Optimizing the Angle of Gaze Elevation for Recording Ocular Vestibular Evoked Myogenic Potential

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This Dissertation is submitted as part fullfillment for the Degree of Master of Science in Audiology University of Mysore, Mysore

May 2015

CERTIFICATE

This is to certify that this dissertation entitled "**Optimizing the Angle of Gaze Elevation for Recording Ocular Vestibular Evoked Myogenic Potential**" is the bonafide work submitted in part fulfillment for the Degree of Master of Science (Audiology) of the student with Registration No: **13AUD028**. This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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CERTIFICATE

This is to certify that this dissertation entitled "**Optimizing the Angle of Gaze Elevation for Recording Ocular Vestibular Evoked Myogenic Potential**" 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.

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DECLARATION

This is to certify that this Master's dissertation entitled "**Optimizing the Angle of Gaze Elevation for Recording Ocular Vestibular Evoked Myogenic Potential**" is the result of my own study under the guidance of Mr. Niraj Kumar Singh, Lecturer 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: 13AUD028

Dedication

Dedicated to my Mamma-Baba, Fathi di, Ali and Shahbaz Bhaiya

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ABSTRACT

The ocular vestibular-evoked myogenic potentials (oVEMP) are short latency biphasic negative-positive myogenic response. These potentials are widely used to assess the otolith function in individuals with several vestibular pathologies. Nevertheless there is a lack of well accepted protocol for recording oVEMP. Among the several studies done for identifying the efficacy of oVEMP in clinical settings, large variability in the use of stimulus and recording parameters can be noticed. One such parameter is the gaze elevation angle. Therefore, the present study aimed at investigating the effect of different gaze elevation angles on oVEMP response parameters and to identify the optimal gaze elevation angle for recording of oVEMP. For this, oVEMPs were recorded for eight gaze angles from -5^{o} to 30^{o} (in steps of 5^{o}; with reference to the horizontal) from both ears of 50 healthy individuals (age range = 18-35 years). Tone-bursts of 500 Hz were presented at 125 dB SPL and the responses were recorded from the electrodes placed beneath the eye contralateral to the stimulus ear. The results revealed significant increase in the response rate, peak-to-peak amplitude and signal-to-noise ratio of the oVEMP waveform with increase in the gaze elevation angle ($p < 0.05$). Further, there was shortening of n1 and p1 latencies with increase in the gaze elevation angle ($p < 0.05$). For most of the oVEMP response parameters, the increase in the gaze elevation angle beyond 20^{o} did not result in any significant variation in the oVEMP response parameters. This implicates that using the gaze elevation angle of 20^{o} is sufficient for clinical recording of oVEMPs and changes beyond this angle will not affect the responses significantly.

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Chapter 1

Introduction

The vestibular system consists of utricle, saccule and the semicircular canals. It is mainly responsible for maintenance of balance during head and/or body acceleration (McCrea, & Cullen, 1992; Cohen, Maruta, & Raphan, 2001). The vestibular system has strong connections with the neck and the eye muscles and the activity in these muscles are modulated by the vestibulocollic reflex and vestibulo-ocular reflex, respectively (Colebatch, Halmagyi, & Skuse, 1994; Rosengren, Todd, & Colebatch, 2005). The vestibulocollic reflex pathway consists of the inferior vestibular nerve originating from the saccule, and travelling to the sternocleidomastoid muscle of the neck via vestibular nuclei (Colebatch et al., 1994; Kushiro, 1999; Todd, Cody, & Banks, 2000; Zhou & Cox, 2004). On the other hand, the vestibulo-ocular reflex pathway ascends from the level of utricle where the superior vestibular nerve emerges and reaches the vestibular nuclear complex, traveling further into the medial longitudinal fasciculus and crossing over to the extraocular muscle via the cranial nerve III, IV and VI (Curthoys et al., 2011; Govender & Colebatch, 2012). The activation of these reflex pathways causes modulations in the activity of the muscles involved (Rosengren, Welgampola, & Colebatch, 2010). Vestibular evoked myogenic potentials (VEMP) are the result of such modulations in neck and eye muscles and therefore have been used for the assessment of these pathways (Colebatch et al., 1994; Kushiro, 1999; Todd et al., 2000; Zhou & Cox, 2004; Hall, 2007).

VEMPs are obtained by presenting high intensity sounds, usually 125 dB SPL or greater, which stimulates the vestibular system, mainly the otolith organs (Colebatch et al., 1994; Murofushi & Curthoys, 1997; Todd et al., 2000; Welgampola & Colebatch, 2001). These responses were earlier recorded only from the sternocledomastoid muscle and were termed as cervical VEMP (Colebatch et al., 1994). The cervical VEMP (cVEMP) consists of an initial positive peak at a latency of around 13 ms which is (labelled as P13 or P1) followed by a negative peak having a latency of around 23 ms labelled as N23 or N1 (Colebatch et al., 1994; Todd et al., 2000). It mainly assesses the functioning of the saccule and the integrity of the saculocollic reflex pathway (Colebatch et al., 1994; Murofushi & Curthoys, 1997; Todd et al., 2000; Welgampola & Colebatch, 2001). VEMP can also be recorded from extra-ocular muscles, mainly the inferior oblique muscle, in which case it is referred as ocular VEMP (Rosengren et al., 2005; Todd, Rosengren, & Colebatch, 2007).

The ocular VEMP (oVEMP) is a biphasic negative-positive myogenic response with a negativity around 10 ms, referred as n1, and positivity at approximately 15 ms, called p1 (Chihara, Iwasaki, Ushio, & Murofushi, 2007; Walther, Rogowski, Hormann, & Lohler, 2011). Elsewhere in literature, these negative and positive peaks are also termed as n10 and p15 respectively (Todd, Rosengren, & Colebatch, 2003) based on their average latency of onset.

The oVEMP responses have been reported to be abnormal in cases with vestibular neuritis (Govender, Rosengren, & Colebatch, 2011; Shin et al, 2012), Menier's disease (Rauch, Zhou, Kujawa, Guinan, & Herrmann, 2004; Timmer et al, 2006), Benign Paroxysmal positional vertigo (Nakahara, Yoshimura, Tsuda, & Murofushi, 2013; Seo, Saka, Ohta, & Sakagami, 2013) etc. Hence, oVEMP can be considered as a reliable and valid tool to assess the functioning of utricle and ocular reflex pathway (Todd, Rosengren, & Colebtach, 2003; Nguyen, Welgampola, & Carey, 2010).

1.1. Need of the study

There are several factors that can affect the amplitude, and to some extent the absolute peak latency, during the oVEMP recording. These can be broadly classified into stimulus related factors and subject related factors. Changes in stimulus related factors like decrease in the stimulus intensity, selecting click over 500 Hz tone-burst, use of tone-burst higher than 1000 Hz, using higher stimulus rate and shortening the stimulus duration have all been shown to reduce the oVEMP response amplitude (Sheykholeslami, Kermany, & Kaga, 2001; Rosengren et al., 2005; Chihara et al., 2007; Welgempola, Migliaccio, Myrie, Minor, & Carey, 2009; Wang, Jaw, & Young, 2009; Park, Lee, Shin, Lee, & Park, 2010; Murnane, Akin, Kelly, Kip & Stephanie, 2011). Likewise subject related factors like advancing age, reduced muscle tonicity, presence of middle ear pathology, selecting ipsilateral recording over contralateral and oVEMPs recorded with patient in supine position have also shown to reduce the response amplitude (Angelaki, 2004; Murnane et al., 2011; Tseng et al., 2010; Nyugen et al., 2010; Piker et al., 2010; Jerin & Gurkoy 2014; Taylor, Xing, Black, Halmagyi, & Welgampola, 2014).

While some of the stimulus and subject related parameters have been reported to alter the oVEMP responses more subtely, others have been found to effect the oVEMP response parameters more drastically. One of the subject related parameters that has been deemed most important for successful recording of oVEMP is the angle of gaze elevation (Govender et al., 2009; Welgampola et al., 2009; Murnane et al., 2011; Rosengren et al., 2013; Kantner, & Gurkov, 2014).

Govender et al (2009) studied the effect of gaze elevation on air-conduction oVEMPs in 10 healthy individuals. Tone-bursts of 500 Hz with rise/fall time of 2-ms were presented at 136-142 dB peak SPL. The oVEMPs were recorded from the eye contralateral to the stimulus ear at various gaze elevation angles ranging from 20^o upward gaze to 20^o downward gaze in 5^o to10^o steps. The results revealed a significant trend for increasing amplitude with increase in upward gaze angle. Further, there was no significant difference in latencies between various gaze angles. However the study did not precisely quantify the angle for the maximum upward or downward gaze or other gaze elevations used for oVEMP recording. Additionally, the conclusions were based on a small sample size which could make generalization eronious.

Later, Murnanre et al (2011) obtained 500 Hz tone-burst evoked oVEMPs from one ear of each subject (17 subjects, 8 right ears & 9 left ears) at gaze elevations of 0^o, 15^o and 30^o. Results revealed a significant increase in the response rate and response amplitude with increase in the gaze elevation angle. They reported that the maximum peak-to-peak amplitude and response prevalence were obtained for contralateral oVEMPs during upward gaze elevation angle of 30^o. However the study evaluated oVEMP responses at only three gaze angles. The use of in between gaze angles might have yielded better understanding of differences in the oVEMP response parameters with changes in gaze elevation angle.

In yet another study, Rosengren et al (2013) investigated the effect of three different angles of gaze elevation on the amplitude of tone-burst evoked oVEMPs in 10 normal volunteers (3 females, 7 males; age range = 26 to 48 years). The angles used were 24^o upward gaze, 0^o neutral gaze and 24^o downward gaze. The results revealed a significant overall decline in oVEMP amplitude with 24^{o} down-gaze and the neutral gaze when compared to the upward gaze. They also reported a significant increase in response latencies in 24^{o} downward gaze when compared to 24^{o} upward gaze and the neutral gaze. Further, no significant difference in latency was found between 24^{o} upward gaze and 0^{o} neutral gaze. However, the study explored only three different gaze angles and it did not address the effect of increase in gaze elevation angle beyond 24^{o} upward gaze on oVEMP responses. Further, like Murnane et al (2011), this study did not examine the effect of steady increase in gaze elevation by using more number of in between angles between steps.

More recently, Kantner and Gurkov (2014) obtained oVEMPs on 32 healthy individuals at 30^{o}, 35^{o} and at maximal gaze elevation angle. Tone-bursts of 500 Hz were presented at 100 dB nHL and the responses were recorded from the electrodes placed beneath the eye contralateral to the stimulus ear. There was a significant increase in the response amplitude with increase in gaze angle from 30^{o} to 35^{o}. However, further increase in the gaze angle to the maximum elevation did not show any significant increase in response amplitude. There was no significant change in the latencies across the 3 gaze elevation angles. However, this study did not investigate the effect of gaze angles lower than 30^{o}.

Most of the above discussed studies were limited by the use of small sample size, especially considering they were normative data. Further, they were limited by the number of gaze elevation angles that were used. Also, most of the studies did not mention a precise method for measuring particular angles of the gaze elevation. Hence, there is a need to overcome these limitations and to have a more precise method of measuring gaze elevation angles to obtain accurate information regarding the effect of gaze elevation on oVEMPs from a large sample size.

1.2. Aim of the study

The study aimed at investigating the effect of different gaze elevation angles on oVEMP response parameters and to identify the optimal gaze elevation angle for recording of oVEMP.

1.3. Objectives of the study

1. To investigate the ear differences, if any, in oVEMP response rate at different gaze angles in healthy individuals.
2. To investigate the effect of gaze elevation on the oVEMP response rate in healthy individuals.
3. To investigate the ear differences, if any, and effect of gaze elevation on n1 and p1 latencies of oVEMP in healthy individuals.
4. To investigate the ear differences, if any, and effect of gaze elevation on the peak-to-peak amplitude of oVEMP in healthy individuals.
5. To investigate the ear differences, if any, and effect of gaze elevation on the signal-to-noise ratio of oVEMP waveforms obtained from healthy individuals.

1.4. Hypothesis

The present study was conducted to test the Null hypothesis (H_0) based on the above mentioned objectives. The Null hypothesis of the study are as follows:

1. There is no significant ear difference in the response rate of oVEMP at any gaze elevation angle in healthy individuals.

2. There is no significant effect of gaze elevation angle on the oVEMP response rate in healthy individuals.
3. There is no significant ear difference and no significant effect of gaze elevation on n1 and p1 latencies of oVEMP in healthy individuals.
4. There is no significant ear difference and no significant effect of gaze elevation angle on peak-to-peak amplitude of oVEMP in healthy individuals.
5. There is no significant ear difference and no significant effect of gaze elevation angle on signal-to-noise ratio of oVEMP waveforms obtained from healthy individuals.

Chapter 2

Literature Review

The inner ear consists of end organs for hearing, called cochlea and also the end organ for balance, called the vestibular system. The vestibular system consists of three semicircular canals and two otolith organs- utricle and saccule. While the utricle and saccule help in maintenance of balance during linear acceleration of head, the semicircular canals are useful in balance sustenance during angular acceleration in various planes (McCrea & Cullen, 1992; Cohen et al., 2001). Whenever there is a dysfunction of anyone or more of these organs, a balance deficit is perceived.

Balance deficits can be assessed by a host of tests, some of which are behavioral in nature where as others include electrophysiological assessment. Some of the well-known tests that include behavioral evaluation of balance function are Romberg test, Fukuda stepping test, Past pointing test and the Tandem gait test. Although these have been found to be useful in assessment of overall balance sustaining ability of an individual (Black, Wall III, Rockette Jr, & Kitch, 1982; Bonnani & Newton, 2006), they do not provide information that could be specific to a particular balance system (among vision, vestibular,& balance systems). This problem is rarely encountered with the use of electrophysiological tests, most of which provide information that are specific to not only vestibular system as a whole, but also specific to sub-components within the vestibular system (Mohsen et al., 2011). One such vestibular measure is VEMP.

VEMP is a vestibular potential that is believed to represent the functionality, or lack of it, of the otolith organs (Colebatch et al., 1994; Todd et al., 2000). It can be recorded from various muscles of the body which includes sternocledomastoid muscle (Colebatch et al., 1994), triceps muscle (Rudisill & Hain, 2008), trapezius muscle (Ferber, Virat, Duclaux, Colleaux, & Dubreuil, 1997) and splenius capitis (Wu, Young, & Murofushi, 1999). When recorded from the SCM muscle in response to intense acoustic, bone-conduction or galvanic stimuli, this myogenic response is called Cervical VEMP (cVEMP).

The cVEMP waveform consists of an initial positive peak (P1) at a latency of about 13 ms which is followed by a negative peak (N1) at a latency of nearly 23 ms (Colebatch & Halmagyi, 1992; Colebatch et al., 1994). It represents the saccule's response to sounds, vibration or electricity (Colebatch et al., 1994; Murofushi & Curthoys, 1997; Todd et al., 2000; Welgampola & Colebatch, 2001). The pathway involved in recording cVEMPs is primarily ipsilateral (Halmagyi & Curthoys, 1999) and involves the inferior vestibular nerve, vestibular nucleus and the medial vestibulo-spinal tract that supplies the neck muscles (Colebatch et al., 1994; Murofushi & Curthoys, 1997; Todd et al., 2000; Welgampola & Colebatch, 2001). As mentioned earlier, VEMPs can also be recorded from the inferior obligue muscle, in which case they are termed as ocular VEMP (Rosengren et al., 2005; Todd et al., 2007).

The oVEMPs are relatively recent advancement in the assessment of vestibular pathways. Initially Todd et al (2003) recorded a vestibular evoked potential from normal hearing individuals using 500 Hz bone-conduction stimulus with peri-ocular electrode.

The response waveform consisted of a negative peak at 10 ms and a positive peak at around 15 ms. Later Rosengren et al (2005) postulated that these responses were evoked by the vestibular system, more specifically from the saccule. They further reported that the responses varied with alteration in the gaze direction. However, later researches confirmed that the response was elicited from the vestibulo-ocular reflex pathway (Rosengren et al., 2005; Todd et al., 2007; Welgampola et al., 2009; Chihara et al., 2009). The more recent studies have tilted the belief in favor of utricle being the main generator end organ (Welgampola & Carey, 2009; Todd, Rosengren, & Colebatch, 2010; Curthoys, Vulovic, & Manzari, 2012)

The vestibulo-ocular reflex pathway ascends from the level of utricle where the superior vestibular nerve emerges and reaches the vestibular nuclear complex, traveling further into the medial longitudinal fasciculus. These fibres decussate at some point, to end at the oculomotor nuclei. The descending fibres then travel via the ocular nerve to reach the extraocular muscles. The activation of these reflex pathways causes modulations in the activity of the involved muscles (Rosengren et al., 2010). Ocular VEMPs are the result of such modulations in the eye muscles and therefore have been used for the assessment of these pathways (Murofushi, Wakayama, & Chihara, 2010; Murofushi, Nakahara, Yoshimura, & Tsuda, 2011; Moon, Lee, Park, & lee, 2012; Khalil & Kabarity, 2014; Singh & Barman, 2015).

There are several factors that affect the oVEMP response parameters. These factors can be mainly categorized into stimulus related and subject related parameters. Changes in the stimulus related parameters like reducing the stimulus intensity

(Rosengren et al., 2005; Chihara et al., 2007; Welgempola et al., 2009; Murnane et al., 2011), using high frequency tone-burst stimulus above 500 Hz (Wang et al., 2009; Chihara et al., 2009; Park et al., 2010), reducing the stimulus duration (Lee et al., 2008; Cheng et al., 2012) and increasing the repetition rate beyond 5.1 Hz (Singh, Kadisonga, & Ashitha, 2014) have all been shown to reduce the oVEMP response rate and response amplitude. However, studies regarding the effect of the above mentioned parameters on n1 and p1 peak latencies have reported variable results. Few studies show a significant prolongation of the peak latency (Rosengren et al., 2005; Chihara et al., 2007; Welgampola et al., 2009), whereas most of the studies report no significant effect of the above mentioned stimulus parameters on the peak latencies (Lee et al., 2008; Chihara et al., 2009; Murnane et al., 2011; Singh et al., 2014).

Along with the stimulus related factors, changes in the subject related factors have also been reported to affect the oVEMP responses. Advancing age, reduced muscle tonicity, presence of middle ear pathology, selecting ipsilateral recording over contralateral and oVEMPs recorded with patient in supine position have also been shown to reduce the response rate and response amplitude (Angelaki, 2004; Taylor et al., 2007; Tseng et al, 2010; Nyugen et al, 2010; Piker et al, 2010; Murnane et al., 2011; Jerin, & Gurkoy 2013). However there are differences among studies regarding to effect of gender on oVEMP. Few studies reported increased response amplitude in males than females but no significant difference in any other oVEMP response parameters (Sung, Cheng, & Young, 2011; Xie, Xu, Bi, Jia, Zheng, & Zhang, 2011), whereas others report no significant gender difference on oVEMP responses (Piker et al., 2011).

One of the subject related parameters that is most important for successful recording of oVEMP is the angle of gaze elevation. There are quite a few studies regarding the effects of gaze angle elevation on oVEMP response parameters (Govender et al., 2009; Welgampola et al., 2009; Murnane et al., 2011; Rosengren et al., 2013; Kantner & Gurkov, 2014), but each of them have used different gaze angles.

Govender et al (2009) studied theeffect of gaze elevation on the oVEMP response parameters. Air-conduction oVEMPs were obtained from 10 healthy subjects using electrodes placed beneath the eyes. The stimuli used were 500 Hz tone-bursts with a rise/fall time of 2 ms that were presented to the ears at 136–142 dB peak SPL. Angles of vertical gaze was varied from maximum downward (-20^o) to maximum upward gaze (+20^o upward gaze) in increments of 5^o–10^o. They reported that increasing the vertical gaze angle increased the oVEMP amplitude. There was a two-three fold increase in amplitude when the gaze elevation angle was increased from 0^o to 20^o. Further, they also found that oVEMP response rate reduced significantly with decrease in gaze elevation angle. However the study did not precisely quantify the angle for the maximum upward or downward gaze or other gaze elevations used for oVEMP recording, as it could vary from individual to individual. Further, the study was limited in its implication owing to the use of a small study sample.

Murnane et al (2011) obtained oVEMPs from one ear of each subject (17 subjects; 8 right ears & 9 left ears) at gaze elevations of 0^o, 15^o and 30^o. Tone-bursts of 500 Hz were presented at an intensity of 125 dB peSPL for eliciting oVEMP. The results revealed a significant effect of gaze angle elevation on both amplitude and latencies of oVEMP. They reported that there was a significant increase in peak-to-peak amplitude, and reduction in p1 latency with increase in gaze elevation angle from 0^o to 30^o. Also, the response rate increased with the increase in the gaze elevation angle from 0^o to 30^o. They concluded that the maximum peak-to-peak amplitude and response prevalence were obtained for contralateral oVEMPs using a 500 Hz tone-burst presented at 125 dB peak SPL during upward gaze of 30^o. However, the study examined the effect of only three gaze elevation angles on oVEMP response. Further, the results of the study cannot be generalized as it included only limited number of subjects, especially considering it was a normative study.

Rosengren et al (2013) evaluated the effect of gaze angle elevation on oVEMPs. Bone-conduction oVEMPs were obtained form 10 normal volunteers (3 female, 7 males; age range 26 to 48 years) at three gaze elevation angles: 24^o upward gaze, 0^o neutral gaze and 24^o downward gaze. A visual target was placed at a distance of 1 meter from the subject, at the above mentioned gaze elevation angles. The subject's task was to fixate the gaze at the target during the recording. Results revealed 100% response rate with the up-ward gaze. The response rate significantly decreased with decrease in gaze elevation angle. They also reported that there was a significant reduction in amplitude with progressive downward gaze. Further the peak latencies were significantly prolonged for oVEMPs recorded with downward gaze when compared to the up-ward gaze. However the study evaluated the effect of only three gaze elevation angles on bone-conduction oVEMPs and it limited its maximum gaze elevation angle to 24^o. Further, the results of the study cannot be generalized as the study included limited number of participants (N=10).

More recently, Kantner and Gurkov (2014) evaluated the effect of gaze elevation on oVEMP response parameters in 32 healthy individuals. Tone-bursts of 500 Hz were presented at 100 dB nHL and the responses were recorded from the electrodes place beneath the eye contralateral to the stimulus ear. The oVEMPs were obtained at three gaze elevation angles: 30^{o}, 35^{o} and maximal gaze elevation angle. Results revealed a significant increase in the response amplitude with increase in gaze angle from 30^{o} to 35^{o}. However, further increase in the gaze angle to the maximum elevation did not show any significant increase in response amplitude. There was no significant change in the latencies across the three gaze elevation angles. Also, there was no significant difference in the oVEMP response rate across the three gaze angles. However, this study did not investigate the effect of gaze angles lower than 30^{o}.

Overall, most of the above discussed studies investigated the effect of only a limited number of gaze elevation angles on oVEMP responses. Further the results of the studies would be difficult to generalize as the sample size used was limited, especially considering normative study. The studies also did not mention a precise method for measuring particular angles of the gaze elevation and fixation. More precise control of gaze angle could provide a more accurate information regarding the effect of gaze elevation on oVEMP.

Chapter 3

Method

3.1. Participants

The study included 50 healthy individuals with normal auditory and vestibular system in the age range of 18-35 years. All the participants produced an informed written consent before they were enrolled to the study and they were not paid for their participation in the study.

3.1.1. Inclusion Criteria

All the participants had normal hearing thresholds as evidenced by their air- and bone-conduction thresholds of ≤15 dB HL in the octave frequency range of 250 Hz to 8000 Hz and 250 Hz to 4000 Hz, respectively. The participants also had normal middle ear functioning as shown by ‘A’ type tympanogram and acoustic reflex thresholds (ipsilateral & contralateral) within normal limits at octave frequencies from 500 Hz to 2000 Hz.

3.1.2. Exclusion Criteria

Individuals with history of otological, vestibular or neurological disorders were excluded from study. Subjects with visual abnormalities such as squints, spontaneous nystagmus or other visual abnormalities were also excluded.Other exclusion criteria included reduced uncomfortable levels (UCL) for speech (< 100 dBHL), presence of diabetes and/or hypertension.

3.2. Instrumentation

A two channel Piano Inventis audiometer, coupled to impedance matched TDH-39 supra-aural headphones housed in MX-41/AR ear cushions was used to obtain air-condition thresholds, speech recognition threshold (SRT), speech identification scores(SIS) and UCL. The same audiometer with Radioear B-71 bone vibrator was used to obtain the bone conduction thresholds. A calibrated immittance equipment with a visual display (Grason - Stadler Incorporated tympstar) was used to carry out tympanometry and reflexometry. Biologic navigator pro version 7.0.0 with impedance matched Etymotic ER-3A insert earphones was used to record click-evoked auditory brainstem response and oVEMP. A wooden measuring scale was used to measure the angle of gaze elevation. The scale consisted of eight markings corresponding to each of the gaze angles used in the study (from -5^0 to $+30^0$). A sliding bar was present to indicate the point of gaze fixation. Two adjacent markings were spaced 8cm apart which corresponded to 5^o angle from a distance of 1metre. The schematic representation of the scale is shown in the Figure 3.2.1.

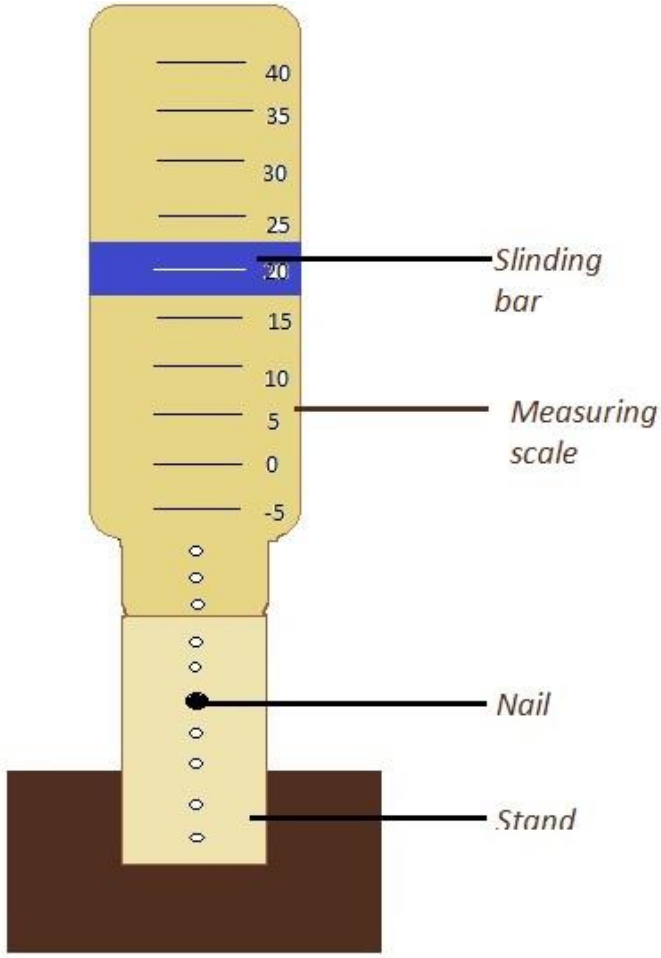

Figure 3.1: A schematic representation of the gaze angle measuring scale that was used in the study.

3.3. Test Environment

All of the tests were conducted in sound treated rooms. The ambient noise levels of the test rooms were well within the limits as per the American National Standard Institution (ANSI S3.1 1999) specifications. While pure-tone and speech audiometry were carried out in a double room set-up, immittance evaluation, ABR recording and oVEMP recordings were done in a single room set-up. The rooms were well illuminated and air-conditioned.

3.4. Procedure

Prior to recording of oVEMP, all the participants underwent audiological and vestibular evaluation for the fulfilment of the subject selection criteria. A detailed structured case history was obtained which was specifically focused on auditory or vestibular disorders or deficits, if any. The tests included otoscopic evaluation, pure tone audiometry, speech audiometry, UCL testing, immitance, ABR, Romberg test, Fukuda stepping test, past pointing test and the Tandem gait test.

Otoscopic examination was done prior to the audiological evaluation for each subject to rule out occlusion of ear canal and ear discharge. Pure-tone thresholds were obtained at octave frequencies from 250 Hz to 8000 Hz and 250 Hz to 4000 Hz for air- and bone-conduction respectively, using modified Hughson Westlake method (Carhart & Jerger, 1959). Speech audiometry included determination of, SRT, SIS and UCL. Obtaining SRT involved the presentation of spondees through use of Bracketing method to arrive at threshold (≥ 50 % criterion) SIS was obtained by presenting the words from the phonemically balanced (PB) word lists in the participants' native language at affixed intensity of 40 dB above their SRT. UCL was obtained for each ear using ascending method.

Immittance evaluation included tympanometry and reflexometry. Tympanometry was carried out with a probe-tone frequency of 226 Hz at 85 dB SPL by varying air pressure in the external ear canal from +200 daPa to -400 daPa at a pump speed of 50 dapa/s. The same probe-tone frequency, along with reflex eliciting signal at octave frequencies from 500 Hz to 2000 Hz, was used to measure ipsilateral as well as contralateral acoustic reflex thresholds.

Two channel ABR was recorded using Biologic Navigator Pro 7.3.0 version. The repetition rate of 11.1/s and 90.1/s were used in order to rule out presence of any retro cochlear pathology. Blackman window gated (2ms rise / fall time and 0ms plateau) click stimuli with rarefaction polarity were used. The subject was seated in a comfortable recline position. The inverting electrode was placed on the mastoid of both the ears. Ipsilateral and contralateral responses were recorded with the non-inverting electrode placed on the vertex and the ground on the forehead (Fpz). The peaks were analysed for absolute latency, interpeak latency, V/I amplitude raito and inter aural wave V latency difference. The difference in absolute latency of wave V between repetition rates of 11.1/s and 90.1/s was also noted. The subjects with normal results in each of the mentioned parameters were considered for the study.

The vestibular system assessment consisted of behavioural screening tests. The behavioural testing consisted of Romberg test, Fukuda stepping test, Past pointing test and the Tandem gait test.

Romberg test was carried out by instructing the participant to keep the feet firmly together and outstretch their hands forward so that they stay apart by chest width and parallel to the ground. The balance of the subject was noted with the subject's eyes open and closed condition for 1 minute. Presence of significant sway during eyes closed condition or inability to maintain balance after closing eyes were considered abnormal responses (Black,Wall, Rockette, & Kitch, 1982; Johnson et al., 2005).

To carry out the Fukuda stepping test, the participant was made to stand inside in the centre of the two concemtric circles. The subject was instructed to march inside the circle, at an appropriate pace, with eyes closed and both hands in front and parallel to the ground (Fukuda 1959). The direction and degree of rotation was noted and any deviation greater than 45^{o} in any direction or movement of < 1 mete was considered abnormal (Harit and Singh 2012).

To carry out Past pointing test, the subject was asked to touch his/her nose tip and clinician's finger tip alternately with his/her index finger.The distance and direction of the clinician's finger was constantly changed. Presence of tremors and/or undershooting/overshooting of the target were considered abnormal responses in Past pointing test.

In tandem gait testing, the participant was asked to walk on an imaginary straight line drawn on the ground with eyes open. The subjects were instructed to place one foot in front of the other making sure that, with each step, the heel of one foot was directly in front of the toes of other foot. Deviation to any side or loss of balance was considered as abnormal (Demyer, 1974; Giorgetti, Harris, & Jette, 1998).

For oVEMP recording the subjects were seated in an upright position. The electrode sites were cleaned using a commercially available abrasive gel to reduce the skin impedance. Silver chloride disc-type electrodes were placed using the commercially available conduction gel and secured in place using surgical plaster. The non-inverting electrode was placed 1 cm below the centre of the lower eyelid, the inverting electrode was placed 2 cm below the inverting electrode and the ground electrode was placed on the forehead. This electrode configuration is similar to those used previously (Singh & Burman, 2014, 2015). Absolute and inter electrode impedance were maintained below 5kΩ & 2kΩ respectively. A monaural single-channel recording was achieved for the contralateral ear stimulation for each participant at different angles of gaze elevations.

The test stimuli used were 500 Hz tone-bursts, with a plateau time of 1 ms and a rise/fall time of 2 ms. Stimuli were presented at an intensity of 125 dB SPL. Rarefaction polarity was used to present the tone-bursts at a rate of 5.1 Hz. The recordings were amplified by a factor of 3000 and were band-pass filtered between 1-1000 Hz as found appropriate by Wang, Jaw and Young (2013). The waveforms were analysed in a time window of 74 ms which was inclusive of a pre stimulus baseline recording of 10 ms. The oVEMPs were recorded for eight gaze angles (-5^{o} to $+30^{o}$), equally spaced at 5^{o} steps. A total of 150 sweeps were averaged for each waveform.

A measuring scale instrument was placed 1metre away from the subject. The subject's eyes were fixed at 0^{o} on the measuring scale. A sliding bar on the scale was used to indicate the point at which the subject had to fixate the gaze, and a wooden stand was used to support the scale. The gaze angles were changed in a random sequence for each recording. A brief interval was given between the recordings to avoid fatigue and eye irritation. This interval was decided based on the subject's preference.

3.5. Waveform Analysis

The peaks were identified by two independent experienced audiologists. The waveforms were analyzed for the individual peak latencies and peak-to-peak amplitude at each of the gaze angles. The SNR for recording corresponding to each gaze angle for both the ears of each participant was obtained using MATLAB software. For the SNR calculation, the MATLAB software uses the formula mentioned below,

$$SNR = 20 \log(RMS_{ep} / RMS_{b})$$

where ‘SNR’ is signal-to-noise ratio in dB, ‘RMS_{ep}’ is the root-mean-square of the oVEMP response in the time range of 7 to 30 ms and ‘RMS_b’ is the root-mean-square of the pre-stimulus baseline.

3.6. Statistical Analysis

The mean peak to peak amplitude and latencies of waveforms at each of the gaze angle were calculated. A commercially available statistical tool, Statistical Package for Social Sciences (SPSS) version 17.0,was used for statistical analyses of the obtained data. The analysed data was subjected to two-way repeated measures analysis of variance (two-way repeated measures ANOVA) for ears and gaze angles. Separate two-way repeated measures ANOVA were used for each of the parameters (n1 & p1 latency, peak-to-peak amplitude, & SNR). In case of a significant difference between the gaze angles on a response parameter, Bonferroni adjusted multiple comparisons were done for pairwise analysis. In addition, the descriptive statistics was done to obtain mean, standard deviation, range and variance for each of the parameters of oVEMP. McNemar test was done to compare the response ratesbetween the ears and between various gaze elevation angles.

Chapter 4

Results

The study aimed to determine the effects of angle of gaze elevation on oVEMP response parameters. For this, oVEMPs were recorded for eight gaze angles (-5^o, 0^o, 5^o, 10^o, 15^o, 20^o, 25^o& 30^o with reference to the horizontal) from both ears of 50 healthy individuals. Figure 4.1 shows the individual averaged and grand averaged oVEMP waveforms corresponding to the eight different gaze angles.

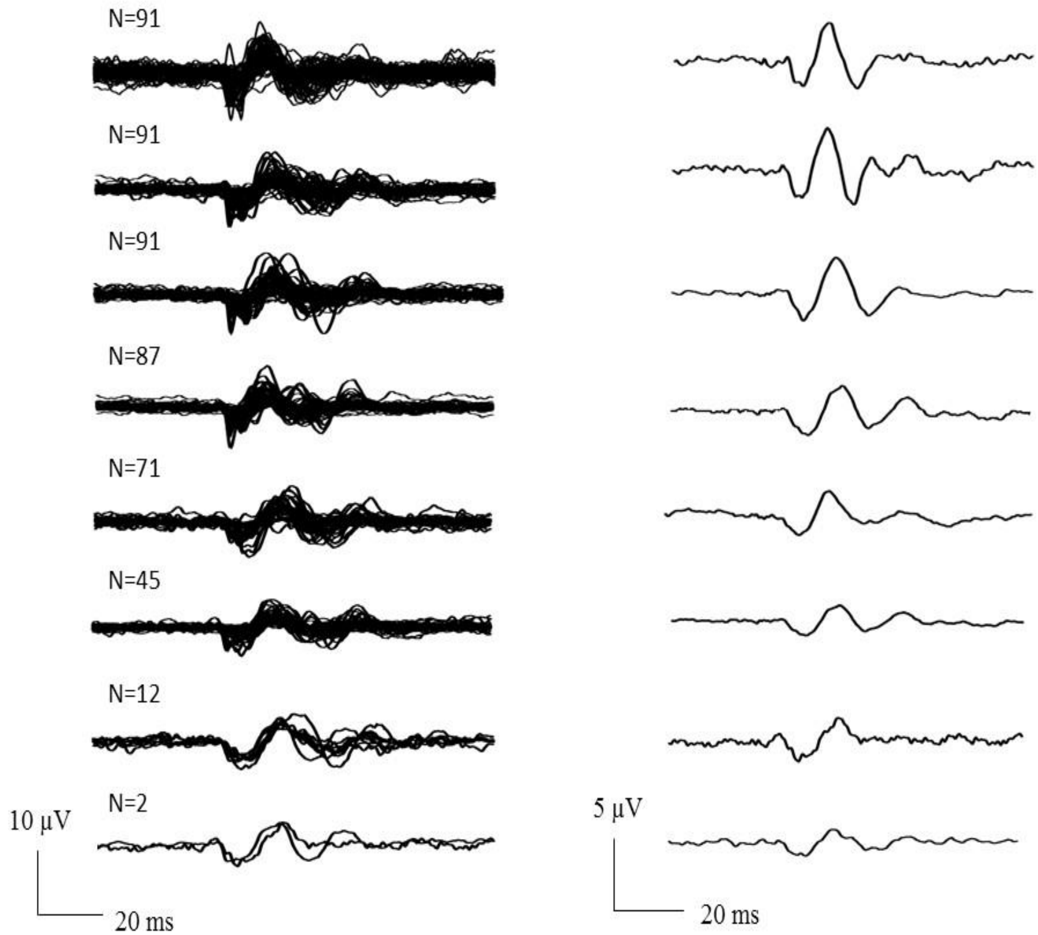

Figure 4.1: Individual averaged (left panel) and grand averaged (right panel) oVEMP waveforms corresponding to the eight different gaze angles. The bottom most waveforms are for -5^{o} and top most for 30^{o} of gaze elevation angle. From bottom to top, the waveforms represent increasing gaze elevation angle in 5^{o} steps.

The waveforms were analyzed for response rate, n1 latency, p1 latency, peak-to-peak amplitude and signal-to-noise ratio. The results are discussed below under each of these parameters.

4.1. Ear differences in response rate of oVEMP at each gaze angle

The response rate was defined as the percentage of ears in which the responses were present at a given gaze angle. The response rates at various gaze elevation angles are given in the Table 4.1.1. It can be observed from the table that there is no apparent difference in the response rates between the ears at any gaze elevation angle, except at a few angles.

Table 4.1: *Response rate of oVEMP for right and left ears at different angles of gaze elevation and outcome of McNemar test for between ears comparison*

Gaze elevation angles	**Right ear**		**Left ear**		$\chi^2(1)$	***p*-value**
	N	RR	N	RR		
-5º	0	0	2	4	0.16	0.78
0º	5	10	7	14	5.19	0.62
5º	25	50	20	40	1.05	0.81
10º	34	68	37	74	0.9	0.77
15º	45	90	42	84	0.48	0.49
20º	45	90	46	92	0.48	0.49
25º	45	90	46	92	0.48	0.49
30º	44	88	47	94	0.59	0.74

Note: ‘N’: number of ears with presence of responses; ‘RR’: response rate in %.

In order to evaluate the statistical significance of the above mentioned observation, McNemar test was done to compare the response rate between the two ears. The results revealed no significant difference in response rate between the ears at any of the gaze angles. The results of McNemar test are also shown in the Table 4.1.1. Figure 4.1.1 shows response rates of oVEMP for right and left ears plotted as a function of gaze angle elevation.

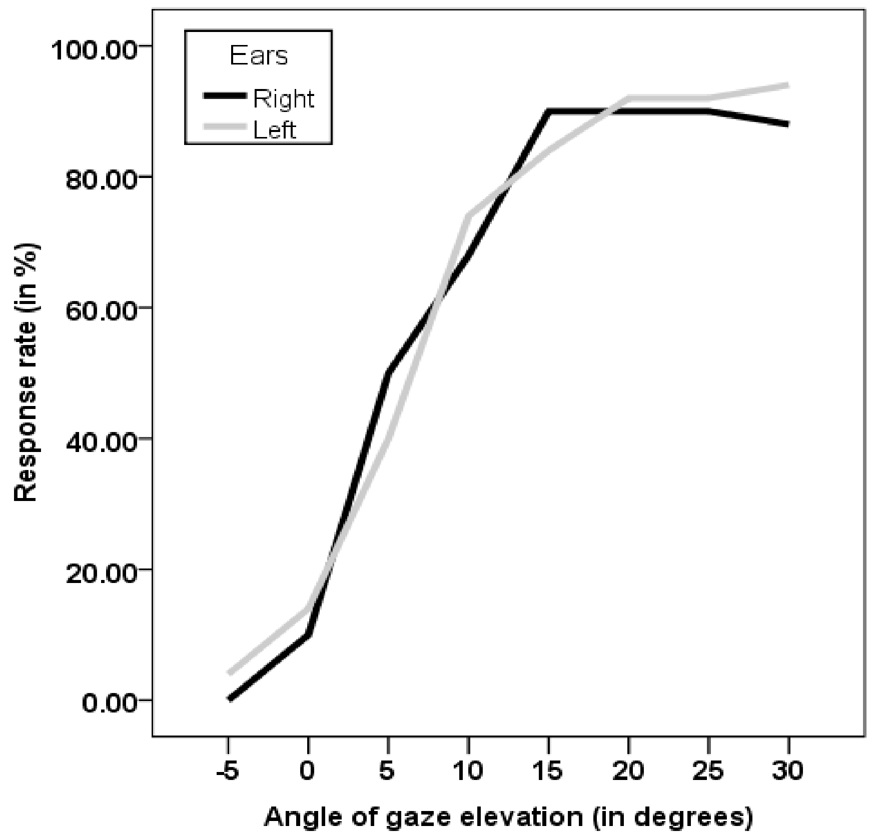

Figure 4.2: Response rate for left and right ear as a function of angle of gaze elevation.

Thus the Null hypothesis (H_0) that there is no significant difference in response rate of oVEMP between the ears at any gaze elevation angle is accepted.

4.2. Effect of gaze elevation angle on response rate of oVEMP

The between ears comparison of response rate revealed no significant difference in response rate between the ears for any of the gaze elevation angles. Hence, for further statistical analysis, the data of the ears were combined. Table 4.2.1 represents the response rate at each gaze elevation angle for both the ears (right and left ear combined). As can be observed, the response rate of oVEMP increased with increase in the gaze elevation angle upto 20^0. Figure 4.2.1 shows the line graph for response rate as a function of gaze elevation angle.

Table 4.2: *Response rates of oVEMP at different gaze elevation angles*

Degree	-5º	0º	5º	10º	15º	20º	25º	30º
N	2	12	45	71	87	91	91	91
Response rate (in%)	2	12	45	71	87	91	91	91

Note: ‘N’: number of ears having responses.

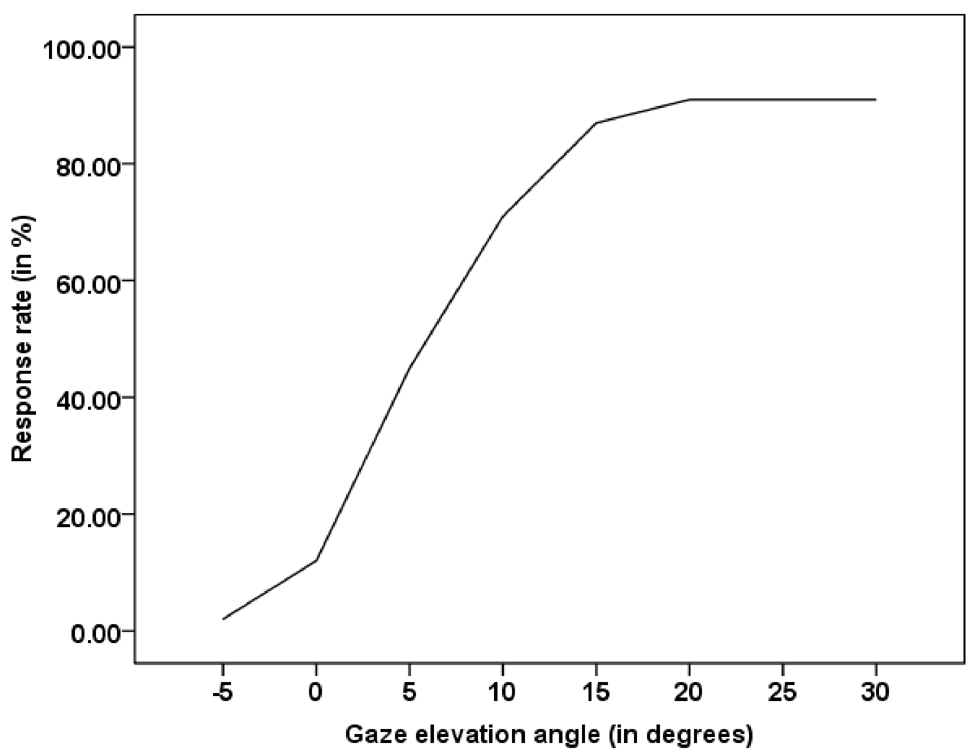

Figure 2.3*:* Response rates (percentage of ears with present responses) of oVEMP as a function of angle of gaze elevation.

In order to examine the statistical significance of the above reported observation, a McNemar test was done. The results demonstrated that the response rate for gaze elevation angles of -5^o, 0^o, 5^o and 10^o were significantly different from each other and significantly lower than all the other angles. However, the response rates for 15^o, 20^o, 25^o and 30^o were significantly not different from each other. Table 4.2.2 shows the results of McNemar test for comparison of response rates between gaze angles.

Table 4.3: *Outcome of McNemar test for comparing response rate of oVEMP between different gaze elevation angles*

Angle of gaze elevation	**0º**	**5º**	**10º**	**15º**	**20º**	**25º**	**30º**
-5º	14.96**	2.30**	0.87***	0.27***	0.20***	0.20***	0.22***
0º		15.37***	3.04***	1.86***	1.34***	1.34***	1.51***
5º			32.80***	12.09***	8.77***	8.77***	9.85***
10º				31.81***	23.07***	23.07***	25.92***
15º					55.36	55.36	48.65
20º						100.00	89.01
25º							89.01

Note: '':p* < 0.05; '**':*p*< 0.01; '***':*p*< 0.001.

Thus, the Null hypothesis (H_0) that there is no significant effect of gaze elevation angle on the response rate of oVEMP is rejected. Hence the Alternative hypothesis (H_1) is that there is a significant effect of gaze elevation angle on the response rate of oVEMP.

4.3. Effect of ear and gaze elevation angle on n1 latency of oVEMP

The waveforms were analysed for n1 latency at the above mentioned eight angles of gaze elevation. The obtained values from all the individuals were subjected to descriptive statistics in order to obtain mean, standard deviation, range and variance. Table 4.3.1 shows the outcome of the descriptive statistics. It can be seen from the table that as the gaze elevation angle increased, the n1 latency reduced.

Table 4.4: *Mean, standard deviation, range and variance of n1 latency of oVEMP at various angles of gaze elevation*

Gaze elevation Angle	N	Mean latency (in ms)	SD (in ms)	Range (in ms)	Variance
-5º	2	11.45	1.03	10.72 - 12.18	2.31
0º	12	11.75	0.90	10.43 - 13.06	0.83
5º	45	12.28	1.14	10.28 - 15.10	1.31
10º	71	11.84	1.11	10.16 - 14.22	1.24
15º	87	11.55	0.94	10.14 - 13.06	0.89
20º	91	11.53	1.06	9.85 - 14.37	1.13
25º	91	11.37	0.96	9.99 - 13.61	0.92
30º	91	11.27	0.89	10.14 - 12.91	0.80

Note: 'SD': standard deviation; 'ms': milliseconds; 'N': number of ears having responses.

In order to examine the statistical significance of the above observation, a two-way repeated measures ANOVA was done for the ears and gaze angles. The gaze angles of -5^o and 0^o were not used for statistical analyses due to presence of responses in ≤ 5 individuals (only 2 individuals had responses at -5^o in left ear; none of the subjects had responses at -5^o in the right ear; only 5 individuals had responses at 0^o in right ear). The results revealed a significant main effect of the angle of gaze elevation on n1 latency [$F(5,14) = 16.32$, $p < 0.001$]. However there was no significant main effect of ear [$F(1,14) = 0.03$, $p > 0.05$] and also no significant interaction between ear and degree of gaze elevation [$F(5,70) = 1.18$, $p > 0.05$] on n1 latency. The Bonferroni adjusted multiple comparisons were done for the pairwise comparison of n1 latency between gaze elevation angles. The n1 latency for 5^{o}gaze elevation was significantly longer than that of 20^o, 25^o and 30^o ($p < 0.05$). Also the n1 latency for 10^{o}gaze elevation was significantly longer than for 25^o and 30^o ($p < 0.05$). There was no significant difference in n1 latency between any of the other gaze angle pairs. The results of the Bonferroni adjusted multiple comparisons for n1 latency are shown in Table 4.3.2. The mean and 95% confidence intervals of n1 latency at gaze elevation angles from 5^o to 30^o are depicted in Figure 4.3.1.

Table 4.5: *The outcome of Bonferroni adjusted multiple comparisons for comparison of n1 latency of oVEMP between various angles of gaze elevation*

Angles of gaze elevation	**10^o**	**15^o**	**20^o**	**25^o**	**30^o**

5º	$p > 0.05$	$p > 0.05$	$\boldsymbol{p < 0.05}$	$\boldsymbol{p < 0.05}$	$\boldsymbol{p < 0.05}$
10º		$p > 0.05$	$p > 0.05$	$\boldsymbol{p < 0.05}$	$\boldsymbol{p < 0.05}$
15º			$p > 0.05$	$p > 0.05$	$p > 0.05$
20º				$p > 0.05$	$p > 0.05$
25º					$p > 0.05$

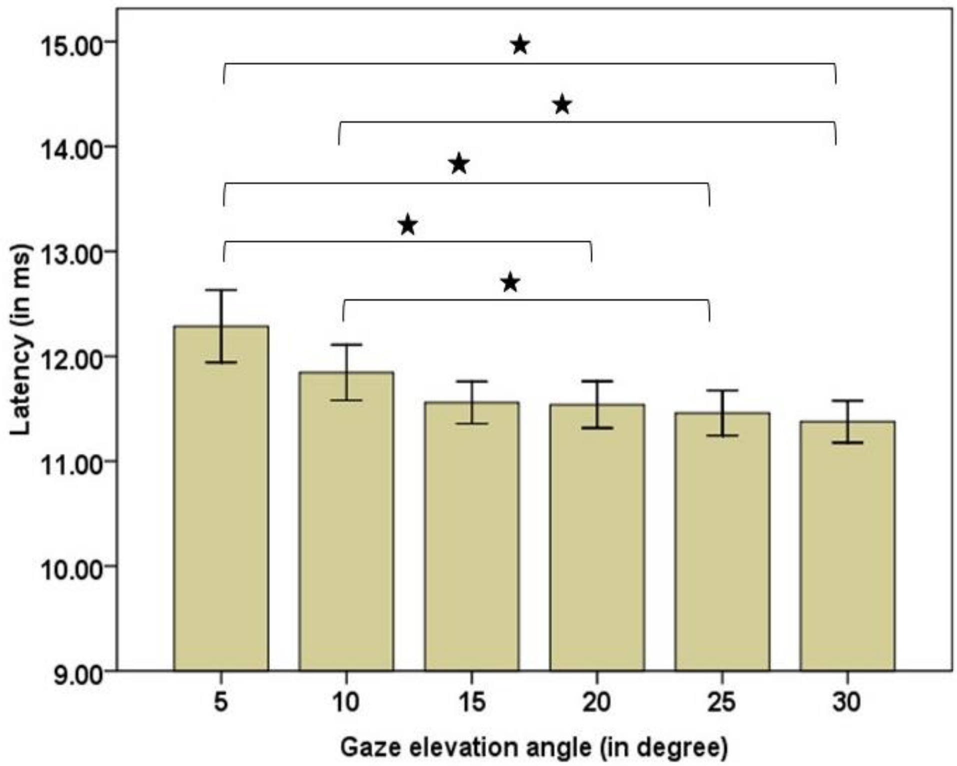

Figure 4.4: Mean and 95% confidence intervals of n1 latency of oVEMP as a function of angle of gaze elevation. The star marked comparisons are statistically significant ($p < 0.05$).

Therefore, the Null hypothesis (H_0) that there is no significant effect of gaze elevation angle on n1 latency of oVEMP is rejected. Hence, the Alternative hypothesis (H_1) is that there is significant effect of gaze elevation angle on n1 latency. However, the

H_0 that there is no significant ear difference in n1 latency at any of the gaze angle is accepted.

4.4. The effect of ear and angle of gaze elevation on p1 latency of oVEMP

Similar to n1 latency, waveforms were also analyzed to obtain p1 latency at the above mentioned eight gaze elevation angles. The observed values from all the individuals were subjected to descriptive statistics to obtain the mean, standard deviation, range and variance. Table 4.4.1 shows the outcome of descriptive statistics for p1 latency of oVEMP. As can be observed from the table, p1 latency reduced with increase in the gaze elevation angle.

Table 4.6: *Mean, standard deviation, range and variance of p1 latency of oVEMP at various angles of gaze elevation*

Angles of gaze elevation	N	Mean latency (in ms)	SD (in ms)	Range (in ms)	Variance
-5º	2	18.45	1.23	17.58 - 19.33	1.76
0º	13	18.80	0.77	17.58 - 19.90	0.60
5º	42	18.75	0.77	16.85 - 19.91	0.60
10º	72	18.3	0.85	15.97 - 20.06	0.73
15º	87	18.03	1.05	13.03 - 20.00	1.10
20º	91	17.72	1.19	10.58 - 20.06	1.42
25º	91	17.4	0.91	15.53 - 19.60	0.83
30º	91	17.04	0.87	15.37 - 19.18	0.76

Note: 'SD': standard deviation; 'ms': milliseconds; 'N': number of ears having responses.

In order to examine the statistical significance of the above observation, a two-way repeated measures ANOVA was done for ears and gaze angles. The results revealed a significant main effect of the degree of gaze elevation on p1 latency [$F(5,65) = 36.68$, $p < 0.001$]. However, there was no significant main effect of ear [$F(1,13) = 2.33$, $p > 0.05$] and also no significant interaction between ear and degree of gaze elevation [$F(5,65) = 0.38$, $p > 0.05$] on p1 latency. The Bonferroni adjusted multiple comparisons were done for the pairwise comparison of p1 latency between the gaze angle pairs. The results revealed a significant difference in p1 latency between several gaze angles. The results of Bonferroni adjusted multiple comparisons are shown in Table 4.4.2. The Figure 4.4.1 depicts the mean and 95% confidence intervals at gaze elevation angles from 5^o and 30^o.

Table 4.7: *The outcome of Bonferroni adjusted multiple comparisons for comparison of p1 latency of oVEMP between various angles of gaze elevation*

Angles of gaze elevation	10º	15º	20º	25º	30º
5º	$p > 0.05$	$\boldsymbol{p < 0.05}$	$\boldsymbol{p < 0.001}$	$\boldsymbol{p < 0.001}$	$\boldsymbol{p < 0.001}$
10º		$p > 0.05$	$\boldsymbol{p < 0.05}$	$\boldsymbol{p < 0.005}$	$\boldsymbol{p < 0.001}$
15º			$\boldsymbol{p < 0.05}$	$\boldsymbol{p < 0.05}$	$\boldsymbol{p < 0.001}$
20º				$p > 0.05$	$\boldsymbol{p < 0.05}$
25º					$p > 0.05$

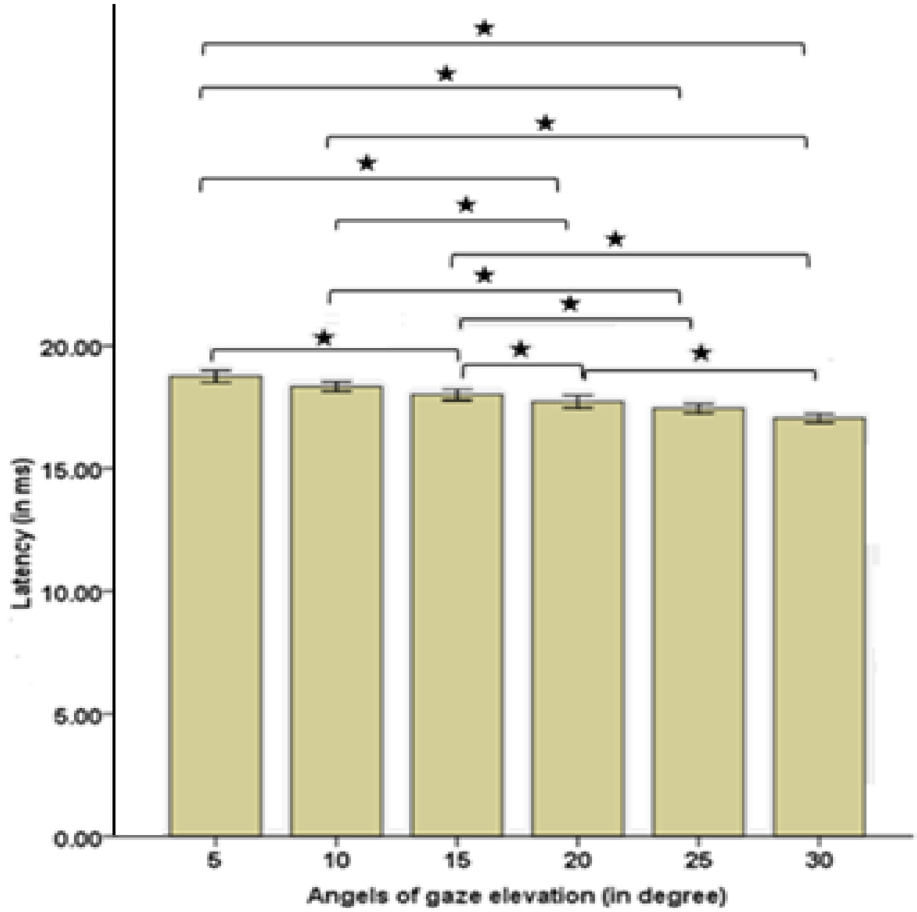

Figure 4.5: Mean and 95% confidence intervals of p1 latency of oVEMP as a function of angle of gaze elevation. The star marked comparisons are statistically significant ($p < 0.05$).

Thus, the Null hypothesis (H_0) that there is no significant ear effect on p1 latency of oVEMP is accepted. However, the H_0 that there is no significant effect of increase in gaze elevation angle on p1 latency is rejected. Therefore, the Alternative hypothesis (H_1) is that there is a significant effect of gaze elevation angle on p1 latency of oVEMP.

4.5. The effect of ear and angle of gaze elevation angle on peak-to-peak amplitude of oVEMP

The oVEMP waveforms were also analyzed for peak-to-peak amplitude at all the eight angles of gaze elevation. The obtained values were subjected to descriptive statistics to obtain the mean, standard deviation, range and variance which are shown in the Table 4.5.1. It can be observed from the table that the amplitude increases with the increase in gaze elevation angle.

Table 4.8: *Mean, standard deviation, range and variance of peak-to-peak amplitude of oVEMP at various angles of gaze elevation*

Angles of gaze elevation	N	Mean peak-to-peak amplitude (in µV)	SD (in µV)	Range (in µV)	Variance
-5º	2	5.53	3.85	2.81 - 8.26	1.2
0º	14	4.71	1.62	2.95 - 9.33	2.63
5º	43	4.80	2.12	1.57 - 11.30	4.31
10º	71	4.93	2.40	1.14 - 11.88	5.78
15º	87	5.47	2.83	1.31 - 14.70	8.04
20º	91	6.66	3.79	1.73 - 19.99	14.41
25º	91	7.55	4.13	1.75 - 20.30	13.06
30º	91	8.56	4.57	2.08 - 25.00	12.09

Note: ‘SD’: standard deviation; ‘µV’: microvolts; ‘N’: number of ears having responses.

In order to examine the statistical significance of the above observation, a two-way repeated measures ANOVA for ears and gaze angles was done. The results revealed a significant main effect of the angle of gaze elevation on peak-to-peak amplitude [$F(5,60) = 41.49$, $p < 0.001$]. However there was no significant main effect of ear [$F(1,12) = 0.33$, $p > 0.05$] and also no significant interaction between ear and angle of gaze elevation [$F(5,60) = 0.42$, $p > 0.05$] on peak-to-peak amplitude. The Bonferroni adjusted multiple comparisons were done for the pairwise comparison of peak-to-peak amplitude between the gaze angles. The results revealed a significant difference in peak-to-peak amplitude between all gaze angles ($p < 0.05$). The only exceptions were the findings of no difference between 20^o and 25^o and also between 25^o and 30^o. The results of the Bonferroni adjusted multiple comparisons are shown in Table 4.5.2. The Figure 4.5.1 depicts the mean and 95% confidence intervals of peak-to-peak amplitude at gaze elevation angles from 5^o to 30^o.

Table 4.9: *The outcome of Bonferroni adjusted multiple comparisons for comparison of peak-to-peak amplitude of oVEMP between various angles of gaze elevation*

Angle of gaze elevation	10^o	15^o	20^o	25^o	30^o
5^o	**$p < 0.05$**	**$p < 0.05$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
10^o		**$p < 0.05$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
15^o			**$p < 0.05$**	**$p < 0.05$**	**$p < 0.05$**
20^o				$p > 0.05$	**$p < 0.05$**
25^o					$p > 0.05$

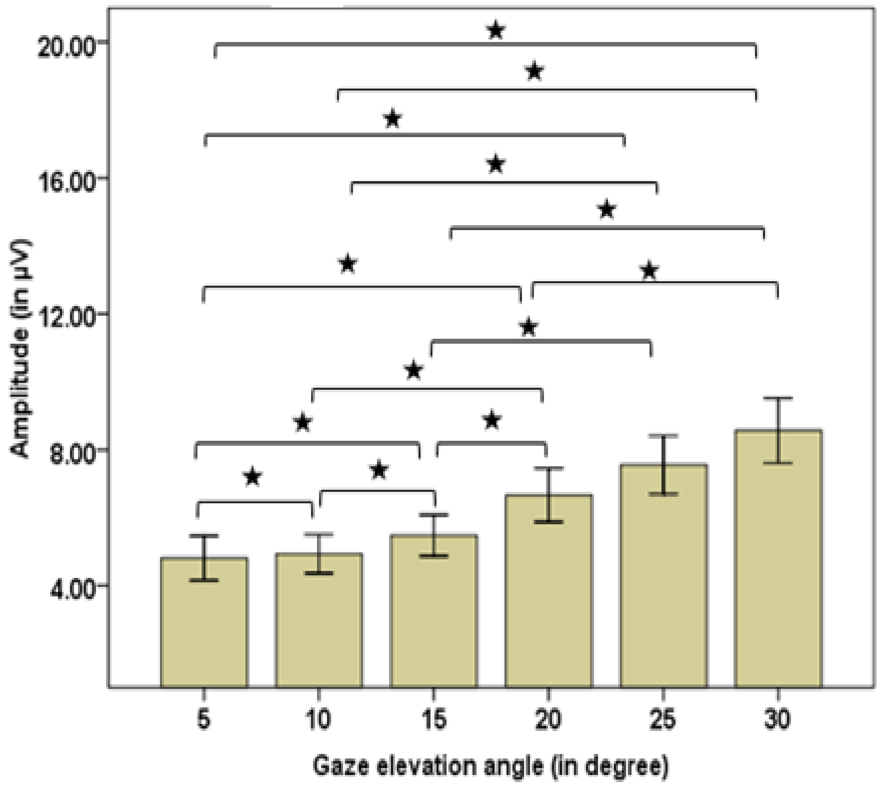

Figure 4.6: Mean and 95% confidence intervals of peak-to-peak amplitude as a function of angle of gaze elevation. The star marked comparisons are statistically significant ($p < 0.05$).

Thus, the Null hypothesis (H_0) that there is no significant effect of gaze elevation angle on peak-to-peak amplitude of oVEMP is rejected. Hence, the alternative hypothesis (H_1) is that there is a significant effect of gaze elevation angle on peak-to-peak amplitude. However, the H_0 that there is no significant ear difference in peak-to-peak amplitude of oVEMP at any gaze angle is accepted.

4.6. The effect of ear and angle of gaze elevation on signal-to-noise ratio of oVEMP waveforms

The oVEMP waveforms were analysed for signal-to-noise ratio (SNR) at the above mentioned eight angles of gaze elevation. The obtained values were subjected to descriptive statistics to obtain the mean, standard deviation, range and variance. The results of descriptive statistics are given in Table 4.6.1. It can be seen from Table 4.6.1 that the SNR increased with the increase in the gaze elevation angle.

Table 4.10: *Mean, standard deviation, range and variance of SNR of oVEMP waveforms at various angles of gaze elevation*

Angles of gaze elevation	N	Mean SNR (in dB)	SD (in dB)	Range (in dB)	Variance
5º	43	17.77	3.08	12.98 - 24.43	9.12
10º	71	18.74	3.16	12.98 - 25.11	10.04
15º	87	23.54	5.30	14.46 - 33.09	18.9
20º	91	26.59	5.97	14.74 - 39.84	15.75
25º	91	26.98	6.84	14.74 - 39.98	26.85
30º	91	27.68	6.29	16.24 - 39.98	18.6

Note: 'SD': standard deviation; 'SNR': signal-to-noise ratio; 'N': number of ears having responses.

In order to examine the statistical significance of the above observation, a two-way repeated measures ANOVA was done for the ears and gaze angles. The results revealed significant main effect of the degree of gaze elevation on SNR [$F(5,34) = 24.78$,

$p < 0.001$]. However there was no significant main effect of ear [$F(1,13) = 2.33$, $p > 0.05$] and also no significant interaction between ear and angle of gaze elevation [$F(5,65) = 0.38$, $p > 0.05$] on SNR. The Bonferroni adjusted multiple comparisons were done for the pairwise comparison of SNR of oVEMP waveforms between the gaze angles. The SNR at 5^o was significantly lower than at all the other gaze elevation angles except for 10^o. Further, the SNR at 10^oelevation angle was significantly lower than all the other angles at except 5^oelevation angle. There was no significant difference in SNR between any of the other gaze elevation angles. The results of the Bonferroni adjusted multiple comparisons are shown in Table 4.6.2. The Figure 4.6.1 shows the mean and 95% confidence intervals at gaze elevation angles from 5^o and 30^o.

Table 4.11: *The outcome of Bonferroni adjusted multiple comparisons for comparison of SNR of oVEMP waveforms between various angles of gaze elevation*

Angles of gaze elevation	**10^o**	**15^o**	**20^o**	**25^o**	**30^o**
5^o	$p > 0.05$	**$p < 0.05$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
10^o		**$p < 0.05$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
15^o			$p < 0.05$	$p > 0.05$	$p > 0.05$
20^o				$p > 0.05$	$p > 0.05$
25^o					$p > 0.05$

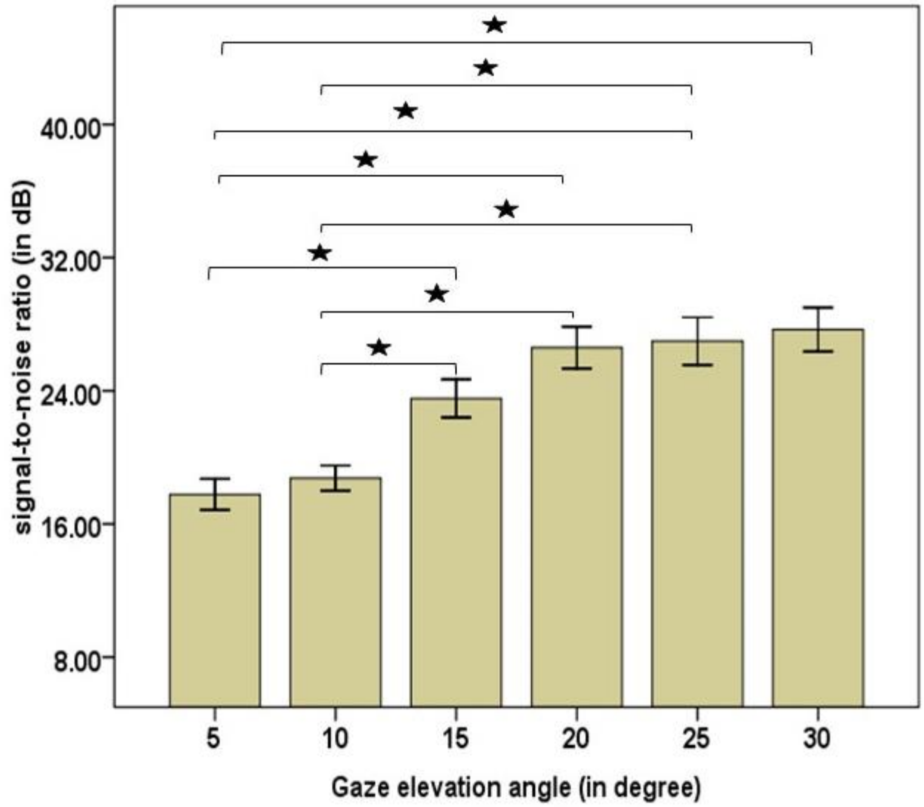

Figure 4.7: Mean and 95% confidence intervals of SNR of oVEMP waveforms as a function of angle of gaze elevation. The star marked comparisons are statistically significant ($p < 0.05$).

Therefore, the Null hypothesis (H_0) that there is no significant effect of gaze elevation angle on SNR of oVEMP waveforms is rejected. Hence the alternative hypothesis (H_1) is that there is a significant effect of gaze elevation angle on SNR of oVEMP waveforms. However, the H_0 that there is no significant ear effect on SNR of oVEMP waveforms at any gaze angle is accepted.

Overall, the results revealed a significant effect of angle of gaze elevation on the oVEMP response rate, n1 latency, p1 latency, peak-to-peak amplitude and SNR.

Generally, increasing the gaze elevation angle caused increase in the response rate, peak-to-peak amplitude and signal-to-noise ratio but decrease in the n1 and p1 latencies.

Chapter 5

Discussion

In the present study, oVEMPs were recorded from 50 healthy individuals in the age range of 18-35 years. The recorded waveforms were evaluated for response rate, n1 latency, p1 latency, peak-to-peak amplitude and signal-to-noise ratio at eight different gaze elevation angles from -5^o to 30^o (in 5^o steps; but the angles were changed randomly between recordings). The findings are discussed under the following headings.

5.1. Ear difference in oVEMP response parameters

The oVEMP response parameters were compared between the ears at various gaze elevation angles. The results showed no significant difference in response rate, peak latencies, peak-to-peak amplitude and signal-noise-ratio between the ears at any gaze elevation angle. Similar results have been found by Iwasaki et al (2008). The findings of no difference in any of the oVEMP response parameters between the ears at any gaze angle could be attributed to the relative symmetry between the two sides' labyrinths which has been demonstrated by the findings of ≤ 20% asymmetry ratio of oVEMP in healthy individuals by a number of studies **(**Murnane et al., 2011; Murofushi et al., 2011; Rosengren et al., 2011; Iwasaki et al., 2013; Singh & Barman, 2014; Singh et al., 2014**)**.

5.2. Effect of gaze elevation on response rate of oVEMP

In general, the response rate of oVEMP increased with increasing gaze elevation angle. There was steeper growth in the response rate with increase in gaze elevation angle from 0^o to 15^o than beyond 15^o. Increase in the gaze elevation angle beyond 20^o did not result in any further increase in response rate. The results are in accordance with the studies that have evaluated the effect of gaze elevation on oVEMP (Govender et al., 2009; Murnane et al., 2011; Rosengren et al., 2013). However, Govender et al (2009) reported a response rate of 83% at 0^o gaze angle in contrast to the 12% response rate found in the present study. This might be attributed to the differences in the stimulus intensity used to record oVEMPs between the present study and that by Govender et al (2009). While Govender et al (2009) used stimulus level of 136 dB SPL and 142 dB SPL, the tone-burst intensity of 125 dB peSPL was used in the present study. Since increase in the stimulus intensity has been shown to increase the response amplitude (Murnane et al., 2011), the use of higher intensity probably would have made the peaks larger thereby improving the possibility of their identification among the mesh of electromyography (EMG) and electroencephalography (EEG) noises.

The finding of increasing response rate with increase in gaze elevation angle could be attributed to increase in the muscle tonicity of the inferior-oblique muscle and increasing vicinity between the muscle and the surface electrode. Obtaining oVEMP requires maintenance of the tonic muscle contraction (Rosengren et al., 2013). The activity of the inferior oblique muscle is maximum at upward gaze angle (Murnane et al., 2011) and decreases with decrease in gaze elevation angle. The decrease in gaze would have made some of the inherently smaller amplitude responses so small that it would be difficult to separate them from the EMG and EEG noises. Therefore, the decrease in the response rate with decrease in the gaze elevation angle can be attributed to the reduction in the tonic activity of inferior oblique muscle. Further, Rosengren et al (2013) reported that the inferior oblique muscle is situated deeper below the surface tissue. Increasing the upward gaze angle brings the muscle closer to the surface electrode. This increase in proximity between the muscle bulk and the surface electrode could be playing important role in response recognition in individuals with inherently lower amplitude of oVEMP. Thus, an increase in the muscle tonicity along with the increase in the proximity between the muscle and the surface electrode could be responsible for higher response rate with increasing upward gaze angle.

5.3. Effect of gaze elevation angle on n1 and p1 latency of oVEMP

Latencies of n1and p1 were compared among various gaze angles and the results revealed significant shortening of n1 and p1 latency with increase in the gaze elevation angle upto 20^{o}. Further increase in the gaze elevation angle did not result in any significant change in the latencies. These results are in agreement with other studies that investigated the effect of gaze elevation angle on oVEMP response parameters (Murnane et al., 2011; Rosengren et al., 2013). However, the findings of the present study are in disagreement with those reported by Kantner and Gurkov (2014), who reported no significant changes in the latencies of oVEMP with changes in the gaze angle. The differences in the two sets of studies could be attributed to the differences in the use of gaze angles between the studies. Kantner and Gurkov (2014) explored the effect of changing the angle of gaze elevation from 30^o to maximum upward gazing. If the results of the present study are taken into perspective, there was no significant change in the latencies upon changing the gaze angle beyond 20^o. Since all the three gaze angles in their study was beyond 20^o, they possibly did not obtain any significant effect on latencies.

The decrease in the peak latencies with increasing gaze elevation might be attributed to the way in which the inferior-oblique muscle changes its position with respect to the surface electrodes. The inferior oblique muscle is reported to move anteriorly and come closer to the surface with the upward movement of the eyes (Demer, Oh, Clark, & Poukens, 2003). This reduces the distance between the muscle and the recording electrode which may have in-turn resulted in earlier peak latencies with upward gazing.

5.4. Effect of angle of gaze elevation on peak-to-peak amplitude

The peak-to-peak amplitude of oVEMP was compared between various angles of gaze elevation. Results revealed significant increase in the peak-to-peak amplitude with increase in gaze elevation angle from 0^o to 30^o. Similar results have been reported in previous studies which evaluated the effect of gaze elevation on amplitude of oVEMPs (Govender et al., 2009; Welgampola et al., 2009; Murnane et al., 2011; Rosengren et al., 2013; Kantner & Gurkov, 2014). Govender et al (2009) and Welgampola et al (2009) reported an amplitude increase by two-three folds when the gaze elevation angle was increased from 0^o to 20^o, whereas Murnane et al (2011) reported a five-fold increase in the response amplitude with increase in gaze elevation angle from 0^o to 30^o. In yet another study, Rosengren et al (2013) reported that the peak-to-peak amplitude of oVEMP recorded at neutral gaze was nearly a quarter of the amplitude of oVEMP obtained at 24^o gaze elevation angle. In the present study, the mean amplitude was 4.71 μV and 8.56 μV at 0^o and 30^o gaze elevation angles. This amounted to a two-fold increase in the response amplitude when the gaze angle of 30^o was compared to 0^o (neutral). Thus, the changes in the amplitude with increase in gaze elevation angle in the present study seems to be well within the range of those reported previously.

The effect of gaze angle elevation on peak-to-peak amplitude could be attributed to two main factors: first tonic muscle contraction and second muscle-electrode distance. As mentioned previously, the tonic activity of the inferior oblique muscle has a significant effect on oVEMP amplitude (Rosengren et al., 2007; Murnane et al., 2011). This extraocular muscle, like any other muscle of the body, acts as an automatic gain control system by virtue of which the response amplitude increases with increase in the tonic muscle contraction (Matthew, 1986). Since the higher upward gazing causes larger muscle contraction, the larger amplitude will consequently result. Overall, increase in gaze elevation angle, increases the muscle force exponentially (Goldstein & Robinson, 1986; Carrizosa et al., 2011) causing increase in response amplitude. However, this is not the only factor that possibly results in increase in oVEMP amplitude with increase in gaze elevation. The inferior oblique muscle is placed deep below the tissue and there is a large distance between the surface electrode placed over the skin and the muscle bulk (Kaufmann & Steffen, 2004). As the eyes move upwards during the upward gaze, the muscle moves anteriorly towards the surface (Demer et al., 2003). This results in the reduction of distance between the muscle and the recording electrode. This would reduce the dampening of the myogenic potentials by the in-between tissues and therefore contribute to the increase in the amplitude with increasing gaze elevation angle (Murnane et al., 2011; Rosengren et al., 2013).

5.5. Effect of angle of gaze elevation on signal-to-noise ratio of oVEMP waveforms

The SNRs of oVEMP response waveforms were calculated for various angles of gaze elevation. The results showed a significant improvement in SNR with increase in gaze elevation angle from 0^o to 20^o. Further increase in gaze elevation angle did not result in any significant increase in the SNR. There are no previous studies investigating the effect of changes in gaze elevation angle on the SNR of oVEMP waveforms. Therefore, the findings of the present study could be considered the first of its kind.

The improvement in SNR with increase in the gaze elevation angle could be attributed to the increase in amplitude as a result of increase in gaze elevation angle. The increase in gaze elevation angle causes increase in the peak-to-peak amplitude (Govender et al., 2009; Welgampola et al., 2009; Murnane et al., 2011; Rosengren et al., 2013), which was also observed in the present study. Although the noise is a random phenomenon, it is likely to remain constant in a noise controlled environment like the acoustically treated rooms with subjects’ movement retricted during the testing. Thus, noise being a constant factor, would not vary across the various gaze elevation angles.

Thus, this might result in improved SNR of oVEMP waveforms with increasing gaze elevation angle.

Chapter 6

Summary and Conclusion

The oVEMP is a biphasic negative-positive myogenic response with a negativity around 10 ms, referred as n1, and positivity at approximately 15 ms, called p1 (Chihara et al., 2007; Walther et al., 2011). They are largely believed to represent the functionality of the utricle and the vestibulo-ocular (otolith-ocular) reflex pathway that initiates from the otolith organs (Todd et al., 2005; Chihara et al., 2007; Curthoys et al., 2011; Govender, & Colebatch, 2012). This makes it an important part of the test battery used for vestibular assessment, as these structures (utricle & otolith-ocular reflex pathway) are not evaluated when using tests like caloric test and cervical VEMP (Todd et al., 2003; Rosengren et al., 2005).

In addition to the pathologies of the utricle and the vestibulo-ocular pathway, oVEMP can also be affected by several stimulus and subject related factors. One of the subject related parameters that has been deemed most important for successful recording of oVEMP is upward gazing (Govender et al., 2009; Welgampola et al., 2009; Murnane et al., 2011; Rosengren et al., 2013; Kantner & Gurkov, 2014). All these studies revealed changes in amplitude and/or latencies with changes in the gaze angle elevation. However, most of these studies were limited by the use of small sample size, especially considering they were normative in nature. Further, they were also limited by the number of gaze elevation angles that they used. Hence, there was a need to overcome these limitations and have a more precise method of measuring gaze elevation angle to obtain accurate information regarding the effect of gaze elevation on oVEMPs. Thus, the present study aimed at investigating the effect of gaze elevation angles on oVEMP response parameters and identify the optimal gaze elevation angle for recording of oVEMP.

In order to fulfil the aim and objectives of the present study, oVEMPs were recorded from 50 healthy individuals in the age range of 18-35 years. The responses were obtained using 500 Hz tone-bursts (plateau time of 1 ms & rise/fall time of 2 ms; intensity of 125 dB peSPL) of rarefaction polarity. The stimuli were presented monaurally to the contralateral ear and the repetition rate of stimulus presentation was set to 5.1 Hz. The recordings were amplified by a factor of 30000 and were bandpass filtered between 1 and 1000 Hz. The waveforms were analyzed in a time window of 74 ms which was inclusive of a pre-stimulus baseline recording of 10 ms. The oVEMPs were recorded for eight gaze angles (-5^o to $+30^o$), equally spaced at 5^o steps. A total of 150 sweeps were averaged for each gaze angle.

The waveforms were analysed for response rate, n1 and p1 latencies, peak-to-peak amplitude and signal-to-noise ratio. Separate two-way repeated measures ANOVA for ears and gaze elevation angles were used for each parameter. Bonferroni adjusted multiple comparisons were done for pairwise analysis in case of significant main effect on the repeated measures ANOVA. McNemar test was used to compare the response rate between the ears and between the various gaze elevation angles.

The results showed significant increase in the oVEMP response rate with increase in the gaze elevation angle upto 15^o. Further increase in gaze elevation angle did not result in any significant change in the response rate. These findings could be attributed to the closer proximity between the muscle and the surface electrode (Rosengren et al., 2013) and increase in the muscle tonicity (Murnane et al., 2011; Rosengren et al., 2013) with increase in the upward gaze angle.

The results of the present study further revealed significant shortening of n1 and p1 latencies with increase in the gaze elevation angle upto 20^o. This could be attributed to the displacement of the inferior oblique muscle (with reference to the surface electrode) as the inferior-oblique muscle has been shown to move anteriorly and closer to the surface with increase in the angle of gaze elevation (Demer et al., 2003). This reduces the distance between the muscle and the recording electrode which may have in-turn resulted in earlier peak latencies with upward gazing.

Further, the results showed significant increase in the peak-to-peak amplitude with increase in the gaze elevation angle from 0^o to 20^o. Increase in the muscle tonicity (Mathew, 1986; Carrizosa et al., 2011; Rosengren et al., 2013) along with the increase in the proximity between the muscle and the surface electrode (Rosengren et al., 2013) with increase in the gaze elevation angle could be responsible for increase in the peak-to-peak amplitude, as explained above.

The signal-to-noise ratio of oVEMP waveforms were compared between the eight gaze elevation angles and the results demonstrated a significant improvement in SNR of oVEMP waveforms with increase in the gaze elevation angle from 0^o to 20^o. This could be attributed to the concept that the signal-to-noise ratio depends on the amplitudes of signal as well as noise. The results of the present study showed an increase in the peak-to-peak amplitude with increase in the gaze elevation angles. Although noise is a random phenomena, the control due to acoustically treated room and a non-moving subject (due to instruction) would have caused the noise to remain more or less constant. Since the amplitude increased and the noise remained relatively constant with the increase in upward gazing angle, the SNR would have improved significantly.

Therefore from the above discussion it can be concluded that the gaze elevation angle has a significant effect on the oVEMP response parameters. For most of the oVEMP response parameters, the increase in the gaze elevation angle beyond 20^o did not result in any significant variation. This implicates that using the gaze elevation angle of 20^o is sufficient for clinical recording of oVEMPs and changes beyond this angle will not affect the responses significantly.

However, the age range used in the study is not of the typical of vestibular patients. Typically vestibular pathologies effect in the 5^{th} and 6^{th} decade of life (Johnson et al., 1972; Walther & Westhofen, 2007). Further, some stimulus parameters like frequency have been reported to interact with age related anatomical changes (Piker et al., 2011). Therefore, future studies might benefit from studying the effect of gaze elevation angle in a broader age range of participants in order to evaluate whether such an interaction does occur. Further, future studies can also be directed at studying the effect of gaze elevation angles in cases with vestibular pathologies like vestibular neuritis, Meneire’s disease etc in order to ascertain that the effects of upward gaze angle on oVEMP remains similar to normal even in individuals with these vestibular pathologies.

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