INTRODUCTION

The cortical auditory evoked potentials (CAEPs) represent the summed neural activity in the auditory cortex in response to sounds ***(Van Dun et al., 2012).*** The peaks of the complex are thought to reflect neural activation of the central auditory system in response to the spectral & temporal properties of a given stimulus ***(Tremblay et al., 2003).***

There has been 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 underlying speech perception. These measures include obligatory evoked potentials such as P1, N1, and P2, and discriminative potentials such as mismatch negativity (MMN) and P300 ***(Kim, 2015).***

The P1-N1-P2 is a transient obligatory auditory evoked potential that can be recorded from surface electrodes placed on the scalp in response to a wide range of stimuli. This potential is typically evoked by brief stimuli such as clicks, tone bursts, and short duration speech tokens. The P1-N1-P2 potential is believed to reflect the neural encoding of a sound signal, but provides no information on sound discrimination ***(Hillyard et al., 1978; Martin et al., 1999; Whiting et al., 1998).***

In children, the N1/P2 complex emerges as a bifurcation from the broad P1 peak as the child ages. While the P1

component of the CAEP response is present at birth, the N1 component cannot be reliably recorded in normal hearing children until approximately seven years of age using an appropriate stimulation rate ***(Sharma et al., 1997; Cunningham et al., 2000; Sharma et al., 2015).***

On the other hand, MMN and P300 have been used to assess sound discrimination using an oddball paradigm ***(Näätänen, et al., 1978; Sutton, et al., 1965).*** However, both of them have limitations. MMN has a small wave amplitude, imprecise latency calculations, and relatively poor reliability ***(Martin et al., 1999; Picton et al., 1995).*** P300 is difficult to record in uncooperative patients because it requires active participation ***(Martin et al., 2008).***

Due to the limitations of MMN and P300, the Acoustic Change Complex (ACC) has drawn considerable attention as another method of investigating auditory discrimination. The ACC is a cortical auditory evoked potential (P1-N1-P2) elicited by a change within an ongoing sound stimulus ***(Martin et al., 1999).*** It has been obtained in response to intensity, frequency, and phase modulations in sustained tones **(e.g., *Dimitrijevic et al., 2008)***. It has also been obtained in response to spectral and intensity changes within speech or speech-like stimuli ***(Tremblay et al., 2003)***. The ACC indicates the encoding of potentially discriminable information at the level of the auditory cortex ***(Martin et al., 1999 &2000; Ostroff et al., 1998).***

Similar to the MMN; ACC does not need the child's attention. However, the ACC has a much larger amplitude (higher signal-to-noise ratio) and requires fewer stimulus presentations because every trial contributes to the response ***(Martin et al., 1999)*****.** Therefore, this may be an advantage of ACC over the MMN ***(Michalewski et al., 2005).***

Since ACC response can be reliably recorded from infants and other children in the absence of attention, it can be recorded in normal hearers, listeners with hearing loss, hearing aids, and cochlear implant users. Moreover, some studies reported reasonable agreement with behavioral measures. These factors are positive for the potential clinical application of the ACC ***(Kim, 2015).***

Different stimuli have been used to elicit ACC. ***Ganapathy et al. (2013)*** used tonal stimuli which changed in frequency from 1KHz to 2 KHz. ***Lister et al. (2007)*** used narrowband noise bursts centered at 1000 or 2000 Hz with a temporal gap introduced into the burst.

Regarding speech stimuli, syllable /sa/ was used by ***Ganapathy et al. (2013)*** to record ACC**.** ***Ostroff et al. (1998)*** recorded cortical potentials in response to three naturally produced speech stimuli (/s/, /ei/, and /sei/). ***Martinez et al. (2013)*** used stimulus alternated between two vowels (/u/ and /a/ for the vowel height contrast and /u/ and /i/ for the vowel place

contrast). ACC was also elicited to (dada/ /daba/ and dada) speech contrasts ***(Chen and Small, 2015).***

The present research is designed to study the ACC in normal hearing children in response to various speech and non-speech stimuli. The aim is to reach the best stimuli that can elicit ACC and provide an objective tool for assessment of cortical auditory discrimination in normal hearers. Hopefully, this will help in evaluation of children at risk for cortical dysfunction. This includes children with suspected auditory processing disorder (APD), whether isolated or in association with peripheral hearing loss. If consistent and valuable, it can be included within the battery of evaluation and monitoring of children and follow up of rehabilitation programs.

Aim of the Work

The aim is to reach the best stimuli that can elicit ACC and provide an objective tool for assessment of cortical auditory discrimination in normal hearing children.

Chapter One

CORTICAL AUDITORY EVOKED POTENTIALS (CAEPS): MATURATION AND CLINICAL APPLICATIONS IN CHILDREN

Definition:

Cortical auditory evoked potentials (CAEPs) represent the summed neural activity in the auditory cortex in response to sounds ***(Van Dun et al., 2012).*** To date, a number of CAEPs have been described in the literature. There has been 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 underlying speech perception. These measures include obligatory evoked potentials such as P1, N1, and P2, and discriminative potentials such as mismatch negativity (MMN), P300 and acoustic change complex (ACC) which all considered long latency auditory evoked potentials (LLAEP) ***(Kim, 2015).***

CAEPs detection versus discrimination:

It is important to understand the difference between auditory detection and auditory discrimination. Auditory detection is the ability to determine the presence or absence of

sound while, auditory discrimination refers to the ability to distinguish between heard sounds ***(Erber, 1982).***

The P1-N1-P2 is a transient auditory evoked potential that can be recorded from surface electrodes placed on the scalp in response to a wide range of stimuli. This potential is typically evoked by a brief stimulus such as clicks, tone bursts, and short duration speech tokens. This obligatory cortical potential consists of three peaks that are recorded within a latency range extending from 50 to 200 msec. The peaks are traditionally labeled individually as P1, N1, and P2. The P1-N1-P2 recorded from the auditory cortex following presentation of an acoustic stimulus is believed to reflect the neural encoding of a sound signal, but this provides no information on sound discrimination ***(Hillyard et al., 1978; Whiting et al., 1998).***

However, the neural processing underlying behavioral discrimination capacity can be measured by modifying the traditional methodology for recording the P1-N1-P2. When obtained in response to an acoustic change within a sound or in response to a stimulus that contains multiple time-varying acoustic changes such as speech, the resulting waveform has been referred to as the acoustic change complex (ACC) ***(Martin et al., 1999).***

MMN and P300 have been used to assess sound discrimination. MMN is evoked by an oddball paradigm, in which infrequent deviant sounds are embedded in a series of

frequent standard sounds. MMN provides an index of the pre-attentive discrimination of two or more sounds. Because the MMN is obtained during passive listening, it may be used to index sound discrimination abilities in those who are difficult to test with conventional methods ***(Martin et al., 1999; Picton, 1995).***

On the other hand, P300 occurs at approximately 300 msec. and is best evoked when the subject is engaged in a discrimination task, using an oddball paradigm. Subjects are instructed to count in response to a deviant or target stimulus embedded in a train of frequent standard stimuli. This may be more useful for clinical assessment of sound discrimination and cognitive processing of cooperative patients as it requires active participation ***(Martin et al., 2008).***

Maturation:

Hearing is a sense existent in the human being from the fifth month of intrauterine life. From that time on, the experiences lived by the individual allow the central auditory nervous system (CANS) to go through neurophysiological changes, through neuronal plasticity, allowing auditory learning. This phenomenon of auditory maturation allows the development of auditory abilities, in other words, allows the individual not only to be capable of hearing, but also for sound stimuli heard to be detected, discriminated, recognized and understood ***(Boéchat et al., 2010).***

In recent decades, Long Latency Auditory Evoked Potentials (LLAEP), traces generated by bioelectric activities from central auditory pathways after acoustic stimulation, have shown themselves to be a resource capable of measuring the neurophysiological modifications resultant from the maturation process ***(Maurer et al., 2002; Fallon et al., 2008).*** Being an exogenous potential, in other words, not dependent on the behavioral response of the individual, they can be a useful tool to evaluate small children who have still not developed auditory and/or cognitive abilities to respond to other evaluations ***(Hall et al., 2006).***

For this reason, studies have utilized this procedure to monitor, objectively, cortical maturation after speech-therapy interventions in children with language problems ***(Datta et al., 2010),*** after training of central auditory processing disorders ***(Tremblay et al., 2001)***, as well as measuring the benefits provided by the use of electronic devices, such as Hearing Aids and Cochlear Implants ***(Sharma et al., 2009).*** It is known that the maturational development of the CANS is highly complex. Given this, it is also understood that there are many individual variables that can favor or hamper this process and, consequently, directly influence the results of the LLAEP. Studies report that around only 41% of variability in latency values can be explained by maturation through the passage of chronological age. The other values correspond to other variables such as gender and individual cognitive abilities ***(Kabel et al., 2009).***

Effect of maturation on CAEPs:

1. P1-CAEP:

The P1-N1-P2 complex elicited by sound onset (a change from silence to sound) shows significant changes in **morphology** with maturation . These changes are dependent on stimulus rate ***(Ceponiene et al., 2002; Gilley et al., 2005).*** After infancy, children show a large, relatively late P1, followed by a broad, slow negativity (N2) ***(Ponton et al., 2000; Sharma, et al., 1997).*** The age at which N1 becomes an expected feature of the CAEP is not precisely known. While it can be evoked in newborn infants ***(Little et al., 1999; Rapin and Graziani, 1967),*** its presence cannot be relied upon. Some studies have indicated that N1 can only be reliably evoked once the age of 9–13 years has been reached ***(Albrecht et al., 2000; Ponton et al., 2000; Sharma et al., 1997)*** but other researchers have shown that it could be consistently evoked, and was the most prominent peak, in 7–9-year-old children when the inter-stimulus interval (ISI) was >700 msec. ***(Ceponiene et al., 1998).*** Because of the increased neural refractoriness in children, the N1 component is only observed when stimuli are presented at very slow rates. Inter-onset intervals needed to elicit N1 are around 800 msec. for 7 to 9 year olds and can be as high as 3 or 4 seconds for younger children ***(Ceponiene et al., 2002; Wunderlich et al., 2006).***

Latency of the P1 wave is thought to reflect the sum of synaptic transmission delays throughout the central auditory

pathways. Hence, latency changes in P1, as a function of increasing age, can be used as a biomarker for maturation of central auditory pathways, and can easily be tracked in individuals over time ***(Eggermont et al., 1997).***

Many studies have already demonstrated that CAEP component peak latencies are shorter in adults than in young infants, children or adolescents ***(Bruneau et al., 1997; Cunningham et al., 2000; McArthur and Bishop, 2002; Ponton et al., 2000; Sharma et al., 1997).*** Increased myelination and neuronal maturation ***(Moore and Guan, 2001; Yakovlev and Lecours, 1967)*** occurring within the first 6 years of life may be so gradual that latency differences may not be apparent within this period of time.

CAEP component latencies were relatively stable from birth to 6 years, but adults demonstrated significantly shorter latencies compared to infants and children. Components P1 and N2 decreased in amplitude, while components N1 and P2 increased in amplitude from birth to adulthood. Words evoked significantly larger CAEPs in newborns compared to responses evoked by tones, but in other age groups the effects of stimulus type on component amplitudes and latencies were less consistent. The participants in this experiment were 10 newborns 19 toddlers (13–41 months), 20 children (4–6 years) and 9 adults (18–45 years) ***(Wunderlich et al., 2006).***

In infants with normal hearing, the average latency of the P1 waveform is about 300 msec. ***(Sharma et al., 1997)***. A rapid decrease in latency occurs during the first few years of life; a normal P1 latency for a 3 year old is about 125 msec. 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 95 msec. The mean P1 latency in middle-aged adults is approximately 60 msec. ***(Nash et al., 2007).***

In young children the dominant features of the cortical response are the P1, which varies in latency as a function of age, and the N2 response ***(Gilley et al., 2005; Sussman et al., 2008).***

There are numerous factors which may influence the magnitude of scalp recorded potentials. Age-related changes in magnitude are assumed to reflect maturation of the neural processes generating the response. For example, the **amplitude** of a peak is thought to rely greatly on synaptic density ***(Eggermont, 1988),*** which, in the primary auditory cortex, doubles over the first 3 months of life ***(Huttenlocher and Dabholkar, 1997).*** With age, increasing neural synchrony may result in a larger averaged response ***(Thomas et al., 1997).*** The magnitude of scalp recorded potentials chronicled over time may also be influenced by changes in the location and/or orientation of the neural substrates ***(Bruneau and Gomot, 1998; Bruneau et al., 1997; Gomes et al., 2001; Pang and Taylor, 2000; Ponton et al., 2000).***

2. MMN:

MMN has been said to develop rather early in comparison to other event-related potential (ERP) waves. It has even been suggested to be the ontogenetically earliest discriminative response of the human brain ***(Cheour-Luhtanen et al., 1996).***

Mismatch responses are different in young infants compared to adults. ***Trainor et al. (2001, 2003)*** found that younger infants showed only an increase in the slow positive wave whereas by 6 months, infants showed a negative response resembling the adult MMN. They proposed that the two responses represent different processes, and that the adult-like MMN response develops with cortical maturation ***(Moore & Guan, 2001). Lee et al. (2012)*** compared 4-, 5- and 6-year-old children, and found that small vowel deviances elicited adult-like MMN responses only in the oldest child group.

The MMN was found to decrease with **latency** by 11 msec/yr from 4 to 10 yr of age. The prominent negativity in children was significantly later than the adult N1 component, and did not change in latency from 4 to 10 yr of age. ***(Shafer et al., 2000). Mahajan and McArthur (2015)*** found that the latency of the MMN remained stable across adolescence. A close examination of ***Bishop et al.(2011)*** data reveals only a marginal decrease (~10 msec.) in latency from childhood to adolescence, and a decline in latency of MMN was evident only in 10–14 years in ***Oades et al. (1997)*** data. The stable latency

trend across adolescence founded by ***Mahajan and McArthur (2015)*** directly supports other research that suggests that by the end of childhood, the MMN latency is mature, and there is little difference between the latency of the MMN between children and adults ***(Csepe et al., 1995; Kraus et al., 1993)***.

As regards amplitude, ***Shafer et al. (2010)*** did not find any difference in magnitude of the MMN amplitude between 4–5-year-old and 6–7-year-old children's responses to vowel changes, suggesting that the amplitude does not increase during these years. In another study, ***Shafer et al. (2000)*** compared the responses for frequency changes in children and adults. There was no difference in the MMN amplitudes between the four age groups (4-year-olds, 5–6-year-olds, 7–8-year-olds, and 9–10-year-olds), or between children and adults. Furthermore, ***Bishop et al. (2011)*** compared 7–12-year-old children to 13–16-year-old teenagers and adults. The responses for frequency and phoneme changes revealed that the MMN amplitude increased with age. Additionally, ***Lovio et al. (2009)*** studied MMN responses of 6–7-year-old children for vowel, vowel duration, consonant, frequency and intensity change. The children's MMN amplitudes were smaller than those observed in adults in a study by ***Pakarinen et al. (2009)*** that used the same multifeature paradigm.

3. P300:

The absolute P300 morphology is predominantly determined by an individual's physiological properties, such as anatomical features of the corpus callosum ***(Huster et al., 2011)*** or skull thickness ***(Frodl et al., 2001).*** Thus despite relative changes by state variables, a person's specific P300 morphology is a remarkably stable measure that shows little variation over recording sessions or experiments ***(Williams et al., 2005).*** In line, P300 morphology has demonstrated a high heritability of approximately 60% (***Van Beijsterveldt and Van Baal, 2002)***.

Research on P300 development across the lifespan has been relatively scarce. However, there is clear evidence that P300 **latency** decreases during the first years of life ***(Polich et al., 1990; Tsai et al., 2012)***, whereas in older adults the parietal P300 latency increases ***(Walhovd et al., 2008; Kuba et., 2012)***.

Findings on early developmental processes in P300 **amplitude** are mixed. P300 amplitudes are found to either increase during childhood or show no change ***(Polich et al., 19990; Sangal et al., 1998; Tsai et al., 2012; Ehlers et al., 2001).*** Capacity of information processing increases rapidly during early childhood, which is expected to enhance the P300 amplitudes. However, an opposing effect on amplitudes may result from an increase in skull thickness, as a thicker skull is related to smaller amplitudes ***(Frodl et al., 2001).*** Indeed, a study by ***Beauchamp et al. (2011)*** found an increasing brain-