one should seek not the evidence and mechanisms of plastic change, but rather the mechanisms that stabilize the brain and prevent plasticity.

1.5 Lacunae in knowledge

Indications for cochlear implantation are expanding. A large variable group of children across different ages are being implanted now but the outcomes are not the same in these children. So far there is no definitive,

objective parameter which can predict the optimal outcomes in these children over time. The commercial software used for programming the implant does not reflect the neural stimulation of the auditory pathway through the implant. Research tools are available to test the implant integrity but these are being used only for trouble shooting and difficult to map children.

There is no standardized objective tool to measure the outcomes of Cochlear Implantation over a period of time. This could necessitate enhancing auditory verbal habilitation catered to the specific needs of the individual child, especially if he is lagging behind.

CAEP is a new tool that has opened a window of opportunity to chronologically and objectively predict the outcomes during the period of habilitation. Though CAEP has been established as a sensitive tool, it has not been clinically implemented. Hence there is a lacuna in the knowledge of the practical application of this valuable tool in the clinical scenario.

1.6 Need for the present study

In the Indian context, in the recent years electrophysiology has been widely discussed among Audiologists at National podia, like the 'Annual Conference of the Cochlear Implant Group of India (CIGI)'.The data has been emerging from various reputed implant centers across India, but there have been no publications or research studies, longitudinally analyzing and documenting the intriguing changes among the cochlear implantees, during the habilitation period. Although results from the western world are widely read and accepted among Indian professionals, indigenous research data is yet to emerge, concurring with the western literature. Though electrophysiological tests like

Evoked Compound Action Potential (ECAP) and Evoked Stapedial Reflex Test (ESRT) and Evoked Auditory Brainstem Reflex (EABR) are provided by implant companies, they do not help to chronologically predict outcomes of cochlear implantation in children over time, as these tests are reflective of the peripheral auditory nerve responses and not of the plasticity of higher auditory centers.

This practical fact triggered the need for a highly specialized tool which would objectively look at neural plasticity after implantation. This is presently possible with CAEP. The present study was conceptualized to evaluate CAEP as a prognosticator in predicting the outcomes among children implanted at different age groups. Such a study would help provide reference values for early identification of implantees with suboptimal auditory stimulation thus enabling to customize the programming and habilitation specific to their needs. This study will also help us to infer the various factors which influence neural plasticity such as age at implantation, pre implant auditory stimulation, syndromic associations, inner ear anomalies, neurodegenerative diseases, Central Auditory Processing Disorder (CAPD), auditory dysynchrony, etc. The present study focuses on assessing the impact of age at implantation and its influence on the neural plasticity provided by auditory stimulation with the implant.

2. AIMS AND OBJECTIVES OF THE STUDY

The aim of the study is to investigate the impact of age at implantation and its influence on the neural plasticity provided by auditory stimulation with the implant.

The objectives of the study are as follows:

1. To assess the pattern of change in the CAEP parameters over time, in the first year of implantation.

2. To assess the impact of age on the CAEP parameters.

3. To correlate the CAEP parameters with subjective outcomes over time.

4. To predict the outcomes across different age groups using CAEP as a prognostic indicator.

Anticipated Outcomes

1. This study would help us develop a guideline, based on the CAEP parameters, to chronologically monitorneural plastic changes in the auditory cortex in response to auditory habilitation over time.

2. To incorporate CAEP as a routine clinical tool in the first year of follow up for early identification of suboptimal or poor performers.

3. The results from the study can be incorporated into the normative data available for the various electrophysiological tests done for the difficult scenario today and for those in the future.

3. REVIEW OF LITERATURE

3.1 Relevant Anatomy and Physiology of Auditory Pathway

The unique ultra-structural organization of the human cochlea has attracted researchers for many years, with innumerable studies being performed to understand the complex behavior of the end organ of hearing in response to various insults.This eventually has led to the innovation of the auditory neural prosthesis. The interesting path-breaking discovery that, despite congenital or acquired damage to the Organ of Corti due to various causes, the spiral ganglion population within the modiolus survives and still remains functional, was the scientific basis upon which the field of cochlear implantation has evolved rapidly to its present day status. Knowledge of the intricate micro-anatomy and patho-physiology of the auditory system remains vital for comprehensively understanding the various electrophysiological and behavioral responses that are evoked by a cochlear implant.

3.1.1 Organization & Function of the Membranous Labyrinth

The compartmentalization of the membranous labyrinth into the ScalaVestibuli, Scala Media and Scala Tympani, provides distinct channels for flow of the endo-cochlear fluids in response to the acoustical impulse.This flow in turn induces mechanical displacement of the Basilar Membrane, thereby triggering the Organ of Corti to create electrical nerve action potentials. The cochlear tonotopicity facilitates temporal stimulation of the various regions of the cochlea, according to the intensity and frequency of the acoustical impulse.This stimulation gets transduced into electrical signals that relay onto

the afferent neuronal fibrils and first order neurons in the spiral ganglion (Fig.3.1)

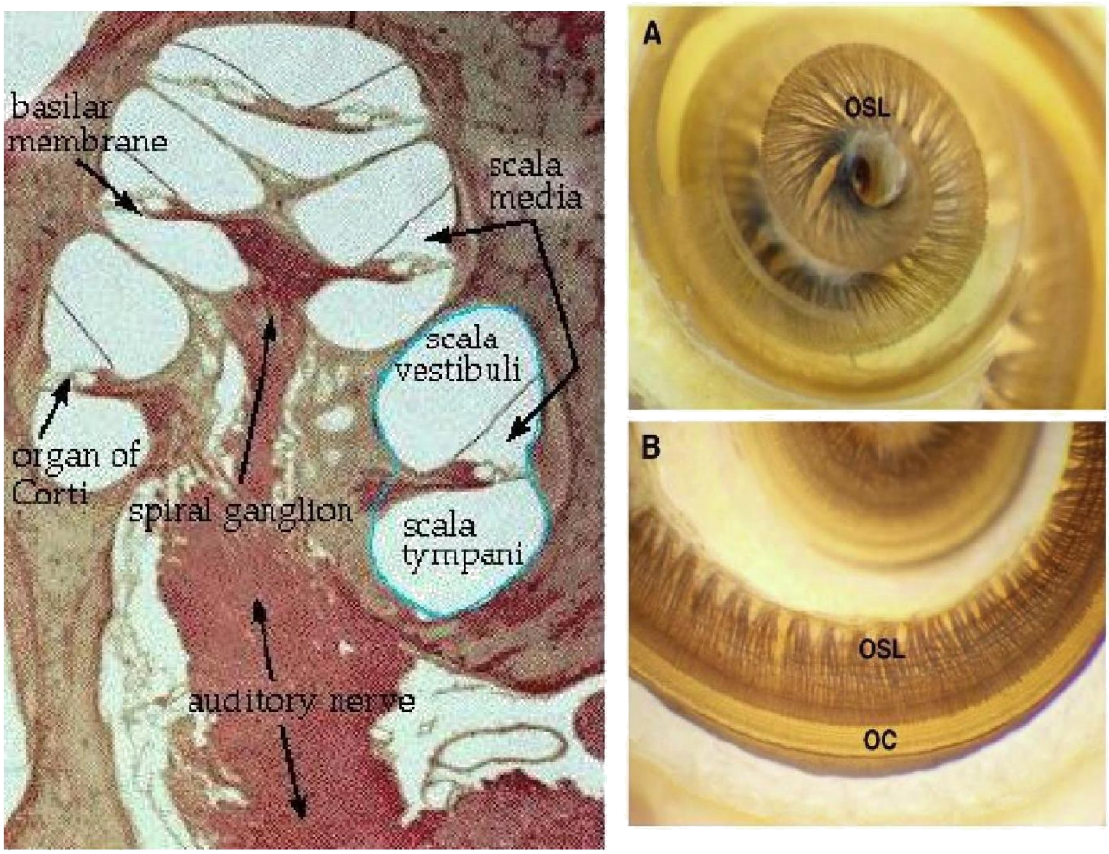


Figure-3.1: *Ultra-structure of cochlea showing the arrangement of afferent neuronal fibrils;*

A. Apical cochlear turn showing myelinated nerve fibers within osseous spiral lamina (OSL)

B. Basal cochlear turn showing Organ of Corti (OC), adjacent to osseous spiral lamina (OSL) [22] (From: Wright CG & Roland PS, 2005)

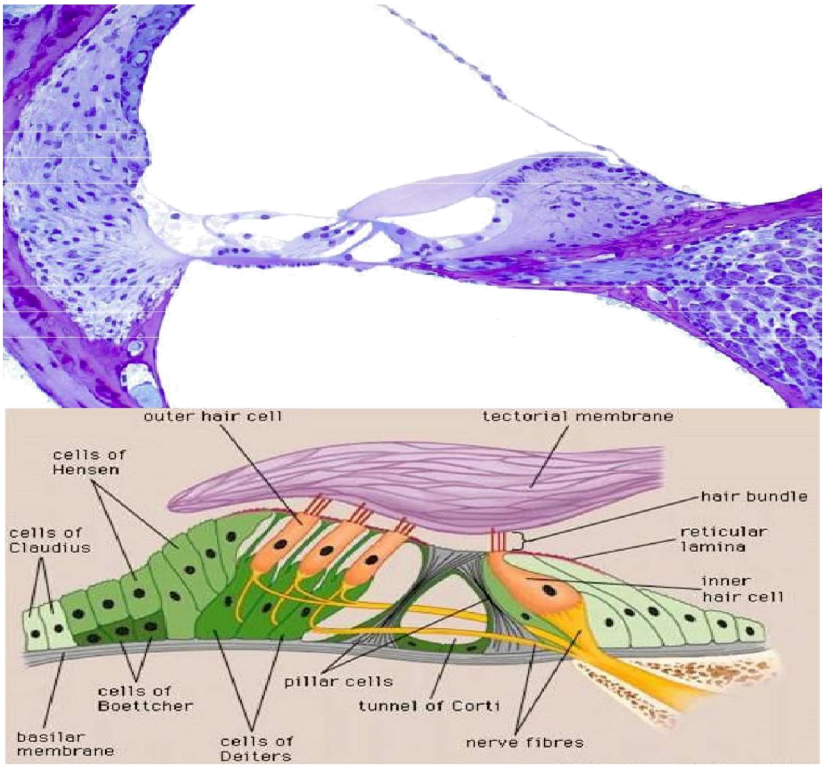


Figure-3.2: *Internal structure of the cochlea showing alignment of the Organ of Corti, inrelation to the Spiral Ganglion within the Rosenthal's canal and the further formation of the Auditory Nerve Fibers in the Modiolus. The survival of functional Spiral Ganglion population, nearly 35,000 in number (in spite of congenital or acquired damage to the Organ of Corti) is paramount for the success of electrical stimulation with cochlear implants [22] (From: Wright CG & Roland PS, 2005)*

The cochlear implant electrode array when placed in situ within the scala tympani, lies underneath and in proximity to the Basilar Membrane. It mimics the natural arrangement of the Basilar Membrane, with the multichannel electrodes serially arranged for stimulation according to the'place-pitch' conduction principle.[23] The major feature of stimulation via these electrodes is the absence of transduction by the Organ of Corti (Fig 3.2) since sound stimuli

externally pre-processed into electrical impulses are directly delivered to their respective regions within the cochlea. They trigger the Spiral Ganglia within the Rosenthal's Canal (bypassing the damaged Organ of Corti) which further conduct these signals to the auditory nerve and onto the auditory cortex where they are perceived as natural sound signals. Hence, the basic requirement for the success of cochlear implant aided hearing is the presence of a surviving spiral ganglion population within the damaged cochlea.[24], [25]

Auditory processing involves the encoding of sound energy into electrical signals. This process begins at the periphery in the cochlea and progresses through the cochlear nerve, the brainstem and the midbrain, and undergoes final integration within the cortex (Fig. 3.3), (Fig.3.4).

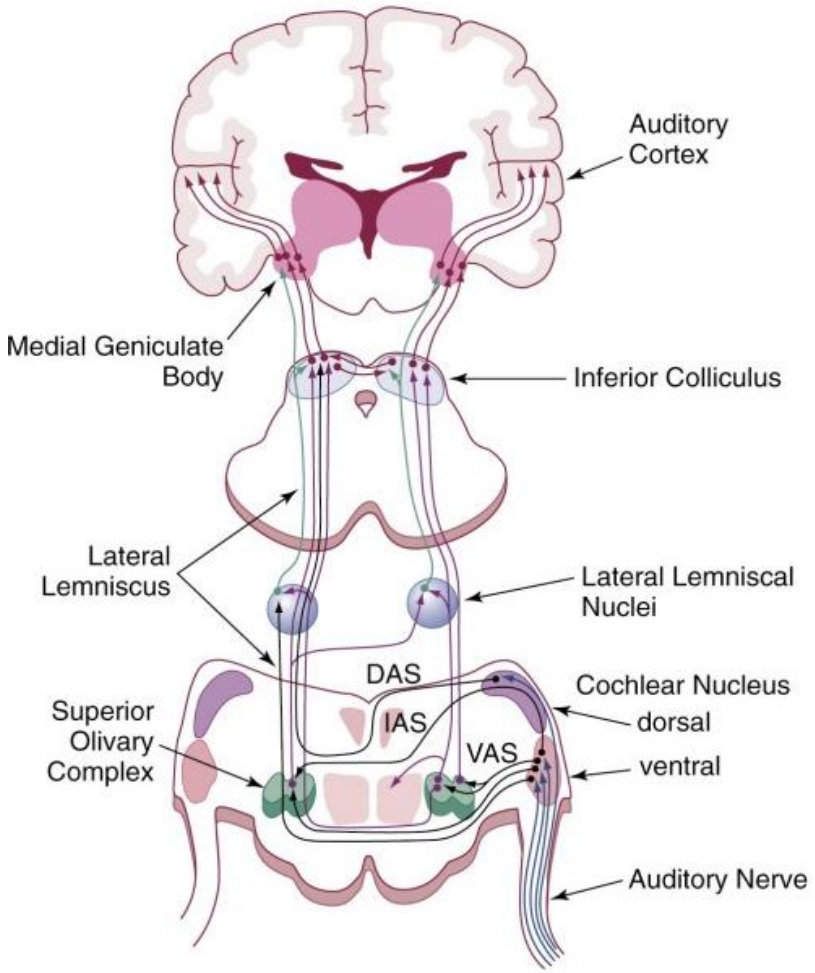


Figure-3.3: Illustration of the major central ascending auditory pathways for sound entering via the right cochlea. Commissural pathways and descending feedback projections from higher centers are not depicted. DAS, dorsal acoustic stria; IAS, intermediate acoustic stria; VAS, ventral acoustic stria. [26] (Cummings, vol 2, part 7, section 1, fig 128-6)

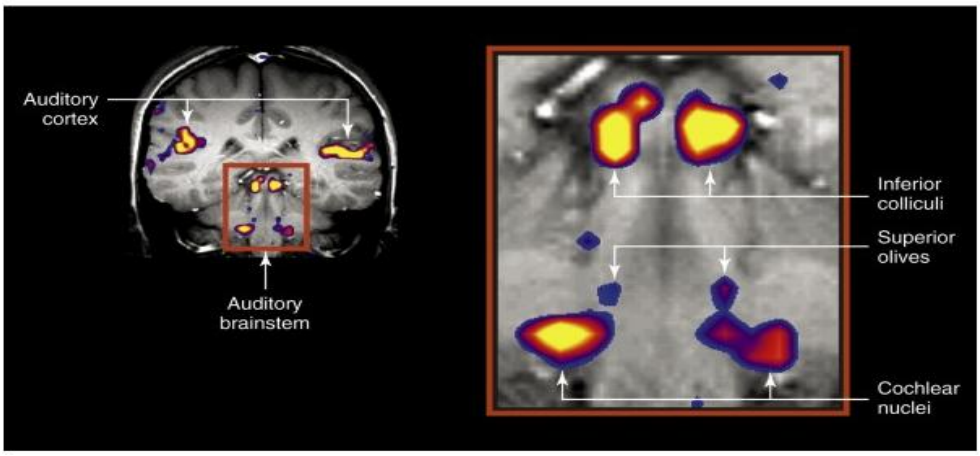


Figure-3.4: Functional magnetic resonance imaging showing the ascending pathways of auditory processing from the auditory brainstem to the auditory cortex. This figure shows activation of the cochlear nuclei (seen as areas of activation in the pontomedullary junction of the dorsolateral brainstem bilaterally), superior olives, inferior colliculi, and auditory cortex during bilateral acoustic stimulation in a normal-hearing adult patient. *[27] (Image courtesy of Jennifer Melcher, PhD)*

3.1.2 Cochlear Nerve

The cochlear nerve, a trunk of the cochleovestibular or eighth cranial nerve, contains afferent fibers transmitting auditory information from the inner and outer hair cells to the brainstem. The cell bodies of these afferent neurons are located within the spiral ganglion of the cochlea, whose neurons are predominantly myelinated.[28], [29] Spiral ganglion neurons are bipolar, with one process extending towards the inner and outer hair cells and the other projecting centrally towards the brainstem. Approximately 90% to 95% of the traversing axons are large myelinated fibers, and the remaining 5% to 10% are thinner, unmyelinated ones.[28], [29]

The afferent auditory neurons are also tonotopically tuned, similar to the basilar membrane and the hair cells. The tuning curves of the basilar membrane, hair cell and afferent neuron have similar attributes. At any given location along the cochlear partition, the basilar membrane, the hair cells, and the afferent neurons all have the same characteristic frequency. When a sound stimulus enters the cochlea, its frequency components are analyzed by the basilar membrane as a series of filters. This frequency information is preserved by the hair cells and the auditory afferent neurons, and transmitted to the central nervous system.

3.1.3 Auditory Brainstem and Midbrain

A. Cochlear Nucleus

The auditory nerve travels along the course of the internal auditory canal to terminate in the second-order neurons of the auditory system located in the cochlear nucleus. The cochlear nucleus is the critical first relay station for all ascending auditory information originating in the ear, and is located in the pontomedullary junction of the dorsolateral brainstem in humans.

The cochlear nucleus is subdivided into the dorsal cochlear nucleus, the anterior ventral cochlear nucleus and the posterior ventral cochlear nucleus. Each subdivision has a restricted population of cell types. The second-order neurons of the cochlear nucleus are tonotopically organized. The spatial representation of frequency-specific information in the cochlea is preserved in the cochlear nucleus.[29]Isofrequencylaminae (sheets of neurons that have the same characteristic frequency) are distributed from dorsal to ventral across each major cochlear nucleus subdivision.[30]

Inputs from the auditory nerve drive multiple cell types in different subdivisions of the cochlear nucleus, with each cell type projecting centrally to different targets in the superior olivary complex, lateral lemniscus nuclei, and inferior colliculus. Because individuals with normal hearing use both ears, sound localization is accomplished by neural processing of intensity and timing cues from each ear in the auditory brainstem. The temporal and spectral features of sound originating in the ear are processed in the cochlear nucleus, which is also the origin of parallel pathways. These pathways project to the auditory brainstem, midbrain, and cortex and integrate information from the ear to determine (1) the identity of the sound source, (2) the intensity of the sound source and (3) the location of the sound source.

The ventral cochlear nucleus contains many different cell types: (1) spherical bushy cells found primarily in the anteroventral cochlear nucleus (rostral), (2) globular bushy and multipolar cells found centrally, and (3) octopus cells found posteriorly (caudal). Spherical and globular bushy cells receive large auditory terminals with multiple synaptic specializations (end-bulbs of Held). This extensive contact allows the second-order neurons (bushy cells) to have primary-like responses to action potentials from the auditory nerve, preserving temporal and spectral information that is sent to higher auditory brainstem nuclei, the thalamus and ultimately, the auditory cortex. The End-bulbs of Held are vulnerable to sensory deprivation and congenital deafness is associated with unambiguous changes in these large synaptic terminals. Specifically, the postsynaptic density is larger and dysmorphic in deaf animals compared with normal-hearing controls,[31],[32] and these

changes may be reversed with electrical stimulation using a cochlear implant. [33]

From the cochlear nucleus, three fiber tracts form the lateral lemniscus and project auditory information to the contralateral inferior colliculus via the superior olivary complex: the dorsal stria (also called the stria of Monaco), the intermediate stria (also called the stria of Held), and the ventral stria (also known as the trapezoid body). These fiber tracts collectively form the lateral lemniscus. (Fig3.3).Some fibers from the cochlear nuclei do not cross the midline and project to the ipsilateral inferior colliculus. There are also connections between the cochlear nuclei of both sides. They represent the most peripheral connections between the two auditory pathways bilaterally. [34].

B. Superior Olivary Complex

The superior olivary complex is located medial to the cochlear nucleus in the caudal portion of the pons. It contains three main nuclei: the medial superior olive, the lateral superior olive and the nucleus of the trapezoid body. The superior olivary complex serves as a relay station for auditory information from both ears as some of the fiber tracts from the cochlear nucleus give off collaterals to the ipsilateral superior olive before forming the lateral lemniscus. Auditory information from both cochlear nuclei is integrated in the superior olivary complex; this region plays an important role in sound localization by analyzing interaural time and amplitude differences.[35]

The processing of auditory information from both ears by the brainstem nuclei not only allows for sound localization, but enhances auditory perception by two additional mechanisms: binaural squelch and summation. *Binaural squelch* refers to the ability of the brainstem auditory nuclei to increase the signal-to-noise ratio of the incoming sound stimulus through information processing.[36]*Summation* refers to the fact that a sound signal received by both ears is greater in amplitude than the same signal received by a single ear. [37]This increase in perceptual loudness is thought to improve speech intelligibility in a noisy environment. Binaural squelch, summation, and the head shadow effect are three mechanisms in binaural hearing that enhance auditory perception,[38] hence the better performance of bilateral implantees compared to unilateral implantees.

C. Lateral Lemniscus

The lateral lemniscus is the principal pathway by which medullary and pontine auditory nerve fibers reach the inferior colliculus. There are two subnuclei associated with this tract (i.e., ventral and dorsal) that receive differential innervation from the ipsilateral and contralateral cochlear nuclei and Superior OlivaryComplex (SOC) subdivisions.[39]

Most fibers from these subnuclei innervate the central nucleus of the inferior colliculus, but minor tracts ascend to the superior colliculus and descend back to the SOC and trapezoid body. The dorsal lemniscal nuclei also send commissural fibers to each other from the contralateral lateral lemniscus. The lateral lemnisci are closely associated with the SOC and play a role in many of the same functions (sound localization and processing)

D.Inferior Colliculus

The inferior colliculus is located in the midbrain just caudal to the superior colliculus. The inferior colliculus, similar to the cochlear nucleus, processes frequency-specific information.[40]It receives projections directly from the cochlear nucleus and also information about interaural time and amplitude differences from the medial superior olive and lateral superior olive. The inferior colliculus also integrates information from auditory and non auditory sources. Anatomic and physiologic studies show that the inferior colliculus receives auditory inputs from the lateral lemniscus, the cochlear nucleus, and the superior olivary complex,[41],[40] and projections from the somatosensory system,[42] and the visual and vestibular systems.[43] The inferior colliculus processes the information it receives and sends fibers to the medial geniculate body of the thalamus. The number of fibers going from the inferior colliculus to the medial geniculate body is about 250,000, which is almost 10 times the number of auditory fibres.[44] This increase in the number of nerve fibers at the level of the inferior colliculus is indicative of the substantial amount of signal processing that occurs in the central auditory system.

Almost all ascending and descending auditory pathways between the brainstem and forebrain synapse within the inferior colliculus.[45] Principal functions of the inferior colliculus involve sound localization, frequency determination, and integration of auditory with non auditory systems.

The inferior colliculusis divided into three main neuronal groups: the central nucleus of the inferior colliculus, the cortex of the inferior colliculus,

and the paracentral nuclei.[46] There is a laminar organization, likely related to the tonotopic map, which subdivides the central nucleus into a pars lateralis, pars centralis and pars medialis. Projections to the central nucleus of the inferior colliculus can be direct and monaural (from the contralateral cochlear nucleus), indirect and binaural (from the cochlear nuclei by way of the SOC) or polysynaptic (via the cochlear nuclei, SOC, and lateral lemniscus).

The cortex of the inferior colliculus is a laminar structure histologically seen to comprise of four layers. This region forms a cap around the dorsal and caudal aspects of the inferior colliculus. Innervations to the cortex of the inferior colliculus are primarily from the forebrain including the primary and secondary auditory cortex. These projections show tonotopic arrangement. There are few fibers to the inferior colliculus cortex from the lower brainstem and typically only from cochlear nuclei. Surrounding non auditory midbrain structures provide additional innervation to the cortex of the inferior colliculus. The paracentral nucleus of the inferior colliculus also receives non auditory innervations, primarily from the somatosensory system.

Ascending fibers from the subnuclei of the inferior colliculus all synapse in the medial geniculate body, where fibers are distributed to multiple auditory and non auditory cortical structures. These tracts are likely the initial pathways for integrating auditory, somatosensory, and special sensory systems. These patterns of innervation argue for the multi-integrative function of the inferior colliculus.

3.1.4 Thalamus and Auditory Cortex

A. Medial Geniculate Body

The medial geniculate body is the thalamic auditory relay center that receives auditory information from the inferior colliculus. It has three divisions: ventral, dorsal, and medial. The ventral division is large and has a stereotyped neuronal organization, the dorsal division is about equal in size and it has many nuclei and a corresponding neuronal diversity and the medial division, the smallest is one nucleus with six types of cells.[47],[48] The ventral division projects to the primary auditory cortex and the dorsal division projects to the auditory association cortex. The auditory processing performed by the medial geniculate body is greatly influenced however by an abundance of inputs from the auditory cortex that is believed to outnumber the projections it receives from the midbrain and lower auditory brainstem.[35] The medial geniculate body is thought to play an important role in sound localization and processing of complex vocal communications, such as human speech.It is the portal for all ascending auditory innervation to the telencephalon. Similar to other auditory centers, it is subdivided into several subnuclei—ventral, medial,and dorsal divisions.[49] Each of these divisions receives innervations from the nuclei of the inferior colliculus and descending fibers from the auditory cortex.

The ventral division of the medial geniculate body is secondarily organized into three distinct regions: the pars lateralis, the pars ovoideaand the marginal zone. The pars lateralis is the dominant region and has a laminar appearance because of the orientation of its large bushy cells and intrinsic interneurons. These layers reflect an underlying tonotopic organization. The bushy cells project to layers III and IV of the auditory cortex, where the

tonotopic map is recapitulated. Similar neuronal populations are found in the pars ovoidea and marginal zone, but with a less distinct laminar appearance.

The dorsal division of the medial geniculate body is a heterogeneous-appearing region comprising 10 subnuclei. The most basic description contains the dorsal, superficial dorsal, and deep dorsal nuclei, and the suprageniculate and posterior limitans nuclei. Inputs to the dorsal division include those from inferior colliculi and other thalamic nuclei. These auditory and non auditory connections may play a role in attending to acoustic stimuli.

The axons of neurons of medial division of the medial geniculate body project to all auditory cortical regions and many non auditory centers. Innervation to the medial division has some auditory origin, but it also receives non auditory contributions from the vestibular nuclei and spinal cord. These varied interconnections may play a role in arousal to auditory stimuli

B. Auditory Cortex

The main auditory portion of the cerebral cortex resides in the temporal lobe, close to the Sylvian fissure. The auditory cortex consists of multiple defined tonotopically organized regions.[50] The two major centers for auditory processing are the primary auditory cortex and the association auditory cortex (Secondary auditory cortex). The primary auditory cortex is located on the superior surface of the temporal lobe (Heschl'sgyrus). This is also known as area A1, and corresponds to Brodmann's area 41. The auditory association cortex is located lateral to primary auditory cortex .It is also known as area A2, and corresponds to Brodmann's areas 22 and 42. It has been shown that the

primary auditory cortex is tonotopically tuned, with high frequencies being represented more medially and low frequencies being represented more laterally (Fig.3.5).[51] These regions are structurally organized, similar to much of the cortex, into layers I through VI, each containing dominant populations of neurons and unique patterns of innervations and projection.

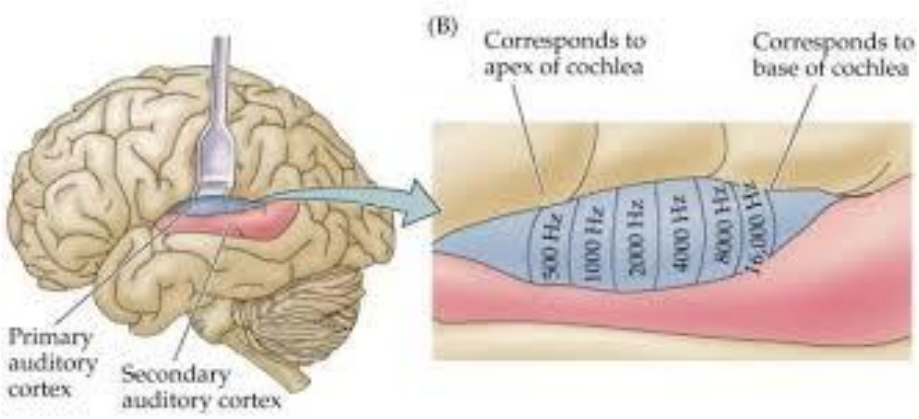


Fig.3.5 Shows Primary and Secondary Auditory cortex (source public domain)

The primary auditory cortex is involved with integrating and processing complex auditory signals, including language comprehension. The auditory association cortex being a part of a language reception area known as Wernicke's area plays an important role in speech perception as evidenced by Functional imaging studies.[52],[53]

Auditory informationfrom subcortical structures also projects to other parts of the brain, such as the amygdala, which is a part of the limbic system. This projection can help explain why sounds such as music can evoke strong emotional responses.

Numerous cortical association areas surround the primary auditory cortex. The posterior aspect of the superior temporal gyrus and the deeper

planumtemporale are known as Wernicke's area (left side) or area 22. Classically, this region has been viewed as a neural substrate for receptive language and is dominant on the left side in most humans. Just posterior to area 22, in the inferior parietal lobe, are the angular gyrus and supramarginalgyrus (areas 39 and 40). These cortical regions integrate auditory, somatosensory, and visual information. Higher orders of language integration, such as in reading and writing, may occur in these areas.

Functional imaging studies also suggest that the angular gyrus may play a role in tinnitus perception.[54] The arcuate fasciculus connects these association areas with the anteriorly located pars triangularis, which is part of the frontal operculum. This region of the inferior frontal gyrus is also known as Broca's area or area 44 and 45. Similar to Wernicke's area, this region apparently is left hemisphere dominant and is important for expressive language, and the perception of musical syntax.[55]

Advances like functional magnetic resonance imaging (MRI), positron emission tomography, and magnetoencephalography have expanded the understanding of cortical processing of complex auditory information, such as music. Reciprocal projections exist between the auditory cortex and lower auditory nuclei. Three principal descending pathways to the thalamus, midbrain, and brainstem have been reported. The primary auditory cortex projects to other cortical regions and to the medial geniculate body.[56] Projections from cortex to SOC and inferior colliculus seem to contact neurons that feedback to higher centers.[57] Direct cortical projections to cochlear

nucleus also have been reported in mammalian models.[58] These pathways may enable the cortex to modulate ascending auditory input.

3.2Plasticity

Plasticity is defined in otology as the inherent ability of the auditory (or vestibular) system to modify or reorganize. Levi-Montalcini R,(1949)[59] observed the anatomic changes to auditory pathways after experimental partial or total auditory deafferentation .These included cell counts, axonal pathway changes and alterations in neural structure. The methods for the evaluation of plasticity of auditory function include various electrophysiologic studies in animal models and in humans[60],[61] and functional neuroimaging methodologies. The latter include positron emission tomography, functional magnetic resonance imaging, and magneto encephalographic studies by Morris JS et al (1998), Pantev C et al (1998).[62],[63]

3.2.1 Time Course of Plastic Change

Plasticity is used to describe changes to the auditory system occurring very rapidly, over a span measured in minutes, weeks, months, and years. In acute plasticity, auditory neuron receptive fields (excitatory and inhibitory frequency tuning curves) have been observed to change within 10 minutes after induction of cochlear lesions or partial deafferentation.[64],[65] More extensive auditory system reorganization seems to occur over a longer time course. Studies show a modification of central tonotopic mapping as a result of cochlear lesions or partial deafferentation.[66],[67],[68],[69]

3.2.2 Historical Background

In neonatal ablation of one cochlea there may be loss or pathologic change, of neurons in brainstem and midbrain.[70] Other studies[71],[72] showed that visual cortical wiring responsible for ocular dominance columns is disrupted in cats if, during an early postnatal period, the animals have had visual input from one eye only (i.e., after neonatal monocular deprivation).

The reorganization of somatosensory maps in cortex after damage or partial deafferentation of the sensory inputs was initially shown after whisker removal in young rodents[73] and after peripheral nerve damage or digit removal in developing and adult animals.[74] These studies also showed that deafferented cortical areas (i.e., no longer receiving input from the periphery) become connected to areas corresponding to the border of the peripheral lesion.

3.2.3 Reorganization of Central Tonotopic Maps after Cochlear Lesions

"Plastic change in otology" explains central tonotopic map reorganization that occurs after lesions are made to the cochlea. It is known that the peripheral activity patterns can influence the establishment and maintenance of central frequency maps. Analogous to the central somatotopicprojections,tonotopic maps can be considered the mainline organizational feature of the auditory system. In the auditory system, the topographic order of afferent neurons is well maintained from the sensory epithelium of the cochlea up to the cortex.[75],[76] This projection system is known as "cochleotopic," analogous to the similarly organized retinotopic visual system and the somatotopic pathways of the somatosensory system.

3.2.4 Tonotopic Map Reorganization in a Developmental Model

Figure 3.6 shows two examples of cortical tonotopic maps in cats given ototoxic aminoglycoside amikacin shortly after birth.[77] This treatment resulted in basal cochlear hair cell lesions. Systemic administration of Amikacin resulted in bilaterally symmetrical cochlear lesions. Histological evaluation in subject A (see Figure. 3.6 – A) showed that the basal region of the cochlea was totally damaged (inner and outer hair cell loss), but in more apical areas, above the 6- to 8-kHz region, a normal sensory epithelium was present. This is consistent with the auditory brainstem response (ABR)–derived audiogram showing normal tone pip evoked ABR thresholds up to the high-frequency cutoff slope. The cortical tonotopic map for this subject is characterized by a normal representation of low frequencies, but the cortical region that has been deprived of normal input by the partial cochlear deafferentation now contains neurons that are all tuned to 6 to 8 kHz (shown as the shaded area). The boundary region of the cochlear lesion is abnormally overrepresented in terms of cortical space. In subject B (see Figure. 3.6-B), the results are more revealing. In this kitten, the cochlear lesion was more extensive, with a severe basal lesion and also scattered hair cell loss up to apical regions. This is reflected in the ABR audiogram that gradually slopes down across all frequencies measured. This kitten also developed a cortical frequency map in which there was a very large isofrequency area (shown as a shaded area) where all neurons have common 6.6-kHz frequency tuning. It seems that a reduced or abnormal stimulus-driven activity pattern from more apical cochlear areas has affected normal mapdevelopment.

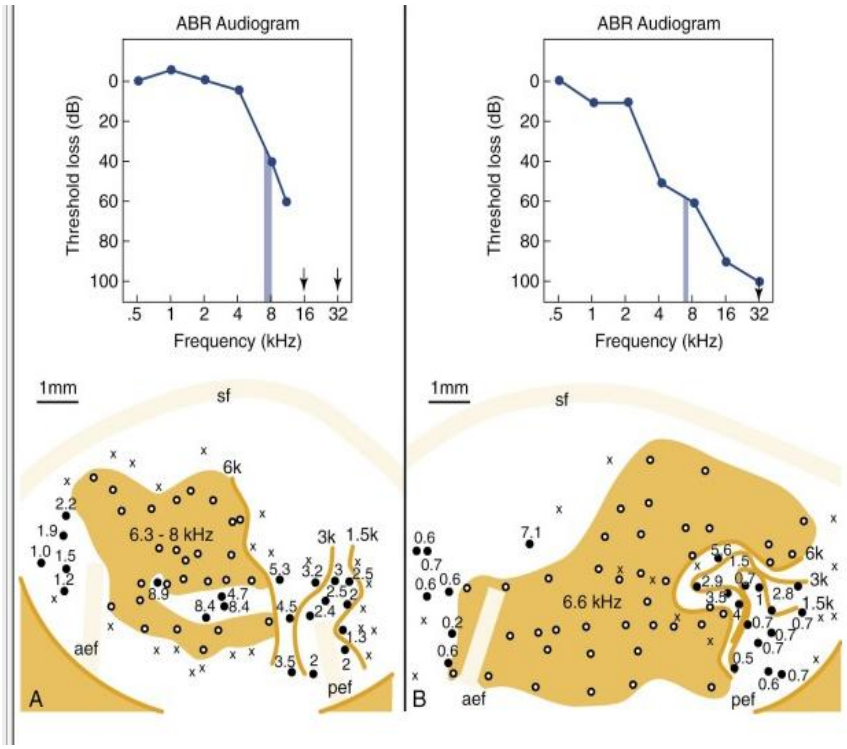


Fig 3.6 (A and B). Cortical tonotopic maps that developed in two cats with neonatal basal cochlear lesions. The kittens were administered the ototoxic aminoglycoside amikacin to produce basal lesions in the cochlea. The effects of such lesions are reflected in the auditory brainstem response (ABR)–derived audiograms (*upper panels*). **A,** In this subject, the cochlear lesion was confined to the basal region. **B,** In this subject, hair cell damage was maximal at the cochlear base, but scattered hair cell loss extended up to

3.2.5 Cortical Frequency Map Reorganization in Adult Subjects

The experimental results shown in Figure 3.7 were from studies in which the cochlear lesions were induced in neonates. Qualitatively similar results are found at the cortical level in adult animals with similar lesions. This was initially

reported by Robertson and Irvine (1989) [78] who were the first authors to report observations of altered central tonotopic maps resulting from peripheral lesions.

Figure 3.7 shows results from an adult chinchilla. Here a normal tonotopic map (Figure. 3.7 -A) is compared with a map recorded from an adult animal (Figure. 3.7-B) with induced cochlear lesions.[68] The anatomic extent of the lesion is shown on the cochleogram and the corresponding ABR audiogram shows the functional consequences- an overrepresentation of neurons with characteristic frequency of approximately 2.5 to 3.5 kHz (shaded area). In the adult animal, as with the developing subject, neurons in deafferented cortical regions seem to become connected to adjacent non interrupted ascending input.

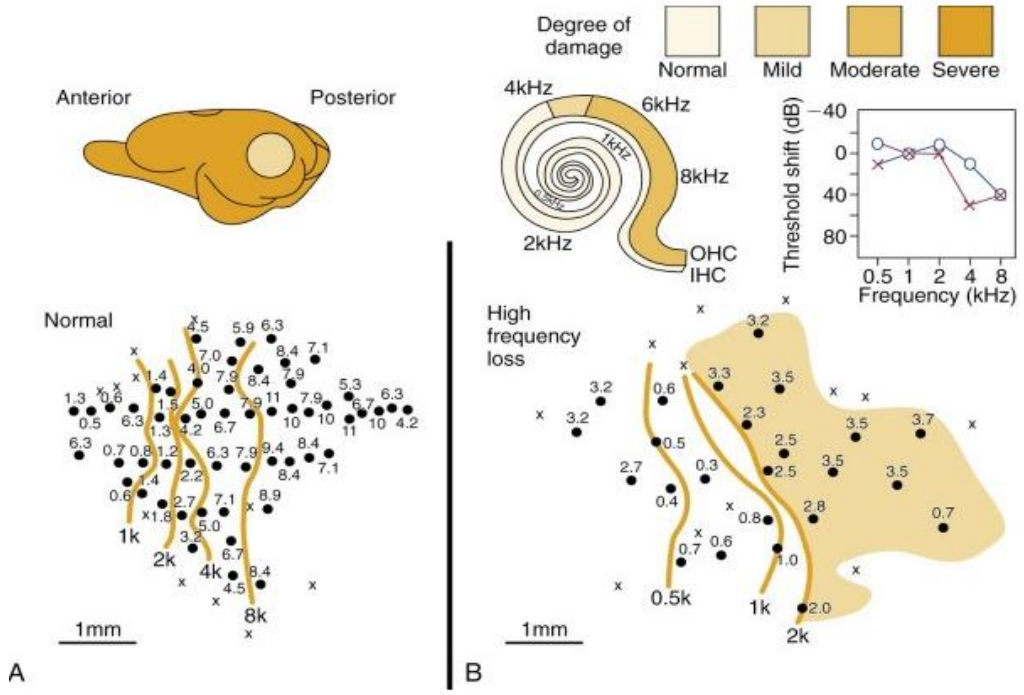


Fig 3.7. Cortical tonotopic maps in a normal adult chinchilla (**A**) and in a subject 4 weeks after inducing cochlear lesions by amikacin administration. (**B**).Isofrequency contours are octave spaced. The peripheral deficit in the chinchilla with cochlear lesion is reflected in the cochleogram and in the auditory brainstem response audiogram(**B**). The *shaded* area in the abnormal cortical map indicates the regions in which most neurons had very similar tuning properties. IHC, inner hair cell; OHC, outer hair cell.*[68] (Adapted from Kakigi A, 2000)*

3.2.6. Tonotopic Map Reorganization at Subcortical Levels

The schematic diagram depicted in Figure 3.8 is helpful in summarizing the differences in tonotopic map connectivity in developmental versus adult models. Unless there is future evidence to the contrary, it would seem that the

plasticity of subcortical regions (in terms of remodeling tonotopic projections) is possible only during an early developmental period. In adults, such plastic change seems to be confined to the cortex (or perhaps the thalamocortical complex). In this sense, these experimental data exhibit an age-related plasticity in the auditory system.

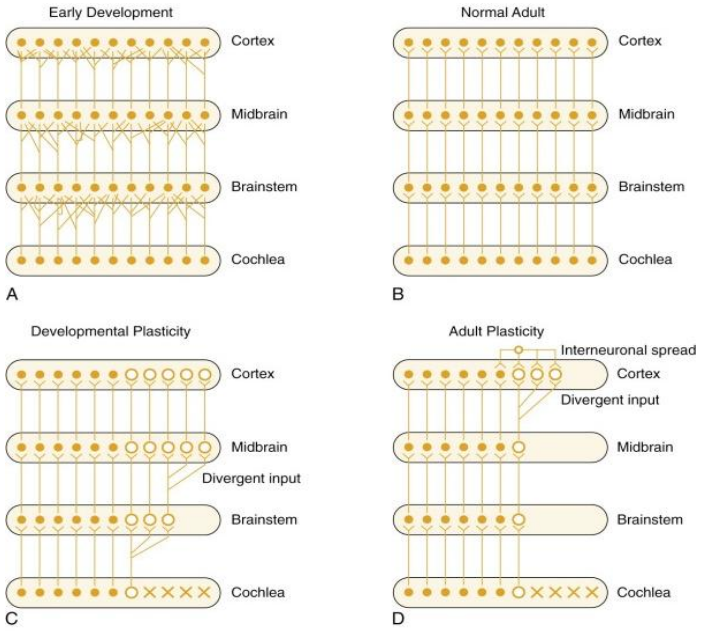


Fig 3.8.A schematic diagram to summarize salient aspects of developmental and adult plasticity experiments, with suggestions for possible neural wiring patterns. Each panel represents the ascending auditory pathway from cochlea to cortex. **A,** Early developmental stage when neural projections between levels have considerable divergence. **B,** Normally developed projection system. It is characterized by good point-to-point connections between auditory nuclei. **C** and **D,** Data from subjects after basal cochlear lesions induced neonatally (**C**) and in an adult (**D**). [79]

3.2.7 Hebb's Postulate

In 1949, Hebb[80] put forward many ideas regarding the conditions that might cause synaptic strengthening. His main postulate was as follows: “When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that *A*'s efficiency, as one of the cells firing *B*, is increased.” This notion has commonly been expressed as: “Cells that fire together, wire together.”

The potential complexity of various mechanisms that might contribute to changing the efficacy of a single synapse is emphasized by Figure 3.9.[81] Any combination of up to six presynaptic or postsynaptic mechanisms can modify the performance of a synapse. A typical auditory neuron may have hundreds of synapses; the possibilities for modification seem limitless.

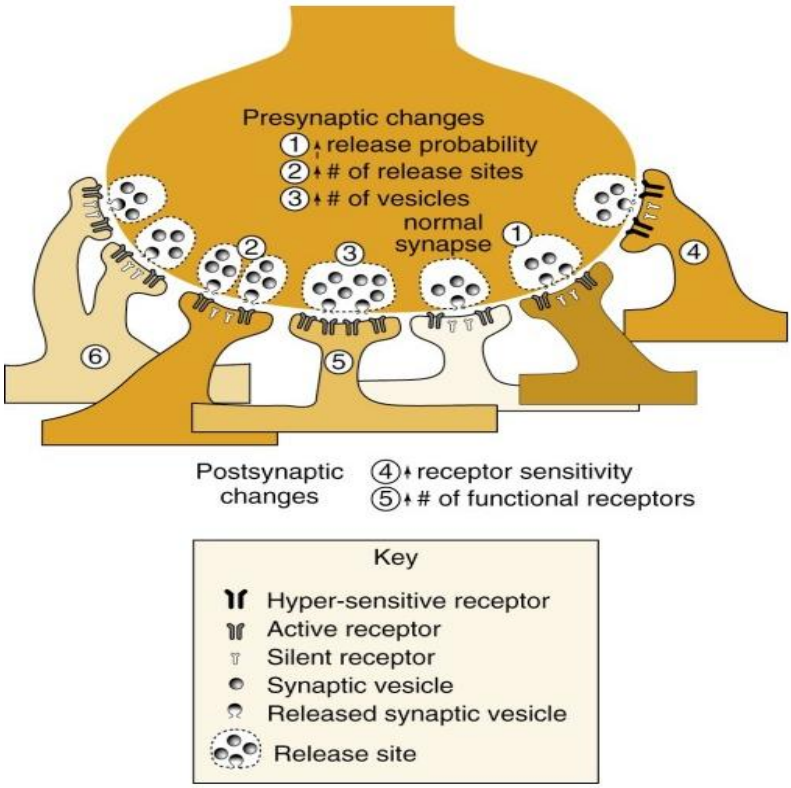


Fig.3.9 Overview of six possible presynaptic or postsynaptic mechanisms for enhancing synaptic efficacy.*1*,More presynaptic vesicles undergo exocytosis at a release site compared with the normal synapse. *2*,An increase in the number of release sites. *3*, Potentiation of a release site because of an increase in number of vesicles available for release.*4*, Increase in the sensitivity of existing postsynaptic receptors. *5*, Increase in the number of receptors. *6*,Synaptogenesis (i.e., new growth of synaptic contacts).[81]

3.3 Cochlear Implantation

3.3.1 Historical Perspective & Current Status

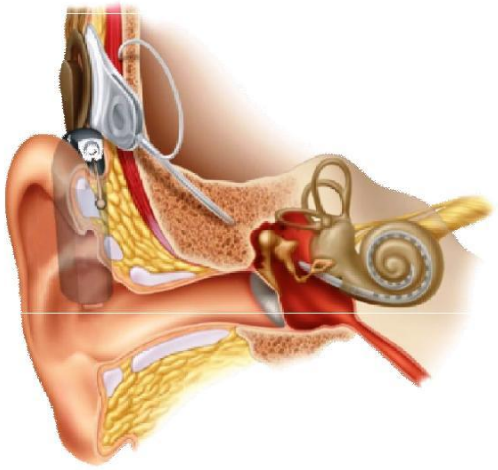


Fig 3.10: Schematic representation of a Cochlear Implant in-situ

The serendipitous discovery of auditory perception following electrical stimulation of the ear, as described in Volta's experiment, in 1790,[82] has today evolved by leaps and bounds, into the unique realm of cochlear implantation. Following Volta's cue of the possibility of electrically stimulating hearing, a string of researchers continued to experiment with electrical hearing over the next 167 years, but with little clinical success. Djourno and Eyries reported their first successful stimulation of the acoustic nerve by direct application of an electrode in a deaf person in 1957. Their achievement brought in an overwhelming wave of interest from various parts of the world and soon a string of similar single channel implantations were performed by House, Doyle, Simmons, and (Table- 3.1). The introduction of multi-channel implants by Prof. Graeme Clark in 1967, led to further advances in micro-electronics and speech

processor designs. Over the next fifty years, technological improvements produced refinements in surgery, miniaturization of implants with better electrode designs & precise speech processing strategies suitable for all environments, leading to the evolution of the present day cochlear implant system (Fig 3.10).[83]

Table-3.1: Historical Landmarks in the Evolution of Cochlear Implants

Year	***Scholar***	***Historical Landmarks in Evolution***
1790	***Alessadro Volta***	Used electrical current to stimulate the inner ear & published his auditory experience
1855	***Duchenne of Boulogne***	Used an alternating electrical current produced by a vibratory circuit to stimulate the inner ear
1868	***Brenner***	Published the effects of altering polarity, rate & intensity of the electrical stimulation on the placement of electrodes. He discovered that hearing quality was better with a negative polarity stimulus
1930	***Wever& Bray***	Demonstrated that the response to the electrodes form the surrounding area of the auditory nerve of a cat was similar in frequency and amplitude to which the ear had been exposed to
1936	***Gersuni&Volokhov***	Found that hearing could still persist after the removal of the tympanic membrane and ossicles, therefore giving an opening for the cochlea to be the site for electrical stimulation

Year	*Scholar*	*Historical Landmarks in Evolution*
1939	***Stevens & Jones***	Showed that electrical stimulus could be transduced linearly or non-linearly into sound vibrations before it reached the inner ear. They proved that the middle ear acted as a transducer converting electrical energy into sound by direct effect on the basilar membrane of the cochlea. Thus a direct stimulation of the auditory nerve produced a basic hearing sensation
1950	***Lundberg***	Performed one of the first attempts to stimulate the auditory nerve using a sinusoidal current during a neurosurgical operation
1957	***Djourno& Eyries***	Were the first to publish results of direct electrical excitation on the auditory nerve, using a trans-cutaneous magnetic inductive link, which laid the foundation for clinical research in human subjects
1961	***William House***	Implanted two patients with the first prototype of short term single electrode implants
1964	***Blair Simmons***	Successfully implanted a six electrode unit in an adult cochlea for the first time, thereby proving the place theory of electrical frequency coding

3.3.2 CI Technology & Surgery: An Overview

Over the last few decades cochlear implants have been established as time-tested electronic devices, used to restore hearing in individuals with severe to profound hearing loss. The last decade has especially seen tremendous progress

and refinement in implant technology and surgical techniques for newer models. The candidacy for cochlear implantation has expanded by leaps and bounds to include very young children, those with multiple handicaps, a spectrum of syndromic associations and also individuals with partial hearing loss.

Fig-3.11: Schematic representation of electrical hearing as provided via a cochlear implant

3.3.3 The Architecture of Cochlear Implants

The cochlear implant system comprises of an external and internal component, connected transcutaneously with a magnet during implant use (Fig3.11). The parts of a CI device include a directional microphone, which receives acoustic impulses from the environment and transmits them onto a speech processor. Here the impulses are converted into frequency specific

electrical signals and transmitted as coded signals, via radiofrequency to a transcutaneous transmitter-receiver/stimulator coil, worn on the mastoid part of the temporal bone. The receiver-stimulator coil in the internal system decodes these signals, producing a pattern of temporally arranged frequency- specific electrical stimuli, which get distributed along the electrode array placed within the cochlea. Since this method follows a pattern of 'place-pitch' stimulation, very similar to the tonotopic arrangement of the normal cochlea, these electrical signals are perceived by the spiral ganglion and first order neurons of the auditory nerve exactly like in normal ears, thereby providing nature-like auditory perception to the higher auditory centers (Laneau J, 2004).[2]

Recent technological improvements like the digitalization of speech processors with high rate stimulation, current steering and stochastic and fine-structure processing of sound signals enable enhanced clarity of complex sound signals in all environments and music perception skills for CI users. This matches a nature-like hearing experience. The speech processor codes the electrical signals digitally but the transmission of information onto the electrode array needs to be done serially in an analogue manner, in order to comprehensively provide a temporally integrated sound across the entire speech spectrum onto the higher centers. This aspect of implant technology is the focus of present day research of delivering digital sound signals directly onto the electrodes. Such an exciting possibility may eventually lead to completely implantable digital CI devices with remote programming options, obviating the need for a radiofrequency interface with an external speech processor.[84]

Ultra-high resolution CT scans of implanted children have now documented the enlargement of Rosenthal's canal, with growth and migration of

spiral ganglion population towards the electrode array over a period of implant use. This promising finding provides numerous possibilities for the restoration of neural elements via a cochlear implant, to alleviate any further intra-cochlear damage in future. Research can be focused on stem cell therapy and neural regeneration factors, which may be delivered via drug eluting electrode arrays to promote hair cell regeneration.[85]

Sound processing strategies represent a set of rules that define how the speech processor analyzes acoustic signals and codes them for delivery to the cochlear implant. These codes are processed in the form of Spectral Information and Fine-Timing / Temporal Information and delivered to the electrodes as Analogue and Pulsatile stimulus waveforms. A complete stimulating strategy should ideally address the number of channels selected to reproduce the original spectrum, the number of electrodes activated to generate each channel, the number of consecutive clock cycles required to deliver selected channels and the scheduling of the activating sequence of electrodes.[86],[87] It is important to adhere to a single strategy for stimulating the implant, while serially programming an individual, since any alteration in strategy between schedules, will unduly influence the current levels configured into the map and thereby induce variabilities in subsequent Mapping.

It is not possible to compare cohorts using different implant devices, or cohorts using the same device but with different speech processor models, since a variable bias gets induced due to differences in the electrode configuration and / or speech processing strategy, which will eventually provide results favoring the advanced models or strategies, used in the comparison.[88],[89]

3.3.4 Cochlear Implantation: the Surgeon's Perspective

With the candidacy for cochlear implantation expanding to include a panorama of difficult conditions, CI surgeons in the present day face a multitude of challenges during surgery in recent times. A meticulous assessment of candidates' temporal bone and cochlear nerve anatomy with high resolution radio-imaging and assessment of co-morbidities and fitness for surgery under general anesthesia are paramount in successfully performing the cochlear implant procedure without any untoward incidents.[90]

High resolution CT and MRI scans greatly aid in exploring the intricate anatomy of the temporal bone and help to identify congenital anomalies of the inner ear like an Incomplete Partition (IP) (Type-I), Mondini Deformity (IP-II), Large Vestibular Aqueduct, Common Cavity, cochleo-vestibular Dysplasia, cochlear ossification (congenital or post-meningiticsequelae), rotated cochlea, cochlear nerves aplasia or an aberrant course of the facial nerve in the middle ear. These scans also help in assessment of the vestibulo-cochlear nerve bundle in order to ascertain the candidacy for cochlear implantation and further decide upon the appropriate per-operative preparations necessary for implantation.[91]

Apart from the routine audiological test battery used to confirm the candidacy for CI, advanced objective electrophysiological tests like the trans-tympanic EABR and Cortical Auditory Evoked Potentials (CAEP) help to judge whether a candidate with a malformed cochlea and / or hypoplastic / thin VIII cranial nerve will benefit from the cochlear implant or not.

Surgery is essentially the same in children and adults because the anatomic structures are of adult configuration at birth. However, in very young

children, there is an increased risk of facial palsy, hypothermia and haemorrhagic shock. (more so, in a simultaneousbilateral CI).

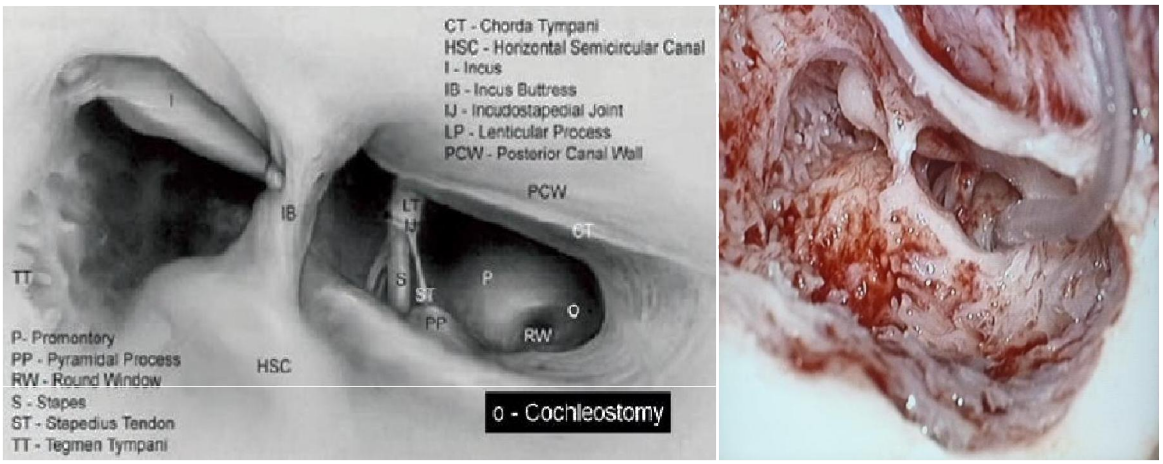


Fig. 3.12. The posterior tympanotomy approach for cochlear implantation

A detailed counseling session is mandatory for the parents & family, for emphasizing the surgical procedure including details regarding the risks involved, and the techniques of 'Switch-On' and programming of the device. The need for intensive Auditory Verbal Habilitation / Therapy (AVH / AVT) for a minimum period of one year should be emphasized in order to match their realistic expectations.

The success of cochlear implantation depends on scrupulous attention to technique at all steps of the procedure. The conventional posterior tympanotomy approach as shown in Fig 3.12is the best approach for access to the cochlea. The ultimate goal of CI surgery is to insert the entire electrode array into the scala tympani, with as little damage as possible to the ultra-structure of the inner ear. This has become possible with newer flexible, atraumatic electrode arrays, through the round window.

For children with congenital or acquired malformations of the cochlea, like the Mondini dysplasia, common cavity malformation or ossified cochlea, specialized electrode arrays (like straight / short / compressed / double / split) are available to provide the best possible intra-cochlear placement of electrodes for optimal stimulation of the viable neural elements within the deformed cochlea. Hence, it prevails upon the experienced CI surgeons, who take up these challenging cases, to judiciously choose the best electrode type to overcome the deformity.

Thus, cochlear implantation is relatively a safe surgery with minimal .complications. It restores the lost sense of hearing and aids the development of speech / language skills, thereby integrating CI users into normal society and leading productive lives.

3.3.5 CI Programming & Habilitation Protocols

The cochlear implant is 'Switched-On' three weeks after the surgery, providing sufficient time for the wound healing and convalescence. For pre-lingual hearing impaired individuals, the 'Switch-On' is a dramatic event, since it is the first experience of auditory perception. Very young children and those with additional handicaps may develop fear and aversion to this experience and may refuse to wear the implant later on. Hence, it requires an experienced audiologist to coax such children to wear the implant and to set the correct mapping levels, based on standard observation techniques. This has to be done periodically in the initial periods of implant use. Subsequently the MAPs have to be fine-tuned according to the individual needs of the implantee, as and when required.

3.3.6 The Art of Mapping

For cochlear implant users to perceive the desired range of acoustic signals from their environment, the features of these sounds must control the electrical stimulation within the cochlea in an appropriate way. Low amplitude speech sounds of different spectral structure should elicit soft percepts and higher amplitude acoustic signals should elicit louder percepts while avoiding uncomfortably loud stimulation. As the useful dynamic range for electrical stimulation is relatively narrow and varies across patients and electrodes, there is a need to tailor the amplitudes of electrical stimulation for each patient. This can be done by assessing the behavioral response to psychophysical and psycho-acoustical stimulation via the cochlear implant, for a wide range of input signals varying in intensity and frequency across the speech spectrum.

Behavioral responses are the 'Gold-standard' method for programming cochlear implants and they are sufficient to obtain accurate electrical threshold and comfort levels for the majority of adults and older children using cochlear implants. Although these levels are reasonably accurate at the time of programming, they tend to change over time.[92] It is normal, to low-set behavioural levels at initial mapping schedules in order to provide adequate psychophysical perceptive signals to the new implantees who would seek to understand and get familiar with the sound signals. These levels are later increased for each electrode along the array in a step-wise manner, with additional psycho-acoustical inputs, in order to provide an enhanced dynamic range of electrical hearing with loudness scaling, pitch ranking and electrode sweeping properties, as the cochlear implantees in due course become more adapted and conducive for higher intensity stimulation.

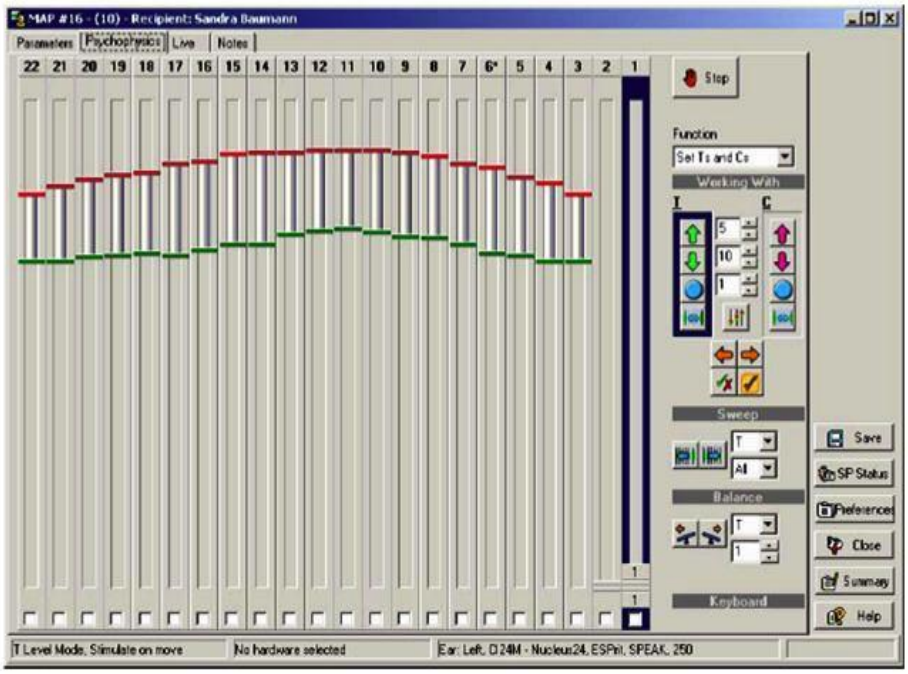


Fig 3.13: A behavioural MAP – The 'Gold-standard' for implant programming

Identifying most comfortable levels forms the basis of behavioural programming, while their threshold levels are auto-set by their map law, at 10% of the comfort levels to provide an adequate dynamic range across electrodes (Fig 313).

Once a series of maps are created, as per the implantees' preference, they are incorporated (fitted) into the speech processor as programs, which control the presentation of encoded sound information through the implant.The maps are within the dynamic ranges for stimulation as set for a particular sound environment.

The threshold and comfort Levels obtained for individual electrodes and

stored in the memory of the speech processor control the implant's function and are based on the loudness of the speech signals in most normal environments. But these levels may not necessarily provide comfortable speech comprehension in noisy environments. Hence stimulation with a particular program may be tolerable for a limited time, but could potentially become uncomfortable over a longer period of implant use. This necessitates regular programming sessions, especially during the first year after implantation, wherein attempts are made to provide a diverse range of maps, so that the implantees gets accustomed to various acoustic environments. Watchful observation of the implantees' auditory verbal skills over time of implant use provides useful feedback for the audiologist, to judge whether the program set for the implantees is optimal or not.

3.3.7 The Auditory Verbal Habilitation Protocol

Cochlear implantees are exposed to intensive auditory verbal habilitation soon after receiving their implants, for a minimum period of one year, in order to make them use the implant optimally and in the right way. Habilitation aims at development of new communication skills, rather than just replacing the lost hearing function. After cochlear implantation, with habilitation given as per the St.Gabriels' Curriculum, development of cognition, intelligence, receptive and expressive language skills occurs in a pre-determined, systematic order. Periodical assessment of these learned skills, are performed by professionally trained habilitationists, using a multitude of standard scoring systems. The most popular of these are the Category of Auditory Performance (CAP) and Speech Intelligibility Rating (SIR) scores[93] which have an ordinal, non-linear scale for assessment of the auditory verbal abilities of the implantees, taking into account

the time taken to achieve the skills.

As the implantees learn to listen with the help of the implant, they climb up an auditory skills pyramid, from a stage of auditory awareness / sound association to a stage of development of auditory processing and comprehension through closed-set and open-set interactions. As this happens, they simultaneously develop their speech skills from a stage of phonating isolatory words, to the formation of full sentences. Acquisition of enhanced auditory receptive skills and useful levels of spoken language attained through cochlear implants provides an opportunity to integrate the implantees into a normal curriculum thereby achieving scholastic skills. This indicates the successful outcome of cochlear implantation. Habilitation is extremely challenging in children with multiple handicaps and complex needs. Hence it is imperative for the habilitationist, to wear a thinking cap and cater to the individual needs of the implantees, by monitoring progress and by setting goals according to his / her areas of strength and weakness. It is paramount for the habilitations to work in tandem with the audiologist who provides the map for stimulation via the implant, as any poor performer needs to be troubleshooted at the earliest, to verify the optimal settings in their maps. If necessary intervention with re-mapping and enhancement of the habilitation protocols need to be pursued in order to eventually match the expected outcomes of cochlear implantation in such individuals.

3.4 Cortical auditory evoked potentials

3.4.1 Auditory Evoked Potentials

AEPs are usually categorized based on their time course or latency, but can also be separated into obligatory AEPs, which depend primarily on the

characteristics of the stimulus, and discriminative AEPs, which result from a change in stimulus characteristics.

Obligatory AEPs include the auditory brainstem response (ABR), the electrocochleogram (ECoG), the middle latency response (MLR), and cortical auditory evoked potentials (CAEP). Obligatory CAEPs are evoked by delivering a series of auditory stimuli (clicks, tone bursts, or speech sounds) while the person listens passively.

Discriminative CAEPs are recorded in response to a different (deviant/oddball) stimulus in the midst of a train of standard acoustic stimuli or in response to a change within an acoustic stimulus. Discriminative potentials include the mismatch negativity (MMN) and P300[94] recorded during passive and active listening, respectively.

CAEPs can be recorded at near-threshold levels.[95],[96] However, the evoked potential of choice for estimating hearing sensitivity in infants would usually be the ABR or Auditory Steady State Responses (ASSR). Currently, CAEPs are primarily used for objective assessment of central auditory function/neural encoding of speech sound.[94] For these applications stimuli are typically presented at suprathreshold intensity levels.

J.W.Hall [97] pointed out that the CAEP was the first auditory electrical response to be recorded from the central nervous system. Hallowell Davis attributed the first recordings of CAEP to his wife and colleague, Pauline Davis in 1939.[98]

The availability of computers and signal averaging in the early 1960s yielded an intensive period of research in CAEP and its potential clinical applications.[97],[98]Several papers on CAEP as a clinical procedure for

objective auditory assessment followed.[99],[100],[101],[102] Hall [97] states however, that interest in the procedure declined sharply following the first clinical reports on ABR in the mid 1970's.The reason for decline in interest was due to the effect of sedation and the state of arousal on the recording of CAEP, whereas the ABR was robust, despite the state of consciousness, and offered a distinct advantage in the pediatric population. Sleep state affects cortical activity and CAEPS are not reliably present during sleep,[103] whereas ABR and auditory steady state response (ASSR) evoked potential testing are usually performed during sleep. CAEPs are recorded while the listener is awake. Adults and older children would typically watch a silent subtitled video during CAEP recording whereas young infants are distracted using age-appropriate toys and books[104]

The auditory P1-N1-P2 complex in CAEP was discovered by Davis P. A. in 1939.[7] The components of the CAEP consist of sequential peaks and troughs labeled as N (negative voltage) or P (positive voltage), including P1, N1, P2, N2, as recorded with a vertex electrode.[97] In adults, the CAEP waveform consists of a series of peak or troughs (labeled P1, N1, P2, N2) that occur at about 50-250 ms. In infants and young children the CAEP waveform has a different morphology and is dominated by a large positivity (P1) at about 100-250 ms followed by a late negativity at about 250-400 ms.At younger ages the N1-P2 component was elicited only at the slowest stimulation rates, and was more clearly apparent at successively faster stimulation rates as age increased.[105]

Central auditory pathways involve all ascending and descending neuronal projections interconnecting the auditory nerve, brainstem, midbrain, thalamus, and cerebral cortex. The output signal from the cochlea travels along the auditory

nerve fibres in the cochlear nerve to reach the brainstem. The impulses travel through several nuclei before reaching the auditory cortex. In ascending order, the most important of these are the cochlear nuclear complex, superior olivary complex, inferior colliculus, medial geniculate nucleus and then auditory cortex.

4. MATERIALS AND METHODOLOGY

The present study was conducted to assess the CAEP parameters in cochlear implantees over a period of time and to assess if there is a relationship between the behavioural outcome scores and CAEP responses in cochlear implantees.

4.1.1 Study Groups:

The study included 64 non-syndromic, pre-lingual, profoundly hearing-impaired children aged less than 6 years, with normal inner ear anatomy and with no additional handicaps. Children with congenital inner ear and auditory nerve anomalies, autistic spectral disorder, auditory neuropathy, mental retardation, dyslexia, multiple handicaps, and other neurological or psychological disabilities were excluded from the study. All the candidates were selected for cochlear implantation as per the standard guidelines formulated in the Consensus Document of the Cochlear Implant Group of India, 2004 available online at www.cigi.in. Prior to inclusion in the study, written and informed consents were obtained from the parents of the candidates in English / their mother tongue, after counseling regarding the test protocols and the anticipated outcomes of the study. The Institutional Ethics Committee provided full approval for this study in July,2012.

The participants, all with Tamil as their mother tongue, were divided into two groups based on age. Group 1 included implantees less than 3 years and Group 2 had implantees between 3 and 6 years of age.

4.1.2 The Study Design: A non-interventional / observational and analytical, prospective Cohort study correlating the standardized clinically available electrophysiological test (CAEP)with subjective responses (CAP and SIR), in two cohorts of cochlear implantees.

4.1.3 Inclusion criteria

- Bilateral severe to profound sensorineural hearing loss.
- Congenital hearing loss
- No other congenital ear anomaly or syndromic associations
- The child must have had an assessment by an audiologist and an otolaryngologist experienced in this procedure indicating the likelihood of success with this device.
- The child must have arrangements for appropriate follow-up care including the long-term habilitation and speech therapy required to exploit the full potential of this device.

4.1.4 Exclusion criteria – Candidates with multiple handicaps, syndromes, inner ear and eighth cranial nerve anomalies, auditory neuropathy, dyslexia, mental retardation, neurological and psychological disabilities and children above 6 years of age.

4.1.5 Study Period: January 2013 – December 2015

4.1.6 Study Center: This single center clinical study was performed at;

Madras ENT Research Foundation (MERF), Chennai and

Cochlear Implant Electrophysiology Lab & Habilitation Clinic,

Madras ENT Research Foundation (MERF), Chennai

4.1.7 Professionals Involved:

The principal investigator – Dr. K. Sathiya, Consultant ENT Surgeon, MERF, Chennai,performed the study under the guidance and supervision of the Research Advisory Board which comprised of Prof. Mohan Kameswaran, Chief Consultant ENT Surgeon, Madras ENT Research Foundation, Chennai (guide), Dr. R. S. Anand Kumar, Senior Consultant ENT Surgeon, Madras ENT Research Foundation, Chennai (co -guide) and Mr.R.Ranjith, Senior Audiologist and Principal, Madras ENT Research Foundation – Institute of Speech and Hearing, Chennai.

The study required assistance from the cochlear implant surgical team, implant audiologist, auditory verbal habilitationists, clinical psychologists and pediatricians. Mrs.Valarmathy Srinivasan, Biostatician, performed the data analysis for this study.

4.1.8 Financial Disclosure: The study required no funding / financial assistance. The electrophysiological testing equipment and programming software required for the study were provided by Madras ENT Research Foundation with no additional cost incurred by the candidates for participating in the study.

4.1.9 Risk Disclosure: This was a non-interventional, observational and analytical study which involved NO RISK to the participants of the study group.

This research was approved by the institutional ethical research review board and an informed written consent from the parents / legal guardians of the

study group was taken prior to their inclusion in the study. All chosen candidates were evaluated with CAEP prior to implantation. They were screened for speech, language and neurological development, and referred to the audiologist, speech / language pathologist, ophthalmologist, occupational therapist and the child psychologist for assessment of higher mental functions and Intelligence Quotient. All the participants in the study group were sent to meet the auditory-verbal habilitation therapist at our institute prior to surgery, to make them adapt to the habilitation program. They were also vaccinated against meningitis two weeks prior to surgery.

4.1.10 Test environment

All the audiological tests were conducted in an air-conditioned sound treated room with noise levels within the permissible limits (ANSI S3.1, 1999).

4.2 EQUIPMENT & TOOLS

4.2.1 INSTRUMENTATION

HEAR Lab ACA was used to record the aided (with implant) late latency response in both the groups. The loudspeaker was calibrated and the participant was made to sit one meter away from the loudspeaker.

4.2.2 TOOLS

CATEGORIES OF AUDITORY PERCEPTION (CAP) (O' Donoghue et al 1999) was used to evaluate the effectiveness of the cochlear implantation in children by assessing auditory perception skills in a natural context and monitoring auditory perception skills across time in everyday life situations. CAP consists of eight categories denoted from 7 to 0, including the criteria of using a

telephone, understanding conversation, discrimination and identification of sound etc. This was monitored during the child's auditory development at 3, 6 and 12 months of implant age. (Appendix-D-3)

SPEECH INTELLIGIBILTY RATING (SIR) (Donoghue et al 1999) was used to assess the speech production skills in the natural context and to monitor the speech production skills over time. It consists of five categories ranging from intelligible speech to unintelligible speech with respect to different speech context. This was monitored during the child's auditory development at 3, 6 and 12 months of implant age.(Appendix D-4).

4.3.1 Procedure

For the purpose of evaluating the objectives, the data collection was done at 3, 6 and 12 months of implant age, recording CAEP parameters and measuring CAP and SIR score(Figure 4.1, Figure 4.2).

Figure 4.1 CAEP testing in progress

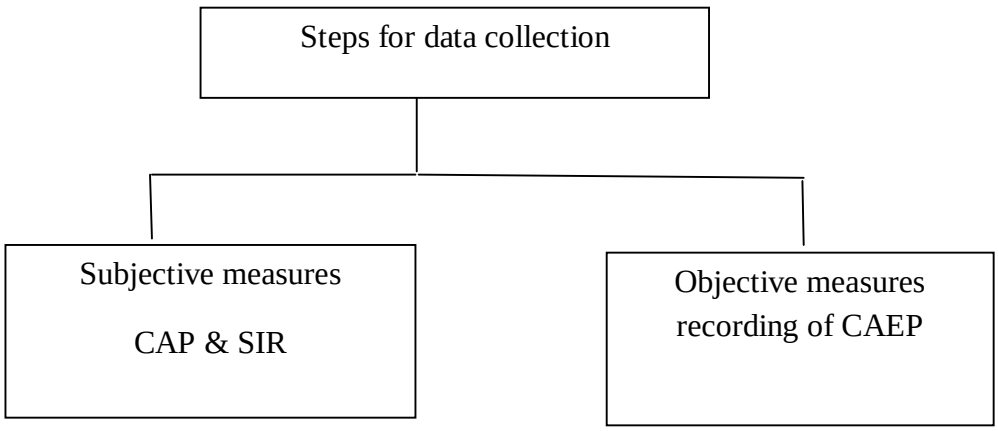


Figure . 4.2 Flow chart for data collection.

Implantees were 'Switched-on' 3 weeks after surgery and habilitated at our Implant clinic for a minimum period of one year. CAEPs were tested in all implantees at 3, 6 and 12 months after surgery. CAEP waveforms were recorded with the NAL HEAR LAB Frye electronics instrument. Cortical assessment module was used to record CAEPs with speech stimuli //m// (low),//g//(mid) and //t//(high)via loud speaker (Figure 4.1). These essentially vowel-free stimuli were chosen because they had a spectral emphasis in the low-, mid-, and high-frequency regions respectively, and thus had the potential to give diagnostic information about the perception of speech sounds in different frequency regions. The test stimuli were presented at the rate of 1.1/s via a loudspeaker at 55dBSPL, 65dBSPL and 75dBSPL. Of the three speech stimuli - //ma//ta//ga.//ta stimuli responses were chosen for analysis as it is the most common speech sound used across different languages. Of the three different intensities - 55, 65, 75 dBSPL, However 65 dBSPL was chosen for analysis because it is equal to the conversation level during speech. (Table 4.1)

Parameters	**Settings**
Test type	Cortical Auditory Potentials
Aided/unaided	Aided (Implant)
Transducer	Loudspeaker
Position of the loudspeaker	1 meter distance with the azimuth of 900.
Electrode sites	Active – vertex upper forehead(Cz) Reference –non test ear mastoid Ground – forehead
No. of epoch	200

Intensity level	65 dB SPL,
Stimulus used	high frequency /t/ (30 ms)
Filter settings	0.16-30 Hz
Polarity	Alternating

Table 4.1: Depicting the protocol used for recording the cortical auditory evoked potentials.

The participants were seated at a distance of 1 meter at 0^0azimuth to the loudspeakers. Speech processors were set to the children's usual program settings. Subjects were seated comfortably in a reclining chair in a sound treated room, watching a muted video or cartoon on a TV placed in front of them. Evoked potentials were collected using CZ as the active electrode. CZ refers to the vertex midline placement. The reference electrode was placed on the mastoid and the ground electrode on the forehead. Time-locked averaging was automatically suspended by the recording computer. The recording window included -200ms pre-stimulus time to +600ms post-stimulus time. Incoming evoked responses were analog filtered from 1-30 Hz. Approximately 200 response sweeps were recorded for each stimulus. The test session including electrode application and evoked response recording lasted approximately 25 minutes. The presence of CAEP responses were defined as the largest positive peak (P1) in the region of 100 ms to 300 ms after stimulus onset. The latency of the peak was measured at the center of the double peak. When the waveform contained a double peak, the latency was measured at the midpoint of the peak. It was made sure that absolute impedance of the electrode was < 5kΩ and inter-

electrode impedance was 2 kΩ prior to testing. Sweeps greater than +/- 30 microvolt were rejected on-line and the remaining sweeps were averaged to compute a final grand-averaged waveform for the individual subject. The same procedure was repeated in all schedules of follow up. Speech and language assessments were done using CAP and SIR scores. All implantees in the study group attended the same habilitation center and the same number of classes (twice weekly).

To eliminate the subjective bias except the investigator the surgeons, implant audiologists and habilitationists were blinded from the study

Overcoming variables during study

1.Electrode Montage: Standard default montage sites were chosen across all subjects

2. Sweeps: Standard 200 sweeps were used across all subjects

3.Time window: Time window was consistently maintained at 300ms across all implantees

4.Response Criteria: This was kept with P value less than.005 for all recordings. Responses above this were rejected

5.Stimulus: Responses of //t// stimulus at 65dBSPL were uniformly used for stastistical analysis in all subjects. The stimuli is a synthesised stimuli synthesised using a KLATT synthesizer by the manufacturer.

6.State of Arousal: All implantees in the study were ensured that they were fully alert during the study by watching a muted video

4.3.2 Procedure for Analysis of Latency, Amplitude and Morphology

The latency and the amplitude of the CAEP waveform were visually inspected by an expert implant audiologist who extracted the latency and the amplitude information and the subjective note on peaks. The audiologist was instructed to mark the presence and absence of peaks and statistical detection of peaks was noted. After the complete evaluation, the scores from all the phases were tabulated and subjected for statistical analysis.

The morphology was visually graded by two independent expert implant audiologists who were blinded from the groups and from the time interval of data collection, to categorize the waveforms as poor (1), fair (2) and good (3). All parameters were assessed at 3, 6 and 12 months and comparisons were done within each group and between the groups.

4.3.3 Statistical analysis

The data obtained were tabulated and statistical analysis was done using Statistical Package for Social Science (SPSS version 21).

1. Quantitative data was given in mean and standard deviation.
2. Qualitative data was given in frequency and percentage.
3. Paired ‘t’ test was used to compare within groups.
4. Independent‘t’ test was used to compare between groups.
5. Pearson Correlation was used to assess the relationship between variables.
6. The Logistic Regression Analysis was done to predict outcome measures in both groups using latency of CAEP as an objective tool for optimal prediction of outcomes.

The following charts are representative examples of our recordings (Fig. 4.3 - 4.8)

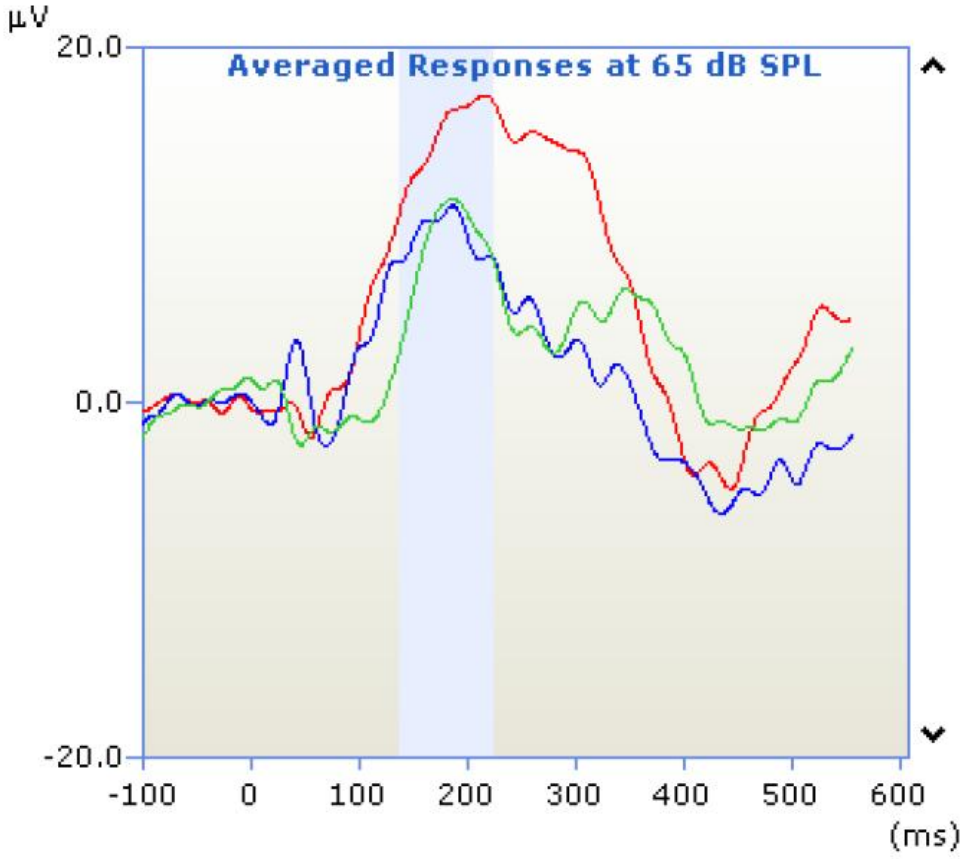


Fig. 4.3. The above CAEP is an example of a normal hearing infant with latency of 200ms

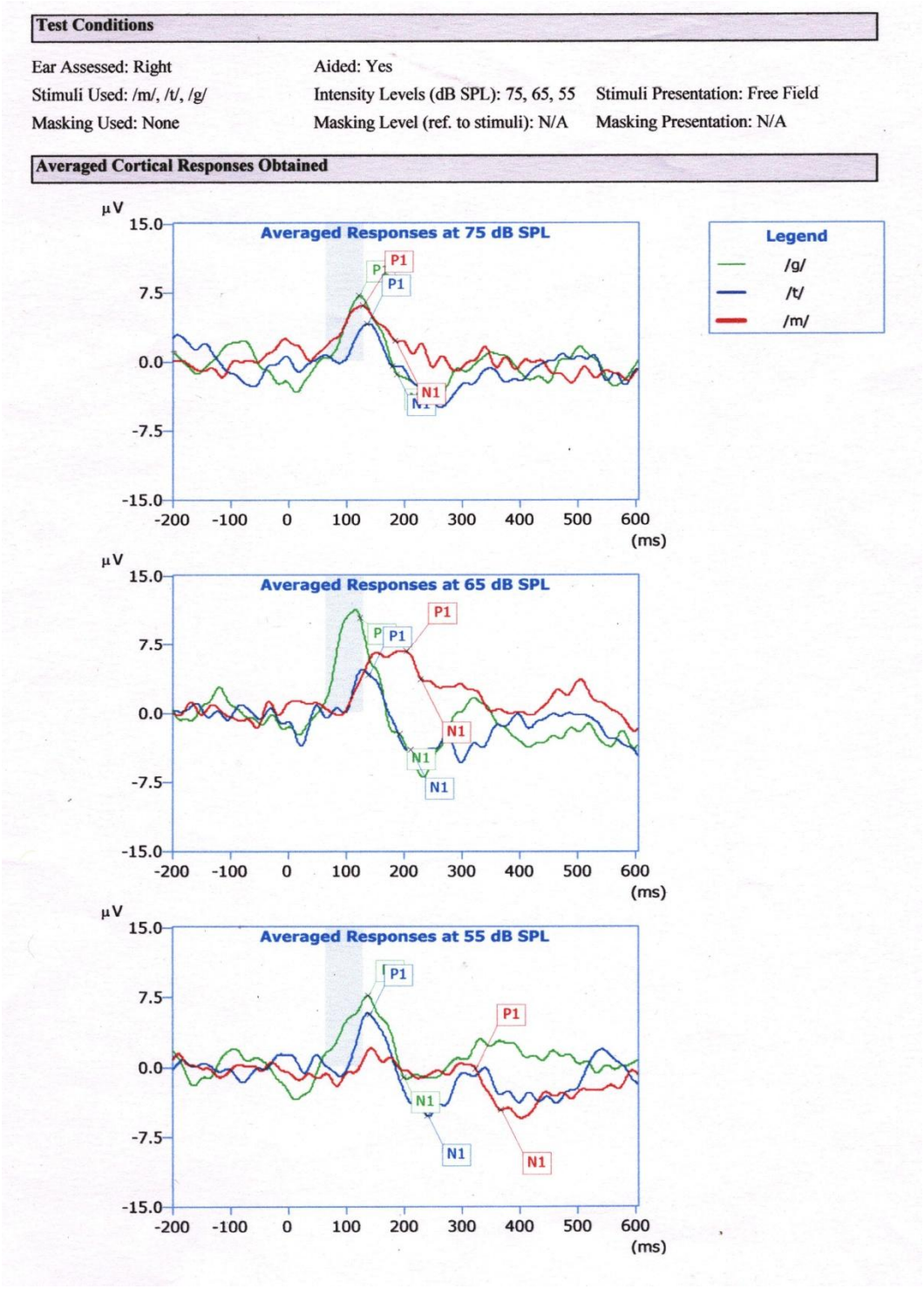


Fig. 4.4 - CAEP waveform depicting the responses to //m//t//g// stimuli at the level of 55, 65 and 75 dBSPL .The amplitude of P1N1 peaks was found to be good. (t stimulus at 65 dB taken for analysis)

Test Conditions

Ear Assessed: Right	Aided: Yes	
Stimuli Used: /m/, /t/, /g/	Intensity Levels (dB SPL): 75, 65, 55	Stimuli Presentation: Free Field
Masking Used: None	Masking Level (ref. to stimuli): N/A	Masking Presentation: N/A

Averaged Cortical Responses Obtained

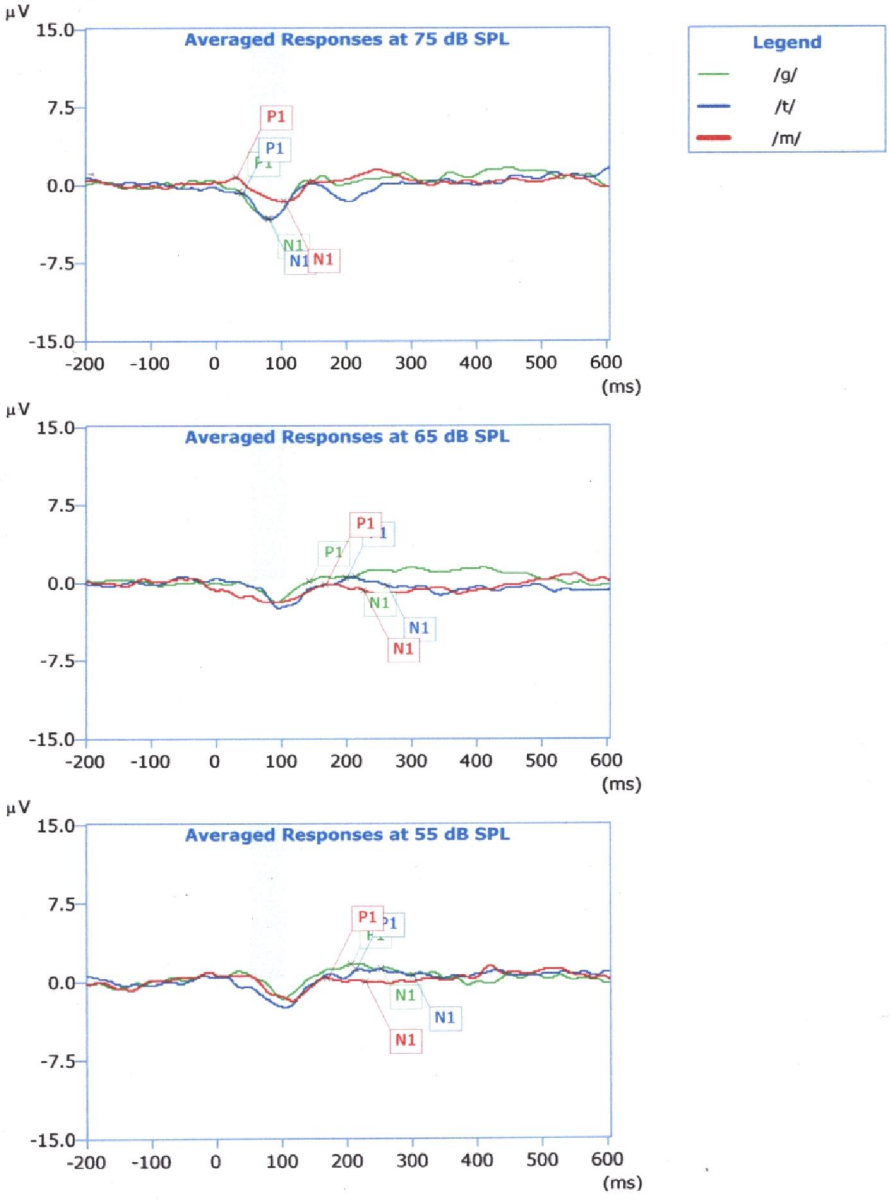


Fig. 4.5 - The Above CAEP waveform depicts the responses to //m//t//g// stimuli at the level of 55,65 and 75 dBSPL .The amplitude of P1N1 peaks was found to be poor. (t stimulus at 65 dB taken for analysis)

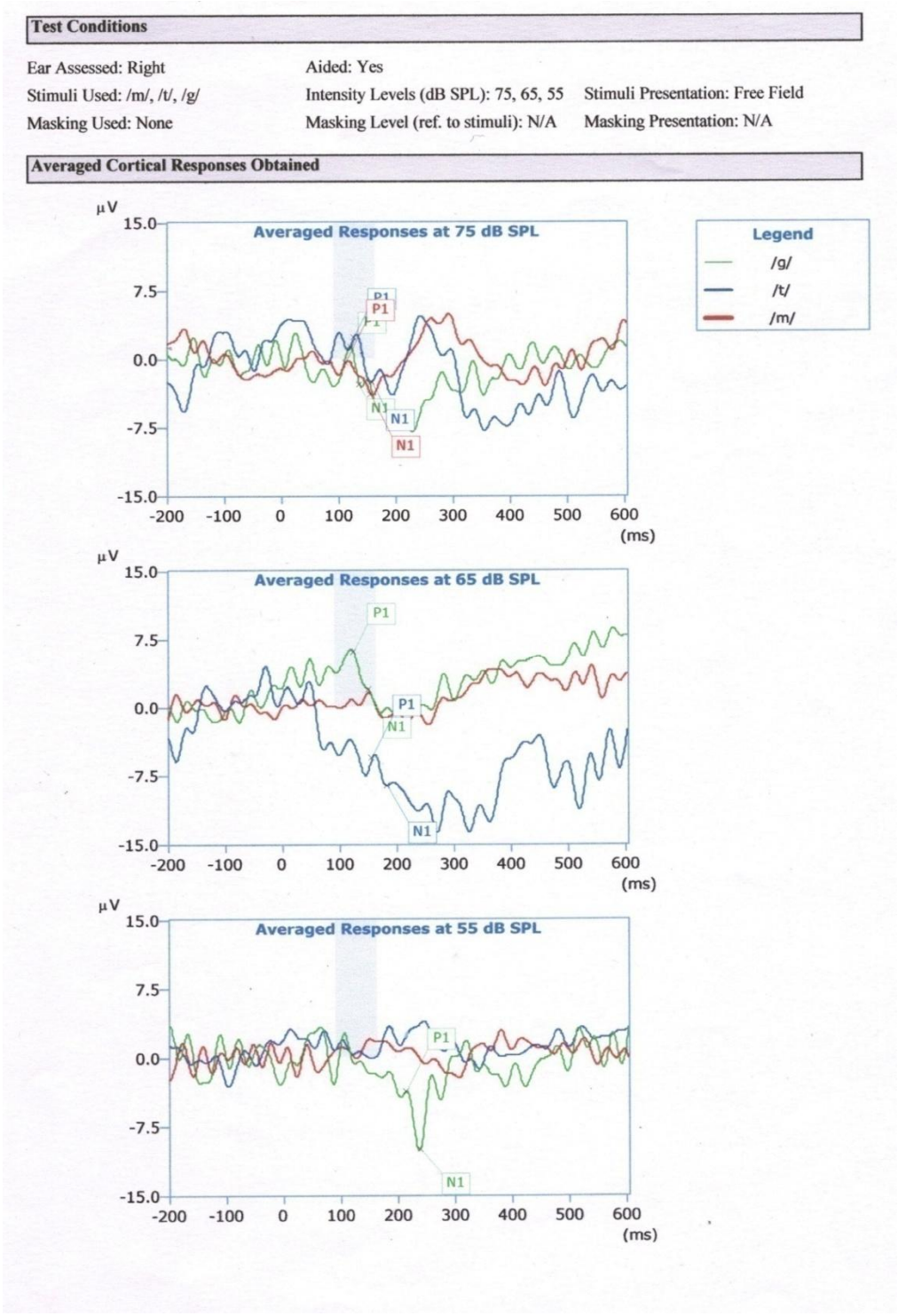


Fig. 4.6- The Above CAEP waveform depicts the responses to //m//t//g// stimuli at 55, 65 and 75 dBSPL .The morphology of P1N1 peaks was found to be poor. (t stimulus at 65 dBSPL taken for analysis)

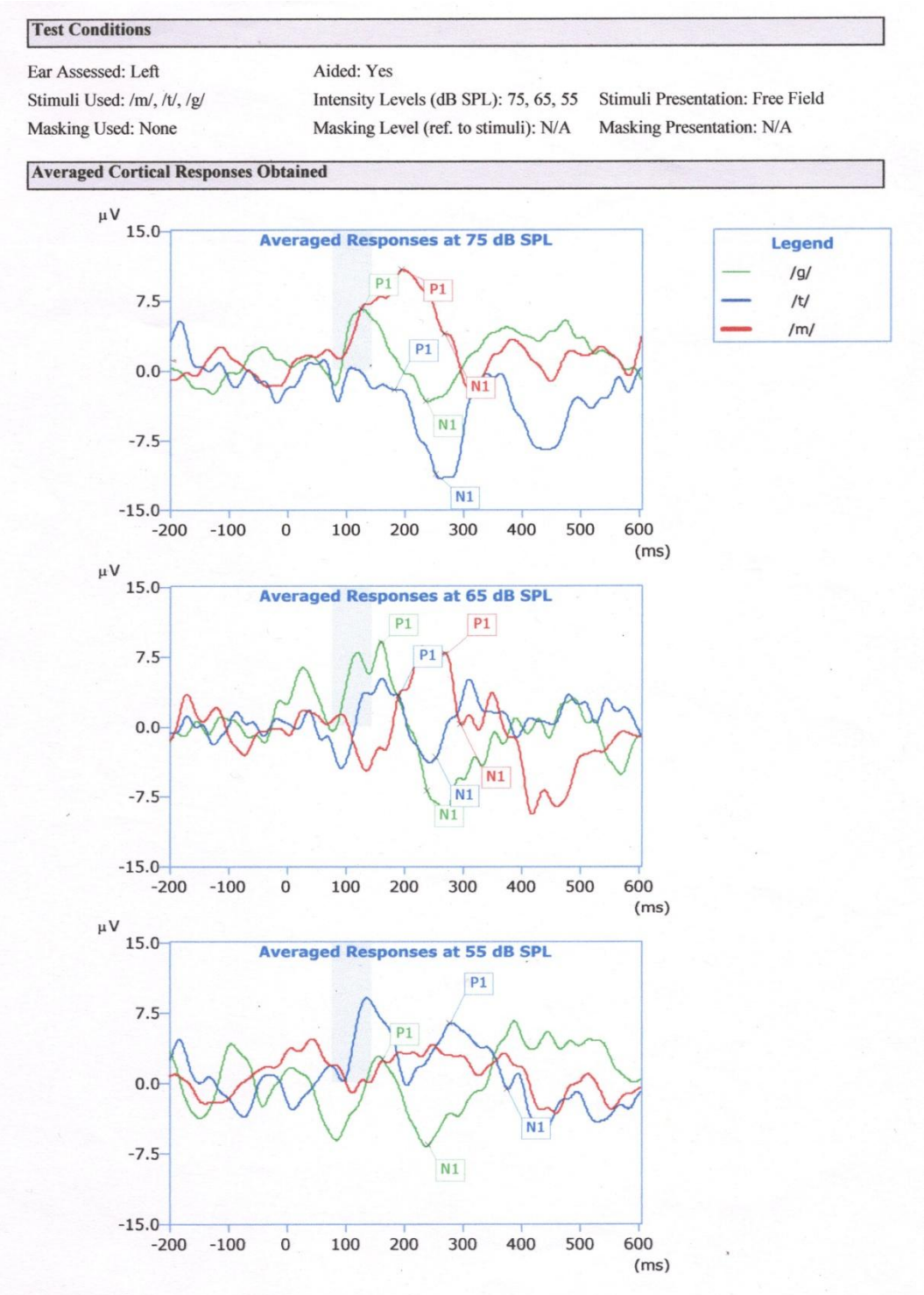


Fig. 4.7 - The Above CAEP waveform depicts the responses to //m//t//g// stimuli at 55, 65 and 75 dBSPL .The morphology of P1N1 peaks was found to be fair. (t stimulus at 65 dBSPL taken for analysis)

Test Conditions

Ear Assessed: Right	Aided: Yes	
Stimuli Used: /m/, /t/, /g/	Intensity Levels (dB SPL): 75, 65, 55	Stimuli Presentation: Free Field
Masking Used: None	Masking Level (ref. to stimuli): N/A	Masking Presentation: N/A

Averaged Cortical Responses Obtained

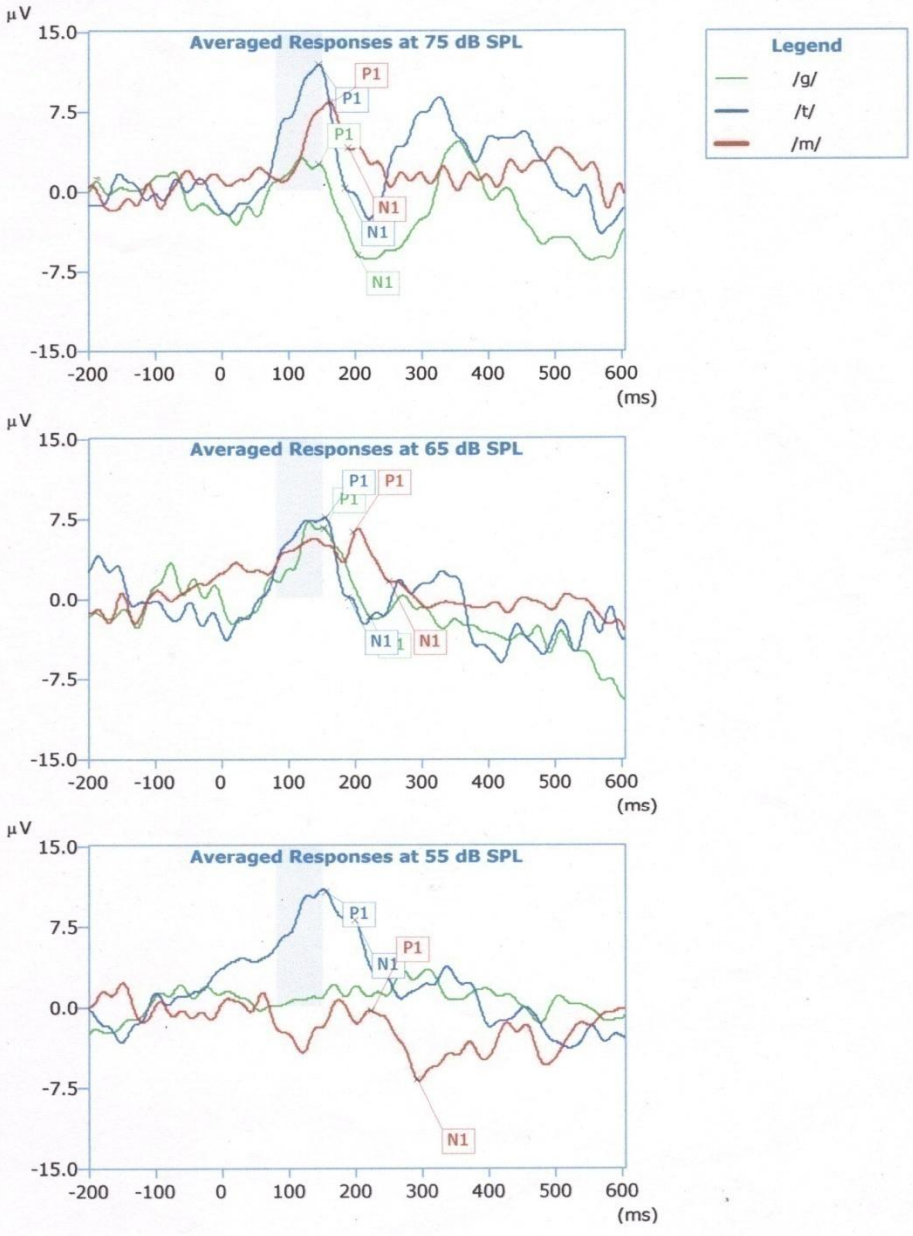


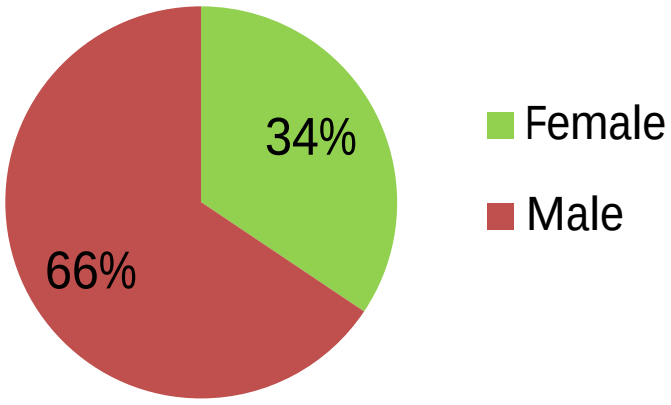
Fig. 4.8 - The Above CAEP waveform depicts the responses to //m//t//g// stimuli at 55, 65 and 75 dBSPL .The morphology of P1N1 peaks was found to be good. (t stimulus at 65 dBSPL taken for analysis)

5. RESULTS AND ANALYSIS

A total of 64 implantees were included in this study which was done in a single center with limited samples over a short follow up duration of 1 year. This was due to logistic reasons like limited availability of ideal candidates and the lack of adequate amount of data for showing statistically significant results. All of them attended the same number of habilitation sessions, i.e. twice a week for one year, at the same habilitation centre. Majority of the implantees 42 (66%) were male children (Figure 5.1). The implantees were divided equally into two groups. Group 1 included implantees less than 3 years of age and Group 2 consisted of implantees between 3 and 6 years of age. CAEP parameters - (latency, amplitude and morphology) were assessed at the time period of 3 months, 6 months and 12 months for both groups, and the CAP and SIR scores were extracted from the habilitation records for the respective time periods.Latency is measured in 'ms' and amplitude in µV.

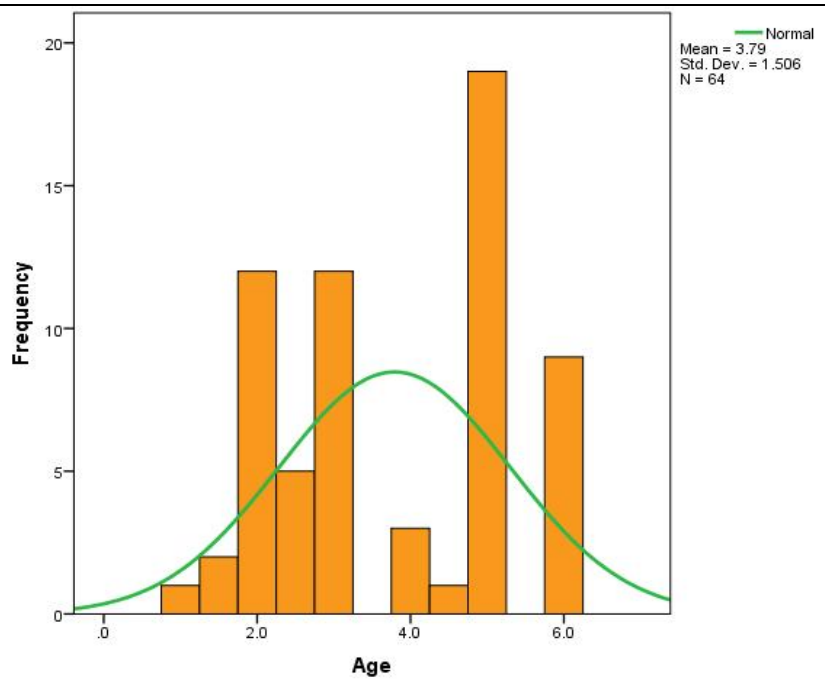
The collected data was tabulated and statistically analyzed using the SPSS Version 21. The results were as follows.

Figure 5.1 -Distribution of Gender



The mean (SD) age of implantees was 3.79 (1.5) ranging from 1 year to 6 years.

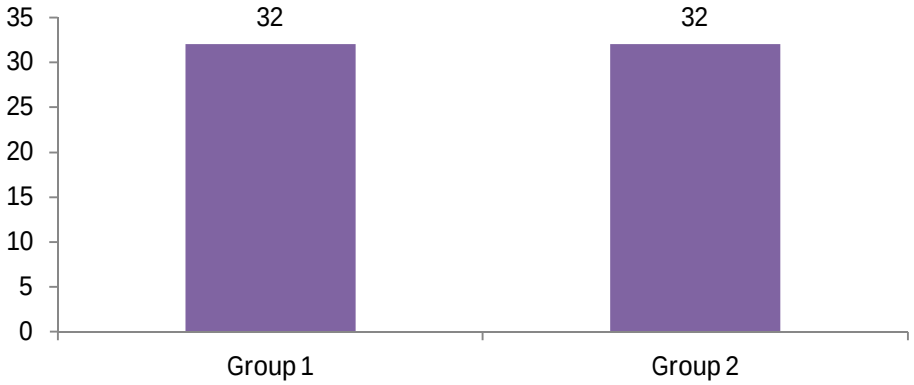
Figure 5.2: Distribution of Age with the Normality Curve



The age is approximately normally distributed since standard deviation is less than half of mean as is depicted in the above figure (Figure 5.2).

The implantees were divided into groups as Group 1 - less than 3 years and Group 2 – between 3 and 6 years of age (Figure 5.3).

Figure 5.3- Distribution of Group



GROUP 1 - DESCRIPTIVE STATISTICS

Descriptive statistical analysis (Mean, Range and SD) was done for each group for the variables at each time point.

LATENCY:

The Mean latency was high, 148.91and SD (6.76) in the third month and it was found to be reduced at the end of 12 months to 98.06(15.45) as in Figure 5.4 and tabulated in Table 5.1.

Figure 5.4- Mean distribution of Latency(ms)

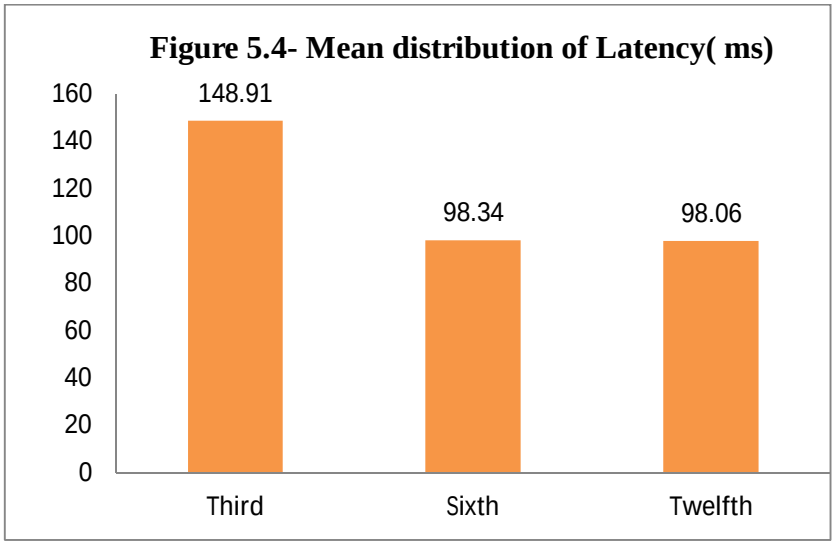


Table 5.1 – Descriptive Statistics				
Latency in ms				
Time	Min	Max	Mean	SD
Third	139	160	148.91	6.765
Sixth	68	136	98.34	15.613
Twelfth	68	134	98.06	15.446

AMPLITUDE:

The Mean amplitude was low, 8.0 and SD (0.84) in the third month and it was found to be increased to 14.36 (1.26) at the end of 12 month, as shown in Figure 5.5 and Table 5.2.

Figure 5.5- Mean distribution of Amplitude

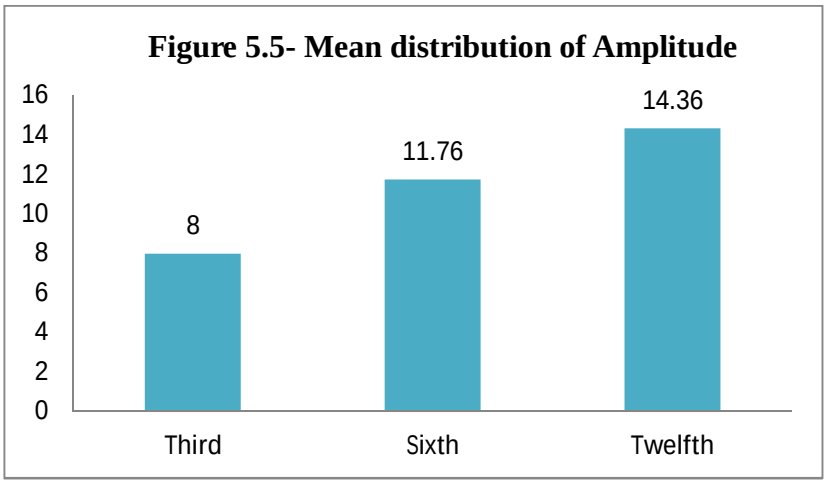


Table 5.2 – Descriptive Statistics for Amplitude µV				
Month	Min	Max	Mean	SD
Third	7	10	8.00	.841
Sixth	9	16	11.76	2.125
Twelfth	11	16	14.36	1.260

CATEGORIES OF AUDITORY PERCEPTION (CAP):

The Mean (SD) CAP was increased from 1.53 (0.621) in third month to 5.22 (0.420) at the end of the twelfth month, as depicted in the Figure 5.6 and Table 5.3.

Figure 5.6 - Mean distribution of CAP

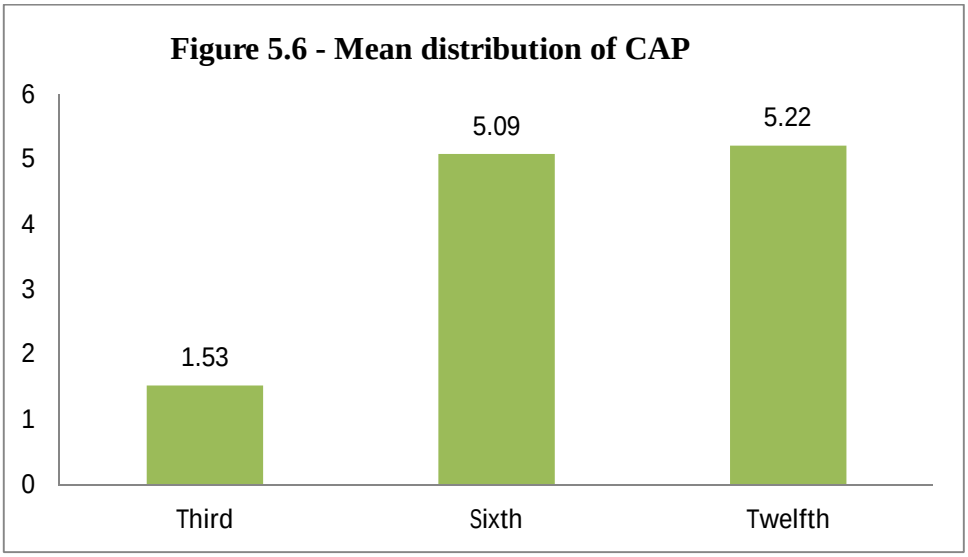


Table 5.3 – Descriptive Statistics for CAP				
Time	Min	Max	Mean	SD
Third	1	3	1.53	.621
Sixth	4	6	5.09	.390
Twelfth	5	6	5.22	.420

SPEECH INTELLIGIBILITY RATING (SIR):

The mean SIR score in the third month (1.06) increased to 2.41 at the end of twelfth month as shown in Figure 5.7 and Table 5.4.

Figure 5.7- Mean distribution of SIR

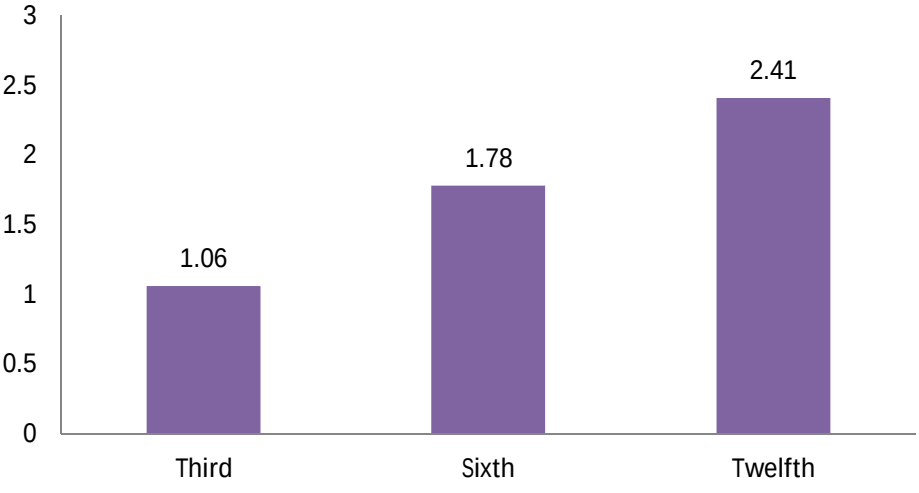


Table 5.4 – Descriptive Statistics for SIR				
Time	**Min**	**Max**	**Mean**	**SD**
Third	1	3	1.06	.354
Sixth	1	2	1.78	.420
Twelfth	2	4	2.41	.665

GROUP 1 - COMPARISON BETWEEN THE TIME POINTS

Paired t test was used to compare the Latency, Amplitude, CAP and SIR between the Time Points within the group.

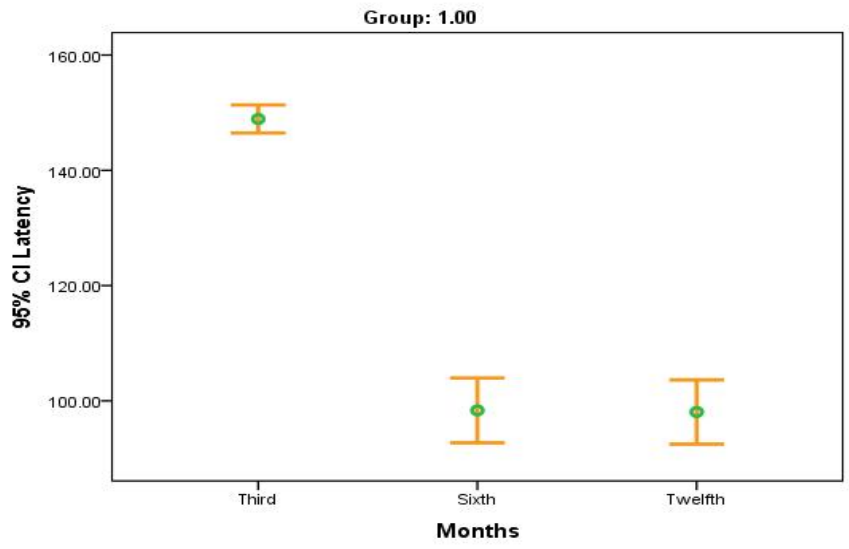
LATENCY:

Mean Differences between the time points of Latency is statistically significant ($p<0.05$). Table 5.5 and Figure 5.8 depicts an overall difference between the third and sixth month, and between the third and twelfth month, whereas there is not much difference between the sixth and twelfth month.

Table 5.5 – Mean differences in Latency between the Time Points

Time	Paired Differences				t	P-Value
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Third vs. sixth	50.563	17.897	44.110	57.015	15.981	.000
Third vs. twelfth	50.844	17.709	44.459	57.229	16.241	.000
Sixth vs. twelfth	0.281	0.581	0.072	0.491	2.738	.010

Figure 5. 8 - Error Plot for 95% confidence Interval of Latency



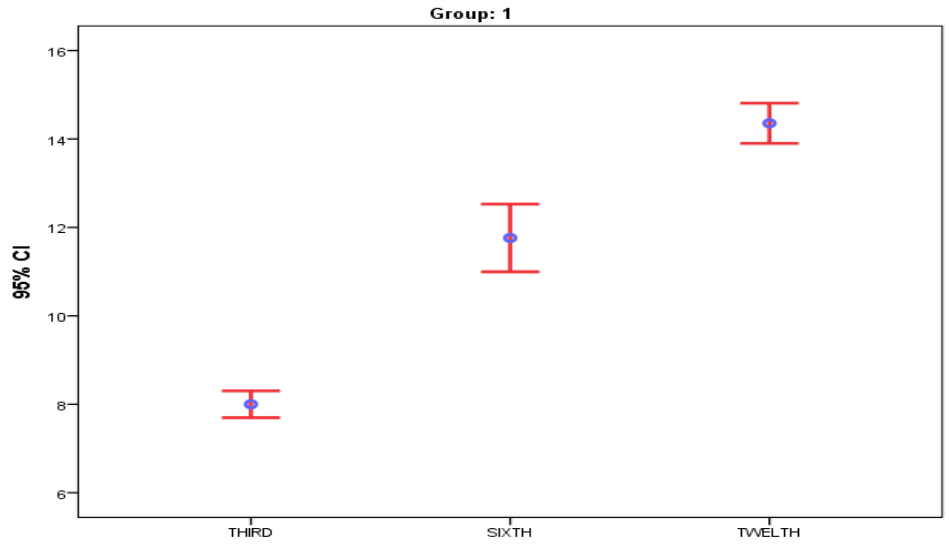
AMPLITUDE:

There are statistically significant ($p<0.05$) Mean Differences between the time points of Amplitude as shown in Table 5.6 and Figure. 5.9

Table 5.6 – Mean differences in Amplitude between the Time Points

Amplitude	Paired Differences				t	P-Value
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Third vs. sixth	3.761	2.103	3.003	4.519	10.117	.000
Third vs. twelfth	6.355	1.186	5.927	6.782	30.299	.000
Sixth vs. twelfth	2.594	2.482	1.699	3.489	5.911	.000

Figure 5.9 -Error Plot for 95% confidence Interval of Amplitude

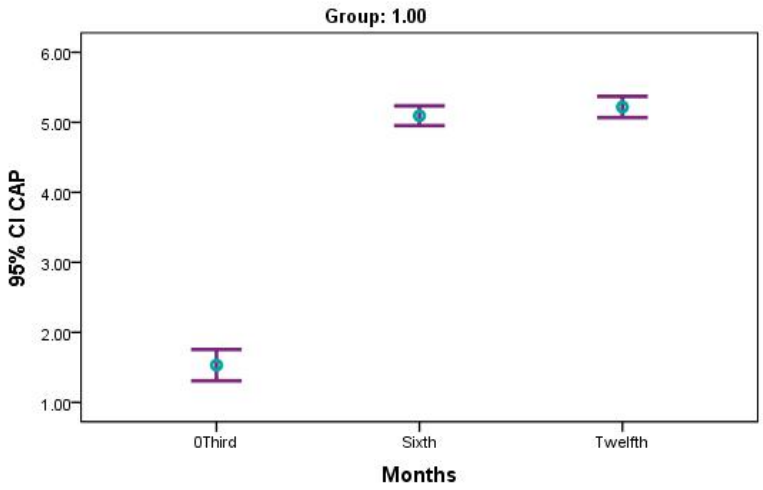


CAP SCORES:

Table 5.7 shows that the Mean Differences between the time points of CAP is statistically significant ($p<0.05$).Figure 5.10 depicts that there is an overall difference between the third and sixth month, third and twelfth month. But there is not much difference between the sixth and twelfth month

Table 5.7 – Mean differences in CAP between the Time Points						
Time	Paired Differences				t	P-Value
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Third vs. sixth	3.563	.716	3.304	3.821	28.161	.000
Third vs. twelfth	3.688	.780	3.406	3.969	26.733	.000
Sixth vs. twelfth	.125	.336	.004	.246	2.104	.044

Figure 5.10 - Error Plot for 95% confidence Interval of CAP



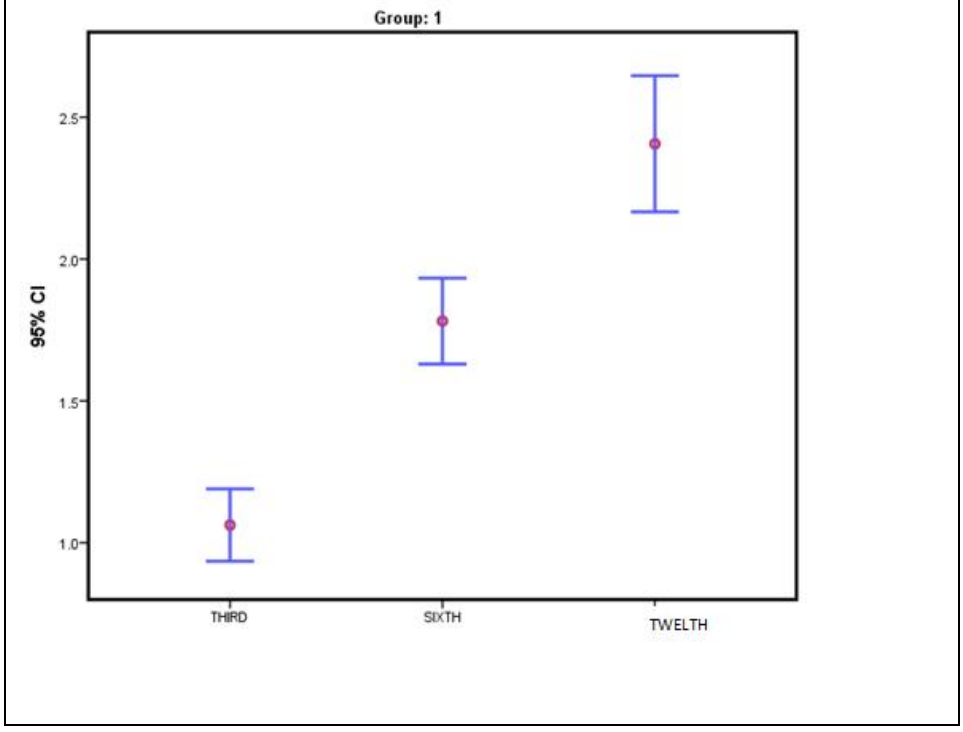
SIR SCORES:

Table 5.8 infers that the Mean Differences between the time points of SIR score is statistically significant ($p<0.05$). Figure 5.11 shows that there is an overall difference between third and sixth month, third and twelfth month

Table 5.8 – Mean differences in SIR between the Time Points

Time	Paired Differences				t	P-Value
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Third vs sixth	1.438	.716	1.179	1.696	11.363	.000
Third vs twelfth	3.031	.647	2.798	3.264	26.511	.000
Sixth vs twelfth	1.594	.665	1.354	1.834	13.552	.000

Figure 5.11 -Error Plot for 95% confidence Interval of SIR



GROUP 2 - DESCRIPTIVE STATISTICS

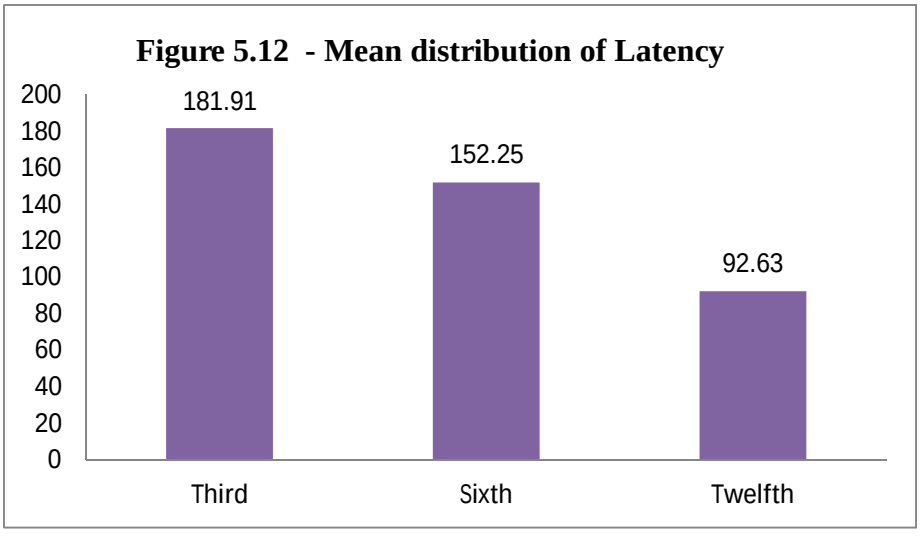
LATENCY:

The Mean (SD) latency was high, 181.91(14.284) in the third month and at the twelfth month it was reduced to 92.63(13.38), as shown in Table 5.9 and Figure 5.12.

Table 5.9 – Descriptive Statistics for Latency(ms)

Latency	Min	Max	Mean	SD
Third	156	224	181.91	14.284
Sixth	139	160	152.25	5.714
Twelfth	68	120	92.63	13.380

Figure 5.12 - Mean distribution of Latency

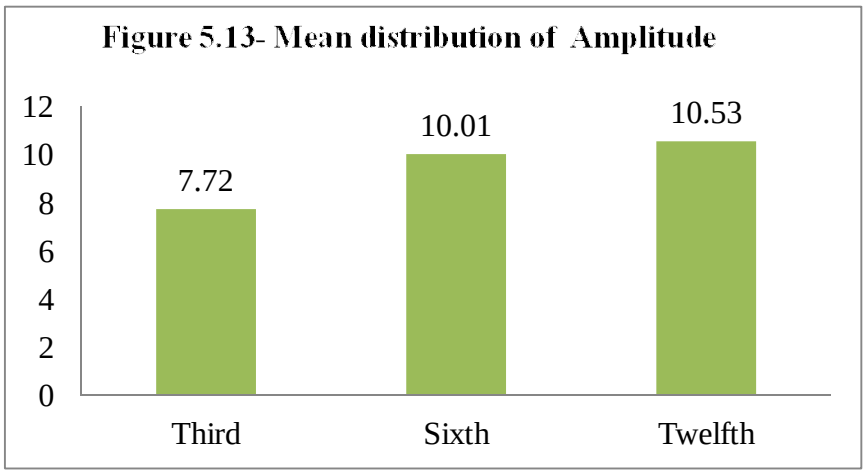


AMPLITUDE:

Table 5.10 shows that there is an increase in the mean value of amplitude from the third month 7.72 (0.679) to the twelfth month 10.53 (0.947). From Figure 5.13 it is very clear that there is a mean difference between the third and sixth, third and twelfth month but there is not much difference in mean between the sixth and twelfth month.

Table 5.10 – Descriptive Statistics for Amplitude(μV)

Amplitude	Min	Max	Mean	SD
Third	6	9	7.72	.679
Sixth	9	11	10.01	.420
Twelfth	9	13	10.53	.947

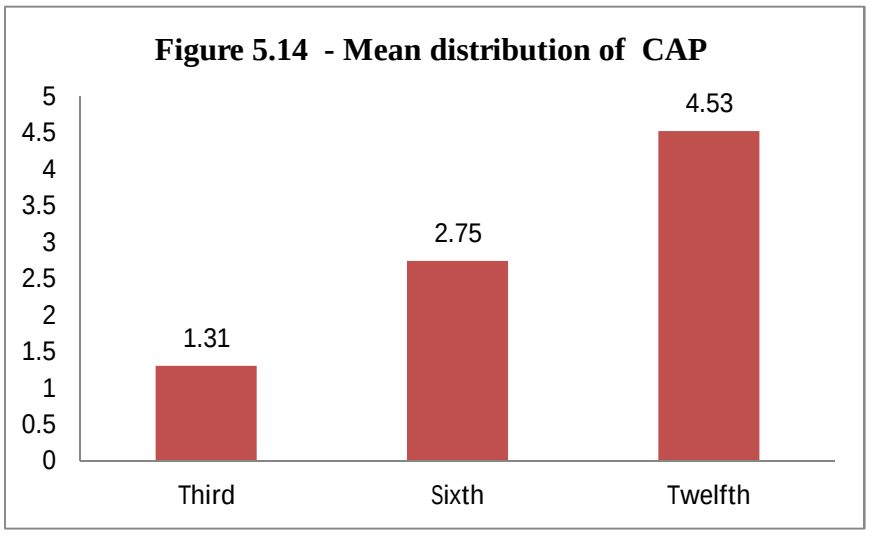


CAP SCORES:

There is a mean increase in CAP score from the third month 1.31 (0.471) to the twelfth month 4.34 (0.483), as shown in Table 5.11 and Figure 5.14.

Table 5.11 – Descriptive Statistics for CAP

CAP	Min	Max	Mean	SD
Third	1	2	1.31	.471
Sixth	2	4	2.75	.672
Twelfth	4	5	4.34	.483



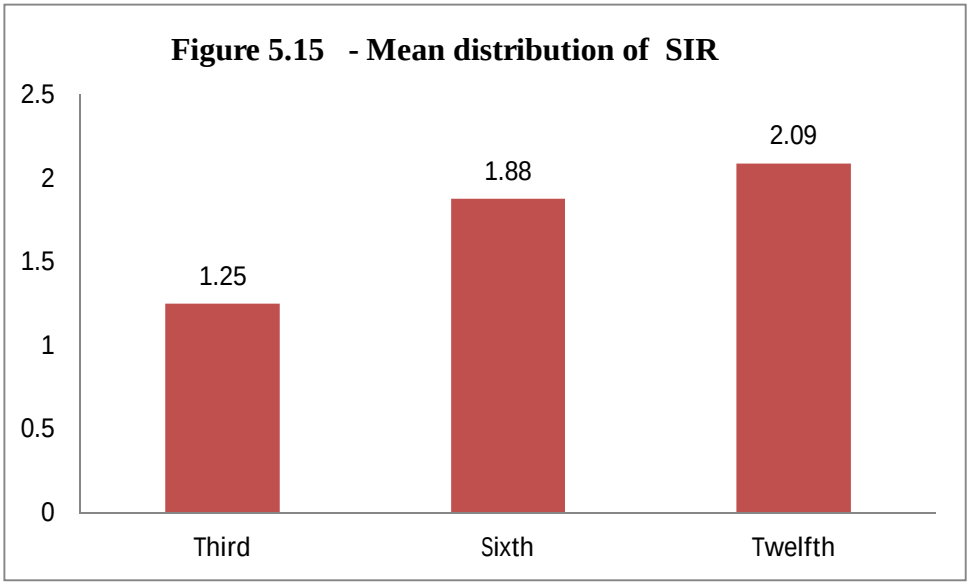
SIR SCORES:

Table 5.12 and Figure 5.15 depicts that there is a mean increase in SIR score from the third month 1.25 (0.622) to twelfth month 2.09 (0.296).

Table 5.12 – Descriptive Statistics for SIR

SIR	Min	Max	Mean	SD
Third	1	4	1.25	.622
Sixth	1	2	1.88	.336
Twelfth	2	3	2.09	.296

Figure 5.15 - Mean distribution of SIR



GROUP 2 - COMPARISON BETWEEN THE TIME POINTS :

Paired t test was used to compare the Latency, Amplitude, CAP and SIR between the Time Points.

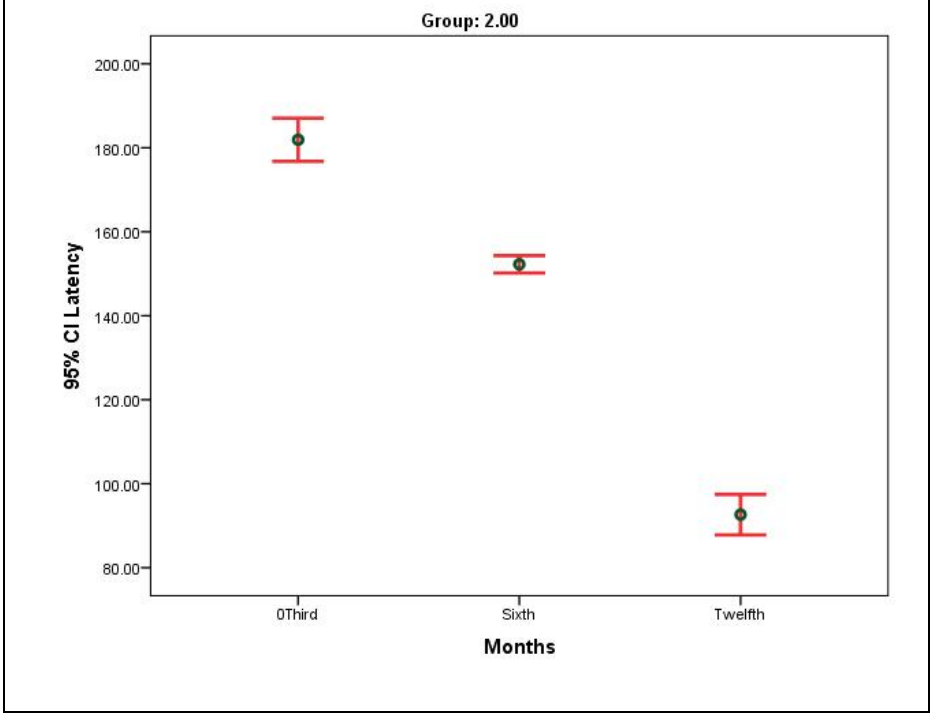
LATENCY:

Mean Differences between the time points of Latency is statistically significant ($p<0.05$) as shown in Table 5.13 and Figure 5.16. However there is an overall difference between third and sixth, sixth and twelfth, third and twelfth month.

Table 5.13 – Mean differences in Latency between the Time Points

Latency	Paired Differences				t	P-Value
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Third vs. sixth	29.656	16.313	23.775	35.538	10.284	.000
Third vs. twelfth	89.281	22.663	81.110	97.452	22.285	.000
Sixth vs. twelfth	59.625	13.531	54.747	64.503	24.928	.000

Figure 5.16 -Error Plot for 95% confidence Interval of Latency



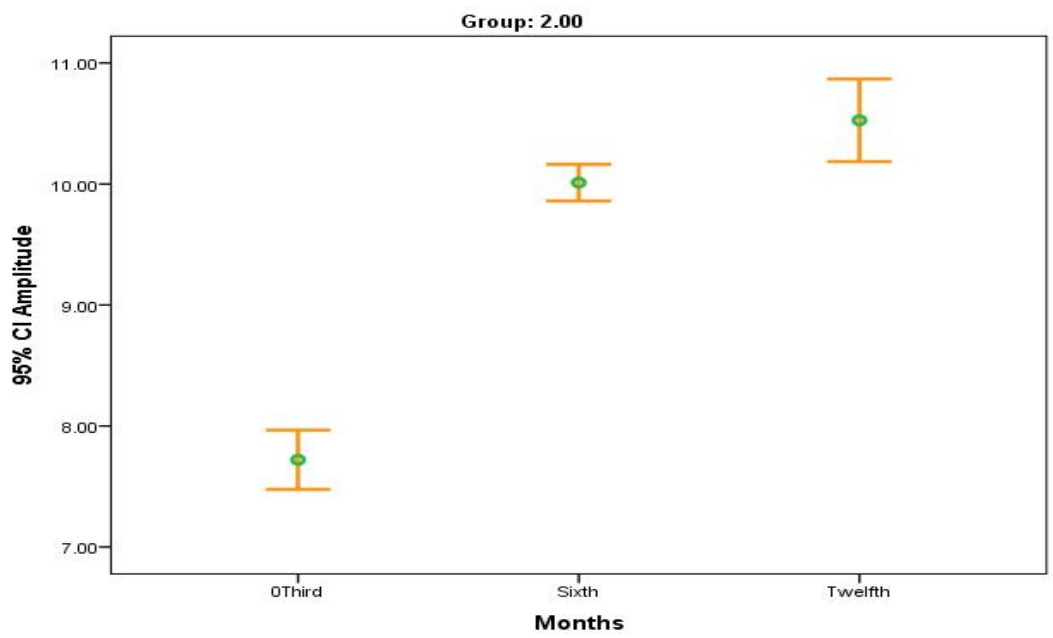
AMPLITUDE:

There is statistically significant ($p<0.05$) Mean Differences between the time points of Amplitude, as shown in Table 5.14. Figure 5.17 depicts there is an overall difference between third and sixth, third and twelfth month.

Table 5.14 – Mean differences in Amplitude between the Time Points

Time	Paired Differences				t	P-Value
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Third vs. sixth	2.290	.783	2.008	2.572	16.557	.001
Third vs. twelfth	2.805	1.236	2.360	3.251	12.841	.001
Sixth vs. twelfth	.515	.964	.168	.862	3.023	.005

Figure 5.17 -Error Plot for 95% confidence Interval of Amplitude



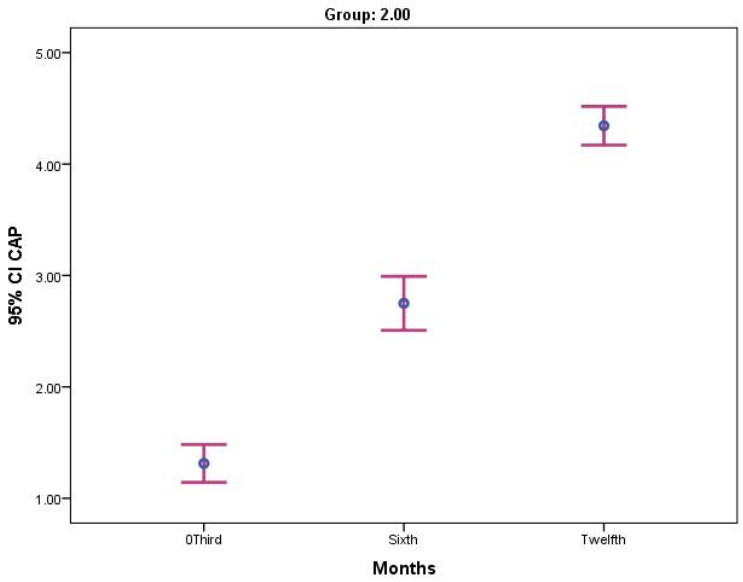
CAP:

Table 5.15 and figure 5.18 shows that the Mean Differences between the time points of CAP is statistically significant ($p<0.05$). However there is an overall difference between third, sixth and twelfth month.

Table 5.15 – Mean differences in CAP between the Time Points

Time	Paired Differences				t	P-Value
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Third vs. sixth	3.563	.716	3.304	3.821	28.161	.000
Third vs. twelfth	3.688	.780	3.406	3.969	26.733	.000
Sixth vs. twelfth	.125	.336	.004	.246	2.104	.044

Figure 5.18 -Error Plot for 95% confidence Interval of CAP

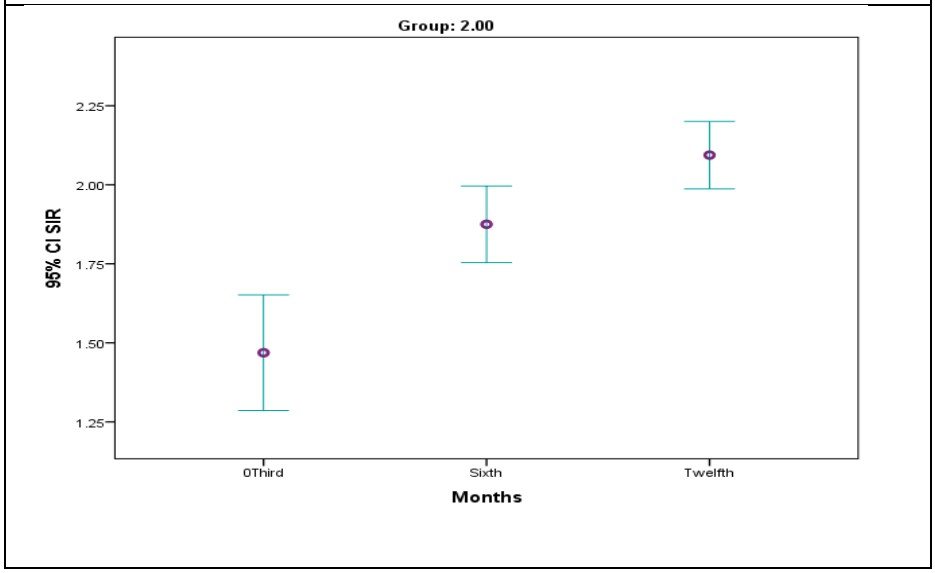


SIR: Table 5.16 infers that the Mean Differences between the time points of SIR is statistically significant ($p<0.05$). Figure 5.19 shows that there is an overall difference between third, sixth and twelfth month**.**

Table 5.16 – Mean differences in SIR between the Time Points

Time	Paired Differences				t	P-Value
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Third vs. sixth	.719	.634	.490	.947	6.411	.000
Third vs. twelfth	1.344	.787	.060	1.628	9.654	.000
Sixth vs. twelfth	.625	.707	.370	.880	5.000	.000

Figure 5.19 -Error Plot for 95% confidence Interval of SIR



Thus sequential comparison of data i.e., latency, amplitude, CAP and SIR scores showed statistically significant improvement in all the parameters over time within each group. This trend shows that CAEP can be used as a prognostic indicator over a period of time to monitor auditory responses.

COMPARISON BETWEEN GROUP 1 AND GROUP 2:

Group 1 and Group2 were compared for mean differences between the variables using Independent t -Test

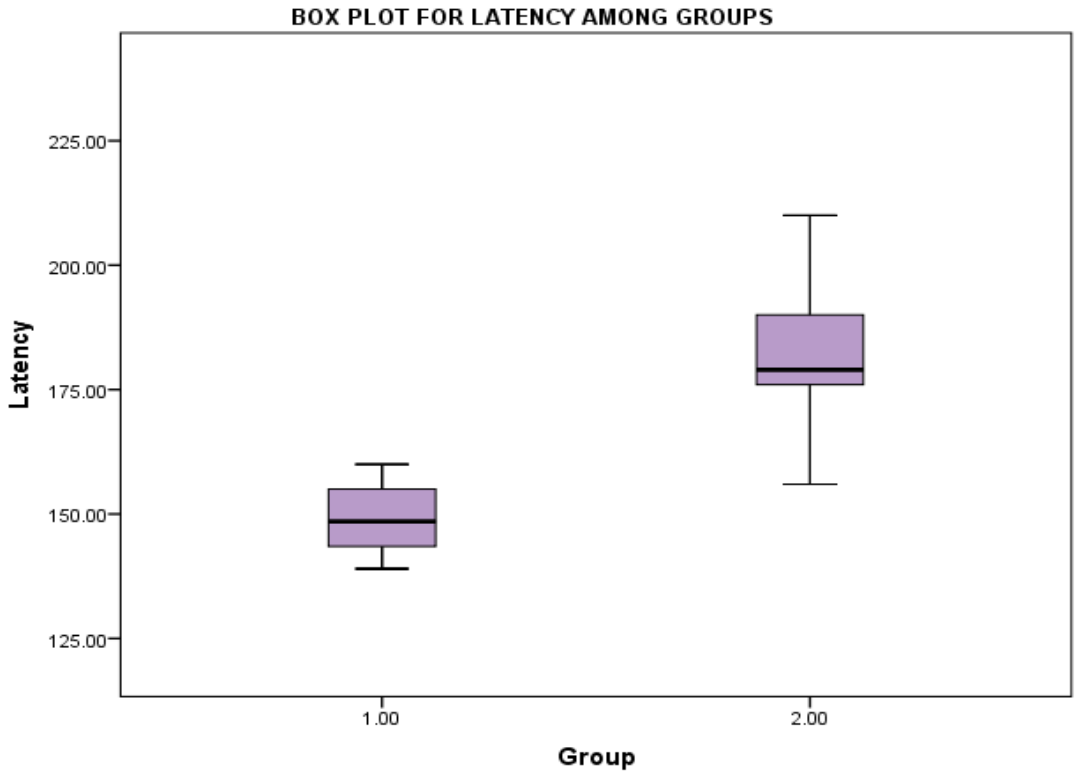
THIRD MONTH

There is statistically significant ($p < 0.05$) mean difference between group 1 and group 2 for the latency in third month whereas the other variables were not found to be significant, as shown in Table 5.17 and Figure 5.20.

Table 5.17 – Mean differences between the Groups in the Third Month

VARIABLES	Group	Mean	SD	Mean Diff.	S.E Diff.	95% C.I For Difference		t value	P value
						Lower	Upper		
Latency	1	148.91	6.765	33.000	2.794	27.415	38.585	11.811	.000
	2	181.91	14.284						
Amplitude	1	8.00	.841	.279	.191	-.103	.661	1.462	.149
	2	7.72	.679						
CAP	1	1.53	.621	.219	.138	-.057	.494	1.587	.118
	2	1.31	.471						
SIR	1	1.06	.354	.188	.127	.065	.440	1.482	.143
	2	1.25	.622						

Figure 5.20 : Comparison Of Latency Among Groups



SIXTH MONTH

There is no statistically significant ($p>0.05$) mean difference between group 1 and group 2 in SIR score in the sixth month whereas the other variables were found to be significant as depicted in Table 5.18 and Figure 5.21, 5.22.

Table 5.18 – Mean differences between the Groups in the Sixth Month

VARIABLES	Group	Mean	SD	Mean Diff.	S.E Diff.	95% C.I For Difference		t Value	P value
						Lower	Upper		
Latency	1	98.34	15.613	53.906	2.939	48.031	59.781	18.341	0.001
	2	152.25	5.714						
Amplitude	1	11.76	2.125	1.750	.383	0.985	2.515	4.571	0.001
	2	10.01	.420						
CAP	1	5.09	.390	2.344	.137	2.069	2.618	17.062	0.001
	2	2.75	.672						
SIR	1	1.78	.420	.094	.095	.096	0.284	.986	0.328
	2	1.88	.336						

Figure 5.21 Comparison of Latency among Groups

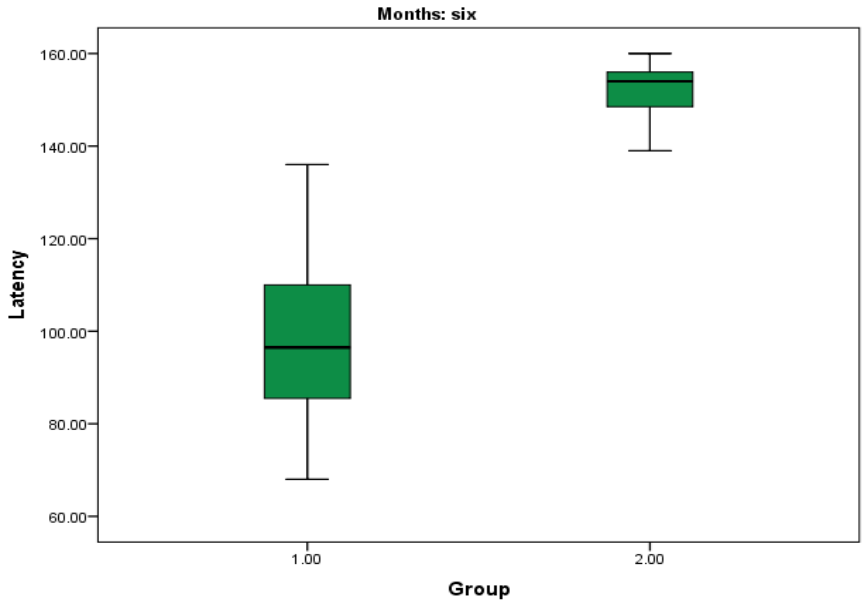
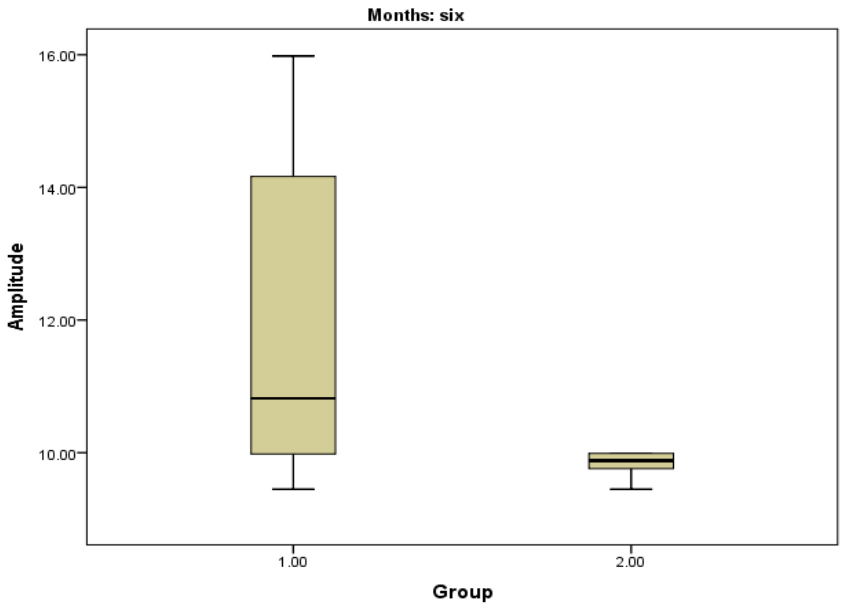


Figure 5.22 Comparison of Amplitude among Groups



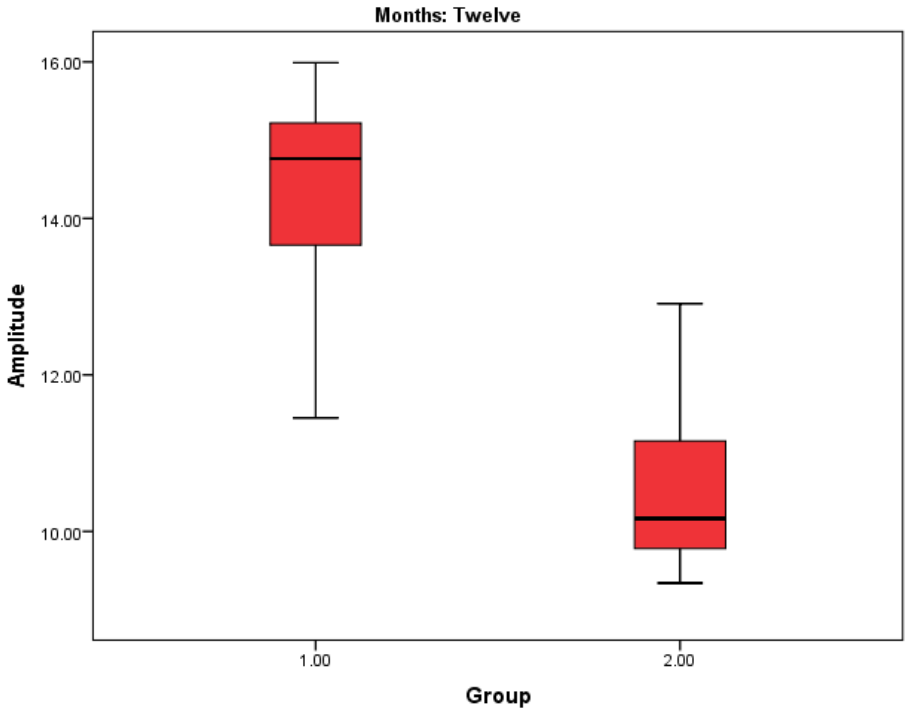
TWELFTH MONTH

Table 5.19 infers that the Mean Differences between the Groups are statistically significant ($p<0.05$) in all variables except latency, which is clearly depicted in Figure 5.23.

Table 5.19 – Mean differences between the Groups in the Twelfth Month

VARIABLES	Group	Mean	SD	Mean Difference	S.E Difference	95% C.I For Difference		t Value	P value
						Lower	Upper		
Latency	1	98.06	15.446	5.438	3.612	1.784	12.659	1.505	0.137
	2	92.63	13.380						
Amplitude	1	14.36	1.260	3.829	.279	3.272	4.386	13.740	0.001
	2	10.53	.947						
CAP	1	5.22	.420	.875	.113	.649	1.101	7.737	0.001
	2	4.34	.483						
SIR	1	2.41	.665	.313	.129	.055	.570	2.428	0.018
	2	2.09	.296						

Figure 5.23: Comparison of Amplitude among groups



CORRELATION OF MEASURES WITHIN EACH GROUP:

Correlation was studied between the subjective and objective measures within each group.

There was a moderate positive correlation between Amplitude & CAP score (0.608), Amplitude and SIR score (0.351) and there was a moderate negative correlation between Latency & CAP score (-0.645), latency & SIR score (-0.455) for group 1. There was a weak positive correlation between Amplitude & CAP score (0.19), Amplitude and SIR score (0.285) in group 2 while there was a weak negative correlation between Latency & CAP score (-0.384), Latency and SIR score (-0.162) – shown in Table 5.20.

Table 5.20 _ Correlations between Groups		
Variables	Group 1	Group2
CAP - AMP	0.608	0.19
SIR - AMP	0.351	0.285
CAP - LAT	-0.649	-0.384
SIR - LAT	-0.455	-0.162

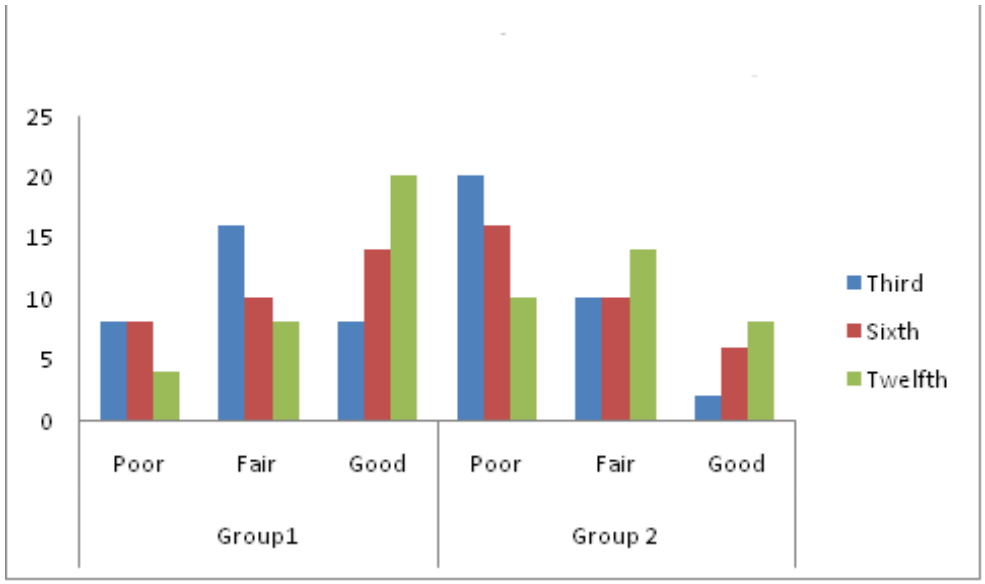
Morphology of P1 wave form

The morphology was visually assessed by two independent expert implant audiologists. They were blinded from the study groups and the time intervals of data collection. They categorized the waveforms as 1 (poor), 2 (fair) and 3 (good). Table 5.21 and Fig 5.24 shows the distribution of P1 morphology.

Table 5.21:- Distribution of Morphology of P1 wave form							
Group	Morphology	Months					
		Third		Sixth		Twelfth	
		N	%	N	%	N	%
Group1	Poor	8	25%	8	25%	4	12%
	Fair	16	50%	10	31%	8	25%
	Good	8	25%	14	44%	20	63%
Group 2	Poor	20	63%	16	50%	10	31%
	Fair	10	31%	10	31%	14	44%
	Good	2	6%	6	19%	8	25%

Morphology in group 1 showed good waveforms when compared to group 2. This trend was maintained throughout the study. In group 1 there is a trend of gradually improving morphology during the course of habilitation. This trend was also seen in group 2 but it was not as pronounced as in group 1. In group 1, shorter latencies correlated with better morphology as confirmed by visual analysis. In Group 2, although latencies were prolonged, the morphology of the waveforms improved over time with adequate habilitation to catch up with group 1 at the end of 12 months.

Figure 5.24:- Distribution of Morphology of P1 wave form



MULTIPLE LOGISTIC REGRESSIONS

Variables found to be clinically meaningful were included in the model of multiple logistic regressions HosmerandLemeshow Goodness of fit was used for assessing how well the model fits the data (Table 5.22**).**It resulted in a non significant value, which is an indication of a model that predicts the population fairly well**.**

Table 5.22- Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	4.281	8	0.831
2	7.038	8	0.533

Assuming Groups as a dependent variable and other factors as independent variables, the backward logistic regression method was selected, which was carried out in two iterative steps. The results are tabulated below (Table 5.23).

Table 5.23 - Backward Logistic Regression

		Odds Ratio	95% C.I.for Odds Ratio		Wald Statistics P value
			Lower	Upper	
Step 1	Latency	2.93	2.59	3.08	.002
	Amplitude	1.38	1.20	2.78	.000
	CAP	25.39	2.35	29.34	.084
	SIR	5.52	1.62	409.81	.404
Step 2	Latency	2.94	2.50	3.09	.001
	Amplitude	1.39	1.21	2.79	.000
	CAP	44.89	2.87	92.23	.041

In the final step it showed that the effectiveness of treatment of group 2 will be affected 2.94 times of Latency, 1.39 times of Amplitude and 44.89 times of CAP as compared to group 1. This is evident from the tabulated results that it was statistically significant (Wald statistics p value < 0.05) and it does not fall in the 95% confidence interval.

The clinical application of this prospective controlled study will be to apply the logistic regression analysis for predicting unknown behavioral responses. For example, in a clinical scenario where a child does not give any

reliable CAP and SIR scores, the habilitationist can make use of the CAEP latency and amplitude at a particular interval of time to statistically predict the anticipated CAP or SIR score which the child should have had at that point of habilitation. Such a reliable objective tool to assess the subjective responses is very valuable in clinical use.

6. DISCUSSION

Congenital deafness leads to atypical organization of the auditory nervous system. In humans, the CAEP provides information about maturation of auditory pathways terminating in auditory cortex, and reflects recurrent cortical activity mediated by cortico-thalamic loops. These recurrent loops mediate subsequent cortico-cortical projections and may be disrupted after auditory deprivation. Restoring function to these modulatory projections may be possible with cochlear implantation, provided the central auditory system remains maximally plastic and the effects of degeneration have not completely taken effect [106].

In our study, we had two groups of participants. Group I included implantees less than 3 years of age and Group 2 included implantees between 3 and 6 years of age. In this study the CAEP parameters were used to objectively assess the maturational changes in cochlear implantees less than 6 yrs. CAP and SIR scores were assessed subjectively. Subjective outcomes were correlated with CAEP parameters like latency and amplitude.

Sharma and colleagues (2002) investigated the maturational changes in the latency of P1 using a broader age range (from 0.1 to 20 years of age) of 136 children with normal hearing and they found the latency of P1 decreases with increasing age, and that this continues until approximately 20 years of age. The changes in P1 latency occur at a more gradual rate in the second decade of life than the rapid decrease seen earlier in life. [12]In the current study the maturational changes were recorded in CI children across both groups and the adequacy of habilitation was monitored using P1 latency and amplitude objectively and CAP and SIR scores subjectively.

Studies have now been published illustrating the use of CAEPs in children and adults with cochlear implants [107], [108,]. Ponton and colleagues (1996) investigated the maturation of CAEPs in six children who received their cochlear implant between 18 months and six years of age, with the average age of implantation being 4.5 years. Their findings suggest both similarities and differences in cortical auditory maturation for normal-hearing and implanted children. For implanted children, the 5 yr delay for maturation of P1 latency roughly corresponds to the average 4.5 yr interval between the onset of deafness and the time of implantation. These findings suggest that during the period of deafness, maturation of cortical auditory function does not progress[108]

Similarly in our study at 3 and 6 months after implantation, there is a significant difference in latency between early(group 1) and late implantees (group 2), p value 0.0001 indicating that latency of p1 wave comes down more rapidly in early implantees than the late implantees. But at the end of one year after intense habilitation there was no significant difference in latency between the 2 groups and the latency in both groups were comparable.

In the studies by Eggermont et al, Ponton et al, they demonstrated that once stimulation is received via the cochlear implant, the central auditory system appears to continue to develop at the same rate as in normal hearing children; however the maturation is delayed proportionate to the length of auditory deprivation [107], [108]. These studies imply that, even after periods of auditory deprivation, the central auditory nervous system still has the ability to continue to mature once appropriate stimulation is received. This study is also comparable with the above mentioned studies.

In my study, in group 2 individuals whose age range was found to be beyond the critical period, the P1 latency matched the Group I individuals at the end of one

year.This infers that neural plasticity is an ongoing process which may proceed beyond the critical age as well when supported optimally with intensive habilitation.

Sharma and colleagues (2002) further investigated the prospect of a sensitive period for the development of the central auditory system in children. They measured CAEPs in 104 children with cochlear implants and compared the waveforms with those measured from 136 children with normal hearing. The children with cochlear implants were divided into three groups, based on their age at implantation: early (before 3.5 years); mid (3.5-6.5 years); and late (after 7 years). P1 latencies of late implantees were outside the 95% confidence limit for age-matched normal-hearing children. The latencies of middle group were outside the range of normal. In contrast, the early group had latencies within the range of normal. The proportion of latencies falling within the range of normal differed significantly between the early-implantees and the late-implantees. [12] The difference between these groups clearly illustrates the existence of a sensitive period up to 3.5 years of age. If appropriate auditory stimulation is provided during this sensitive period, the auditory system is able to recover from deprivation fairly early.[12] This is similar to our results in which the early implantees (before 3 years) had P1 latency better than late implantees group (3 to 6 yrs) at 3 and 6 months of implant age. Age matched comparison was not done in our study for want of normative data. All our patients were less than 6 yrs and hence latencies were comparable at 1 yr post implantation in both groups after adequate habilitation

The early implantees had more rapid decrease in latency at 3 months and 6 months post implantation. The early implantees also had a better CAP score at 6 months which was statistically significant. At 1 year also there is a statistically significant difference in CAP and SIR scores between the early and late implantees, thus showing the sensitive period in our study to be 3 yrs of age. This is consistent with the study by

Sharma A et al 2002 [109] in which the development of cortical response latencies for the implanted children was more rapid than for their normal hearing age-matched peers in early implantees within 8 months.

Dorman et al. assessed the P1 latency in 245 congenitally deaf children fitted with cochlear implants following various periods of auditory deprivation. They concluded that if children experienced less than 3.5 years of auditory deprivation before implantation, their P1 latencies fell within the range of normal children after 3–6 months of electrical stimulation. Children who had experienced greater than 7 years of auditory deprivation, however, generally did not develop normal P1 latencies, even after years of stimulation via the implant and their waveforms were markedly abnormal. [110] In our study all the children were less than 6 years of age and they had residual neural plasticity and hence the latency in group 2 implantees matched those of group 1 after intense rehabilitation.

CAEP measurements could therefore be clinically useful to confirm the functioning of the auditory pathways. Such information would be clinically valuable for determining whether appropriate stimulation was being provided by a hearing aid or cochlear implant, particularly in hard-to-test populations, including young infants. Sharma and colleagues (2005) studied 21 children who received cochlear implants. They were divided into early implantees(less than 3.5 yrs) and late implantees (more than 7 yrs).CAEP latencies reduce with CI experience in children, particularly in early-implanted children. [111] This is consistent with our study in which the decrease in latency in group 1 at 3 months post implantation was more marked than in group 2 and was statistically significant.

The morphology and latency of CAEPs in early and late implanted children have been further investigated by Sharma et al. [111]

The amplitude of this negativity decreases after stimulation is received from the cochlear implant. The morphology of the waveforms of early implanted children differed markedly and much better during the first year of electrical stimulationwhile in late implantees it remained atypical after 12-18 months of implant use. [111]

In our study morphology in Group 1 showed good wave forms when compared to Group 2. This trend was maintained throughout the study. In early implantees there is a gradual trend of improving morphology over time with habilitation. This trend was also seen in late implantees but not as pronounced as in early implantees where shorter latencies correlated with better morphology as confirmed by the visual analysis. In late implantees although latencies were prolonged the morphology of waveforms improved over time to catch up with early implantees at 12 months of habilitation.

The amplitude of early implantees at 3 months after habilitation in our study was better than late implantees but was not statistically significant. However at 6 and 12 months, statistically significant difference in the amplitude was seen between the two groups.

Despite various studies supporting the use of CAEPs in children with cochlear implants, the maturation of evoked potentials is still not well understood. In particular, there is conflicting evidence from the two major researchers in this field. Ponton and colleague's data demonstrate a delay in the maturation of CAEP responses equal to the time that the child spent without adequate auditory stimulation [108] This is in direct contrast with Sharma et al, who illustrated that CAEP responses develop to the point of becoming age-appropriate once appropriate auditory stimulation is provided [111].

If CAEPs in children with cochlear implants were found to continue to mature at a normal rate, albeit delayed because of the time spent with inadequate auditory stimulation, then our study would support the importance of providing appropriate auditory stimulation as early as possible. Our data supported the fact that CAEPs are able to recover if appropriate stimulation is provided prior to 3 years of age, thus indicating the need for early intervention during this sensitive period in order to get the maximum benefit. It is hoped that this information would help us understand the early maturation of CAEPs in children who receive cochlear implants prior to 3.0 years of age. This will also assist in developing protocols by which these objective measures can be used to support an early implantation and ensure that adequate stimulation is being received.

Gordon and colleagues (2005) found a relationship between CAEP morphology and speech perception outcomes in children with CIs. Children displaying atypical types of responses were implanted at a wide range of ages and had significantly poorer behavioral speech perception scores ($P<0.05$) than their peers with expected waveforms. [112] However in my study, the morphology was not correlated with the speech outcome. There is also some evidence that CAEPs are predictive of speech perception and functional outcomes for children [113], with Auditory Neuropathy Spectrum Disorder (ANSD) [114]. In our study, group 1 had 63% with good morphology while group 2 had only 25% at the end of 12 months of implantation. So the CAEP morphology was definitely better in group 1. CAEPs show promise as a clinical tool for either predicting CI outcomes or optimizing CI settings.

Several studies have shown correlations between CAEP latencies or amplitudes and speech scores in adult CI users [115], [116], [117]. In normal children, the canonical

babbling of well established syllables appear between age 7 and 10 months. Prior to implantation, the babbling was observed to be delayed and poor morphology and latency was recorded. Multi-channel cochlear implant fitted in two female children (at age 5 months and 7 months) showed that the acquisition of rapid increase in canonical vocalizations occurred within 3 months of implant fitting. In my study, amplitude and latency were correlated with speech outcomes and both were found to better in group 1 implantees than group 2 implantees. In my study speech intelligibility score for group 1 was better than group 2 and was statistically significant by the end of 1 year of habilitation.

Speech and language studies by Geers, 2006, Kirk et al., 2002have consistently shown that children implanted under age 3–4 years show significantly better speech and language skills than children implanted after 6–7 years. [118], [119]. In general, implantation at younger ages results in better speech and language outcomes for cochlear implanted children [120], [121]. This is consistent with our results, in which CAP scores at 6 months were significantly better in group 1. At 12 months both CAP and SIR scores were better in group 1 than in group 2 implantees and were found to be statistically significant. It can therefore be concluded that early implantation results in better speech and language development. With early implants hearing-impaired children develop like normal individuals in speech and language aspects as per Sharma et al (2004) [122]. However in our study the data was not age-matched with normal children

Limitations of the study

1. The CAEP parameters ,CAP and SIR were not age matched with normal children

2.The follow up in my study is limited to 1 year only. Longer follow up is needed to assess the prognosis especially in the late implantees as they may improve significantly after intense habilitation and may even become comparable with early implantees.

7. SUMMARY AND CONCLUSION

SUMMARY

The sequential comparison of data i.e., latency, amplitude, CAP and SIR scores showed statistically significant improvement in all the parameters over time within each group. This trend shows that CAEP can be used as a prognostic indicator over a period of time to monitor auditory responses.

Independent t test was used to compare Group 1&2 showed the following results. At 3 months, there is a statistically significant mean difference between the Groups 1&2 for the latency whereas the other variables were not significant. At 6 6months, in Group 1 the latency, amplitude and CAP scores were found to be statistically significant when compared with group 2(except SIR). At 12 months, latency was comparable in both groups but the other parameters were found to be statistically significant in Group 1when compared with Group 2.

This study has successfully achieved the four objectives stated in the aims

and objectives.:

1. The trend in latency, morphology and amplitude of CAEP has been objectively monitored for 12 months post implantation.
2. The influence of two different age groups on CAEP parameters has been documented.
3. The correlation of CAEP parameters with subjective habilitation outcomes was also shown.
4. The Logistic Regression Analysis has shown in both groups that latency of CAEP can be used as an objective tool for optimal prediction of outcomes.

CONCLUSION

Cochlear implants represent one of the most successful interventions for restoring an absent special sense. Restoration of auditory function directly translates into establishment of speech and language skills in a child, provided the intervention falls within the period of neural plasticity. Conventional electrophysiological tests like brainstem evoked responses are helpful to document peripheral auditory stimulation but do little to demonstrate and study the phenomenon of auditory cortical maturation. Cortical auditory evoked potentials seem to be the most reliable method of studying the cortical maturation. In fact it is the only biomarker for auditory cortical maturation. This study looks at the correlation between the objective measurement of cortical maturation namely cortical auditory evoked potential with behavioural responses and shows the statistical validity of this comparison.

8. RECOMMENDATIONS

The anticipated outcomes of the study have been achieved to clinically reflect the **impact of the study** as below.

1. The data set of reference values obtained from this study can be used as normatives for developing future studies.

2. CAEP has now been incorporated in our institution as a routine follow up, especially for early identification of suboptimal performers.

The evidence from the study has contributed to the existing knowledge of CAEP and its clinical applications. It has influenced change in clinical practice. This will be valuable evidence for future habilitation programmes. A multicentric study in future will create a larger input so as to change the protocols of habilitations across India. Recommendations can be put forward to Cochlear Implant Group of India, for incorporating CAEP into the implant guidelines.

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APPENDICES

INFORMATION SHEET FOR PARTICIPANTS OF STUDY GROUP

Description of the Study:

This research work is entirely performed as per the guidelines formulated by the "Cochlear Implant Group of India", which is the governing body dealing with all issues related to Cochlear Implantation in India. The CIGI Consensus Document, providing all information regarding Cochlear Implantation is available with the Principal Investigator of this study and is also accessible online at www.cigi.in for your reference if needed. In this study we propose to analyze the clinical correlations between subjective Behavioral responses and multi-modal objective Electrophysiological tests performed among Cochlear Implantees, after their surgery during the first year of follow up. The multi-modal Electrophysiological test battery has been included into the standard Cochlear Implantation Habilitation protocol, in anticipation of obtaining the best possible & most ideal outcomes for the Cochlear Implantees of our study group.

You are / your child has been, selected as a participant in our study group, after fulfilling the eligibility criteria for Cochlear Implantation, as advocated by *'The CochlearImplant Group of India'* in its Consensus Document. On induction into the study group, you /your child will be explained in detail about the type of research methodology adopted for this study in addition to the standard Cochlear Implant counseling provided prior to surgery. On agreement of your participation in our research work, you / your child will undergo additional Electrophysiological test (CAEP) during Auditory Verbal Habilitation at periodic follow ups for a minimum period of 12 months after surgery. These tests will be performed by qualified & well trained Implant Audiologists of the research team at the Cochlear Implant facilities at MERF / MERF-ISH

You will be provided with complete details of your / your child's Electrophysiological test results, Habilitation performance & the eventual outcomes at the completion of your participation period.

Possible Risks to the participant:

There are NO risks involved in this study. This specialized & advanced electrophysiological test are done using very safe, internationally standardized testing equipment for research purpose, with the principal aim of giving the best outcomes for your child.

Possible Benefits to the participant:

At the time of enrollment into this study, no guarantee or assurance has been given by anyone, as to the possible results that may be obtained at the time of completion of the candidates' participation period. This research work is undertaken with the principal hypothesis that the participants will be benefited by obtaining the most ideal & anticipated outcomes of Cochlear Implantation, due to the inclusion of advanced, objective & periodic Electrophysiological test to assess their performance at regular intervals during their 12 month follow up period.

Appendix A

Cost and Payments to the participant:

There is no additional cost for undergoing these Electrophysiological tests or for participation in this study. All your / your child's tests will be performed free of cost. No payment will be provided for participation in the study.

Voluntary consent by the participant:

Participation in this study is completely voluntary and your consent with signature is required before you / your child can participate in this study.

Confidentiality:

All participants / parents will be counseled by the Research Team members prior to induction into the study. They shall contribute to the Proforma of this study & sign the informed consent in the presence of the Principal Investigator, who will be available to clarify any further issues related to this study. Information obtained thus, in this study will remain strictly confidential. You / your child will be assigned a research number, along with the name, which will be recorded on the Study Proforma & Assessment Forms thereon. Your / your child's name will not be used while reporting the analysis of study results & while reporting the statistical information in publications or conference presentations.

Participants' right to withdraw from the study:

You have the right to refuse to participate in this study, the right to withdraw from the study and the right to have your data destroyed at any point during or after the study, without any penalty.

Thank You for Your Participation

** For any further clarifications or queries, you are advised to contact the Principal Investigator whose details are given below.*

Signature of Principal Investigator

Name: Dr.K. sathiya
Consultant ENT Surgeon,
Madras ENT Research Foundation,
No.1, 1st Cross street, off 2nd Main road, Ph: +91- 9840140648
Opposite Indian Bank, Raja Annamalaipuram, E-mail: sathiyadr@gmail.com
Chennai – 600028. Date:

Appendix A

INFORMED CONSENT FORM FOR COCHLEAR IMPLANTATION WITH PARTICIPATION IN RESEARCH WORK

Name: Date:

Date of Birth: Age: Sex:

Name of Parent:

Address: Tel No:

Hospital / ID No.:

I ---------- the candidate / parent of the candidate (---------- who has been) diagnosed to have Bilateral Severe / Profound Sensori-neural Hearing Loss of Cochlear origin, based on the multitude of objective Audiological tests performed upon me/ my child, hereby provide Consent for me / for my child to undergo Cochlear Implantation Surgery.

I have been thoroughly explained in the language best understood by me, about the above procedure in clear detail by my ENT doctor & Audiologist. I have fully understood the procedure of Cochlear Implantation, the Auditory Verbal Habilitation process & the anticipated outcomes of Habilitation.

I hereby fully agree & give consent (to permit my child) to participate in the study group of this (Ph.D.) doctoral research work undertaken by Dr. K.Sathiya (PrincipalInvestigator) & her research team, which will include additional electrophysiological test at periodic follow ups, for a minimum period of twelve months during the Auditory VerbalHabilitation process following surgery.

All these tests have been explained to me in full detail by the Principal Investigator of this research work in person. I understand that these specialized & advanced electrophysiological tests are done using very safe, internationally standardized testing equipment for research purpose, with the principal aim of giving the best outcomes for me / my child. I have been informed that some of these advanced electrophysiological tests are only available at the Madras ENT Research Foundation / MERF Institute of Speech &Hearing and I will need to visit the Electrophysiological Lab at MERF / MERF-ISH for thesame as per the periodic instructions given to me by the research team. I also understand that, I do not have to incur any additional cost for undergoing these tests.

Appendix B-1

I have read this consent form (or it has been read to me) and I fully understand the contents of this document and voluntarily consent / permit my child, to participate in this study. All of my questions concerning this study have been answered. If I have any questions in the future about this study, they will be answered by the principal investigator & her research team during the participation period. I also understand that the results of my participation will remain strictly confidential & will be provided to me at the end of the study period and this consent shall end at the conclusion of my participation in this study.

I have fully understood the nature & purpose of the various tests & procedures to be performed upon me / my child during the Habilitation & I hereby give my full cooperation & commitment for active participation in this ongoing (Ph.D.) doctoral research work. By signing this form, I fully agree to / permit my child to participate in this study. A copy of this form has been given to me.

Signature of Candidate / Parent
Name:
Date:

Consent Witnessed & Supervised by,
Name:
Date:

Appendix B-1

CERTIFICATION OF INFORMED CONSENT

I hereby certify that I have explained the nature and purpose of this study to the above named individual and I have fully discussed the potential benefits of participation in this study. The questions that the individual had about this study have been answered and our research team will always be available to address any future questions

Signature of Principal Investigator

Name: Dr. K. Sathiya,
Consultant ENT Surgeon,
Madras ENT Research Foundation,
No.1, 1st Cross Street, off 2nd Main road,
Opposite Indian Bank, Raja Annamalaipuram,
Chennai – 600028.
Ph: +91- 9840140648
E-mail: ssathiyadr@gmail.com
Date

காக்லியர் இம்பிளேண்ட் அறுவை சிகிச்சை மற்றும் ஆராய்ச்சியில் பங்கு பெறுவதற்கான ஒப்புதல் படிவம்

பெயர்: தேதி:

பிறந்த தேதி: வயது பால்

பெற்றோரின் பெயர்:

முகவரி :

தொலைபேசி எண். :

மருத்துவமனை/ அடையாள எண்.

..... என்கிற நான் / ..... என்பவருடைய பெற்றோர் ஆகிய நான் என் மீது/ என் குழந்தையின்மீது / நடத்தப்பட்ட பல்வேறு மிக நுணுக்கமான அதிநவீன கேட்பியல் பரிசோதனைகளின் அடிப்படையில், இரண்டு உட்காதுகளும் நோயினால் பாதிக்கப்பட்டு, மிகுந்த காது கேளாண்மை நோய் கண்டறியப்பட்டுள்ளதை அறிகிறேன்.

இதற்கு சிகிச்சையாக எனக்கு / என் குழந்தைக்கு காக்லியர் இம்பிளேண்ட் அறுவை சிகிச்சை செய்வதற்கு முழு ஒப்புதல் அளிக்கிறேன்.

காது, மூக்கு, தொண்டை மற்றும் கேட்பியல் நிபுணரால் எனக்கு நன்கு அறிந்த மொழியில் இந்த கருவியின் செயல் முறைகள் பற்றி மிக தெளிவாக விளக்கப்பட்டுள்ளது.

காக்ளியர் இம்பிளேண்ட் அறிவியல் சிகிச்சை, கேட்பியல் வாய்மொழி கற்றல் செயல்பாடு முறை மற்றும் அதன் எதிர்பார்க்ககூடிய முடிவுகள் பற்றி நான் முழுவதுமாக புரிந்துக் கொண்டுள்ளேன்.

இந்த சிகிச்சை முறையில், Ph.D. மருத்துவ ஆராய்ச்சி மேற்கொண்டுள்ள Dr.K.சத்யா (முதன்மை ஆய்வாளர்) மற்றும் அவரது மருத்துவகுழு நடத்தும் ஆராய்ச்சியில் நான் / என் குழந்தையை பங்கு எடுத்துக் கொள்ள முழுமையாக ஒப்புக் கொண்டு என் சம்மதத்தை அளிக்கிறேன்.

இந்த ஆராய்ச்சியில் கூடுதலான, அதிநவீன நுணுக்கமான, மின் இயல்பியல் ஆய்வுகள் அறுவை சிகிச்சையின் பொழுதும், அதன்பின் கேட்பியல், வாய்மொழி, கற்றலின் பொழுதும் குறைந்தது, 18 மாத காலம் பரிசோதிக்கப்படும் என்று அறிவேன். இந்த தேர்வு முறைகள் பற்றி, இந்த ஆராய்ச்சியை மேற்கொண்டுள்ள முதன்மை ஆய்வாளர், எனக்கு முழு விவரத்தையும், நேரடியாக, விளக்கமாக தெரிவித்துள்ளார்.

எனக்கு / என் குழந்தைக்கு, காது கேளாண்மை நோயிலிருந்து மிக சிறந்த நிவாரணம் அளிப்பதற்காக உலக அளவில் அங்கீகாரம் பெற்ற ஆய்வு கருவிகளில் மூலம், மிக பாதுகாப்பான முறையில், இந்த விஷேசமான அதிநவீன, மின் இயல்பியல் ஆய்வுகள் நடத்தப்படுகின்றன என்று நன்கு அறிந்துள்ளேன்.

இந்த அதிநவீன பரிசோனைகள் செய்யும் வசதி மெட்ராஸ் இ என் டி ஆராய்ச்சி நிறுவனத்தில் உள்ளதையும் அறிவேன்.

இந்த ஆராய்ச்சிக்காக தேவைப்படும் போது, ஆராய்ச்சிக் குழு என்னை / என் குழந்தையை சோதனை கூடங்களுக்கு அழைப்பார்கள் என்று தெரிவித்துள்ளனர். மேலும் இந்தபரிசோதனைகளுக்காக நான் எந்த தொகையையும் செலவு செய்ய தேவையில்லை என்பதையும் புரிந்துக் கொண்டேன்.

நான் இந்த ஒப்புதல் படிவத்தை படித்து / அல்லது எனக்கு படிக்கப்படடு, இதில் உள்ள விஷயங்களை முழுவதுமாக புரிந்துக் கொண்டு, இந்த ஆய்வுக்கு சம்மதிக்கிறேன் / என் குழந்தையை அனுமதிக்கிறேன். இந்த ஆய்வுக் குறித்து என் கேள்விகள் அனைத்திற்கும் மிகவும் தெளிவாக பதிலளிக்கப்பட்டுள்ளன.

எனது / எனது குழந்தையின் பரிசோதனை முடிவுகள் மிக ரகசியமாக பாதுகாக்கப்பட்டு, முடிவில் எனக்கு தெரிவிக்கப்படும் என்பதை அறிவேன்.

மேலும் எதிர்காலத்தில் வேறு ஏதேனும் கேள்விகள் எழுந்தால் அவற்றிற்கு முதன்மை ஆய்வாளரும், அவரது ஆய்வு குழுவும் தேவையான விளக்கங்களை அந்த அந்த நேரத்தில் அளிப்பார்கள் என்பதை அறிவேன்.

இந்த ஒப்பந்தம், இந்த ஆராய்ச்சியில் என்னுடைய பங்கு நிறைவேறியவுடன், முடிந்துவிடும் என்பதையும் அறிவேன்.

இந்த ஒப்புதல் படிவத்தில் கையெழுத்திடுவதின்மூலம் , இந்த ஆய்வுக்கு நான் முழுமனதுடன் ஒப்புக் கொள்கிறேன் / என் குழந்தையை ஆய்வில் பங்குகொள்ள அனுமதிக்கிறேன். இந்த ஒப்புதல் படிவத்தின் ஒரு நகல், எனக்கு கொடுக்கப்பட்டுள்ளது.

இந்த ஆய்வு மற்றும் செயல்பாடுகளின் இயல்பு மற்றும் நோக்கத்தை நான் முழுமையாக உணர்ந்து கொண்டு, இது தொடர்பாக Ph.D. மருத்துவ ஆராய்ச்சி நடவடிக்கைகளுக்கு என்னை / என் குழந்தையை முழு மனதுடன் ஈடுபடுத்தி பூரண ஒத்துழைப்பை அளிப்பேன் என்று உறுதி கூறுகிறேன்.

பங்கு பெறுவோர் கையொப்பம்/
பெற்றோரின் கையொப்பம்

பெயர் :
தேதி :

ஒப்புதல் அளித்ததை
கண்காணித்து சாட்சி
அளித்தவர்.

பெயர் :
தேதி :

Appendix B2

அறிவிக்கப்பட்ட ஒப்புதல் படிவ சான்றிதழ்

நான், மேலே குறிப்பிட்ட நபருக்கு, இந்த ஆய்வின் இயல்பு மற்றும் நோக்கத்தை முழுமையாக விளக்கியுள்ளதாக சான்றுரைக்கிறேன். மேலும் இதனால் விளையக்கூடிய எதிர்பார்க்கும் நன்மைகளையும் முழுமையாக அவரிடம் விவாதித்துள்ளேன். இந்த ஆய்வு குறித்து அவர் எழுப்பிய வினாக்களுக்கு முழுமையாக விடையளிக்கப்பட்டுள்ளது. எதிர்காலத்தில் அவர் ஏதேனும் வினாக்களை எழுப்பினால், அவருக்கு பதிலளிக்க எங்களுடைய ஆராய்ச்சிக்குழு தயாராக உள்ளது.

முதன்மை ஆய்வாளரின் கையொப்பம்

பெயர் : **டாக்டர். க.சத்யா**
காது, மூக்கு, தொண்டை அறுவை நிபுணர்,

மெட்ராஸ் இ. என். டி. ஆராய்ச்சி நிறுவனம்,
எண்.1, முதல் குறுக்குத்தெரு, 2வது மெயின் தெரு அருகில்,
இந்தியன் வங்கி எதிரில்,
இராஜா அண்ணாமலைபுரம், சென்னை - 600 028.
தொலைபேசி எண். 9840140648

ஆராய்ச்சி மேலாளர்

டாக்டர். மோகன் காமேஸ்வரன்
தலைவர் - காது மூக்கு தொண்டைபிரிவு,
மெட்ராஸ் இ. என். டி. ஆராய்ச்சி நிறுவனம்,
எண்.1, முதல் குறுக்குத்தெரு, 2வது மெயின் தெரு அருகில்,
இந்தியன் வங்கி எதிரில்,
இராஜா அண்ணாமலைபுரம், சென்னை - 600 028.

ஆராய்ச்சி துணை - மேலாளர்

டாக்டர். இரா.ச. ஆனந்த குமார்
மெட்ராஸ் இ. என். டி. ஆராய்ச்சி நிறுவனம்,
எண்.1, முதல் குறுக்குத்தெரு, 2வது மெயின் தெரு அருகில்,
இந்தியன் வங்கி எதிரில்,
இராஜா அண்ணாமலைபுரம், சென்னை - 600 028.

PROFORMA FOR RESEARCH WORK

Name: Date:

Date of Birth: Age / Sex:

Hospital / ID No.:

Name of Parent:

Address: Tel No:

History of Presentation –

Hearing Loss detected at age of:

Onset & Duration of Hearing Loss:

Delayed Speech & Language Development: Yes / No
Details –

Delayed Milestones: Yes / No
Details –

H/o Amplification (Monaural / Binaural) &Benefits: Yes / No

Duration of Hearing Aid Usage:

Communication Mode:

H/o Special Education / Schooling:

H/o Additional Disabilities: Yes / No

Associated Medical / Surgical Illness: Yes / No
Details –

Family History of Hearing Loss: Yes / No

H/o Consanguinity: Yes / No (if so) Degree: Order of Sibling:

Ante-natal, Peri-natal & Post-natal History:

Previous ENT Assessment Details & Hearing Test reports:

Protocol for Clinical Evaluation –

ENT – Head & Neck Clinical Examination:

Audiological Test Battery Reports:
Pure Tone Audiometry / Behavioural Observation Audiometry –
Free-Field Audiometry / Conditioned Play Audiometry – Impedance Audiometry & Reflexometry –
Oto Acoustic Emissions –
Auditory Brainstem Responses –
Auditory Steady State Responses –
Cortical Auditory Evoked Potentials –

Hearing Aid Optimization & Amplification Assessment with Aided Audiometry: Performance Report wit Best Fitting / Powerful Hearing Aids:

Speech & Language Evaluation Report:

Radiological Investigations: HRCT Scans of Temporal Bones & MRI Inner Ears Details -

Paediatricians Evaluation + Immunization Status – BCG, Polio, MMR, Others: Pre-operative Immunization Status (Meningococcal / Pneumococcal / H1b):

Cardiologists Evaluation: Yes / No Ophthalmologists Evaluation: Yes / No

Clinical Psychologists / Child Counselors Assessment Details:

Diagnosis –

Etiology of Hearing Loss – Congenital / Acquired:

Degree of Hearing Loss:

Communication Status: Pre-lingual / Peri-lingual / Post-lingual

Fulfillment of Candidacy Criteria : Yes / No
For Cochlear Implantation (as per CIGI Guidelines)
Pre-operative Counseling given for : Yes / No
Cochlear Implantation to Candidate + Parents / Family
Awareness to parents about CI Technology, Surgery : Yes / No
Habilitation & Outcomes

Appendix C

Regular visits to Cochlear Implant Clinics : Yes / No

Interaction with other Implantees : Yes / No

Participation in Auditory Verbal Habilitation : Yes / No

Family / Parental Commitment & Motivation for active participation in Habilitation Process : Yes /No

Parental / Candidates Consent given for Cochlear Implantation : Yes / No

Consent given for participation in this Research Study : Yes / No

Consent given for Post-operative Assessment with Electrophysiological Test : Yes / No

Consent given for Periodic & Regular Follow up at Cochlear Implant clinic for a minimum period of 12 months after surgery : Yes / No

Details of Cochlear Implant Surgery –

Date of Implantation –

Implanted Side:(Left Ear / Right Ear)

Make & Type of Implant used – Serial No. of Implant:

Surgery – Uneventful / Eventful (if so - Details):
Number of Electrodes within Cochlea:
Full Insertion / Partial Insertion (Reason):

Post-operative Recovery – Uneventful / Eventful (Details):

Post-operative Test Schedules

Team Members Involved –

Name of Implant Audiologists:

Name of Auditory Verbal Teacher habilitating the Candidate:

First Schedule – (3 months post surgery)

Date of 'Switch-On' & Mapping:

Research Test Battery Dates:

Procedural Details:

CAEP Procedure: Latency Amplitude, Morphology

Habilitation outcome: CAP, SIR scores

Second Schedule – (6 months post surgery)

Research Test Battery Dates:

Procedural Details:

CAEP Procedure: Latency Amplitude, Morphology
Habilitation outcomes: CAP, SIR scores

Third Schedule – (12 months post surgery)

Research Test Battery Dates:

Procedural Details:

CAEP Procedure: Latency Amplitude, Morphology
Habilitation outcome: CAP, SIR scores

FINAL IMPRESSION –

- Comments on CAEP responses :
- Remarks on Auditory Verbal Habilitation Performance :

Signature of Principal Investigator **Signature of the Guardian**

Name: **Name:**
Date: **Date:**

Appendix C

DATA SHEETS

RAW DATA GROUP - 1												
SR. NO	LAT3M	LAT6M	LAT12M	AMP3M	AMP6M	AMP12M	CAP3M	CAP6M	CAP12M	SIR3M	SIR6M	SIR12M
1	155	96	96	9.67	10.66	15.66	2	5	5	1	2	2
2	142	111	110	8.34	14.45	14.99	3	5	5	1	2	2
3	139	93	92	8.21	9.45	15.45	1	6	6	1	2	3
4	148	110	110	7.91	9.68	15.88	2	5	5	1	2	2
5	160	111	111	7.21	10.64	14.65	2	6	6	1	2	2
6	159	94	94	8.73	15.98	14.89	1	5	5	1	2	2
7	156	68	68	6.78	9.79	13.99	1	6	6	1	2	2
8	154	82	80	7.55	10.67	12.87	1	5	5	1	2	2
9	145	84	84	8.98	9.87	12.97	2	5	5	1	2	2
10	144	104	104	6.76	9.97	13.88	2	5	5	1	1	2
11	156	116	116	7.56	10.54	14.87	1	5	5	1	2	2
12	155	110	110	8.54	9.56	15.85	1	5	5	1	2	3
13	139	97	96	7.87	9.76	14.96	1	4	5	1	1	2
14	143	102	102	6.89	10.85	14.88	1	5	6	1	2	4
15	149	94	94	7.98	10.88	14.79	2	5	5	1	2	3
16	152	96	96	8.43	14.88	13.88	1	5	5	1	2	4

RAW DATA LEGEND:

LAT – LATENCY

AMP – AMPLITUDE

CAP – CAP SCORE

SIR – SIR SCORE

Appendix D-1

RAW DATA GROUP – 1 contd												
SR. NO	**LAT3M**	**LAT6M**	**LAT12M**	**AMP3M**	**AMP6M**	**AMP12M**	**CAP3M**	**CAP6M**	**CAP12M**	**SIR3M**	**SIR6M**	**SIR12M**
17	155	78	78	7.66	9.99	12.67	2	5	5	1	2	2
18	148	136	134	7.88	14.99	11.45	3	5	5	3	1	2
19	147	135	134	8.69	10.57	13.56	1	5	5	1	2	2
20	144	88	88	8.96	10.87	14.77	2	5	6	1	1	2
21	139	118	118	9.55	12.65	15.64	1	5	5	1	2	2
22	139	80	80	9.74	12.76	15.79	1	5	5	1	2	2
23	146	99	98	8.44	13.88	15.99	1	5	6	1	1	2
24	156	90	90	7.29	10.77	15.87	2	5	5	1	2	4
25	154	85	85	7.89	10.79	14.57	1	5	5	1	2	2
26	139	111	111	8.32	14.87	14.88	1	5	5	1	2	2
27	155	84	84	6.98	10.88	11.98	1	5	5	1	2	3
28	158	100	100	6.77	9.88	11.68	1	5	5	1	1	2
29	153	99	99	7.23	14.99	13.54	2	6	6	1	2	3
30	140	86	86	7.31	14.89	14.76	2	5	5	1	2	2
31	147	108	108	7.55	10.96	13.99	2	5	5	1	2	3
32	149	82	82	8.34	14.99	13.76	2	5	5	1	1	3

RAW DATA GROUP 2												
SR. NO.	LAT3M	LAT6M	LAT12M	AMP3M	AMP6M	AMP12M	CAP3M	CAP6M	CAP12M	SIR3M	SIR6M	SIR12M
1	180	155	80	8.87	9.66	9.76	2	3	4	1	2	2
2	156	149	82	8.81	9.45	9.89	1	4	5	1	2	2
3	165	159	98	8.22	9.45	10.35	1	3	4	1	2	3
4	170	158	82	6.51	9.68	11.38	2	3	4	1	2	2
5	176	160	112	8.67	10.64	11.75	2	3	4	1	2	2
6	176	159	120	8.55	9.98	10.43	1	3	4	2	2	2
7	178	156	99	6.42	9.79	10.93	1	2	4	1	2	2
8	160	154	100	6.87	9.67	12.91	1	2	5	1	2	2
9	156	145	90	7.14	9.87	9.88	2	2	4	1	2	2
10	178	154	98	7.56	9.97	9.97	2	2	4	1	1	2
11	174	156	106	7.44	10.54	10.03	1	3	4	1	2	2
12	170	155	98	8.56	9.56	10.14	1	2	4	1	2	3
13	178	139	90	8.86	9.76	9.79	1	3	4	1	2	2
14	178	153	98	7.66	10.85	9.77	1	3	4	4	2	3
15	176	149	94	7.21	10.88	9.54	2	3	5	1	2	2
16	178	152	82	7.68	9.88	10.04	1	2	4	1	2	2

Appendix D-1

RAW DATA GROUP 2 contd												
SR. NO.	LAT3M	LAT6M	LAT12M	AMP3M	AMP6M	AMP12M	CAP3M	CAP6M	CAP12M	SIR3M	SIR6M	SIR12M
17	176	155	118	7.64	9.99	10.19	2	3	5	1	2	2
18	180	148	86	7.13	9.99	10.77	1	2	4	1	2	2
19	184	147	88	8.99	10.57	11.92	1	3	4	1	2	2
20	182	144	104	7.68	10.87	12.01	2	4	5	1	2	2
21	200	159	70	7.23	9.65	11.88	1	3	5	2	2	2
22	210	139	82	7.11	9.76	10.76	1	4	5	1	2	2
23	224	146	80	7.98	9.88	10.56	1	2	4	1	1	2
24	196	156	68	7.13	9.77	9.76	2	4	4	1	2	2
25	190	154	97	7.88	10.79	12.08	1	3	5	1	2	2
26	194	159	88	7.32	9.87	11.78	1	3	4	2	2	2
27	188	155	70	7.71	9.88	9.77	1	2	5	2	2	2
28	190	158	94	7.49	9.88	9.57	1	2	4	1	1	2
29	188	153	118	7.44	9.99	9.34	1	3	5	2	2	2
30	192	150	86	7.66	9.89	9.45	1	2	4	1	2	2
31	190	147	88	7.88	9.96	9.89	2	3	5	1	2	2
32	188	149	98	7.77	9.99	10.55	1	2	4	1	1	2

DATA Group - 1 - Morphology							
S. No.	**3 Months**	**6 Months**	**12 Months**	**S. No.**	**3 Months**	**6 Months**	**12 Months**
1	3	3	3	17	2	2	3
2	3	3	3	18	2	2	3
3	3	3	3	19	2	2	3
4	3	3	3	20	2	2	2
5	3	3	3	21	2	2	3
6	3	3	3	22	2	2	3
7	3	3	3	23	2	2	2
8	3	3	3	24	2	2	2
9	2	3	3	25	1	1	1
10	2	3	3	26	1	1	1
11	2	3	3	27	1	1	1
12	2	3	3	28	1	1	2
13	2	3	3	29	1	1	2
14	2	3	3	30	1	1	1
15	2	2	2	31	1	1	2
16	2	2	3	32	1	1	2

DATA Group - 2 – Morphology							
S. No.	**3 Months**	**6 Months**	**12 Months**	**S. No.**	**3 Months**	**6 Months**	**12 Months**
1	3	3	3	17	2	2	2
2	1	2	2	18	1	1	1
3	1	1	1	19	2	3	3
4	1	1	2	20	1	1	1
5	2	3	3	21	1	1	2
6	1	2	2	22	1	1	1
7	1	2	2	23	2	2	3
8	3	3	3	24	1	1	2
9	2	2	2	25	2	3	3
10	1	1	2	26	1	1	1
11	2	2	2	27	2	2	2
12	1	1	1	28	1	1	1
13	2	3	3	29	1	2	2
14	1	1	1	30	1	1	1
15	2	2	3	31	1	1	2
16	1	1	1	32	1	1	2

Categories of Auditory Performance

The CAPwas used to measure the speech perception performance of the implanted children. It measures supraliminal performance, which reflects everyday auditory performance in a more realistic way. The CAP comprises a hierarchical scale of auditory perceptive ability ranging from 0 “displays no awareness of environmental sounds” to 7 “can use the telephone with a familiar talker”.

0. No awareness of environmental sound
1. Awareness of environmental sounds
2. Responds to speech sounds
3. Recognizes environmental sounds
4. Discriminates at least two speech sounds
5. Understands common phrases without lip-reading
6. Understands conversation without lipreading with a familiar talker
7. Can use the telephone with a familiar talker

Ref: Archbold S, Lutman ME, Marshall DH (1995) Categories of Auditory Performance. Ann Otol Rhinol Laryngol Suppl 166: 312–314

Speech Intelligibility Ratings

The SIR was used to measure the speech intelligibility of the implanted children by quantifying their everyday spontaneous speech. It is a time-effective global outcome measure of speech intelligibility in real-life situations. SIR consists of five performance categories ranging from “prerecognizable words in spoken language” to “connected speech is intelligible to all listeners”

1. Prerecognizable words in spoken language (the child’s primary mode of everyday communication may be manual)
2. Connected speech is unintelligible; intelligible speech is developing in single words when context and lip reading cues are available
3. Connected speech is intelligible to a listener who concentrates and lip-reads within a known context
4. Connected speech is intelligible to a listener who has little experience of a deaf person’s speech; the listener does not need to concentrate unduly
5. Connected speech is intelligible to all listeners; the child is understood easily in everyday contexts

Ref:Allen MC, Nikolopoulos TP, O'Donoghue GM (1998) Speech intelligibility in children after cochlear implantation. Am J Otol 19: 742–746?

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ETHICAL COMMITTEE

Dr.K.Sathiya,MBBS.,DNB.,DLO.,MNAMS., 24/07/2012
Con.ENT Surgeon,
Madras ENT Research Foundation (P)Ltd., Chennai-28.

EC Ref Number: MERF/PHD/0002/12

Dear Dr.Sathiya,
This is to inform that your research entitled **"Factors influencing Cortical Auditory Evoked Potentials in Cochlear Implantees"** has been approved by the ethical committee of Madras ENT Research Foundation (P) Ltd and MERF Institute of Speech and Hearing. Approval was granted after thorough review by the following board members.

Any change to the existing protocol should receive changes from the Board.
Yours Sincerely,

Prof.Mohan Kameswaran, DSc,MS, FRCS(Ed), FICS, FAMS, DLO.,
Chairman, Ethical Committee.

Clinician In-house:
Dr.R.S.Anand Kumar, MS, FICS, MAMS,DLO., ...

Clinician Other Institutions:
Prof.M.C.Vasudevan, MD, DNB(NS)., ...
Neuro Surgeon

Prof.S.Suresh, MBBS, FRCOG(Hon)., ...
Foetal Medicine

Basic Medical Scientist:
Dr.Saranya Narayan, MD., ...
Micro Biologist

Contd....PTO

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Institute of Internal Medicine
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Appendix E

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Dr.Shankar Bhagavad Pada
Spiritual Teacher

Lay Person:
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Audiologist & Speech Language Pathologist

Dr. S. SIVARAM KANNAN, M.D.,
Reg No 55814,
Asst Professor of Medicine
Institute of Internal Medicine
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Chennai 600 003

LIST OF PUBLICATIONS & PRESENTATIONS

ORIGINAL ARTICLE

COMPARISON OF OUTCOMES FOLLOWING COCHLEAR IMPLANTATION IN EARLY AND LATE IMPLANTEES

SathiyaMurali, ShyamSudhakarSudarsan, SenthilVadivuArumugam, Kiran Natarajan, Mohan Kameswaran

ABSTRACT

Introduction: Cortical auditory evoked potentials (CAEPs) is a non-invasive tool that can provide objective information on the functioning of the auditory pathways. In our study, we study CAEP parameters like P1 latency and amplitude as a tool for measure of auditory cortical maturation following continuous electrical stimulation following cochlear implantation and compare the values in children implanted below 3 years of age and between 3-6 years of age. Furthermore, in our study, we also recorded Category of Auditory Perception (CAP) and Speech Intelligibility Ratio (SIR) scores for subjectively assessing post-implantation outcomes and correlated the values with CAEP parameters. The results of our study are discussed.

Patients and Methods : 64 congenitally deaf children were enrolled for the study. They were divided into 2 groups (A-below 3 yrs of age & B-between 3 and 6 yrs). 6 monthly follow-up for a period of 1 year after cochlear implantation.CAEP parameters (P1 amplitude and latency), CAP and SIR scores were recorded. Students paired and un-paired t-tests, Pearson's correlation were the statistical tools used.

Observation and results : Investigation of CAEP parameters – P1 amplitude(except P1 latency)along with CAP and SIR scores in both the groups (A&B) showed statistically significant difference at 12 months post-implantation, indicating, that earlier the implantation better the outcomes.

Conclusion : Overall outcomes except CAEP P1 latency, early cochlear implantees showed significant improvement following implantation at 12 months than late implantees and values improve with increased use of implant. Thus earlier the implantation, earlier the maturation of auditory cortex.and stress on intensive auditory-verbal habilitation after implantation must also be appropriately explained to the care-givers / parents. The correlation between CAP, SIR with P1 latency, amplitude are discussed.

KEY WORDS – Cortical Auditory Evoked Potential (CAEP), CAP, SIR, early implantee, late implantee.

INTRODUCTION

As normal function of the auditory pathway is a precondition for normal development of speech and language skills, children with hearing loss are at higher risk of abnormal development of these skills.[1]Cortical Auditory Evoked Potentials (CAEPs) are auditory evoked potentials that are evoked by sound and processed in or near the auditory cortex and therefore they are referred to as CAEP.There is a considerable clinical and scientific interest in CAEPs to probe threshold and suprathreshold auditory processes because they are believed to reflect the neural detection and/or discrimination of sound.[2]

Cochlear implants (CIs) bypass peripheral cochlear damage, directly stimulate cell bodies in the spiral ganglion and make it possible, in principle, to avoid the deleterious effects of stimulus deprivation. From this point of view, children and adults who receive CIs provide a platform from which we can examine the time course of and constraints on, plasticity in central auditory system.[2]

We studied CAEP parameters like P1 latency and amplitude as a tool for measure of auditory cortical maturation following continuous electrical stimulation following cochlear implantation and compare the values in children implanted below 3 years of age and between 3-6 years of age. Furthermore, in our study, we also recorded Category of Auditory Perception (CAP) and Speech Intelligibility Ratio (SIR) scores for subjectively assessing post-implantation outcomes and correlated the values with CAEP parameters. The results of our study are discussed below.

COMPONENTS OF P1N1P2 COMPLEX

P1 is the first major component of P1N1P2 complex (Fig. 1). It is a vertex positive voltage deflection that often occurs approximately 50milliseconds (ms) after sound onset. P1 is usually small in amplitude in adults but large in young children and may dominate their response. Generators of P1 have traditionally been identified in the primary auditory cortex and specifically Heschl's gyrus.[3] The latency of P1 changes during infancy and childhood. P1 is generated by

auditory thalamic and cortical sources.[4] In normal hearing newborns the mean P1 latency is approximately 300 ms. Over the first 2–3 years (yrs) of life there is a rapid decrease in latency (to approximately 125 ms at age 3) and then a more gradual decrease into the second decade of life. The mean P1 latency in normal hearing adults (ages 22–25 yrs) is approximately 60 ms.[5] Because P1 latency varies as a function of chronological age, P1 latency can be used as a biomarker to infer the maturational status of auditory pathways in infants and children. Of particular interest are infants and children with significant hearing loss.[4]

N1 appears as a negative peak approximately 100ms after sound onset. N1 latency can be larger in some cases depending on the duration and complexity of the signal used. Compared to P1, N1 is relatively large in amplitude in adults (typically 2-5microvolts). In young children N1 generators may be immature and therefore the response absent. N1 is known to have multiple generators in the primary and secondary auditory cortex and therefore described having atleast 3 components.[2] N1 is maximally recorded from electrodes in midline central scalp locations.

P2 is a positive wave-form that occurs approximately 180ms after sound onset. It is relatively large in amplitude in adult (2-5micro volts or more) & may be absent in children. P2 appears to have generators in multiple auditory areas including the primary auditory cortex, secondary auditory cortex and the mesencephalic reticular activating system.[2] P2 is not as well understood as P1 and N1 components.

PATIENTS & METHODS

The aim of this study is to examine cortical responses to speech stimuli in children who received cochlear implants using P1N1P2 complex in CAEP. Auditory bold activation is identified and described in relationship to the P1 latency, amplitude and morphology as well as patient characteristics such as subject age at the time of implantation.

This prospective clinical study is done in children who receive cochlear implantation at our institute (Madras ENT Research Foundation Pvt Ltd) from Jan 2013The sample size was 64 implantees (32 less than 3yrs and 32 between 3 and 6 yrs) and they were sequentially followed-up at 6 monthly intervals for a period of 12 months after implantation. The candidates were chosen based on the following criteria.

Inclusion criteria

1. Child with bilateral severe to profound sensorineural hearing loss determined by pure tone Audiometry
2. Congenital hearing loss
3. Normal inner ear
4. No syndromic associations
5. A subgroup of our study to include bilateral sequential implantees to look at the differences if any between this group and single side implantation.
6. The child must have had an assessment by an audiologist and from an otolaryngologist experienced in this procedure indicating the likelihood of success with this device; and
7. The child must have arrangements for appropriate follow-up care including the long-term habilitation and speech therapy required to take full advantage of this device.

Exclusion criteria

1. Peri-lingual and post-lingual deafness
2. Associated mental retardation
3. Using sign language

This research was approved by the institutional ethical research review board and an informed written consent from the parents / legal guardians of the study group was taken prior to their inclusion in the study. All chosen candidates were evaluated with CAEP prior to implantation. All children were screened for speech, language and neurological development and referrals made to the audiologist, speech / language pathologist, ophthalmologist, occupational therapist and the child psychologist for assessment of higher mental functions and Intelligence Quotient. All the participants in the study group were sent to meet the auditory-verbal habilitation therapist at our institute prior to surgery, to make them adapt to the habilitation program. All the children were vaccinated against meningitis two weeks prior to surgery.

Implantees were 'Switched-on' 3 weeks after the surgery and habilitated at our Implant clinic for a minimum period of one year. CAEPs were tested in all these implantees at 6 monthly intervals. CAEP waveforms were recorded with NAL HEAR LAB Frye electronics instrument. Aided cortical assessment module were used to record CAEPs with speech stimuli m/(low),/g/(medium) and /t/(high)via loud speaker. These essentially vowel-free stimuli were chosen because they had a spectral emphasis in the low-, mid-, and high-frequency regions, respectively, and thus had the potential to give diagnostic information about the perception of speech sounds in different frequency regions. The test stimuli were presented at rate of 1.1/s via a loudspeaker at 55dBSPL, 65dBSPL and 75dBSPL.

The participants were seated at a distance of 1 meter at 00 azimuth to the loudspeakers. Speech Processors were set to children's usual program settings. Subjects would be seated comfortably in a reclining chair placed in a sound booth and they were watching a muted video tape or cartoon

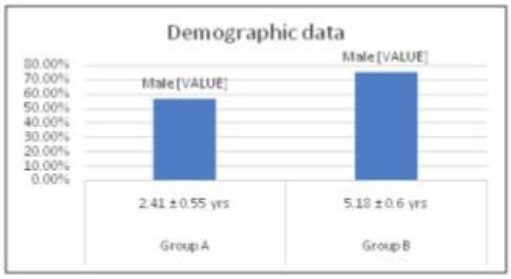
Appendix F-1

on a TV monitor placed in front of them. Evoked potentials were collected using Cz as the active electrode. Cz refers to the vertex midline placement. The reference electrode would be placed on the mastoid and a ground electrode on the forehead. Time-locked averaging were automatically suspended by the recording computer. The recording window will include -200ms pre-stimulus time to +600ms post-stimulus time. Incoming evoked responses were analog filtered from 1-30 Hz. Approximately 200 response sweeps would be recorded for each stimulus. The test session including electrode application and evoked response recording, will last approximately for about 25 minutes at each schedule. The presence of CAEP responses were defined as the largest positive peak (P1) in the region of 100 ms to 300 ms after stimulus onset. The latency of the peak was measured at the center of the peak. When the waveform contained a double peak, the latency was measured at the midpoint of the peak. It was made sure that absolute impedance of the electrode was < 5kΩ and inter-electrode impedance was 2 kΩ prior to testing.

Sweeps greater than +/- 30 microvolt were rejected on-line and the remaining sweeps were averaged to compute a final grand-averaged waveform for the individual subject. The same procedure was repeated in all schedules of follow up. Speech and language assessments were done using CAP and SIR scores.

OBSERVATION & RESULTS

The demographic data of the implantees in both groups are as below (table 1).



In our study, the observed values of the groups A & B are as below. Values expressed as mean ± standard deviation.

Group A	6m	12m	p value
Latency	98.34 ± 15.6	198.06 ± 15.45	0.01
Amplitude	8 ± 0.84	14.36 ± 1.26	0.0001
CAP	5.09 ± 0.39	5.22 ± 0.42	0.044
SIR	1.78 ± 0.42	2.41 ± 0.67	0.0001

Table 1 : Paired t-test: Statistical comparison of 6m and 12m group values

Group A	6m	12m	p value
Latency	282.78 ± 27.67	92.63 ± 13.38	0.0001
Amplitude	3.78 ± 0.93	10.53 ± 0.95	0.0001
CAP	2.75 ± 0.67	4.34 ± 0.48	0.0001
SIR	1.88 ± 0.34	2.09 ± 0.3	0.006

Table 2. Paired t-test values for Groups A & B

Unpaired t-test: Statistical comparison between 6m and 12m values of Group A, Group B (table 3)

6m	Group A	Group B	p value
Latency	98.34 ± 15.61	282.78 ± 27.67	0.0001
Amplitude	8 ± 0.84	3.78 ± 0.93	0.0001
CAP	5.09 ± 0.39	2.75 ± 0.67	0.0001
SIR	1.78 ± 0.42	1.88 ± 0.34	0.328
12m			
Latency	98.06 ± 15.45	92.63 ± 13.38	0.137
Amplitude	14.36 ± 1.26	10.53 ± 0.95	0.0001
CAP	5.22 ± 0.42	4.34 ± 0.48	0.0001
SIR	2.41 ± 0.67	2.09 ± 0.3	0.018

Table 3. Paired t-test values for Groups A & B

Correlation between observed Amplitude & Latency values of both groups with CAP and SIR scores **(table 4)**

Correlation	Group A	Group B
CAP - AMP	0.608	0.19
SIR - AMP	0.351	0.285
CAP - LAT	-0.649	-0.384
SIR - LAT	-0.455	-0.162

Table 4. Correlation between CAP, SIR scores with Latency, Amplitude in Groups A & B

Analysis of results:

1. There is a statistically significant difference between the CAEP latency ($p < 0.01$), CAEP amplitude ($p < 0.0001$) at 6 months and 1 year of group A candidates showing auditory cortical maturation following implantation was progressively improving.
2. When the CAP ($p < 0.044$) and SIR ($p < 0.0001$) scores of group A candidates were compared, there is a statistically significant difference between 6 months and 1 year values showing the outcome of cochlear implantation was progressively improving with time.
3. There is a statistically significant difference between the CAEP latency ($p < 0.0001$), CAEP amplitude ($p < 0.0001$) at 6 months and 1 year of group B candidates showing auditory cortical maturation following implantation was progressively improving even in late

Appendix F-1

implanted candidates.

4. When the CAP ($p < 0.0001$) and SIR ($p < 0.006$) scores of group B candidates were compared, there is a statistically significant difference between 6 months and 1 year values showing the outcome of cochlear implantation was good in late implanted candidates.
5. When the 6 month values of candidates of both the groups (A & B) were compared, there is a statistically significant difference in the parameters such as CAEP latency, amplitude and CAP scores, but there is no statistically significant difference in SIR scores. This implies the earlier the implantation, earlier the better results (within 6 months itself). But SIR score takes a longer time for better outcome.
6. When the 12 month values of candidates of both the groups (A & B) were compared, there is a statistically significant difference in the parameters such as CAEP amplitude, CAP and SIR scores, but there is no statistically significant difference in CAEP latency. This implies the earlier the implantation, better the outcome. But CAEP latency of late implantation group (Group B) matches with the earlier implantation group (Group A) by 12 months.
7. When CAEP amplitude and latency of both the groups were Correlated with CAP and SIR scores, there is a moderate positive correlation between Amplitude & CAP (0.608), SIR (0.351) scores of group A. There is a moderate negative correlation between Latency & CAP (-0.645), SIR (-0.455) of group A.
8. When CAEP amplitude and latency of both the groups were Correlated with CAP and SIR scores, there is a weak positive correlation between Amplitude & CAP (0.19), SIR (0.285) scores of group B. There is a weak negative correlation between Latency & CAP (-0.384), SIR (-0.162) of group B.

DISCUSSION:

Cochlear implantation is a surgery performed to restore hearing in a profoundly hearing impaired person. The clinical scores generally applied are CAP, SIR, MUSS, MAIS, etc., but these are subjective tests. CAEP is the latest objective tool used to study the changes in evoked potentials in a normal hearing and hearing impaired subjects and those with restored hearing either by hearing aid or cochlear implant. This study used CAEP in predicting outcomes of CI as this was an objective non-invasive tool to assess patients' post implantation outcome.

CAEPs are a measure of the maturity of central auditory pathways. Because P1 latencies vary as a function of chronological age, they are used to infer the maturational status of auditory pathways in congenitally deaf children who regain hearing after being fit with a cochlear implant. Our data suggest that in the absence of normal stimulation there is a sensitive period of about 3 years during which time the human central auditory system remains maximally plastic. Plasticity remains in some, but not all children until approximately age [6].

The central auditory pathway of a child with a cochlear implant is, therefore, stimulated in a different manner to those children with normal hearing or with hearing aids. However, once the auditory nerve is stimulated by the electrode array, the auditory nervous system function should presumably proceed as normal.[6]

Our study involved 64 children, aged between 1-6 years (divided equally into Group A 1-3 years and group B 3-6 years) who underwent cochlear implantation and were followed up for period of 1 year at 6 monthly intervals. The CAP and SIR scores were extracted from AVT records. P1 latency and amplitude values were correlated with CAP and SIR at 12 months of implantation.

Compared to our study, 2 studies [Dorman, Anu Sharma] have longitudinally researched 245 and 21 congenitally deaf children respectively.[7,8] The mean age of the children in our study groups were 2.41 ± 0.55 years (Group A) and 5.18 ± 0.6 years (Group B) and the chronological age was ≤ 6 years. In a study by Connor,the chronological age of the children were 1 – 10 years and were distributed into 4 groups based on age at implantation.[9] However, in a study by Anu Sharma, the age cut-offs were < 3.5 years & > 7 years for early and late age of implantation, respectively.[8]

The sex distribution in our study was 1:1.91 (female: male). The tool used for assessment of cochlear implantation outcomes in our study was CAEP, similar to that used in studies by Dorman and Anu Sharma, but in a study by Connor, the tools for outcome assessment were CAP and SIR scores.[7,8,9]

The CAEP parameters compared in our study were P1 latency and amplitude with age of implantation (6 monthly intervals for a period of 1 year) and correlated with CAP and SIR scores. The maturation of auditory cortex as demonstrated by P1 latency and amplitude in children implanted below 3 years of age showed that the values fall within normal range following 6 months of electrical stimulation. Furthermore, the decreases seen in the latency of P1 were larger than children implanted after 7 years of age, and continued to occur after the first month of stimulation, for the children who received their cochlear implant before 3.5 years of age, reaching normal limits within six to eight months. These results are in agreement with those of previous studies.[8]

Ponton and colleagues (1996) in their study, investigated the maturation of CAEPs in six children who received their cochlear implant between 18 months and six years of age, with the average age of implantation being 4.5

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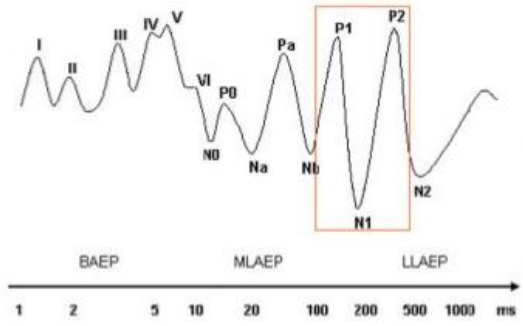

Figure 1. Cortical Auditory Evoked Potential components

years.[10] They found that the CAEPs, and in particular, the peak latency of P1, appeared to mature at the same rate as in children with normal hearing.

However, the maturation seemed to be delayed by the corresponding length of auditory deprivation, as also witnessed in children implanted between 3-6 years of age (group B) in our study.[11] These children demonstrated age-appropriate P1 latencies at 12 months post-implantation only.

In another study, Anu Sharma recorded CAEPs in 3-year-old congenitally deaf children after they were fitted with cochlear implants. Over the next few months after implantation, the cortical evoked responses showed rapid changes in morphology and latency that resulted in age-appropriate latencies by 8 months after implantation.[12] Hence, in agreement with such studies, it can be observed that cortical reorganization stimulated by deprivation is likely to be a significant factor in both variation in the latency and morphology of the cortical evoked response to sound for children fit with a cochlear implant and variation in the development of oral speech and language function.[7]

The CAP scores obtained from our study pointed out that there was a significant gain for speech perception outcomes when children were implanted before 3 years of age. They were able to achieve a minimum level of 5 at 6 months post-implantation itself. This however maintained over 12 months post-implantation. The SIR scores however showed progressive significant improvement at 6 and 12 months post-implantation. These values may considerably improve on further follow-up, i.e. over a period of 2 -5 years post-implantation.

The CAEP latency scores of children implanted between 3-6 years of age were comparable with early implantees (< 3 years of age) at 12 months post-implantation suggesting that these children can achieve better results provided they receive intensive auditory habilitation. This can probably be explained by residual neural-plasticity as our late implantees were less than 6 years of age. These results are in agreement with previous studies by Anu Sharma and Holt.[8,13]

CONCLUSION:

Pre-lingual / congenital deaf children who are implanted before 6 years of age develop speech perception and speech intelligibility abilities. Overall CAP and SIR scores along with CAEP parameters appear to improve with increased used of cochlear implant. However, the results of the present study strongly suggests that congenitally deaf children should receive cochlear implantation as early as possible (preferably < 3 years of age) to facilitate and maximize the gain from the surgical intervention. Since both the groups (A&B) showed comparable results with P1 latency at 12 months post-implantation, stress on intensive auditory-verbal habilitation after implantation must be appropriately explained to the care-givers / parents especially in late implantees

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ORIGINAL ARTICLE

CORTICAL AUDITORY EVOKED POTENTIALS - A REFLECTION OF AUDITORY MATURATION AN OVERVIEW

Sathiya K., Kiran Natrajan, Senthil Vadivu, Arpana Shekhar, Mohan Kameshwaram

INTRODUCTION

Normal maturation of central auditory pathways is essential for the development of speech and language skills in children. Auditory stimulation results in acoustical tagging of the temporal cortex. Hearing loss results in changes in the higher auditory centers. There is a 'developmental sensitive' period, during which the auditory cortex is highly plastic. If sensory input is deprived to the auditory system during this sensitive period, then the central auditory system is susceptible to large scale reorganization. Restoring input to the auditory system at an early age can provide the stimulation necessary to preserve the auditory pathways. In children with congenital bilateral profound hearing loss, cochlear implantation increases auditory sensitivity by direct electrical activation of auditory nerve fibers, enabling phonemic awareness, discrimination and identification ultimately yielding speech understanding. The emphasis is to implant early as early implantation stimulates a brain that has not been re-organized and will therefore be more receptive to auditory input & greater auditory capacity. Cortical auditory evoked potentials (CAEPs) have enabled us to objectively study this phenomenon. CAEPs were described by Hyde in 1997 and were obtained from the scalp potential complex when perceived in sound field.[1] The advent of CAEP has objectively proved that there is a critical age for stimulating the auditory brain via cochlear implantation. If auditory input is not restored during this developmental period, then the cross-modal reorganized pathways may exhibit abnormal functional characteristics as observed in recorded P1 amplitude, latencies and morphologies of CAEPs.

Cortical Auditory Evoked Potentials

The P1 auditory evoked potential has been characterized as a biological indicator of auditory neurodevelopment in normal hearing children and in children with cochlear implants.[2] The P1 is a robust, easily identified positive response occurring at about 100-300ms post-implantation, depending on the age of the child. The parameters analyzed are amplitude of P1 wave (microvolts), latency of P1 wave (milliseconds) and morphology of P1 wave (good, distorted & polyphasic). The latency of the P1 wave is thought to reflect the sum of synaptic transmission delays through out the central auditory pathways. Latency changes in the P1, as a function of increasing age and reflects the maturation of central auditory pathways occurring in response to auditory stimulation.[3] In infants with normal hearing, the average latency of P1 waveform is

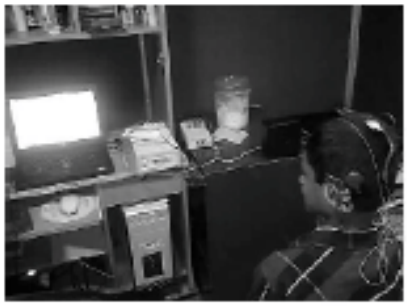

Fig.1: CAEPs being recorded in a cochlear implantee

about 300ms. A rapid decrease in latency occurs during the first few years of life; a normal P1 latency for a 3 years old child is about 125ms. A smaller decrease in P1 latency is expected from that time on; by the age of 15 years the average P1 latency decreases to approximately 95ms. The mean P1 latency in middle aged adults is approximately 60ms. This variation of P1 latency according to age can be used to infer the developmental status of the central auditory pathways and can easily be tracked in individuals over time. The latency and morphology of the P1 will vary depending upon the amount of time the central auditory system has been without adequate auditory input. The period during which the central auditory system remains most plastic is about 3.5 years after birth. A child who receives stimulation via cochlear implant within the first 3.5 years of life will have P1 latency that enters the normal range within the first 6 months after implant activation.[3]

If the auditory system does not receive adequate stimulation within 8 years after birth, it is likely that the higher order auditory cortex gets reorganized due to neural scavenging. CAEP latencies generally remain abnormal and the overall chances for normal speech and language while using a cochlear implant decrease significantly. This may be due to a lack of activity in the infragranular layers of the cortex in response to sound and decoupling of communication between the primary and secondary auditory areas.[4] Auditory deprivation also causes morphological changes to the P1 wave form. Early deprivation related wave form negativities, polyphasic morphology and low amplitude wave form have often been observed in children who have not received adequate input to their central auditory pathway.

PROCEDURE

CAEP response is recorded in response to synthesized speech syllables of /m/, /g/, & /t/. The stimuli are presented via a loudspeaker placed at an angle of 0 (zero) degree in front of the child. **(Fig.1)** Speech processors are set up to the child's usual program settings. The subject is seated comfortably in a reclining chair placed in a sound booth and watches a video tape or cartoon on a TV monitor placed in front in the sound booth. Video tape audio levels are kept below 45db SPL. The patient's state of attention needs to be such that they are awake or alert during CAEP measures. Evoked potentials are collected using Cz as the active electrode. Cz refers to the vertex midline placement. The reference electrodes are placed on the mastoid and a ground electrode on the forehead. Averaging is automatically suspended by the recording computer.[5] The recording window includes -200ms pre-stimulus time to +600ms post-stimulus time. Incoming evoked responses are analog filtered from 1-30 Hz. Approximately 300 response sweeps are collected for each subject. The test session including electrode application and evoked response recording lasts for about 45 minutes at each schedule. Sweeps greater than +/- 30 microvolt are rejected off-line and the remaining sweeps are averaged to compute a final grand averaged waveform for the individual subject. P1 is defined as the first robust positive cortical auditory evoked potential waveform in the 50-175ms range.[5]

CLINICAL APPLICATIONS OF CAEPS

CAEPs reflect recurrent cortical activity mediated by cortico-thalamic loops. These recurrent loops mediate subsequent cortico-cortical projections that may be disrupted after auditory deprivation. Cortical auditory evoked potentials can therefore be used to objectively assess hearing sensitivity, central auditory processing, and neural encoding of speech sound.[5] Restoring function to these modulatory projections may be possible with cochlear implantation, as long as the central auditory system remains maximally plastic and the effects of degeneration have not completely taken effect.[7] CAEPs may be useful for objectively predicting cochlear implant outcomes as well as improving candidacy and implant programming. A child who receives stimulation via cochlear implant within the first 3 years of life will have P1 latency that enters the normal range within the first 6 months after implant activation whereas this is not noted in late implantees. **(Fig.2, 3, 4)**

Cortical auditory evoked potentials have been used to estimate hearing thresholds.[8] CAEPS correlate with behavioral thresholds in individuals with hearing loss. Obtaining a good morphology

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on CAEPs using aided audiometry in children fitted with hearing aids confirms optimal function of hearing aids.[9] In combination with other objective hearing test results, such as ABR, it can provide considerable improvement to the efficacy of infant hearing aid fitting.

The auditory brainstem implant (ABI) has become a well established management option for children with bilateral absent or hypoplastic cochlea or cochlear nerves. The ABI helps bypass the hypoplastic or absent cochlear nerves and stimulates the cochlear nucleus in the brainstem, thereby restoring auditory sensation. The conventional tool for objective assessment of optimal function of ABI has been Electrically Evoked Auditory Brainstem responses (EABR). CAEPs provide us a way of identifying the tonotopicity within the cochlear nucleus and reflect re-organization of the higher auditory centers when stimulated via ABI. They can be used to identify optimum electrode placement and functioning of ABI. Unlike EABR which requires a tedious setup and a sedated or co-operative patient, CAEPs provide an easier and faster method to assess the optimal function of the ABI. **(Fig.5)** The morphology of P1 wave is somewhat similar to that obtained in a cochlear implantee. Amplitude of the CAEP may help as a guide to program young children with ABI. Absence of CAEPs via ABI may possibly indicate the absence of proper contact of electrode with the cochlear nucleus and may also help as a vital trouble shooting tool to identify device failure.[10] CAEPs may also be a good prognosticator for long term assessment of the performance of ABI.

CAEPs are predictive of speech perception and functional outcomes for children with Auditory Neuropathy Spectrum Disorder (ANSD). Children with ANSD may have normal P1 responses, delayed P1 response latencies and smaller amplitudes or absent P1 responses. P1 responses may be a good predictor of behavioral outcome in ANSD patients and provide a clinical tool for guiding intervention choices.[11] Absent speech-evoked CAEPs while wearing high-powered hearing aids facilitates an early decision about cochlear implantation. Thus, CAEPs show promise as a clinical tool for either predicting CI outcomes or optimizing CI settings in children with ANSD.

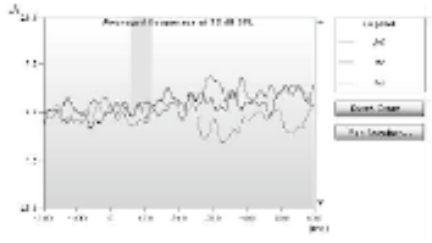

Fig.2: Pre-cochlear implant CAEP

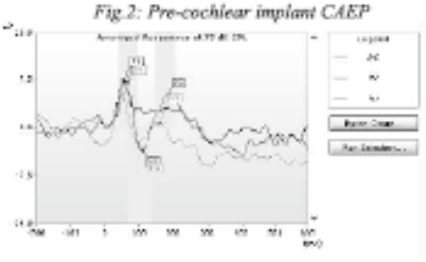

Fig.3: Post-cochlear implant CAEP at 1 year

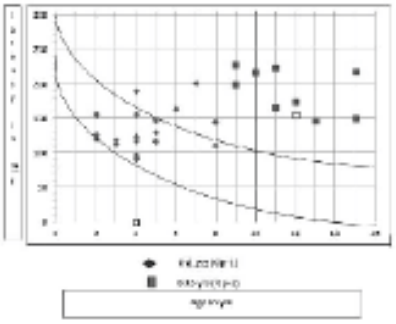

Fig.4: Early implantees have shorter P1 latencies than late implantees

CAEPs can be used to determine cases of cortical hearing loss, where hearing impairment is a consequence of underdevelopment of the central nervous system.[12] CAEPs may be an early indicator of cognitive impairment e.g. dementia.[13] However, the most important application of CAEPs is in cochlear implants. Candidates with early onset good CAEP morphology have been found to have better auditory verbal outcomes with habilitation than late cochlear implantees.[14]

CONCLUSION

Cortical auditory evoked potentials are proving to

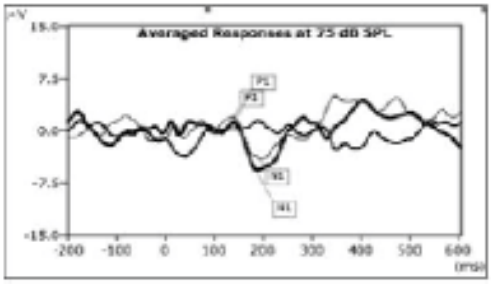

Fig.5: CAEPs after ABI

be a very useful investigative modality with clinical applications in the implant field. CAEPs are primarily used for objective assessment of central auditory function/neural encoding of speech sounds. There is a developmental sensitive period, during which the auditory cortex is highly plastic. The optimal time to implant a congenitally deaf child is within the first 3 years of life, when central auditory pathways are maximally plastic. If auditory stimulation is withheld for a period of 8 years or longer, the plasticity of the central auditory pathway is greatly reduced. CAEPs have proved to be a good prognosticator for the objective assessment of optimal functioning of the cochlear implant, providing an easy & efficient way to assess long term outcomes of cochlear implantation. They may be useful in assessing the functioning of auditory brainstem implants and to verify their correct placement in the brainstem. Hence, CAEP is a window to the auditory brain which can objectively assess the influence of auditory implants on the central auditory system.

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The Association of Otolaryngologists of India

South Zone Branch

(Regd. No. 122 of 2006)

CERTIFICATE

This Certificate of appreciation is presented to

Dr. Sathiya Murali

of ..... for receiving the

"AOI Andhra Pradesh (AP) Medal for Senior Consultant" during the AOI TS & SO CTI ZONE 2016 Annual Conference of AOI Southzone held at HOTEL PATRIYA TOWERS HYDRABAD on 7th & 8th OCTOBER 2016

President Dr. Ramana chary

Secretary General Dr. K.V. DEVADAS

Chairman Steering Committee

Org. Secretary

Awarded gold medal by the Association of Otolaryngologists of India, South zone Hyderabad (October 2016)

Topic: Comparisons of outcomes of cochlear implantation in early and late implantees.

Appendix G-1

CIGI
THE COCHLEAR IMPLANT GROUP OF INDIA

CIGICON 2015

13th Annual Conference of Cochlear Implant Group of India

26th - 27th September 2015
SMS Medical College, Jaipur

Certificate of Appreciation

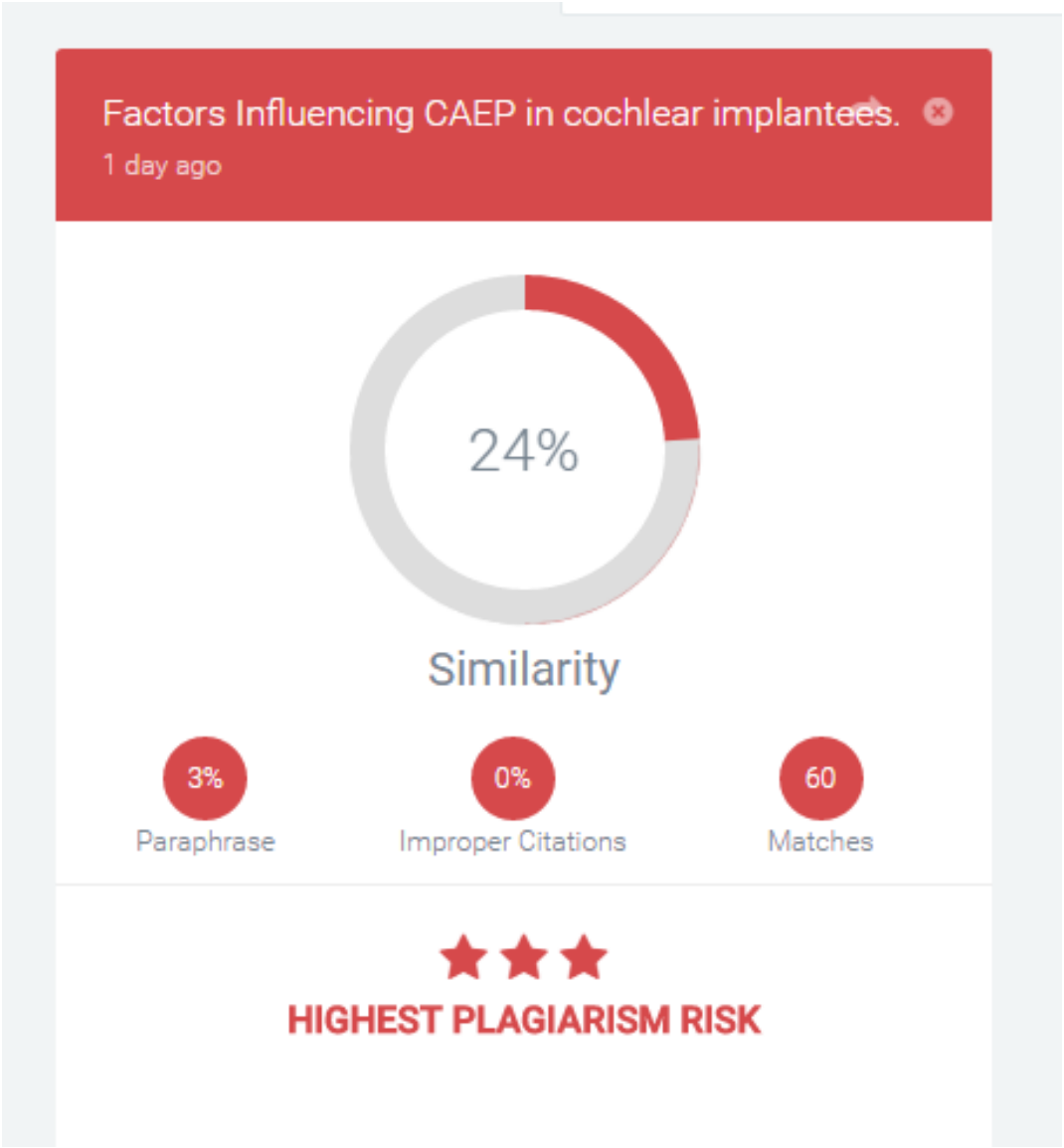
Awarded to

for securing Second position in
Oral Poster (Audiology Rehabilitation)

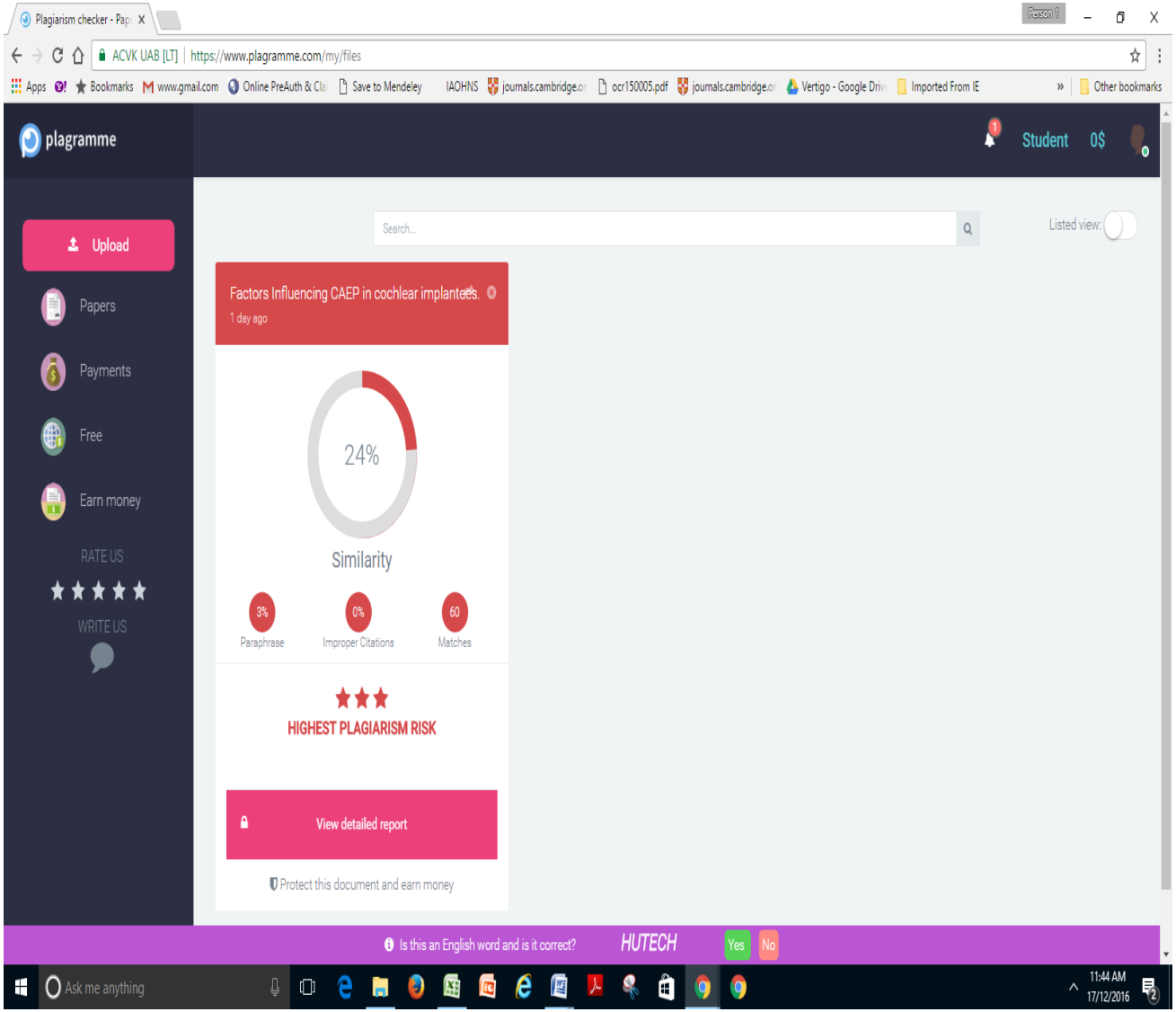
Dr. Man Prakash Sharma (Organizing Chairperson)	Dr. Mohnish Grover (Organizing Secretary)	Dr. Shashank Nath Singh (Treasurer)	Dr. Nishi Sonkhya (Scientific Chairperson)	Dr. Kalyani Mandke (CIGI President)	Dr. Ameet Kishore (CIGI Secretary)

Awarded silver medal in 13th Annual conference of cochlear implant group of India, (September 2015) Topic: Factors influencing CAEPs in cochlear implantees.

Plagiarism Certificate



Appendix H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Appendix H