TEST RETEST RELIABILTY OF MISMATCH NEGATIVITY USING SPEECH STIMULUS

Sowmya M

13AUD024

A Masters Dissertation Submitted in part fulfillment of final year

Master of Science (Audiology)

University of Mysore,

Mysore

All India Institute of Speech and Hearing,

Manasagangothri, Mysore - 570 006

May, 2015

CERTIFICATE

This is to certify that this dissertation entitled "**Test Retest Reliabilty of Mismatch Negativity using Speech Stimulus**" is the bonafide work submitted in part fulfillment for the Degree of Master of Science (Audiology) of the student with Registration No: **13AUD024**. 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.

Dr. S. R. Savithri

Director
All India Institute of Speech and Hearing,
Manasagangothri, Mysore- 570 006.

Mysore,
May, 2015.

CERTIFICATE

This is to certify that this dissertation entitled "**Test Retest Reliabilty of Mismatch Negativity using Speech Stimulus** " has been prepared under my supervision and guidance. It is also certified that this has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Dr. Sandeep M.

Guide
Reader in Audiology,
Department of Audiology,
All India Institute of Speech and Hearing,
Manasagangothri, Mysore- 570 006.

Mysore,
May, 2015.

DECLARATION

This is to certify that this Master's dissertation entitled "**Test Retest Reliabilty of Mismatch Negativity using Speech Stimulus** " is the result of my own study under the guidance of Dr. Sandeep M, Reader in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore, and has not been submitted earlier in other University for the award of any Diploma or Degree.

Mysore,
May, 2015.

Register No: 13AUD024

Dedication

This work is dedicated to my family and my guide….

AKNOWLEGDEMENT

I am sincerely thankful and grateful to my dissertation guide ***Dr. Sandeep M,*** Lecturer, Department of Audiology, All India Institute of Speech and Hearing, Mysore, for his valuable and constant guidance throughout the study. Without him this study would not have been completed. Sir, I am very proud of having done dissertation under your guidance. I am greatly inspired by the your knowledge, patience and I must thank you for all the encouragement.

My sincere gratitude to ***Dr. S. R. Savithri***, Director, All India Institute of Speech and Hearing, Mysore for giving me an opportunity to take up this dissertation.

My grateful thanks ***Mr. Naike Gnanatheja*** and ***Mr. Sreaker***, Junior Research Staffs for your constant support and source of information. Without you both I would not have completed my data collection and thank you so much for spending your valuable time throughout study.

Appaji and ***Amma***, I would like to thank you both for giving everything in my life. You both are my life and you are my world. Thank you so much for your constant support, inspiration and encouragement in each and every moment of life. ***Mahi*** and ***Kavu*** you both are my best buddies for ever. I love my family.

I would like to thank all my dissertation subjects **Tulsi, Madhu, Gopika, Preethi, Shruti, Pooja, Keshav, Shanthala, Anina, Shama, Swathi, Sindhu, Basi, Nadeer, Srujan, Akil, Adithi, Mala, Vinodhini, Janani.**

I would like to thank my all classmates especially **Priyanka, Vinodini, Swathi, Tulsi, Aisha, Preetha, Himanshu, Sneha, Zeena, Madhuri, Aitha, Salome**….

Vinu, zeena, swathi, Tulsi, Tenzi for all fun and laughter. I really enjoyed with u all throughout my Msc. Thanku guys.

A special thanks to **vinu and priyanka** for ur help, support and encouragement.

If I don't thank **Sumanth , Swathi akka, Mala ,Ravi sir** my dessertaion wont be complete.

I would like to thank my dissertation partneres **Kiran and Shreyank** for their support throughout my dissertation. Thanku **Indira chechi and Priya mam.**

I should thank my brother **(Mr. Gunda)** for giving fun and support all the time and **Mahanthesh,** for his guidance and encouragement.

Sorry if I missed out anyones name….

Finally I would like to thank God all Mighty for each and everything that got in life.

Abstract

The aim of the present study was to establish the test retest reliability of speech elicited MMN. Twenty normal hearing adults in the age range of 18 to 25 years participated in the study. MMNs were recorded for /da/-/ga/ and /da/-/ta/ stimulus pairs, from Cz and Fz sites. In each participant, MMN was recorded 3 times (in 3 trials) with 1 hour gap between the first and second trial, and 1 week gap between the second and third trial. Results showed that the prevalence of MMN varied from 50% to 70%. Results reliability measures (Intra Class Correlation & Cronbach's alpha) indicated poor reliability of MMN in both intra and inter session comparison. Based on the results it was concluded that MMN is not a clinical tool in its present form. However, it has good group level reliability and therefore is a reliable research tool provided one does group comparisons.

Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction

Mismatch negativity (MMN) is an event related potential generated primarily for the difference in acoustic property of an infrequent stimulus compared that in a frequent stimulus. MMN can be generated for speech as well as tonal stimulus and is generated by multiple generators involving cortical and sub cortical structures.

MMN denotes an automatic pre-attentive change detection generated in response to an acoustic change in a repetitive stimulus sequence (Naatanen, Gaillard & Mantysalo, 1978; Naatanen, Simpson & Loveless, 1982). MMN is elicited using an odd ball paradigm in which an infrequent stimulus (the "deviant") is presented within a series of repeated standard stimulus. MMN has been reported to be present for changes in frequency, intensity, or duration of a sound (Naatanen, 1992) and also in response to more complex changes, as that in speech stimuli (Aaltonen, Niemi, Nyrke & Tuhkanen, 1987, 1994; Cheour et al., 1995; Cheour, Alho, Sainio, Reinikainen, Renlund & Aaltonen, 1997; Cheour, Alho, Ceponiene, Reinikainen, Sainio & Pohjavuori, 1998; Naatanen & Tiitinen, 1998; Naatanen & Winkler, 1999).

The generators of MMN are the bilateral auditory cortices, although right frontal cortex is also a contributor (Giard, Perrin, Pernier & Bouchet, 1990). MMN represents the biological function of monitoring and detecting any change in ongoing auditory stimulation, especially when attention is directed away from the stimulus. The MMN

subcomponent generated in supratemporal areas is an auditory-cortex marker of a change that occurs automatically and pre-perceptually (Naatanen & Michie, 1979). The frontal MMN subcomponent reflects that the frontal cortical mechanisms recruited to attend to the change in stimulus (involuntary attention switching) have been activated (Naatanen & Michie, 1979; Giard et al., 1990; Escera, Alho, Winkler & Naatanen, 1998; Escera, Yago & Alho, 2001; Rinne, Alho, Ilmoniemi, Virtanen & Naatanen, 2000).

MMN is shown to be an objective index of the discrimination accuracy that correlates well with the behavioural discrimination thresholds. Lang, Nyrke, Aaltonen, Raimo and Naatanen (1990) recorded MMN to a frequency deviance and correlated it to a behavioral discrimination task. They divided their participants into three groups (good, poor & intermediate) based on their performance in the behavioural discrimination task and found that MMN was present for a smaller frequency deviance in the good performance group. On the other hand, in poor performers group, MMN was elicited with a greater frequency deviance.

MMN can be elicited for speech as well as non-speech stimuli. Among the non-speech stimuli, MMN has been successfully elicited for changes in frequency (Hari, Hamalainen, Ilmoniemi, Kaukoranta & Reinikainen, 1984), intensity (Naatanen, Gaillard & Mantysalo, 1978), timbre (Winkler, Tervaniemi & Naatanen, 1997), duration (Korpilahti & Lang, 1994) and spatial location (Paaviainen, Karlsson, Reinikainen & Naatenan, 1989). MMN has also been evoked by speech sounds. Sandeep and Vanaja (2003) studied the effect of stimulus type on amplitude and latencies of MMN and found

that when speech was used as a stimulus, greater amplitudes and shorter latencies were obtained compared to when tonal stimulus was used. Endrass, Mohr and Pulvermuller (2004) compared MMN to words and pseudowords, and found larger amplitude MMN for words reflecting the existence of memory traces for spoken words.

The acoustic versus phonetic nature of MMN has been debated upon since few decades. One school of thought considers MMN to be sensitive to the acoustic differences between speech sounds, rather than phonetic differences (Aaltonen, Niemi, Nyrke & Tuhkanen, 1987; Sams, Aulanko, Aaltonen & Naatanen, 1990; Maiste, Wiens, Hunt, Scherg & Picton, 1995; Sharma & Dorman, 1999), whereas the other suggests that MMN reflects the phonetic differences too (Naatanen, Lehtokoski, Lennes, Cheour, Huotilainen & Iivonen, 1997; Winkler, Lehtokoski, Alku, Vainio, Czigler & Csepe, 1999a; Winkler, Kujala, Tiitinen, Sivonen, Alku & Lehtokoski, 1999b; Shafer, 2004).

1.1 Justification for the Study

In the last few decades a number of studies have demonstrated utility of MMN in understanding normal as well as pathological aspects of auditory processing. In fact studies have even shown that MMN can be used as predictor of dyslexia and the associated auditory processing disorder. In spite of this strong research evidence, the clinical utility of MMN has been questionable due to its uncertain test re-test reliability. Most of the research evidence has demonstrated its utility on the group data. But MMN to be a powerful clinical tool, across-trial and across-subject variations need to be authenticated. Tervaniemi, Lehtokoski, Sinkkonen, Virtanen, Llmoniemi and Naatanen

(1999) investigated the test re-test reliability for frequency, intensity and duration deviances and reported that most replicable waves were elicited for 66% decrement in duration.

Most clinical recording of MMN is done using speech stimuli as this gives a quick idea about the deficits in the pre-attentive discriminative processing. However, there is no reliability data established for MMN elicited by speech stimuli. For a careful interpretation of the clinical data, it is important to establish the test re-test reliability of MMN to speech stimulus. Further, most of the earlier studies have used high resolution EEG system like Neuroscan to test the stability of response. Whereas the clinical equipments are much lower in terms of technology. Therefore a reliability data established using a high density EEG systems cannot be generalized to a clinical equipments. Most of the reliability data has been derived from the group data. However for MMN to prove a useful clinical tool, reliability based on individual data needs to be established. Hence the present study is taken up.

1.2 Objectives of the Study

1. To establish the reliability index of MMN response parameters for /da –ga/ and /da –ta/ stimulus pairs at Cz and Fz sites.
2. To test the groupwise stability of MMN response parameters.
3. To test the reliability of MMN response parameters in the individual data.

1.3 Hypothesis

There is no significant difference in the latency, amplitude and area of MMN across three trials of recording.

Chapter 2

Literature Review

The Mismatch negativity (MMN) is an event related cortical potential which depicts the preconscious detection of change in specific component of the auditory stimuli (Naatanen, Gaillard & Mantysalo, 1978). Commonly used stimuli for eliciting MMN is an oddball paradigm which consists a train of standard and deviant stimuli. There is a neural trace that is formed for the standard stimuli and that is stored in echoic memory (Naatanen 1990, 1992). When the deviant stimulus is detected, an event related MMN response occurs due to mismatch between the two traces (Naatanen, 1995). In an averaged response, MMN appears as a negative displacement of the LLR wave which is obtained by subtracting the event related potential to the standard stimuli from that of deviant stimuli (Walker et al., 2001). MMN is known to have fronto-centrally distributed topography showing negativity at the midline, and positivity at the mastoids (Gomes et al., 1999). The cortical generators of MMN are located bilaterally at the supra – temporal auditory cortex and frontal cortex majorly from right hemisphere (Giard, Perrin, Pernierc & Bouchet, 1990). The supratemporal component of MMN is associated with pre-perceptual change detection and frontal component is related to involuntary attention switch for auditory change (Naatanen & Michie, 1979; Giard, Perrin, Pernier & Bouchet, 1990; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000 ; Escera, Alho , Winkler & Näätänen, 1998; Schroger, 1996)

MMN appears around 100ms after the stimulus onset with a duration of 50 to 200ms (Mantysalo & Naatanen, 1987) and its amplitude is around 3miro Volts (Licht & Horsley, 1998). The MMN peak latency becomes shorter with the increasing magnitude of stimulus change (Sams, Paavilainen, Alho, & Naatanen, 1985; Tiitinen et al., 1994; Naatanen, Paavilainen, Alho, Reinikainen & Sams, 1989; Amenedo & Escera, 2000). MMN can be obtained for both speech and non speech signals.

2.1 MMN for Non Speech Stimuli

MMN reflects several brain processes and analyses features of a sound (e.g. frequency, intensity, duration speech cues) and extracts invariance in the multiple acoustic stimuli. Hence, MMN can be obtained using tones which vary in terms of frequency, intensity and duration. Several authors have reported MMN for non speech signals like tones differing in terms of frequency (Sams et al., 1985), duration (Ponton, Don, Eggermont & Kwong, 1997), intensity (Schroger, 1996), spatial and location (Winkler & Czigler, 1998). Sams et al. studied MMN for frequency deviance in six subjects. The stimulus were presented in blocks which consisted 80% of standard stimuli (1000 Hz) and 20 % of deviant stimuli (either 1002 Hz, 1004 Hz, 1008 Hz, 1016 Hz or 1032 Hz) in each block. The inter stimulus interval was kept constant i.e. 1 sec and the stimulus order was randomized. There were two conditions ; discrimination condition and ignore condition. In the ignore condition, the peak latency of MMN was obtained around 170ms for 1016Hz and 1032Hz whereas for 1008Hz, small MMN was obtained. In discrimination condition, an extra negative component, N2b appeared in addition to

MMN which had longer latency due to activation of the posterior region (i.e., parietal lobe).

Korpilahi and Lang (1994) obtained MMN for duration changes in 12 normal children. Standard stimulus used was 1000Hz tone of 50ms and deviants were 1000 Hz tone of 110 ms and 500 ms. It was observed that as the physical difference between standard and deviant stimuli was increased (50/110 ms versus 50/500 ms) the peak amplitude of MMN was also increased.

Colin et al. (2009) measured effect of sound duration contrasts on MMN. They used oddball paradigm where 100, 200, and 250 ms were used as standard stimulus duration and deviants were 50% longer or shorter in duration of the standard stimulus. The results revealed that there was no effect of duration deviance on MMN latency, whereas amplitude of MMN is affected by duration deviance. Amplitude of MMN was larger for shorter duration deviance when compared to longer duration deviance.

Kujalo, Kallio, Kervaniem and Naatanen (2001) recorded MMN in passive oddball paradigm where standard stimulus (P = 0.79) was a tone pair with 120 ms silent-inter-stimulus interval (ISI) and deviant stimuli (P=0.07) were tone pairs with ISI of 100, 60 and 20 ms in two sessions separated by 4-21 days and behavioral responses in a separate session for 10 adults. They found that the 20 and 60 ms ISI deviant tone pairs elicited good MMN and could be discriminated behaviorally when compared to 100 ms ISI deviant pair which was not discriminated behaviorally. Further the replicability of MMN was high with 20ms ISI deviant pairs (r =0.75) than 60ms ISI deviant pair (r

=0.60) and significant correlation was seen between MMN and reaction times for 20 and 60ms ISI deviant pairs. Therefore it was concluded that the discrimination accuracy of temporal sound intervals are reflected in MMN.

2.2 MMN for Speech Stimuli

MMN is an objective measure of speech perception. It acts as a tool to study neurobiological mechanisms in humans and processes that are involved during speech perception. MMN can be elicited for different units of speech such as acoustic cues required for speech perception, phonological units (phonemes), words and even for prosody and semantic feautres (Shtyrov, Pulvermuller, Naatanen & Ilmoniemi, 2003).

MMN for speech can be elicited by changing variables such as formant transition (Martin, Sigal, Kurtzber & Stapells, 1997; Sams et al., 1990), formant duration (Krauel, Schott, Sojka, Pause & Ferstl, 1999) and voice onset time (Tremblay, Kraus, Carrell, & McGee, 1997).

Kraus, McGee, Sharma, Carrell and Nicol (1992) examined MMN in children and young adults for speech stimuli (/da/ as standard and /ga/ as deviant) at Fz. MMN was seen at approximately 235 ms for both adults and young children. Pang et al. (1998) measured MMN in 10 adults and 8 month old normal awake infants for consonants /da/ and /ta/. MMN was recorded from 11 electrode sites (Fz, Cz, Pz, C3, C4, T3, T4, T5, T6, P3 & P4). The standard stimuli /da/ was presented with probability of 80% and deviant stimuli /ta/ with 20% probability. It was observed that at C3 and T3 electrode sites, a clear MMN was present for infants, whereas for adults better MMN was present at Fz,

Cz, Pz, C3 and C4 sites. MMN was largest for infants at T3 and for adults it was at Cz and C3. This suggested that neural systems involved in the generation of MMN are different in infants and they show developmental changes.

Tervaniemi, Schroger, Saher and Naatanen (2000) recorded MMN for 2.5% pitch change in pure tones of 500Hz and with tones which are spectrally rich with three (500-1500Hz) and five (500-2500Hz) harmonic partials. Stimuli were of 100 to 250ms. They observed that the amplitude was good with both the spectrally rich sounds compared with pure tones and the long duration sound did not affect the MMN. So this suggests that the spectral information facilitates pitch processing of spectrally rich sounds compared to temporal information. Hence they concluded that the complex stimuli results in larger MMN when compared to pure tones but in contrast, Naatanen et al. (1997) reported that complex sounds resulted in smaller amplitude than simple sounds.

Naatanen et al. (2000) studied MMN in native and non -native Finnish speakers and observed maximum amplitude at 150ms for finnish speakers than non-native Finnish speakers. This suggested the presence of memory traces for spoken words in the human brain.

Chhabra and Maruthy (2013) studied perceptual differences for three Malayalam nasal contrasts on native and non native speakers of Malayalam. The behavioural disvrimination of the stimulus was compared with the MMN response for the same stimuli. The results revealed that there was a relation between behavioural discrimination

and MMN prevalence, and indicated that the discrimination scores were better for individuals who had presence of MMN and vice versa.

Kraus et al. (1992) recorded MMN for normal school age children and, adults for different variants of speech phoneme /da/. Peak latency and duration were similar in children and adults whereas peak to peak amplitude and area were significantly better in children than adults. They also noted that minimal acoustic stimulus changes in complex speech signals can elicit MMN in school-age children and suggested that MMN can be used as a tool to study deficient auditory perception in children.

Wunderlich and Cone-Wesson (2001) studied the effect of stimulus frequency and stimulus complexity (words and consonant –vowel combination differentiated based on formant change) on MMN from 12 normal listeners. They found that MMN was larger in its area for low frequency contrasts. For speech sounds, MMN had smaller area compared to tones.

Korpilahti, Krause, Holopainen and Lang (2001) elicited MMN for complex tones, pseudo words and naturally spoken words. For tone, early MMN was obtained at 150-200ms whereas for words it was around 400-450ms represented as strong late MMN. Overall MMN was found to be weaker for pseudo words when compared to words because the system which encodes memory trace automatically detects the words in their own language according to the author.

Cheour et al. (1998) compared MMN in pre-term infants (30-35 weeks of conceptional age), full term new-borns and full term 3-month- old infants for Klatt-synthesized Finnish vowels /y/ and /i/. They observed decrease in the latency with age, but no much latency difference was noted in response between 3month old infants and adult responses of the previous study. There was no significant differences in the amplitude of MMN the age groups.

Other variables that affect MMN include probability of deviant stimulus, magnitude of the deviation and the length of inter stimulus interval (Naatanen, 1992). MMN appears to be large for the smaller deviant stimulus probability, larger magnitude of the deviation and shorter inter stimulus interval.

2.3 Correlation of MMN with Behavioral Discrimination

Lang, Nyrke, Ek, Aaltonen, Raimo and Natatanen, (1990) correlated MMN amplitude with behavioral discrimination using two tonal stimuli which differed in terms of frequency in 17 year old adolescents. For behavioral discrimination, the subjects were asked to respond by saying same or different. Based on the behavioral performance, the participants were categorized into good, moderate and poor performers. They found that in good performers, 19Hz of frequency change was required to elicit MMN response whereas poor performers required 100Hz deviance for recordable MMNs.

Kraus, McGee, Carrell, Zecke, Nicol and Koch (1996) elicited behavioral and MMN response using /da -ga/ and /ba- wa/ stimulus pair. It was found that only those

children who could discriminate the two syllables behaviorally, got MMN response for /da/-/ga/ contrast. Whereas, MMN was found to be robust in all the children for /ba/-/wa/ contrast since it was easy to discriminate.

Parkarinen, Takegata, Rinne, Huotilainen and Naatanen (2007) recorded MMN responses for duration, intensity, and frequency changes using multi-feature paradigm in young adults along with behavioral discrimination. They obtained significant MMNs for all the changes in the stimuli and also found increased amplitude and decreased latency with increase in magnitude of the sound change. Further they concluded that the amplitude and latency of MMN can predict the detection accuracy and speed of the changes by the subject.

Novitski, Tervaniemi, Huotilainen and Naatanen (2004) compared the neural and behavioral discrimination for frequency changes that ranged from 250 to 4000Hz. MMN was used as a neural frequency change detector. In behavioral task, the subjects were asked to indicate whenever they perceived changes in the stimuli. The results of their study revealed that the MMN amplitude and latencies correlated with behavioral response reaction time and hit rate of the response and a good correlation was found between behavioral (hit rate) and MMN amplitude.

2.4 MMN and Categorical Perception

Dehaene -Lambertz (1997) reported that MMN can be used as an evidence to show the language specific memory. MMN was recorded for syllables varying in terms of

place of articulation in a continuum. It was observed that MMN response was enhanced if the syllable change was present in their native language.

Sharma and Dorman (1999) used /da/ and /ta/ stimulus pair which varied in terms of voice onset time (VOT) in a continuum. It was observed that for all the subjects, the behavioral categorical boundary was at the same location. They also reported that within category of /ta/ discrimination of VOT changes were not accurate whereas in across category (/da/-/ta/) discrimination was more accurate. The amplitude of MMN was larger for across- category change rather than within-category change and this enhanced MMN was observed at /da/-/ta/ phonetic boundary.

2.5 Clinical Applications of MMN

MMN has two attractive features for clinical use. First, it can be elicited passively without any attention or response from the listener. As a result it can be used to assess the individuals who are not willing or not able to participate for tests that require active response. Second, the presence of MMN indicates that the person is able to differentiate the deviant stimulus from standard stimulus. Hence it can be used as an objective measure to check the discrimination ability of an individual (Naatanen et al., 1978; Kraus et al., 1993; 1996). It is the most popular measure in investigating neurological and psychiatric disorders such as schizophrenia, memory disorders, dyslexia, coma outcomes etc. (Naatanen et al., 1978; Naatanen et al., 2007; Duncan et al., 2009). MMN is used in assessing adult psychiatric disorders such as aphasia and dementia (Naatanen, 1995; Escera, 1997) and child psychiatry as in attention deficit disorder (Korpilahti & Lang,

1994; Kemner, Verbaten, Cuperus, Camffermanand & Van Engeland, 1998), language impairment (Holopainen, Korpilahti, Juottonen, Lang & Sillanpaa, 1997), dyslexia (Schulte-Korne et al., 2001). MMN is also a good clinical tool to evaluate the effectiveness of auditory training in individuals with hearing loss.

Naatanen et al. (2011) studied MMN using frequency, duration and speech-sound changes in repetitive background stimulation by making the patients to read books or watch videos. They noted longer latencies and reduction in MMN amplitude majorly in neurodevelopmental, neurological and neuropsychiatric disorders, also in normal but aged individuals. Apart from the reduced discrimination accuracy, the MMN response in these individuals reflect reduced sensory memory duration, poor attention control, abnormal perception and cognitive decline irrespective of specific aetiology and symptomatology. *N*-methyl-D-aspartate (NMDA) receptor function deficiency was found to affect memory trace information and hence cognition in these disorders.

Cheour et al. (1999) compared MMN response between 9 neonates with cleft palate and 8 healthy neonates of same age group using 1000 Hz as standard stimuli and 1100Hz as deviant stimuli. They noted that the MMN which was elicited in 3 of the 9 infants with cleft palate was reduced in amplitude than the MMN responses of the healthy neonates. This indicated brain dysfunction in neonates with cleft palate which lead to cognitive disabilities. So they suggested that MMN can be helpful to start rehabilitation by identifying cognitive disabilities early.

Schulte- Korne, Deimel, Bartling and Remschmit (2001) elicited MMN in 12 adults with Dyslexia and normal subjects using passive oddball paradigm for both speech and tones. They found that the tonal stimuli lead to two MMN components for both the groups. For speech stimuli, three components of MMN was obtained. Multivariate testing between groups yielded significant difference between two groups. Hence the authors suggested that speech perception should be measured on early, pre-attentive level which helps in assessing Dyslexia not only in children but also in adults.

2.5.1. MMN as an Index of Temporal Processing

Kujalo, Kallio, Kervaniem and Naatanen (2001) recorded MMN in passive oddball paradigm where standard stimulus (P=0.79) was a tone pair with 120 ms silent-inter-stimulus interval (ISI) and deviant stimuli (P=0.07) were tone pairs with ISI of 100, 60 and 20ms in two sessions separated by 4-21 days and behavioral responses in a separate session for 10 adults. They found that the 20 and 60 ms ISI deviant tone pairs elicited good MMN and could be discriminated behaviorally when compared to 100 ms ISI deviant pair which was not discriminated behaviorally. Further the replicability of MMN was high with 20ms ISI deviant pairs (r=0.75) than 60ms ISI deviant pair (r = 0.60) and significant correlation was seen between MMN and reaction times for 20 and 60 ms ISI deviant pairs. So they concluded that the discrimination accuracy of temporal sounds intervals is reflected in MMN and a highly reliable MMN can be obtained if the difference between the standard and the deviant tone pair in temporal domain is large.

2.5.2 MMN as Tool to Measure Training Effects

Several investigations (Kraus et al., 1995; Tremblay et al., 1997) demonstrated the effect of listening training on MMN and they concluded that behavioral training can change the neurophysiological representation for speech sounds. As a result, it was suggested that MMN reflects the physiologic plasticity associated with auditory training.

Tremblay et al. (1997) studied discrimination and identification of VOT contrast after training in English speaking normal adults where VOT contrast does not occur in their language. Identification and discrimination of VOT contrast was trained with bilabial context (training condition) and later it was transferred to alveolar context (transfer condition). The evaluation was done before and after training. It was found that the MMN area and duration were increased for training condition compared to transfer condition. Behaviorally after training, all the subjects could identify and discriminate both training and transfer contrasts.

So far MMN has been used in research but it is also a tempting assessment tool for clinical use because of its versatile nature. Before using MMN as a clinical tool, it is necessary to demonstrate that (a) it is detectable in all the normal individuals who are able to differentiate the eliciting stimuli and (b) it is replicable over sessions within an individual. However unlike other auditory evoked potentials, MMN is not yet used for clinical applications because of its questionable reliable measures (Kujala et al., 2007).

2.6 Incidence of MMN

Dalebout and Fox (2000) identified MMN in normal adults for three stimulus conditions (one control condition and two contrast conditions) using /da/-/ga/ continuum. The waveforms were presented to the examiners for analysis. In each condition the examiner assessed hit rate, a false alarm rate and d' based on identification of MMN. Hit rate was found to be low and false rate was relatively higher which resulted in small d values. They also found poor relationship between behavioral discrimination and MMN.

Dalebout and Fox (2001) recorded MMN for synthetically generated speech contrast (/da/-/ga/) from 12 normal adults during four biweekly sessions. The standard and deviant stimluli varied in terms of place of articulation. They reported that MMN was not detectable in the responses obtained from all the individuals. They found that the MMN identification rate was too low (29%) to check the reliability.

2.7 Reliability of MMN

Many studies have reported intersession reliability of MMN (Chertoff, Goldstein, & Mease, 1988; Pekkonen, Rinne, & Naatanen, 1995; Lang et al., 1995; Escera & Grau, 1996; Frodl –Bauch, Kathmann, Moller & Hegerl, 1997; Joutsiniemi et al., 1998; Kathmann et al., 1999; Tervaniemi et al., 1999; Escara, Yago, Polo, & Grau, 2000). Overall it has been found that reliability of MMN is in group studies but this is not seen in single subject measurements (Escara & Grau, 1996; Tervaniemi et al., 1999).

2.7.1 Reliability of MMN for Tonal Stimuli

The test retest reliability of MMN was first reported by Pekkonen et al. (1995) and Lang et al. (1995). Pekkonen et al. (1995) studied the correlation between mean amplitudes of two test sessions (one month apart) in 10 young adults by varying deviant types (frequency and duration), inter stimulus interval (0.5 and 1.5 sec) and at different electrode sites. They found significant correlation for duration deviance with inter stimulus interval of 0.5 seconds when compared to frequency deviance. Overall stability of MMN was found by taking grand average waves for both duration and frequency with two inter stimulus interval and obtained $p < 0.05$ in paired Student's test. To check intra subject stability at individual level, Pearson product-moment correlation coefficient ($r=0.57$, $p < 0.09$) was used separately for each electrode site, between two sessions for MMN amplitude. The results revealed that at group level, test retest reliability of MMN amplitude was fairly good for both types of changes in stimulus, whereas at individual level, test retest stability was significantly obtained for duration MMN.

Escera and Grau (1996) evaluated short term replicability of MMN in a sample of 11 adults. They recorded MMN in two sessions, with two hours of interval between first and second session, using Neuroscan. Probability of 92% and 8% were presented to all the subjects. The grand average for first and second sessions were taken and two way analysis of variance was done and it did not reveal significant difference between the two sessions ($p = 0.162$). Pearson's product moment correlation was carried out to check individual short term replicability between two sessions and separately for different electrode sites. They found significant ($r = 0.65$, $p = 0.02$) correlation coefficient for C3 and ($r = 0.598$, $p = 0.04$) for F4 electrode sites. For group data, between the two sessions,

there was no significant difference found in terms of amplitude or latency of MMN. Whereas MMN replicability was found to be poor for individual data between the two sessions. Results indicated good replicability of MMN at group level when compared to individual level replicability.

Frodl–Bauch et al. (1997) compared MMN for frequency and duration deviances concerning test retest reliability of amplitudes and source of potential location. The effect of attention on test retest reliability was also studied. There were two groups of subjects. One group of subjects were given visual task during reading whereas the other group was not given any task. MMN was recorded twice with 3 weeks of interval between two sessions. It was found that test retest reliability was high for frequency MMN and low for duration MMN.

Deouell and Bentin (1998) compared spatial distribution, amplitude and latency of MMN for frequency and intensity deviances and also assessed inter and intra subject variability at various electrode sites. For each dimention paired t tests were carried out to check for significant difference. Post hoc univariate comparison was done to compare between dimentions and found that MMN was larger for frequency ($F = 8.09$, $p < 0.05$) than other dimensions. They also obtained better reliability for frequency deviance at individual level but good test retest-reliability at group level for all the dimensions.

Tervaniemi et al. (1999) compared test retest reliability of MMN for duration, frequency and intensity deviances of sound from 15 normal hearing adults for 1 to 27 days. Results revealed that among all the deviances tested MMN was more replicable for

duration decrement. The reliability of MMN has been reported to be influenced by the attentional conditions along with deviance type.

Kathmann, Frodl-Bauch, and Hegerl (1999) recorded MMN from 45 subjects for duration and frequency changes in test retest sessions. Subjects were divided into two groups where one group of subjects were involved in active visual attention task while other group was instructed to ignore the task. As a result they found that amplitude and replicability of MMN increased for duration changes for both with and without focused visual attention task and also obtained above 0.8 test-retest correlation coefficients at all frontal scalp sites. However the study concluded that stability and replicability of MMN depends on deviant types and attentional conditions. Hence it is essential to choose appropriate task conditions while testing MMN for group comparisons.

Escera, Yago, Polo, and Grau (2000) studied replicability of MMN in six electrode sites for short and long ISI from ten young subjects in two recording sessions separated by one month. The stimuli used were pure tone of 700Hz where standard tone had duration of 75ms and deviant tone with 25ms. They used Neuroscan to record MMN .The subjects were presented with trains of 3 stimuli with probability of 16.7%. In a train, stimuli were separated by 300ms short interval. In separate blocks, the trains of stimulus were presented with short ISI of 0.4seconds or long ISI of 4.0seconds. To compare overall peak amplitude and latency for each session and inter stimulus interval, ANOVA was used. For individual replicability between sessions for each ISI at each electrode site, Pearson product moment was tested and found highly significant correlation between

sessions (r = 0.85, p = 0.02) for all six electrode sites. High individual replicability of MMN was obtained for short ISI i.e 0.4 seconds when compared to long ISI condition. Hence it was concluded that MMN is reliable for short ISIs.

Kujala et al. (2001) evaluated replicability of MMN for inter-stimulus intervals between paired tones. MMN was obtained in two sessions separated by 4 to 21 days using oddball paradigm from 10 adults. The standard stimuli had an inter stimulus interval of 120 ms whereas deviant stimuli had varied inter stimulus interval of 100, 60, and 20ms. The behavioral response was obtained using button press technique for target stimuli. The results showed that during both sessions tone pairs with inter stimulus interval of 20 and 60 ms elicited significant MMN and the subjects could also discriminate behaviorally, whereas for 100ms ISI pair, neither MMN was significantly elicited nor was it behaviorally discriminated. It was also found that for 20ms ISI, MMNs were highly replicable (r = 0.75) and for 60ms ISI, it was less (r = 0.60). It was concluded that MMN reflects temporal sound interval discrimination.

Tervaniemi et al. (2005) investigated test-retest reliability of MMN magnetically using whole head magnetometer consisting 122 channels in 15 normal young adults for level, frequency and time deviances and analyzed right and left hemispheres separately. The responses were measured in terms of latency, strength of generator loci and dipole moment. Their results revealed statistically significant test retest-reliability for all the parameters of magnetic MMN in right hemisphere (r =0.4 -0.89) and in left hemisphere (r = 0.61 – 0.82). Thus the results encourage MMN for both research as well as clinical use.

However it is difficult to generalize the finding of these studies to that of speech elicited MMN. MMN for speech stimuli is known to differ from non-speech stimuli in number of dimensions such as latency, amplitude and scalp distribution.

2.7.2 Reliability of MMN for Speech Stimuli

Uwer and Suchodoletz (2000) studied the stability of MMN in 15 children for tones varying in terms of frequency and duration and for /ba/ and /ga/ speech stimuli. The stimuli were presented in balanced order. For frequency deviance, standard tone of 1000Hz with 175ms and deviant stimuli of 1200Hz with 175ms were used .In MMN obtained for duration deviance 1000Hz, 175 was used as standard and 1000Hz, 100ms as deviant stimuli. Using correlation coefficients, reliability of MMN amplitude within one session and stability between the sessions were determined. The results revealed significant individual stability for duration deviance and one of the syllable (/ga/). But there was decrease in mean amplitude of MMN for frequency deviance and other speech stimuli. They also concluded that MMN stability is poor in children when compared to adults.

Dalebout and Fox (2001) recorded MMN for synthetically generated speech contrast (/da/-/ga/) from 12 normal adults during four biweekly sessions. The standard and deviant stimuli varied in terms of place of articulation. They reported that MMN was not detectable in the responses obtained from all the individuals. They also found good replication of standard and deviant waveforms across sessions but poor replicability of

the derived difference waveform and concluded that the MMN identification rate was too low (29%) to check the reliability.

Pakarinen et al. (2009) recorded MMN for changes in consonant and vowel. They also studied MMN for changes in syllable frequency, intensity and vowel length using multi feature paradigm. They compared these MMNs with that obtained for traditional oddball paradigm. The reliability of MMN was also examined for multi feature paradigm where after the first recording, MMN was repeated for the same individuals after 1-7 days. There was similarity obtained between multi feature paradigm and oddball paradigm. The results on replicability of MMN revealed that across two recordings there was only minor differences obtained in amplitude of MMN.

Overall, evidences related to reliability doesn't convince as it is influenced by stimulus used, task involved and the method of analysis. Most of the earlier studies have tested reliability of non speech MMNs and by using conventional paradigm wherein the frequent wave is subtracted by the infrequent wave. Speech MMNs are characterized by different scalp distribution, latency and amplitude compared to non speech MMN. Depending on the contrast used, they may involve different generators and possess different scalp distribution compared to non speech MMN. Therefore reliability data of non speech MMN does not help in understanding the reliability of speech MMN.

Secondly, in the present study it was aimed to use a different method to derive the difference waveform compared to conventional method. Therefore as the literature suggests MMN detectability could vary and in turn its reliability.

Finally, all the studies in the literature have used high density EEG systems which have sophisticated signal processing technology compared to clinical EEG equipments. Therefore one can expect, different reliability of MMN due to difference in the technology in clinical EEG equipments compared to earlier reports.

Chapter 3

Method

The present study aimed to investigate the test retest reliability of Mismatch Negativity (MMN) for two stimulus pairs, at two electrode sites, across three trials. It tested the null hypothesis that there is no significant difference in the Latency, amplitude and area of MMN across three trials of recording. Repeated measures design was implemented in the study wherein the same participant was tested at different time points to check the test retest reliability of MMN. The following method was used to test the hypothesis of the study.

3.1 Participants

Twenty normal hearing adults in the age range of 18 to 25 years participated in the study. The participants were bachelors and masters students of speech and hearing. Prior to the MMN recording, they were assessed to rule out hearing loss, middle ear dysfunction, auditory processing disorder and the presence of any neurological deficits. They had:

- Pure tone thresholds of less than 15 dB HL at octave frequencies between 250 Hz and 8000 Hz.

- Speech recognition thresholds of less than 25 dB HL (for word list in Kannada given by Rajashekar & Vyasamurthy, 1976) and speech identification scores of

more than 90% (for PB word list in Kannada given by Yathiraj & Vijayalakshmi, 2005).

- Normal middle ear functioning as reflected by type-A tympanogram and the presence of ipsilateral and contralateral reflexes at normal sensation levels.

- No history or presence of any speech, language, psychological, neurological and auditory processing problems as revealed by a structured interview.

Geographically they were from different parts of India and in their native language /da/, /ga/ & /ta/ syllables were phonetically relevant. Participants were explained about the purpose of the study and a written consent was taken prior to their participation in the study.

3.2 Test Environment

All the audiological evaluations were carried out in an air conditioned sound treated room with ambient noise levels within permissible limits ANSI S3.6 (1999). The room used for recordings of MMN was also electrically shielded.

3.3 Instrumentation

For preliminary evaluations various technical equipments were used such as a calibrated two channel diagnostic audiometer (OB-922) and a calibrated Immittance meter (GSI - Tympstar). For recording MMN, Intelligent Hearing System (IHS) EEG

recording system with Smart EP software (version 2.39) was used. A laptop computer with Adobe Audition and Praat softwares were used for stimulus editing.

3.4 Test Stimuli

MMNs were recorded for 2 pairs of stimuli /da/-/ga/ and /da/ -/ta/ in order to check for processing of place and voicing cues. In the /da/ -/ga/ pair, /da/ served as frequent stimulus and /ga/ as the infrequent stimulus. Acoustically these two stimuli differed in their F2 transition. Similarly in /da -/ta/ pair, /da/ served as frequent stimulus while /ta/ was the infrequent stimulus which differed in VOT.

In a sound treated room all the syllables /da/, /ga/ and /ta/ were recorded using a unidirectional recording microphone which was connected to a laptop computer. These were uttered by a native speakers of Kannada who had normal oromotor mechanism, articulation, voice and fluency. For this purpose, Praat software (version 4.5.18) was used and the recordings were digitized with a sampling frequency of 44,100 Hz and 16 bit digitization. The total duration of each stimulus was 200ms.

The recorded stimuli were played back to 10 normally hearing listeners to rate the clarity, loudness and pitch of the stimulus using a 3 point rating scale where 1 indicates adequate, 2 as almost adequate and 3 indicates not adequate. Eight out of ten listeners rated the samples as adequate or almost adequate in terms of its quality and intelligibility. Using Adobe Audition software (version 3) the stimuli were normalized based on RMS

amplitude. Figure 3.1 shows the waveform and spectrogram of /da/, /ga/ and /ta/ stimuli used in the present study for recording MMN.

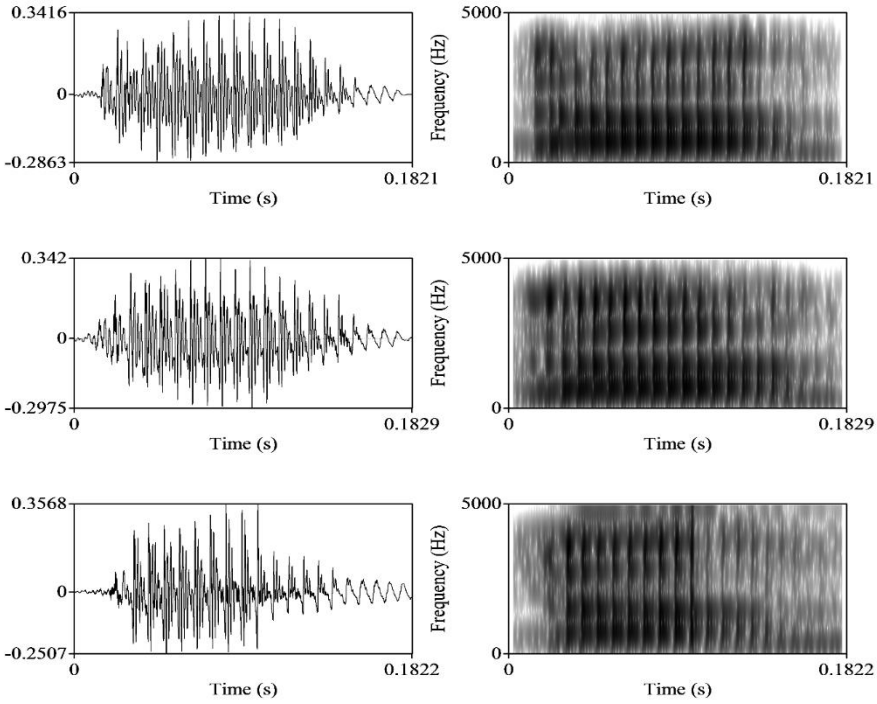

Figure 3.1: Waveform and spectrogram of the syllables /da/,/ga/ and /ta */ used in the present study or recording MMN.*

3.5 Test Procedure

3.5.1 Preliminary Audiological Evaluations

Pure tone thresholds in the air conduction mode were obtained at octave frequencies between 250 Hz and 8000 Hz using modified Hughson –Westlake procedure (Carhart & Jerger, 1959). Speech audiometry was carried out to obtain speech recognition thresholds (for word list in Kannada given by Rajashekar & Vyasamurthy, 1976) and

speech identification scores (using PB word list in Kannada given by Yathiraj & Vijayalakshmi, 2005). Tympanogram was obtained using 226 Hz probe tone and, static admittance and peak pressure were noted down. Ipsilateral and contralateral reflexes at 500, 1000, 2000, and 4000 Hz were recorded. In order to rule out auditory processing deficits a structured interview was carried out. Only those individuals who had normal hearing sensitivity, normal speech perception and normal middle ear functioning, and reportedly normal auditory processing proceeded to be participants for the MMN recording.

3.5.2 Recording of MMN

Two pairs of speech stimuli were used to record MMN. Stimuli were presensted binaurally using an ER-3A insert phones with an intensity of 70dBSPL. MMN was recorded using two channels in vertical montage with Cz and Fz as the positive electrodes referenced to the nape of the neck. The ground electrode was placed on the lower forehead. A third channel was used to record the eye blink response. The sweeps with large eye blink artifacts were eliminated from the averaging.

Stimuli were presented in the odd ball paradigm with the probability of standard and deviant stimulus being 80% and 20% respectively. The stimuli were presented in the rarefaction polarity with a repetition rate of 1.1/second. The response was averaged for 200 sweeps (200 infrequent stimuli + the corresponding number of frequent stimuli) from -50 to 500 ms. The filter was set to band pass between of 0.1 and 30 Hz, while the input EEG was amplified with a gain of 50,000. Artifact rejection was kept at 25 μV. For

ocular channel, artifact rejection window was adjusted until eye blink artifact was being rejected following its detection.

The participants were seated comfortably in order to minimize muscular artifacts and were made to watch a silent movie in order to facilitate passive listening. The skin surface of the target electrode sites were cleaned and disc electrodes were placed. The recording was started only if the absolute impedance was less than 5 kΩ and inter-electrode impedance was less than 2 kΩ. For each stimulus pair, MMN was recorded twice to ensure the replicability.

Apart from recording MMN in the conventional paradigm for each stimulus pair, LLRs were recorded for the respective infrequent stimulus at the rate of 1.1/sec for 200 presentations. This again was recorded twice to ensure the replicability. LLRs for infrequent stimulus of each contrast was obtained in order to analyze the presence or absence of MMN by comparing the infrequent waveforms of MMN and LLR of respective infrequent stimuli. This method was used to control the stimulus difference effect on MMN analysis.

In each participant, MMN to each stimulus pair was repeated twice; once after one hour of the first recording, within the same session (intrasession) and second time within a week, in a different session (intersession). Totally recordings were made on 3 occasions.

3.6 Response Analysis

To eliminate the stimulus effects on MMN, the averaged wave recorded for infrequent /ga/ in the /da-ga/ sequence was compared with the LLR wave recorded for the /ga/ stimuli. Similarly, the wave recorded for infrequent /ta/ in the /da-ta/ sequence was compared with the wave recorded for the /ta/ in the LLR paradigm. Difference waves were then obtained by subtracting LLR for /ga/ from infrequent /ga/ wave and LLR for /ta/ from infrequent /ta/ wave. MMN was located in the difference wave to note down its onset latency, peak latency, offset latency, peak amplitude and the area. Figure 3.2 shows a representative group of waves that include a standard wave (/da/), deviant wave (/ga/), LLR for deviant stimulus (/ga/) and the difference waveform. MMN is marked in the difference waveform.

Each difference waveform was separately analyzed visually by 3 experienced audiologists. Only if all the audiologists agreed upon, presence of MMN and its location were considered. At the beginning of the negativity in the difference waveform, onset latency was taken and at the end point where negativity stopped was considered as offset latency. Peak latency was marked at the point where there was maximum negativity. Peak amplitude was obtained by subtracting absolute amplitude at the tip of negativity and amplitude at the beginning of the negativity. Once the two extremes of MMN were marked, the area under the curve was calculated by the software itself. This procedure was used for recordings at Cz as well as Fz electrode sites.

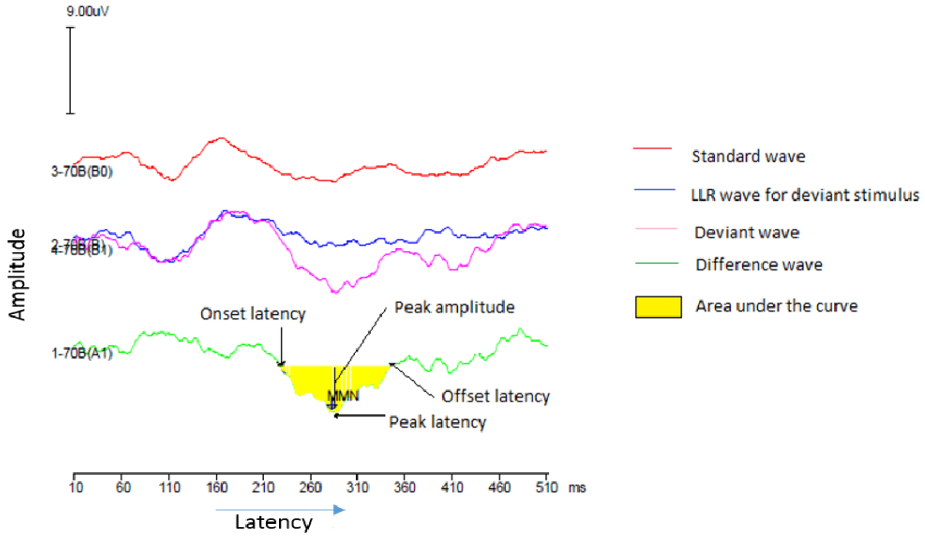

Figure 3.2: *Representative waveform of MMN and its parameters (onset latency, offset latency, peak latency, peak amplitude and area under the curve) recorded for /da/-/ga/ stimuls pair.*

3.7 Data Analysis

The group data was analyzed statistically for the prevalence of MMN, stability of group data and the stability of individual data.

Chapter 4

Results

The purpose of the present study was to examine the test-retest reliability of speech elicited Mismatch negativity (MMN). Considering that the responses were recorded in 20 participants, at 2 electrode sites, for 2 stimulus pairs, in 3 trials, there were 480 LLRs recorded of which 240 were for frequent stimuli and 240 were for infrequent stimuli. The infrequent waveforms and the corresponding LLRs were compared to derive the MMN. Two forty difference waveforms were analysed for the presence of MMN and if MMN was present, onset latency, offset latency, peak latency, peak amplitude and area under the curve were noted down from the individual difference waveform. The group data thus obtained was statistically analysed using repeated measures ANOVA, and Crombach's alpha to verify the hypothesis of the study. The results of the study are reported under the following headings.

1. Prevalence of MMN
2. Results of normality test
3. Comparison of MMN between the electrode sites
4. Comparison of MMN across the three trials
5. Test for Reliability

4.1 Prevalence of Mismatch Negativity

Prevalence of MMN operationally means the number of individuals who showed presence of MMN out of the total number of individuals (which is 20). This was determined separately for each of the 3 trials, for the two stimulus pair and for the data

from two electrode sites (Cz & Fz). Table 4.1 represents presence or absence of MMN for the two stimulus pairs, at the two electrode sites for /da/ - /ga/ stimulus pair, in the three trials.

Table 4.1: *Representation of presence or absence of MMN for /da/ - /ga/ stimulus pair at two electrode, sites, in the three trials*

	Fz			**Cz**		
Participants	**Trial 1**	**Trial 2**	**Trail 3**	**Trial 1**	**Trial 2**	**Trail 3**
1	P	A	A	P	A	A
2	P	P	A	P	P	A
3	P	A	P	P	A	P
4	P	P	A	P	P	A
5	P	P	P	P	P	P
6	A	A	P	A	P	P
7	P	P	P	P	P	P
8	P	P	A	P	A	A
9	P	P	A	P	P	A
10	A	P	A	A	P	A
11	P	A	A	P	A	A
12	P	P	P	P	P	P
13	P	A	P	P	A	P
14	P	P	A	P	P	A
15	A	P	P	A	P	P
16	A	P	P	A	P	P
17	A	A	P	A	A	P
18	P	A	A	P	P	A
19	P	P	P	P	P	P
20	A	A	A	A	A	A
Total	**14/20**	**12/20**	**10/20**	**14/20**	**13/20**	**10/20**

For the /da –ga/ stimulus pair the percentage of individuals with presence of MMN varied from 50 % to 70 %. This was considering both the electrode sites and the three trials. Further, it can be observed from the table that only in 4 participants, MMN was present in all the three trials. This was true for both Fz and Cz sites. There was only

one participant in whom MMN was absent in all the trials at both Fz and Cz sites. In most instances, (15/20 times in Fz and Cz) MMN was present only in one or two trials. In the Fz site, it was present in 6 participants only in one trial while it was present in 9 participants in two trials. On the other hand, at Cz site, 5 participants had MMN only in one trial and 10 participants had MMN in two trials.

Table 4.2: *Representation of presence or absence of MMN for /da/ - /ta/ stimulus pair at two electrode site in the three trials*

	Fz			**Cz**		
No .subjects	**Session 1**	**Session 2**	**Session 3**	**Session 1**	**Session 2**	**Session 3**
1	P	A	A	P	A	A
2	A	P	P	P	P	P
3	P	A	P	P	A	P
4	P	P	A	A	P	A
5	P	P	P	P	P	P
6	A	P	P	A	P	P
7	P	P	P	P	P	P
8	A	P	A	A	P	A
9	P	P	A	P	P	A
10	A	A	A	A	A	A
11	P	A	P	P	A	P
12	A	P	A	A	P	A
13	A	P	P	A	P	P
14	P	A	A	P	A	A
15	P	P	P	P	P	P
16	A	P	P	A	P	P
17	A	A	P	A	A	P
18	A	A	A	A	A	A
19	A	P	A	A	P	A
20	P	A	A	P	A	A
Total	**10/20**	**12/20**	**10/20**	**10/20**	**12/20**	**10/20**

Table 4.2 shows the presence or absence of MMN for /da/ - /ta/ stimulus pair at two electrode sites, in the three trials. In the /da/ - /ta/ stimulus pair, the percentage of participants showing presence of MMN varied between 50 % and 60 %. This was

considering both the electrode sites and the three trials. It can be observed that 3 participants had MMN in all the three trials at Fz site, while in 7 participants it was present only in one trial and in 8 participants MMN was present in two trials. On the other hand at Cz site, 4 participants had MMN in all the three trials, 8 participants had only in one trial and 6 participants had MMN in two trials. There were 2 participants in whom MMN was absent in all the three trials at Cz site.

4.2. Results of Normality Test

The data obtained was tested for its distribution using one-sample Kolmogorov-Smirnov test of normality. The data of each electrode site, each stimulus pair and each trial was separately tested for normality. Results showed that the data was normally distributed in both electrode sites, both stimulus pair and in each trial. This supported the use of parametric statistical tests with the present data.

4.3. Comparison of MMN between Electrode Sites

Table 4.3 gives the mean and standard deviation of the parameters (Onset latency, offset latency, peak latency, peak amplitude and area under the curve) of MMN in the three trials, for both Fz and Cz sites, for /da/-/ta/ stimulus pairs and /da/-/ta/.

Table 4.3: *Mean and Standard deviation (SD) of the parameters of MMN (Onset latency, offset latency, peak latency, peak amplitude and area under the curve) in the three trials, for both Fz and Cz sites, for /da / - /ga/ and /da/ -/ta/ stimulus pairs*

Trial	MMN parameters	Electrode site	/da-da/		/da-ta/	
			Mean	Standard deviation	Mean	Standard deviation
1	Onset latency (ms)	Fz	196.42	42.89	185.10	49.06
		Cz	201.57	44.77	179.30	45.09
	Offset latency (ms)	Fz	300.85	46.49	266.70	58.07
		Cz	302.71	51.42	263.90	61.10
	Peak latency (ms)	Fz	245.57	42.28	225.70	49.90
		Cz	248.07	42.85	223.20	53.93
	Peak amplitude (µV)	Fz	2.54	1.02	2.35	1.38
		Cz	2.23	0.74	2.50	1.21
	Area under the curve (ms x µV)	Fz	150.67	88.47	117.07	100.80
		Cz	119.46	58.57	114.10	93.79
2	Onset latency (ms)	Fz	179.36	54.97	179.83	45.92
		Cz	194.53	60.06	189.25	45.52
	Offset latency (ms)	Fz	259.54	56.76	274.08	52.29
		Cz	262.69	64.08	264.33	53.79
	Peak latency (ms)	Fz	213.00	55.94	229.83	42.53
		Cz	226.30	59.39	227.33	45.76
	Peak amplitude (µV)	Fz	2.11	0.73	2.58	1.08
		Cz	2.14	0.76	2.30	0.79
	Area under the curve (ms x µV)	Fz	94.32	46.49	139.94	93.27
		Cz	85.40	63.50	94.43	39.14
3	Onset latency (ms)	Fz	200.00	40.49	213.70	33.54
		Cz	208.00	47.22	210.20	35.31
	Offset latency (ms)	Fz	310.80	39.65	303.10	28.89
		Cz	303.90	36.00	301.20	26.57
	Peak latency (ms)	Fz	252.70	26.96	253.80	25.28
		Cz	257.60	29.65	258.20	24.03
	Peak amplitude (µV)	Fz	2.28	0.49	2.37	0.93
		Cz	2.18	0.78	1.97	0.75
	Area under the curve (ms x µV)	Fz	127.77	54.70	135.05	114.94
		Cz	128.98	81.75	117.28	107.97

For /da/- /ga/ stimulus pair, in all the three trials, mean MMN latency (onset latency, offset latency and peak latency) were prolonged in Cz compared to Fz. No such uniform trend was seen for the mean amplitude and area under the curve across the three

trials. On the other hand, for /da/ -/ta/ stimulus pair, the latency of the MMN parameters (onset

Table 4.4: *Results of Paired Sample t-test comparing MMN between Fz and Cz sites in three trials, for /da-ga/ and /da-ta/ stimulus pairs.*

Trial	Parameter	/da/ -/ga/		/da/-/ta/	
		t	**df**	**T**	**df**
1	Onset latency (ms)	-2.12	13	0.46	8
	Offset latency (ms)	-0.39	13	0.10	8
	Peak latency (ms)	-0.85	13	0.49	8
	Peak amplitude (µV)	1.40	13	-0.02	8
	Area under the curve (ms x µV)	1.66	13	0.41	8
2	Onset latency (ms)	-0.57	10	-1.14	11
	Offset latency (ms)	2.25	10	0.88	11
	Peak latency (ms)	-0.91	10	0.44	11
	Peak amplitude (µV)	-0.87	10	0.86	11
	Area under the curve (ms x µV)	0.44	10	1.81	11
3	Onset latency (ms)	-2.16	9	0.78	9
	Offset latency (ms)	0.798	9	0.58	9
	Peak latency (ms)	-1.64	9	-1.08	9
	Peak amplitude (µV)	0.50	9	1.73	9
	Area under the curve (ms x µV)	-0.08	9	1.40	9

Note: *The 'p' value was corrected by dividing 0.05 from the total no. of comparison i.e.,15*

latency, offset latency and peak latency) were prolonged for Fz when compared to Cz in first trial whereas no such trend was seen in the other two trials. The peak amplitude was higher in second and third trial but lesser in first trial compared to Cz. Area under the curve was larger in all the three trials at Fz compared to Cz. To test whether the observed mean differences between Fz and Cz sites were significantly different, paired- t test was carried out. The results of the paired -t test are given in Table 4.4.

The table shows that there is no statistically significant difference between MMN recorded at Cz and Fz sites. This was true with all the parameters for both the stimulus pairs and in all the three trials. Since there was no significant difference between the two sites, for the all future statistical analysis, the data of Fz and Cz were combined. This lead to increase in the number of data to check for the reliability of the individual data.

4.4. Comparison of MMN across the Three Trials

Table 4.5. gives the mean and standard deviation of MMN response parameters (Cz & Fz data combined) obtained in the 3 trials for the /da-ga/ and /da-ta/ stimulus pairs. Inspection of the table reveals that, in /da-ga/ stimulus pairs, the latency was maximum in the third trial followed by the first trial and least in second trial. Peak amplitude and area were maximum with second trial followed by third trial and least in the first trial. On the other hand, MMN elicited for /da-ta/ stimuli showed a different trend. Comparison across the three trials showed that in mean offset and peak latency, MMN prolonged from first trial to third trial. Whereas mean onset latency was maximum in second trial followed by third trial and least in I trial.

To test whether these mean differences across the three trials were significantly different, repeated measures ANOVA was carried out. The results of Repeated Measures ANOVA for the combined data of Cz and Fz electrode sites, for all the parameters of MMN, for two stimulus pairs are given in the Table 4.6. It was found that there was no significant difference in MMN response parameters across the three trials for both /da/-/ga/ and /da/ - /ta/ stimulus pairs.

Table4.5: *Mean and Standard deviation (SD) of the parameters of the MMN (Onset latency, offset latency, peak latency, peak amplitude and area under the curve) in three the trials for /da / - /ga/ and /da/ -/ta/ stimulus pair*

MMN Parameter	Number of trial	/da-ga/		/da-ta/	
		Mean	Standard Deviation	Mean	Standard Deviation
Onset latency (ms)	1	186.50	52.20	182.14	61.63
	2	161.50	56.05	208.28	12.61
	3	221.00	27.46	199.42	37.04
Offset latency (ms)	1	294.62	59.00	286.57	76.75
	2	252.00	66.55	287.42	34.38
	3	319.00	19.69	296.85	20.82
Peak latency (ms)	1	242.12	50.25	236.14	65.17
	2	202.37	55.21	238.71	14.11
	3	261.12	13.44	260.14	10.79
Peak amplitude (µV)	1	2.16	0.37	3.76	1.24
	2	2.68	0.92	2.59	0.92
	3	2.26	0.80	2.15	0.82
Area under the curve (ms x µV)	1	120.69	41.95	205.23	114.47
	2	132.03	66.61	118.78	60.18
	3	127.52	71.03	135.97	104.63

Table4.6: *Results of Repeated Measures ANOVA comparing MMN parameters across the three trials, for /da/-/ga/ and /da/ -/ta/ stimulus pairs*

MMN parameters	/da-ga/			/da-ta/		
	F	df (error)	P	F	df (error)	p
Onset latency (ms)	2.24	1.14 (8)	0.17	1.07	1.09 (6.53)	0.34
Offset latency (ms)	2.37	1.01 (7.08)	0.16	0.11	2 (12)	0.82
Peak latency (ms)	2.59	1.04 (7.30)	0.15	0.85	1.13 (6.80)	0.40
Peak amplitude (µV)	1.35	2.00 (14)	0.28	5.58	2.00 (12)	0.09
Area under the curve (ms x µV)	0.06	2.00 (14)	0.93	1.53	2.00 (12)	0.25

4.5. Results of Reliability of MMN

The present study aimed to test both intra and inter session reliability of MMN. Reliability is the stability of response across trials. Intra session reliability is the stability

of response between two recordings made within a single session without altering subject position, electrode placement, insert receiver etc. whereas, inter session reliability is the stability of response between two recordings made in two different sessions within a week using the same measurement parameters.

In this study, intra session reliability was evaluated for all the data which had MMN response in both first and second trial. Including data from both Cz and Fz sites, totally 18 data were available for /da/ -/ga/ stimulus pair and 11 data were available for /da/ -/ta/ stimulus pair. To test the stability of MMN parameters at the individual level, statistical tests of reliability (Cronbach's alpha and interclass correlations) were used. Reliability was tested separately for the two stimulus pairs. Figure 4.1 shows the representative MMN waveforms of an individual across three trials, for two stimulus pair (/da/-/ga/ & /da/-/ta/).

Results of the reliability measures showed that there was no significant correlation between the data of two trials obtained within the same session. Also, Cronbach's alpha showed that the intra session reliability is poor.

To derive inter session reliability, those data wherein MMN was present in first as well as third or second as well as third trials were considered. Totally 15 such data were available for /da/ -/ga/ stimulus pair and 18 data were available for /da/ -/ta/ stimulus pair. To test the stability of the MMN parameters at the individual level, tests of reliability was used. Reliability (Cronbach's alpha and interclass correlations) was tested repeatedly for the two stimulus pair. The results are given in the Table 4.7.

Table 4.7: *Results of Cronbach's alpha and Intra class correlation for analysis of intra inter session reliability across all the parameters of MMN for /da/ -/ga/ and /da/ -/ta/ stimulus pair*

MMN parameter	/da-ga/				/da-ta/			
	Cronbach's alpha		Intra class correlation coefficient		Cronbach's alpha		Intra class correlation coefficient	
	Intra-session	Inter-session	Inter-session	Inter-session	Intra-session	Inter-session	Intra-session	Inter - session
Onset latency (ms)	-0.98	-0.73	-0.98	-0.73	-0.31	0.43	-0.31	0.43
Offset latency (ms)	-0.44	-0.20	-0.44	-0.20	0.27	0.28	0.27	0.28
Peak latency (µV)	-0.22	-0.29	-0.22	-0.29	-0.84	0.28	-0.84	0.28
Peak amplitude (µV)	-0.16	-0.29	-0.16	-0.18	-0.19	-0.16	-0.19	-0.16
Area under the curve (ms x µV)	0.37	-0.18	0.37	-0.63	-0.54	-0.21	-0.54	-0.21

Overall, the results of reliability showed that the data of the two sessions did not correlate ($p > 0.05$) and the reliability was poor.

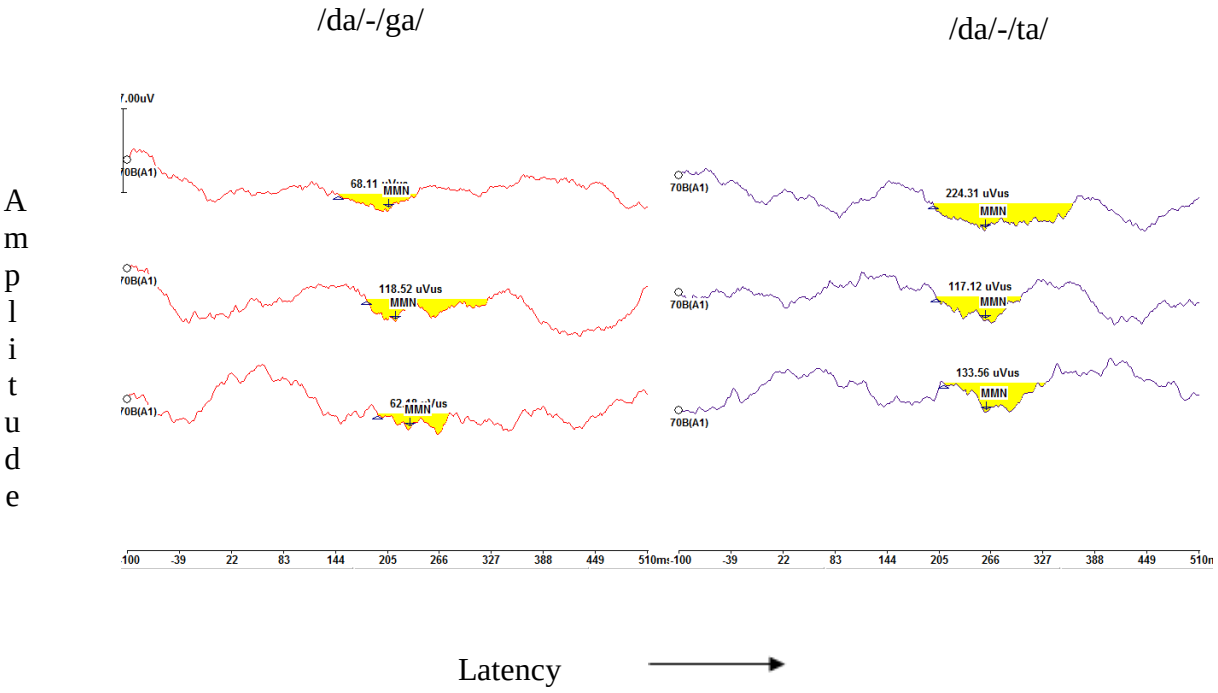

Figure 4.3.Representation of the MMN waveforms of an individual across three trials, for two stimulus pair (/da/-/ga/ & /da/-/ta/).

Chapter 5

Discussion

Mismatch Negativity (MMN) is one of the well known event related potential in auditory neuroscience that has potential to be a very good clinical tool in the audiological test battery. Literature reveals that MMN is an effective tool in identifying individuals with neurogenic and psychogenic disorders. However, such effectiveness is more so in a group comparison than at the individual level. For MMN to be a potential clinical tool, it is necessary that it has good test retest reliability apart from high sensitivity.

In the present study, attempt was made to test reliability of MMN elicited for speech stimuli. The stimuli used were chosen based on the literature. The two stimulus pairs (/da/-/ga/ & /da/- /ta/) are phonemic in most of the Indian languages, and differed in place and voicing features respectively. MMN for these two stimulus pairs were recorded from Fz and Cz electrode sites as these two sites are known to show higher amplitudes (Naatanen & Miche, 1979; Alain, Woods & Knight, 1998).

To test the reliability, MMNs recorded in three trials were compared (trial 1- the first recording, trial 2 - recording after one hour of the first trial, trial 3- recording after a week of first trial) and in the results, there were some interesting findings. The findings of the present study are discussed under following headings:

5.1 Prevalence of MMN

In the present study, MMN was present in about 50% to 70% of the total number of recordings. This prevalence varied across the three trials and between the two stimulus pairs. However, prevalence did not vary much between two electrode sites. Considering all the participants of the present study were ensured for normal hearing, middle ear functioning and normal auditory processing, one would expect that the MMN is present in 100% of the individuals. Further the contrasts taken as the stimuli were phonemic to all the participants in this study, and were easily behaviourally discriminable due to which again one would expect MMNs to be present in each of the recordings. The absence of MMN, in spite of controlling stimulus and subject related factors would suggest that the MMN is not a reliable measure for clinical use. However, the present data of prevalence lower than 80% is supported by the findings of the earlier studies. Dalebout and Fox (2001) reported a prevalence of 29% among 12 listeners. Uwer and Suchodoletz (2000) have visually observed the presence of MMN in 64% of the 15 children tested. There was also a difference in the prevalence across the three trials. This means in some of the individuals who had presence of MMN in one trial did not have in the other trials. This further supports that the reliability of MMN is not very good. The lower prevalence of MMN was true in the presence of obligatory responses in 100% of the recordings.

The exact reason for the absence of MMN in some of the normal individuals is not known. However one can speculate that due to its low amplitude nature (Licht & Horsley, 1998), it is difficult to obtain recordable MMNs in some of the individuals. Further, it has been reported in literature that the addition or subtraction of any two waveforms adds extraneous noise to the difference waveforms (Hall, 2007). MMN is always identified in the difference waveform derived from subtraction of frequent waveform from infrequent waveform. This probably is adding some kind of noise to the difference waveform which masks the low amplitude MMN. The third possibility for MMN being absent may be because, the currently used stimulus paradigm and the recording techniques are not ideal to get recordings of the MMN in 100% of the cases.

However, in the present study there was difference in the prevalence of MMN across the three trials. This difference cannot be justified by any of the above three reasons. The difference in prevalence across the three trials only means that there is inherent variability linked to MMN.

The absence of MMN in some of the normal individuals proves against MMN being a clinical tool. That is, if MMN is present, it means that the pre attentive sound discrimination is normal in that particular individual. But, if MMN is absent, it may not confirm the presence of an abnormality, as some of the normal individuals are also likely to have absent MMNs.

Overall, the results of the present study on prevalence of MMN, do not support its use as a clinical tool. However, if future research are attempted towards improving the recording techniques, one may find better prevalence of MMN.

5.2 Reliability of MMN

In the present study, reliability was tested on the group data as well as on individual data. The test-retest reliability was tested by comparing the MMNs across the three trials. Both intra session and inter session reliability was tested in the present study on group as well as individual data.

The comparison of the presence or absence of MMN across the three trials showed that there was a consistency in the MMN in terms of its presence or absence in only 4 of the 20 participants. That is, three of them showed presence of MMN in all three trials while one participant showed absence of MMN in all three trials. Rest of the participants were inconsistent across the three trials in terms of the presence of MMN. They showed the presence of MMN only in one or two trials. Therefore, going by the consistency of presence or absence of the MMN across the three trials, MMN is not a reliable response for clinical use.

Reliability at the group level was tested using repeated measures ANOVA, by comparing the group data across the three trials. Results revealed no significant difference in any of the 5 parameters of MMN, for both the electrode sites. This means that the group data obtained in the three trials were comparable and implies that there is a

good group level reliability of MMN. Earlier studies have shown that at group level, the test retest reliability of MMN was good (Pekkonen et al., 1995; Frodl –Bauch, Kathmann, Moller & Hegerl 1997; Joutsiniemi et al., 1998; Kathmann et al., 1999; Tervaniemi et al., 1999; Escara, Yago, Polo & Grau, 2000; Deouell & Bentin, 1998) for non speech stimuli. These studies varied frequency, duration and intensity deviances. Most of these studies obtained good reliability of MMN for duration deviance compared to frequency deviance. On the other hand, for speech stimuli, study done by Uwer and Suchodoletz (2000) have also reported that at group level reliability of MMN is good. The present study is in agreement with these studies.

The finding that there is a good group level reliability of MMN has important implication for research in MMN. This means that MMN is a reliable tool if one considers the group data. In research studies that compare across different groups or in those that compare across several conditions within the same group, MMN is expected to provide reliable and useful information. In short, it qualifies to be a good research tool provided one compares the group data.

The primary aim of the present study was to establish the test-retest reliability of MMN in the individual data. The reliability at the individual level was tested using Cronbach's alpha and Intra-Class Correlation (ICC). From the data of the present study, both intra-session and inter-session reliability were derived. The present study found that there is no correlation of MMN response across sessions at individual level for both intra and inter session comparisons. This means that the reliability of MMN at individual level

was found to be poor. The poor reliability was characteristic of all the parameters of MMN for both intra and inter-session comparisons. In support to the present study, Escera and Grau (1996) reported that replicability of MMN was poor for individual data across two sessions in spite of group level reliability being good.

The present finding of the reliability of MMN at the individual level is alarming to audiologists. MMN has been proven to be abnormal in several of the psychogenic and neurogenic disorders, such as schizophrenia, memory disorders, dyslexia, comatose patients etc. (Naatanen et al.,1978; Kujala, Kallio, Tervaniemi & Näätänen**,** 2007; Naatanen et al., 2007; Duncan et al., 2009). MMN has been used in assessing adult psychiatric disorders such as aphasia and dementia (Naatanen, 1995; Escera, 1997) and child psychiatry as in attention deficit disorder (Korpilahti & Lang, 1994; Kemner, Verbaten, Cuperus, Camffermanand, & Van Engeland, 1998), language impairment (Holopainen, Korpilahti, Juottonen, Lang & Sillanpaa, 1997), dyslexia (Schulte-Korne et al., 2001). Having known the vast utility of MMN, as in the literature, one would be tempted to use it as a clinical tool. For clinical purposes, the results of MMN would be used to infer about the auditory neural functioning at the individual level. Going by the results of the present study, it will not provide reliable information and therefore may mislead the clinical analysis of the condition and its interpretation. Therefore, based on the present findings, it is not advised to use MMN as a clinical tool. However, if future studies attempt to modify the test protocol so as to improve the reliability at the individual level, one would have to reconsider the present recommendation.

MMN has also been used as a tool to evaluate the effectiveness of auditory training in individuals with hearing loss. The change in the neural plasticity secondary to auditory training has been monitored using MMN. However, one is cautioned again about the poor test-retest reliability while using such a paradigm at the individual level. For example, if one gets a poor MMN before the training and a good MMN after the training, it can't be confirmed that the observed positive change is a training related improvement in MMN. The difference may be a mere coincident due to inherent variability of MMN.

There was no significant difference in the prevalence and the reliability of MMN elicited by /da/-/ga/ and /da/-/ta/ stimulus pairs. /da/- /ga/ differed in F2 transition and /da/-/ta/ differed in terms of voicing. Studies have shown that the reliability varies in terms of contrasts used (Kathmann, Frodl-Bauch & Hegerl, 1999). However in the present study there was no significant difference observed between the two stimulus pairs.

There were two electrode sites (Cz & Fz) used in the present study to record MMN. It was found that there was no significant difference between those two electrode sites. This may be because, the Cz and Fz may share the same scalp distribution for the stimulus used in the present study. Secondly, the standard deviation obtained for the data was more due to inherent variability of MMN. Hence there was no significant difference observed between Cz and Fz electrode sites.

Chapter 6

Summary and Conclusion

Mismatch negativity (MMN) is among the most researched event related potentials in the auditory neuroscience. There is enormous literature that has reported MMN as a sensitive tool in identifying neurogenic and psychogenic disorders. In spite of such strong literature support, its clinical utility is still questionable. In order to validate MMN as a clinical tool, it is important to establish its test-retest reliability. Therefore, aim of the present study was to establish the test retest reliability of speech elicited MMN.

Twenty normal hearing adults in the age range of 18 to 25 years participated in the study. MMNs were recorded in oddball paradigm using /da/-/ga/ and /da/-/ta/ stimulus pairs. They were recorded using standard acquisition parameters from Cz and Fz electrode sites.

In each participant, MMN was recorded 3 times (in 3 trials) with 1 hour gap between the first and second trial, and 1 week gap between the second and third trial. In each trial, apart from recording MMN in the oddball paradigm, an additional LLR was recorded for the stimulus used as infrequent in the oddball paradigm. The LLR and the infrequent wave of the MMN recording were then compared and a difference wave was derived by subtracting one from the other. The difference wave was independently analysed by 3 experienced audiologists to identify the MMN. If MMN was found to be

present, the response was analysed to note down its onset latency, peak latency, offset latency, peak amplitude and the area. The responses recorded in the 3 trials were analysed using repeated measures ANOVA and reliability measures (Crombach's Alpha and intra class correlations) to determine the group level and the individual level reliability of MMN and its parameters. The results of the present study can be summarised as follows,

1. The prevalence of MMN varied from 50% to 70% among the two stimulus pairs, two electrode sites (Cz & Fz) and across the three trials. The prevalence was different among the three trials.

2. There was no significant between the two electrode sites in any of the MMN response parameters. Results of repeated measures ANOVA did not reveal any significant difference in the MMNs elicited across three trials.

3. Results of Intra Class Correlation showed that there was no correlation among the MMNs recorded in two different trials. This was true in both intra session and inter session comparisions.

4. Results of Cronbach's alpha indicated poor reliability of MMN in both intra and inter session comparison.

The prevalence found in the present study is comparable with that of the prevalence reported in the literature. The lower prevalence can be attributed to the lower amplitude of MMN, addition of noise during subtraction process and inadequate

recording techniques. The difference in the prevalence of MMN across the three trials indicates that the MMN is characteristically has higher variability.

The comparable group data across the three trials as tested by repeated measures ANOVA indicates good group level reliability of MMN. This is in consensus with all the studies in the literature which have used correlational statistics and ANOVA and found good group level reliability. However, earlier studies speaks only about reliability of non-speech MMN while the present study speaks about speech MMN.

Results of the present study also showed poor individual level reliability of MMN in both intra and inter session comparisions. This was true for MMNs elicited for both the pairs of stimuli. This finding is again in agreement with the studies in the literature wherein poor individual reliability has been reported for non-speech MMNs.

From the findings of the present study, it can be concluded that MMN can not be a clinical tool in its present form. However, it has good group level reliability and therefore is a good research tool provided one does group comparisons.

References

Aaltonen, O., Niemi, P., Nyrke, T., & Tuhkanen, J. M. (1987). Event related brain potentials and the perception of a phonetic continuum. *Biological Psychology, 24*, 197–207

Alain, C., Woods, D. L., and Knight, R. T. 1998. A distributed cortical network for auditory sensory memory in humans. *Brain Res.* **812:**23–37.

Amenedo, E., & Escera, C. (2000). The accuracy of sound duration representation in the human brain determines the accuracy of behavioural perception. *European Journal of Neuroscience*, *12*(7), 2570-2574.

American National Standards Institute. (1999). Maximum permissible ambient noise levels for audiometric test rooms. ANSI S3.1- 1999 (R2003). New York: *ANSI*, Inc.

Carhart, R., & Jerger, J. (1959). Preferred method for clinical determination of pure-tone thresholds. *Journal of Speech & Hearing Disorders*, *24*, 330-345.

Cheour, M., Alho, K., Ceponiene, R., Reinikainen, K., Sainio, K., Pohjavuori, M., Aaltonen, O., Näätänen, R. (1998). maturation of mismatch negativity in infants. *International Journal of Psychophysiology, 29*, 217-226.

Cheour, M., Alho, K., Sainio, K., Reinikainen, K., Renlund, M., Aaltonen, O., ... & Näätänen, R. (1997). The mismatch negativity to changes in speech sounds at the age of three months. *Developmental Neuropsychology*, *13*(2), 167-174.

Cheour, M., Čeponien, R., Hukki, J., Haapanen, M. L., Näätänen, R., & Alho, K. (1999). Brain dysfunction in neonates with cleft palate revealed by the mismatch negativity. *Clinical neurophysiology*, *110*(2), 324-328.

Cheour-Luhtanen, M., Alho, K., Kujala, T., Sainio, K., Reinikainen, K., Renlund, M., Aaltonen, O., Eerola, O., Näätänen, R. (1995). Mismatch negativity indicates vowel discrimination in newborns. *Hearing Research, 82*, 53-58.

Cheour-Luhtanen, M., Alho, K., Sainio, K., Rinne, T., Reinikainen, K., Pohjavuori, M., Aaltonen, O., Eerola, O., & Näätänen, R. (1996). The ontogenetically earliest discriminative response of the human brain. *Psychophysiology*, *33*, 478–481.

Chertoff, M. E., Goldstein, R., & Mease, M. R. (1988). Early event-related potentials with passive subject participation. *Journal of Speech, Language, and Hearing Research*, *31*(3), 460-465.

Chhabra, V., & Maruthy, S. (2013). Mismatch Negativity for Nasal Contrasts in Native and Non native Individuals. Unpublished Master's Dissertation, University of Mysore

Colin, C., Hoonhorst, I., Markessis, E., Radeau, M., de Tourtchaninoff, M., Foucher, A.,

Colleta, G. & Deltenre, P. (2009). Mismatch negativity (MMN) evoked by sound duration contrasts: an unexpected major effect of deviance direction on amplitudes. *Clinical neurophysiology*, *120*(1), 51-59.

Dalebout, S. D., & Fox, L. G. (2000). Identification of the mismatch negativity in the responses of individual listeners. *Journal-American academy of Audiology*, *11*(1), 12-22.

Dalebout, S. D., & Fox, L. G. (2001). Reliability of the mismatch negativity in the responses of individual listeners. *Journal American academy of Audiology*, *12*(5), 245- 253.

Dehaene-Lambertz, G. (1997). Electrophysiological correlates of categorical phoneme perception in adults. *NeuroReport*, *8*(4), 919-924.

Deouell, L. Y., Bentin, S., & Giard, M. H. (1998). Mismatch negativity in dichotic listening: evidence for interhemispheric differences and multiple generators. *Psychophysiology*, *35*(04), 355-365.

Deouell, L. Y., Bentin, S., & Giard, M. H. (1998). Mismatch negativity in dichotic listening: evidence for interhemispheric differences and multiple generators. *Psychophysiology*, *35*(04), 355-365.

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Näätänen, R., & Van

Endrass, T., Mohr, B. & Pulvermüller, F. (2004). Enhanced mismatch negativity brain response after binaural word presentation. *European Journal of Neuroscience, 19,* 1653-1660.

Escera, C., & Grau, C. (1996). Short-term replicability of the mismatch negativity. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *100*(6), 549-554.

Escera, C., Alho, K., Winkler, I., & Näätänen, R. (1998). Neural mechanisms of involuntaryattention to acoustic novelty and change. *Journal of cognitive neuroscience*, *10*(5), 590-

Escera, C., Yago, E., & Alho, K. (2001). Electrical responses reveal the temporal dynamics of brain events during involuntary attention switching.*European Journal of Neuroscience*, *14*(5), 877-883.

Escera, C., Yago, E., Polo, M. D., & Grau, C. (2000). The individual replicability of mismatch negativity at short and long inter-stimulus intervals.*Clinical Neurophysiology*, *111*(3), 546-551.

Frodl-Bauch, T., Kathmann, N., Möller, H. J., & Hegerl, U. (1997). Dipole localization and test-retest reliability of frequency and duration mismatch negativity generator processes. *Brain Topography*, *10*(1), 3-8.

Giard, M. H., Perrin, F., Pernier, J., & Bouchet, P. (1990). Brain Generators Implicated in the Processing of Auditory Stimulus Deviance: A Topographic Event-Related Potential Study. *Psychophysiology*, *27*(6), 627-640.

Gomes, H., Sussman, E., Ritter, W., Kurtzberg, D., Cowan, N., & Vaughan Jr, H. G. (1999). Electrophysiological evidence of developmental changes in the duration of auditory sensory memory. *Developmental psychology*, *35*(1), 294.

Hall, James Wilbur. *New handbook of auditory evoked responses*. Pearson, 2007.

Hari, R., Hämäläinen, M., Ilmoniemi, R., Kaukoranta, E., Reinikainen, K., Salminen, J., Alho, K., Näätänen, R. & Sams, M. (1984). Responses of the primary auditory cortex to pitch changes in a sequence of tone pips: neuromagnetic recordings in man. Neuroscience *Letters*, *50*, 127-132.

Holopainen, I. E., Korpilahti, P., Juottonen, K., Lang, H., & Sillanpää, M. (1997). Attenuated auditory event-related potential (mismatch negativity) in children with developmental dysphasia. *Neuropediatrics*, *28*(5), 253-256.

Joutsiniemi, S. L., Ilvonen, T., Sinkkonen, J., Huotilainen, M., Tervaniemi, M., Lehtokoski, A., Rinne, T. & Näätänen, R. (1998). The mismatch negativity for duration decrement of auditory stimuli in healthy subjects. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *108*(2), 154-159.

Kathmann, M., Bauer, U., Schlicker, E., & Göthert, M. (1999). Cannabinoid CB1 receptor-mediated inhibition of NMDA-and kainate-stimulated noradrenaline and dopamine release in the brain. *Naunyn-Schmiedeberg's archives of pharmacology*, 359(6), 466-470.

Kathmann, N., Frodl-Bauch, T., & Hegerl, U. (1999). Stability of the mismatch negativity under different stimulus and attention conditions.*Clinical Neurophysiology*, *110*(2), 317-323.

Kemner, C., Verbaten, M. N., Cuperus, J. M., Camfferman, G., & Van Engeland, H. (1998). Abnormal saccadic eye movements in autistic children.*Journal of Autism and Developmental Disorders*, *28*(1), 61-67.

Korpilahti, P., & Lang, H. (1994). Auditory ERP components and mismatch negativity in dysphasic children. *Electroencephalography and Clinical Neurophysiology*, *91*, 256–264.

Korpilahti, P., & Lang, H. A. (1994). Auditory ERP components and mismatch negativity in dysphasic children. *Electroencephalography and Clinical Neurophysiology*, *91*(4),256- 264.

Korpilahti, P., Krause, C. M., Holopainen, I., & Lang, A. H. (2001). Early and late mismatch negativity elicited by words and speech-like stimuli in children.*Brain and language*, *76*(3), 332-339.

Krauel, K., Schott, P., Sojka, B., Pause, B. M., & Ferstl, R. (1999). Is there a mismatch negativity analogue in the olfactory event-related potential?.*Journal of Psychophysiology*, *13*(1), 49-55.

Kraus, N., McGee, T. J., Carrell, T. D., Zecker, S. G., Nicol, T. G., & Koch, D. B. (1996). Auditory neurophysiologic responses and discrimination deficits in children with learning problems. *Science*, *273*(5277), 971-973.

Kraus, N., McGee, T., Carrell, T. D., King, C., Tremblay, K., & Nicol, T. (1995). Central auditory system plasticity associated with speech discrimination training. *Journal of Cognitive Neuroscience*, *7*(1), 25-32.

Kraus, N., McGee, T., Ferre, J., Hoeppner, J. A., Carrell, T., Sharma, A., & Nicol, T. (1993). Mismatch negativity in the neurophysiologic/behavioral evaluation of auditory processing deficits: a case study. *Ear and hearing*,*14*(4), 223-235.

Kraus, N., McGee, T., Sharma, A., Carrell, T., & Nicol, T. (1992). Mismatch negativity event-related potential elicited by speech stimuli. *Ear and hearing*, *13*(3), 158-164.

Kujala, T., Aho, E., Lepistö, T., Jansson-Verkasalo, E., Nieminen-von Wendt, T., von Wendt, L., & Näätänen, R. (2007). Atypical pattern of discriminating sound features in adults with Asperger syndrome as reflected by the mismatch negativity. *Biological psychology*, *75*(1), 109-114.

Kujala, T., Kallio, J., Tervaniemi, M., & Näätänen, R. (2001). The mismatch negativity as an index of temporal processing in audition. *Clinical Neurophysiology*, *112*(9), 1712-1719.

Kujala, T., Karma, K., Ceponiene, R., Belitz, S., Turkkila, P., Tervaniemi, M., & Näätänen, R. (2001). Plastic neural changes and reading improvement caused by audiovisual training in reading-impaired children. *Proceedings of the National Academy of Sciences*, *98*(18), 10509-10514.

Kujala, T., Tervaniemi, M., & Schröger, E. (2007). The mismatch negativity in cognitive and clinical neuroscience: theoretical and methodological considerations. *Biological psychology*, *74*(1), 1-19.

Lang, A. H., Eerola, O., Korpilahti, P., Holopainen, I., Salo, S., & Aaltonen, O. (1995). Practical issues in the clinical application of mismatch negativity. *Ear and Hearing*, *16*(1), 118- 130.

Lang, H., Nyrke, T., Ek, M., Aaltonen, O., Raimo, I., & Näätänen, R. (1990). Pitch discrimination performance and auditory event-related potentials.*Psychophysiological brain research*, *1*, 294-298.

Licht, R., & Horsley, T. M. (1998). Mismatch Negativity as a tool in studying auditoty phonological processing in reading disability. *Child Neuropsychology, reading Disability and more. Delft: Eburon*, 85-105.

Maiste, A., Wiens, A. S., Hunt, M. J., Scherg, M., & Picton, T. W. (1995). Event-related potentials and the categorical perception of speech sounds. *Ear and Hearing, 16*, 68–90.

Mäntysalo, S., & Näätänen, R. (1987). The duration of a neuronal trace of an auditory stimulus as indicated by event-related potentials. *Biological psychology*, *24*(3), 183-195.

Martin, B. A., Sigal, A., Kurtzberg, D., & Stapells, D. R. (1997). The effects of decreased audibility produced by high-pass noise masking on cortical event-related potentials to speech sounds/ba/and/da. *The Journal of the Acoustical Society of America*, *101*(3), 1585-1599.

Maruthy, S., & Vanaja, C. S. (2003). Auditory log latency responses in children with learning disability, Unpublished Master's Dissertation, University of Mysore, Mysore.

Na¨a¨ta¨nen, R., and Michie, P. T. 1979. Early selective-attention effects on the evoked potential: A critical review and reinterpretation.*Biol. Psychol.* **8:**81–136.

Na¨a¨ta¨nen, R., Gaillard, A. W. K., and Ma¨ntysalo, S. 1978. Earlyselective-attention effect on evoked potential reinterpreted. *ActaPsychol.* **42:**313–329.

Na¨a¨ta¨nen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A., Valnio, A., Alku, P., Ilmoniemi, R. J., Luuk, A., Allik, J., Sinkkonen, J., and

Alho, K. 1997. Language-specific phoneme representations revealed by electric and magnetic brain responses. Nature 385: 432–434.

Näätänen, R. (1990). The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. Behavioral and Brain Sciences, 13, 201–288.

Näätänen, R. (1992). Attention and Brain Function. *Hillsdale*, NJ: Lawrence Erlbaum Associates.

Näätänen, R. (1992). *Attention and brain function*. Psychology Press.

Näätänen, R. (1995). The mismatch negativity: a powerful tool for cognitive neuroscience. *Ear and hearing*, *16*(1), 6-18.

Näätänen, R. (2000). Mismatch negativity (MMN): perspectives for application. *International Journal of Psychophysiology*, *37*(1), 3-10.

Näätänen, R., & Alho, K. (1995). Mismatch negativity: A unique measure of sensory processing in audition. International Journal of Neuroscience, 80, 317–337.

Näätänen, R., & Escera, C. (2000). Mismatch negativity: Clinical and other applications. Audiology and Neuro-Otology, 5, 105–110.

Näätänen, R., & Michie, P. T. (1979). Early selective-attention effects on the evoked potential: a critical review and reinterpretation. *Biological psychology*, *8* (2), 81-136.

Näätänen, R., & Winkler, I. (1999). the concept of auditory stimulus representation in cognitive neuroscience. *Psychological Bulletin*, *6*, 826–859.

Näätänen, R., Gaillard, A. W. K., & Mantysalo, S. (1978). Early selective attention effects on the evoked potential reinterpreted. *Acta Psychologia*, *42*, 313-329.

Näätänen, R., Kujala, T., Kreegipuu, K., Carlson, S., Escera, C., Baldeweg, T., & Ponton, C. (2011). The mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing. *Brain*, *134*(12), 3435-3453.

Näätänen, R., Lehtoskoskl, A., Lennes, M., Cheour, M., Huotilainen, M., Ilvonen, A., Vainio, M., Alku, P., Ilmoniemi, R., Luuk, A., Allik, J., Sinkkonen, J., & Alho, K. (1997). Language-specific phoneme representations revealed by electric and magnetic brain responses. *Nature, 385,* 432–434.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K., & Sams, M. (1989). Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain?. *Neuroscience letters*, *98*(2), 217-221.

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clinical Neurophysiology, 118*(12), 2544-2590.

Näätänen, R., Simpson, M., & Loveless, N. E. (1982). Stimulus deviance and evoked potentials. *Biological Psychology, 14,* 53-98.

Novitski, N., Tervaniemi, M., Huotilainen, M., & Näätänen, R. (2004). Frequency discrimination at different frequency levels as indexed by electrophysiological and behavioral measures. *Cognitive Brain Research,20*(1), 26-36.

Paavilainen, P., Karlsson, M. L., Reinikainen, K. & Näätänen, R. (1989). Mismatch negativity to change in spatial location of an auditory stimulus. *Electroencephalography and Clinical Neurophysiology, 73,* 129- 141.

Pakarinen, S., Lovio, R., Huotilainen, M., Alku, P., Näätänen, R., & Kujala, T. (2009). Fast multi-feature paradigm for recording several mismatch negativities (MMNs) to phonetic and acoustic changes in speech sounds. *Biological psychology*, *82*(3), 219-226.

Pakarinen, S., Takegata, R., Rinne, T., Huotilainen, M., & Näätänen, R. (2007). Measurement of extensive auditory discrimination profiles using the mismatch negativity (MMN) of the auditory event-related potential (ERP).*Clinical Neurophysiology*, *118*(1), 177-185.

Pang, B., Lee, L., & Vaithyanathan, S. (2002, July). Thumbs up ?: sentiment classification using machine learning techniques. In *Proceedings of the ACL-02 conference on Empirical methods in natural language processing*, *10* (79-86). Association for Computational Linguistics.

Pang, E. W., Edmonds, G. E., Desjardins, R., Khan, S. C., Trainor, L. J., & Taylor, M. J. (1998). Mismatch negativity to speech stimuli in 8-month-old infants and adults. *International Journal of Psychophysiology*, *29*(2), 227-236.

Pekkonen, E., Rinne, T., & Näätänen, R. (1995). Variability and replicability of the mismatch negativity. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *96*(6), 546-554.

Petten, C. (2009). Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology*, *120*(11), 1883-1908.

Ponton, C. W., Don, M., Eggermont, J. J., & Kwong, B. (1997). Integrated mismatch negativity (MMN i): a noise-free representation of evoked responses allowing single-point distribution-free statistical tests. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *104*(2), 143-150.

Ponton, C. W., Eggermont, J. J., Kwong, B., & Don, M. (2000). Maturation of human central auditory system activity: evidence from multi-channel evoked potentials. *Clinical Neurophysiology*, *111*(2), 220-236.

Rajashekar & Vyasamurthy, M. N. (1976). Development and Standarization of A Picture SRT Test For Adults and Children In Kannada. Unpublished Master's Dissertation, University of Mysore, Mysore.

Rinne, T., Alho, K., Ilmoniemi, R. J., Virtanen, J., & Näätänen, R. (2000). Separate time behaviors of the temporal and frontal mismatch negativity sources. *Neuroimage, 12*(1), 14-19.

Sams, M., Aulanko, R., Aaltonen, O., & Näätänen, R.(1990). Event-related potentials to infrequent changes in phonetic features of synthetic CV stimuli. *Journal of Cognitive Neuroscience, 2*, 344–357.

Sams, M., Hämäläinen, M., Antervo, A., Kaukoranta, E., Reinikainen, K., & Hari, R. (1985).Cerebral neuromagnetic responses evoked by short auditory stimuli. *Electroencephalography and clinical neurophysiology*, *61*(4), 254-266.

Sams, M., Paavilainen, P., Alho, K., & Näätänen, R. (1985). Auditory frequency discrimination and event-related potentials. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *62*(6), 437-448.

Schroger, E. (1996). Interaural time and level differences: integrated or separated processing *Hearing research*, *96*(1), 191-198.

Schulte-Körne, G., Deimel, W., Bartling, J., & Remschmidt, H. (2001). Speech perception deficit in dyslexic adults as measured by mismatch negativity (MMN). *International Journal of Psychophysiology*, *40*(1), 77-87.

Schulte-Körne, G., Deimel, W., Bartling, J., & Remschmidt, H. (2001). Speech perception deficit in dyslexic adults as measured by mismatch negativity (MMN). *International Journal of Psychophysiology*, *40*(1), 77-87.

Shafer, V. L. (2004). Language specific memory traces of consonants in the brain. Cognitive Brain Research, 18 (3), 242- 254.

Sharma, A., & Dorman, M. F. (1999). Cortical auditory evoked potential correlates of categorical perception of voice-onset time. *Journal of the Acoustical Society of America, 106,* 1078–1083.

Sharma, A., & Dorman, M. F. (2000). Neurophysiologic correlates of cross-language phonetic perception. *The Journal of the Acoustical Society of America*, *107*(5), 2697-2703.

Shtyrov, Y., Pulvermüller, F., Näätänen, R., & Ilmoniemi, R. J. (2003). Grammar processing outside the focus of attention: an MEG study. *Journal of Cognitive Neuroscience*, *15*(8), 1195-1206.

Tervaniemi M, Kujala A, Alho K, Virtanen J, Ilmoniemi RJ, Näätänen R. (1999). Functional specialization of the human auditory cortex in processing phonetic and musical sounds: A magnetoencephalographic (MEG) study. *Neuroimage*, 9,330–336.

Tervaniemi, M., Just, V., Koelsch, S., Widmann, A., & Schröger, E. (2005). Pitch discrimination accuracy in musicians vs nonmusicians: an event-related potential and behavioral study. *Experimental brain research*, *161*(1), 1-10.

Tervaniemi, M., Lehtokoski, A., Sinkkonen, J.,Virtanen, J., Ilmoniemi, R. J., and Näätänen, R. (1999). Test-retest reliability of mismatch negativity for duration, frequency, and intensity changes. *Clinical Neurophysiology, 110*, 1388–1393.

Tervaniemi, M., Schröger, E., Saher, M., & Näätänen, R. (2000). Effects of spectral complexity and sound duration on automatic complex-sound pitch processing in humans–a mismatch negativity study. *Neuroscience letters*, *290*(1), 66-70.

Tiitinen, H., May, P., Reinikainen, K., & Näätänen, R. (1994). Attentive novelty detection in humans is governed by pre-attentive sensory memory.

Tremblay, K., Kraus, N., & McGee, T. (1998). The time course of auditory perceptual learning: europhysiological changes during speech-sound training. *Neuroreport*, *9*(16), 3557- 3560.

Tremblay, K., Kraus, N., Carrell, T. D., & McGee, T. (1997). Central auditory system plasticity: generalization to novel stimuli following listening training.*The Journal of the Acoustical Society of America*, *102*(6), 3762-3773.

Tremblay, L., Valenza, F., Ribeiro, S. P., Li, J., & Slutsky, A. S. (1997). Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *Journal of Clinical Investigation*,*99*(5), 944.

Uwer, R., & von Suchodoletz, W. (2000). Stability of mismatch negativities in children. *Clinical Neurophysiology, 111*(1), 45-52.

Vanaja, C. S., Sandeep, M. (2003). Auditory long latency response in children with learning disability. *Departmental Project*, University of Mysore, Mysore.

Walker, L. J., Carpenter, M., Downs, C. R., Cranford, J. L., Stuart, A., & Pravica, D. (2001). Possible neuronal refractory or recovery artifacts associated with recording the mismatch negativity response. *Journal of the American Academy of Audiology*, 12, 348-356.

Winkler, I., & Czigler, I. (1998). Mismatch negativity: deviance detection or the maintenance of the 'standard'. *NeuroReport, 9*(17), 3809-3813.

Winkler, I., Kujala, T., Tiitinen, H., Sivonen, P., Alku, P., Lehtokoski, A. (1999). Brain responses reveal the learning of foreign language phonemes. *Psychophysiology, 36*, 638–42.

Winkler, I., Lehtokoski, A., Alku, P., Vainio, M., Czigler, I., Cse´pe, V. (1999). Preattentive detection of vowel contrasts utilizes both phonetic and auditory memory representations. *Cognitive Brain Research ,7*, 357–69.

Winkler, I., Tervaniemi, M., & Näätänen, R. (1997). Two separate codes for missing-fundamental pitch in the human auditory cortex. *The Journal of the Acoustical Society of America*, *102*(2), 1072-1082.

Winkler, I., Tervaniemi, M., and Näätänen, R. (1997). two separate codes for missing-fundamental pitch in the human auditory cortex. *Journal of Acoustical Society of America, 102,* 1072–1082.

Wunderlich, J. L., & Cone-Wesson, B. K. (2001). Effects of stimulus frequency and complexity on the mismatch negativity and other components of the cortical auditory-evoked potential. *The Journal of the Acoustical Society of America, 109*(4), 1526-1537.

Yago, E., Escera, C., Alho, K. & Giard, M. H. (2001). Cerebral mechanisms underlying orienting of attention towards auditory frequency changes. *Neuroreport, 12*(11), 2583- 2587.

Yathiraj, A., & Vijayalakshmi, C.S. (2005). Phonemically Balanced wordlist in Kannada. Material developed in department of Audiology, All India Institute of Speech & Hearing, Mysore.