The effect of Coffee on Ocular Vestibular Evoked Myogenic Potentials

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CERTIFICATE

This is to certify that this dissertation entitled "**The effect of coffee on ocular vestibular evoked myogenic potentials**" is a bonafide work submitted in part fulfillment for the Degree of Master of Science (Audiology) of the student (Registration No.: 12AUD019). This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any of the University for the award of any other Diploma or Degree.

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CERTIFICATE

This is to certify that this dissertation entitled "**The Effect of Coffee on Ocular Vestibular Evoked Myogenic Potentials**" has been prepared under my supervision and guidance. It is also certified that this has not been submitted earlier in other University for the award of any Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled "**The Effect of Coffee on Ocular Vestibular Evoked Myogenic Potentials**" is the result of my own study under the guidance of Mr. Kishore Tanniru, 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.

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CHAPTER 1

INTRODUCTION

The Vestibular Evoked Myogenic Potential (VEMP) is an objective neurophysiological assessment techinique to assess the functioning of utricle and saccule, which are the primary sensory organs for balancing (Colebatch, Halmagry & Skuse, 1994). The Vestibular Evoked Myogenic Potential was first recorded from posterior neck muscles in response to loud clicks (Bickford, Jacobson, Cody, & Lambert, 1964). Currently VEMP is considered as an essential tool in diagnosis/ differntial diagnosis of a varieties of vestibular disorders like acoustic neuroma (Murofushi, Matsuzaki & Mizuno, 1998), vestibular neuritis (Bajda, 2005), Meniere's disease (Bajda, 2005), multiple sclerosis (Yang, Sun, Kim, Huhn, Lee, Dae & Sang 2008), Benign paroxismal positional vertigo and superior semicircular canal dehiscence syndrome (Manzari, Burgess, McGarvie, & Curthoys, 2012). Vesibular evoked myogenic potentials(VEMP) were initially recorded in late 1970s and are recorded from the sternocleido mastoid muscles. These VEMPs are named as Cervical VEMP (cVEMP). Later it was found that the responses can also be successfully recorded from inferior oblique muscles and these were named as Ocular vestibular evoked myogenic potentials(oVEMP).

Thus there are two varieties of VEMP exists for clinical use. The oVEMP assesses the functioning of vestibulo ocular pathway while cVEMP assesses the functioning of vestibulo collicular pathway. Further oVEMP is a crossed ascending uriculo occular excitatory response recorded from inferior rectus and inferior oblique muscle. The neural pathway for the generation of oVEMP is represented in figure 1.1.

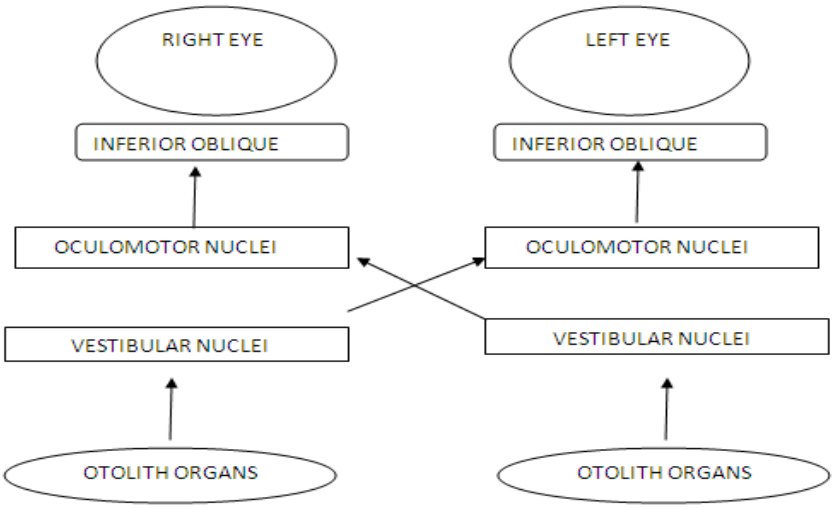

Figure 1.1*: Neural pathways of oVEMP*

oVEMP is a generally recorded as biphasic response with first negative component occurs at a latency of 10ms (n10), and another positive peak usually present at a latency of 16ms (p16) (Chihara, Iwasaki, Ushio, & Murofushi, 2007; Walther, Hormann, Lohler, 2011; Piker, 2012). oVEMPs can be recorded from almost 100 percentage of neurogicaly and otologicaly healthy subjects (Chihara et al; Erin, Piker, Gary, Jacobson, Devin, McCaslin, & 2011). However, there are different factors that could influence the recordings of oVEMP, which could be grouped as subjective factors, recording factors and extraneous factors.

Some of the subjective factors which can affect oVEMP recording are age, eye elevation and gender etc. The effect of age related changes in oVEMP was investigated by Piker et al (2011); Singh, Kashyap, Supreetha, & Sahana (2013) and the result revealed a greater effect on oVEMP above 50 years . Similar findings were reported by

Tseng, Chou & young (2010). The another major subjective factor which affect the recording of oVEMP is eye elevation during the time of recording. Murnane, Akin, Kelly, & Byrd, (2011) noticed an increase in amplitude of n1-p1 with increase in eye elevation up tp 30 degree from the horizontal axis in upright position. Other factor such as gender has slight difference in n1- p1 peak to peak amplitude between males and females, while the latency remained same (Sung, cheng & Young, 2011).

Likewise, in the recording parameters factors related to stimulus and recording protocol had major influence on oVEMP waveforms. Murnane et al (2011) compared oVEMP response to different stimulus intensity level from 100 dB peak SPL to 125 dB peak SPL between different frequencies. The result showed better amplitude and improved prevalnce of response at 125 dB peak SPL for tone burst at 500 Hz. Singh & Barman (2013) studied frequency tuning properties of air conducted stimulus on oVEMP recording. The results indicated that the responses had maximum amplitude and lowest thresholsd at 500Hz. Similarly Lee, Han, Jung, Kwak, Park, & Jung (2008) investigated the effect of plateau and rise/ fall time on oVEMP amplitude and latency parameters. The result showed better response for 0.5 to 1 ms rise/ fall time along with 2 ms plateau time. The maximum amplitude for n1-p2 component was recorded from contra lateral inferior oblique and inferior rectus muscle to the ear of presentation (Wang, Jaw, & Young, 2008).

Along with the above described factors some of extraneous variables like intake of psychoactive drugs which could affect the respnse latency and amplitude parameters of neural responses (Dixit, Vaney, & Tandon, 2006). Caffeine is a one of the most commonly used psychoactive drug which is seen in the leaves of tea plants and seeds of

coffee plants, and being used most commonly all around the world. The effect of this psychoactive drug on oVEMPs were not well explored.

Caffeine, the common name for 1, 3, 7- trimethylxanthine, was derived from the German word “Kaffee” and the French word “cafe”, each meaning coffee. Caffeine is a bitter, white crystalline xanthine alkaloid and a stimulant drug. This is most abundant in the seeds of coffee plant. In humans, caffeine demonstrated significant effect, on sensory evoked potentials, indicating an effect on central nervous system and brainstem. (Shalini, Selvi, & Kumar, 2012; Dixit, Vaney, & Tandon, 2006).

According to United States Department Of Agriculture (USDA), 1.8g of instant coffee contains 57mg of caffeine. The brewed variety contains 56 to 100mg of caffeine per 100ml of coffee. (Nawrot, Jordan, Eastwood, Rotstein, Hugenholtz, & Feeley, 2003). In 1958, Food and Drug Administration (FDA) carefully studied about caffeine and placed them in the list of Generally Recognized As Safe (GRAS). The safest amount of caffeine that can be consumed by a normal healthy person per day is 400mg (FDA, 2013; Heckman, Weil, & Mejia, 2010). The maximum amount of absorption of caffeine to the blood stream from the gastro intestinal tract happens within 1 to 1.5 hours after the intake and does not last more than 5 hours (Nawrot et al., 2003). The caffeine crosses blood brain barrier, through the placenta into the amniotic fluid within 1 to 1.5 hours of consumption. The use of caffeine result in improved alertness and concentration, improved flow of thoughts, better body concentration, reduced physical fatigue etc. The amount of caffeine needed to produce these effects will be different for different people. There are several studies which evaluates the effect of caffeine on central nervous system functions like alertness, reaction time, memory tests, vigilance etc. but research studies

which detailed the effect of caffeine on myogenic potentials are very limited. Thus the main aim of current study is to investigate the effect of caffeine on oVEMPS.

1.1: NEED FOR THE STUDY

There are limited number of studies revealed the effect of caffeine on cortical and brainstem evoked potentials. One such study by Dixit et al(2006) observed the effect of caffeine on auditory brainstem responses, middle latency responses and slow vertex responses . The latency, absolute amplitude and inter peak latencies were compared before and after the intake of caffeine (3mg/ kg) for Auditory Brainstem Responses (ABR), Middle Latency Responses (MLR) and Slow Vertex Responses(SVR). The results showed the latencies of wave IV and V, wave IV- V inter peak latencies in ABR were decreased significantly, which was accompanied by a significant increase in wave V amplitude. The Pa, Na latencies of middle latency responses also showed statistically significant decrement after caffeine intake. The latency of P1 in SVR showed significant decrement in latency after caffeine intake. Similarly Ruijter, De Ruiter, & Snel (2000); Deslands, Veiga, Cagy, Pieda, Pompeu, & Ribero (2004) found a decrement in late wave latencies and an increase in absolute wave amplitudes after the intake of caffeine. These studies indicate that the intake of caffeine showed a prominent change in higher order cortical potentials (Seidl, Peryl, Nicham & Hauser, 2000; Azcona, Barbanoj, Torrent & Jane 1995; Clubley, Bye, Henson, Teck, & Riddington 1979).

In the other modality apart from auditory, Shalini et al., (2012) showed a decrease in p100 absolute latency in Visually Evoked Potentials (VEP).The findings from these studies reveal that the caffeine has an excitatory function on neural synapses. Some of the

research in the direction of the physiological processes at synapses suggest, increase level of Glutamate and Dopamine (an excitatory neurotransmitter) levels which may result in faster conduction through the nerve fibers. This faster conduction may result in decrement of absolute and inter peak latencies of various evoked potentials. (Solinas, Ferre, Kubicha, Popoli, & Goldberg, 2002).

There is a dearth of studies in the direction of caffeine effect on myogenic potentials. Thus further exploration in this direction is much needed.

1.2: AIM AND OBJECTIVES OF THE STUDY

AIM

- To investigate the influence of caffeine intake on ocular vestibular evoked myogenic potentials

OBJECTIVES

- To find out whether any difference is there in effect of caffeine between two genders and between ears.
- To find out whether any difference is there in functioning of caffeine on vestibular system with change in duration of time after the intake.
- To find out the influence of caffeine on vestibular system in regular and non-regular users of caffeine.

CHAPTER 2

REVIEW OF LITERATURE

There are many scientific studies revealed different mechanisms of action by caffeine on human body. Explanation from Pesta, Angadi, Burtscher, & Roberts (2013) indicated the major function of caffeine can be divided inhibitory and oxidizing property. The caffeine acts as an inhibitory agent upon adenosine receptors and thereby decreasing the vascularity towards the cerebral hemispheres. Similarly, the caffeine improves the production of many enzymes which is essential for the metabolism of glucose and lipids because of its inhibitory action upon phosphodiesterase. It also acts as an enhancer of glycogen level in muscles and thereby improves the physical activity. Along with It also enhances the release of Calcium ions from sarcoplasmic reticulum. It is clear from its natural mechanism of action that the caffeine can have different functioning at different systems of human body, which can be grouped in to function of caffeine at the level of cardiovascular system, nervous system, musculoskeletal system etc. The studies which investigate its effect on sensory evoked potentials are also very limited.

2.1: Effect of caffeine on cardiovascular system

James, Lane, Pieper, Barbara, Bute, Bryant, & Kuhn (2002) investigated the effect of caffeine on ambulatory blood pressure and heart rate. The result revealed an increase in ambulatory blood pressure and decrease in heart rate after the administration of caffeine. This study showed a clear evidence of effect of caffeine on cardiovascular system.

2.2: Effect of caffeine on Nervous system

Diukova, Ware, Smith, Evans, Murphy, Rogers, & Wise (2012) compared the BOLD FMRI and visually evoked potential at occipital area and auditory odd ball p300. The result showed a change in BOLD FMRI at visual, and primary motor cortex, while the potentials generated by visual stimuli at occipital region remains unaffected even after the administration of caffeine. But there was a significant reduction in latency of p300 evoked by auditory stimuli after the intake of caffeine. Dixit, Goyal, Thavani, & Vaney (2012) investigated the effect of caffeine on reaction time and attention. The result showed a decrease in reaction time and improvement in attention after the intake of caffeine.

2.3: Effect of caffeine on musculoskeletal system

The effect of caffeine on physical activity in soccer players were investigated by Lara , Gonzalez, Salinero, Abian, Areces, Barbero, Munoz, & Delcoso (2014). The result revealed an improvement in running speed and distance after the administration of caffeine, which was not evident in placebo group. Similar findings were reported by Abian, Puente, Salinero, Gonzalez, Areces, Munoz, & Del coso (2014) in volleyball players as well.

2.4: Effect of caffeine on evoked potentials

Shalini et al. (2012) investigated the effect of caffeine on visual and auditory evoked potentials in six healthy volunteers by administering pure caffeine powder (2mg/kg of body weight) mixed with milk and sugar. The result showed a decrease in latency and increase in amplitude of visually evoked P100 after caffeine consumption.

The auditory brainstem responses were also showed the same trend as that of visually evoked p100. Further decrease in latencies after the intake of caffeine was lesser in females than males, and more in smokers as compared to non smokers.

Dixit et al. (2005) evaluated the effect of caffeine on auditory cortical responses using an odd ball paradigm in forty normal subjects. As in the earlier studies, this study also involved intake of pure caffeine powder (3mg/kg of body weight), which was mixed with milk powder and sugar in 100 ml of water, was given to all the subjects to study the effect on various evoked potentials. The results indicated significant decrease in the latency of P1 and non significant decrease in the latency of N1, P2 and N2 after the intake of caffeine.

Dixit, Vaney, Tandon (2006) further assessed effect of caffeine on auditory evoked brainstem responses, slow vertex responses and middle latency responses in 40 male subjects. The results revealed that the latencies of IV, V peaks, I- V inter-peak latencies of auditory evoked brainstem responses, P1 latency of slow vertex responses were decreased significantly after the intake of caffeine. There was an improvement in amplitude of wave V after the consumption of caffeine, which was statistically significant.

Felipe, Correia, Utsch and Cotta (2005) investigated the effect of caffeine on vestibular tests in nineteen females having vestibular symptoms. The subjects were regular users of coffee (3cups /day) and they have undergone vestibular testing in two

different conditions as before and after stopping consumption of coffee and other caffeine containing substances. Results mainly emphasized that the subjects showed more anxiety, head ache and other vestibular symptoms in vestibular tests when the subjects were stopped the intake of coffee or other caffeine containing products than when they were in regular use.

Most of the above mentioned studies indicated significant latency or amplitude changes on intake of caffeine. And majority of the studies used laboratory methods to administer caffeine content. And moreover, up to the authors' knowledge there are no reports of studies on effects of caffeine in oVEMP recordings. It would be wise to observe the effect of the same when administered in more natural way of intake. Thus the current study was taken up to with the main aim of noticing coffee affects on oVEMP recordings, and coffee was administering as detailed in the following chapters.

CHAPTER 3

METHOD

The aim of this present study was to investigate the effect of coffee on oVEMP parameters within three groups across four different conditions. The subjects participated in this study were graduate and post graduate students at All India Institute of Speech and Hearing. All of them participated voluntarily and were informed about the aim of this study prior to participation. A written consent was taken from the subjects before taking part of the study. The following methodology was incorporated to evaluate the aim of the study.

3.1: Participants

A total number of 30 healthy normal hearing subjects with age ranging between 18 to 30 years (mean age of 23.59 years) including both males and females in equal numbers were considered. All the subjects were divided into regular and non- regular users of coffee based on history about frequency of consumption of coffee over past three years (assessed through formal interview method). Subjects having history of consuming of less than one cup of coffee per week (around 40 to 150mg/ of caffeine in150ml of coffee) similar to the criteria employed by Dixit , Vaney & Tandon (2006) were considered as non- regular users of coffee. Subjects with an habit of taking coffee more than one cup in a day were treated as regular users of coffee. The non- regular users were further divided into two groups for noting placebo effect. Thus all the participants were grouped in to regular users of coffee, non regular users of coffee and placebo group

The subjects having history/ presence of middle ear pathologies, conductive hearing loss, and having vestibular symptoms were not considered for further participation. Habit of smoking, alcohol consumption, history of medical conditions like diabetic mellitus, epilepsy, liver diseases, CNS and mental illness, history of recent surgical and medical illness were also excluded from the study. Immitance evaluation was carried out using GSI Tympstar before oVEMP recording to rule out middle ear pathologies.

3.2: Instrumentation and environmental factors

All the testing procedures were conducted in a sound treated room according to specifications by ANSI S3.1, 1999 specifications. A well calibrated GSI Tympstar was be used to assess the middle ear condition of all the subjects. A well calibrated Bio-Logic Navigator Pro auditory evoked potential unit with amplifier was used for oVEMP recordings. All the equipments were calibrated according to ANSI standards, precautions were taken on placement of instruments used and subject positions to avoid the interference of electromagnetic fields generated from other electronic instruments.

3.3: Recording protocol for oVEMP

Prior to the recording, the designated electrode sites were cleaned using skin preparation gel and cotton. Five gold plated cup electrodes were used for the recording the oVEMP potentials. The electrode sites considered for recording oVEMP responses were 1 cm below the lower eye lid of both the eyes for non inverting electrode, 2 cm below for inverting electrodes and lower forehead for ground electrode. The inter electrode impedance was maintained below 2K Ohms and absolute electrode impedance

was less than5K Ohms throughout the recording period. Contralateral oVEMP recordings were considered for all conditions, ie when stimuli presented to right/ left ear, the electrical responses from electrodes placed opposite side were collected. Monaural presentation of acoustic stimulus was used for all oVEMP recordings.

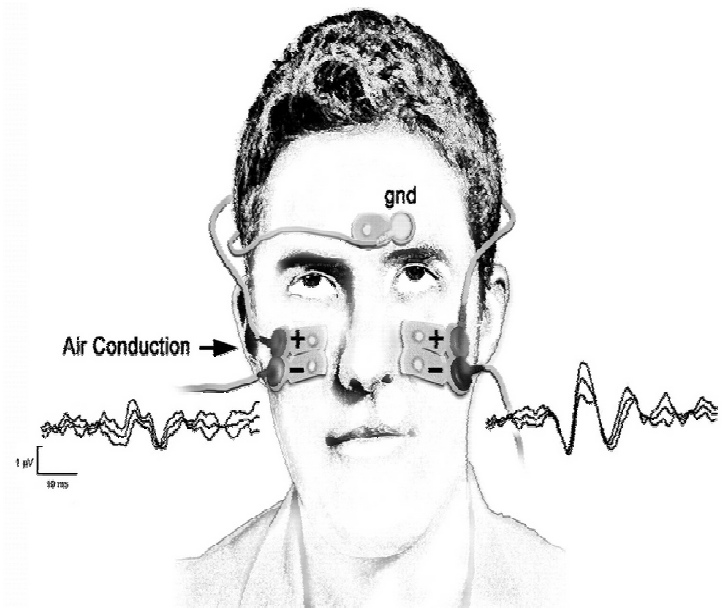

Figure 3.1*: Electrode montage for oVEMPrecording, [from Akin &Murnane (2009)]*

All subjects were instructed to sit in upright position and gaze to an object which is 30 degree above the horizontal plane of vision during the recording (as described in Murnane et al., 2011). Subjects were instructed to maintain the same throughout recording time. Each recording were repeated twice to see the replicability of the response. All the recordings were taken in one session from each subject (approximately lasting for 50min). ER 3A insert receivers were used for delivering 500Hz tone burst at

125dB peak SPL. The filter settings used for recording the responses were 1 to 1000Hz and responses were averaged for 200 sweeps. The other stimulus and recording parameters used for oVEMP recordings are tabulated in Table 3.1.

Table 3.1 *Stimulus and Acquisition protocol used for oVEMP recording*

Type of parameter	Parameter	Specifications
Stimulus	Type	Tone burst of 2-0-2 ms
	Frequency	500Hz
	Intensity	125dB peak SPL
	Polarity	Alternating
	Rate	5.1/ sec
	No of sweeps	200
Recording	Filter settings	1 to 1000Hz
	Amplification	30,000 times
	Analysis time	10 ms pre stimulus and 70ms post stimulus
	Transducer	ER 3A insert receiver with 0.8ms delay
	Electrode montage	Non inverting 1cm below the lower eye lid, Inverting at 2cm below the active electrode, ground on lower forehead

3.4: Experimental Procedure

All the subjects participated in this study were asked to avoid the intake of caffeine containing food products and beverages 12 hours before the participation. Two base line recordings (B1 & B2) of oVEMP were taken from all the participants with an interval of 10 minutes before intake of coffee or placebo. oVEMP recordings were

repeated after five minutes and twenty minutes (T5 & T20) successively soon after intake of coffee or placebo for all the subjects. Thus were a total of four conditions namely B1 (Base line 1), B2 (Base line 2), T5 (Recording the response at 5 min after the intake of coffee/ placebo), T20 (Recording the response at 20 min after the intake of coffee/ placebo).

For all subjects the right ear was tested initially followed by left ear in all four conditions. Thus recording happened at exactly 5 and 20 minutes in right ear while it was delayed by an average time of 3 min in left ear in both T5 and T20 conditions.

3.5: Procedure of administering caffeine/ Placebo

1.8 g instant coffee powder (available for regular use) containing 57% of coffee and 43% of chicory was used for the study. This was mixed with 1 table spoon of milk powder (partly skimmed milk and sucrose) and sugar (according to taste) in 100 ml of hot water. Subjects in placebo group were asked to intake a solution containing only made with 1 table spoon of milk powder and sugar (according to taste) in 100 ml of hot water.

3.6: Analysis

Later, all the wave forms collected during the recordings were printed on to hard paper and presented to two experienced professional for marking n1 and p1. From the marking n1 latency, p1 latency, n1-p1 peak to peak amplitude, asymmetric ratio between two ears were calculated. Latency parameters are calculated in msec and amplitude parameters in micro volts. The asymmetric ratio can be calculated using the formula given below.

$$AR = \left(\frac{amp\ in\ left\ ear - amp\ in\ right\ ear}{amp\ in\ left\ ear + amp\ in\ right\ ear}\right) X100$$

Where AR= Asymmetric ratio

amp in right ear = n1-p1 peak to peak to amplitude measured in micro volts in right ear

amp in left ear = n1-p1 peak to peak to amplitude measured in micro volts in left ear.

CHAPTER 4

RESULTS AND DISCUSSION

The aim of the current study is to find out the effect of coffee on different parameters of oVEMP recordings. Prior to the analysis, all oVEMP recordings of all subjects were presented to two experienced professionals separately for marking n1 and p1. As both professional's markings of n1 and p1 are identical in all recordings, no statistical measure was performed between the markings and from the markings n1 latency, p1 latency and n1-p1 amplitude were directly computed. These findings indicate a clear morphology in all oVEMP recordings obtained in normal healthy hearing subjects.

In this present study every subject acted as his /her own control as two baseline measurements of oVEMP recordings obtained prior to administering either placebo or coffee powder orally. Hence results obtained were discussed separately for three groups (namely placebo group, regular user of coffee and non regular users of coffee). Before beginnings with main affect, a Mann Whitney U test was conducted for comparing results of both genders across all the parameters in each group. The result showed no significant difference between results obtained by males and females on any of the recording parameters at a significance level of less than 5%. Hence the data obtained from both males and females were combined for further analysis.

For further all statistical measures, considered dependent variables in each group were n1 latency, p1 latency and n1-p1 peak to peak amplitude along with independent variables were effect of time interval, and ear effects. Together with these variables, for

comparison between ears for each subject, asymmetric ratio was considered for analysis. All statistical measures were performed using SPSS software (version 17).

4.1: Placebo group:-

For subjects participated under placebo group, only a mixture of milk added with sugar (according to the taste) was given without coffee. The mean and standard deviation of latency measures in msec for both n1 and p1 across first baseline (B1), second baseline (B2), tested after 5min (T5) and tested after 20min (T20) were decimated to three values. The same were shown in table 4.1.

Table 4.1 *Mean and SD values for n1 latency and p1 latency for both right and left ear for four conditions within placebo group.*

Ear		n1 latency (msec)				p1 latency (msec)			
		B1	**B2**	**T5**	**T20**	**B1**	**B2**	**T5**	**T20**
Right	**Mean**	11.102	11.276	11.334	11.248	16.350	16.323	16.234	16.936
	SD	0.299	0.311	0.391	0.532	1.511	1.251	1.217	1.632
Left	**Mean**	11.218	11.276	11.276	11.334	16.496	16.468	16.350	16.701
	SD	0.427	0.340	0.311	0.391	1.028	1.026	1.053	1.142

From table 4.1 it is evident that very less n1/ p1 latency shifts noted across different recordings.

4.1.1: Latency measures across recordings in placebo group:-

Two way repeated measures of ANOVA (4 conditions X 2 ears) was performed to find out significant difference in n1 latency/ p1 latency obtained in different conditions (time intervals). The results were shown in table4.2. Thus the results indicate

that there is no significant difference in both n1 and p1 latencies before and after the intake of placebo. Similar findings were observed between right and left ear also.

Table 4.2 *Results of two way repeated measures of ANOVA placebo group*

	n1	**p1**
Across ears	[F (1, 9) = 0.234, P=0.640] NSD	[F (1, 9) = 0.019, p = 0.893] NSD
Across conditions	[F (3, 27) = 1.238, P = 0.315] NSD	[F (3, 27) = 3.91, p = 0.520] NSD

NSD= No significant difference at a value less than 0.05.

Grossly the results indicate that there is no significant difference in both n1 and p1 latencies before and after the intake of placebo and also there are no difference of affects between right and left ear.

4.1.2: Amplitude Measures across recordings in placebo group:-

Peak to peak amplitude from n1 to p1 was calculated in microvolts. The mean and standard deviation of such n1-p1 peak to peak amplitude for subjects under placebo group across B1, B2, T5 and T20 were tabulated in Table 4.3.

Table 4.3 *Mean and SD values for n1-p1 peak to peak amplitude for both right and left ear for four different conditions within placebo group.*

Ear		n1-p1 peak to peak amplitude			
		B1	**B2**	**T5**	**T20**
Right	**Mean**	8.635	9.909	10.645	8.366
	SD	5.722	5.518	7.318	5.056
Left	**Mean**	17.953	15.273	17.271	15.456
	SD	11.915	8.960	10.637	8.303

It can be easily understood from the table 4.3 that variations in n1-p1 peak to peak amplitude data across subjects in placebo group is quite higher, indicating that amplitude measures are highly variable across subjects. Thus both parametric and non-parametric tests were used for the analysis. Under parametric tests, two way repeated measures of ANOVA (4 conditions X 2 Ears) were performed to compare the n1-p1 peak to peak amplitude within placebo group across different conditions (Time intervals) or between two ears. The results indicated that there is no significant difference across 4 conditions [$F(3, 27) = 1.185$, $p = 0.334$], but there is a significant difference between ears [$F(1, 9) = 7.586$, $p = 0.022$] revealed. Thus further Paired sample t test was considered to reveal significant difference in n1-p1 peak to peak amplitude across ears. The result indicated significant difference in right ear and left ear n1-p1 peak to peak amplitude in all three conditions except at time interval of 5 min at 0.05 level of significance.

On non parametric tests Fried man test revealed a significant difference in right ear n1-p1 peak to peak amplitude across four conditions [$X^2(3) = 10.440$, $p = 0.015$], but there is no significant difference in left ear's n1-p1 amplitude. Further analysis was carried using Wilcoxon Signed Ranks Test and the output showed a significant difference

in n1-p1 peak to peak amplitude in right only between B1 and T5 at 0.05 level of significance (Z=0.017). Wilcoxon Signed Ranks Test was also used to analyze the difference in n1-p1 peak to peak amplitude between left and right ear within same condition (time interval). The result showed that there is significant difference in n1-p1 peak to peak amplitude for all the pairs selected between two ears for same condition at a significance level of less than 0.05.

Overall one can conclude that on amplitude measures there is high variability across subjects and also between ears with and without intake of placebo. In all the conditions the right ear recordings shown lesser n1-p1 amplitude compared to the left ear. However only in right ear significantly lowered amplitudes than left ear were recorded before and after placebo intake. No further conclusions were made due to large variability in the obtained amplitude measures.

4.1.3: Asymmetric ratio across recording in placebo group:-

Asymmetric ratio was calculated by using equation described in method chapter. The values obtained were in percentages and decimated to three points. The mean and standard deviation values for asymmetric ratio in placebo group across different conditions are given in table 4.4. All positive values indicated that peak to peak amplitude in left ear recordings were higher than that of right ear as shown in the amplitude measures.

Table 4.4 *Mean and SD values for asymmetric ratio in placebo group.*

	Asymmetric ratio			
	B1	**B2**	**T5**	**T20**
Mean	37.601	26.991	32.366	36.431
SD	23.634	20.140	23.724	21.414

It is apparent from the values that the Standard deviation values asymmetric ratio were higher. So both parametric and non parametric tests were performed to correlate the results obtained across conditions. Repeated measures of ANOVA were performed to compare asymmetric ratio within placebo group in different conditions (time intervals). The result showed that there is no significant difference in asymmetric ratio across different conditions (time intervals) [$F(3, 27) = 1.890$, $p > 0.05$] at 0.05 significance level. On non parametric tests, Fried man test result [$X^2(3) = 5.400$, $p > 0.05$] was also yielded similar results of the parametric test results.

It can be concluded from the above results that similar to latency measures, asymmetric ratio failed to show any significant differences before and after intake of placebo. Thus clearly one can understand that intake of placebo did not change/ influence the studied oVEMP parameters.

4.2: Regular users of coffee group:-

Subjects with a history of frequent intake of caffeine contained food habits were grouped into this group. For all subjects under this group a regularly used coffee powder mixed with milk was given orally. oVEMP was recorded before and after intake of coffee. The mean and standard deviation of oVEMP latency measures in msec for both n1 and p1 across first baseline (B1), second baseline (B2), tested after 5min (T5) and tested after 20min (T20) were decimated to three values. The same were shown in Table 4.5.

Table 4.5 *Mean and SD values for n1 latency and p1 latency for regular users of coffee*

Ear		n1 latency				p1 latency			
		B1	**B2**	**T5**	**T20**	**B1**	**B2**	**T5**	**T20**
Right	**Mean**	11.044	11.043	11.159	11.130	15.943	15.855	15.680	16.031
	SD	0.414	0.535	0.565	0.422	0.769	0.679	0.780	0.860
Left	**Mean**	11.131	11.160	11.044	11.131	15.826	16.002	15.681	15.767
	SD	0.347	0.361	0.366	0.420	0.824	0.586	0.818	0.775

From table 4.5 it is clear that very less n1/ p1 latency shifts noted across different recordings and also across the ear there is very little changes. And also variability in all latency measures is comparatively lower.

4.2.1: Latency measures across recordings in regular users of coffee group:-

Two way repeated measures of ANOVA (4 conditions X 2 ears) was performed to find out significant difference in n1/ p1 latency obtained in different conditions (time intervals). The results were mentioned in table 4.6.

Table 4.6 *Results of two way repeated measures of ANOVA in regular users of coffee group*

	n1	**p1**
Across ears	[F (1, 9) = 0.133, P=0.724] NSD	[F (1, 9) = 0.146, p = 0.712] NSD
Across conditions	[F (3, 27) = 0.134, P = 0.939] NSD	[F (3, 27) = 1.322, p = 0.284] NSD

NSD= No significant difference

These results show no change in n1/ p1 latencies between conditions or ears in regular users of coffee group also (similar result obtained in placebo group).

4.2.2: Amplitude Measures across recordings in regular users of coffee:-

The mean and standard deviation of n1-p1 peak to peak amplitude for subjects under regular users of coffee group across B1, B2, T5 and T20 were depicted in Table 4.7.

Table 4.7 *Mean and SD values for n1-p1 peak to peak amplitude in regular users of coffee group*

Ear		n1-p1 peak to peak amplitude			
		B1	**B2**	**T5**	**T20**
Right	**Mean**	12.263	13.708	15.252	13.744
	SD	6.761	8.183	9.554	8.712
Left	**Mean**	12.813	13.071	14.187	13.887
	SD	5.954	5.513	8.150	7.160

It is markedly clear from table 4.7 that the variations in n1-p1 peak to peak amplitude across subjects in regular users of coffee group is larger. Thus both parametric and non-parametric tests were used for the analysis. Two way repeated measures of ANOVA (4 conditions X 2 Ears) were performed to compare the n1-p1 peak to peak amplitude within regular users of coffee group across different conditions (Time intervals). The results showed no significant differences across conditions [F (3, 27) = 0.134, P = 0.939] as well as across ears [F (3, 27) = 1.750, p= 0.181] at significant level of 0.05.

Non parametric tests (Fried man test) also results showed no significant difference in peak to peak amplitude across four conditions [$X^2(3) = 7.970$, p = 0.1.345]. This indicates that there is no clear change in n1-p1 peak to peak amplitude in regular users of coffee across four conditions / between two ears after the intake of coffee.

4.2.3: Asymmetric ratio across recording in regular users of coffee group:-

Similar to the asymmetric ratio measures calculated for placebo group, for subjects categorized under regular group also computed. The mean and standard deviations obtained were shown in below Table 4.8.

Table 4.8 *Mean and SD values for asymmetric ratio in regular users of coffee group.*

	Asymmetric ratio			
	B1	**B2**	**T5**	**T20**
Mean	16.105	19.752	12.944	17.489
SD	12.796	11.804	8.931	15.736

Repeated measures of ANOVA were performed to compare the n1-p1 peak to peak amplitude asymmetric ratio within regular users of coffee group in different conditions (time intervals). The result showed that there is no significant difference in asymmetric ratio across different conditions (time intervals) [F (3, 27) = 1.087, p = 0.372] at 0.05 significance level. Non parametric test Fried man test was also administered to confirm the results obtained through parametric tests. The Fried man test result [$X^2(3) = 6.000$, p = 0.112] also yielded similar results of the parametric test results.

Summarizing all the results obtained in regular users, the main affect of coffee on regular users is not significant across all latency and amplitude measures of oVEMP. Thus one can conclude that for regular users of coffee, intake of coffee before oVEMP recording would does not alter the results significantly.

These results are in contra indication to the results obtained by Shalini et al (2012) & Dixit et al (2005 & 2006) in the field of evoked potentials. These differences would indicate differential coffee affect on evoked potentials and myogenic potentials. But these differences could also be due to differences in the methodological procedures followed.

4.3: Non regular users of coffee group:-

The oVEMP data obtained from **s**ubjects with no prominent history of taking coffee contained food product regularly were considered under this group. The mean and standard deviation of latency measures in msec for both n1 and p1 across first baseline (B1), second baseline (B2), tested after 5min (T5) and tested after 20min (T20) were decimated to three values. The same were given in Table 4.9.

Table 4.9 *Mean and SD values for n1 latency and p1 latency in non regular users of coffee group.*

Ear		**n1 latency**				**p1 latency**			
		B1	**B2**	**T5**	**T20**	**B1**	**B2**	**T5**	**T20**
Right	**Mean**	11.538	11.683	11.712	11.624	16.430	16.410	16.351	16.525
	SD	0.495	0.562	0.756	0.436	1.095	0.889	1.258	1.208
Left	**Mean**	11.597	11.626	11.800	11.770	16.527	16.440	16.556	16.993
	SD	0.690	0.715	0.854	0.620	1.117	1.112	1.264	0.982

From table 4.9 it can be observed that very less n1/ p1 latency shifts noted across different recordings.

4.3.1: Latency measures across recordings in non regular users of coffee group:-

Two way repeated measures of ANOVA (4 conditions X 2 ears) was performed to find out significant difference in n1/p1 latency obtained in different conditions (time intervals) or between two ears. The results were shown in the following table 4.10.

Table 4.10 *Results of two way repeated measures of ANOVA in non regular users of coffee group*

	n1	**p1**
Across ears	[F (1, 9) = 0.424, P=0.531] NSD	[F (1, 9) = 1.389, p = 0.269]. NSD
Across conditions	[F (3, 27) = 0.904, P = 0.452] NSD	[F (3, 27) = 1.694, p = 0.192] NSD

NSD= No significant difference

Thus one can conclude that there is no change in n1/ p1 latencies in non regular users of coffee across four conditions or between two ears after intake of coffee powder (similar affect as observed in other two groups as well).

4.3.2: Amplitude Measures across recordings in non regular users of coffee:-

The n1-p1 amplitude measures were measured in micro volts. The mean and standard deviation of such n1-p1 peak to peak amplitude for subjects under non regular users of coffee group across B1, B2, T5 and T20 were tabulated in Table 4.11

Table 4.11 *Mean and SD values for n1-p1 peak to peak amplitude in non regular users of coffee group*

Ear		n1-p1 peak to peak amplitude			
		B1	**B2**	**T5**	**T20**
Right	**Mean**	8.798	8.757	7.330	9.125
	SD	7.733	7.275	2.923	4.543
Left	**Mean**	10.843	10.569	8.598	10.904
	SD	9.324	9.470	8.277	9.733

It is very much evident from table 4.11 that the variations in n1-p1 peak to peak amplitude across subjects in non regular users of coffee group is quite higher, indicating that amplitude measures are highly variable across subjects. Thus both parametric and non-parametric tests were used for the analysis. However, two way repeated measures of ANOVA (4 conditions X 2 Ears) were performed to compare the n1-p1 peak to peak amplitude within non regular users of coffee group across different conditions (Time intervals). The results indicated that there is no significant difference across 4 conditions [$F (3, 27) = 1.431$, $p= 0.255$] and also across ears [$F (1, 9) = 0.636$, $P=0.446$]. On non parametric tests Fried man test revealed there is no a significant difference in right ear n1-p1 peak to peak amplitude across four conditions [$X^2(3) = 3.000$, $p = 0.392$].

From this result we can conclude that there is no change in n1-p1 peak to peak amplitude across different conditions and between two ears after the intake of coffee in non regular users of coffee.

4.3.3: Asymmetric ratio across recording in non regular users of coffee group:-

Similar to the other two groups, asymmetric ratio calculated between ears for subjects considered under non regular users. The mean and standard deviation values of the same were cited in table 4.12.

Table 4.12 *Mean and SD values for asymmetric ratio in non regular users of coffee group.*

	Asymmetric ratio			
	B1	**B2**	**T5**	**T20**
Mean	20.802	25.438	34.997	30.368
SD	22.604	20.587	23.249	25.996

Repeated measures of ANOVA were performed to compare across different conditions (time intervals). The result showed that there is no significant difference in asymmetric ratio across different conditions (time intervals) [F (3, 27) = 3.123, p = 0.432] at 0.05 significance level. Non parametric test (Fried man test) was also administered to confirm the results obtained through parametric tests. The Fried man test result [$X^2(3) = 8.640$, p = 0.132] also yielded similar results of the parametric test results.

These results reveal that regularly used coffee powder of 1.8g is not enough to make a change in latency or amplitude parameters in both regular and non regular users of coffee across different conditions.

4.4: Between group comparison

As the main affect of coffee in different groups is not significant (i.e.) ruled out**,** further no statistical measures were performed to compare different parameters of oVEMP across three groups. But the data obtained were depicted in the figures 4.1, 4.2 and 4.3. For the depiction of these figures, simple statistical measures as Mean and standard deviation were computed by combining data obtained in both ears.

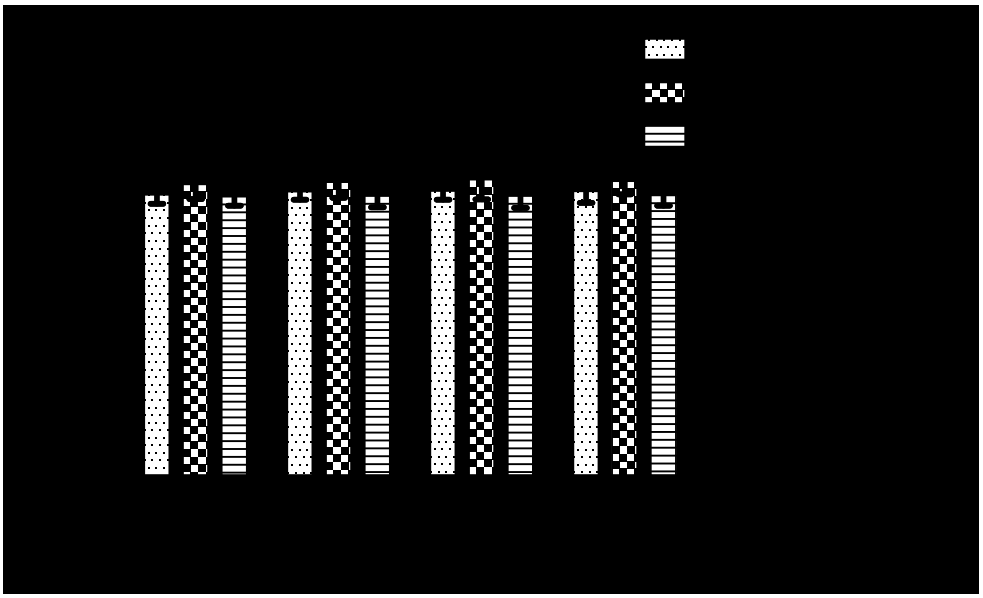

Figure 4.1: Comparison of n1 latency across three groups

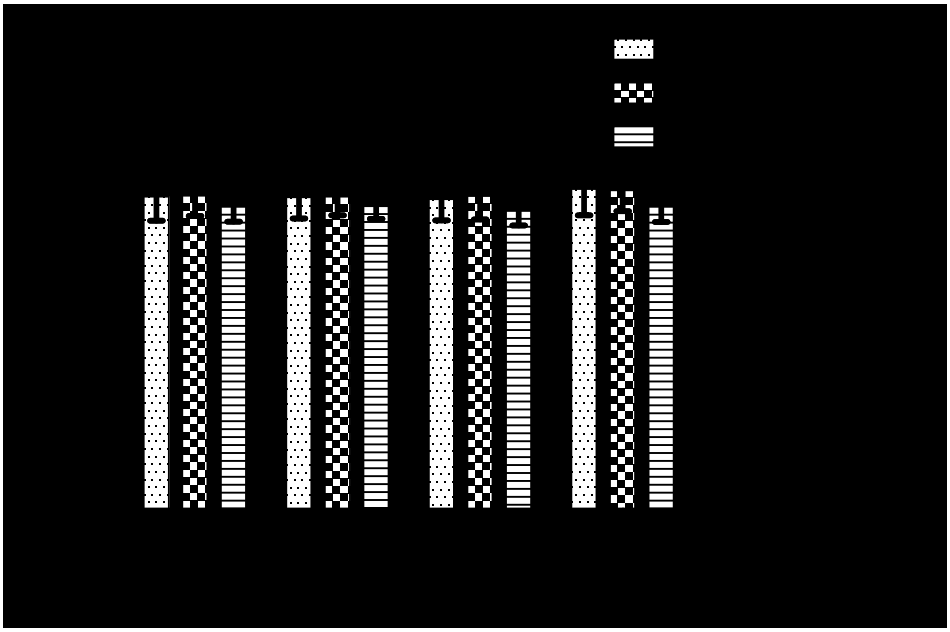

Figure 4.2: Comparison of p1 latency across three groups

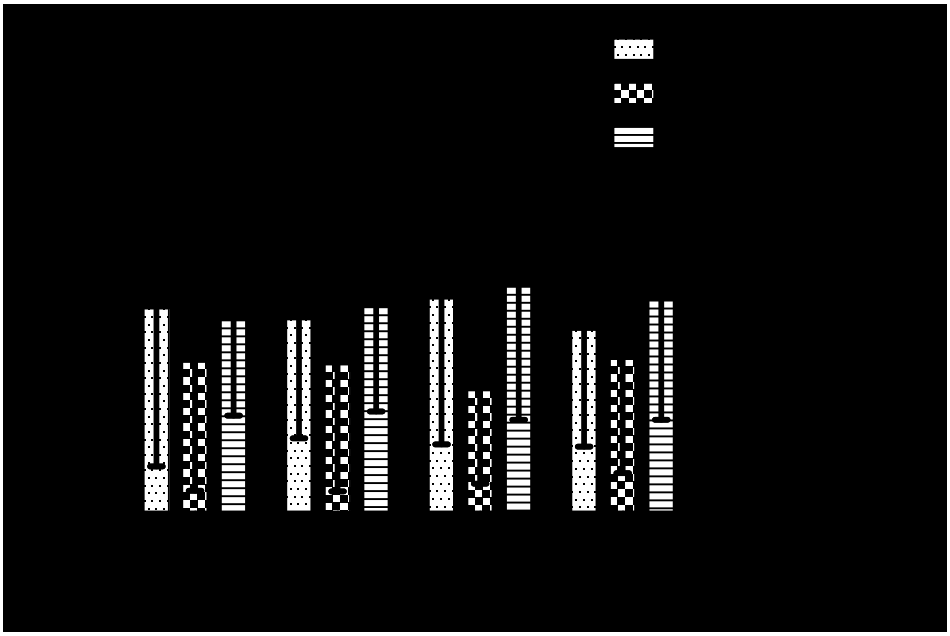

Figure 4.3: Comparison of n1- p1 peak to peak amplitude across three groups

It can be seen from the above figures that n1 latencies are little longer in non regular users of coffee from other two groups, while the p1 latencies are shorter comparatively. However considering variations possible in each peak these differences might not be significantly different. Similarly, the peak to peak amplitudes are lower in non regular users of coffee than other two groups. But as the variability is too large no conclusion could be inferred.

From the figure 4.3 it is clearly evident that non regular users showed a clear reduction in the amplitude. This might indicate possible reduction in peak to peak amplitude in non-regular user if coffee been administered. Thus it can be concluded that one time intake of coffee is not sufficient to make a changes in the oVEMP findings.

CHAPTER 5

SUMMARY AND CONCLUSIONS

The present study was considered to investigate the effect of coffee intake on oVEMP parameters like n1 latency, p1 latency, n1-p1 peak to peak amplitude and asymmetric ratio when taken as in regular usage. From the results it was understood that the administered coffee had very small impact on oVEMP and were not statistically significant. It was also clear that amplitude measures of oVEMP are highly variable across subjects and potential to show changes after consumption of coffee.

Though there were no statistically significant changes across three groups, it can be inferred that n1-p1 peak to peak amplitude was consistently (before and after intake of coffee) smaller in non regular users of coffee compared to other two groups. These variations in amplitude between regular and non- regular group could be due to the long time effects of coffee (i.e) long term use of coffee might lead to have higher inter-peak amplitude in oVEMP, but for non-regular users it would have diminishing affects on amplitude after intake of one time coffee. Thus there is always a factor of smaller amplitudinal changes, which needed to be unfolded in further studies.

However other studies like Dixit et al. (2006), Shalini et al. (2012) showed a significant difference in latencies and amplitude parameters of auditory brainstem responses and visually evoked p100 responses. These differences could also be due to methodological differences in administration of caffeine. Dixit et al. (2006), Shalini et al. (2012) investigated their studies under laboratory conditions while this study was

conducted in natural method of coffee intake. These differences also provide insights into differentials affects of coffee on evoked potentials different from myogenic potentials.

Apart from the above results there are many noticeable negative effects due to high dose levels of coffee. Thus the authors indicate potential of dangers affects if abused.

5.1: Limitations of the study

The few limitations in this study include

1) Amount of coffee administered can be based on their daily usage amount (or) according to their body mass index (However 1.8g of coffee powder for 100ml of milk is considered to be tolerable, higher amounts lead to have bitter taste in unusual way).
2) Coffee affects on clinical groups was not considered.

5.2: Future directions

1) Similar study could be conducted in subjects with vestibular symptoms to find out differential effects of coffee between normal subjects and subjects with vestibular symptoms.

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