Cervical vestibular evoked myogenic potentials: A systematic review and meta-analysis

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Cervical vestibular evoked myogenic potentials: A systematic review and meta-analysis

by

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Abstract

Objective: A systematic literature review and meta-analysis was performed to determine the effect of stimulus type, sternocleidomastoid (SCM) muscle activation method, transducer type and method to control SCM muscle electromyography (EMG) level on response parameter values for 0.1 ms click evoked and 500 Hz tone burst cervical vestibular evoked myogenic potentials (cVEMPs). A description of normative response values was attempted.

Method: An electronic systematic literature review was performed to obtain normative cVEMP response data. Subsequently a meta-analysis was conducted to determine significant effects on cVEMP response parameters and to obtain norms.

The scientific database, Scopus, was used to identify reports containing normative data. Reports were selected based on inclusion and exclusion criteria determined beforehand. Weighted means were calculated and compared to identify significant effects on response parameters and normative data for cVEMP interpretation.

Results: Sixty six reports were included in the systematic review and most prevalent stimulus and recording parameters are identified and tabulated as guidelines for conducting and interpreting cVEMPs in the clinic. Stimulus type had a statistically significant effect on all response parameters (latency P1, latency N1, raw amplitude, corrected amplitude, asymmetry ratio and threshold), where larger latencies were noted for 500 Hz tone burst cVEMPs (TBVs). Stimulus duration was confirmed to produce larger latencies. Larger raw amplitude values were found for TBVs and visual monitoring levels of at least 40 µV is suggested. Larger asymmetry ratios for 0.1 ms click cVEMPs (CVs) were found and upper limits of normality of 14.2% (CVs) and 10.05% (TBVs) are suggested. Higher threshold values were found for CVs and threshold ranges of 89 dB HL (SD 0.88) for CVs and 81.02 (SD 2.03) for TBVs are suggested. SCM muscle activation method, transducer type and method to control SCM muscle EMG level had statistically significant effects on all response parameters, indicating that one method to perform the cVEMP should be chosen and used consistently for accurate interpretation of results.

Conclusions: Optimal stimulus and recording parameters suggested by previous research are confirmed by the current systematic review and meta-analysis and are suggested for clinical use. Response parameter values are influenced by variations in stimulus and recording parameters and normative response values are suggested as guideline for cVEMP interpretation.

Keywords

Vestibular Evoked Myogenic Potential

SCM muscle activation method

Method to control SCM muscle EMG level

Transducer

Normative data

List of abbreviations

AR	**asymmetry ratio**
BPPV	**benign paroxysmal positional vertigo**
CI	**confidence interval**
cm	**centimetre**
CV	**click evoked cVEMP**
cVEMP	**cervical Vestibular Evoked Myogenic Potential**
dB	**decibel**
EMG	**electromyography**
ENG	**electronystagmography**
FL	**force level**
Hz	**Hertz**
mA	**milli-Ampere**
MRV	**mean rectified voltage**
ms	**millisecond**
mV	**micro Volt**
N_1	**first negative peak**
nHL	**normal hearing level**
P_1	**first positive peak**
pSPL	**peak sound pressure level**
SCM	**sternocleidomastoid**
SD	**standard deviation**

SEH	**supine, head elevated**
SETC	**supine, elevate and rotate head contralaterally**
SPF	**seated, push head forward**
SPL	**sound pressure level**
SRH	**supine, head rotated**
SSCD	**superior semicircular canal dehiscence**
STC	**seated, turn head contralaterally**
TBV	**500 Hz tone burst evoked cVEMP**
VOR	**vestibulo-ocular reflex**
VSR	**vestibulo-spinal reflex**

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Chapter 1: Introduction

"In order to obtain the maximum benefit from VEMP testing, examiners need to know the ideal techniques for conducting testing and established ranges of normal results."
(Bush, Jones, & Shinn, 2010, p.170)

Vestibular assessment is both a challenging and exciting field in the practice of audiology (Kocunik, Beck, & Khalil, 1993). It is a technically demanding area which has become more sophisticated mainly because of our increased understanding of the underlying pathophysiology of vestibular disorders combined with advances in technology (Paydarfar & Goebel, 2000). However, a lack of uniform test procedures and response values used for interpretation of test results are evident even in office evaluation tests, which require no additional technology than present in the standard audiology office.

Most audiologists come in contact with individuals complaining of dizziness and disequilibrium (Desmond, 2004). In fact, these symptoms constitute a significant portion of the clinician's caseload and are described as a very frequent chief complaint of individuals by various authors (Desmond, 2004; Hamid, 2000; Horak, Wrisley, & Frank, 2009; Jackson, Morgan, Fletcher Jr, & Krueger, 2007; Phillips, FitzGerald, & Bath, 2009). It is no surprise then, that the American Speech Language and Hearing Association [ASHA] (ASHA, 2004) and the Health Professions Council of South Africa [HPCSA] (HPCSA, 2009) include the prevention, diagnosis and intervention of the vestibular system as part of the role of the audiologist.

1.1 The vestibular system

The vestibular or balance system as a whole can be viewed as a three part structure when described in a simplistic manner. The three parts are depicted by Domínguez and Magro (2009) as the data input system, the data processing system and the motor response system. Data input depends on the visual system, somatosensorial system and the peripheral vestibular system. The peripheral vestibular system includes the labyrinth and vestibular nerve (Barin, 2009). The labyrinth has a bony and membranous component, filled with perilymphatic and endolymphatic fluid, respectively (Desmond, 2004). Two types of sensors, the

semicircular canals and the otolith organs, are housed in the membranous labyrinth (Furman & Cass, 2003). The cristae ampullaris are housed one in each of the three semicircular canals. They are sensitive to angular movement of the head and detect rotation of the head in the “pitch”, “yaw” and “roll” planes. The otolith organs include the utricle and saccule which are housed in two cavities within the membranous labyrinth (Desmond, 2004). These two organs are mainly responsible for detecting linear motion in three dimensions and the direction of gravity per se (Barin, 2009) in order to maintain postural control (Desmond, 2004).

In the central nervous system, data collected from the various sensory systems are processed. Sensory information from the peripheral vestibular organs regarding head movement is transmitted via the vestibular portion of the eighth cranial nerve to the vestibular nuclei (Furman & Cass, 2003). The vestibular nuclei constitute the central component of the vestibular system (Barin, 2009) and receive not only direct vestibular input, but also afferent input from other sensory systems and areas of the central nervous system (Jacobson, Newman, & Kartush, 1997).

Ascending and descending pathways extend from the vestibular nuclei which contribute to the motor response system. Although cortical and neurovegetative responses are components of the motor response system, there are at least three important reflexes the audiologist should be aware of (Barin, 2009; Domínguez & Magro, 2009; Furman & Cass, 2003). The vestibulo-ocular reflex (VOR) is a mechanism whereby head movement results in a reflexive corrective eye movement in order to establish gaze stabilization during movement of the head (Barin, 2009; Desmond, 2004; Furman & Cass, 2003). Another reflex, the vestibulospinal reflex (VSR) contributes to the various motor control mechanisms which are responsible for maintaining postural stability (Barin, 2009). Thirdly, the vestibulocollic reflex (VCR) aims to stabilize the head by acting on the neck muscles (Hain, 2011). Since it is not possible to directly evaluate the input system (except for evoked potentials that merely provide information on isolated function), or data processing, the audiologist must rely on responses of the motor response system to identify possible vestibulopathies (Barin, 2009; Domínguez & Magro, 2009).

The ear is a compound organ sensitive to both sound and acceleratory forces. This is evident in the inescapable anatomical link between the auditory and peripheral vestibular system where the cochlea and vestibular labyrinth are immediately adjacent to each other (Furman & Cass, 2003). The endolymphatic and perilymphatic fluid of these two structures share common fluid spaces and are thus in communication with one another. Furthermore, the inner ear shares a common blood supply where the labyrinthine artery divides into the anterior vestibular artery and common cochlear artery, which again divides into the main cochlear artery and vestibular-cochlear artery. A further branch of the vestibular-cochlear artery is the posterior vestibular artery. Blood supply to the vestibular labyrinth and cochlea is thus a series of interconnected blood vessels, supplying various parts of the cochlea and vestibular labyrinth simultaneously. The anatomical link is also evident in the fact that both the cochlear and vestibular labyrinths are neurologically innervated by the eighth cranial nerve, which branches into a vestibular and cochlear segment (Barin, 2009).

Given the above-mentioned information, it is not surprising that disorders of the vestibular system may also affect the cochlea. In fact, the presence of an associated sensori-neural hearing loss is noted as the single strongest incriminator when identifying a possible lesion in the vestibular organ (Shepard, 2009). Accompanying otologic symptoms that are probable in the case of a vestibulopathy, include aural fullness, otalgia and tinnitus and may be useful in the lateralization of the vestibular lesion (Desmond, 2004; Furman & Cass, 2003). These complementary symptoms emphasize the importance of diagnostic audiological testing and the role the audiologist plays in the identification and lateralization of vestibular disorders. Yellin (2000) confirms this major role of audiologists in evaluation of the vestibular system “because of the link between the auditory and vestibular systems and the audiologist’s expertise in these areas”.

The described anatomical link has also been used by researchers to justify the use of vestibular function assessment in children with hearing impairment. A study by Nandi and Luxon (2008) describes vestibular development and the importance of vestibular function assessment in children with profound hearing loss and those with delays in postural control and locomotor milestones. This is imperative for habilitation or rehabilitation to commence as soon as possible.

Thus, based on the anatomical link between the cochlea and vestibular system and the described physiopathology of the vestibular system, assessment for vestibular disorders should include thorough diagnostic audiological testing, as well as a comprehensive neurologic history and office vestibular assessment procedures (Shepard, 2009). Laboratory vestibular function assessment procedures (such as electronystagmography and videonystagmography) are described as important by Shepard (2009) and add further dimensions to the assessment in complex cases. Since vestibular function testing falls well within the scope of practice of audiologists, thorough test procedures, normative data for test interpretation and clinical skills pertaining to these laboratory tests are imperative for evidence based practice.

1.2 Vestibular function testing

Electronystagmography (ENG) commonly consists of a battery of tests. Typically, tests in the ENG battery focused mainly on assessment of the lateral semicircular canals and the superior vestibular nerve. However, vestibular function testing has evolved in such a manner that vertical semicircular canals and the otolith organs can also be investigated. In other words, not only lateralization of lesions is now possible, but also deducing which part within the vestibular labyrinth is affected.

A thorough discussion of the neurotologic history precedes vestibular function testing, since the test selection and course of management depends greatly thereon. Testing then proceeds with either laboratory or bedside evaluations, or a combination of the two. Laboratory testing usually include ENG testing, videonystagmography (VNG) testing, rotational chair testing and/or computerized dynamic posturography (CDP). ENG-testing usually consists of oculomotor testing (including smooth pursuit tracking, saccade analysis, gaze fixation and optokinetic simulation), test for spontaneous nystagmus, rapid positioning tests (i.e. Dix-Hallpike maneuver), tests for positional nystagmys and caloric irrigations. The ENG test battery is useful in determining whether a central or peripheral lesion is present, and may also aid in determining the exact location of the lesion in the vestibular system. Rotational chair testing is used to expand the evaluation of the peripheral vestibular system and is needed for defining the degree of bilateral peripheral lesions. CDP adds valuable

information on postural control of patients and is helpful to design a rehabilitation program in some cases (Shepard, Solomon, Ruckenstein, & Staab, 2002).

The bedside evaluation tests usually include a physical examination of the eyes (sometimes with the use of Frenzel's glasses), the test for skew deviation, the head thrust test, the head-shake test, the dynamic visual acuity test, positional tests, pressure testing, visual tracking tests, saccadic eye movement tests and stance and gait tests (i.e. Romberg tests) (Tusa, 2005).

A relatively recent addition to the test battery for evaluating vestibular function is the cervical Vestibular Evoked Myogenic Potential (VEMP) (Akin & Murnane, 2008; Rosengren, Welgampola, & Colebatch, 2010). In short, the cVEMP can be described as an inhibitory potential recorded from the sternocleidomastoid (SCM) muscle due to saccular activation in response to loud sounds (Zhou & Clarke Cox, 2004; Akin & Murnane, 2008). From an evolutionary point of view, the cochlea is a late development in humans (Ferber-Viart, Dubreuil, & Duclaux, 1999; Todd, Cody, & Banks, 2000; McCue & Guinan, 1997). In the absence of a cochlea, the saccule has been noted as an acoustic-sensitive organ in lower species such as the fish (Popper, Platt, & Saidel, 1982). Although the cochlea has replaced the saccule as primary organ for hearing over time, it has been reported that the saccule retained some auditory function in amphibians, birds, guinea pigs, cats and squirrel monkeys (Todd et al., 2000). Some authors speculate that for humans, the saccule has retained an ancestral acoustic sensitivity (Todd et al., 2000; McCue & Guinan, 1997), but Carey and Amin (2006) states that there are no known afferents between the saccule and auditory nuclei and thus, the cVEMP reflects a pressure-mediated vestibular response to acoustic stimulation.

Although direct recording of auditory-evoked neurogenic responses has been done in animal research, it is not ethically viable in human studies (Zhou & Clarke Cox, 2004). Thus, researchers altered their focus to that of recording muscular responses (Zhou & Clarke Cox, 2004). The work of Dr. Pietro Tullio on alert animals paved the way for studying the acoustic sensitivity of the vestibular system, but in 1935 von Békésy was the first to describe sound-evoked vestibular responses in normal human subjects (Welgampola & Colebatch, 2005; Akin & Murnane, 2008). He reported

observing small head movements toward the stimulated ear evoked by loud sounds (122-134 dB SPL) and provided evidence that these movements were not mediated by the cochlea, since they were evident even after stimulation induced temporary deafness. He suggested that the responses were the result of fluid displacement in the otolith organs (Akin & Murnane, 2008; Welgampola & Colebatch, 2005; Rosengren et al., 2010).

In 1958, Geisler, Frishkopf and Rosenblith (1958) recorded short-latency responses to auditory clicks at the inion. They suggested that these responses were of cortical origin. Bickford, Jacobson and Cody extended this research in 1964 and made various significant conclusions regarding the characteristics of averaged inion responses to clicks. Firstly, the myogenic origin of the response was confirmed, since responses were exclusively recorded during extension of the neck musculature and absent following curarisation thereof. They also noted that the response amplitude was directly proportional to stimulus and tonic electromyography (EMG) level. Secondly, they confirmed that the responses were mediated by the vestibular system (as opposed to the cochlear system), since the responses were present in deaf patients with normal vestibular function and absent in a deaf patient with loss of vestibular function (Bickford et al., 1964). Their attempts at identifying the activation organ was narrowed down further and subsequent studies on selective inner ear lesions proved the saccule to be the origin of the inion response (Cody & Bickford, 1969; Townsend & Cody, 1971). However, the inion response was described as being too non-specific for clinical use (Meier-Ewert, Gleitsmann, & Reiter, 1974).

More recently Colebatch and Halmagyi (1992) and Colebatch, Halmagyi and Skuse (1994) revised the recording settings and measured EMG activity from the SCM muscle in response to high-level, air-conduction clicks. This established a reliable procedure to record myogenic potentials evoked by clicks and the cVEMP became a practical, clinical test. The authors confirmed a short-latency response and its dependence on level of tonic EMG. The response could be depicted as an initial positive peak (p13 or P1), followed by successive positive and negative peaks (n23/N1, p34, n44). Also, the response was recorded from the ipsilateral SCM muscle, as is also described by Basta et al. (2005) who conducted an intra-operative study. A “crossed response” has been noted by some researchers, where an inverted peak

was observed in the contralateral SCM muscle. However, it is thought that this response may be produced by spread of the stimulus to other vestibular afferents with bilateral projection to the SCM muscles, such as the utricle (Rosengren et al., 2010; Welgampola & Colebatch, 2001b). Brantberg and Mathiesen (2004) pointed out that the response is abolished after inferior vestibular nerve resection, indication that the response must originate in the saccule (as opposed to the utricle).

In summary, the described animal and human neurophysiological and clinical data suggest that the cVEMP is mediated by an ipsilateral anatomical pathway that includes the saccular macula, inferior vestibular nerve, lateral vestibular nucleus in the brainstem, descending medial vestibulospinal tract and the motorneurons in the ipsilateral SCM muscle (Akin & Murnane, 2008; Akin, et al., 2004; Cody & Bickford, 1969). Although VEMPs are currently also measured over the ocular muscles, the present document will refer to the described cervical VEMP (cVEMP) recorded from the SCM muscle.

Although the vestibular afferents are sensitive to head acceleration, they are also responsive to acoustic, vibratory and electric stimulation (Welgampola & Colebatch, 2005). These are imposed head accelerations and are characteristically non-physiological, implying that they do not replicate natural conditions. Notwithstanding, in effect, any stimulus that is intense enough and of transient nature will be adequate to cause a brief pressure gradient over the saccule. This will stimulate the hair cell bed of the saccule which in turn will activate the vestibulospinal reflexes that aid in maintaining tone in the anti-gravity muscles. When an acoustic stimulus is used to provoke a cVEMP response, the mentioned pressure gradient is thought to be the result of a large displacement of the stapes footplate, since anatomically the stapes and saccule are in close proximity of each other (Rosengren et al., 2010; Zapala, 2007; Welgampola & Colebatch, 2005).

The cVEMP is a manifestation of the vestibulo-collic reflex. When measuring the cVEMP, tonic SCM muscle contraction generates background EMG which is interrupted briefly due to a short period of inhibition (Welgampola & Colebatch, 2005; Rosengren et al., 2010). It is likely that this inhibition is the result of the central vestibular system interpreting the activation from the saccule as a temporary loss of

postural tone. The system then reacts with a reflexive increase in extensor muscle activity and decrease in flexor (SCM) muscle activity (Carey & Amin, 2006).

1.3 SCM muscle activation

It seems that there are two basic techniques used to activate the SCM muscles during cVEMP testing; one being head rotation and the other neck flexion. Both can be done with the patient either sitting or in a supine position, although the latter is preferable for neck flexion. (Wang & Young, 2006; Zapala, 2007; Akin, et al., 2004; Rosengren et al., 2010). Rotating the head in a sitting position involves having the patient turn their head to the contralateral side of stimulation. This way, the ipsilateral SCM muscle is flexed and activated for recording (Zapala, 2007). The minimal level of effort acquired for this method makes it suitable for testing the aged, newborn and debilitated populations according to some literature (Eleftheriadou & Koudounarakis, 2011). The head rotation method can also be used in a supine position, where the patient rotates his/her head towards the contralateral shoulder as head down in the yaw plane (Wang & Young, 2006). Thus, the rotation method will predominantly assure unilateral recordings.

The neck flexion method has several variations and SCM muscle activation is achieved by having the patient lift his/her head against gravity. In the supine position, patients can be instructed to lift the head from the horizontal plane and to keep the head in the midline. Bilateral SCM muscle activation has also been achieved by having patients pushing the head forward against a padded bar whilst in the sitting position (Welgampola & Colebatch, 2005). By applying these procedures, simultaneous recording from both ears can be done (Ozdek, Tulgar, Saylam, Tatar, & Korkmaz, 2009; Akin, et al., 2004). The bilateral neck flexion method has been described as advantageous for the elderly and paediatric populations, since simultaneous stimulation of both ears may reduce test time and possible muscle fatigue (Akin, et al., 2004). However, Rosengren et al. (2010) found that these populations are able to maintain proper SCM muscle activation, provided that the upper body is positioned approximately 30° from horizontal with the head only slightly lifted and that secondly, sufficient rest breaks should be allowed. The authors prefer

this method of stimulation, since possible contralateral responses can be revealed and recorded.

Another variation of the neck flexion method is having the patient in a supine, semi-recombinant position with the head turned to the side about 45° (Zapala, 2007). This will allow for unilateral recordings. According to Zapala (2007), an advantage of this method is that the weight of the head of the patient is a constant, meaning that muscle contraction should be equal for each ear that is tested. However, since other muscles may aid in lifting the head, active EMG monitoring is essential to ascertain this assumption. Isaacson, Murhpy and Cohen (2006) compared three methods of SCM muscle activation and found that eliciting cVEMPs with the patient in the supine position with the head turned to the contralateral side of stimulation leads to the most robust amplitudes.

Wang and Young (2006) compared the head rotation method in the sitting position and the head elevation method with the head in the midline position. They obtained a lower response rate and recorded smaller cVEMP amplitudes with the head rotation method, which discourages the use of this method as a screening procedure. However, when combining results of both the head elevation and head rotation methods, a higher response rate was obtained compared to using either method alone. Thus, the rotation method should be used to reduce false-negative results in patients who cannot sustain SCM muscle activation with the head elevation method. These results are also confirmed by Ozdek et al. (2009), who compared the two methods in children using logon stimulus.

1.4 Stimulation mode

Various stimulation modes can be utilized to evoke cVEMP responses, which include air conduction, bone conduction and transmastoid galvanic stimulation. The physiologic response to air conduction stimuli has been described and includes mechanical stimulation of the saccule due to large stapes footplate displacement (Welgampola & Colebatch, 2005). Air conduction clicks and tone bursts are used most

frequently and can be delivered via head or insert phones (Rosengren et al., 2010; Eleftheriadou & Koudounarakis, 2011).

The last decade has been marked with studies attempting to identify whether air conduction clicks or tone bursts are best suited for clinical use. Cheng, Huang and Young (2003) reported that click-evoked cVEMPs revealed a higher response rate, shorter latency and larger amplitude when compared to short tone burst evoked cVEMPs. A study conducted by Bush et al. (2010) concluded that the type of stimulus used had no statistically significant effect on amplitude asymmetry, however, only a small study group of 8 participants was included. It seems that the majority of data indicate short tone bursts to be superior to click stimuli when attempting to evoke cVEMP responses. Already in 1999 and 2001, Welgampola and Colebatch (2001a) and Murofushi, Matsuzaki and Wu (1999) illustrated that 500 Hertz (Hz) tone bursts evoke the largest cVEMP amplitudes, making tone bursts an adequate stimulus for clinical use. Basta, Todt and Ernst (2005) confirmed large differences between cVEMP latencies evoked by clicks and tone bursts and Wu, Shiao, Yang and Lee (2007) substantiated these findings. The authors recommended the use of short tone bursts, since a large inter-laboratory variability concerning click-evoked cVEMP latency and amplitude was evident. More recently, Viciana and Lopez-Escamez (2012) indicated that 500 Hz short tone bursts elicited consistently larger amplitudes and had better reliability across recording sessions.

Since high intensity levels are required to elicit cVEMPs, care must be taken with calibration of stimuli. If possible, the physical sound energy content should be indicated, such as the A-weighted intensity or $L_{Aeq.}$ Rosengren, Govender and Colebatch (2011) matched click and tone burst stimuli by using decibel (dB) L_{Aeq} and still found tone burst evoked responses to be larger in amplitude, more frequent and had a lower threshold than clicks. Similarly, these authors proved that the use of a 500 Hz tone burst will maximize the prevalence and amplitude of cVEMP responses for a given sound pressure level (SPL) (2009). Given this information, it seems that tone bursts require a lower intensity for cVEMP eliciting and will maximize patient comfort during testing. Overall, the use of air conduction clicks or tone bursts are contra-indicated when the patient experiences tinnitus (Welgampola & Colebatch, 2005).

Normal middle ear function is a prerequisite for elicitation of air conduction cVEMPs (Eleftheriadou & Koudounarakis, 2011). This implies difficulty eliciting a cVEMP response in the presence of a conductive hearing loss. As with pure tone audiometry, bone conduction stimuli can be utilized to bypass the middle ear system in order to stimulate the vestibular afferents (Yang & Young, 2003). The vibration will be transmitted through the skull bones and also the external auditory meatus and middle ear cavity, middle ear ossicular inertia, cochlear fluid inertia and pressure transmission from the cerebrospinal fluid (Rosengren et al., 2010). Bone conduction stimuli can be induced by using either vibration (by means of a clinical bone conductor) or skull taps (by means of a clinical reflex hammer) (Rosengren et al., 2010). Vibration stimuli are preferred above taps, since they are consistently present in healthy individuals and can be calibrated (Welgampola, Rosengren, Halmagyi, & Colebatch, 2003).

Sheykholeslami, Kermany and Kaga (2000) and Welgampola et al. (2003) proved the presence of a short-latency, biphasic (P1-N1) responses in subjects with normal hearing and conductive or sensorineural loss and proved the vestibular origin of the responses. Bone conduction cVEMPs are typically bilateral (as opposed to air conducted tones) since interaural attenuation is negligible, but larger amplitudes and earlier latencies are usually recorded from the ipsilateral SCM muscle (Welgampola et al., 2003). Significantly lower threshold levels are also obtained with bone conduction stimulation which may be contributed to both utricular and saccular activation (Welgampola et al., 2003).

Calibration is also essential for bone conduction and dB force level (FL) where a 1 micro Newton reference is typically used. Usually, bone conduction cVEMPs are obtained using 200-250 Hz tone bursts with a duration of 7 to 12 milliseconds (ms), and they are mostly absent at frequencies above 1000 Hz (Akin & Murnane, 2008). Wave morphology is best when the bone oscillator it placed 3 centimetres (cm) posterior and 2 cm superior to the external auditory canal (Welgampola et al., 2003). Bone conduction stimulation is a useful method for patients with conductive hearing loss or where loud air conduction stimuli is contra-indicated (e.g. infants or patients with hyperacusis) and has also been proved useful in identifying the possible stage of otosclerosis (Akin & Murnane, 2008; Yang & Young, 2006).

Another mode of cVEMP elicitation is galvanic vestibular stimulation. This method is less reported on in the literature and includes a cathode electrode placed on the mastoid and an anode electrode positioned on the forehead. Cheng, Yang, Huang and Young (2008) found a 5 mA (milli-Ampere) electrical stimulus with a duration of 1 ms to produce optimal response rates and amplitudes. Briefly, galvanic cVEMPs are thought to be substantiated by a reflex pathway that bypasses the vestibular end-organs and can be used to differentiate labyrinthine and retro-labyrinthine pathology (Rosengren et al., 2010).

1.5 Stimulus parameters

Stimulus parameters for air conduction 500 Hz tone bursts and clicks vary across clinics, but optimal parameters have been suggested by some studies. For click stimuli, reports recommend optimal stimulus levels between 90 and 105 dB normal hearing level (nHL), which translates roughly into 129 – 145 dB peak sound pressure level (pSPL). A relatively slow repetition rate is indicated of 5-7 Hz and Wu and Morufushi (1999) went on to prove 5 Hz to be the optimal stimulation rate for clinical use. Although a 0.1 ms click seems to be the most prevalent, Huang, Su and Cheng (2005) indicated a 94% response rate when using a 0.1 ms duration. They recommend a 0.5 ms click to be the optimal stimulus for eliciting cVEMPs. Concerning 500 Hz tone bursts, 90 – 95 dB nHL intensity levels are indicated at a rate of 5 Hz. Some authors prefer a 1 ms rise interval with a 2 ms plateau, while others prefer a two cycle rise and fall with no plateau (Akin & Murnane, 2008; Zhou & Clarke Cox, 2004; Zapala, 2007; Young, 2006; Wuyts, Furman, Vanspauwen, & Van de Heyning, 2007). Cheng and Morufushi (2001a; 2001b) conducted studies specifically to determine optimal rise, fall and plateau times and concluded that 1 ms rise and fall times combined with 2 ms plateau time would elicit best possible 500 Hz cVEMP responses.

1.6 Recording parameters

As with stimulus parameters, some variability concerning recording parameters is evident across the literature. Cervical VEMPs are obtained using a two-channel

recording with electrodes placed on various sites. A popular electrode montage includes placing the active electrode over the upper third or half of the SCM muscle with the reference electrode over the lateral end of the upper sternum and several researchers adopted this montage in their studies (Zhou & Clarke Cox, 2004; Cheng & Morufushi, 2001a; Cheng & Morufushi, 2001b; Welgampola & Colebatch, 2001a). Young (2006) and Sheykholeslami, Murofushi and Kaga (2001) confirmed the upper half and middle third respectively of the SCM muscle as optimal electrode placement in studies dedicated to establish superior cVEMP stimulation techniques. Zapala (2007) indicated that when the reference electrode is placed over the sternum, it is best to position the active electrode over the upper quarter of the SCM muscle. This way, the muscle belly is between the two electrodes which ensures optimal response amplitudes. Recordings with this type of montage will lead to P1 being an upward deflecting wave and N1 downward deflecting. Interestingly, the author also indicates that positioning the active electrode on the forehead with the reference electrode over the belly of the SCM muscle will result in slightly smaller cVEMP amplitudes, but with less variability between responses.

Recording epochs are typically 50 to 100 ms post-stimulus since the entire SCM muscle myogenic potential lasts about 40 ms and pre-stimulus recording time is necessary for determining estimated EMG level (Zapala, 2007; Akin & Murnane, 2008). The number of sweeps are generally between 64 and 256 and not more than 500 for each run or waveform, which is typically repeated (Akin & Murnane, 2008; Zhou & Clarke Cox, 2004; Welgampola & Colebatch, 2005). Artifact rejection is turned off, since muscle responses are considered artifacts when a signal average for neurogenic activity (commonly used in the clinic for cVEMPs) is used. This will allow for muscle responses to be included for averaging (Zapala, 2007; Akin & Murnane, 2008). Filter settings are usually between 10 and 2000 Hz, since the dominant energy of EMG signals are between 40 and 150 Hz and amplifier gain is typically set at 5000 times (Akin & Murnane, 2008; Zapala, 2007; Welgampola & Colebatch, 2005).

The normal cVEMP waveform is characterized by a biphasic positive-negative curve and usually the peaks and troughs are labelled by lowercase letters preceded with the mean latency, although “P1” and “N1” is also a common appellation. The initial positive-negative complex is labelled P1-N1 and is present in most of the

subjects participating in studies where cVEMPs are elicited (Zhou & Clarke Cox, 2004). The latencies used were based upon the mean response latencies to click stimulation evoked by Colebatch and Halmagyi (1992). Mc Nerney and Burkard (2011) more recently found similar results to air conduction 500 Hz tone bursts presented at 120 dB pSPL with mean latencies of 13.48 ms (standard deviation = 0.86) and 21.8 ms (SD = 1.56). Later potentials (n34-p44) may be recorded in some participants, but they have been found to be present in only 60% (Eleftheriadou & Koudounarakis, 2011) and 40% of participants (Colebatch et al., 1994) of normal healthy subjects and they probably originate from cochlear afferents. Therefore, this second complex is not conventionally used for normal cVEMP interpretation (Zhou & Clarke Cox, 2004).

1.7 Response parameters

The response parameters used to describe and interpret the P1-N1 complex include P1 and N1 latency, P1-N1 amplitude, threshold and asymmetry ratio (Akin & Murnane, 2008). As described in the previous paragraph, latency values for P1 and N1 seem to fall within close range of the 13 and 23 ms used to describe the waveform. Test-retest reliability has been proven to be good for latency and intra-subject variations are described as being small (Versino, Colnaghi, & Cosi, 2001; Eleftheriadou & Koudounarakis, 2011). Tone burst and click latencies have been described as similar to each other, as long as tone burst duration was kept at a constant (Akin & Murnane, 2008; Basta et al., 2005). However, some studies have indicated that click evoked cVEMPs yield shorter latencies than 500 Hz tone bursts (Wu et al., 2007; Cheng et al., 2003). Also, Huang et al. (2005) found that absolute latencies were prolonged as click duration increased. The standard deviation of latencies was largest when using a 1 ms click, contra-indicating it to be the ideal stimulus for eliciting cVEMPs.

Unlike response amplitude, latency does not act as a function of stimulus level or tonic EMG obtained, which is probably due to the reflexive nature of the response (Colebatch et al., 1994; Akin, et al., 2004). Conversely, tone burst duration (rise and fall time and plateau) alter latencies recorded, where an increase in either of these

parameters lead to an increase in latency (Cheng & Morufushi, 2001a; Cheng & Morufushi, 2001b). Neck length seems to play a role in latency as well, where the adult range of cVEMP latencies can be expected if the neck length is longer than 15.3 cm (Wang, Yeh, Chang, & Young, 2008).

Raw, unrectified amplitude values vary widely leading to great inter- and intra-subject variability. Various parameters have a direct influence on amplitude measurements and studies are encumbered with differences in tonic EMG level, dB reference levels, stimulus intensity levels and stimulus frequency. Regarding stimulus intensity, there is a general agreement across studies that an increase in intensity will lead to a corresponding increase in response amplitude. It is suggested that this phenomenon is the result of a larger number of motor units that are activated in response to the increase in stimuli (Wit & Kingma, 2006). This has been proven for tone bursts (Welgampola & Colebatch, 2001a) as well as click-evoked responses (Colebatch et al., 1994). Although Cheng et al. (2003) evoked higher amplitudes with click stimuli, Welgampola and Colebatch (2001a) indicated that tone bursts require a lower intensity level than clicks to produce equivalent response amplitudes.

Stimulus frequency also has a definite effect on cVEMP response amplitude. cVEMP responses show a frequency tuning and the saccule exhibits maximum resonance at lower frequencies (Todd et al., 2000; Park, Lee, Shin, Lee, & Park, 2010). The majority of literature supports the use of 500 Hz tone bursts for evoking cVEMP responses since larger amplitudes are consistently evoked in comparison with clicks for a given SPL and better reliability is obtained across recording sessions (Viciana & Lopez-Escamez, 2012; Akin, et al., 2004; Rosengren et al. 2009). Rosengren, et al. (2009) also indicated three factors which majorly influence cVEMP amplitude, of which vestibular frequency tuning is one.

A linear relationship between stimulus duration and cVEMP amplitude is indicated by various researchers. Generally, an increase in tone burst plateau and rise and fall time, as well as overall click duration will lead to an increase in response amplitude (Welgampola & Colebatch, 2001a; Cheng & Morufushi, 2001b; Cheng & Morufushi, 2001a). However, it should be noted that there seems to be a cut off point for optimal amplitude elicitation concerning stimulus duration. This is due to stapedial

reflex activation in the middle ear. Cheng and Morufushi (2001b; 2001a) found a rise fall time of 1 ms and 2 ms respectively to elicit optimal response amplitudes and Welgampola and Colebatch (2001a) indicated that a 7 ms stimulus will not evoke the stapedial reflex, making it optimal for clinical use.

The leading cause of variability among cVEMP responses is perhaps differences in tonic EMG measured over the SCM muscles. It has been well-documented that amplitude scales in proportion to tonic EMG activity (Colebatch et al., 1994; Akin, et al., 2004; Isaacson et al., 2006). Thus, differences in muscle tension will lead to differences in amplitude measured and raw amplitude values are rarely used for cVEMP interpretation. Since the cVEMP is a useful test of determining unilateral pathology, interaural differences are used for clinical interpretation. Therefore, SCM muscle activity needs to be as similar as possible in both ears to eliminate false-positive results. Monitoring the tonicity of the SCM muscle is thus a prerequisite for proper cVEMP recording (Akin, et al., 2004).

Rosengren et al. (2010) describe three functions of SCM muscle activity monitoring: adequate levels of SCM muscle activation can be ensured, head position can be adjusted to allow for equal EMG levels on both sides and background EMG levels can be measured and used for corrected amplitudes. The authors suggest using a two-channel system where the mean rectified EMG is indicated on one of the channels. An important factor is to rectify each trace prior to averaging, seeing that rectifying averaged signals will lead to a continuous decrease in EMG average. By following this method, the EMG channel allows for direct visual monitoring of muscle activation. Subsequently, the mean rectified activity can be measured for the pre-stimulus time interval and this value is then used to calculate normalized or corrected amplitudes (P1-N1 amplitude divided by pre-stimulus mean rectified EMG). Using rectified EMG values as described will allow for comparison between studies. The authors indicate mean rectified EMG levels of at least 40 micro Volt (mV) and up to 150 – 200 mV as adequate for recordings.

Akin et al. (2004) found that amplitude responses are least variable when EMG targets of 30 mV or 50 mV is used. They also describe monitoring EMG levels as obligatory and suggest either direct control of the EMG level and keeping the rectified

EMG at a constant or calculating the corrected amplitude by implementing a correction algorithm that takes pre-stimulus muscle tension into consideration. By using the latter, equal muscle contraction for left and right stimulation is not required since they are corrected for. Isaacson et al. (2006) also found the method of SCM activation to have no significant effect on cVEMP amplitude when the corrected amplitude is calculated. In order to monitor EMG levels as described, recording systems that are not routinely found in all clinics are required (Tourtillott, Ferraro, Bani-Ahmed, Almquist, & Deshpande, 2010; Maes, et al., 2009).

Since tonic EMG level is induced by SCM muscle activation, researchers sought to solve this monitoring dilemma by controlling the amount of SCM muscle activity in the absence of sophisticated recording systems. In 2006, Vanspauwen, Wuyts and Van de Heyning (2006) described using a blood pressure manometer for visual feedback as a valid alternative to EMG measurement when simultaneous mean rectified voltage (MRV) and cVEMP recording is not feasible. Mean rectified voltage values prior to cVEMP testing and during cVEMP testing have been proven to be similar, meaning that when simultaneous measurement is impossible, MRV values measured before cVEMP testing can be applied as indicators for SCM muscle contraction during testing. Subsequently, cuff pressures that result in the same MRV values are estimated for left and right sides. Indicated cuff pressures are then maintained during cVEMP testing. Using this method has resulted in significantly lower amplitude variation.

However, the method described by Vanspauwen et al. (2006) still included a supplementary control where pre-stimulus MRV was measured together with the feedback method. Maes et al. (2009) showed that combining the blood pressure feedback method with carefully controlled head positioning and SCM muscle activation is a reliable method to perform cVEMP testing when background muscle contraction cannot be measured or software-related correction amplitudes are not available, in other words, when *only* a feedback mechanism is accessible. They found excellent within-session and between-session reliability and that their method of unilateral activation delivered acceptable left-right differences when compared to a bilateral muscle contraction combined with EMG monitoring. However, they note that using corrected amplitudes is still the preferred method for interpreting cVEMP responses.

Monitoring tonic EMG to obtain equal muscle tensions within and between subjects is another good technique, provided that exact EMG values can be provided.

Cervical VEMP threshold is defined as the lowest stimulus intensity where a clear biphasic response can be elicited and seems to be a useful and reliable parameter (Eleftheriadou & Koudounarakis, 2011). For click-evoked cVEMPs, thresholds have been found to be within 75-85 dB nHL (Colebatch et al., 1994). Similarly, Welgampola and Colebatch (2001b) found a threshold range of 75-100 dB nHL (mean 89.6 ± 6.9) in a group of subjects ranging from 25 to 85 in age. For tone bursts, the frequency tuning effect of the saccule leads to lowest thresholds obtained in response to 500 Hz stimuli (Park et al., 2010; Tourtillott et al., 2010). Zapala (2007) notes that thresholds obtained from left and right ears should be within 10 dB from each other to indicate normal results.

As described, large intersubject variability regarding cVEMP amplitude is evident due to various factors. Consequently, clinicians express the side-to-side difference in amplitude as a percentage. This asymmetry ratio (AR) is calculated by the following formula: $AR = 100 \times (A_L - A_S) / (A_L + A_S)$, where A_L equals the larger P1-N1 amplitude and A_S the smaller P1-N1 amplitude. The AR can also be calculated when using corrected amplitudes. Regardless of method used to account for differences in tonic EMG, it seems that AR range from 0- 40% normal individuals (Akin & Murnane, 2008). Wu et al. (2007) found no statistically significant AR differences between click- and tone burst-evoked VEMPs and Li, Houlden and Thomlinson (1999) found an AR value of ≤ 37% when monitoring EMG activity. Welgampola and Colebatch (2001a) found an average AR of 13.9% for individuals under 60 years old when using corrected amplitude values and an AR of 16.3% for the same age group when using uncorrected amplitude values. Similarly, Maes et al. (2009) indicated an AR percentage of 12% (SD = 10) when eliciting cVEMPs with 500 Hz tone bursts for the age group 19-39 years. Since the AR is still dependent on amplitude values and substantial variations between ears are evident in even normal subjects, care must be taken when interpreting cVEMP results according to ARs and a monitoring or correction method is still preferable in conjunction with this calculation (Lee, et al., 2008a).

1.8 Effect of age

Aging has a definite effect on the vestibular system and the changes in cVEMP responses have been well-documented. Although cVEMPs have been successfully recorded in neonates, children and the elderly, comparisons between these age-groups and normal healthy adults have revealed several differences in response parameters (Akin & Murnane, 2008). Vestibular hair cell loss, vestibular nerve fibre loss and a decrease of cell bodies in Scarpa's ganglion have been reported since the 1970's (Tourtillott et al., 2010) and backed the argument that a decrease in cVEMP responses with age is due to morphological changes in the vestibular system, rather than the elderly being unable to obtain sufficient SCM muscle contraction. This was proven by studies indicating that although tonic EMG remained constant across age-groups in the experiment, decreased amplitudes in cVEMP responses were obtained (Basta et al., 2005). Several studies indicated that response amplitude decreases and threshold increases with an increase in age and that latency and inter-aural difference is not significantly influenced by the aging process (Basta et al., 2005; Tourtillott et al., 2010; Ochi & Ohashi, 2003; Lee, Cha, Jung, Park, & Yeo, 2008b).

When Maes et al. (2009) evaluated the effect of aging on various laboratory vestibular function tests, the result was that aging had the most significant effect on the cVEMP test. There seems to be a general consensus in the literature that cVEMP responses can be reliably evoked up until the age of 60 and thereafter, if present, cVEMPs should be interpreted with great care in terms of amplitude and threshold (Welgampola & Colebatch, 2001b; Lee et al., 2008b; Rosengren et al. 2011; Su, Huang, Young, & Cheng, 2004).

1.9 Effect of gender

Unlike the effect of age, gender does not seem to induce significant changes on cVEMP response parameters, especially with regards to amplitude and threshold (Tourtillott et al., 2010; Welgampola & Colebatch, 2001b). Although some studies suggest that gender has an effect on latency values (Lee et al., 2008b) these results

are contradictory to other results (Basta et al., 2005). At this stage, it seems that gender effects are not significant enough to alter cVEMP interpretation, but further research is recommended (Tourtillott et al., 2010).

1.10 Clinical significance of the cVEMP test

Clinical significance of the cVEMP has been demonstrated in various areas, but the majority of research has been on identifying the potential application of the cVEMP test in patients with Ménière's disease. Although findings vary across studies, some trends can be identified. Akin and Murnane (2008) conducted a literature review from 1994 to 2006 on various pathologies and indicated that cVEMP responses were normal and present in 51% of Ménière's subjects across studies included in the review where cVEMP testing has been done. Abnormal cVEMPs in Ménière's subjects seem to be characterized by either absent cVEMP responses, or mainly a decrease in threshold, loss of tuning or increased amplitude (in the beginning stages). Taylor et al. (2011) found significant abnormalities in cVEMP responses to air conduction stimuli (as opposed to bone conduction stimuli) in Ménière's patients, which is indicative of saccular involvement.

Since endolymphatic hydrops is suspected as the underlying pathology of Ménière's disease, some researchers have attempted to utilize a dehydration mechanism as treatment for the disease. Seo, Node, Yukimasa and Sakagami (2003) found that cVEMP amplitude increased in 40% of ears diagnosed with Ménière's disease following furosemide injection. Also, cVEMP responses appeared in some ears post-furosemide testing where cVEMPS were absent pre-furosemide testing. Similar results have been obtained by glycerol testing (Magliolo, Cianfrone, Gagliardi, Cuiuli, & D'Amico, 2004). A recent study on intratympanic gentamicin for Ménière's disease patients by Gode et al. (2011) indicated that cVEMPs are significant predictors of subjects' dizziness status six months post-treatment. Timmer et al. (2006) found cVEMP responses more likely to be absent in ears with Ménière's disease and most likely to be absent in Ménière's ears where the patients experience drop attacks. Frequency tuning was also found to change with the course of Ménière's disease,

suggesting that cVEMP measurement may be a valuable technique to monitor disease progress.

Cervical VEMP responses have also been found to be abnormal in patients with migrainous vertigo, where normal wave formation was significantly lower in both ears than with the control group (Hong, Kim, Park, & Lee, 2010). Baier, Stieber and Dieterich (2009) found significantly bilaterally reduced cVEMP amplitudes in patients with vestibular migraine and suggested that both peripheral and central structures contribute to vertigo in vestibular migraine. However, it has been suggested that migraine-associated vertigo share a common pathophysiology with Ménière's disease and that differentiating between the two may prove challenging (Murofushi, Ozeki, Inoue, & Sakata, 2009; Zuniga, Janky, Schubert, & Carey, 2012).

The Tullio phenomenon is induced by loud sounds and leads to symptoms of vertigo, nystagmus, oscillopsia and/or postural imbalance and the most common disorder associated with this occurrence is superior semicircular canal dehiscence (SSCD) (Akin & Murnane, 2008). The dehiscence in the bone covering the super semicircular canal leads to a route of lowered impedance, or "third window" with a resulting increase in vestibular sensitivity. During VEMP testing, this manifests as a lowered VEMP threshold and enlarged amplitude (Akin & Murnane, 2008; Welgampola & Colebatch, 2005). A study done by Welgampola, Myrie, Minor and Carey (2008) proved that VEMP thresholds normalize after corrective surgery to the semicircular canal. Since air conduction VEMPs are usually abolished in the case of conductive hearing losses, the presence of VEMP responses in the case of air-bone gaps with pure tone audiometry can be an indicator of SSCD (Akin & Murnane, 2008).

Another valuable clinical application of the cVEMP is with identification of vestibular schwannomas. The most prevalent type of tumor of the eighth nerve usually occurs on the vestibular portion thereof and the cVEMP has become a potential useful means to determine the status of the inferior vestibular nerve (Akin & Murnane, 2008). In a study of 170 patients diagnosed with vestibular schwannomas, 78.8% displayed sacculo-collic pathway pathology where cVEMP responses were either absent or abnormally low on the affected side (Patko, Vidal, Vibert, Ba Huy, & de Waele, 2003).

The study further indicated that short 500 Hz tone bursts are the most effective stimulus for the sacculo-collic pathways. No significant changes in latency were noted.

Vestibular neuritis is usually a unilateral impairment and the superior vestibular nerve is most commonly affected (Akin & Murnane, 2008; Govender, Rosengren, & Colebatch, 2011). The literature review by Akin and Murnane (2008) indicated that this disorder is most commonly recognized by absent cVEMP responses and the response is absent in nearly half of the subjects included in the review. Govender et al. (2011) found that air conduction stimuli were associated with low abnormality rates of cVEMPs, which is consistent with sparing of inferior vestibular nerve function in vestibular neuritis. Cervical VEMPs were found to be absent or have a decreased amplitude, but also to normalize more rapidly than canal-related tests after vestibular neuritis in a study conducted by Kim et al. (2008).

It is common for benign paroxysmal positional vertigo (BPPV) to occur secondary to vestibular neuritis (Akin & Murnane, 2008). Several studies confirm cVEMP abnormalities when patients present with BPPV, including increased cVEMP latencies and decreased amplitudes (Yang, Kim, Lee, & Lee, 2008; Akkuzu, Akkuzu, & Ozluoglu, 2006; Hong, Park, Yeo, & Cha, 2008).

Air conduction cVEMPs are most often absent in the presence of a conductive hearing loss. This is due to attenuation of the required high sound pressure level necessary to evoke cVEMP responses (Akin & Murnane, 2008). In the case of otosclerosis, Yang and Young (2006) concluded that the presence of an air conduction cVEMP may indicate an earlier stage of otosclerosis and when used in conjunction with bone conduction cVEMPs, later stages of the condition can be identified. Wang et al. (2009) reported a significant increase in cVEMP responses after surgery for chronic otitis media patients and Yang and Young (2003) suggested the tapping method to elicit cVEMP responses in the absence of air conduction VEMPs due to chronic otitis media.

The effect on cVEMP responses has also been studied in patients with neurologic pathologies. Although cervical dystonia causes involuntary, sustained contraction of the neck muscles, Rosengren and Colebatch (2010) reliably recorded

cVEMP responses from 21 patients diagnosed with cervical dystonia. In 54 patients with idiopathic Parkinson disease, 20 had absent unilateral responses and four had bilateral absent cVEMP responses. Normal latency values were obtained when compared with healthy controls (Pollak, Prohorov, Kushnir, & Rabey, 2009). Patients with multiple sclerosis presented with decreased cVEMP amplitudes and an increase in P1 latency in studies conducted by Gazioglu and Boz (2012) and Patko, Simo and Aranyi (2007). The cVEMP test is also recommended for the early diagnosis of Alzheimer disease, where mean latency of P1 was increased and mean response amplitude was lowered in a group of 30 individuals with Alzheimer disease (Birdane, Incesulu, Gurbuz, & Ozbabalik, 2011).

1.11 Rationale

This review highlights the controversy surrounding best recording method of the cVEMP and resonates well with the findings of Eleftheriadou and Koudadounarakis' (2011), where they conclude that there is still no consensus across the literature pertaining to standard recording and interpreting procedures and values. Basta et al. (2005) also proved that response characteristics depend for the most part on stimulus parameters and suggested the evaluation of cVEMP responses by using normative data obtained with the same stimulus parameters.

Even though several studies have attempted to describe the best stimulus and recording parameters, relatively small sample sizes were used. In an effort to overcome this problem, statistical methods can be employed to compensate for small study groups. One such manner is the use of a meta-analysis, which is the statistical analysis of a large collection of results to integrate findings (Glass, 1976). This pooling of data can lead to more precise estimates and facilitates consistency of evidence across studies.

1.12 Problem statement

Therefore, based on the possibility of facilitating standard test procedures for performing and interpreting cVEMPs, this study aimed to determine the most prevalent trends in stimulus and recording parameters by performing a systematic literature review. Also, it aimed to combine normative data to determine significant effects of stimulus type, SCM muscle activation method, transducer type and method to control SCM muscle EMG level on cVEMP results by performing a meta-analysis and to obtain normative guidelines for cVEMP interpretation.

Chapter 2: Methodology

2.1 Research aims

The method to determine most prevalent trends and the effect of certain stimulus and recording parameters on cVEMP results are discussed below:

Main aim

The main aim of the study was to systematically determine most prevalent air conduction 0.1 ms click and 500 Hz tone burst cVEMP stimulus and recording parameters by performing an electronic database search and subsequently suggest normative response parameters for interpretation based on peer-review articles.

Sub-aims

Three sub-aims were formulated to accomplish the main aim of the study:

- *Sub-aim 1:* To determine the most prevalent 0.1 ms click and 500 Hz tone burst cVEMP stimulus and recording parameters by systematically reviewing relevant cVEMP reports.
- *Sub*-aim *2*: To determine the effect of stimulus type, SCM muscle activation method, transducer type and method to control SCM muscle EMG level on 0.1 ms click and 500 Hz tone burst cVEMP response parameters by performing a meta-analysis.
- *Sub*-aim *3*: To determine normative response parameters for 0.1 ms click and 500 Hz tone burst cVEMP interpretation by performing a meta-analysis.

2.2 Research design

Although optimal cVEMP stimulus and recording parameters have been suggested by various studies in the literature, relatively small sample sizes were used seeing that it is mostly control group data which is described (Eleftheriadou &

Koudounarakis, 2011). Thus, this study used a systematic literature review where relevant current publications in peer-reviewed journals were identified and reviewed through a computerized literature search to obtain most prevalent 0.1 ms click and 500 Hz tone burst cVEMP stimulus and recording parameters.

In addition, a meta-analysis was performed to combine cVEMP response parameter results from the individual studies to determine significant effects of stimulus type, SCM muscle activation method, transducer used and method to control SCM muscle EMG level, as well as normative data for 0.1 ms click and 500 Hz tone burst cVEMP interpretation. This combining of data will facilitate more precise suggestions for normative cVEMP response parameters values (Glass, 1976).

2.3 Ethical considerations

Ethics are central to any research study and various principles and guidelines should prevail throughout the entire research process, especially when human beings are involved (Babbie, 2008). Since only published reports are used in this study and not human subjects, the ethics pertaining to human studies were irrelevant. However, the following ethical principles were adhered to and applied in the current study:

Plagiarism:

Plagiarism implies that another researcher's work is falsely presented as if it were your own (Babbie, 2008). Full acknowledgement was given to all the sources used in this study.

Reliability and validity of research:

Leedy and Ormrod (2010) describe reliability as being concerned with the consistency of a measurement and validity as being concerned with the

trustworthiness of the conclusions drawn from a research project. To ensure that these two principles were applied to the quantitative data collected in this study, all included reports were chosen according to an exact inclusion criteria from peer-reviewed literature. When queries regarding inclusion of certain reports arose, the researcher asked for the opinion of the supervisors to ensure reliability and validity.

2.4 Selection criteria for research material

As mentioned above, a certain set of selection criteria is imperative to assure validity and reliability of research but it is also necessary to answer the research question at hand. The following exclusion and inclusion criteria were applied:

Inclusion criteria

- Reports published from 1974 – 14 April 2012, when the systematic review was performed, were included;
- reports where normative control group data were reported were included;
- control group participants had to present with normal hearing and no history of vestibular function deficits;
- reports that explicitly aimed to determine normative data were included;
- participants had to be between the ages of 18 and 60 years;
- reports where participants were male or female were included;
- only reports where 0.1 ms click or 500 Hz tone burst cVEMPs were conducted via air conduction stimuli were included;
- only reports where the SCM muscle was used were included;
- only English reports were included and
- only reports with human participants were included.

Thus, the implied inclusion criteria consisted of the following:

Exclusion criteria

- Non-English reports were excluded;
- reports where no normative data were indicated were excluded;
- duplicates, reviews, letters, notes, dissertations and conference papers were excluded;
- reports irrelevant to the study field were excluded;
- reports where participant age was not indicated were excluded;
- paediatric reports were excluded;
- animal studies were excluded;
- oVEMP reports were excluded;
- reports using bone conduction, galvanic stimulation, skull taps or logon stimulus were excluded;
- reports where musculature other than the SCM muscle was used were excluded;
- reports where response parameters were not clearly indicated or inconsistent with the study were excluded;
- reports where abnormal recording conditions were present were excluded;
- reports on tone burst cVEMPS where a stimulus frequency other than 500 Hz was used, or where stimulus frequency was not indicated were excluded;
- reports on click cVEMPS where a stimulus duration other than 0.1 ms was used, or where stimulus duration was not indicated were excluded and
- reports where stimulus level was not indicated were excluded.

2.5 Data collection procedures

The data collection procedure for the systematic review and meta-analysis is systematically indicated below:

The scientific database, Scopus, was used to enable a multi-pronged search strategy, seeing that it covers multiple health-related databases and has full Medline and PubMed coverage. The indicator “VEMP” was entered as search term for all years up until 2012. Reports from 1974 – 14 April 2012 were sourced. Reports adhering to the exclusion criteria stipulated above were excluded and it was attempted to retrieve the full text for all remaining reports.

2.6 Data analysis procedures

Systematic review:

After the full-text reports were reviewed to determine whether they meet the inclusion criteria, they were divided into two main groups: those dealing with 0.1 ms clicks and those dealing with 500 Hz tone bursts. Each report in these two main groups was then carefully analysed with respect to the following dimensions:

- report title;
- year of publication;
- number of participants;
- mean age of participants;
- device used for cVEMP testing;
- SCM muscle activation method (seated, turn head contralaterally *‘STC’;* supine, head elevated *‘SEH';* supine, elevate and rotate head contralaterally *‘SETC’;* seated, push head forward *‘SPF’;* supine, head rotated *‘SRH*);
- electrode montage;
- transducer used;
- method to control SCM muscle activation (rectified cVEMPs, visual monitoring only, rectified cVEMPs and visual monitoring, the blood pressure feedback method only or controlling method not indicated);
- stimulus parameters (stimulus type, frequency, polarity, level, rate, duration, rise and fall time, plateau, gating);
- recording parameters (amplifier gain, filter settings, time window, number of sweeps, number of channels) and

- response parameters (mean latency P1, mean latency N1, mean amplitude, mean asymmetry ratio, mean threshold).

Thus, all reports from the systematic review indicating normative means for latency, amplitude, asymmetry ratio and threshold were included.

Meta-analysis:

Microsoft Excel was used to perform the meta-analysis measures for 0.1 ms click cVEMPs (CVs) and 500 Hz tone burst cVEMPs (TBVs).

Documented means of all response parameters (latency P1, latency N1, raw amplitude, corrected amplitude, asymmetry ratio and threshold) and number of participants in each study were used to calculate weighted means, standard deviations and 95% confidence intervals (CI) for CVs and TBVs. This was done to establish possible normative values for cVEMP interpretation.

A corresponding T-stat at the 95% CI was calculated to determine statistically significant differences in the weighted means of response parameters when compared to each other. These calculations were done to determine significant effects of stimulus type (click compared to tone burst), SCM muscle activation method (5 positions as indicated above), transducer type (headphone compared to insert earphone) and method to control SCM muscle activation on cVEMP response parameters.

Chapter 3: cVEMPS: A systematic review and meta-analysis

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3.1 Abstract

Objective: A systematic literature review and meta-analysis was performed to determine the effect of stimulus type, SCM muscle activation method, transducer type and method to control SCM muscle EMG level on response parameter values for 0.1 ms click-evoked and 500 Hz tone burst cVEMPs. A description of normative response values was attempted.

Design: An electronic systematic literature review was performed to obtain normative cVEMP response data. Subsequently a meta-analysis was conducted to determine significant effects on cVEMP response parameters and to obtain norms.

Study Sample: Scopus was used to identify reports containing normative data. Reports were selected based on inclusion and exclusion criteria determined beforehand. Weighted means were calculated and compared to identify significant effects and normative data.

Results: Sixty six reports were included in the systematic review. Stimulus type, SCM muscle activation method, transducer type and method to control SCM muscle EMG level had significant effects on all response parameters.

Conclusions: Optimal stimulus and recording parameters suggested by previous research are confirmed by the current systematic review and meta-analysis and are suggested for clinical use. Response parameter values are influenced by variations in stimulus and recording parameters and normative response values are suggested as guideline for cVEMP interpretation.

3.2 Introduction

Vestibular function testing commonly consists of a battery of tests. A relatively recent addition to the test battery for evaluating vestibular function is the Vestibular Evoked Myogenic Potential (VEMP) (Rosengren et al., 2010).

Although the work of Dr. Pietro Tullio on alert animals paved the way for studying the acoustic sensitivity of the vestibular system, von Békésy (in 1935) was the first to describe sound-evoked vestibular responses in normal human subjects (Welgampola & Colebatch, 2005). More recently, Colebatch and Halmagyi (1992) and Colebatch et al. (1994) measured electromyographic (EMG) activity from the sternocleidomastoid (SCM) muscle in response to high-level, air-conduction clicks. This established a reliable procedure to record myogenic potentials evoked by clicks and the cervical or collic “cVEMP” became a practical, clinical test. The response could be depicted as an initial positive peak (p13 or P1), followed by a successive negative peak (n23 or N1). Although VEMPs are currently also measured over the ocular muscles, the present study will refer to the described cVEMP.

In short, the cVEMP can be described as an inhibitory potential recorded from the SCM muscle due to saccular activation in response to loud sounds (Zhou & Clarke Cox, 2004). When measuring the cVEMP, tonic SCM muscle contraction generates background EMG which is interrupted briefly due to a short period of inhibition (Welgampola & Colebatch, 2005; Rosengren et al., 2010).

The last decade has been marked with studies attempting to identify whether air conduction clicks or tone bursts are best suited for clinical use. It seems that the majority of data indicate short tone bursts to be superior to click stimuli when attempting to evoke cVEMP responses, since they produce larger cVEMP amplitudes, have better reliability across recording sessions and have smaller inter-laboratory variability (Welgampola & Colebatch, 2001a; Murofushi, Matsuzaki, & Wu, 1999; Basta et al., 2005; Wu et al., 2007; Viciana & Lopez-Escamez, 2012).

Stimulus parameters have definite effects on cVEMP response parameters and optimal parameters are suggested by various studies (Zhou & Clarke Cox, 2004; Zapala, 2007; Young, 2006; Wuyts et al., 2007). Some variability concerning recording parameters is also evident across the literature. This includes SCM muscle activation method, electrode montage, transducer type, amplifier gain, filter settings, time window for recording, number of sweeps and tone burst frequency (Zhou & Clarke Cox, 2004; Cheng & Morufushi, 2001a; Cheng & Morufushi, 2001b; Welgampola & Colebatch, 2001a). Evidence-based stimulus and recording parameters still need to be suggested.

There are two basic techniques used to activate the SCM muscles during cVEMP testing; one being head rotation and the other neck flexion. Both can be done with the patient either in a sitting or a supine position. The neck flexion method has several variations and SCM muscle activation is achieved by lifting the head against gravity in the supine position or by pushing the head forward against a padded bar whilst in the sitting position (Ozdek et al., 2009; Akin, et al., 2004; Welgampola & Colebatch, 2005). Isaacson and colleagues (2006) compared three methods of SCM muscle activation and found that eliciting cVEMPs with the subject in the supine position with the head turned to the contralateral side of stimulation leads to the most robust amplitudes. Wang and Young (2006) compared the head rotation method in the sitting position and the head elevation method with the head in the midline position and found that when combining results of both the head elevation and head rotation methods, a higher response rate was obtained.

The response parameters used to describe and interpret the P1-N1 complex include P1 and N1 latency, P1-N1 amplitude, threshold and asymmetry ratio. Lately,

corrected P1-N1 amplitude and threshold values are used more often to interpret cVEMP responses. However, latency is a robust parameter since test-retest reliability has been proven to be good and intra-subject variations are described as being small (Versino et al., 2001; Eleftheriadou & Koudounarakis, 2011).

Raw, unrectified amplitude values vary widely leading to great inter- and intra-subject variability. There is a general agreement across click and tone burst evoked studies that an increase in intensity will lead to a corresponding increase in response amplitude, under the condition of an equal SCM muscle contraction level throughout all recordings (Wit & Kingma, 2006; Welgampola & Colebatch, 2001a; Colebatch et al., 1994). Stimulus frequency also has a definite effect on cVEMP response amplitude and the saccule exhibits maximum resonance at lower frequencies (Todd et al., 2000; Park et al., 2010). A linear relationship between stimulus duration and cVEMP amplitude is expected where an increase in tone burst plateau and rise and fall time, as well as overall click duration will lead to an increase in response amplitude (Welgampola & Colebatch, 2001a; Cheng & Morufushi, 2001b; Cheng & Morufushi, 2001a).

Perhaps the leading cause of variability among cVEMP responses is differences in tonic EMG measured over the SCM muscles. It has been well-documented that amplitude scales in proportion to tonic EMG activity (Colebatch et al., 1994; Akin, et al., 2004; Isaacson et al., 2006). Therefore, monitoring the tonicity of the SCM muscle is a prerequisite for accurate cVEMP recording. Vanspauwen, et al. (2006) described using a blood pressure manometer for visual feedback as a valid alternative to EMG measurement when simultaneous MRV and cVEMP recording is not feasible.

Cervical VEMP threshold is defined as the lowest stimulus intensity where a clear biphasic response can be elicited and seems to be a useful and reliable parameter (Eleftheriadou & Koudounarakis, 2011). For click-evoked cVEMPs, thresholds have been found to be within 75-85 dB nHL (Colebatch et al., 1994), but Welgampola and Colebatch (2001b) found a threshold range of up to 100 dB nHL to be normal. A normative threshold range across studies has not been established.

Due to large inter-subject variability regarding cVEMP amplitude, clinicians express the side-to-side difference in raw or corrected amplitude as a percentage. This asymmetry ratio (AR) is calculated by the following formula: $AR = 100 \times (A_L - A_S) / (A_L + A_S)$, where A_L equals the larger P1-N1 amplitude and A_S the smaller P1-N1 amplitude. Although Wu et al. (2007) found no statistically significant AR differences between click- and tone burst-evoked cVEMPs, the AR is still dependent on amplitude values and substantial variations between ears are evident in even normal subjects (Lee, et al., 2008a). Several researchers have suggested norms, but they vary widely between studies (Li, Houlden, & Thomlinson, 1999; Welgampola & Colebatch, 2001a; Maes, et al., 2009). Thus, as with latency, amplitude and threshold, normative data are still needed.

Aging has a definite effect on the vestibular system and the changes in cVEMP responses with age have been well-documented. There seems to be a general consensus in the literature that cVEMP responses can be reliably evoked up until the age of 60. Thereafter, if present, cVEMPs should be interpreted with great care in terms of amplitude and threshold (Welgampola & Colebatch, 2001b; Lee et al., 2008b; Rosengren et al., 2011; Su et al., 2004).

Eleftheriadou and Koudadounarakis (2011) concluded that there is a lack of consensus on procedures for cVEMP recording and interpretation. Even though several studies across the literature have attempted to describe the best stimulus and recording parameters, relatively small sample sizes were used. In an effort to overcome this problem, a meta-analysis can be performed to compensate for small study groups (Glass, 1976). This pooling of data can lead to more precise estimates and facilitates consistency of evidence across studies. Therefore, this study aimed to determine the most prevalent trends in stimulus and recording parameters by performing a systematic literature review. Also, it aimed to combine normative data to determine significant effects of stimulus type, SCM muscle activation method, transducer type and method to control SCM muscle EMG level on cVEMP results by performing a meta-analysis and to obtain normative guidelines for cVEMP interpretation.

3.3 Method

Systematic Review: Relevant current publications in peer-reviewed journals were sourced electronically through a computerized literature search to obtain normative response data. The Scopus database was used to enable a multi-pronged search strategy, seeing that it covers multiple health-related databases and has full Medline and PubMed coverage. The indicator "VEMP" was entered as search term for all years up until 2012. Reports from 1974 – 2012 were sourced. Non-English reports, duplicates, reviews, letters, notes, dissertations and conference papers were excluded. Full-text articles were then retrieved for all remaining studies.

Reports were only included if normative control group data were reported and control group participants had to present with normal hearing with no history of vestibular function deficits. Additionally, reports that explicitly aimed to determine normative data were included. Participants had to be between the ages 18 and 60 to exclude possible vestibular function deterioration due to aging. Males and females were included, since there is no clear indication that gender has an effect on cVEMP results (Tourtillott et al., 2010; Welgampola & Colebatch, 2001b). Only studies where cVEMPs were conducted via air conduction stimuli were included.

After the full-text reports were reviewed to determine whether they meet the inclusion criteria, they were divided into two main groups: those dealing with clicks and those dealing with tone bursts. Each report in these two main groups was then carefully analysed with respect to the following dimensions: report title; year of publication; number of participants; mean age of participants; device used for cVEMP testing; SCM muscle activation method (seated, turn head contralaterally *'STC';* supine, head elevated *'SEH';* supine, elevate and rotate head contralaterally *'SETC';* seated, push head forward *'SPF';* supine, head rotated *'SRH*); electrode montage; transducer used; rectified cVEMPs, visual monitoring only, rectified cVEMPs and visual monitoring, the blood pressure feedback method only or controlling method not indicated; stimulus parameters (stimulus type, frequency, polarity, level, rate, duration,

rise and fall time, plateau, gating); recording parameters (amplifier gain, filter settings, time window, number of sweeps, number of channels) and response parameters (mean latency P1, mean latency N1, mean amplitude, mean asymmetry ratio, mean threshold).

Meta-analysis: A meta-analysis was performed to combine cVEMP test results from the individual studies to determine significant effects of stimulus type, SCM muscle activation method, transducer used and method to control SCM muscle EMG level, as well as normative data for cVEMP interpretation. Thus, all reports from the systematic review indicating normative means for latency, amplitude, asymmetry ratio and threshold were included. Microsoft Excel was used to perform the meta-analysis measures for 0.1 ms click cVEMPs (CVs) and 500 Hz tone burst cVEMPs (TBVs).

Documented means of all response parameters (latency P1, latency N1, raw amplitude, corrected amplitude, asymmetry ratio and threshold) and number of participants in each study were used to calculate weighted means, standard deviations and 95% confidence intervals (CI) for CVs and TBVs. In order to calculate the weighted means, a weight was assigned to each study according to the number of participants in each study ($w_i = \frac{n_i}{N}$, where n_i is the number of participants in study i, and N is the total number of participants across all the studies). The original means were then re-weighted ($\mathrm{x}_i = w_i \times x_i$, where x_i is the un-weighted mean of study i). The weighted sample mean of each response parameter was then determined ($E(\bar{\mathrm{x}}_j) = \frac{\sum w_i x_i}{\sum w_i}$, where i is the particular study, w_i is the proportion of participants in study i and x_i is the un-weighted mean of study i). The standard deviations for each response parameter was determined by $s_j = \sqrt{(\frac{1}{n-1})\sum(x_i - \bar{\mathrm{x}}_j)^2}$, and the 95% CI by $CI_{95\%} = (\bar{\mathrm{x}}_j) \mp [1.96 \times \sqrt{\frac{s_1^2}{n_1}}]$. This was done to establish possible normative values for cVEMP interpretation.

A corresponding T-stat at the 95% CI was calculated ($t_{stat} = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$, where $\bar{x}_j$ the weighted sample is mean of parameter j and s_j is the standard deviation of parameter j) to determine statistically significant differences in the weighted means of response parameters when compared to each other. If the 95% CI ($CI_{95\%} = (\bar{x}_1 - \bar{x}_2) \mp [1.96 \times \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}]$) calculated from the difference between two compared weighted means did not enclose the value "0" within the 95% CI range, it was regarded as statistically significant. This corresponds with a p-value of < 0.05. These calculations were done to determine significant effects of stimulus type (click compared to tone burst) on cVEMP response parameters.

Likewise, weighted means were calculated and used with a two-sample t-test to determine the effect of SCM muscle activation method on CV and TBV results. A loop-calculation was used to compare the weighted means of the four different positions for CVs and 5 positions for TBVs. For example, the loop-calculation for positions of CVs compared the weighted means of each response parameter in the following order: *STC with SEH; STC with SETC; STC with SPF; SHE with SETC; SHE with SPF and SETC with SPF.*

The effects of different transducers on response parameters were also determined for CVs and TBVs. Calculated weighted means of cVEMP response parameters were determined for studies using supra-aural headphones and compared to studies using insert earphones. Lastly, the effect of method to control SCM muscle EMG level on cVEMP response parameters were determined with a loop-calculation as indicated above for positioning.

3.4 Results

Systematic Review: Five hundred and thirty seven reports were initially identified with the database search and the procedural outcomes are indicated in Table 1. It was attempted to retrieve full text for 374 reports, which included some studies without control groups since abstracts do not always indicate whether control groups were included or not. The full text for two reports were still in press and eight could not be retrieved, even when attempted to source them on other databases. From the 364 full text reports, 75 reports were initially included in the analysis. These 75 reports were included based on the aim of the study to determine the effects of stimulus and recording parameters on normal responses, and hence only studies where control group data were indicated or where the study per se determined normative data were included. Also, to limit the amount of variables, only studies where air conducted tone burst or click cVEMPs over the SCM muscle in human adults (age 18 – 60) were measured, were included. The resulting excluded studies are systematically indicated in Table 1:

Table 1. Systematic review procedures of inclusion and exclusion

	Number of reports
Database search results (DBSR)	537
DBSR excluding non-English reports	450
DBSR excluding duplicates	444
DBSR excluding reviews, letters, notes, dissertations or conference papers	408
DBSR excluding reports irrelevant to the study field	374
DBSR excluding articles in press	372
DBSR excluding reports where full text is unavailable	364
DBSR excluding studies with no control group or studies where no normative data were indicated	221
DBSR excluding reports where participants were cochlear implanted	220
DBSR excluding reports where participant age was not indicated	207
DBSR excluding reports where participant age >60	175
DBSR excluding paediatric reports	143
DBSR excluding animal studies	132
DBSR excluding oVEMP reports	118
DBSR excluding bone conduction reports	106
DBSR excluding galvanic stimulation reports	102
DBSR excluding logon stimulus reports	101
DBSR excluding skull tap reports	97
DBSR excluding reports where musculature other than SCM muscle used	95
DBSR excluding reports where response parameters were not clearly indicated or inconsistent with current study	76
DBSR excluding reports with abnormal recording conditions	75
DBSR excluding TBV reports with a stimulus frequency other than 500 Hz or stimulus frequency was not indicated	72
DBSR excluding CV reports with a stimulus duration other than 0.1 ms or stimulus duration was not indicated	69
DBSR excluding reports where stimulus level was not indicated	66

Of all the remaining reports using click stimuli, two reports used a stimulus duration other than 0.1 ms (0.5 ms and 125 µsec) and one did not indicate the stimulus duration. They were excluded. For the tone burst group, two reports used a stimulus Figure 1frequency other than 500 Hz (750 and 1000 Hz) and one did not indicate the stimulus frequency. They were also excluded. A final three reports in the tone burst group did not indicate stimulus level and were excluded.

Sixty six reports remained and were included to be used for the meta-analysis. Twenty four reports used 0.1 ms click stimuli exclusively, 36 used 500 Hz tone burst stimuli exclusively and six reports used both of these stimuli. Thus, 30 reports were included for CVs and 42 for TBVs.

The stimulus and recording parameters of included reports are indicated in Supplementary Digital Content Table 1. Most reports used 95 dB nHL as stimulus level (10 CV reports and 31 TBV reports) and a stimulus rate of 5 Hz (17 CV reports and 32 TBV reports). The duration for CVs was kept at a constant of 0.1 ms and most TBV reports used a rise/fall and plateau time of 1 and 2 ms respectively (25 reports). Regarding recording parameters, the *supine, elevate head (SEH)* position was used most prevalently for both CVs and TBVs (16 CV reports and 19 TBV reports). Most CV reports used (23 reports) while most TBV reports used insert earphones (25 reports). Only three CV reports indicated the amplifier gain values (1000, 2000 and 2500 Hz), but TBV reports mostly amplified input 5000 times (6 reports). Although a wide variety of filter settings was reported on, 20 – 2000 Hz were used most for CVs (11 reports) and TBVs (16 reports). Most reports indicated that EMG was visually monitored during cVEMP recording (16 CV reports and 22 TBV reports). Most prevalent stimulus and recording parameters in the systematic review are summarized in Table 2:

Table 2. Suggested stimulus and recording parameters of 0.1 ms click and 500 Hz tone burst cVEMPs

	0.1 ms click cVEMP	500 Hz tone burst cVEMP
Stimulus parameters		
Level	95 dB nHL	95 dB nHL
Rate	5 Hz	5 Hz
Duration	0.1 ms	1 ms rise and fall, 2 ms plateau
Recording parameters		
Device	Across different devices	Across different devices
Positioning	Across different positions (no significant effect was indicated)	Across different positions (no significant effect was indicated)
Electrode montage	Active electrode: upper half and middle third of SCM; Reference: lateral end of upper sternum; Ground: forehead	Active electrode: upper half and middle third of SCM; Reference: lateral end of upper sternum; Ground: forehead
Transducer	Insert earphone	Insert earphone
Amplifier gain	5000	5000
Filter settings	20 - 2000 Hz	20 - 2000 Hz
Time window	50 - 100 ms	50 - 100 ms
Number of sweeps	256	256
Visual monitoring	Recommended: minimum level of 40 µV	Recommended: minimum level of 40 µV

Since the meta-analysis would be done on the response parameters (latency P1, latency N1, raw amplitude, corrected amplitude, asymmetry ratio and threshold), the means for these parameters obtained from the participants in each study were carefully recorded underneath each heading. Where response parameters were indicated for the left and right ears separately, the mean of the two together was calculated and used for analysis (see Supplementary Digital Content Table 2).

Meta-analysis: Table 3 summarizes the weighted means, SDs and 95% CIs for CVs and TBVs. Concerning the effect of stimulus type on cVEMP results, a significant difference was evident between all response parameters of CVs and TBVs.

Table 3. Meta-analysis of weighted means between response parameters of 0.1 ms click and 500 Hz tone burst cVEMPs

	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Latency P1 (ms)				
0.1 ms click	26	660	12.19 (0.19)*	12.18 - 12.21
500 Hz tone burst	37	744	14.44 (0.20)*	14.42 - 14.45
Latency N1 (ms)				
0.1 ms click	26	660	19.90 (0.28)*	19.88 - 19.93
500 Hz tone burst	37	744	22.89 (0.39)*	22.86 - 22.92
Raw amplitude (µV)				
0.1 ms click	15	443	92.94 (11.18)*	91.90- 94.00
500 Hz tone burst	22	511	122.16 (13.82)*	120.97 - 123.36
Corrected amplitude				
0.1 ms click	2	24	2.61 (0.26)*	2.51 - 2.72
500 Hz tone burst	10	140	1.77 (0.10)*	1.75 - 1.78
Asymmetry ratio (%)				
0.1 ms click	10	258	14.06 (1.23)*	13.91 - 14.21
500 Hz tone burst	11	231	9.89 (1.27)*	9.73 - 10.05
Threshold (dB nHL)				
0.1 ms click	4	83	89.27 (0.88)*	89.08 - 89.46
500 Hz tone burst	8	228	81.02 (2.03)*	80.76 - 81.29

** $p < 0.05$*

n = total number of participants in the indicated number of included studies

Participant age = 18 - 60 years

Asymmetry ratio = 100 x (A_L – A_S) / (A_L + A_S), where A_L equals the larger P1-N1 amplitude and A_S the smaller P1-N1 amplitude

Table 4 indicates the weighted means, SDs and 95% CIs for CVs and TBVs for different SCM muscle activation methods. For CVs, the SCM muscle activation method had a statistically significant effect on latency P1 and N1, raw amplitude, corrected amplitude and asymmetry ratio. Only when comparing the *SEH* and *STC* methods, the *STC* and *SPF* and lastly the *SEH* and *SPF* methods for latency N1 were no significant differences noted. However, since the weighted latency N1 means of these methods were significantly different from all the other methods, it should rather be noted in a holistic fashion, that SCM muscle activation method has a significant effect on cVEMP latency N1 values. No comparisons could be made regarding effect of SCM muscle activation method on CV threshold values, since only the *SEH* method indicated these values.

For TBVs, statistically significant differences in the weighted means of each response parameter of the various SCM muscle activation methods were evident. Overall, the P1 and N1 latencies of TBVs are distinctly larger than those of CVs.

Table 4. Meta-analysis of 0.1 ms click and 500 Hz tone burst cVEMP response parameters for different SCM muscle activation methods

0.1 ms click	*Number of studies*	*n*	*Weighted mean (SD)*	*95% CI*
Latency P1 (ms)				
STC	5	213	13.06 (0.09)*	13.04 - 13.07
SEH'	15	341	11.75 (0.20)*	11.73 - 11.77
SETC	3	39	12.27 (0.12)*	12.24 - 12.31
SPF	2	49	11.82 (0.10)*	11.79 - 11.85
Latency N1 (ms)	-	-	-	-
STC	5	213	19.86 (0.19)*	19.84 - 19.89
SEH'	15	341	19.85 (0.35)*	19.81 - 19.89
SETC	3	39	20.43 (0.13)*	20.39 - 20.47
SPF	2	49	19.91 (0.14)*	19.87 - 19.95
Raw amplitude (µV)				
STC	3	166	36.01(7.64)*	34.85 - 37.18
SEH'	11	259	112.70 (11.96)*	111.20 - 114.10
SETC	0	-	-	-
SPF	0	-	-	-

	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Corrected amplitude				
STC	1	12	3.5*	-
SEH'	1	12	1.72*	-
SETC	0	-	-	-
SPF	0	-	-	-
Asymmetry ratio (%)				
STC	3	138	10.80 (0.93)*	10.64 - 10.95
SEH'	3	74	20.19 (1.72)*	19.79 - 20.58
SETC	3	28	14.34 (0.46)*	14.16 - 14.51
SPF	0	-		-
Threshold (dB nHL)				
STC	0	-	-	-
SEH'	1	11	96	-
SETC	0	-	-	-
SPF	0	-	-	-

500 Hz Tone burst

	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Latency P1 (ms)				
STC	11	331	14.63 (0.16)*	14.61 - 14.65
SEH'	19	296	14.05 (0.22)*	14.03 - 14.08
SETC	3	41	14.18 (0.10)*	14.15 - 14.21
SPF	2	31	15.24 (0.27)*	15.15 - 15.34
SRH	1	20	15.1*	-
Latency N1 (ms)				
STC	11	331	23.45 (0.40)*	23.41 - 23.49
SEH'	19	296	22.27 (0.37)*	22.23 - 22.31
SETC	3	41	21.83 (0.35)*	21.72 - 21.94
SPF	2	31	23.81 (0.54)*	23.62 - 24.00
SRH	1	20	24.2*	-
Raw amplitude (µV)				
STC	7	195	130.82 (5.92)*	129.99 - 131.65
SEH'	7	134	137.94 (22.30)*	134.16 - 141.71
SETC	3	53	156.80 (13.11)*	153.72 - 160.33
SPF	1	20	70.58*	-
SRH	2	40	123.6 (1.95)*	123.00 - 124.20

	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Corrected amplitude				
STC	4	78	1.65 (0.05)*	1.64 - 1.66
SEH'	5	51	2.00 (0.13)*	1.97 - 2.04
SETC	0	-	-	-
SPF	1	11	1.5*	-
SRH	0	-	-	-
Asymmetry ratio (%)				
STC	4	173	4.96 (0.86)*	4.82 - 5.10
SEH'	5	68	16.78 (1.86)*	16.34 - 17.22
SETC	2	30	17.75 (1.03)*	17.38 - 18.12
SPF	0	-	-	-
SRH	0	-	-	-
Threshold (dB nHL)				
STC	4	143	4.96 (0.86)*	4.82 - 5.10
SEH'	0	-	-	-
SETC	1	20	104.35*	-
SPF	0	-	-	-
SRH	0	-	-	-

** p < 0.05*
n = total number of participants in the indicated number of included studies
Asymmetry ratio = 100 x (A_L – A_S) / (A_L + A_S), where A_L equals the larger P1-N1 amplitude and A_S the smaller P1-N1 amplitude

STC	Seated, turn head contralaterally
SEH	Supine, head elevated
SETC	Supine, elevate and rotate head contralaterally
SPF	Seated, push head forward
SRH	Supine, head rotated

Table 5 shows the effect of transducer type on response parameters for CVs and TBVs. For CVs, 23 studies made use of a supra-aural headphone and 5 studies made use of insert earphones. A statistically significant effect of transducer type was indicated for latency p1, latency n1, asymmetry ratio and threshold. No comparisons could be made for raw amplitude, since only reports using a headphone indicated raw amplitude values. Corrected amplitude values were not indicated in any of the reports selected for determining the effect of transducer type.

A total of 13 studies in the TBV group used supra-aural headphones and 23 used insert earphones. One study did not indicate which transducer was used. Transducer type had a statistically significant effect on latency P1, latency N1, corrected amplitude and asymmetry ratio. Only reports using insert earphones indicated threshold values and could not be compared to reports using a headphone as transducer. It is worth noting that the latency values for TBVs are once again larger in comparison with those of CVs.

Table 5. Meta-analysis of 0.1 ms click and 500 Hz tone burst cVEMP response parameters for different transducers

0.1 ms click	*Number of studies*	*n*	*Weighted mean (SD)*	*95% CI*
Latency P1 (ms)				
Headphone	19	521	12.25 (0.13)*	12.24 - 12.26
Insert earphone	5	120	11.63 (0.14)*	11.60 - 11.66
Latency N1 (ms)				
Headphone	19	521	19.67 (0.20)*	19.65 - 19.68
Insert earphone	5	120	20.77 (0.46)*	20.69 - 20.85
Raw amplitude (μV)				
Headphone	12	388	94.47 (10.08)	93.47 - 95.47
Insert earphone	0	-	-	-
Corrected amplitude				
Headphone	0	-	-	-
Insert earphone	0	-	-	-
Asymmetry ratio (%)				
Headphone	8	224	12.38 (0.68)*	12.30 - 12.47
Insert earphone	2	60	25.12 (1.65)*	24.56 - 25.67
Threshold (dB nHL)				
Headphone	2	23	95.06 (0.27)*	94.95 - 95.17
Insert earphone	2	60	51.00 (6.63)*	49.32 - 52.68

500 Hz tone burst

	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Latency P1 (ms)				
Headphone	14	189	13.95 (0.25)*	13.91 - 13.98
Insert earphone	23	555	14.61 (0.18)*	14.59 - 14.62
Latency N1 (ms)				
Headphone	14	189	22.41 (0.54)*	22.34 - 22.49
Insert earphone	23	555	23.06 (0.32)*	23.03 - 23.08
Raw amplitude (µV)				
Headphone	4	86	122.10 (11.34)	119.7 - 124.5
Insert earphone	17	405	121.70 (14.65)	120.30 - 123.10
Corrected amplitude				
Headphone	7	84	1.58 (0.05)*	1.57 - 1.59
Insert earphone	3	56	2.05 (0.09)*	2.03 - 2.08
Asymmetry ratio (%)				
Headphone	3	29	14.45 (0.46)*	14.28 - 14.62
Insert earphone	8	212	9.26 (1.27)*	9.09 - 9.43
Threshold (dB nHL)				
Headphone	0	-	-	-
Insert earphone	8	228	81.02 (2.03)	80.76 - 81.29

** $p < 0.05$*

n = total number of participants in the indicated number of included studies

Participant age = 18 - 60 years

Asymmetry ratio = $100(A_L – A_S) / (A_L + A_S)$, where A_L equals the larger P1-N1 amplitude and A_S the smaller P1-N1 amplitude

Table 6 indicates the effect of method to control SCM muscle EMG level on cVEMP response parameters. For CVs, these methods included reports that indicated only rectifying cVEMP responses, only visually monitoring EMG level and visually monitoring and rectifying cVEMP responses. Statistically significant differences can be seen for latency P1, latency N1 and asymmetry ratio. Only studies using the visual monitoring method indicated raw amplitude values, and no statistical inferences could be drawn. Likewise only studies using rectification alone indicated corrected amplitude values and only studies using the visual and rectifying methods indicated threshold values. No comparisons could be made for them.

The TBV group in Table 6 indicates that method to control SCM muscle EMG level has a significant effect on all cVEMP response parameters.

Table 6. Meta-analysis of 0.1 ms click and 500 Hz tone burst cVEMP response parameters for different methods to control SCM muscle EMG level

0.1 ms click				
	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Latency P1 (ms)				
Rectified	1	12	10.92 (0.00)*	-
Monitored	15	422	12.00 (0.12)*	11.99 - 12.01
Rectified and Monitored	2	21	12.84 (0.08)*	12.87 - 12.80
Latency N1 (ms)	-	-	-	-
Rectified	1	12	19.55 (0.00)*	-
Monitored	15	422	19.78 (0.30)*	19.76 - 19.81
Rectified and Monitored	2	21	21.02 (0.22)*	20.93 - 21.12
Raw amplitude (µV)				
Rectified	0	-	-	-
Monitored	9	268	92.17 (3.36)	91.77 - 92.57
Rectified and Monitored	0	-	-	-

	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Corrected amplitude				
Rectified	1	12	1.72 (0.00)	-
Monitored	0	-	-	-
Rectified and Monitored	0	-	-	-
Asymmetry ratio (%)				
Rectified	1	12	34.5 (0.00)*	-
Monitored	5	115	16.34 (0.16)*	16.31 - 16.37
Rectified and Monitored	0	-	-	-
Threshold (dB nHL)				
Rectified	0	-	-	-
Monitored	2	60	87.05 (0.01)	87.04 - 87.04
Rectified and Monitored	0	-	-	-

500 Hz tone burst				
	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Latency P1 (ms)				
Rectified	6	67	13.65 (0.08)*	13.63 - 13.66
Monitored	20	458	14.37 (0.04)*	14.36 - 14.37
Rectified and Monitored	6	91	14.82 (0.10)*	14.80 - 14.83
Feedback method	4	112	14.60 (0.05)*	14.59 - 14.61
Latency N1 (ms)	-	-	-	-
Rectified	6	67	21.27 (0.22)*	21.22 - 21.32
Monitored	20	458	22.91 (0.07)*	22.90 - 22.92
Rectified and Monitored	6	91	23.04 (0.22)*	23.00 - 23.09
Feedback method	4	112	23.34 (0.08)*	23.33 - 23.36
Raw amplitude (µV)				
Rectified	1	18	90.70 (0.00)*	-
Monitored	15	345	123.90 (3.81)*	123.50 - 124.30
Rectified and Monitored	0	-	-	-
Feedback method	4	112	129.73 (2.45)*	129.28 - 130.18
Corrected amplitude				
Rectified	6	80	1.77 (0.05)*	1.76 - 1.78
Monitored	0	-	-	-
Rectified and Monitored	4	60	3.28 (0.78)*	3.08 - 3.47
Feedback method	0	-	-	-

	Number of studies	*n*	*Weighted mean (SD)*	*95% CI*
Asymmetry ratio (%)				
Rectified	3	31	21.59 (1.46)*	21.07 - 22.10
Monitored	5	128	7.91 (0.69)*	7.79 - 8.03
Rectified and Monitored	0	-	-	-
Feedback method	3	61	10.76 (1.25)*	10.44 - 11.07
Threshold (dB nHL)				
Rectified	0	-	-	-
Monitored	5	146	85.50 (0.89)*	85.35 - 85.64
Rectified and Monitored	0	-	-	-
Feedback method	3	61	73.46 (0.24)*	73.40 - 73.52

** $p < 0.05$*

n = total number of participants in the indicated number of included studies

Participant age = 18 - 60 years

Asymmetry ratio = $100(A_L – A_S) / (A_L + A_S)$, where A_L equals the larger P1-N1 amplitude and A_S the smaller P1-N1 amplitude

Chapter 4: General discussion and conclusion

Note: *Part of this chapter was edited according to the guidelines provided by the International Journal of Audiology (IJA) and the editorial style may differ from the other chapters of this dissertation. The "Discussion of the results" section included below is as written in the IJA.*

4.1 Discussion of results

A systematic review and meta-analysis was performed to determine the effect of stimulus type, SCM muscle activation method, transducer type and method to control SCM muscle EMG level on cVEMP response parameters for participants between the ages of 18 and 60 years. The systematic review revealed most prevalent trends in stimulus and recording parameters which are suggested for clinical use. Relatively large sample sizes are included as a pooling result of the meta-analysis and normative values for cVEMP interpretation are suggested.

Most prevalent stimulus and recording parameters in the systematic review are summarized in Table 2 which correlates well with optimal parameters suggested by previous research: The stimulus level used most frequently in the systematic review was 95 dB nHL, which correlates well with 95 – 100 dB nHL and 90- 95 dB nHL suggested for CVs and TBVs respectively by Akin and Murnane (2008). The indicated stimulus rate of 5 Hz for both CVs and TBVs was also suggested by Wu and Morufushi (1999) to be optimal. As suggested by Welgampola and Colebatch (2005), a 0.1 ms click seems to be used most which is reflected in the systematic review where only 3 reports out of the initial 24 CV reports indicated a different click duration. The previously suggested stimulus duration for TBVs is a 1 ms rise interval with a 2 ms plateau, while others prefer a two cycle rise and fall with no plateau (Zhou & Clarke Cox, 2004; Young, 2006; Wuyts et al., 2007; Welgampola & Colebatch, 2005). Cheng and Morufushi (2001a; 2001b) conducted studies specifically to determine optimal rise, fall and plateau times and concluded that 1 ms rise and fall times combined with 2 ms plateau time would elicit the best possible 500 Hz VEMP responses. It is clear from Table 2 that this is preferred by most clinicians and is recommended for clinical

use. Onset phase or polarity was not reported on regularly in the systematic review and only 21 of the 66 reports indicated using rarefaction.

The popular montage where electrodes are placed over the upper third or half of the SCM muscle (active) with the reference electrode over the lateral end of the upper sternum (Zhou & Clarke Cox, 2004; Cheng & Morufushi, 2001a; Cheng & Morufushi, 2001b; Welgampola & Colebatch, 2001a) is confirmed in the meta-analysis. Although slightly diverse descriptions were given, most of them corresponded with the above-mentioned montage reported in literature.

A fifty millisecond time window was used by most CV reports in the systematic review (see Table 2). Eight TBV reports used a 60 ms time window and another 9 used 100 ms. Since the entire SCM myogenic potential lasts about 40 ms and pre-stimulus recording time is necessary for determining estimated EMG level, a 50 to 100 ms time window is recommended (Zapala, 2007). The number of sweeps is generally between 64 and 256 and not more than 500 for each run or waveform (Zhou & Clarke Cox, 2004; Welgampola & Colebatch, 2005). This corresponded well with systematic review results where the maximum number of indicated sweeps was 512 for CVs and 256 for TBVs.

Artefact rejection is turned off, since muscle responses are considered artefacts when a signal average for neurogenic activity (commonly used in the clinic for cVEMPs) is used (Zapala, 2007). Filter settings are usually between 10 and 2000 Hz, since the dominant energy of EMG signals is between 40 and 150 Hz and amplifier gain is typically set at 5000 times (Zapala, 2007; Welgampola & Colebatch, 2005). Table 2 indicates that the majority of reports for both CVs and TBVs indicated using a 20 – 2000 Hz filter and amplifier gain of 5000 times.

The possible effect of stimulus type on response parameters has been a great point of interest in the study. Cheng et al. (2003) reported that CVs revealed shorter latencies when compared to TBVs. Basta et al. (2005) confirmed large differences between CV and TBV latencies and Wu et al. (2007) substantiated these findings. Results of the meta-analysis (see Table 3) confirm the shorter latency for CVs in comparison to TBVs and also indicate that stimulus type had a significant effect on all

response parameters. Tone burst duration (rise and fall time and plateau) alters latencies recorded, where an increase in duration leads to prolonged latencies (Cheng & Morufushi, 2001a; Cheng & Morufushi, 2001b). Seeing that CV duration in the systematic review and meta-analysis was 0.1 ms and TBV duration much longer (most of the studies used a rise/fall time of 1 ms and a plateau of 2 ms), the overall increase in TBV latency is understood in terms of stimulus duration and confirms findings of previous reports.

Already in 1999 and 2001, Welgampola and Colebatch (2001a) and Murofushi et al. (1999) illustrated that 500 Hz tone bursts evoke the largest VEMP amplitudes. These authors recommended the use of short tone bursts, since a large inter-laboratory variability concerning click-evoked cVEMP latency and amplitude was evident. Most recently, Viciana and Lopez-Escamez (2012) indicated that 500 Hz short tone bursts elicited consistently larger amplitudes. The meta-analysis in the current study concurred with these findings, where CVs had a weighted mean of 92.94 µV (11.18) and TBVs a larger weighted mean of 122.16 µV (13.82). A linear relationship between stimulus duration and cVEMP amplitude is confirmed by the meta-analysis, since the TBVs have a longer stimulus duration than CVs and TBV weighted amplitude means were larger than CV weighted amplitude means.

Most reports used visual EMG and/or µV level monitoring (see Supplementary Digital Content Table 1). All reports applying monitoring used levels of more than 40 µV. Rosengren et al. (2010) prescribe EMG levels of at least 40 µV and up to 150 – 200 µV. A minimum level of 40 µV for EMG monitoring is recommended in Table 2. Since a significant effect of method to control SCM muscle EMG level is noted on all response parameters in Table 6, care should be taken to perform one method only in the clinic. Also, since the reports in the systematic review and meta-analysis mostly represent the visual monitoring method, the suggested norms in Table 3 should be considered when performing this method to control SCM muscle EMG level (versus rectifying or the feedback method).

The meta-analysis indicated that the type of stimulus has a significant effect on AR. This is contrary to a study conducted by Bush et al. (2010). Table 3 suggests upper limits of normality for CVs to be 14.21% and 10.05% for TBVs (upper limit of

normality = upper value of 95% CI as determined statistically and not by simply adding 2 SDs). This is much less than the usual 30% - 40% which is commonly used in clinical settings.

Click-evoked cVEMP thresholds have been found to be within 75-85 dB nHL (Colebatch et al., 1994). Similarly, Welgampola and Colebatch (2001b) found a threshold range of 75-100 dB nHL (mean 89.6 ± 6.9) in a group with subjects ranging from 25 to 85 in age. The current meta-analysis suggested weighted threshold means of 89.27 dB nHL (SD 0.88) with a range of 89.08 - 89.46 to be accepted as normal for CVs (95% CI in Table 3).

For TBVs, the frequency tuning effect of the saccule leads to lowest thresholds obtained in response to 500 Hz stimuli (Park et al., 2010; Tourtillott et al., 2010). This is also the stimulus frequency used in the meta-analysis and a weighted mean of 81.02 dB nHL (SD 2.03) with a range of 80.76 - 81.29 is suggested as normal. Zapala (2007) notes that thresholds obtained from left and right ears should be within 10 dB from each other to indicate normal results.

The number of reports for each method of SCM muscle activation method that was used for CVs and TBVs are indicated in Table 4. From the meta-analysis, it can be seen that the SCM muscle activation method had a significant effect on VEMP response parameters. Adequate SCM muscle contraction with similar EMG levels for both sides seems to be the most important outcome regarding positioning.

Not much is indicated in the literature regarding the effect of type of transducer used on cVEMP response parameters. The systematic review included reports where either a headphone or insert earphones were used. As can be seen from Table 5, a significant effect of transducer type on cVEMP response parameters was found. Since the goal of cVEMP testing includes delivering high intensity sounds, insert earphones may prove to be a better option in order to prevent unwanted stimulus attenuation due to headphone displacement during testing.

Although latency does not clinically act as a function of stimulus level or tonic EMG obtained, which is probably due to the reflexive nature of the response (Colebatch et al., 1994), a statistically significant difference was noted for all response parameters with different methods to control SCM muscle EMG level. Thus, a standard method to control SCM muscle EMG level in the clinic is suggested.

4.2 Clinical implications and recommendations

Optimal stimulus and recording parameters have been suggested by previous research. The current systematic review and meta-analysis confirmed most of these findings by pooling results from a number of studies. Table 2 summarizes these parameters and they are suggested for clinical use as evidence-based practice. Response parameter values obtained from the meta-analysis covered a larger sample size than performed in any single study with weighted means and weighted standard deviations. Therefore, although not all stimulus and recording parameters were kept at a constant, the normative response values indicated in Table 3 are suggested as a guideline for cVEMP interpretation when using stimulus and recording parameters similar to those indicated in Table 2. Since stimulus type had a significant effect on latency values, CV and TBV are to be interpreted with their own set of suggested norms.

4.3 Critical evaluation

An objective, critical evaluation of the research project should be performed to identify possible strengths and limitations of the study. After careful scrutiny, the following points were identified:

Strengths of the study

To date, no summative data on cVEMP stimulus, recording and response data was available. Since the pooling of data leads to more precise estimates of these parameters, the study suggested stimulus and recording parameters for performing cVEMPs and also normative data for cVEMP interpretation which may be used across clinics. Data from 1974 were used, leading to not only a large number of studies included, but also to inclusion of data that are seminal to cVEMP execution and interpretation.

Limitations of the study

Limitations of the study include the following: paediatric data were excluded from the study and the parameters suggested for clinical use are only representative of the age group 18 to 60 years. Due to the nature of the explicit inclusion and exclusion criteria, no recommendations are available for bone conduction cVEMPs, tone burst cVEMPs with a stimulus frequency other than 500 Hz or click cVEMPs with a stimulus duration other than 0.1 ms.

4.4 Future research

This study suggested stimulus, recording and response parameter values for 0.1 ms click and 500 Hz tone burst cVEMPs. As indicated by the limitations section of the study, suggestions regarding cVEMP stimulus, recording and response parameters for the paediatric population need to be explored. Also, since bone conduction cVEMPs can prove to be useful in patients with middle ear pathologies, standard bone conduction cVEMP execution techniques and normative data across a large number of participants need to be established.

4.5 Conclusion

This study addressed the controversy surrounding best recording method of 0.1 ms and 500 Hz tone burst cVEMPs and lack of summative normative data for interpretation purposes. Guidelines are suggested for performing cVEMPs and norms are suggested for the interpretation thereof. The same outcomes for bone conduction cVEMPs and the paediatric population remains to be determined.

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Appendices

Appendix A

Supplementary Content Table 1

Appendix 1: Supplementary Digital Content Table 1.
Stimulus and recording parameters of included 0.1 ms click and 500 Hz tone burst cVEMP reports

0.1 ms click cVEMP			**500 Hz tone burst cVEMP**	
		Number of reports		*Number of reports*
Stimulus parameters				
Level	*Range of 75 - 110 dB nHL:*		*Range of 90 - 110 dB nHL*	
	75 dB nHL	1	90 dB nHL	2
	90 dB nHL	3	95 dB nHL	31
	95 dB nHL	10	100 dB nHL	3
	97 dB nHL	1	105 dB nHL	2
	100 dB nHL	7	107 dB nHL	1
	103 dB nHL	1	110 dB nHL	3
	105 dB nHL	5		
	110 dB nHL	2		
Rate	*Range of 3 - 10 Hz:*		*Range of 4 - 6 Hz:*	
	3 Hz	1	4 Hz	1
	4 Hz	1	4.3 Hz	1
	5Hz	17	5 Hz	32
	6 Hz	1	5.1 Hz	3
	10 Hz	1	5.26 Hz	1
	NI	3	6 Hz	1
			NI	3
Duration	0.1 ms	30	*Range of different rise/fall (R/F) and plateau times (P):*	
			R/F: 1 ms; P: 2 ms	25
			R/F: 1 ms; P: 5 ms	2
			R/F: 1 ms; P: 6 ms	1
			R/F: 2 ms; P: 2 ms	5
			R/F: 2 ms; P: 1 ms	1
			Unclear / not fully described	8

Recording parameters

Device	Across different devices		Across different devices	
SCM muscle activation method	a) Seated, turn head contralaterally (STC)	5	a) Seated, turn head contralaterally (STC)	12
	b) Supine, head elevated ('SEH')	16	b) Supine, head elevated ('SEH')	19
	d) Supine, elevate and rotate head contralaterally (SETC)	5	c) Supine, head rotated (SRH)	2
	e) Seated, push head forward (SPF)	2	d) Supine, elevate and rotate head contralaterally (SETC)	5
	f) NI	2	e) Seated, push head forward (SPF)	2
			f) NI	2
Electrode montage	Across different montages		Across different montages	
Transducer	a) Headphone	23	a) Headphone	16
	b) Insert earphone	5	b) Insert earphone	25
	c) NI	2	c) NI	1
Amplifier gain	*Range of 1000 - 2500:*		*Range of 1000 - 10 000:*	
	1000	1	1000	2
	2000	1	2500	1
	2500	1	5000	6
	NI	27	10 000	1
			NI	32
Filter settings	*Range:*		*Range:*	
	1 - 1000 Hz	1	1.6 - 800 Hz	1
	10 - 1000 Hz	2	8 - 1600 Hz	1
	20 - 2000 Hz	11	5 - 2000 Hz	1
	5 - 1500 Hz	2	10 - 1200 Hz	1
	8 - 1600 Hz	2	10 - 1500 Hz	6
	8 - 4000 Hz	1	10 - 3000 Hz	3
	10- 1600 Hz	1	20 - 1500 Hz	2
	10 - 3000 Hz	1	20 - 2000 Hz	16
	5 - 1000 Hz	1	30 - 1500 Hz	1

	5 - 1500 Hz	1	30 - 3000 Hz	9
	30 -1500 Hz	1	NI	1
	30 - 3000 Hz	1		
	20 - 10 000 Hz	3		
	NI	2		
Time window	*Range of 40 – 220 ms:*		*Range of 40 -120 ms*	
	40 ms	1	40 ms	1
	50 ms	10	50 ms	8
	53 ms	1	53.3 ms	1
	80 ms	1	55.5 ms	2
	100 ms	4	60 ms	8
	120 ms	2	100 ms	9
	200 ms	1	120 ms	2
	220 ms	1	NI	11
	NI	9		
Number of sweeps	100 - 512		100 - 256	
Method to control SCM muscle activation				
	Rectified	1	Rectified	8
	Visually monitored	16	Visually monitored	22
	Visually monitored and rectified	2	Visually monitored and rectified	6
	Feedback method alone	0	Feedback method alone	4
	NI	4	NI	2
EMG monitoring levels	50 - 200 mV	9	50 -200 mV	6
	Measuring resistance against examiner's hand	1	Measuring resistance against examiner's hand	1
	Levels not indicated	6	60 -80 mV	1
			100-400 mV	1
			Levels not indicated	15
NI = Not indicated				

Appendix B

Supplementary Digital Content Table 2

Appendix 2: Supplementary Digital Content Table 2.
Included reports for 0.1 ms click cVEMPs

Authors	Title	Year	Nr of Participants	Latency						Amplitude			Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Gazioglu S., Boz C.	Ocular and cervical vestibular evoked myogenic potentials in multiple sclerosis patients	2012	35	12,25	20,8								15,6	
Gode S., Celebisoy N., Akyuz A., Gulec F., Karapolat H., Bilgen C., Kirazli T.	Single-shot, low-dose intratympanic gentamicin in Meniere disease: Role of vestibular-evoked myogenic potentials and caloric test in the prediction of outcome	2011	40	12,7	22					112,7	145,6	129,15	17,5	
Boldingh M.I., Ljostad U., Mygland A., Monstad P.	Vestibular sensitivity in vestibular migraine: VEMPs and motion sickness susceptibility	2011	30	11,9	20,9									87
Jin Y., Munetaka U., Hayasi A., Takegoshi H., Nakajima Y., Kaga K.	Vestibular myogenic potentials of athletes for the deaf olympic games with congenital profound hearing loss	2010	10	11,6	19,7								15,5	

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Nguyen K.D., Welgampola M.S., Carey J.P.	Test-retest reliability and age-related characteristics of the ocular and cervical vestibular evoked myogenic potential tests	2010	12	10,92	19,55							1,72	34,5	
Rosengren S.M., Govender S., Colebatch J.G.	The relative effectiveness of different stimulus waveforms in evoking VEMPs: Significance of stimulus energy and frequency	2009	11	12,6	20,5									
Rosengren S.M., Todd N.P.M., Colebatch J.G.	Vestibular evoked myogenic potentials evoked by brief interaural head acceleration: Properties and possible origin	2009	10	13,1	21,6									
Chuang Y.-M., Chen C.-C., Lin C.-P.	Vertebral artery hypoplasia may contribute to abnormal vestibular evoked myogenic potentials	2009	26	12,1	24,8							102,3		

Authors	Title	Year	Nr of Participants	Latency						Amplitude			Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Bektas D., Gazioglu S., Arslan S., Cobanoglu B., Boz C., Caylan R.	VEMP responses are not affected in non-insulin-dependent diabetes mellitus patients with or without polyneuropathy	2008	21	12,73	21,06	12,86	12,6	20,99	21,13	218	230	224		
Hong S.M., Park D.C., Yeo S.G., Cha C.I.	Vestibular evoked myogenic potentials in patients with benign paroxysmal positional vertigo involving each semicircular canal	2008	63	13,3	18,9							16,5	3,87	
Seo T., Miyamoto A., Node M., Sakagami M.	Vestibular evoked myogenic potentials of undiagnosed dizziness	2008	10										14,8	
Lee S.K., Cha C.I., Jung T.S., Park D.C., Yeo S.G.	Age-related differences in parameters of vestibular evoked myogenic potentials	2008	63	13,3	18,775							16,4		

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Versino M., Ranza L., Colnaghi S., Alloni R., Callieco R., Romani A., Bergamaschi R., Pichiecchio A., Bastianello S., Cosi V.	The N3 potential compared to sound and galvanic vestibular evoked myogenic potential in healthy subjects and in multiple sclerosis patients	2007	31	11,45	19,4	11,7	11,2	19,9	18,9					
Driscoll C., Bekessy A., Bui V., Fox D., Harvey M., Mackenzie D.	Vestibular evoked myogenic potentials: Clinical implications of a normative investigation	2007	30	10,65	18,32									87,09
Wu H.-J., Shiao A.-S., Yang Y.-L., Lee G.-S.	Comparison of short tone burst-evoked and click-evoked vestibular myogenic potentials in healthy individuals	2007	22	12,43	19,85							81,23	20	
Sazgar A.A., Akrami K., Akrami S., Karimi Yazdi A.R.	Recording of vestibular evoked myogenic potentials	2006	18	12,45	20,8									

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Huang T.-W., Su H.-C., Cheng P.-W.	Effect of click duration on vestibular-evoked myogenic potentials	2005	17	11,31	18,44							111,38		
Huang T.-W., Young Y.-H., Cheng P.-W.	Eliciting constant and prominent waves n34-p44 of vestibular-evoked myogenic potentials	2004	27	11,905	19,105							108,2		
Su H.-C., Huang T.-W., Young Y.-H., Cheng P.-W.	Aging effect on vestibular evoked myogenic potential	2004	40	11,53	19,015							117,6	16	
Cheng P.-W., Huang T.-W., Young Y.-H.	The influence of clicks versus short tone bursts on the vestibular evoked myogenic potentials	2003	29	11,45	19,17							119,55		
Nong D.X., Ura M., Kyuna A., Owa T., Noda Y.	Saccular origin of acoustically evoked short latency negative response	2002	12											94,2

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Versino M., Colnaghi S., Callieco R., Cosi V.	Vestibular evoked myogenic potentials: Test-retest reliability	2001	13	11,515	19,14	11,51	11,52	18,93	19,35	216,65	199,15	207,9		
Brantberg K., Fransson P.-A.	Symmetry measures of vestibular evoked myogenic potentials using objective detection criteria	2001	23	11,4	18,18							66,6		
Ochi K., Ohashi T., Nishino H.	Variance of vestibular-evoked myogenic potentials	2001	18	11,26	20,23							264,1	13,5	
Streubel S.-O., Cremer P.D., Carey J.P., Weg N., Minor L.B.	Vestibular-evoked myogenic potentials in the diagnosis of superior canal dehiscence syndrome	2001	11											96
Sasaki O., Asawa S., Katsuno S., Usami S., Taguchi K.	The effects of intense click sounds on velocity storage in optokinetic after-nystagmus	2000	12	14,05	20,8	13,1	15	20,4	21,2	3,9	3,1	3,5		
De Waele C., Tran Ba Huy P., Diard J.-P., Freyss G., Vidal P.-P.	Saccular dysfunction in Meniere's disease	1999	34	11,5	19,3							80,5		

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Murofushi T., Matsuzaki M., Mizuno M.	Vestibular evoked myogenic potentials in patients with acoustic neuromas	1998	8										12,3	
Robertson D.D., Ireland D.J.	Vestibular evoked myogenic potentials	1995	7	14,6	21,3							10,2		

Included reports for 500 Hz tone burst cVEMPs

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
McNerney K.M., Burkard R.F.	The vestibular evoked myogenic potential (VEMP): Air- versus bone-conducted stimuli	2011	22	13,48	21,8							81,96		

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Murofushi T., Nakahara H., Yoshimura E., Tsuda Y.	Association of air-conducted sound oVEMP findings with cVEMP and caloric test findings in patients with unilateral peripheral vestibular disorders	2011	7	15,1	23,7								16,4	
De Oliveira Barreto A.C., Colafemina J.F., De Lemos Menezes P.	Saccular sensitivity function measured by vestibular evoked myogenic potential	2011	78	14,15	24,17									
Tourtillott B.M., Ferraro J.A., Bani-Ahmed A., Almquist E., Deshpande N.	Age-related changes in vestibular evoked myogenic potentials using a modified blood pressure manometer feedback method	2010	11	16,1	24,5							168,5	10,1	76,8

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Sazgar A.A., Yazdani N., Rezazadeh N., Yazdi A.K.	Vestibular evoked myogenic potential (VEMP) in patients with auditory neuropathy: Auditory neuropathy or audiovestibular neuropathy?	2010	30	14,47	23,79							114,09		
Jin Y., Munetaka U., Hayasi A., Takegoshi H., Nakajima Y., Kaga K.	Vestibular myogenic potentials of athletes for the deaf olympic games with congenital profound hearing loss	2010	10	13,6	23,9								12,9	
Nguyen K.D., Welgampola M.S., Carey J.P.	Test-retest reliability and age-related characteristics of the ocular and cervical vestibular evoked myogenic potential tests	2010	12	12,96	20,79							2,76	31,6	

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Maes L., Dhooge I., D'Haenens W., Bockstael A., Keppler H., Philips B., Swinnen F., Vinck B.M.	The effect of age on the sinusoidal harmonic acceleration test, pseudorandom rotation test, velocity step test, caloric test, and vestibular-evoked myogenic potential test	2010	51	14,5025	23,515							147,0525	2,1675	71,875
Park H.J., Lee I.-S., Shin J.E., Lee Y.J., Park M.S.	Frequency-tuning characteristics of cervical and ocular vestibular evoked myogenic potentials induced by air-conducted tone bursts	2010	20	14,2	21,6							87,7	24	74
Rosengren S.M., Govender S., Colebatch J.G.	The relative effectiveness of different stimulus waveforms in evoking VEMPs: Significance of stimulus energy and frequency	2009	11	14,3	21,1									

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Murofushi T., Ozeki H., Inoue A., Sakata A.	Does migraine-associated vertigo share a common pathophysiology with Meniere's disease? Study with vestibular-evoked myogenic potential	2009	8	13,7	22							1,76		
Vanspauwen R., Wuyts F.L., Van De Heyning P.H.	Vestibular evoked myogenic potentials: Test-retest reliability and normative values obtained with a feedback method for the sternocleidomastoid muscle contraction	2009	30	15,4	24,1							1,84		
Buyuklu F., Tarhan E., Ozluoglu L.	Vestibular functions in motion sickness susceptible individuals	2009	20	15,98	25,25	15,94	16,02	25,13	25,37	78,97	62,19	70,58		
Kawashima Y., Noguchi Y., Ito T., Kitamura K.	Vestibular evoked myogenic potentials in patients with the mitochondrial A1555G mutation	2009	20									132,2		

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Chou C.-H., Wang S.-J., Young Y.-H.	Feasibility of the simultaneous ocular and cervical vestibular-evoked myogenic potentials in unilateral vestibular hypofunction	2009	20	14,5	22							84,6		
Fujimoto C., Karino S., Ito K., Murofushi T.	Existence of possible functional interaction between the saccule and the posterior semicircular canal in humans	2009	14	13	18,5							1,63		
Maes L., Vinck B.M., De Vel E., D'haenens W., Bockstael A., Keppler H., Philips B., Swinnen F., Dhooge I.	The vestibular evoked myogenic potential: A test-retest reliability study	2009	61	14,97	23,41							147,34	0,12	77
Wang S.-J., Yeh T.-H., Chang C.-H., Young Y.-H.	Consistent latencies of vestibular evoked myogenic potentials	2008	14	13,9	20,9							1,9		
Erbek S., Erbek S.S., Yilmaz S., Yucel E., Ozluoglu L.N.	Vestibular evoked myogenic potentials in Behcet's disease	2008	25	15,4	22,4							46,1		

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Isaradisaikul S., Strong D.A., Moushey J.M., Gabbard S.A., Ackley S.R., Jenkins H.A.	Reliability of vestibular evoked myogenic potentials in healthy subjects	2008	20	14,4075	21,1975							163,2825	20,175	104,35
Welgampola M.S., Myrie O.A., Minor L.B., Carey J.P.	Vestibular-evoked myogenic potential thresholds normalize on plugging superior canal dehiscence	2008	20									1,29		
Basta D., Todt I., Ernst A.	Characterization of age-related changes in vestibular evoked myogenic potentials	2007	44									59,4		
Driscoll C., Bekessy A., Bui V., Fox D., Harvey M., Mackenzie D.	Vestibular evoked myogenic potentials: Clinical implications of a normative investigation	2007	30	14,8	24,22									97,12

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Murofushi T., Iwasaki S., Ozeki H., Ushio M., Chihara Y.	Tone burst-galvanic ratio of vestibular evoked myogenic potential amplitudes: A new parameter of vestibular evoked myogenic potential?	2007	12	13,9	23,5							1,6	14,6	
Chang C.-H., Tsung-Lin Yang, Wang C.-T., Young Y.-H.	Measuring neck structures in relation to vestibular evoked myogenic potentials	2007	20	13,8	20,85	14,1	13,5	20,9	20,8					
Wu H.-J., Shiao A.-S., Yang Y.-L., Lee G.-S.	Comparison of short tone burst-evoked and click-evoked vestibular myogenic potentials in healthy individuals	2007	22	14,83	22,54							198,53	13	
Ito K., Karino S., Murofushi T.	Effect of head position on vestibular evoked myogenic potentials with toneburst stimuli	2007	14	16,3	26,6							1,78		

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Yang T.-L., Young Y.-H.	Vestibular-evoked myogenic potentials in patients with otosclerosis using air- and bone-conducted tone-burst stimulation	2007	10	14	22,8							87,7		
Tal D., Hershkovitz D., Kaminski G., Bar R.	Vestibular evoked myogenic potential threshold and seasickness susceptibility	2006	15	14,45	23,24							365,7	12,4	77,33
Bhagat S.P.	Properties of binaural vestibular evoked myogenic potentials elicited with air-conducted and bone-conducted tone bursts	2006	18									90,7		
Wang C.-T., Young Y.-H.	Comparison of the head elevation versus rotation methods in eliciting vestibular evoked myogenic potentials	2006	20	13,625	21,175							104,725		81,25

Authors	Title	Year	Nr of Participants	Latency						Amplitude			Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Karino S., Ito K., Ochiai A., Murofushi T.	Independent effects of simultaneous inputs from the saccule and lateral semicircular canal. Evaluation using VEMPs	2005	11	13,9	21,2							1,5		
Young Y.-H., Kuo S.-W.	Side-difference of vestibular evoked myogenic potentials in healthy subjects	2004	14	13,3875	20,3875	13,48	13,295	20,46	20,315					
Brantberg K., Lofqvist L., Fransson P.-A.	Large vestibular evoked myogenic potentials in response to bone-conducted sounds in patients with superior canal dehiscence syndrome	2004	5	14,35	23,8	14,5	14,2	24,1	23,5	1,9	1,77	1,835		
Wang S.-J., Young Y.-H.	Vestibular evoked myogenic potentials using simultaneous binaural acoustic stimulation	2003	14	14,46	21,825									
Cheng P.-W., Huang T.-W., Young Y.-H.	The influence of clicks versus short tone bursts on the vestibular evoked myogenic potentials	2003	29	12,49	19,97							102,84		

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Takegoshi H., Murofushi T.	Effect of white noise on vestibular evoked myogenic potentials	2003	20	15,1	24,2							115		
Cheng P.-W., Murofushi T.	The effects of plateau time on vestibular-evoked myogenic potentials triggered by tone bursts	2001	13	14,4	24,27									
Akin F.W., Murnane O.D.	Vestibular evoked myogenic potentials: Preliminary report	2001	2	14,3	20,3							150,2		
Cheng P.-W., Murofushi T.	The effect of rise/fall time on vestibular-evoked myogenic potential triggered by short tone bursts	2001	13	13,7	23									
Sheykholeslami K., Murofushi T., Kaga K.	The effect of sternocleidomastoid electrode location on vestibular evoked myogenic potential	2001	15									227,46		

Authors	Title	Year	Nr of Participants	Latency							Amplitude		Asymmetry Ratio	Threshold
				Mean Latency P	*Mean Latency N*	*Mean Latency P Left*	*Mean Latency P Right*	*Mean Latency N Left*	*Mean Latency N Right*	*Mean Amplitude R*	*Mean Amplitude L*	*Mean Amplitude L + R*	*Mean Asymmetry (%)*	*Mean threshold*
Wu C.-H., Young Y.-H., Murofushi T.	Tone burst-evoked myogenic potentials in human neck flexor and extensor	1999	16	16,6	25,2							54,6		

Appendix C

Proof of acceptance of article

Appendix 3: Proof of acceptance of article

From: <roeser@utdallas.edu>
Date: 28 Sep 2014 8:03 PM
Subject: International Journal of Audiology - Decision on Manuscript ID TIJA-2013-11-0340.R2
To: <nathaliebarnard@gmail.com>
Cc: <LeenK.Maes@ugent.be>

MS: "cVEMPs: A systematic review and meta-analysis"
MS#: TIJA-2013-11-0340.R2

Dear Mrs. Meyer:

Dr Maes has reviewed your revised manuscript. Based on the revisions made, it is a pleasure to accept it for publication in the International Journal of Audiology. Note that due to the number and size of tables in the paper, they will be placed on online. This will avoid having you to pay an excessive page charge.

At this time your manuscript is being sent to the publisher for final production. Page proofs will be sent to you during the production process. It is very important that you read your page proofs carefully and return them promptly so that your paper will be processed on schedule. Currently, it requires about 5-6 months for accepted papers to appear in a printed issue of the journal. However, the finished article will appear in electronic form and all readers will be notified through alerts that it is available shortly after you return your page proofs. The electronic posting represents a formal publication.

Thank you for your fine contribution. On behalf of the Editors of the International Journal of Audiology, we look forward to your continued contributions to the Journal. Of particular importance is that you consider accepting the offer to review papers for IJA if/when asked. Finding seasoned authors to review papers is a critically important component of the peer review process and your assistance in this area would be most appreciated.

Sincerely,

Ross J. Roeser, PhD
Editor-in-Chief
International Journal of Audiology
roeser@utdallas.edu

Cc: Leen Maes, PhD
IJA Associate Editor