Central Auditory Processing Abilities in Children with Non-Syndromic Cleft Lip and Palate: An Electrophysiological Study

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CERTIFICATE

This is to certify that this dissertation entitled "**Central Auditory Processing Abilities in Children with Non-syndromic Cleft Lip and palate: An Electrophysiological Study**" is a bonafide work submitted in part-fulfillment for the degree of Master of Science (Audiology) of the student with Registration Number: P01II21S0060. This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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CERTIFICATE

This is to certify that this dissertation entitled "**Central Auditory Processing Abilities in Children with Non-syndromic Cleft Lip and Palate: An Electrophysiological Study**" has been prepared under my supervision and guidance. It is also certified that this dissertation has not been submitted to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled "**Central Auditory Processing Abilities in Children with Non-syndromic Cleft Lip and Palate: An Electrophysiological Study**" is the result of my own study under the guidance of Dr. Chandni Jain, Associate Professor in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysuru, and has not been submitted earlier to any other University for the award of any Diploma or Degree.

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Abstract

The present study compared the central auditory processing abilities in children with non-syndromic cleft lip and palate (NSCLP) and their age-matched craniofacially typical counterparts. Thirty children aged 7 to 15 years were recruited for the study, with 15 children in each group. Electrophysiological tests, including auditory brainstem responses (ABR), binaural interaction component (BIC) of ABR, Auditory late latency responses (ALLR), and P300 were assessed. The results showed deviant responses in ABR, BIC, and ALLR in children with NSCLP compared to craniofacially typical counterparts. However, no significant difference was observed in P300 between the two groups. Hence, it can be concluded from the study that children with NSCLP are at higher risk of central auditory processing disorder due to their abnormal neural transmission in the auditory nervous system. Also, assessing auditory processing abilities in children with NSCLP should include electrophysiological tests in the test battery for additional information regarding neural transmission.

Keywords: Non-syndromic cleft lip and palate, cental auditory processing disorder, electrophysiological test.

Chapter 1

Introduction

Cleft lip and palate (CLP) are craniofacial malformations caused due to abnormal fetal development. In 70% of cases, CLP occurs without significant craniofacial malformations and is termed non-syndromic cleft lip and palate (NSCLP) (Ma et al., 2016a). Children with NSCLP usually experience hearing loss with middle ear deficits often caused by Eustachian tube dysfunction (Bluestone & Doyle, 1988; Sheer et al., 2012). These individuals have hearing loss which is usually bilateral, mild to moderate in severity, and fluctuating in nature (Yang & McPherson, 2007), which also leads to academic difficulties (Conrad et al., 2014; Persson et al., 2012; Richman et al., 2012). Collett et al. (2010) noticed that children with NSCLP had poor scores on tasks requiring reading and related skills, and they hypothesized that this could be primarily linked to their associated hearing deficits.

Multiple researchers have concluded that a history of conductive pathology cannot be the primary reason attributing to the severity of language and academic difficulties exhibited in children with NSCLP (Conrad et al., 2014; Hubbard et al., 1985; Jocelyn et al., 1996). Studies that included individuals with CLP with conductive pathologies have found abnormalities in Auditory brainstem response (ABR) findings (Viswanathan et al., 2008), but studies excluding conductive hearing loss have found mixed results. Yang et al. (2012) found no differences between infants with NSCLP and their craniofacially normal counterparts when conductive hearing loss was excluded. In contrast, Ma et al. (2016a) discovered substantial variations in absolute latency of wave III and V and interpeak latency of I-V in ABR results between children with NSCLP and craniofacially typical peers. The perceptual abnormalities might result from structural abnormalities in children with NSCLP, as imaging studies support it

(Nopoulos et al., 2000, 2001, 2002, 2007; Shriver et al., 2006; Yang, McPherson, Shu, Xie, et al., 2012).

Few studies have revealed that compared to their peers without craniofacial defects, infants with NSCLP had structural abnormalities in their brains that were frequently discovered in the left hemisphere's superior temporal plane, the location of the primary auditory cortex and the auditory association regions (Yang, McPherson, Shu, Xie, et al., 2012). These abnormalities may result in central auditory processing disorder (CAPD).

CAPD refers to the deficits in the neural processing of auditory information in the central auditory nervous system (CANS) as demonstrated by poor performance in one or more of the skills such as sound localization and lateralization, auditory discrimination, auditory pattern recognition,auditory performance in competing acoustic signals and and auditory performance with degraded acoustic signals, and temoral processing (ASHA, 2005). CAPD is assumed to be the outcome of compromised brainstem/cortical function.

CAPD can be assessed through questionnaires, behavioral, and electrophysiological tests. Prior to a diagnostic evaluation, questionnaire-based screening tools can be used by parents, teachers, speech-language pathologists, or psychologists to measure behavioral characteristics based on personal opinion (American Academy of Audiology, 2010). Studies have reported that children with NSCLP perform poorly on various central auditory processing tests, including temporal processing, speech perception in noise, and binaural processing abilities (Feng & Lu, 2016; Hofer-martini et al., 2021; Lemos et al., 2008; Maximino et al., 2022; Zarei et

al., 2021). Children with NSCLP also show difficulties in sound localization and sequential memory abilities (Do Amaral et al., 2010).

The electrophysiological assessment offers a window into auditory function and compared to behavioural hearing tests it requires lesser cooperation from listeners. Additionally, a variety of different auditory evoked potentials (AEP) represent neural activity from different anatomical structures along the auditory pathway and help to locate the lesion in the auditory system (Eggermont, 2007). Electrophysiological tests are objective, lower linguistically demanding and do not require patient response. Hence, there is a widespread agreement that CAPD diagnostic battery is incomplete without them (Bellis, 2011; Liasis et al., 2003).

ABR has been used on infants with NSCLP before 12 months of age, and it was found that most infants with NSCLP exhibited mild to moderate conductive hearing loss at an early age (Hélias et al., 1988). Aside from ABR, Mismatch negativity (MMN) was employed as a measure by researchers from the University of Helsinki to assess the auditory cortex function of infants with CLP (both NSCLP and CLP with syndrome) and was compared with craniofacially typical peers (Ceponienė, Haapanen, Ranta, Näätänen, & Hukki, 2002; Ceponiene et al., 1999, 2000; Cheour et al., 1997, 1999). In these studies, the infants with CLP without a history of any hearing disorder demonstrated shorter auditory memory span time (Cheour et al., 1997). In addition, infants with cleft palate exhibited more abnormal MMN responses compared to cleft lip and palate. (Ceponiene et al., 1999, 2000).

In another study, the absolute and interpeak latency of ABR, N1 latency, and N1-P2 amplitude of ALLR were significantly different between the NSCLP and the control group. However, P300 latency and amplitude did not differ between the two

groups (Ma et al., 2016a). This implies that children with NSCLP may have delayed neuronal transmission between the auditory nerve and the brainstem. Furthermore, delayed myelination and synaptic development may have a deleterious effect on auditory processing abilities in this group. (Ma et al., 2016a).

All these studies show abnormalities related to processing abilities in children with NSCLP, which could affect the child's ability to learn, communicate, and speech and language skills; hence, it is necessary to have a comprehensive CAPD test battery to assess the children with NSCLP to check if they are at risk for central auditory processing disorder.

1.1 Need for the Study

Children with NSCLP, particularly those with cleft palate, have a higher prevalence of CAPD (Ma et al., 2016a). Assessment of CAPD can be done utilizing questionnaires, behavioral tests, and electrophysiological tests. It is necessary to include electrophysiological measures along with behavioral assessment as these tests are objective and less linguistically demanding than behavioral tests (Liasis et al., 2003).

Electrophysiological assessments make the CAPD diagnostic battery more comprehensive as these tests help locate the lesion in the auditory system (Burkard et al., 2007). Few electrophysiological studies have been conducted to assess CAPD in children with cleft lip and palate and reported significant differences between the control and NSCLP populations (Ceponiene et al., 2000; Ma et al., 2016a; Yang, McPherson, Shu, & Xiao, 2012). MMN amplitude was significantly smaller in infants with cleft lip and palate than in the control group (Ceponiene et al., 2000). In another study, substantial differences have been found between the NSCLP group and the

control group for absolute wave latencies and interpeak latency in ABR, the latency of N1 wave, and N1-P2 amplitude in ALLR (Ma et al., 2016a). This suggests that the neural transmission time between the peripheral auditory nerve and the brainstem is slower in children with NSCLP.

However, all the tests have not been done together, and there are no pieces of evidence of the binaural interaction component (BIC) test executed in children with NSCLP. Also, as per the author's knowledge, no study assesses auditory processing abilities in children with NSCLP in an Indian context. With the evidence of abnormal BIC in children with CAPD (Delb et al., 2009; Gopal & Pierel, 1999), there is a need to assess BIC children with NSCLP. Thus, the present study is aimed to assess auditory processing abilities in children with NSCLP using electrophysiological tests.

1.2 Aim of the Study

The study aimed to assess auditory processing abilities in children with NSCLP through electrophysiological tests.

1.3 Objective of the Study

1. To record ABR in individuals with NSCLP and age-matched craniofacially normal individuals.
2. To record the BIC of ABR in individuals with NSCLP and age-matched craniofacially normal individuals.
3. To record ALLR in individuals with NSCLP and age-matched craniofacially normal individuals.
4. To record P300 in individuals with NSCLP and age-matched craniofacially normal individuals.

5. To compare the latency and amplitude measures of various electrophysiological tests between the individuals with NSCLP and age-matched craniofacially normal individuals.

Chapter 2

Review of Literature

Cleft lip and palate (CLP) is a common congenital craniofacial anomaly, and the global prevalence of CLP is 0.45 in every 1000 live births (Salari et al., 2022). Among all the orofacial cleft disorders, 70% occur without any associated syndromes and are called non-syndromic cleft lip and/or palate (NSCLP) (Stanier & Moore, 2004). Peripheral hearing loss is common in children with NSCLP, possibly due to direct or indirect effects of Eustachian tube dysfunction. Auditory processing disorder (APD), which has also been reported as a hearing deficiency in children with NSCLP, may also be a factor in learning and language delays in this population.

2.1 Eustachian tube dysfunction (ETD) and Otitis media in children with CLP

Children with cleft palate are more likely to develop ETD. As a result of this malfunction, negative pressure builds up in the middle ear, leading to otitis media as a disease progression (Berryhill, 2016).

Using tympanometry, Gudziol and Mann (2006) evaluated 40 patients with unilateral cleft lip and palate with an average age of 19.9 years. ETD was identified in 25% of patients bilaterally and 6% unilaterally, whereas chronic otitis media was diagnosed in 32% bilaterally and 12% unilaterally. Muscular insufficiency in opening the eustachian tube was attributed to be the reason behind ETD.

Sheer et al. (2012) studied three-dimensional (3D) finite element (FE) modeling techniques to study biochemical and anatomical changes influencing the opening of eustachian tubes in infants and children with cleft palate. The subjects exhibited reduced sensitivity to tensor veli palatini muscle forces (TVPM), and as the eustachian tube is highly sensitive to TVPM forces, it seems to result in ETD.

Rajion et al. (2012) conducted a study using 3D computed tomography (CT) to examine the skeletal components of the nasopharyngeal area in patients with cleft lip and palate. CT scans of 29 patients with cleft lip and palate aged between 0 and 12 months were obtained and compared with their normal counterparts. They discovered an enlarged nasopharyngeal space in the cleft population, which may cause the eustachian tube to be compressed and result in recurrent middle ear infections.

Thus, ETD can lead to recurrent middle ear infections in developmental years, affecting children's auditory processing abilities (Khavarghazalani et al., 2016).

2.2 Hearing loss in children with CLP

Hearing loss is often seen in children with cleft lip and palate and is usually caused by otitis media with effusion. The prevalence of audiological problems is influenced by numerous factors, including age, gender, ethnicity, type of cleft, and the repair status of CLP.

Handzic et al. (1996) compared haring levels in patients with different types of cleft, including bilateral cleft lip and palate (BCLP) (57 patients), unilateral cleft lip and palate (UCLP) (124 patients), and cleft palate only (62 patients) across wide age group from 1 to 34 years (median age, 6). Results showed that conductive hearing loss was found in 59.7% of the population, whereas others had normal hearing sensitivity. They also observed an age-related change in the frequency of hearing impairment. The hearing loss was higher in younger children (81% in 1-3 years) than older children (47% in 7-9 years). Among children with BCLP, UCLP, and cleft palate, 57%, 61.7 %, and 58.1 % had conductive hearing loss, respectively. They concluded that most of the cleft population suffer from bilateral moderate conductive hearing loss by age 6, and sensorineural hearing loss is rare in them. Early diagnosis and repair of cleft are essential for normal hearing and speech and language development.

Broen et al. (1996) conducted a longitudinal study on 28 children with cleft palate (18 boys and 10 girls) and 29 children without cleft with an age range of 9 to 30 months at a three-month interval. The mean age of cleft repair was 13.3 months (range from 9 to 22 months). Tympanometry and hearing screening were performed to assess hearing status. Hearing screening was performed at 500, 1000, and 2000 Hz using warble tones in the sound field and through visual reinforcement audiometry. They reported that all children with cleft failed tympanometry before the primary palatal surgery, and even after the surgery, only a few children had normal middle ear function. Only 5.9 % of children with cleft palate had normal tympanograms. Also, it was reported that children with cleft palate failed the hearing screening in every stage of the study more than children without cleft.

In a systematic review study, Yang and McPherson (2007) reported that children with non-syndromic clefts usually exhibited conductive hearing loss. In contrast, the study also noted that conductive and sensorineural hearing loss were common in children with syndromic clefts.

In a cross-sectional cohort study, Do Amarel et al. (2010) assessed hearing abilities in 44 children with CLP aged 8 to 14. Hearing evaluation results revealed that 77.27% of the children had normal hearing, 13.6% and 2.2% had conductive hearing loss and mixed hearing loss, respectively. Tympanogram results showed that C-type tympanogram was seen in 21.2%, B-type in 7.1%, Ad-type in 3.5% and A-type in 68.2% of the CLP children.

Thus, conductive hearing loss is common in children with CLP, and recurrent otitis media is usually a causative factor. Middle ear infections are more frequent before the primary palatal surgery but persist in some individuals even after surgery, leading to subsequent hearing loss.

2.3 Central auditory processing deficits in children with CLP

CAPD is a perceptual disorder suspected to be caused by impaired brainstem/cortical function. Many behavioral assessments (Boscariol et al., 2009; Ma et al., 2015) and questionnaires (Cayres Minardi et al., 2004; Ma et al., 2016b) have been administered to children with NSCLP indicating deficits in auditory processing abilities in this population compared to their age-matched craniofacially normal individuals.

Lemos et al. (2008) compared the performance of 27 children with CLP in dichotic listening tests (directed attention mode) to the performance of 25 age-matched normal controls. The children were in the age range of 7 to 7.11 years. Children with cleft had no co-morbid conditions like hearing deficit, intellectual impairment and attention deficit hyperactive disorder (ADHD). The authors reported that the CLP group scored lower than the controls in both ears. They concluded the study by attributing the listening experience during critical development as a key role in achieving optimized neural connections and listening skills.

Ma et al. (2015) investigated and compared the auditory processing abilities of one hundred and forty-one children with NSCLP and sixty age-matched craniofacially normal controls. The children were aged between 6 and 15.67 years. Central auditory processing abilities were assessed for temporal resolution and picture identification in noise. The result revealed that children with NSCLP performed poorly in both tests, indicating that children with NSCLP might have poor temporal resolution and auditory closure abilities.

Ma et al. (2016b) used Fisher's auditory problem checklist (FAPC) to investigate the prevalence of auditory processing disorders in children with NSCLP.

The children were divided into different cleft types, including cleft lip, cleft palate, and cleft lip and palate. Caregivers of one hundred and forty-seven school-going children with NSCLP and 60 craniofacially normal children were recruited for the study. The results revealed that children with cleft palate scored lowest on the FAPC questionnaire, indicating that children with cleft palate might be at higher risk of CAPD than children with only cleft lip and children with cleft lip and palate.

Feng and Lu (2016) investigated the central auditory abilities of eighteen children with NSCLP aged 7 to 15 years with normal hearing sensitivity and compared it with age-matched controls. Both groups underwent the following CAPD tests: dichotic digits test (DDT), gap in noise test (GIN), and hearing in noise test (HINT). Results revealed that children with NSCLP performed poorly in the GIN and HINT tests, indicating poor temporal resolution and auditory closure, respectively. However, DDT scores were comparable between the two groups, indicating that binaural integration and separation might be normal in the NSCLP group.

MacDonald et al. (2019) studied the prevalence of spatial processing disorders in twenty children with cleft palate (with or without cleft lip) aged between 6 and 16 years with normal hearing sensitivity. Listening in Spatialized Noise-Sentences (LiSN-S) test was used to assess spatial processing. Authors reported that 40% of them exhibited spatial processing deficit, indicating that children with cleft palate might be at risk of spatial processing disorder, and they attributed this deficit to a history of recurrent otitis media.

Hofer-Martini et al. (2021) investigated auditory processing abilities in forty-eight children with NSCLP aged 5 to 16 years using speech intelligibility in noise, dichotic speech discrimination, auditory short-term memory, and parental

questionnaire. Although most parents did not report any problems in the parental questionnaire, 69% scored poor scores in the speech intelligibility in noise test, and 16.7% showed poor results in dichotic speech discrimination and the auditory short-term tests. This indicated that children and adolescents with NSCLP might be at risk of CAPD.

Zarei et al. (2021) assessed the auditory processing abilities of Persian-speaking twenty-three children with NSCLP in the age range of 8 to 12 years, along with their normal counterparts. The study used the GIN test, a Persian version of dichotic digit (DDT) test, and Persian version of monaural selective attention test (mSAAT). DDT score revealed that children with NSCLP scored higher in the right ear than the control group. However, no difference was found in the left ear scores between the two groups. GIN and mSAAT scores were poorer in children with NSCLP than in the control group. This indicates that children with NSCLP might have poor monoaural low redundancy and temporal resolution skills in children with NSCLP.

Thus, multiple domains of auditory processing abilities are affected in children with NSCLP, as shown through behavioral measures to assess auditory processing abilities. Eustachian tube dysfunction and its complications resulting in otitis media in the developing years might alter the functional aspect of hearing and lead to central auditory processing disorder.

2.3.1 Electrophysiological test findings in children with CLP

Electrophysiological assessment provides information on auditory functions in relation to neural connections of auditory pathways. Previous investigations have been done to evaluate central auditory processing abilities in children with CLP through

electrophysiological measures (Ma et al., 2016a; Yang, McPherson, Shu, & Xiao, 2012).

In their experimental study, Yang et al. (2012) performed auditory brainstem response (ABR) and mismatch negativity (MMN) in infants with NSCLP. They compared it to normal controls to identify the central auditory nervous system response to acoustic stimuli. Thirty-four infants with NSCLP aged 6 to 24 months and an equal number of age-matched normal controls were included in the study. ABR was performed at a 19.3/s stimulus rate at 80 dB nHL. The absolute latency of wave I, III, and V and I-V interpeak latency were analyzed. Results indicated that absolute and interwave latencies of infants with NSCLP were comparable to normal controls. For studying MMN, a tone burst of 1000 Hz was used as a standard stimulus along with an 1100 Hz deviant stimulus. The recoding was done at an intensity of 80 dB nHL with a ratio of 9:1 for the standard and deviant stimuli. The result revealed diminished MMN response in children with NSCLP compared to the control group indicating impaired processing abilities at the cortical level.

Ma et al. (2016a) performed ABR, ALLR and P300 in 146 children (98 males and 48 females) with NSCLP and 60 craniofacially normal children aged between 6 and 15 years. The NSCLP group was further divided into four subgroups by cleft type: 37 children with cleft lip (CL), 26 children with cleft palate (CP), and 83 children with cleft lip and palate (CLP). The CLP group was further subdivided into unilateral (UCLP) and bilateral (BCLP) groups. ABR was recorded at a 44.1/s stimulus rate with an intensity of 80 dB HL. The comparison between NSCLP and the control group revealed that waves III and V were significantly prolonged in the NSCLP group. In addition, I-V interpeak latency was also longer in children with NSCLP. Gender disparities were also found, and wave III, wave V, and I-V interpeak latency was

significantly prolonged in males compared to females. Comparison between different cleft revealed that compared to CL group, children with CP, UCLP, and BCLP had significantly prologed wave I latencies. Wave III latency was significantly different for CL vs. CP and CL vs. UCLP; wave V was prolonged only in the case of UCLP compared to the CL subgroup.

In ALLR, the latency of N1 and amplitude of the N1-P2 complex was examined. The result revealed that the N1 latency of the NSCLP group was significantly longer than the control group, and there was a significant difference in the amplitude of the N1-P2 complex in children with NSCLP compared to the control group. N1 latency changed with the age in the NSCLP group, and there was a significant difference in the age groups: 6-8 years vs. 12-15 years and 9-11 years vs. 12-15 years. A decrease in the amplitude of the N1-P2 complex with age was also observed in the NSCLP group.

For assessing P300, a standard stimulus of 1000 Hz at 60 dB nHL and a deviant stimulus of 2000 Hz at 90 dB HL were presented in a 4:1 ratio. Children were instructed to count the rare stimuli. After obtaining the waveform, P300 latency and amplitude were compared between the two groups. The results revealed no significant difference in the P300 parameters between the two groups. The authors suggested that the auditory processing abilities relevant to attention and memory issues available in craniofacially typical children were similar to those with clefts.

This evidence gives insight into the dysfunction of neural transmission in the auditory nerve and lower and upper brainstem in the NSCLP group, leading to processing difficulties. Researchers suggested that the deviated response in ABR indicates delayed central auditory system maturation in children with NSCLP. They

have also concluded that N2 response might be a marker of neural deficits in children with CAPD.

In everyday life, binaural hearing distinguishes selected signals from surrounding noise and localizes a target sound in a noisy environment. Behavioral studies have investigated binaural hearing extensively. One common electrophysiological test for investigating binaural hearing is the auditory evoked potentials' binaural interaction component (BIC) (Fowler, 2004). According to the authors' knowledge, there are no studies done in children with NSCLP regarding BIC. Hence, with the evidence of abnormal BIC in children with CAPD (Delb et al., 2009; Gopal & Pierel, 2009), there is a need to assess BIC children with NSCLP.

Thus, electrophysiological assessment provides information on auditory functions with minimal response from listeners compared to any behavioral hearing tests. Additionally, detecting hearing loss and the localization of auditory system lesions are supported by a series of unique AEP peaks appearing after different latencies representing neuronal activity from various anatomical structures along the auditory pathway (Burkard et al., 2007). Hence, from the above studies, it can be concluded that children with NSCLP show deviated responses from typically developing children and might be at risk of CAPD. More electrophysiological studies need to be conducted in these populations for generalization.

2.4 Brain abnormalities in individuals with NSCLP

Studies have shown that patients with NSCLP have different brain architecture than their craniofacially normal counterparts (Nopoulos et al., 2000, 2001, 2002, 2007; Yang, McPherson, Shu, Xie, et al., 2012). Isolated clefts are not limited to facial defects; abnormalities in the brain accompany them (Nopoulos et al., 2007).

Radiological evidence of structural abnormalities in these children's cortical structures suggests that it can lead to processing difficulties (Yang, McPherson, Shu, Xie, et al., 2012).

Nopoulos et al. (2000) studied the brain morphology in 14 adult men with isolated cleft lip and palate. Patients were selected from the University of Iowa's cleft lip and palate service programme. The control subjects were selected from healthy volunteers with Magnetic resonance imaging (MRI) scans and neuropsychological collected via the Mental Health Clinical Research Centre. They were matched to patients by age, gender, and parental socioeconomic background. MRI was obtained on a 1.5 Tesla GE Sigma MR scanner, and three different sequences were acquired for each subject. The measures of the brain were further compared between the two groups. The analysis revealed no significant difference between the two groups in intracranial volume, total brain tissue, and total cerebrum volume; however, both groups' regional distribution of tissue within cerebrum was significantly different. Compared with the controls, patients with facial cleft had larger frontal lobes and smaller temporal and occipital lobes. The volume of the cerebellum also showed a significant group differences. The researchers highlighted the relationship between the growth and development of the brain and face and concluded that craniofacial anomaly could result in brain abnormalities and vice versa.

Nopoulos et al. (2001) studied the midline of the brain of 49 adult men (to reduce the impact of gender and age on the brain morphology) with CLP and compared it with 75 healthy controls. The MRI of both groups was done and analyzed. The results revealed that the adult men with NSCLP had an enlarged Cavum septi pellucidi (CSP). The incidence of enlarged CSP was 8% in CLP patients and 1% in healthy controls. Researchers concluded that individuals with NSCLP do not always have enlarged CSP.

Still, in this population with no other congenital anomalies, it can be suggested that the brain abnormality may be specifically related to facial cleft. Researchers also linked this structural abnormality of CSP to cognitive dysfunction in individuals with NSCLP, which is a primary brain problem rather than a complication of other factors such as poor hearing or psychological problems.

Noupoulos et al. (2002) compared the brain morphology of adult males with NSCLP to that of a matched healthy control group. The brain structure was quantified by analyzing MRI. Subjects with NSCLP had severe abnormalities in brain morphology, including abnormally enlarged anterior cerebrum regions and decreased volumes of the posterior cerebrum and cerebellum. Overall, the left temporal lobe was the most seriously afflicted region. Furthermore, these anatomical anomalies were linked to cognitive impairment. Hence, they concluded that these findings emphasize the critical link between facial and brain development.

Nopoulus et al. (2007) studied the brain structure in children with NSCLP as their previous study was only on men, limiting the interpretation to generalize to both the genders and children. In their study, 50 boys and 24 girls with NSCLP were recruited for the study. The cleft type was categorized into the cleft of the lip only (CLO) (n=18), cleft of the lip and palate (CLP) (n=33) and cleft palate only (CPO) (n=23). Age and gender-matched healthy normal controls were recruited. MRI was obtained for all on a 1.5 Tesla GE Sigma magnetic resonance scanner and three different sequences were obtained for each subject: T1, T2 and proton density. After analyzing images between the two groups, it was found that children with NSCLP had significant abnormalities in their brain structure. They had reduced head circumference with smaller brain tissue volumes in the cerebrum and cerebellum. A gender-specific abnormality was found in males as they had abnormal tissue distribution and reduced

cerebrum volume compared with controls. They concluded that the cerebrum volume in individuals with NSCLP might eventually reach a normal measure. Still, the tissue distribution within the cerebrum was abnormal in children and adults with NSCLP.

Researchers have also studied the brain structures of infants with NSCLP and compared them to normals. In their study, Yang et al (2012) looked at probable structural anomalies of the central auditory system in children with non-syndromic cleft lip and palate. They studied twenty-seven Chinese infants with NSCLP aged 6 to 24 months, and the central auditory nervous system (CANS) morphological MRI measurements of infants with NSCLP were analyzed and compared to those of age- and gender-matched normal controls. There were no significant group differences in typical brain parameters, such as brain stem and right hemisphere volumes. However, infants with NSCLP had statistically considerably reduced volumes of the left thalamus and left auditory cortex and significantly decreased thickness of the left auditory cortex.

Chollet et al. (2014) also studied the brain structures in children with NSCLP. They recruited ninety-six children, 57 children with NSCLP and 39 controls aged between 7 to 17 years. Of these, 35 had cleft lip and palate, and 22 had cleft palate only. MRI was obtained with 1.5 Tesla Signa magnetic resonance scanner using a T1 sequencing protocol. The result of the study showed similar results as the findings of Nopoulus et al. (2007). Brain volume was smaller in children with NSCLP than in the control group. Within the brain, the tissue was abnormally distributed such that the cerebellum, frontal lobe, and caudate nucleus were smaller, and the occipital lobe was larger than normal. They also identified dysmorphology patterns specific to the type of cleft. The cleft palate-only group was associated with cerebral heightening, narrowing of the frontal lobe, reorientation of the Broca's area, and displacement of the superior colliculus and the splenium. The cleft lip and palate group was associated with shifts in

the occipital and temporal poles, inferior pons displacement, and cerebellum shortening. They concluded that the cognitive deficits associated with cleft lip and/or plate may be due to abnormal brain structures.

This evidence suggests that the abnormal molecular pathways that cause this condition play a role in facial and brain development. Furthermore, the data here support the theory that cognitive problems associated with cleft lip and/or palate are caused by aberrant brain structure.

Chapter 3

Method

The present study aimed to assess auditory processing abilities in children with non-syndromic cleft lip and palate (NSCLP) through electrophysiological tests.

3.1 Research Design

The within and between-group experimental research design compared the electrophysiological findings between children with NSCLP and craniofacial normal children.

3.2 Participants

Thirty participants in the age range of 7 to 15 years participated in the present study. Participants were divided into two groups; the clinical group (children with NSCLP) comprised 15 children (mean age: 10.75 years), and the control group (craniofacially typical peers) comprised 15 children (mean age: 11.02 years) with normal auditory processing skills. Table 3.1 shows the age, gender, and type of cleft of children in clinical group.

Table 3.1

Age, gender, and type of cleft of children in clinical group

Subject No	Age (years)	Gender	Cleft type
1	7.1	M	Bilateral RCLP
2	7.2	F	RCP (soft palate)
3	7.6	M	Bilateral RCP
4	8.10	F	Bilateral RCP
5	10.3	M	RCP (soft palate)
6	10.3	F	Unilateral RCLP
7	10.4	F	Unilateral RCLP
8	10.9	M	Unilateral RCLP
9	11.3	M	RCP (soft palate)
10	11.4	F	Bilateral RCLP
11	11.9	F	Bilateral RCP
12	12	M	Unilateral RCLP
13	13.7	M	Bilateral RCLP
14	14.10	F	Unilateral RCLP
15	15	M	Unilateral RCLP

3.2.1 Participant inclusion criteria for clinical group

Inclusion criteria:

- Children with non-syndromic cleft lip and palate with no active middle ear infection.
- Children with normal hearing sensitivity in both ears.

Exclusion criteria:

- Syndromic conditions and other sensory impairments such as hearing loss and intellectual disability.

3.2.2 Participant inclusion criteria for the control group

Inclusion criteria:

- Craniofacially normal children with normal hearing sensitivity and no active middle ear infection.
- Participants who passed 'Screening Checklist for Auditory Processing (SCAP) developed by Yathiraj and Mascarenhas (2002) were recruited for the study.

Exclusion criteria:

- Children with any structural abnormalities and active middle ear infections.
- Children with any sensory impairments like hearing loss, intellectual disability and developmental delay.

3.3 Test environment

The study was conducted in an acoustically treated air-conditioned room (ANSI S3.1 1991). Pure tone audiometry was performed in a two-room setup, while immittance evaluation, optoacoustic emissions (OAEs), and P300 were carried out in a single-room setup.

3.4 Instruments

The following instruments were used in the study:

- A calibrated diagnostic audiometer, GSI-61 (Grason-Stadler, Eden Prairie, USA), dual-channel audiometer with TDH-39 headphones, and B-71 bone vibrator was used for routine audiological evaluation.
- A calibrated Immittance meter, GSI-Tympstar pro (Grason-Stadler, Eden Prairie, USA), was used for tympanometry and acoustic reflex threshold measurement.
- OAE instrument ILO-V6 Echoport (Otodynamics Ltd., UK) was used to assess outer hair cell functioning.
- Screening Checklist for Auditory Processing (SCAP) Yathiraj and Mascarenhas (2002) was used to screen children's auditory processing abilities in the control group.
- Biologic Navigator Pro (Natus Medical Incorporated, Illinois, USA) version 7.0.0 with ER-3A insert earphones were used to record auditory evoked potentials.

3.5 Test Procedure

3.5.1 Routine Audiological Evaluation

Pure tone audiometry was performed to establish air conduction thresholds between 250 to 8000 Hz and bone conduction thresholds from 250 to 4000 Hz. To exclude any middle ear pathology, immittance evaluation was performed. Tympanometry was performed using a 226 Hz probe-tone by altering the air pressure in the ear canal from +200 to -400 daPa. Using the same probe tone frequency as before, ipsilateral and contralateral acoustic reflex thresholds were measured at octave

frequencies from 500 Hz to 4000 Hz. Transient evoked otoacoustic emissions (TEOAEs) were recorded to rule out any outer hair cell dysfunction.

3.5.2 Electrophysiological tests

This study examined the auditory pathway from the eighth nerve to the cortical level in clinical population and compared it to the control group using ABR, BIC of ABR, ALLR, and P300.

The participants were seated in a recliner chair and were instructed to avoid any movements during the test. Single channel recording was obtained in a vertical montage and electrode placement were as follows: the non-inverting electrode was placed on Cz, an inverting electrode on the mastoid of the recording ear, and the ground electrode was placed on the mastoid of the non-recording ear. The absolute impedance of 5k Ω and inter-electrode impedance of 2k Ω was maintained, respectively.

Auditory brainstem response recording: ABR was used in the study to check the integrity of the auditory pathway from the auditory nerve to the brainstem level. For ABR, 100 µs click stimuli were delivered using insert earphones at 11.1 and 90.1/s at 80 dB nHL. An averaging window of 10 ms was used with 1500 sweeps. The evoked electrical signals were amplified 100,000 times, and the filter setting used was 30-3000 Hz. The sensitivity/artifact rejection level was kept at ± 23 µV. Wave I, III, V and I-V interpeak latency were taken into considered while assessing the waveforms. The robustness of the signal led to the choice of the ABR wave latencies, which are virtually unaffected by the placements of the recording electrodes. Previous studies on ABR show mixed results while comparing children with cleft and the control group at a lower repetition rate. In this study, a 90.1/s was also included to check for the difference in absolute and interpeak latencies of ABR at a higher rate.

Binaural interaction component of ABR recording: For BIC, the binaural response was obtained by recording ABR binaurally at an 11.1/s rate, and all other parameters were the same as ABR recording. The ABR was recorded separately for the right and left ear, and binaural recording was also done. The right and left waveform was added to get a summed-up waveform. BIC was calculated with the mentioned formula:

Summed-up waveform – binaural waveform = BIC

BIC wave V was chosen in the study as they are valid and confirmed responses that show binaural interaction and indicate ongoing binaural processing (Gopal & Pierel, 2009), and children with NSCLP might have deviated response as they are at risk of CAPD.

Auditory late latency response recording*:* For ALLR, the same equipment and electrode placement were used as the ABR. The stimuli to elicit ALLR was a 1000Hz tone burst presented at 0.5/s at an intensity of 80 dB nHL. The filter setting was 1-30 Hz with an analysis window from -100 to +400 and 200 sweeps. With the understanding that N1 amplitude varies with stimulus length and rise-fall time and decreases if the stimulus duration is longer than 30 ms and rise-fall time are longer than 50 ms, the stimuli used in current study were tone bursts with a rise-fall times of 20 ms and plateau time of 20 ms (Alain & Woods, 1997; Onishi & Davis, 1968). Children were given counting the stimulus task during the recording for active attention. Absolute latency and baseline-to-peak amplitude of waves P1, N1, P2, and N2 were assessed as the N1-P2 wave latency prolongs and amplitude decreases in children with CAPD. Hence, ALLR was included in the study as children with NSCLP expecting a deviated response as they are at risk of CAPD.

P300 recording: Stimuli used for P300 recording were 2000 Hz tone bursts as deviant (infrequent) tones embedded randomly in a series of 1000 Hz standard (frequent) stimuli. The standard and deviant tone ratio used was 4:1. The late AEPs were recorded in active mode, and counting rare stimuli in P300 were the tasks given to the children. P300 latency and amplitude were evaluated in the study to assess the participant's ability to detect acoustic changes in the signal and then decide on the similarity or difference in the signals linked to attention and memory, respectively. A detailed summary of stimulus and acquisition parameters of all the electrophysiological tests used in the study is given in Table 3.2.

Table 3.2

AEP recording protocol: stimulus and acquisition parameters settings

Stimulus and Acquisition parameters	**ABR and BIC**	**ALLR**	**P300**
Stimulus	100 µs click	1000 Hz tone burst	1000 Hz tone burst (standard) 2000 Hz tone burst (deviant) 4:1
Rate	11.1/s 90.1/s	0.5/s	0.5/s
Polarity	Rarefaction	Rarefaction	Rarefaction
Transducer	Insert earphones	Insert earphones	Insert earphones
Intensity	80 dB nHL	80 dB nHL	80 dB nHL (standard) 80 dB nHL (deviant)
Filters	30-3000 Hz	1-30 Hz	0.1-30 Hz
Analysis window	10 ms	-100 to +400 ms	-100 to +700 ms
Sweeps	1500	200	100
Gain	1,00,000	50,000	50,000

3.6 Statistical analysis

The data was analyzed using Statistical Software for the Social Sciences (SPSS V.26). The descriptive statistics were done to obtain the mean and standard deviation of the latency and amplitude measures of different AEPs. Shapiro-Wilks normality test was done to analyze the normality distribution of this study. An independent t-test was conducted to compare the means of various electrophysiological tests between the control and the clinical group.

Chapter 4

Results

The current study aimed to compare the central auditory processing abilities through electrophysiological tests in children with NSCLP and craniofacially typical peers. The electrophysiological tests included in the study were ABR, BIC of ABR, ALLR, and P300. The electrophysiological responses were compared between 15 participants in the clinical group and 15 in the control group. The clinical group included different types of cleft; 6 had a cleft palate, 6 had unilateral cleft lip and palate, and 3 had bilateral cleft lip and palate.

The Shapiro-Wilk test was done to check the normal data distribution for all the tests. The Shapiro-Wilk test result revealed that the data were normally distributed ($p>0.05$), and hence, a parametric test was used to analyze data. Ear-wise analysis was done initially for all the electrophysiological measures for both groups. The paired t-test showed no significant difference in all the measures between the two ears. Hence, the ear-wise data was combined for further analysis for ABR, ALLR, and P300.

4.1 ABR comparison between the clinical and control group

Table 4.1 shows the mean and standard deviation (SD) for ABR peaks at 11.1 and 90.1/s rates for both groups. A representative waveform of ABR at 11.1/s and 90.1/s for both groups is shown in Fig 4.1 and 4.2. The Table and Figures show that the latency of all the peaks is delayed for clinical group than the control group.

Table 4.1

The mean and SD of ABR at 11.1/s and 90.1/s rate for the control and the clinical group

Parameters	Rate	Control (N=30)		Clinical (N=30)	
		Mean	SD	Mean	SD
Wave I latency (ms)	11.1/s	1.431	0.125	1.553	0.186
	90.1/s	1.653	0.153	1.708	0.151
Wave III latency (ms)	11.1/s	3.416	0.151	3.679	0.221
	90.1/s	3.686	0.159	3.945	0.254
Wave V latency (ms)	11.1/s	5.349	0.126	5.540	0.205
	90.1/s	5.778	0.176	5.955	0.230
I-V interpeak latency (ms)	11.1/s	3.917	0.180	3.991	0.180
	90.1/s	4.128	0.205	4.240	0.230

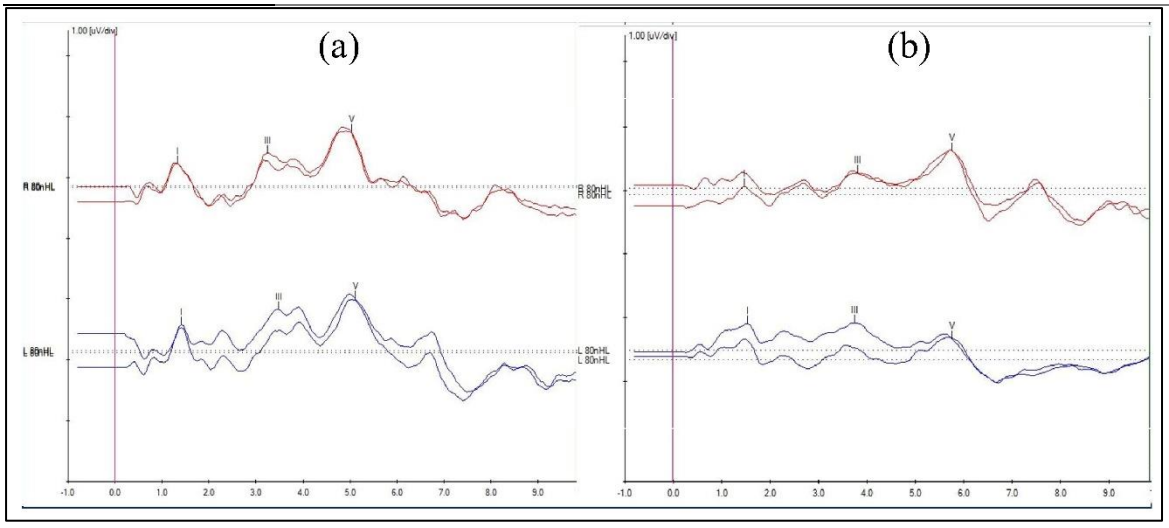

Figure 4.1 *The representative waveform of ABR at 11.1/s rate for the (a) Control and (b) Clinical group*

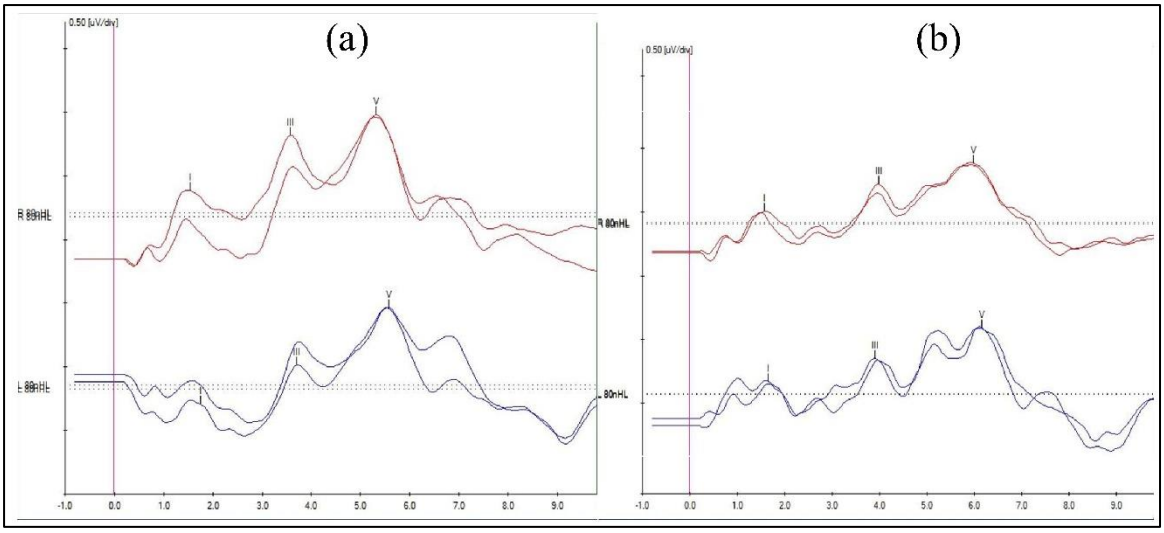

Figure 4.2 *The representative waveform of ABR at 90.1/s rate for the (a) Control and (b) Clinical group*

Further, an independent t-test was done to compare if the difference in ABR latencies at the rate of 11.1 and 90.1/s between the clinical and control group was significant. Results showed that the clinical group had significant delayed absolute latencies for ABR at 11.1/s for all three waves {wave I ($t=-2.964$, $p<0.05$), III ($t=-5.363$, $p<0.05$), and V ($t=-4.328$, $p<0.05$)} and for wave III ($t=-4.680$, $p<0.05$) and V ($t=-3.328$, $p<0.05$) in ABR 90.1/s; however, no significant difference was found for the I-V interpeak latencies in both the rates {at 11.1 rate ($t=-3.196$, $p>0.05$ and at 90.1 rate ($t=-1.963$, $p>0.05$)}. Also, Table 4.2 shows the mean and SD for ABR peaks at 11.1 and 90.1/s rates for different types of cleft. It can be noted that children with bilateral RCLP and unilateral RCLP had prolonged ABR latencies than children with RCP. In contrast, the I-V interpeak latency was comparable for all types of cleft. However, the statistical analysis could not be performed due to the fewer participants in each group.

Table 4.2

The mean and SD of ABR at 11.1/s and 90.1/s rate across different types of cleft

Parameters	Rate	B/L RCLP		U/L RCLP		RCP	
		Mean	SD	Mean	SD	Mean	SD
Wave I latency (ms)	11.1/s	1.643	0.144	1.610	0.237	1.450	0.079
	90.1/s	1.816	0.161	1.764	0.156	1.608	0.068
Wave III latency (ms)	11.1/s	3.745	0.171	3.735	0.222	3.589	0.226
	90.1/s	4.030	0.232	4.041	0.226	3.822	0.251
Wave V latency (ms)	11.1/s	5.620	0.235	5.59	0.149	5.450	0.221
	90.1/s	6.015	0.099	6.022	0.124	5.858	0.321
I-V interpeak latency (ms)	11.1/s	3.978	0.240	3.980	0.253	4.008	0.203
	90.1/s	4.201	0.197	4.253	0.215	4.249	0.271

4.2 BIC comparison between the clinical and control group

Click-evoked ABR was done using monaural stimulation (left and right ear alone) and binaural stimulation in both groups. Both monaural and binaural stimulation waveforms showed good morphology in both groups. BIC was calculated for both groups. Table 4.3 depicts the mean and SD for both groups' summed-up monoaural response, binaural response, and BIC of ABR. Figure 4.3 shows the representative BIC waveform for both groups. It can be noted from Table 4.3 and Figure 4.3 that the BIC latency is delayed and amplitude is lesser in the clinical group.

Table 4.3

The mean and SD of BIC of ABR at 11.1/s rate for the control and the clinical group

Parameters		Control		Clinical	
		Mean	SD	Mean	SD
Summed up	Latency (ms)	5.324	0.128	5.519	0.163
	Amplitude (μV)	1.124	0.507	0.988	0.195
Binaural	Latency (ms)	5.314	0.138	5.549	0.203
	Amplitude (μV)	0.801	0.491	0.774	0.224
BIC	Latency (ms)	5.340	0.135	5.498	0.169
	Amplitude (μV)	0.285	0.303	0.046	0.313

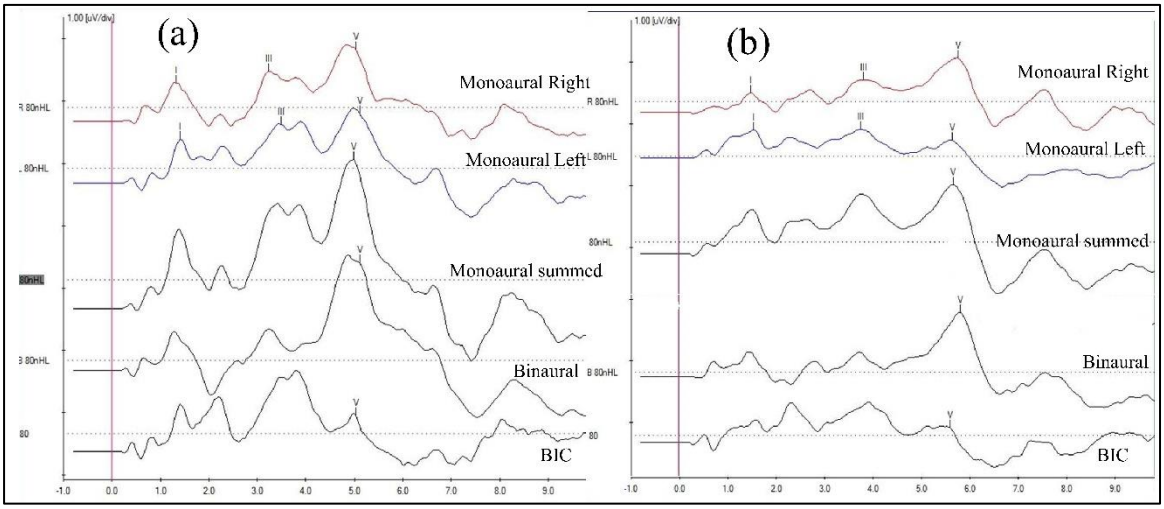

Figure 4.3 *The representative waveform of BIC at 11.1/s rate for (a) Control and (b) Clinical group*

Further, an independent t-test was done to assess the significant difference in BIC component between the two groups. Results showed a significant difference in the summed-up monoaural latency (t=-3.636, p <0.05) and binaural latency (t=-3.701, p<0.05) of wave V between the two groups. However, summed-up monoaural

amplitude (t=0.974, p>0.05) and binaural amplitude (t=0.196, p>0.05) of wave V showed no significant difference between the two groups. Results also revealed that a significant difference was found in the BIC latency (t=-2.836, p<0.05) and amplitude (t=2.123, p<0.05) of wave V between the two groups. Also, Table 4.4 shows the mean and SD of summed-up monoaural response, binaural response, and BIC of ABR for different types of cleft. It can be noted that BIC was prolonged in bilateral and unilateral RCLP when compared to the RCP group. The amplitude was more affected in children with bilateral RCLP and the mean value obtained was negative. However, the statistical analysis could not be performed due to the fewer participants in each group.

Table 4.4

The mean and SD of BIC of ABR at 11.1 rate across different types of cleft

Parameters		**B/L RCLP**		**U/L RCLP**		**RCP**	
		Mean	SD	Mean	SD	Mean	SD
Summed up	Latency (ms)	5.543	0.100	5.560	0.145	5.466	0.209
	Amplitude (μV)	0.926	0.064	0.885	0.192	1.121	0.177
Binaural	Latency (ms)	5.613	0.109	5.555	0.143	5.511	0.293
	Amplitude (μV)	0.873	0.215	0.620	0.192	0.878	0.196
BIC	Latency (ms)	5.516	0.160	5.546	0.135	5.441	0.210
	Amplitude (μV)	-0.11	0.125	0.086	0.278	0.083	0.416

4.3 ALLR comparison between the clinical and control group

Table 4.5 depicts the mean and SD of different components of ALLR for the two groups. The representative waveform of ALLR for the control group and the clinical group is shown in Figure 4.4. It can be noted from the Figure and Table that the latency of N1 and P2 waves is delayed in the clinical group compared to the control group. Also, the amplitude difference between the two groups can be seen for the N1 wave.

Table 4.5

The mean and SD of ALLR for the control and the clinical group

Parameter		Control		Clinical	
		Mean	**SD**	**Mean**	**SD**
Wave P1	Latency (ms)	64.248	12.110	62.781	17.02
	Amplitude (μV)	0.911	1.278	1.130	1.882
Wave N1	Latency (ms)	98.040	9.639	106.403	20.302
	Amplitude (μV)	-2.357	1.538	-4.198	2.105
Wave P2	Latency (ms)	159.849	12.668	172.592	23.685
	Amplitude (μV)	4.421	2.719	3.992	2.342
Wave N2	Latency (ms)	232.130	14.785	235.338	23.268
	Amplitude (μV)	-3.486	2.106	-3.069	1.818

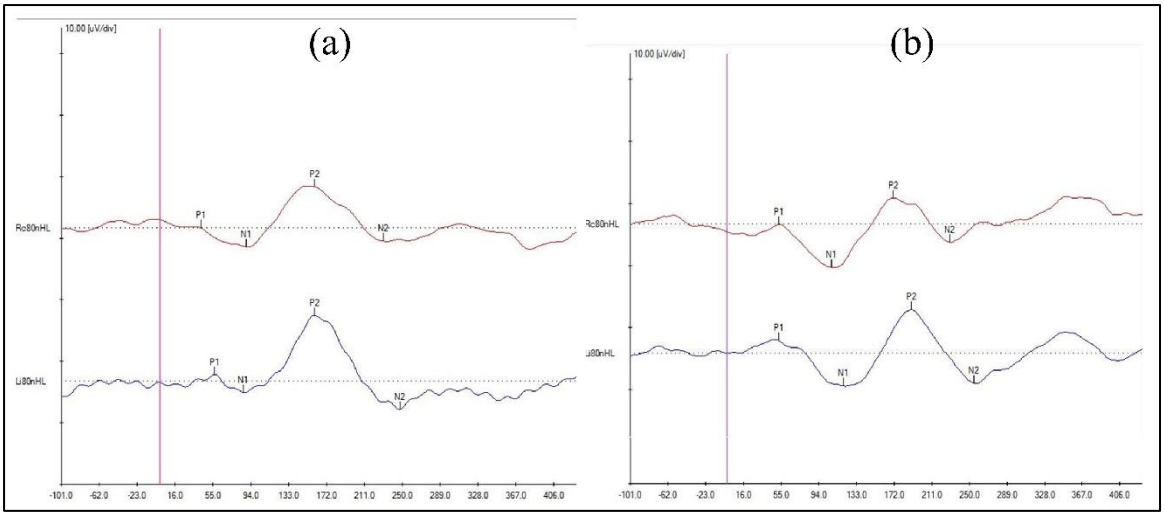

Figure 4.4 *The representative waveform of ALLR of (a) Control and (b) Clinical group*

Further, an independent t-test assessed the two groups' significant differences in ALLR components. Results showed a significant difference between the two groups for N1 ($t=-2.038$, $p<0.05$) and P2 ($t=-2.958$, $p<0.05$) latencies. However, the two groups' amplitude was significantly different only for the N1 wave ($t=3.868$, $p<0.05$). Also, Table 4.7 shows the mean and SD of ALLR for different types of cleft, and it can be noted that P1 wave latency was higher in the RCP group than the other groups, and the amplitude of P1 was lesser in bilateral RCLP. N1 wave latency was affected in the unilateral RCLP group and RCP group. P2 and N2 wave latency was similar across all cleft types. However, the statistical analysis could not be performed due to the fewer participants.

Table 4.6

The mean and SD of ALLR across different types of cleft

Parameter		B/L RCLP		U/L RCLP		RCP	
		Mean	SD	Mean	SD	Mean	SD
Wave P1	Latency (ms)	52.935	19.04	56.835	7.292	73.649	18.044
	Amplitude (μV)	0.790	1.073	1.116	1.227	1.313	2.685
Wave N1	Latency (ms)	99.435	30.531	107.706	13.887	108.585	20.893
	Amplitude (μV)	-3.185	1.956	-5.401	2.020	-3.502	1.787
Wave P2	Latency (ms)	163.458	35.094	177.368	9.954	172.382	27.380
	Amplitude (μV)	4.581	2.924	4.864	1.724	2.825	2.257
Wave N2	Latency (ms)	232.685	19.272	234.926	18.772	237.077	29.980
	Amplitude (μV)	-3.670	2.099	-2.760	1.838	-3.078	1.741

4.4 P300 comparison between the clinical and control group

Table 4.5 depicts the mean and SD of P300 latency and amplitude of the control and the clinical groups. Figure 4.5 shows the representative waveforms of P300 for both groups. It can be noted from the Table and Figure that there is not much difference in the latency and amplitude of P300 between the two groups.

Table 4.7

The mean and SD of P300 of the control and the clinical group

Parameters	Control		Clinical	
	Mean	SD	Mean	SD
P300 latency (ms)	358.142	29.383	354.331	37.214
P300 amplitude (µV)	3.056	1.952	2.666	1.319

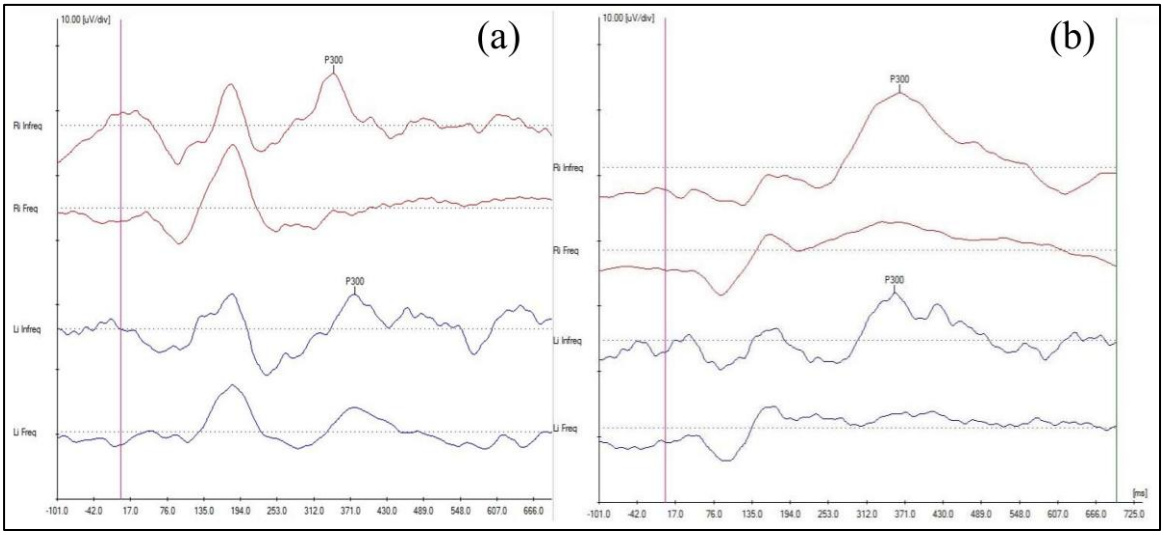

Figure 4.5 *The representative waveform of P300 of (a) Control and (b) Clinical group*

Further, an independent t-test assessed the two groups' significant differences in P300 components. Results showed that the P300 latency (t=0.440, >0.05) and amplitude (t=0.905, p>0.05) between the two groups did not show any significant difference. Table 4.8 shows the mean and SD of P300 latency and amplitude for different types of cleft. It can be noted that latency was more in bilateral RCLP and RCP than in unilateral RCLP, and amplitude was lesser in the RCP group than in the

other two groups. However, the statistical analysis could not be performed due to the fewer participants.

Table 4.8

The mean and SD of P300 latency and amplitude across different types of cleft

Parameters	B/L RCLP		U/L RCLP		RCP	
	Mean	SD	Mean	SD	Mean	SD
P300 latency (ms)	375.393	52.302	335.765	30.653	362.365	27.921
P300 amplitude (µV)	2.840	1.741	3.156	1.103	2.090	1.163

Chapter 5

Discussion

The present study aimed to assess auditory processing abilities in children with NSCLP through electrophysiological tests. All the children underwent routine audiological evaluation to rule out peripheral hearing loss. In clinical group, children with cleft were recruited from the Unit for Structural and Orofacial Anomalies (USOFA) clinic of All India Institute of Speech and Hearing (AIISH) Mysore. In the control group, a screening checklist for auditory processing (SCAP) was administered to check if they were at risk of CAPD and were recruited if they passed on SCAP. In the present study, auditory brainstem response (ABR), binaural interaction component (BIC) of ABR, auditory late latency responses (ALLR), and P300 were compared between the clinical and control group.

5.1 ABR in children with NSCLP

ABR is a non-invasive electrophysiological tool that determines the activity of various regions of the auditory pathway from the cochlea to the brainstem. This neurophysiological test has been used to detect aberrant brain activity characterized by prolonged peak latencies and decreased peak amplitude (Kwon et al., 2007). Changes in neural synchronization may be associated with poor temporal processing and further decline in speech recognition performance, which may be observed in individuals with central auditory processing disorders (CAPD) (Anderson et al., 2012; Tremblay & Billings, 2012).

In the present study, a significant difference was found in the ABR latencies at 11.1/s for wave I, III, and V, and in ABR latencies at 90.1/s for wave III and V between the clinical and the control group. There was no significant difference found in I-V

interpeak latency in both the rates. The present study also noted that prolonged ABR latency was seen for children with cleft lip and palate (CLP) than cleft palate (CP). Similar findings were reported in a study by Ma et al. (2016a), where they assessed ABR in children with NSCLP and compared with craniofacially typical peers. They also found a significant difference in ABR latencies for waves III and V and the I-V interpeak latency. The same study also reported that children with CP and CLP had longer latencies than only the CL population.

However, Yang and his colleagues (2012) observed contrary results in their study on infants with NSCLP. They found no significant difference in absolute ABR latencies and interpeak latency in children with NSCLP compared to craniofacially typical peers. Though there is contrary evidence of ABR being normal or deviated in children with NSCLP, the studies regarding brain imaging in individuals with NSCLP highlight brain abnormalities including reduced head circumference, smaller temporal lobe, and abnormal distribution of tissue within cerebellum, enlarged brain midline structures, decreased volumes of the cerebrum and cerebellum, reduced volume of left thalamus and left auditory cortex, and shift in temporal lobe position (Chollet et al., 2014; Nopoulos et al., 2000, 2001, 2002, 2007; Yang, McPherson, Shu, Xie, et al., 2012). These brain abnormalities might affect the neural transmission in the brain, leading to pronged latencies and reduced amplitude.

Prolongations in the ABR latencies indicate increased neural transmission times in the auditory pathway, and it can be inferred that the children with NSCLP may have auditory nerve and brainstem dysfunction leading to central auditory processing disorder.

5.2 BIC of ABR in children with NSCLP

Binaural hearing is an important process for localizing sound sources and aids in the perceptual separation of sound from background noise (Middlebrooks & Green, 1991). However, psychoacoustic binaural and spatial hearing measures such as localization/lateralization and binaural fusion can evaluate processing difficulties; BIC of ABR is a potential objective measure of binaural hearing function (Laumen et al., 2016).

In the present study, a significant difference in BIC's latency and amplitude of wave V was seen between the clinical and the control group. Reduced amplitude and prolonged latencies were observed in the clinical group, and five among fifteen NSCLP children had negative BIC amplitude. As per the author's knowledge, no study has been done on BIC in children with NSCLP. However, abnormal BIC has been documented in the literature in children with CAPD.

Gopal and Pierel (2009), who performed BIC on nine children at risk of CAPD and compared it to nine typically developing children, found a significant reduction in the BIC amplitude of ABR V peak, and negative BIC amplitude was found in four children in CAPD group. Children with persistent otitis media can show binaural and spatial hearing impairments even after the condition is resolved (Whitton & Polley, 2011). Thus, children with NSCLP might be at risk of binaural and spatial hearing impairments, as evident from the present study's result.

5.3 ALLR in children with NSCLP

ALLR originates in the auditory cortex and is regarded as a biomarker for central auditory system maturity and may, therefore, be relevant in diagnosing children with central auditory processing disorder (Macaskill et al., 2022).

In the present study, ALLR significantly differed between the clinical and control group for N1 and P2 latency and N1 amplitude. Prolonged N1 and P1 latencies and reduced N1 amplitude were observed in the clinical group. These findings are in consensus with the literature (Liasis et al., 2003; Ma et al., 2016a). In their study, Ma et al. (2016) compared the ALLR of children with NSCLP with their age-matched craniofacially typical peers. N1-P2 amplitude was smaller, and N1 latency was prolonged in the NSCLP group. These researchers hypothesized that the abnormal data showed slower processing or delayed maturation of the central auditory system within the NSCLP group.

Brain abnormalities in individuals with NSCLP might lead to abnormal neural transmission in them and leading to abnormal ALLR waveforms. Prolonged ALLR latencies and reduced amplitude in the NSCLP group might be an indication of temporal processing difficulties in them. Hence, ALLR needs to be included in the test battery of CAPD assessment in children with NSCLP to give information regarding their neural transmission. It will also be helpful to record progress pre and post-therapy when provided CAPD management.

5.4 P300 in children with NSCLP

P300 is a cortical potential elicited in an oddball paradigm when subjects detect target stimuli in a regular sequence of standard stimuli (Picton, 1992). P300 represents auditory processing abilities for signals using attention and memory. Hence, P300 is obtained by instructing the subject to actively listen and count the deviant stimuli (Ma et al., 2016a).

In the present study, no significant difference was observed between the clinical and control group in the latency and amplitude parameters of P300. These findings are

in consensus with the previous study by Ma et al. (2016a), who compared P300 in children with NSCLP and age-matched normal controls and found no significant difference between the two groups on amplitude and latency parameters.

P300 is a cortical potential that is associated with the recognition of novel stimuli. The generation site of P300 is more complex than other obligatory AEP responses, and it can provide information regarding processing abilities for stimuli by using auditory attention and memory. That is why the subject is asked to actively listen to the sound and attend to deviant sounds by counting or pressing a buzzer. P300 is an important parameter in identifying children with processing difficulties, and there is evidence of deviated response in children at risk of CAPD, especially children with Learning disability (LD) (Diniz et al., 1997; Holcomb et al., 1986; Maciejewska et al., 2014) and Attention Deficit and Hyperactive disorder (ADHD) (McPherson & Salamat, 2004; Schochat et al., 2002; Szuromi et al., 2011). But in the case of children with NSCLP, P300 seems to be unaffected. Although there is not enough evidence regarding P300 in the NSCLP group, it can be concluded from the few studies that skills like attention and memory required for obtaining P300 are not affected in children with NSCLP.

Thus, it can be concluded that electrophysiological tests, especially ABR, BIC of ABR, and ALLR, have shown deviated responses in children with NSCLP. Hence, electrophysiological tests must also be included in a comprehensive CAPD test battery for children with NSCLP because they are objective and have a lower linguistic demand than many behavioral tests (Liasis et al., 2003).

Chapter 6

Summary and Conclusion

The present study assessed the central auditory processing abilities in children with non-syndromic cleft lip and palate (NSCLP) through electrophysiological tests. The study compared the central auditory processing abilities of children with NSCLP with age-matched craniofacially typical peers. Fifteen participants were recruited in both groups between the age of 7 to 15 years. The electrophysiological tests conducted in the study were auditory brainstem responses (ABR), binaural interaction component (BIC) of ABR, auditory late latency responses (ALLR), and P300. The results revealed a significant difference in absolute ABR latencies of children with NSCLP at lower and higher stimulation rates compared to age-matched craniofacially normal peers. However, I-V interpeak latencies were comparable between the two groups at both rates. BIC of ABR and ALLR showed diminished amplitude and prolonged latencies in the cleft population. However, no significant difference between the two groups was found in P300 parameters. The effect of gender and cleft type could not be studied due to fewer participants. Thus, the comprehensive CAPD assessment tool should include electrophysiological and behavioral tests to give more insights into neural transmission in children with NSCLP.

6.1 Implication of the Study

- A CAPD screening checklist for all children with NSCLP is recommended. It is also advised that behavioral and electrophysiological diagnostic CAPD tests be administered for children with NSCLP for early identification and rehabilitation.

- As children with NSCLP might be at risk of CAPD and exhibit academic difficulties, parents should be counseled regarding diagnosing and managing CAPD in children with NSCLP.

6.2 Future direction

- More studies on a larger population with NSCLP are required to assess central auditory processing difficulties using electrophysiological measures.
- Future research on the effect of gender and different types of clefts on various electrophysiological measures needs to be studied.
- Longitudinal studies are required from infancy till adolescence to give insight into changes in the neural aspect of the auditory system.

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