MASTER THESIS

OPTIMIZING OCULAR VESTIBULAR EVOKED MYOGENIC POTENTIALS: ELECTRODE MONTAGE AND STIMULUS FREQUENCY

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Abstract

Introduction

The ocular Vestibular Evoked Myogenic Potentials (oVEMP) test is a functional vestibular test that can evaluate the function of the utricle and the superior vestibular nerve by measuring the potentials of the inferior oblique muscle. Large vibratory devices such as the minishaker can be used to evoke oVEMPs. Most literature uses the "standard" electrode montage to record the responses, an alternative, the belly-tendon montage, is hypothesized to yield larger responses than the standard montage, thereby benefiting clinical evaluation. Additionally, it is unclear with which stimulus frequency oVEMP responses can be best evoked using a minishaker setup.

Objective

The aim of this study is to investigate the optimal electrode montage and stimulus frequency for obtaining oVEMP responses evoked with a minishaker.

Methods

Two experiments were conducted, both in 15 healthy volunteers. The first experiment investigated the influence of the electrode montage (standard or belly-tendon), the second experiment investigated the optimal stimulus frequency (250, 500, 750, 1000 Hz). The main outcome parameters were response rate, threshold and n1p1 peak-to-peak amplitude. The secondary parameters were n1 and p1 latency and the inter-ocular ratio. The reproducibility and interobserver variability were examined in a subset of 8 subjects.

Results

There was a 100% response rate for 500 and 750 Hz stimuli with the belly-tendon montage. The response rate to 1000 Hz stimuli was 40% and no responses could be evoked to 250 Hz stimuli. Using the standard montage, no response could be evoked in one subject. The threshold to 500 Hz stimuli with the belly-tendon montage was significantly lower compared to all other conditions. The amplitude was also significantly larger compared to the standard montage. The reproducibility and interobserver variability were high, except for a 2-3 dB difference in the determined thresholds.

Conclusion

The belly-tendon montage yields larger amplitudes and lower threshold compared to the standard montage and is therefore the preferred method for measuring oVEMPs. The most optimal oVEMP responses are acquired with 500 Hz stimuli. 750 Hz stimuli are a good alternative, but higher or lower frequencies are unsuitable to the current setup. The most objective clinical parameter is the n1p1 amplitude at a fixed intensity, as there is a grey area in the threshold determination.

Keywords

Ocular Vestibular Evoked Myogenic Potentials; Evoked Potentials; Vestibular function; Utricle

Samenvatting

Achtergrond

De oculaire *Vestibular Evoked Myogenic Potential* (oVEMP) is een relatief nieuwe evenwichtstest waarmee de functie van de utriculus en de n. vestibularis superior gemeten kan worden. Bij deze test wordt gebruikt gemaakt van de vestibulo-oculaire reflex: er worden er luide auditieve of botgeleide trillingen aangeboden die het evenwichtssysteem stimuleren, en wordt de spierpotentiaal van de m. obliquus inferior gemeten. In de meeste literatuur wordt deze potentiaal gemeten volgens de zogeheten standaardmontage, maar de alternatieve *belly-tendon* montage geeft potentieel grotere potentialen en daarmee een beter meetresultaat.

Daarnaast is onduidelijk met welke geluidsfrequentie de grootste potentialen opleveren. In deze studie is gebruik gemaakt van een grote botgeleider, ofwel de *minishaker.*

Onderzoeksdoel

Het doel van deze studie is om te onderzoeken of de gekozen opzet voor het meten van oVEMPs met de minishaker werkt en welke electrodemontage en stimulusfrequentie de optimal response geven.

Methode

Na de proof-of-concept zijn er twee experimenten uitgevoerd, beide in 15 gezonde vrijwilligers. In het eerste experiment is gekeken naar de invloed van de elektrodemontage op de uitkomstpotentialen, waarbij de standaard en belly-tendon montage zijn vergeleken op 500 Hz stimuli. Het tweede onderzoek betrof de stimulusfrequentie, waarbij de response op 250, 500, 750 en 1000 Hz stimuli gemeten met de belly-tendon montage zijn vergeleken. De belangrijkste uitkomstwaarden zijn de respons rate, drempelwaarde en responsamplitude. Secundair is er gekeken naar de latentiewaarden en de inter-oculaire ratio. Ten slotte is er gekeken naar reproduceerbaarheid en inter-observer variabiliteit.

Resultaten

De response rate voor 500 en 750 Hz stimuli met de belly-tendon montage was 100%. Voor 1000 Hz was dit 40%, op 250 Hz zijn geen responsen gevonden. Met de standaarmontage waren er responsen en 14/15 proefpersonen. De drempelwaarden voor 500 Hz stimuli met de belly-tendon montage waren statistisch significant lager vergeleken met alle andere condities. Per intensiteit was de amplitude ook significant hoger vergeleken met de standaardmontage. De reproduceerbaarheid en interobserver variabililteit waren groot, behalve voor een verschil van 2 a 3 dB FL in de gevonden drempelwaardes.

Conclusie

De belly-tendon montage geeft grotere amplitude en lagere drempels vergeleken met de standaardmontage, en heeft daarom de voorkeur bij het meten van oVEMPs. De beste responsen zijn gevonden op 500 Hz stimuli. De 750 Hz response zijn ook betrouwbaar en kunnen als alternatief worden gebruikt. De andere frequenties zijn in deze opstelling niet betrouwbaar. De meest objectieve klinische parameter is de piek-piek amplitude, omdat er rondom de drempelwaarde een klein grijs gebied is.

Table of Contents

List of abbreviations

CI	Cochlear implant/implantation
cVEMP	cervical Vestibular evoked Myogenic Potentials
dB FL	decibel force level
dB HL	decibel hearing level
dB SPL	decibel sound pressure level
EMG	Electromyography
Hz	Hertz
MD	Menière’s disease
oVEMP	ocular Vestibular evoked Myogenic Potentials
SSCD	Superior Semicircular Canal Dehiscence
TB	Tone Burst
VEMP	Vestibular evoked Myogenic Potentials
VS	Vestibular Schwannoma

Chapter 1. Introduction

Until recently, of the five different vestibular end organs (horizontal, anterior and posterior semicircular canals, and the saccule and utricle otolith organs), vestibular functional evaluation was mostly limited to the horizontal semicircular canals. This vestibular end organ can be assessed by several functional vestibular tests, such as calorimetry, the velocity step test, torsion swing or the head impulse test [Wuyts et al., 2015]. For other vestibular organs, clinically applicable tests have become available in recent years. The video Head Impulse Test was developed based on a clinical test to objectively analyze the vestibulo-ocular reflex of the horizontal semicircular canal, and was later expanded to include evaluations of the anterior and posterior semicircular canals [Halmagyi et al., 1988; Aw et al., 2001; Wuyts et al., 2008; Murnane et al., 2014]. Direct clinical evaluation of the otolith organs, saccule and utricle, is possible since the development of Vestibular Evoked Myogenic Potential (VEMP) tests. The cervical Vestibular Evoked Myogenic Potential (cVEMP) was developed first [Watson & Colebatch, 1998]. In this test, the electrical activity of the sternocleidomastoid muscle is measured in response to auditory stimuli. It evaluates the function of the saccule and the inferior vestibular nerve and is well integrated in the modern balance clinic. At the Radboudumc, cVEMP is employed in the assessment of superior semicircular canal dehiscence (SSCD).

The focus of this Master's thesis is on the newest entry to the functional vestibular test battery: the ocular Vestibular Evoked Myogenic Potential (oVEMP), first described in 2005 [Rosengren et al., 2005]. This test is closely related to cVEMP but instead of the sternocleidomastoid muscle, a recording of an eye muscle, the inferior oblique is made.

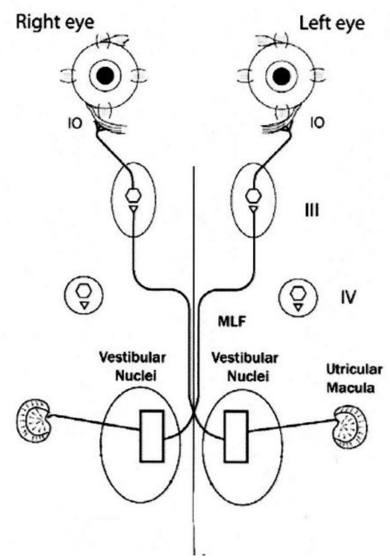

Figure 1 Pathway of oVEMP response. Upon activation of the utricular macula, the response is send through the superior vestibular nerve and the vestibular nuclei in the brainstem towards the medial longitudinal fasciculus (MLF) and oculomotor nerve (III) and ultimately reached the inferior oblique muscle (IO) contralateral to the side of activation. (Figure adapted from Curthoys et al., 2014)

The origin of the oVEMP has not been conclusively proven, but most evidence points towards the oVEMP response being predominantly of utricular origin and conducted through the superior vestibular nerve (see Figure 1) [Suzuki et al., 1969; Isu et al., 2000; Curthoys et al., 2012]. Although it is known that some saccular afferents are present in the superior vestibular nerve and a saccular component has not been decisively excluded [Curthoys et al., 2012; Todd, 2014; Weber & Rosengren, 2015]. It was shown that VEMPs were preserved in patients with profound hearing loss, proving that the response is independent of cochlear function [Wu et al., 2002; Chihara et al., 2009b]. Recent studies in humans with vestibular neuritis and known dysfunctions has provided further evidence that the oVEMP responses are predominantly of utricular and superior vestibular nerve origin [Manzari et al., 2010a; Govender et al., 2015]. Regarding the question of which potentials are measured with oVEMP, Chihara et al. provided evidence that the oVEMP response comes from the extraocular muscles, as the response was preserved in patients with facial palsy or after exenteration of the eye, but lost when the extraocular muscles were removed [Chihara et al., 2009b]. Via the utricular-ocular pathway, unilateral utricular activation causes small torsional and vertical eye movements. These eye movements have been detected in humans, although these movements are too small to be clinically useful and the EMG response of the inferior oblique muscle is a better indicator of utricular function [Cornell et al., 2009; Cornell et al., 2015]. Ipsilateral to the side of activation, eye movements are mediated by the superior oblique and to a lesser extent by the superior rectus muscle. The contralateral response is larger and here the inferior oblique is activated more strongly than the inferior rectus in response to electrical nerve stimulation [Suzuki et al., 1969]. Another study showed that the superior and inferior oblique muscles are not dependent on saccular activation [Isu et al., 2000]. Considering all physiological evidence, this test can be considered a clinical indicator of utricular and superior vestibular nerve function.

In figure 2, a typical oVEMP response is shown. A response consists of an initial negative deflection, called the n1 or n10, occurring around 10 ms after stimulation and a subsequent peak, p1 (or p15) around 15 ms. Aside from the presence or absence of a response, the n1 and p1 latency and n1p1 peak-to-peak amplitudes are used for clinical evaluation.

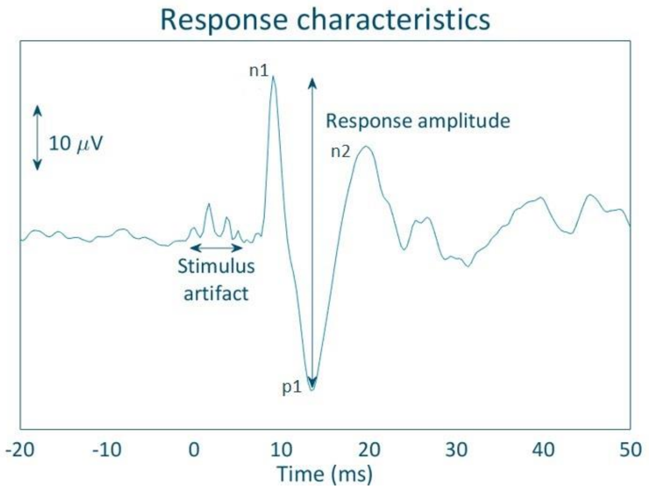

Figure 2 A typical oVEMP response to a vibratory stimulus. A stimulus artefact is visible from 0 to ~6 ms, corresponding to the length of the stimulus. This is followed by the main response complex of n1 and p1 and a secondary n2 peak.

Ocular VEMP may be a valuable tool in the diagnosis and monitoring of specific vestibular disorders, such as superior semicircular canal dehiscence, vestibular schwannoma, or in the evaluation of vestibular symptoms after cochlear implantation [Weber & Rosengren, 2015; Abuzayd et al., 2016]. However, as oVEMP is a relatively new measurement technique, there is no standardized measurement protocol and many technical difficulties exist in performing consistent and reliable oVEMP measurements.

In this introductory chapter, first a literature review of the different oVEMP measurement protocols will be presented, followed by a review of its clinical significance in selected pathologies.

Chapters 3 and 4 detail the main study of this thesis. In this study, oVEMPs were recorded in 30 healthy volunteers with the aim of developing a clinically usable measurement protocol and obtaining normative data. The study focused on 2 parameters on which the literature was inconclusive: the optimal frequency for evoking oVEMPs and the optimal electrode montage. Chapter 5 gives the discussion of the study and recommendations for further methodological and clinical research. Finally, chapter 6 gives the overall conclusion of this Master's thesis.

1.1 Ocular Vestibular Evoked Myogenic Potentials: How to measure?

There is no standardized method for evoking and measuring oVEMP. Responses can be evoked by auditory stimuli, bone-conducted vibration and tendon hammer taps. The mode of stimulation and (for bone-conducted vibration) site, the type and frequency of the stimulus and patient position all show variance in the literature and have different outcomes and response rates [Iwasaki et al., 2008; Kantner & Gürkov 2014; Holmeslet et al., 2015]. Of the acquisition parameters, the electrode montage for capturing the EMG response and the level of gaze elevation have been shown to affect the recording [Sandhu et al., 2014]. Differences in these parameters all affect the oVEMP recording and there is no standardized method or protocol for recording oVEMPs.

This section provides an overview of the various stimulus and acquisition methods for oVEMP recordings and discusses optimal settings. First the stimulus mode and compares air conduction to the various vibratory stimuli are discussed, followed by a review of the stimulus itself, including a discussion of the optimal frequency for Tone Burst stimuli and paragraphs on the stimulus phase and on chirp stimuli, which has been employed in a few recent studies. The final subsection deals with acquisition and recording parameters and discusses the electrode montage and filter settings.

1.1.1 Stimulus mode

Comparison of air conducted and vibratory stimuli

Bone conducted vibration stimuli can be transmitted via classical bone-conduction transducers (e.g. the B71 or B81 (Radioear, USA)), large vibratory shakers (e.g. the type 4810 "minishaker" or V201 (both Bruel & Kjær, Denmark)) or with a tendon hammer. Compared to air conducted stimuli, bone conducted vibrations have a higher response rate in healthy persons and yield higher amplitudes [Wang et al., 2009; Weber & Rosengren 2015; Piker et al., 2013]. An additional advantage of bone conducted stimuli is that these are not impaired by a conductive hearing loss. Therefore, bone conducted oVEMPs are generally preferred over air conduction.

The intensity level necessary for evoking potentials, in the range of ~140 dB FL, is a limiting factor in oVEMP research. Classical bone-conduction transducers have a lower maximum output and therefore a limited capacity in eliciting oVEMP responses. The maximum output of large vibratory shakers, combined with additional pre-amplification results in a higher intensity level and these devices show higher response rates compared to classical bone conduction devices [Iwasaki et al., 2008]. One study revealed a response rate of just 65% in healthy subjects to bone conduction with the B71, compared to 92% with the minishaker [Rosengren et al., 2011]. Iwasaki et al., could not reliably evoke oVEMP responses in healthy subjects with the Radioear B71 and concluded that only the minishaker gave consistent, reliable responses [Iwasaki et al., 2008]. An alternative large vibratory shaker is the V201 shaker, which has specifications comparable to the 4810 but has a higher maximum output. This device was also shown capable of evoking reliable oVEMP responses [Wang et al., 2009; Lin et al., 2010].

An oVEMP response can also be evoked with a tendon hammer [Iwasaki et al., 2008; Rosengren et al., 2011; Weber & Rosengren 2015]. In this setup, the tendon hammer is applied manually to a site on the skull, while a pressure trigger in the hammer is linked to the recording to obtain a time-locked response. An important disadvantage is that it is difficult to obtain a consistent force output, resulting in a large variation in the measured response. For this reason, Iwasaki et al. found the results with a tendon hammer inferior to the minishaker [Iwasaki et al., 2008].

Stimulus site for bone conducted vibration

When using a bone conducted stimulus to evoke oVEMP signals, the placement of the transducer is crucial. Small displacements of a bone conduction transducer can have a large effect on latency and amplitude of the oVEMP response and exact placement remains one of the technical pitfalls of conducting oVEMP measurements [Wang et al., 2009; Li et al., 2014; Curthoys et al., 2012].

Early studies have focused on stimulation of the mastoid. Due to the short path to the vestibule, the large amplitudes and short latencies to oVEMP responses are an advantage of this placement [Rosengren et al., 2005; Rosengren et al., 2009; Cornell et al., 2009; Tseng et al., 2012 Cornell et al., 2015]. For this reason, some researchers prefer mastoid stimulation over the midsagittal sites [Todd 2014]. A disadvantage of mastoid placement is that because the placement of the vibratory device cannot be precisely controlled there will be small differences in placement when testing both sides, which makes a bilateral comparison very difficult [Curthoys et al., 2012]. Partly to circumvent this issue, several midsagittal sites have been explored as alternatives to mastoid stimulation, including Fz (forehead), Iz (the inion), Fpz (just above the glabella) and Cz (vertex) [Iwasaki et al., 2008; Lin et al., 2010; Wang et al., 2009; Rosengren et al., 2013; Kantner & Gürkov, 2014; Holmeslet et al., 2015]. In a study comparing these different stimulation sites, Lin et al. found that oVEMPs could be elicited from all sites, but that Fpz exhibited the shortest latencies and largest magnitudes, even though the absolute distance to the vestibule was shortest at the inion [Lin et al., 2010]. They therefore concluded that Fpz was the preferred midsagittal stimulus site. In contrast, Holmeslet et al. prefer the vertex as a site of stimulation, with the patient in a sitting position, and argue that the smaller amplitude and longer latencies of oVEMPs at that site are compensated by the relative ease of using a BC vibrator at the vertex compared to other sites [Holmeslet et al., 2015]. Another recent paper compared Fz stimulation to a setup where the minishaker was attached to a bitebar, for direct stimulation of the teeth to low frequency (100 Hz) stimuli [Parker-George et al., 2016]. They found larger and more prolonged responses to teeth stimulation compared to Fz and hypothesize this difference is due to the absence of soft-tissue attenuation.

1.1.2 Stimulus characteristics

Stimulus frequency

Air conducted oVEMPs can be evoked by TB stimuli. In a large study to determine the optimal frequency to evoke oVEMPs, Murnane et al. determined that 500 Hz TB stimuli gave the highest response rate and largest response amplitude compared to other frequencies in octave bands from 250 to 4000 Hz [Murnane et al., 2011]. 1000 Hz stimuli also gave large responses, but the response rates were significantly poorer to lower or higher frequency stimuli. All stimuli were 4 ms in duration and delivered with insert earphones at 125 dB SPL. In the same study, a mean threshold of ~119 dB SPL to 500 Hz TB was found. A similar study was performed by Singh and Barman, investigating frequencies of 250 to 2000 Hz and including a 750 Hz stimulus [Singh & Barman, 2014]. They confirmed that the largest responses were found in response to 500 Hz stimuli, yet found larger responses in 250 and 750 Hz compared to 1000 Hz, all in response to 4 ms 125 dB SPL stimuli. Interestingly, the latter study found lower thresholds than Murnane et al., at 103 dB SPL for 500 Hz stimuli. The reported lower thresholds and higher response rates at other frequencies as well, but still found significantly poorer responses to stimuli >1000 Hz. Together, these studies suggest that the range of interest for air-conducted oVEMP responses is 250 to 1000 Hz, where 500 Hz seems to be the optimal frequency for evoking a response. One study investigating age-related characteristics of VEMP responses, found that the ideal frequency for evoking oVEMPs may be age-dependent, with older individuals benefitting from a higher frequency, such as 750 or 1000 Hz tone bursts [Piker et al., 2013]. The stimulus length is also a factor in the response amplitude, with response amplitudes to 500 Hz stimuli of 6 ms significantly larger compared to 4 ms stimuli [Kantner et al., 2014].

For vibratory stimuli, the most common stimulus is the 500 Hz TB [see e.g. Li et al., 2014], although there is an ongoing discussion about the optimal stimulus frequency with both lower and higher frequency stimuli championed as giving optimal responses. Todd et al., developed a model to show that utricle-derived vestibular responses are highly tuned to low-frequency vibratory stimuli [Todd et al., 2008; Todd et al., 2009; Chihara et al., 2009a]. The largest responses were found to 100 Hz stimulation. This response is thought to be predominantly utricular, in contrast with the saccule which seems most highly tuned to air-conduced stimuli around 500 Hz [Todd et al., 2009]. This frequency tuning effect was exploited by others to obtain large oVEMP responses to bone conducted stimuli [Holmeslet et al., 2015; Parker-George et al., 2016]. The responses to low-frequency BC pulses may be less age-dependent than higher frequency or air-conducted stimuli [Rosengren et al., 2011; Colebatch et al., 2013; Weber & Rosengren, 2015].

Stimulus phase

Iwasaki et al., reported oVEMP responses to 500 Hz tone bursts at Fz, an initial negative phase gave a longer latency and lower magnitude compared to a starting positive deflection [Iwasaki et al., 2008]. They hypothesized that a mechanical limitation of the B&K 4810 Mini-Shaker is at least partly responsible for this, and that this difference does not necessarily reflect a physiological phenomenon. However, later studies showed a definite link between the direction of head acceleration caused by vibratory stimuli and the latency of the response [Cai et al., 2011; Jombik et al., 2011]. The direction of head movement depends on the position of the bone conduction device and on the initial deflection of the stimulus. Cai et al found that lateral or medial acceleration, caused by mastoid stimulation, has a significant effect on the response latency, an effect which persisted at Fz [Cai et al., 2011]. Jombik and colleagues showed responses of opposite phase when comparing forward or backward acceleration of the head, with similar findings in forehead stimuli with a positive deflection and inion stimuli with a negative deflection [Jombik et al., 2011].

Chirp stimuli

Several studies have compared the response of chirp stimuli as an alternative to tone bursts for ocular and cervical VEMPs [Wang et al., 2014; Özgür et al., 2015; Walther & Cebulla, 2016a]. These studies have all used air-conducted stimuli. When comparing the latency and amplitude outcomes of these studies, chirps were quite comparable to regular stimuli (tone burst or pip) in each case. However, fewer stimuli may be required to obtain a reproducible response for both cervical and ocular VEMP when chirps are used [Walther & Cebulla, 2016a]. Walther and Cebulla designed a chirp specifically for VEMP measurements, a narrow-band chirp centered around 500 Hz in a 2-octave band (range of 250-1000 Hz) of 10 ms duration which they called the CW-chirp [Walther & Cebulla, 2016a, b]. Discounting low-frequency tuning characteristics, this is the frequency range where the highest response rates and oVEMP amplitudes can be found [Murnane et al., 2011; Singh & Barman, 2014]. The CW-chirp is currently being developed for the Eclipse system by Interacoustics and will become available in a future release [prof. dr. L. Walther, personal communication].

The physiological advantage of a chirp stimulus compared to a tone burst is not immediately clear. Auditory chirps were specifically designed based on the travelling wave delay model of the cochlea and their use for audiometric purposes is well documented [Elberling et al., 2010; Maloff & Hood, 2014]. In contrast, the otoliths lack a comparable time-dependent frequency-specificity, but may still benefit from a broader frequency range [Walther & Cebulla, 2016b]. However, the common assumption that tone burst stimuli are frequency specific may be wrong. Spectral analysis has shown that tone bursts contain smaller harmonic components and other contamination caused by windowing and are therefore not entirely frequency-specific [Walther & Cebulla, 2016b]. The literature on chirp stimuli for VEMP and especially oVEMP is still very limited. Studies on chirp-evoked VEMPs in different pathologies or evoked with vibratory stimuli are necessary before the potential advantage of chirp stimuli can be evaluated.

1.1.3 Acquisition parameters

Electrode configuration

Several studies have analyzed the position of the electrode montage for oVEMPs [Rosengren et al., 2013; Sandhu et al., 2013; Kantner & Gürkov, 2014]. The most commonly used electrode configuration is the standard bipolar montage [Rosengren et al., 2005; Iwasaki et al., 2008; Sauter, 2008; Holmeslet et al., 2015]. Here, the active electrode is placed on the infra-orbital ridge just below the eye, with a reference electrode approximately 15 to 20 mm below the active electrode. The location of the ground electrode differs in the literature, but may be on the sternum, the forehead or the chin.

An alternative electrode configuration is the belly-tendon montage, first described by Sandhu [Sandhu et al., 2013]. In this montage, the active electrode is placed on the infero-lateral orbit between the inferior edge and the lateral canthus and the reference electrode placed adjacent to the medial canthus, thereby roughly following the anatomy of the inferior oblique muscle. This montage was shown to yield larger responses than the standard montage in response to 500 Hz stimuli for both vibratory and air conducted stimuli [Sandhu et al., 2013; Vanspauwen et al., 2016; Govender et al., 2016a; Leyssen et al., 2017]. It was also shown to yield larger response amplitudes compared to other montage configurations where an active electrode on various positions on the orbit was compared to a reference electrode placed according to the standard montage [Sandhu et al., 2013; Govender et al., 2016a].

Finally, electrode montages with a more distally placed common reference have been investigated, where an active electrode is placed on the infra-orbital ridge of the eye like in the conventional configuration and a reference placed on the chin [Zuniga et al., 2014] or the sternum [Vanspauwen et al., 2016]. The chin-reference electrode was compared in patients with unilateral superior semicircular canal dehiscence and gave larger amplitudes than the standard montage in both affected and non-affected ears. However, the researchers encountered a difficulty in measuring chin-referenced responses in patients with facial hair [Zuniga et al., 2014]. The sternum montage gave significantly larger n1p1 peak-to-peak amplitudes compared to the standard montage, and had a similar amplitude as the belly-tendon configuration [Vanspauwen et al., 2016].

Eye and head position

The amplitude of the oVEMP response is significantly affected by the level of gaze elevation [Rosengren et al., 2005; Murnane et al., 2011; Rosengren et al., 2013; Kantner & Gürkov, 2014]. An upwards gaze is necessary to improve the response amplitude and improve the signal-to-noise ratio. Elevating the eyes has the effect of placing the belly of the inferior oblique muscle closer to the surface of the skin and the surface electrodes and of increasing the EMG amplitude of this muscle [Iwasaki et al., 2008]. Rosengren suggests that this second effect of increasing tonic activity is the dominant contributor to larger responses of gaze elevation [Rosengren et al., 2013]. The largest responses, at least in response to AC stimuli, were found at 30° to 35° gaze elevation [Murnane et al., 2011; Kanter & Gürkov, 2014]. Response amplitudes are up to 75% smaller with the eyes in neutral position, and absent completely with downwards gaze [Rosengren et al., 2013]. The need for a target for this upwards gaze was shown by Kantner and Gürkov, who showed a significant increase in the response amplitude when the gaze angle was changed just a few degrees [Kantner & Gürkov, 2014]. To ensure intrasubject reproducibility, it is important that the subject maintains a constant gaze angle with the aid of a visual target. The latencies of n1 and p1 are not affected by the degree of upward gaze [Kantner & Gürkov, 2014].

Filter settings

Prefiltering of VEMP responses is necessary to reduce drift and high frequency noise components and therefore improve the signal-to-noise ratio, yet filtering reduces the overall response amplitude, which might make identification of a response more difficult [Wang et al., 2013]. Different studies have used different filter settings, with high pass filters ranging from 1-20 Hz and low pass filters between 300 and 2000 Hz [Rosengren et al., 2005; Rosengren et al., 2013; Li et al., 2014; Holmeslet et al., 2015]. A study comparing different band-pass filters for the acquisition of air-conducted oVEMPs found responses typically have the largest frequency component around 100 Hz, they found that a broad bandpass filter of 1-1000 Hz produced the largest amplitudes [Wang et al., 2013].

1.2 Clinical applications of ocular and cervical Vestibular Evoked Myogenic Potentials

Ocular Vestibular Evoked Myogenic Potential (oVEMP) measurement are still a relatively new measurement technique, but its clinical significance for some patient groups has already been established [Weber & Rosengren, 2015; Venhovens et al., 2015]. The test can be used either as a sole indicator or in combination with other functional vestibular tests, notably cVEMP. It is used both as an indicator of utricular function, and to investigate the superior vestibular nerve. In this section, the clinical evidence for oVEMP in four selected pathologies is discussed. The selection of these pathologies is based on those which have most clinical relevance in the Radboudumc clinic: Vestibular Schwannoma (VS), Cochlear Implantation (CI), Superior semicircular canal dehiscence (SSCD) and Menière's disease (MD). Ocular and cervical VEMP provide complementary information about the vestibular system and are often research simultaneously. Therefore, this review will also focus on both measurement techniques.

1.2.1 Vestibular Schwannoma

Vestibular Schwannoma (VS), also known as acoustic neuroma is a benign intracranial tumor arising from the Schwann cells of the vestibulocochlear nerve. It is associated with symptoms of hearing loss, tinnitus and vestibular problems. Magnetic Resonance Imaging is the gold standard for diagnosis [Wagner et al., 2011; Babu et al., 2013; Carlson et al., 2015]. Functional vestibular tests, such as caloric tests and VEMP measurements, primarily have a role in the monitoring of vestibular function and objectification of vestibular symptoms [Fortnum et al., 2009; Weber & Rosengren 2015; Brooker et al., 2017].

Several studies have examined a combination of functional vestibular tests to determine which nerves are affected, either by comparing cVEMP to caloric test results [Day et al., 2008; Suzuki et al., 2008; Ushio et al., 2009a & b; Kinoshita et al., 2013; He et al., 2016] or by combining c- and oVEMP [Kinoshita et al, 2013; Chiarovano et al., 2014; Lin et al., 2014; Taylor et al., 2015]. In these studies, cVEMP is an indicator of inferior vestibular nerve function, and caloric tests or oVEMP is an indicator of the function of the superior vestibular nerve. Kinoshita compared both the caloric and oVEMP tests and found that the results were well correlated in VS patients [Kinoshita et al., 2013]

A link between tumor size and vestibular functional outcomes is well established, and reduced or absent responses for both cVEMP and oVEMP (or caloric testing) is associated with larger tumors than when either response is preserved [Day et al., 2008; Suzuki et al., 2008; Wagner et al., 2011]. Lin et al., found that for small tumors (diameter <2 cm), either oVEMP or cVEMP may be intact, while in larger tumors both responses are generally reduced or absent [Lin et al., 2014]. The same study showed no correlation between tumor size and audiometric outcomes. Taylor et al. combined the VEMP tests with the video head impulse test (vHIT) to obtain information of all individual vestibular end-organs [Taylor et al., 2015]. They also found a correlation between abnormal test results and tumor size.

The correlation between the nerve of origin of the Schwannoma and the post-surgical outcomes of functional vestibular tests has been investigated, with early studies reporting that the nerve of origin cannot be accurately determined based on vestibular tests alone, as commonly both nerves will be affected [Suzuki et al., 2008; Ushio et al., 2009a]. A recent study by He et al. found that in a subgroup of VS patients where the nerve of origin was known, an intact cVEMP response in patients diagnosed with VS (and reduced or absent caloric responses) indicates a tumor originating from the inferior vestibular nerve, and intact caloric responses (with reduced or absent cVEMP) indicates a tumor originating from the superior vestibular nerve [He et al., 2016]. In addition, hearing preservation was more common in Schwannomas originating in the superior vestibular nerve and intact cVEMPs were an important predictor for postsurgical hearing preservation.

In conclusion, vestibular functional tests, especially c- and oVEMP have a role in the monitoring of Vestibular Schwannoma, as they are indicators of inferior and superior vestibular nerve function, respectively. When both tests are abnormal, this is associated with larger tumors than when either is preserved. In some cases, VEMP tests can be used to indicate the nerve of origin of the VS and intact cVEMP responses may be an indicator of hearing preservation.

1.2.2 Cochlear Implantation

The risk of vestibular damage following cochlear implantation (CI) has long been known [Huygen et al., 1995; Buchmann et al., 2004]. In recent years, this complication has received increased interest, as the indication for CI has broadened, including the possibility of bilateral implantation [Wagner et al., 2010]. The reported incidence of vestibular function loss after CI varies widely, with estimations ranging from 6-80% of patients [Abouzayd et al., 2016]. This is further complicated by the prevalence of preoperative vestibular dysfunction in this patient group and the fact that subjective vertigo symptoms are often transient in nature, or may first appear only months after implantation [Filipo et al., 2006; Rah et al., 2016]. Different studies stress the importance of informing patients about the risk of vestibular dysfunction, yet maintain that the benefits of CI outweigh this risk [Melvin et al., 2009; Rah et al., 2016]. The role of vestibular function testing in CI patients has mostly been to help determine the optimal ear for unilateral CI surgery, when there is no preference based on auditory outcomes [Filipo et al. 2006]. Until recently, conventional caloric irrigation testing has been the most common technique for determining vestibular loss post CI. However, this technique has limited sensitivity for vestibular symptoms in CI patients [Abuzayd et al., 2016]. Therefore, it is necessary to look beyond caloric irrigation for vestibular function testing in CI patients.

Of the newer vestibular function tests, cVEMP is perhaps most promising. Histopathological studies have shown that the saccule is the vestibular structure that is most frequently damaged after CI [Tien & Linthicum 2002; Handzel et al., 2006]. Several studies on cVEMP responses in CI patients have been performed. Most studies have focused on adults [Basta et al., 2008; Todt et al., 2008; Melvin et al., 2009; Wagner et al., 2010; Katsiari et al., 2013; Meli et al., 2016], while only a few have studied children [Licameli et al., 2009; Xu et al., 2015]. In a large meta-analysis study, Abouzayd and colleagues reported a sensitivity of cVEMP testing for vestibular function of 32% [Abouzayd et al., 2016]. However, the included studies had several methodological differences, including the choice of stimulus (click or tone burst), conduction mode (air or vibratory) and level of stimulation, optimization of the cVEMP protocol may be possible. An overview on the cVEMP settings used in these studies can be found in appendix D. Basta et al. found that air conducted cVEMPs disappeared in all patients post-CI, but that bone conducted cVEMP was preserved in a few patients [Basta et al., 2008]. Other studies reported a less drastic percentage of patients with saccular function loss, but agree that the VEMP signal disappears in a majority of patients postoperatively, indicating an impaired saccular function [Wagner et al., 2010; Xu et al., 2015].

The utricle has received little attention in the literature regarding cochlear implants. One study on pediatric CI recipients aged 3 to 12 found that oVEMP potentials disappeared in a majority of patients [Xu et al., 2015]. To the best of my knowledge, this is currently the only study to investigate oVEMP responses in a CI population.

Overall, it seems unlikely that one vestibular function test will be sufficient to diagnose vestibular function loss in CI recipients. In the available literature, none of the techniques has a good individual correlation to subjective symptoms, which implies that the etiology of vestibular loss post-CI is diverse. A vestibular test battery that includes an evaluation of all individual vestibular end organs will provide more insight in the etiology of vestibular deterioration after CI. The value of oVEMP in vestibular evaluation of CI patients should be further investigated, as little is known of utricular function in this patient category.

1.2.3 Menière's disease

The diagnosis of Menière’s disease (MD) is based on the presence of clinical symptoms, namely recurrent, spontaneous vertigo attacks and associated fluctuating hearing loss and tinnitus in the affected ear. The disease is episodic, with a gradual worsening of symptoms over time, late-stage Menière’s disease is characterised by a permanent vestibular function loss and hearing loss.

VEMP findings in MD patients are dependent on disease stage, and show variance between quiescent and acute periods [Weber & Rosengren, 2015]. In quiescence, patients with MD show higher rates of absent or reduced oVEMP responses in response to air conducted stimuli compared to normal controls [Winters et al., 2011; Hassaan 2011]. One study found that responses are also reduced in the unaffected ear compared to controls [Winters et al., 2011]. However, the control group in this study was not age-matched and later studies could not reproduce this finding [Hassaan 2011; Jerin et al., 2014]. Patients may also show larger asymmetry between the affected and unaffected ears compared to controls [Taylor et al., 2012]. The rate of abnormal findings increases as the disease progresses, with BC oVEMP relatively unaffected in the early stage but reduced or absent in later stages of MD [Hassaan 2011; Winters et al., 2011]. Cervical VEMPs display similar patterns as oVEMPs, with decreased response rates and amplitudes as the disease progresses, although oVEMP and cVEMP responses may be dissociated in patients with MD, suggesting individual variance in disease pattern [Chiarovano et al., 2011]. In contrast with these findings in quiescence, Manzari et al. found that the oVEMP amplitude in response to BC stimuli may be enhanced in the affected in the acute phase of the disease, showing significantly larger responses compared to oVEMPs recorded in a latent period, while cVEMP amplitudes were decreased [Manzari et al., 2010b]. Finally, frequency tuning characteristics of the utricle have come under scrutiny for MD. One study found enlarged oVEMP responses to 1000 Hz auditory TB stimuli, and suggested the amplitude ratio of 500/1000 Hz responses as a diagnostic tool to aid the diagnosis of MD [Jerin et al., 2014]. In this study, 500 Hz responses were significantly reduced, but 1000 Hz responses unchanged in affected compared to healthy ears in patients with unilateral MD.

In summary, VEMP responses are affected in MD patients, and will be reduced or absent dependent on the stage of the disease. In early stages or during acute attacks, the oVEMP amplitude may be amplified.

1.2.4 Superior Semicircular Canal Dehiscence

SSCD is a pathology characterized by a low-frequency pseudoconductive hearing loss, tinnitus, autophony (i.e. loud perception of own voice) and vestibular symptoms in response to loud auditory stimuli. It is caused by a thinning of the superior semicircular canal. The diagnosis is based on high resolution CT scans with a preliminary or supplemental role for both cervical and ocular VEMP testing [Weber & Rosengren, 2015].

Increased ocular and cervical VEMP amplitude and lower thresholds compared to normal subjects are characteristic findings in patients affected by SSCD [Janky et al., 2012; Manzari et al., 2012; Taylor et al., 2012; Zuniga et al., 2012; Taylor et al., 2014; Govender et al., 2016b; Verrecchia et al., 2016; Hunter et al., 2017]. These VEMPs can be evoked via both an air conduction or vibratory pathway [Janky et al., 2012; Manzari et al., 2013; Govender et al., 2016b]. Janky et al., compared air and bone conduction for both VEMP modalities, and found that the amplitude of AC oVEMP responses was the best indicator of SSCD [Janky et al., 2012]. Others have found the amplitude of AC oVEMPs to be more sensitive to SSCD than cVEMP thresholds [Zuniga et al., 2012]. However, both oVEMP amplitudes and cVEMP thresholds are sensitive tests for the diagnosis of SSCD [Govender et al., 2016b; Hunter et al., 2017]. Although AC stimulation generally has a higher sensitivity for abormalities than BC, this can also be used reliably, especially when the minishaker is employed [Janky et al., 2012; Manzari et al., 2012; Govender et al., 2016b]. Finally, there are indications that the frequency specificity for oVEMP responses is altered in SSCD patients compared to healthy subjects, as SSCD patients can show oVEMPs at frequencies where healthy controls have a flat response [Taylor et al., 2012; Manzari et al., 2013; Verecchia et al., 2016]. One article recommended a 4000 Hz stimulus as a fast indicator of SSCD abnormality for both air and bone conduction, which had a very high response rate for SSCD patients but where responses were not detected in healthy volunteers [Manzari et al., 2013]. In contrast, another study found significantly higher responses in SSCD patients compared to normal subjects with a 125 Hz bone conducted stimulus [Verecchia et al., 2016].

In conclusion, both c- and oVEMP show highly characteristic patterns in SSCD patients and can be used supplemental to CT scans in diagnosis. The sensitivity and specificity of the tests for SSCD is dependent on a number of protocol parameters such as stimulus frequency and conduction mode, and the debate on the optimal method to distinguish normal from dehiscent ears is ongoing.

Chapter 2. Aims

Based on the available literature on oVEMP a research setup using vibratory stimuli presented with a minishaker (type 4810, Bruel & Kjær, Denmark) was chosen for further investigation, as this device was shown to provide the most consistent oVEMP responses.

The first aim of the thesis was to investigate the viability of this setup. This was addressed in a small preliminary study, attached in Appendix B. This study showed that evoking oVEMPs was possible using this setup, but left open a few questions regarding the optimal method for oVEMP recordings.

The main aims of this thesis were to assess under which conditions ocular Vestibular Evoked Myogenic Potentials can be measured optimally, with the ultimate goal of developing a clinically viable measurement protocol.

The literature review and preliminary study identified two parameters for further study: the electrode configuration and the stimulus frequency that provides the best oVEMP responses.

These parameters are addressed in two separate experiments in the main study of this thesis. The first experiment focuses on the optimal electrode montage and compares the oVEMP responses recorded with the standard montage or the belly-tendon montage. The second experiment focusses on the optimal stimulus frequency and compared tone burst stimuli of 250, 500, 750 and 1000 Hz. As a secondary aim, the consistency of the minishaker setup was investigated by evaluating the reproducibility and interobserver variability.

Chapter 3. Methods

3.1 Subjects

Adult volunteers (aged 18-30) with a clear vestibular and neuro-otological history were included in the study. Thirty subjects were included in the main study, divided equally over the different experiments: 15 for the montage comparison and 15 for the frequency comparison. In a subset of eight subjects the measurement was repeated at different occasions to test the intrasubject reproducibility. All subjects gave informed consent and this research was reviewed and approved by a local medical ethics committee.

3.2 Materials

The oVEMP stimuli were administered with a large bone-conducted vibration transducer, the 4810 “minishaker” connected to a type 2735 amplifier (both Bruel & Kjær, Denmark). The minishaker was fitted with a hard plastic cap. The responses were acquired with Ag-AgCl electrodes and recorded by the VEMP modality of an Eclipse EP 25 system (Interacoustics, Denmark). The calibration report of this minishaker setup is attached in Appendix A.

Figure 3 Left: the Belly-Tendon electrode montage. The active electrode lies on the inferio-lateral orbit and a common reference is placed on the nasion. Right: the Standard electrode montage with the active electrode on the inferior orbit of the eye and separate references 15-20 mm below the active electrode. The ground electrode is placed on the chin in both configurations.

3.3 Procedures

The measurements were performed according to the protocol attached in Appendix C. After disinfection with alcohol and light scrubbing with an abrasive agent, the surface EMG electrodes were placed on the subject’s skin, according to either the standard or belly-tendon montage (see

Figure 3Figure 3). For the standard electrode montage, the active electrode was placed on the inferior orbit of the eye and a reference electrode on the cheek 15-20 mm below the active electrode. This required separate reference electrodes for the left and right side. The Belly-Tendon montage has an active electrode placed on the inferio-lateral orbit of the eye, on the belly of the inferior oblique muscle, and a common reference electrode placed on the nasion. For both montages, the ground electrode was placed on the chin or sternum. The electrical impedances were maintained below 5 kOhm.

The recordings were performed with the subject in supine position. Subjects were instructed to focus their eyes on a target on the ceiling at a ~30^{o} angle to ensure a constant upward angle and obtain a sufficient upwards gaze of the eyes. The total examination time, including preparation of the electrodes, was about 40 minutes.

3.3.1 Stimulus parameters

Tone Burst (TB) stimuli at a frequency of 250, 500, 750 or 1000 Hz were used for the measurements. The stimuli were presented to the subject at a rate of 5.1 Hz with the minishaker held manually at a right angle to the forehead (Fz position). An overview of the stimulus characteristics is shown in Table 1. The length of the TB stimulus was chosen to minimize the chance of overlap between the stimulus artefact and the evoked potentials, which had an expected latency of around 10 ms. Due to differences in calibration, the maximum sound intensity was frequency dependent and can be seen in
Table 2. For more details on the stimulus and calibration of the research setup, please refer to appendix A: calibration report of the 4810 minishaker.

Table 1 An overview of the main stimulus and acquisition parameters for oVEMP measurements

Parameter	Value
Acquisition time (ms)	100
Sample rate (Hz)	3000
Number of stimuli per recording	60
Stimulus rate (Hz)	5.1
Band pass filter (Hz)	10-1000

3.3.2 Acquisition parameters

Each recording consisted of 60 stimuli and at least two recordings were averaged to ensure that the response was reproducible. After a reproducible response was found, the examination was repeated at a lower sound intensity until a threshold (i.e. a sound level without a measurable EMG response) was reached. The EMG was recorded from 20 ms before to 80 ms after the stimulus and bandpass filtered (10-1000 Hz). The latency and mean amplitude were used for further analysis. Both sides were evaluated separately.

3.4 Experiment 1 (n=15): Comparison of standard and belly-tendon montage

For the first experiment, an intrasubject comparison between the standard and the common-reference belly-tendon montage was made in 15 subjects. The effect of the electrode montage on the n10 and p15 latency, n10p15 peak-to-peak amplitude and response threshold was examined. For the belly-tendon measurements, recordings of both eyes were made simultaneously. Standard montage recordings were performed sequentially. A 500 Hz TB stimulus was used for all measurements in this experiment and the order of the electrode placement was randomized between subjects.

3.5 Experiment 2 (n=15): Optimal frequency

To determine the optimal stimulus frequency, an intrasubject comparison between four different TB stimulus frequencies in the range of 250-1000 Hz was made. The order of measurement was randomized between subjects and the belly-tendon montage was used for each recording. The length of the TB stimuli was kept around 6 ms, the exact characteristics differed for each frequency. Table 2 gives an overview of the stimulus characteristics.

3.6 Reproducibility and inter-observer variability

In a subset of eight test subjects, the reproducibility of oVEMP responses was tested for the 500 Hz condition with the belly-tendon montage. This repeated measurement took place two to eight weeks after the initial recording. In the same group, the inter-observer variability was investigated for both measurements, by comparing the evaluations of two different observers for this dataset.

Table 2 Stimulus characteristics of the TB stimuli at different frequencies.
A detailed report of the calibration of the research setup can be found in appendix A.

Frequency (Hz)	Duration (ms)	Rise/fall (cycles)	Plateau (cycles)	Maximum intensity (dB FL)
250	12	1	1	127
500	6	1	1	141
750	5.33	1	2	142
1000	6	2	2	141

3.7 Analysis

All data was processed and analyzed in MATLAB (version 2014b, The MathWorks, Inc., USA). The exported VEMP data from Eclipse contains 2 separate curves (A and B) for each recording, into which responses to the stimuli are saved alternatingly. Using the A and B curves, a Pearson's correlation was calculated to determine the internal correlation of each recording, as a measure of reproducibility. The time window for this correlation was set at 8 to 18 ms after the start of the stimulus. This window was chosen to include the likely range of a n1p1 and n2 response while excluding both stimulus artefacts (which occur from 0 to 6 ms) and possible longer latency peaks (which occur starting at ~20 ms). If the correlation was below 60%, an oVEMP response was considered unreliable for the purpose of threshold determination.

When a recording was reproducible and had a visible response, the n1 and p1 peaks were determined manually, from which the n1 and p1 latencies (ms), the interpeak latency (ms), and n1-p1 peak-to-peak amplitude (µV) were calculated. The n1 and p1 were defined as the first large negative and positive deflection after the stimulus artifact, respectively. When multiple peaks were visible, or one of the peaks appeared biphasic, the first peak was always selected. Finally, the inter-ocular ratio (IOR), an asymmetry value based on the absolute difference in amplitude between sides, was calculated:

$$\frac{|V_L - V_R|}{V_L + V_R}$$

where V_L and V_R are the n1-p1 amplitude for the left- and right-sided vestibular function, respectively. The asymmetry ratio was not calculated for the standard montage, as these measurements were not performed simultaneously.

3.8 Statistics

In the first experiment, there were two different testing conditions (standard montage or belly-tendon montage for 500 Hz TB). There were four different conditions in the second experiment (250, 500, 750 and 1000 Hz TB stimuli for the belly-tendon montage). Each experiment had 15 subjects. In all 30 subjects, the 500 Hz TB belly-tendon condition was measured and these were combined in the determination of the normal values for this condition.

For each condition, the response rate and mean thresholds (dB FL) were determined. Normal values (mean +/- std) were calculated for the threshold, latencies and amplitudes for each condition and possible left/right differences were investigated using a paired t-test.

For the montage comparison, paired t-tests were performed for the threshold intensity and the n1p1 amplitude between the belly-tendon and standard electrode montage at each intensity. The thresholds of the different stimulus frequencies where compared using paired t-tests. Normal values for the above parameters were recorded at fixed stimulus levels for each frequency.

In a subset of eight subjects, the repeated measures reproducibility was tested for the thresholds and the latencies and amplitudes at 136 dB FL, using paired-t tests. In the same subgroup, the inter-observer variability was determined for the same parameters. Left and right sided measurements were evaluated separately.

Chapter 4. Results

4.1 Subjects

A total of 30 subjects were included, all with a clear otological history (see Table 3). VEMP responses could be evoked in all these subjects for at least one condition.

Table 3 ***Subject characteristics***

	Total	Exp 1	Exp 2
N =	30	15	15
Female	15	6	9
Male	15	9	6
Age (years) (std)	24.8 (2.0)	24.6 (2.5)	25.1 (1.4)

4.2 Response rate and thresholds

No responses were found to 250 Hz TB stimuli in any recording, due to the limited attenuation of the setup at that frequency. This condition will not be discussed further here.

There were no significant left/right differences in threshold for any condition. For the belly-tendon montage, the 500 Hz and 750 Hz TB stimuli could evoke responses in all subjects. At 500 Hz, a mean threshold of 126.7 ± 3.2 dB FL was found and a 100% response rate was achieved at 136 dB FL. At 750 Hz, measurements were initially performed at 137 dB FL (73% response rate), and when no response was found, the measurement was repeated at a higher intensity. There was a 100% response rate at 142 dB FL and a mean threshold of 135.1 ± 4.3 dB FL. The response rate was lower for the 1000 Hz stimulus, where a response was found bilaterally in 6/15 subjects (40%) at maximum stimulus intensity and bilaterally absent in all other recordings.

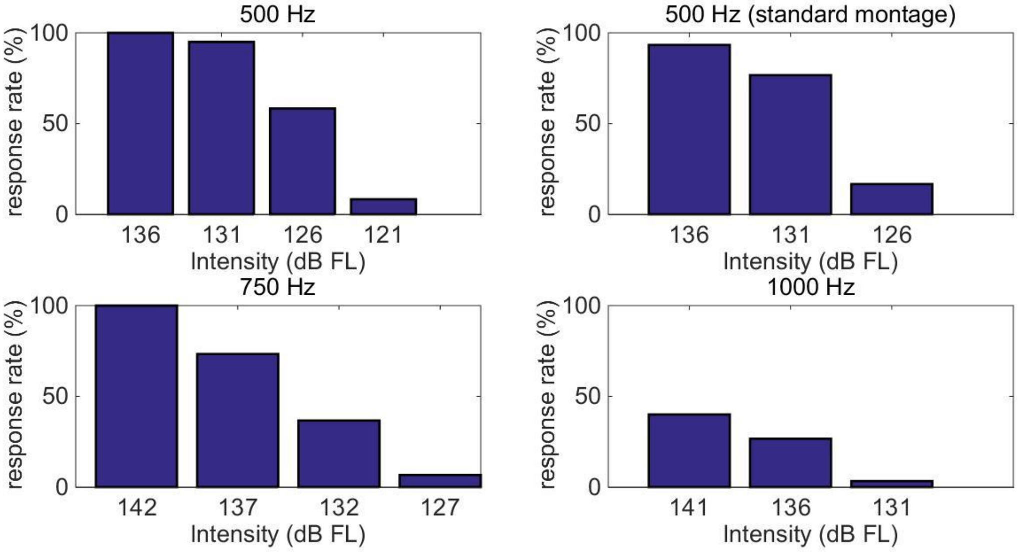

Figure 4 Response rates for different oVEMP frequencies and stimulus levels (n=30 ears). For the standard montage (upper right graph) there was no measurable response in 1 subject at maximum intensity. 100% response rates were found at 500 and 750 Hz. At 1 kHz, there was only a 40% response rate at maximum intensity.

For the standard electrode montage, no response could be discerned in one subject at maximum intensity, while a response was found for the belly-tendon montage. For each condition, the response rate drops for lower intensities, as is shown in Figure 4. Figure 5 shows the mean thresholds for the different conditions. For the belly-tendon montage at 500 Hz, the response threshold was significantly lower compared to all other frequencies conditions (paired t-tests, p<0.05).

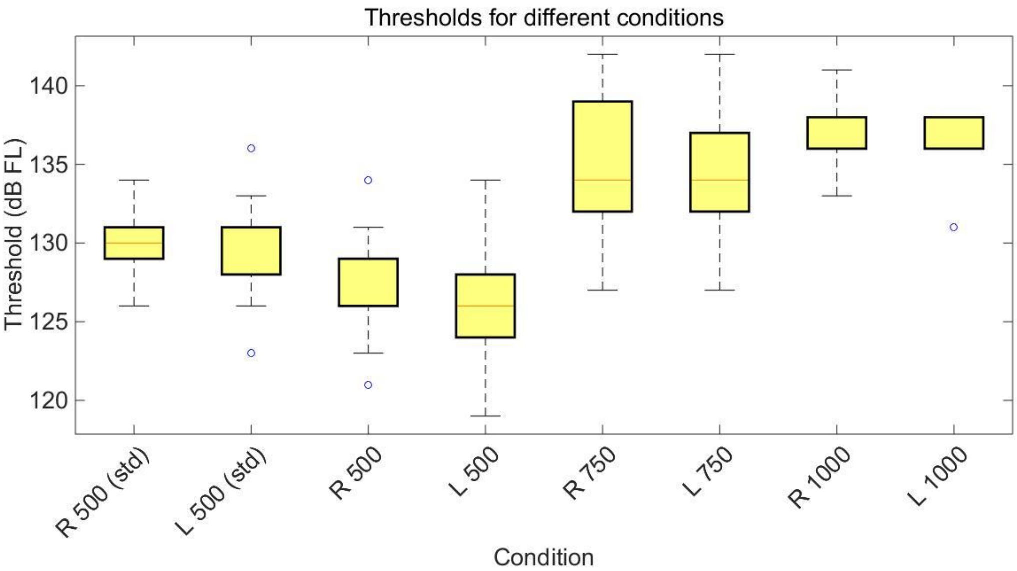

Figure 5 The mean oVEMP threshold for left and right sided utricular function for each condition. There was no significant left/right difference in threshold for any condition. The thresholds at 500 Hz TB with the belly-tendon montage was significantly lower compared to the thresholds with the standard montage and for 750 and 1000 Hz stimuli (p < 0,05). Abbreviations: R: right utricle, L: left utricle, std: standard montage

4.3 Experiment 1: standard and belly-tendon montage

Table 4 Response rate and amplitude comparison between the belly-tendon and standard montage at different intensities. Based on 15 ears (left or right) for each condition. *Statistically significant difference (paired t-test, p<0.05); no statistics performed for the 126 or 124 dB FL conditions, because of the low response rate in the standard montage.

Intensity (dB FL)	**belly-tendon**		**standard montage**	
	N *(%)*	**Amplitude (µV)** *mean (std)*	**N** *(%)*	**Amplitude (µV)** *mean (std)*
136 L	15 *(100)*	23.11 (10.16)	14 *(93)*	9.12 (6.34)*
134 R	15 *(100)*	18.43 (8.36)	14 *(93)*	9.51 (4.49)*
131 L	14 *(93)*	8.92 (5.12)	11 *(73)*	4.44 (2.59)*
129 R	12 *(80)*	8.53 (4.46)	7 *(47)*	4.51 (2.14)*
126 L	9 *(60)*	5.06 (2.61)	2 *(13)*	2.83 (0.83)
124 R	5 *(33)*	4.18 (1.79)	0 *(0)*	-

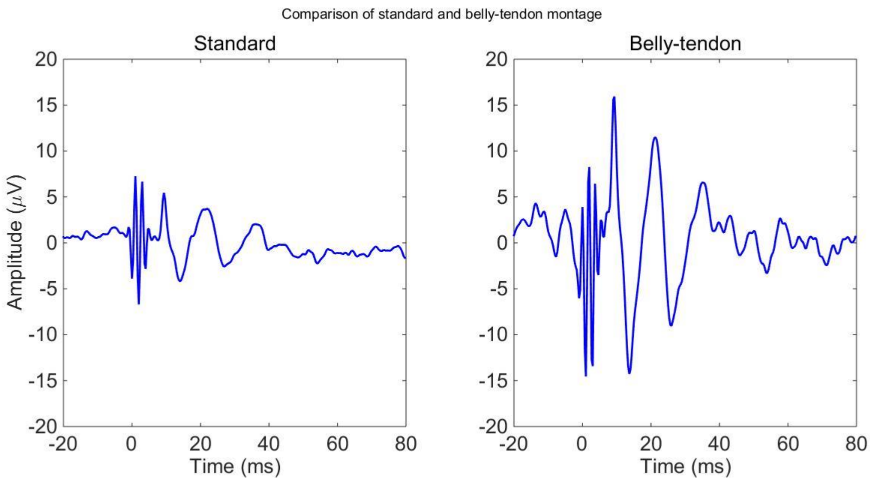

Figure 6 A typical example of oVEMP recordings in a single subject. Left: recording with the standard montage. Right: recording with the belly-tendon montage. Both recordings were made on the eye and at the same intensity. The n1 amplitude is noticeably higher in the belly-tendon montage. Also note the presence of secondary peaks around 20 ms.

Figure 6 shows a comparison of the standard and belly-tendon recordings in a single subject. Due to attenuation differences between the left and right insert sockets at 500 Hz (a 2 dB difference), a left/right comparison for the standard montage was not possible. With paired t-tests, the amplitude difference between the standard and belly-tendon montage recordings was determined at different intensities for left and right ears. Left ears were compared at 136, 131 and 126 dB FL and right ears at 134, 129 and 124 dB FL. An overview of the different intensities is given in Table 5. There were no significant n1 or p1 latency differences between both electrode montages at any intensity. At 136, 134 and 129 dB FL, the amplitude of the belly-tendon montage was significantly larger than the amplitude obtained by the standard montage. No statistical test was possible at 126 or 124 dB FL because these were below threshold for the standard montage in most or all subjects.

Table 5 Response rate, mean latencies and amplitudes for TB stimuli at 500 (60 ears), 750 and 1000 Hz (both 30 ears) recorded with the belly-tendon montage. The top 3 rows give the parameters for 500 Hz at 3 different intensities. The bottom rows give the values for 750 Hz at 137 dB FL and for 1000 Hz at 141 dB FL. The IOR is the amplitude difference between the left and right recordings. Abbreviations: std: standard deviation; IOR: inter-ocular ratio. * Significantly different from the 136 dB FL condition, for p < 0,05.

Intensity (dB FL)	**N (ears)**	**n1 latency (ms)** *(mean (std))*	**p1 latency (ms)** *(mean (std))*	**n1p1 amplitude (μV)** *(mean (std))*	**N (subjects)**	**IOR (%)** *(mean (std))*
136	60	9.0 (0.4)	13.4 (1.0)	22.86 (10.59)	30	8.9 (6.3)
131	58	9.2 (0.4)	13.9 (1.3)*	9.78 (5.45)*	28	9.2 (7.9)
126	34	9.3 (0.5)*	14.5 (1.7)*	4.60 (2.07)*	15	11.7 (8.5)
137 (750 Hz)	22	8.5 (0.6)*	13.3 (1.7)	10.01 (5.13)*	10	7.4 (6.1)
141 (1000 Hz)	12	8.7 (1.7)	12.1 (1.8)	9.8 (2.7)	6	5.1 (3.8)

4.4 Experiment 2: Frequency comparison

Figure 8 shows the averaged responses to 500 , 750 and 1000 Hz stimuli to stimuli at 136, 137 and 141 dB FL, respectively. Each response consists of a n1, p1 and n2 deflection, and some later latency peaks occur in a subset of the recordings. The mean values for the 500 Hz belly-tendon montage for different intensity levels are reported in

Table 45. Typically, the n1 peak occurs around 9 ms and the p1 peak around 13 ms after the start of the stimulus, with a slight (but statistically significant) latency increase at lower stimulus intensities. Across the measurements, the p1 showed a larger variability than n1, as reflected by the larger

standard deviation. At 750 Hz, there was a significantly shorter n1 latency compared to 500 Hz, but no difference in the latency of p1. The peak-to-peak amplitude was also significantly lower, despite the slightly higher stimulus intensity. The decrease in amplitude for lower stimulus intensities was statistically significant with $p<0.05$. Finally, the IOR was not affected by stimulus intensity and was around 10% for all conditions.

4.5 Reproducibility

The n1 and p1 latencies and the peak-to-peak amplitude were highly reproducible. In the subgroup where reproducibility was tested, no significant differences were found for n1 and p1 latency or peak-to-peak amplitude using paired-t tests. However, the repeated measurement tended to find lower thresholds. This was significant in the right-sided ears (128.4±3.2 dB FL vs 125.3±3.3 dB FL, $p<0.05$), and there was a trend for lower thresholds in the left ears 127.1±3.6 dB FL vs 125.3± 3.6 dB FL).

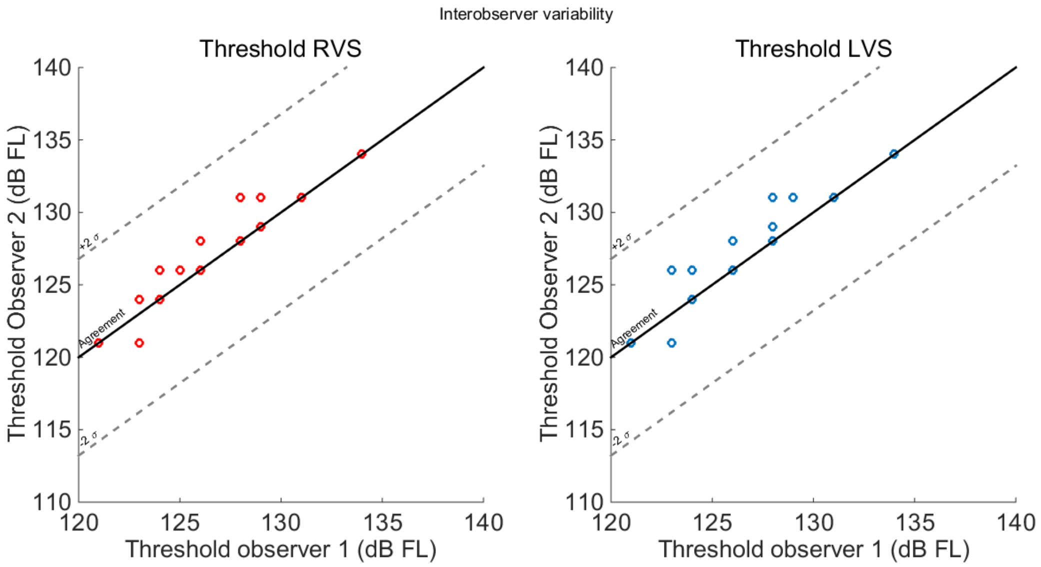

Figure 7 Interobserver variability. This scatter plot shows the determined oVEMP thresholds determined by both observers. The thresholds of observer 1 are plotted on the x- and of observer 2 on the y-axis. The left graph (red dots) shows the outcomes for the right vestibular system (RVS), the right graph (blue dots) show the outcomes for the left vestibular system (LVS). The black line represents perfect agreement between the two observers, the dotted gray lines represent twice the standard deviation (2σ). This figure shows that observer 2 tended to place the threshold slightly higher than observer 1.

4.6 Inter-observer variability

The inter-observer correlation was high, with no significant differences for n1 or p1 latency and peak-to-peak amplitude at 136 dB FL. However, there was a small but significant difference in the determined thresholds, with one researcher tending to a higher threshold determination than the other, as seen in the scatter plot (Figure 7).

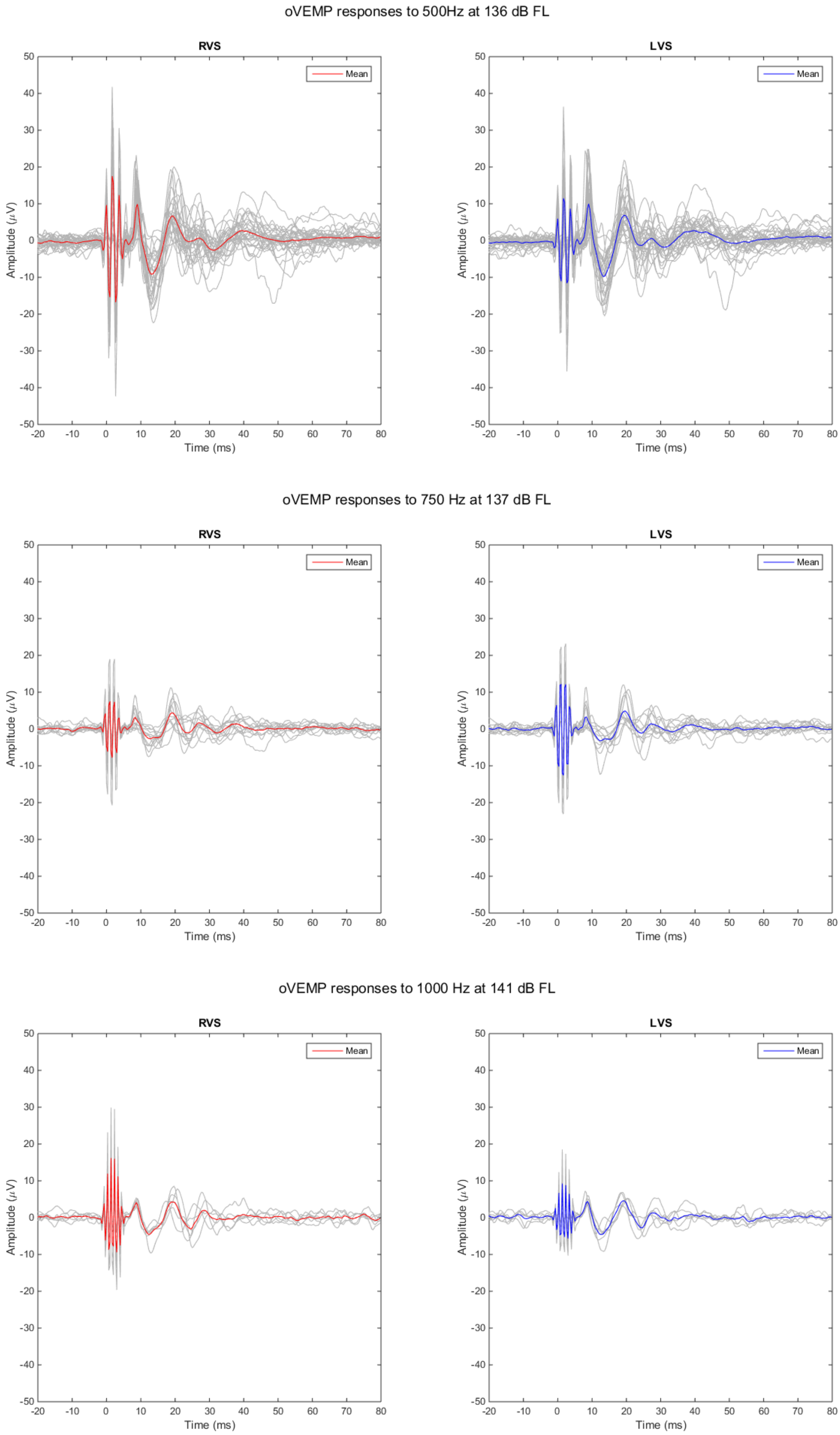

Figure 8 Combined oVEMP responses to 500, 750 and 1000 Hz stimuli recorded with the belly-tendon montage of all subjects. Each grey line represents one subject, the red and blue lines represent the averaged response for the right and left vestibular systems, respectively. The upper two graphs are the responses to the 500 Hz stimulus at 136 dB FL (n=30), the middle graph shows the responses to a 750 Hz stimulus at 137

dB FL (n=11) and the bottom graphs show the responses to 1000 Hz stimuli at 141 dB FL (n=6). These figures show that a response always consists of a n1, p1 and n2 peak. Deflections with a longer delay can be seen in a subset of the subjects. Abbreviations: RVS: right vestibular system; LVS: right vestibular system. Additional graphs at other stimulus intensities can be found in Appendix D.

Chapter 5. Discussion & Recommendations

5.1 Standard vs belly-tendon montage

Larger amplitudes were found with the belly-tendon montage compared to the standard configuration, which corresponds to the available literature on this subject [Sandhu et al., 2014; Vanspauwen et al., 2016; Govender et al., 2016a; Leyssens et al., 2017]. Of the previous studies on the belly-tendon montage, two looked at minishaker evoked oVEMPs [Vanspauwen et al., 2016; Govender et al., 2016a], the others used an air conduction method. All studies investigated only 500 Hz stimuli and did not compare thresholds.

The larger amplitudes found with the belly-tendon montage make identification of the response easier. In this study, the response thresholds for the belly-tendon montage were significantly lower compared to the standard montage, corresponding to the larger amplitudes at fixed intensities. Vanspauwen and colleagues reported larger amplitudes for both electrode configurations compared to this study [Vanspauwen et al., 2016]. However, their stimulus intensity was also higher at 140 compared to 136 dB FL, which is likely the main factor in this difference. There is a larger variance in the stimulus intensity to which oVEMPs have been evoked with the standard montage, ranging from 131 to 148 dB FL [Rosengren et al., 2011; Rosengren et al., 2013]. The thresholds found in this study of ~126 dB FL for the belly-tendon electrode configuration show that there is quite a large margin to response threshold compared to the intensity values reported in some studies – at least in healthy subjects. The present study shows that these high stimulus intensities may be unnecessarily taxing on the subjects, especially when the belly-tendon configuration is used.

Apart from the belly-tendon montage, several electrode configurations have been investigated over the years as possible improvements over the standard configuration. The belly-tendon montage was shown to have significantly better responses compared to configurations with the active electrode on different orbital sites [Sandhu et al., 2014; Govender et al., 2016a]. Other montages include the chin-referenced and sternum-referenced electrodes, which also gave results superior to the standard montage [Zuniga et al., 2014; Vanspauwen et al., 2016]. A small downside of the chin-reference is that it cannot always be evoked when the subject has facial hair [Zuniga et al., 2014]. Between the belly-tendon and sternum-reference configurations, no significant difference in amplitude was shown [Vanspauwen et al., 2016].

The hypothesis that the belly-tendon montage yields the optimal response rates has an anatomical basis. This configuration places the active electrode near or on the belly of the inferior oblique and the reference near the insertion site of this same muscle. Based on the results of this study, and of the other available studies on this subject, this hypothesis can be confirmed. The belly-tendon montage is superior compared to the standard montage for recording oVEMP, as this method finds both larger response amplitudes and lower thresholds. Extrapolating from this, the belly-tendon may find reliable responses with fewer repetitions or at lower stimulus intensities than the standard configuration, reducing the strain of the measurement and patient discomfort.

5.2 Stimulus frequency

There was a 100% response rate for 500 and 750 Hz stimuli with the belly-tendon montage, with 500 Hz responses obtained at a significantly lower threshold. Poor response rates were found at 1000 Hz. This contrasts with available literature on air-conducted oVEMP, where 100% response rates were found at this frequency [Murnane et al., 2011; Singh & Barman, 2014]. The stimuli were all delivered at roughly the same sound intensities, so attenuation is not the limiting factor here.

Both the lowest intensity at which a 100% response rate was achieved, and the mean threshold value were significantly lower at 500 Hz compared to other frequencies. Therefore – discounting frequency tuning effects [Todd et al., 2008], which were not explored in this study, 500 Hz stimuli are the optimal responses for evoking oVEMP. However, there are indications that the optimal response frequency is age-dependent, with older patients benefiting from a higher frequency stimulus [Piker et al., 2013]. Although this effect was not shown for minishaker evoked oVEMPs specifically [Rosengren et al., 2011]. The current study was limited as the subjects were all relatively young with a mean age of ~25 years, therefore a possible age-dependent effect could not be explored. As most clinical applications only the presence or absence of a VEMP response is significant, it is certainly recommended to provide higher frequency stimulus when no response can be discerned at 500 Hz. 750 Hz stimuli were shown to have good response rates and amplitudes in the current study, and is therefore the primary recommendation when no or poor responses are found to 500 Hz.

The n1 latency to 750 Hz stimuli was significantly shorter than the latencies to 500 Hz tone bursts in contrast to other literature, where latency was not frequency dependent [Barman & Singh, 2014]. However, the 750 stimuli were slightly shorter than the stimuli to 500 or 1000 Hz tone bursts (5.3 vs 6 ms). This difference could account for the small latency gap. No latency difference was found for p1.

5.3 Reproducibility

The repeated measurements reproducibility for n1 and p1 latencies and amplitude was high at 136 dB FL. However, there was a discrepancy of 2-3 dB in the found thresholds. The factors discussed above - minishaker angle and position and gaze elevation could account for this effect.

There was a high interobserver correlation for the n1 and p1 latencies when judged by different observers. This was expected, as these were strictly defined in the protocol (n1 is defined as the first peak of the response and p1 first subsequent trough). However, there was a small discrepancy in thresholds, with one observer systematically defining lower thresholds. A possible explanation for this difference is in experience – as the more experienced observer achieved lower thresholds. Experience plays a role in the identification and interpretation of peaks, especially near threshold. However, the difference in threshold between observers was quite small, around 2-3 dB, which is equal to the stepsize used in threshold determinations. It shows that there is a small gray area in whether near-threshold recordings are marked as a response. There remains a subjective component in VEMP analysis and this is especially evident near threshold.

Fortunately, the discrepancies in repeated measurements or between observers are small. The 2-3 dB difference is equal to the stepsize employed in threshold determinations, so this difference is equal one intensity step. While the variability of the parameters affecting amplitude and the gray area of interpreting oVEMP responses near thresholds should be taken into account in clinical application, the small discrepancy found in this study is unlikely to be of clinical significance.

A method to reduce the variability in thresholds requires that the presence or absence of a response must be determined more objectively. In this setup, the Pearson's correlation was explored for this purpose. This coefficient was based on internal reproducibility and was generally high (>95%) at maximum intensity. At lower intensities, and especially near threshold, the coefficient tended to drop, signifying a worse signal-to-noise ratio. A somewhat arbitrarily chosen cutoff of 0.60 was used to determine whether a response was present, however, this cutoff functioned more as a guideline in practice, with responses slightly below 0.60 sometimes marked if the observer found the response very evident. The cutoff chosen here was lower than the 0.80 reported elsewhere [Walther & Cebulla, 2016b]. However, this study had a different setup and did not look near thresholds.

It is my opinion that a method for separating responses from noise is desired for VEMP measurements, and Pearson's correlation coefficient may be suited for this purpose. The correlation coefficient is built in to Eclipse, but unfortunately the time window is not very customizable as it is currently implemented. In practice, it is often inevitable to include some component of stimulus artifact or secondary peaks in the selection window, leading to an over- or underestimation of the response inter-reproducibility. Unless the coefficient is determined solely over the range of interest (roughly 8-16 ms), then it is not suitable as a parameter to objectify whether a response is present. Even then, it is probably better served as a guideline, where very low coefficients mean that the response should be considered as noise, even when a (small) peak complex is visible. More research would be necessary to determine which cutoff value is appropriate.

5.4 Response characteristics

5.4.1 Inter-ocular ratio

A degree of variability in amplitude existed between subjects and between measurements on the same subject. In the study setup, there are at least two parameters that can explain this. The first is the angle and position of the minishaker. This was difficult to control precisely in practice, especially between subjects. While the clinician can and should attempt to maintain a constant position and a right angle of the minishaker on the skull, in practice, small displacements are inevitable. This means that there will be some variability in the resulting force exerted on the skull at Fz. An additional between-subject effect is the absolute distance from the stimulation site to the inner ear, which also has a degree of variability between subjects [Iwasaki et al., 2008]. Together, these effects contribute to small intra- and intersubject differences in the intensity of the stimulus that reached the utricle. The exact magnitude of this variability is unknown, but likely small. In the calibration, differences of ~1 dB FL where found in response to small displacements of the shaker, this range is likely similar for clinical measurements. This difference can have an effect on the recorded amplitude. Fortunately, n1 and p1 latencies are mostly independent of stimulus intensity, as this study showed with the comparison of responses to 136, 131 and 126 dB FL stimuli at 500 Hz, where the latency shift over a 10 dB FL decrease in intensity was minimal (although statistically significant).

Another, likely larger influence on the oVEMP amplitude is the level of gaze elevation. During the measurements, subjects lay supine and were asked to direct their gaze towards a target on the ceiling at a ~30^{o} upwards gaze angle. However, this angle was not calibrated exactly and small inter- and intra-measurement differences in elevation are likely. Different studies have shown that even small changes in gaze angle result in a significant change in amplitude [Murnane et al., 2011; Rosengren et al., 2013; Kantner & Gürkov, 2014]. This also corresponds to the findings in the preliminary study. For longer measurements, gaze fatigue might play a role, leading to lower amplitude responses for repeated measurements. To reduce intrasubject variability of EMG amplitude, the level of gaze elevation should be precisely controlled and the measurement time should be kept short to prevent fatigue.

However, even with the above precautions, some variability between measurements probably cannot be eliminated, which means that the n1p1 amplitude alone is not reliable clinical parameter for inter-person comparisons, unless the difference in amplitude is profound such as may be the case in SSCD. A related parameter is the inter-ocular ratio. The advantage of this parameter is that it does not suffer from gaze- and angle related variability, at least for simultaneous recordings as performed in this study.

This setup showed a variability in inter-ocular ratio of 0-25% in the normal subjects. This range corresponds to earlier findings using this montage [Vanspauwen et al., 2016; Leyssens et al., 2017]. Based on these findings, an asymmetry ratio of > 25% can be considered abnormal and may be indicative of a unilateral pathology. However, more tests on patients with known pathologies (e.g. SSCD) are necessary to determine if this effect is also clinically significant.

Due to amplitude variability between measurements, it is clear that the variance between measurements due to gaze elevation and minishaker position can have a significant effect on the measured amplitude. Therefore, the IOR is likely less reliable when it is determined over separate left- and right sided measurements. Simultaneous recordings as employed in this study for all belly-tendon montage conditions do not have this problem, and further research on the viability of the IOR as a clinical parameter should focus on these simultaneous recordings.

5.4.2 Additional n-peaks

An oVEMP response consists of an initial negative deflection, n1 around 9 ms after the stimulus, a p1 peak followed by a secondary n2 deflection. After this initial complex, secondary and sometimes tertiary or quaternary peaks were seen in a number of subjects, although not always present. These peaks were always ~10 ms apart from each other. Figure 9 gives a typical example of this behavior. Secondary peaks in response to both air- and bone-conducted stimuli have been described previously, although there is a discussion about their origin [Rosengren et al., 2013; Singh & Barman, 2014].

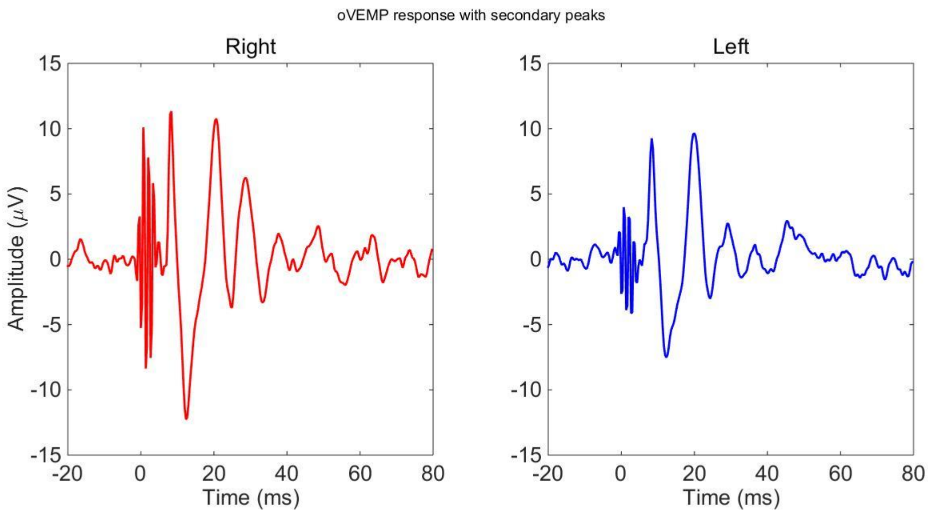

Figure 9 An example of secondary peaks in response to a 750 Hz TB stimulus at 137 dB FL. After the initial reaction around 9 ms, several later responses are visible, starting at ~20 ms. The right figure shows the response to right vestibular and the left figure shows the response to left vestibular activation. Both recordings were made simultaneously.

Firstly, the additional peaks can be a result of frequency tuning in the utricle [Todd et al., 2008]. Although the utricle is most highly tuned to low frequency stimuli of 100 Hz, a similar yet smaller effect may exist that amplifies the 500 Hz stimuli as used in the present study. Adding to this hypothesis is that the tone bursts are not necessarily frequency-specific and a 500 Hz stimulus also contains lower frequency components [Walther & Cebulla, 2016b].

Another possibility is that later peaks are a result of activity of different ocular muscles. Intramuscular needle EMG showed that both the inferior oblique and inferior rectus activate in response to oVEMP stimuli, both with a pattern of multiple contractions about 10 ms apart [Weber et al., 2012]. This activation pattern is consistent with the pattern of additional peaks shown here. However, other ocular muscles may also play a role in the longer latency reactions. In the same paper, Weber et al., showed that the inferior rectus has a ~5 ms latency delay compared to the inferior oblique [Weber et al., 2016]. Secondary oVEMP components could reflect the activity of this muscle, or of delayed potentials from the ipsilateral superior rectus or superior oblique, which have been shown to activate to a small degree in response to inferior nerve stimulation [Suzuki et al., 1969].

5.4.3 Biphasic peaks

Figure 10 shows an example of an oVEMP with a biphasic n1 complex. Similar complexes were seen in a minority of the measured subjects. The origin of this pattern could not be discerned with certainty in the course of this study, but our hypothesis is that this pattern is caused by highly time-specific utricular activation. The latency difference between the two n1s is roughly equal to one cycle of the tone burst stimulus. The separate peaks are therefore probably a response to different cycles of the stimulus. Threshold measurements often showed one of these peaks disappearing until a single n1 remained. For the purpose of this study, when this biphasic complex appeared, the latency of the response was always marked as the latency of the first peak, even if it was slightly smaller as shown in the blue trace of Figure 10.

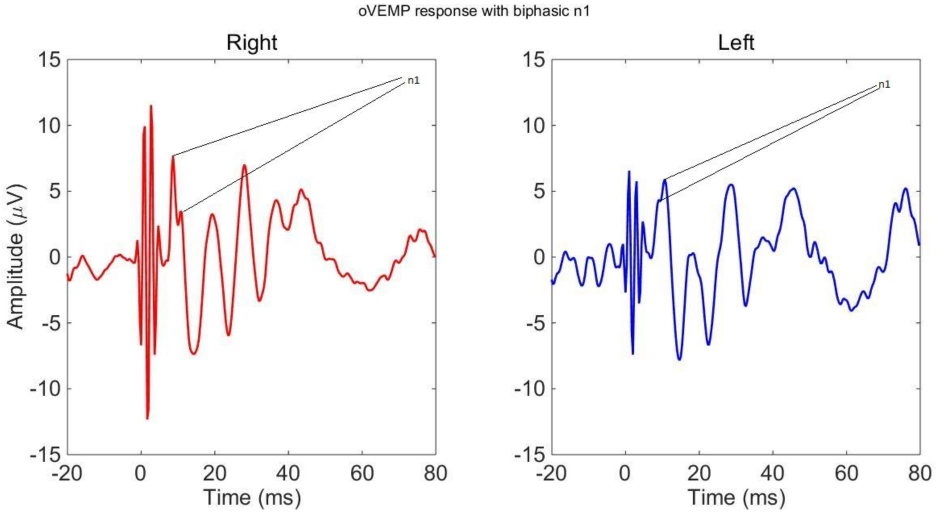

Figure 10 Example of a biphasic n1 peak in response to a 500 Hz stimulus at 136 dB FL. These right and left-sided oVEMPs were recorded simultaneously in one subject. In the right oVEMP, the initial response has the higher peak, in the left oVEMP, the response is larger in the second peak. Both responses are considered part of the same n1 complex

5.5 Tolerance of testing conditions

During preliminary testing, no qualitative difference between the responses to different stimulus rates could be determined. However, the 3 subjects where this comparison was made all reported that a stimulus rate of 8 Hz distinctly more uncomfortable than a rate of 5.1 Hz. Because the potential saved time with faster stimulation is quite small (~4.5s per 60 stimuli), the 5.1 Hz stimulus, which is well tolerated, is preferred.

Prolonged testing leads to discomfort, based both on the weight of the minishaker and because the subject has to maintain an elevated gaze throughout the measurement, which leads to muscle fatigue. In addition, several of the early test subjects reported headaches after the measurements. One subject in the preliminary reported a sensation of vertigo during exposure to high-intensity stimuli. This was not reported by any subject in the main study and may have been in response to sound intensities higher than in the final setup. It is still a reminder that the measurement may not be tolerated well by every subject, which should be remembered in clinical application. The tolerance to stimulation may be worse in certain patient groups, such as in SSCD patients who experience sound-induced vertigo.

Overall, the measurements were well tolerated and discomfort from the measurements was minimal. Still, oVEMP requires loud sound intensities and further minimizing the exposure time to these stimuli is of great benefit as it both reduces patient discomfort and minimizes the effect of muscle fatigue.

5.6 Limitations of the setup

During the study, we encountered several limitations in the hardware and software of the Eclipse system (Interacoustics, Denmark) and in the calibration and attenuation of the set up. This limited the application of the oVEMP measurements in the setup used in this study to a degree. These will be discussed in this section. An abbreviated list of these limitations and recommendations was compiled earlier and communicated with Interacoustics.

5.6.1 Stimulation limitations

The minishaker could not be inserted in the bone conduction socket of the Eclipse, because this socket is calibrated to a B81 bone conductor and has a limited output (maximum attenuator of 60 dB) to a degree that oVEMP responses cannot be evoked. Instead, the air conduction sockets were used. A practical disadvantage was that the socket had to be changed every time the measurement is switched from left-sided to right-sided. Additionally, the Eclipse system could not be calibrated for the minishaker specifically, as changing the calibration settings would also affect the calibration for other devices using the same socket. Both sockets are calibrated separately, and a 1 and 2 dB difference in calibration was found at 250 and 500 Hz, respectively. Unfortunately, this discrepancy was discovered only after the inclusion period was finished and therefore could not be corrected for pre-recording. This difference had to be corrected for in the report to report accurate threshold values. For the belly-tendon montage, a left-right comparison for different parameters was made by analyzing the contralateral data in MATLAB. However, a left/right comparison at the same intensity was not possible for the standard montage, which is why this data is missing from the report.

Finally, there was a different intensity attenuation for different stimulus frequencies. This difference was small for 500-1000 Hz, where the intensities are comparable. However, at 250 Hz, the attenuation was too low to evoke oVEMP responses. In the preliminary setup, a more powerful amplifier (B&K type 2718) was used that had a roughly 20 dB higher maximum amplification and this could overcome the limited attenuation level. Figure 11 shows an example of an oVEMP response to a 250 Hz stimulus , obtained during the preliminary study. This amplifier was changed for the type 2735 in the main study based on safety considerations.

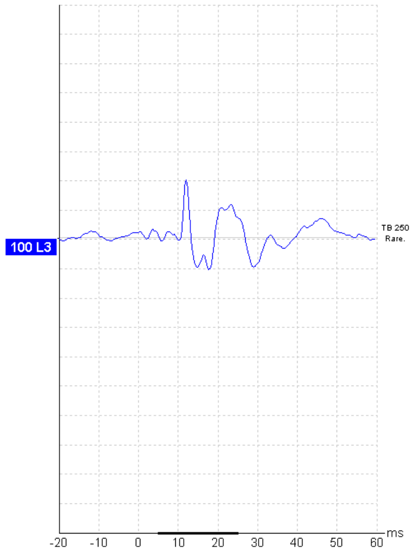

Figure 11 Example of an oVEMP response to a 250 Hz TB stimulus.

Unfortunately, the exact intensity at which the response was evoked is unknown, because the preliminary setup was not properly calibrated and contained a variable gain amplification. However, this still shows that oVEMP responses can be evoked at 250 Hz, and that the failure to do so in the current setup is due to hardware limits. The case can be made that for 1000 Hz stimuli, a higher response rate may be achieved at a higher attenuation setting, although this would require higher intensities than what was shown sufficient for 500 and 750 Hz.

5.6.2 Acquisition limitations

For a midsagittal stimulation site such as Fz as employed in this study, separate left- and right sided recordings are theoretically unnecessary as both vestibular systems are stimulated equally and are recorded simultaneously. However, in this situation the software provided by Interacoustics is the limiting factor, as the 'contralateral' EMG (i.e. the side opposite of the stimulating insert socket) is recorded but cannot be evaluated within the software.

A MATLAB script was written to evaluate the contralateral side, in addition to some other parameters, but this script is not (yet) suitable for clinical applications, as processing the data is relatively time consuming. Therefore, separate bilateral recordings are probably a necessity in the short term.

Another hardware limitation is that Eclipse can handle just a single reference electrode, whereas 2 are required for the standard montage, and 2 references are also used in the belly-tendon montage as described in the literature [Sandhu et al., 2013; VanSpauwen et al., 2016; Leyssens et al., 2017]. In this study, the reference electrode was changed manually for the standard montage to make both recordings. A different workaround was chosen for the belly-tendon montage, instead of placing references on the inner canthi of both eyes, as first described by Sandhu [Sandhu et al., 2013], we used a setup with a single reference on the nasion, equidistant from both active electrodes.

5.7 Recommendations

5.7.1 Methodological research

This study has shown that the setup with the minishaker gives reliable responses, but there are several areas in which the responses may be further optimized. The most interesting developments in recent literature are the chirp stimulus and the possibility of simultaneous c- and oVEMP recordings. Research with low – frequency stimuli is not possible in the current setup, but would be interesting to explore in the future.

Firstly, several papers have explored VEMP recordings in response to air conducted chirp stimuli [Wang et al., 2014; Özgür et al., 2015; Walther & Cebulla, 2016a]. It was found that chirp stimuli require fewer stimuli are required to obtain a highly reproducible response, potentially reducing the required measurement time. A logical next step would be to compare these chirp stimuli to tone bursts for vibratory conduction. The effect of chirp stimuli on physiological (i.e. age) and pathological conditions is another area of research, especially for those conditions where frequency-dependent attenuation has been shown, such as Menière's disease or SSCD.

Secondly, the effects of frequency tuning to 100 Hz stimuli has been ignored in this thesis. While this effect is described in some literature, several adaptations are necessary to test this in the setting employed at the Radboudumc, as 100 Hz stimuli cannot currently be given. It would be interesting to develop a low frequency stimulus to explore these characteristics at our centre. The same technical limitation exists for 250 Hz stimuli; a better attenuation will probably give responses.

The electrode montage has been explored extensively, and I am convinced that the belly-tendon montage yields the best responses. Although this study used a slightly different setup by employing a common reference on the nasion, compared to separate references on the inner canthi [Sandhu et al., 2013]. While I do not expect this small adaptation leads to significantly different responses, it would be sound to investigate whether it truly makes no difference in response amplitude and threshold.

Another point where development is possible is in the stimulus mode. The minishaker – or similar large vibratory devices are currently the most consistent mode for evoking oVEMPs as clinical bone transducer B71 gives insufficient output for reliable responses [Lin et al., 2010]. However, this transducer has the advantage that it easier to apply in clinical situations and also widely available. The successor to the B71, the B81 is under continuing development, and may provide sufficient output in the future. If this improved B81 becomes available, it is worthwhile to compare its reliability to evoke oVEMP with the minishaker.

Regarding the cervical VEMPs, these responses are preferentially performed using auditory stimuli of 500 Hz, as they are most highly tuned to this conduction mode and frequency [Todd et al., 2008]. However, there is a clinical limitation in auditory stimuli for VEMP measurements when a conductive hearing loss is present. Therefore, the viability of bone conducted cVEMP measurements, for instance with the minishaker, is useful – if only to provide an alternative clinical option when auditory cVEMPs are not reliable.

Finally, there has been a little research on performing cervical and ocular VEMPs simultaneously [Silva et al., 2016]. This requires that both are evoked under the same conditions (so both auditory or both vibratory), which means that the conduction method will be suboptimal for one of the VEMP modes. However, the potential saved time may be worth this suboptimal response, if the responses are sufficiently reliable. The hardware setup in this study was not suitable for these simultaneous measurements, but it can perhaps be explored in the future. A first step would be to develop a measurement protocol for simultaneous recording that is usable in clinical practice and minimizes discomfort. However, there is also a practical disadvantage to simultaneous measurements, as it requires more complex patient instruction and cooperation, and the reliability of these simultaneous recordings is unknown. The advantages and disadvantages of simultaneous setup should be carefully weighed before possible clinical implementation.

5.7.2 Vestibular Schwannoma

In vestibular schwannoma (VS), it was shown that a combination of c- and oVEMP can be used to determine whether the inferior and/or superior vestibular nerves are affected and sometimes determine the nerve of origin [Weber & Rosengren, 2015]. In the Radboudumc, there is a group of VS patients who present with normal results on the caloric tests, but a deficit of the posterior semicircular canal under the Head Impulse Test. This indicates that the superior vestibular nerve is compromised, yet the inferior nerve intact. VEMP results in these patients should show impaired cVEMPs, but intact oVEMPs. A study on this phenomenon is clinically significant, because it shows that early vestibular impairment can be missed when only calorimetric testing is performed. The nerve of origin is potentially important, as one study correlated intact cVEMP and impaired oVEMP (i.e. a VS originating from the inferior vestibular nerve) with postsurgical hearing preservation [He et al., 2016]. If this finding is reproducible, than VEMP testing has a clinical role in predicting symptoms and in counseling patients before they receive a surgical intervention. On the other hand, there is an increasing trend towards a wait-and-scan policy in the management of VS, rather than surgical intervention and VEMP testing may have a role in this protocol as well. Similar to pre- and postoperative comparisons, it would be interesting to explore a role for c- and oVEMP in the monitoring of VS, in combination with the standard follow-up CT-scans. As VEMP tests provide functional vestibular information rather than anatomical, they are complementary to imaging techniques and may be a predictor of disease progress.

5.7.3 Cochlear implantation

While vestibular function loss after cochlear implantation (CI) receives increasing attention in the literature, very little is known about utricular function after cochlear implantation (CI). This despite the fact that available functional vestibular tests are often a poor predictor of postoperative vestibular symptoms [Abuzayd et al., 2016]. The different studies on this topic have used widely different tests and methodologies to assess vestibular function, and very little – if any studies on vestibular symptoms in CI recipients have included evaluations of all vestibular end organs. A study on vestibular symptoms in CI recipients that includes oVEMP evaluations may provide new insights in postsurgical vestibular pathology of CI. Ideally, such a study should make a pre- and postoperative comparison and include assessments of subjective vestibular symptoms with a (standardized) questionnaire (such as the Dizziness Handicap Questionnaire – [Jacobson & Newman, 1990] and of all separate vestibular end organs. This setup would provide information on the entire vestibular system and may help to better understand the vestibular symptoms that CI recipients present with.

5.7.4 Menière’s Disease

Abnormal o- and cVEMPs have been recorded in patients with Menière’s Disease (MD). These abnormalities (absent or reduced responses) are not highly specific for this pathology, and patient history remains the most important parameter in the diagnosis of MD. However, there is a considerable overlap in symptoms with another vestibular pathology – vestibular migraine. Like MD, the pathophysiological causes of vestibular migraine are not well understood, and very little is known about VEMP patterns in this disease [Venhovens et al., 2015]. However, the origin is vestibular migraine is likely central, compared to the peripheral endolymphatic hydrops of MD. Depending on the anatomical location of vestibular migraine (brainstem or cortical), VEMP responses may be unaffected. If this is the case, VEMPs could be used to differentiate MD from vestibular migraine when patient history alone is not indicative. More research of both pathologies is necessary to discover whether such a distinction can be made.

5.7.5 Superior Semicircular Canal Dehiscence

Firstly, this thesis showed that for superior semicircular canal dehiscence (SSCD) patients, oVEMP can be used as an alternative for – or complementary to cVEMP. This is especially clinically useful when the latter is less reliable, for instance with the presence of a conductive hearing loss, or when the patient has difficulty maintaining a sufficient contraction of the sternocleidomastoid muscle, which is required for cVEMP measurements. The research on this topic is not extensive, but there are indications favoring vibratory oVEMPs as a diagnostic measure in this patient group [Janky et al., 2012]. A case report of a SSCD patient analyzing the different oVEMP characteristics is presented below. The measurement condition that best separates SSCD from the healthy condition can be further explored, especially with regards to the ideal stimulus frequency [Manzari et al., 2013]. Another interesting topic of research may be perioperative VEMP monitoring in SSCD patients. SSCD is treated with surgical plugging of the superior semicircular canal, after which symptoms are reduced and VEMP responses normalize [Welgampola et al., 2008]. This normalization of VEMP threshold and amplitude occurs immediately and perioperative monitoring of ocular or cervical VEMP could show this normalization and show whether the intervention is complete.

Case report

A 70 year old woman presented to our clinic with complaints of spinning vertigo after sneezing or coughing, with attacks lasting around one minute. She had a sense of pressure in the ear and experienced autophonia (unnaturally percieved sound of own voice). She did not have headache or tinnitus complaints. Audiometry results showed a pre-existing perceptive hearing loss, with a low-frequency pseudo-conductive component in her right ear (see Figure 12).

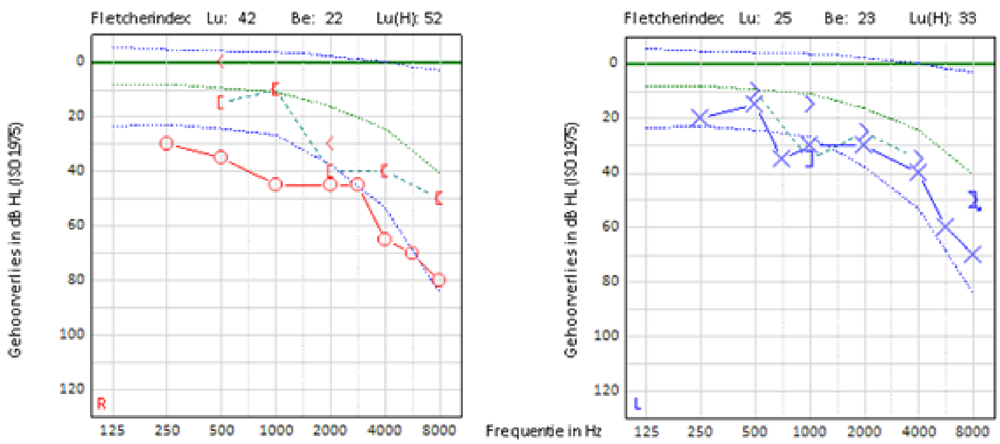

Figure 12 Audiometric results of a 70 year old woman with symptoms indicative of SSCD. Her right ear shows a (pseudo)conductive hearing loss.

This history is indicative of superior semicircular canal dehiscence (SSCD) in the right ear, and for this reason a CT scan and VEMP tests were scheduled to test this diagnosis. In this case, the cVEMP thresholds, shown in Figure 13, were not indicative of SSCD and an oVEMP measurement was performed subsequently (see Figure 14). This measurement used the belly-tendon montage and 500 Hz TB stimuli starting at 131 dB FL until a threshold was found.

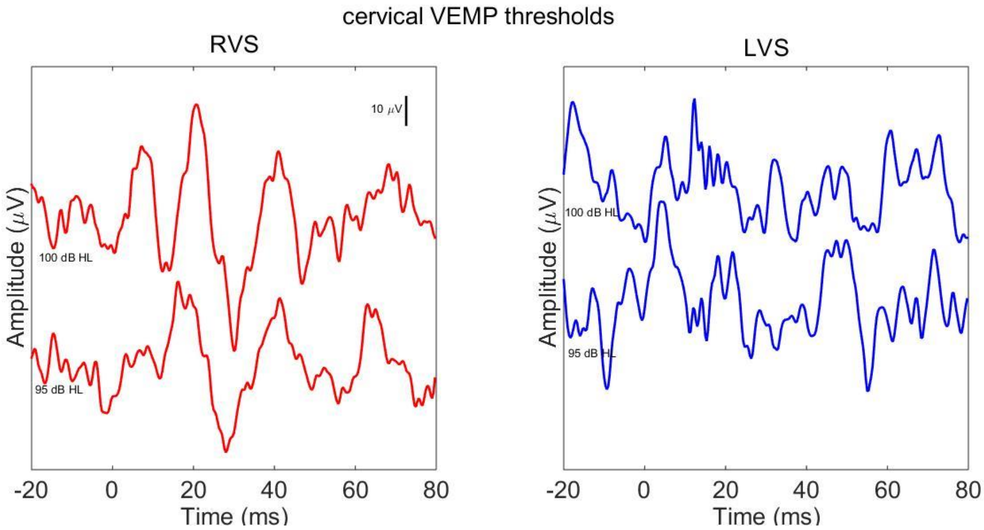

Figure 13 cVEMP thresholds of the selected patient showing a reproducible recording at the RVS to 100 dB HL, with a peak around 12 ms. The threshold was 100 dB HL for the RVS (Pearson's correlation of 0.89), as the response was not reproducible at 95 dB HL (0.40). There was no reproducible cVEMP for the LVS. These values fall within the normal range and are not indicative for SSCD, where lower thresholds (<85 dB HL) are expected.

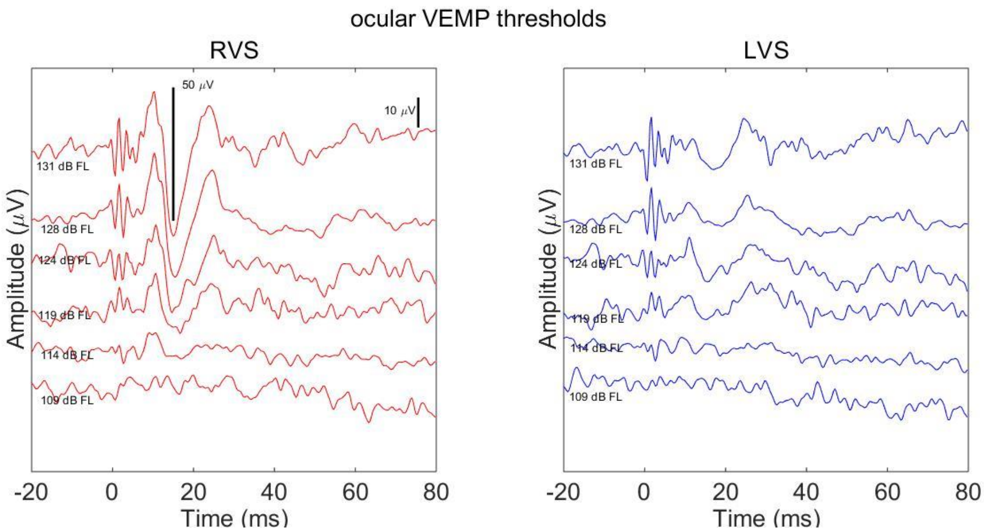

Figure 14 An oVEMP measurement in a patient with suspected SSCD. Recordings were made at different threshold intensities, marked in the figure. The affected right side has significantly larger amplitudes and a lower response threshold compared to the unaffected side. At 131 dB FL, the IOR was 65%. Abbreviations: RVS: right vestibular system; LVS: left vestibular system.

Janky et al. described two methods of diagnosing SSCD based on VEMP responses: larger amplitudes and low thresholds compared to normative data [Janky et al., 2012]. In addition to these parameters, inter-ocular ratio – a degree of asymmetry, may also serve as an indicator of SSCD, so long the disease is unilateral.

These parameters can be applied to the present case. Firstly, the right sided amplitude was significantly higher to the normative data of healthy subjects collected in the main study. At 131 dB FL, the peak-to-peak amplitude of the right utricle was ~50μV, compared to the ~9±5 μV found at this level in the normative data. The left utricle gave a peak-to-peak amplitude of ~10 μV, which falls within the normal range. Unfortunately, this normative data was not age-matched. It is recommended that age-matched normative data is used for oVEMP measurements, as several age-dependent effects have been shown [Rosengren et al., 2011; Piker et al., 2013], although the minishaker may be relatively insensitive to age-related changes [Rosengren et al., 2011; Colebatch et al., 2013]. However, oVEMP responses are generally reduced with age, so the amplitude discrepancy will likely be larger for an age-matched control group.

Secondly, the oVEMP right vestibular threshold was lower compared to the normative group. The threshold was found at 114 dB FL, where the Pearson's correlation was 0.64 in the 8 to 18 ms time window. At 124 dB FL (0.90 correlation) the left vestibular threshold lay in the normal range. In the control group, a mean threshold of 126±3 dB FL was found, with no responses below 121 dB FL. Finally, the left-right asymmetry in this patient was shown using the inter-ocular ratio. The IOR was 65% at 131 dB FL, which is also significantly larger than the 0-25% range in the normative group.

In conclusion, the large response amplitudes, low threshold and large asymmetry in this oVEMP measurement are all indicative of a right vestibular SSCD. This shows that oVEMP is a valuable tool in the diagnosis of SSCD.

Chapter 6. Conclusions

Vibratory stimuli with the minishaker can readily evoke oVEMPs in healthy subjects and the minishaker setup employed in this study is potentially suitable for clinical application. This study has shown that the belly-tendon montage for the acquisition of oVEMP responses is superior to the standard montage (experiment 1). It yields larger amplitudes and lower n1 thresholds, both of which facilitate the identification of responses, and this configuration can be used for simultaneous measurements of both vestibular systems, so that left/right comparisons can be made. The presence or absence of a response, or a comparison of the n1p1 amplitude to normative data at a fixed intensity is the most reliable parameter. Thresholds can be used and are reasonably consistent, but there is a grey area in this parameter, as shown by the discrepancy in repeated measurements and and interobserver variability.

In a comparison of different stimulus frequencies, the 500 Hz tone burst stimulus gave larger peak-to-peak amplitudes and lower thresholds than 750 Hz and 1000 Hz stimuli (experiment 2). Responses to 750 Hz were also adequate and can be a good backup when no responses are found at 500 Hz. Due to the poor response rates, the current setup is not suitable for measuring oVEMP responses to 1000 Hz or 250 Hz stimuli.

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Appendix A: Calibration report 4810 vibration shaker

J.B. van der Heijdt & M.J. Boonstra

This report shows the method and results of calibration of the research setup with a vibratory shaker. Values are reported in dB FL (force level). The employed method of calibration is sensitive to small variations in the setup. As described in this report, several steps were taken to limit this influence and to keep the error < 1 dB.

A.1 Methods

Setup

Tone Burst (TB) stimuli were delivered with the EP25 Eclipse system (version 4.4.0.57, Interacoustics, Denmark) controlled from a desktop computer that has OtoAccess (version 1.2.1, Interacoustics) installed. This system was connected to the 2715 amplifier (Bruel & Kjær, Denmark) with a jack to BNC converter cable from a jack socket that is reserved for insert earphones. The amplifier was set to the maximum amplification of *20 dB* and connected to the vibratory shaker 4810 "Mini-shaker" (Bruel & Kjær) with a coax cable. The Mini-shaker was fitted with a small hard plastic cap. The Mini-shaker was placed on the plastic cap at a right angle to the center of the surface membrane of an artificial mastoid (type 4930, Bruel & Kjær) and the frequency specific intensity component was read out using an analyzer (Investigator type 2260, Bruel & Kjær), which reads out in dB SPL (sound pressure level).

Measurement

TB stimuli were delivered according to the overview in Table A.1. These stimuli were given at an attenuator level from 50 to 75 dB. The frequency specific intensity component was recorded. Each measurement was repeated; the average is used in this report. If the difference between consecutive measurements was larger than *1.5* dB, the measurement was repeated to minimize the margin of error. Right and left insert sockets were evaluated separately.

Table A.1 Overview of the different Tone Burst (TB) input stimuli

TB Frequency (Hz)	Duration (ms)	Rise/fall (cycles)	plateau (cycles)
250	12	1	1
500	6	1	1
750	5,3	1	2
1000	6	2	2

Correction of error in artificial mastoid

To determine the correct factor in the calibration of the artificial mastoid, pure tone responses of a calibrated B71 bone conductor were compared to the measured output for each frequency. The correction factor for each frequency is stated in Table A.2 and taken into account during the calibration of the Mini-shaker.

Table A.2 Frequency specific correction factor and offset for the artificial mastoid. The correction factor is based on the mean error of two calibrated B71 transducers in response to pure tones. The offset is based on force sensitivity level in the calibration report of the artificial mastoid.

Frequency (Hz)	Correction factor (dB)	Offset (dB)
250	1,2	-19,2
500	-6,7	-19,1
750	-3	-19,0
1000	-1,3	-18,8

Calculation

The Investigator displays the outcomes in dB SPL. These values were converted into dB FL via voltage, using the calibration constant of the artificial mastoid (referenced to 94 dB = 50 mV) and the device specific force sensitivity. Before this conversion, a frequency-dependent correction for the offset of the artificial mastoid was applied (Table 1). This offset is caused by a difference in sensitivity of the Investigator and the artificial mastoid, the amount of delivered force on the mastoid is higher than the measured SPL values of the Investigator. The formulas for converting the Investigator output to dB FL are as follows:

$$V = p_0 \times 10^{\frac{L_{SPL}}{20}} \; [V]$$

$$F = V/F_{sens} \; [N]$$

$$L_{FL} = 20 \times \log \frac{F}{F_0} \; [dB\ FL]$$

with reference pressure $(p_0) = 1\ \mu Pa$, force sensitivity $(F_{sens}) = 114{,}5\ mV$ and reference force $(F_0) = 1\ \mu N$.

A.2 Results

Figure A.1 shows the linear correlation of the input and output of the setup. There is a small difference in attenuation of the 500, 750 and 1000 Hz stimuli and a larger attenuation difference at 250 Hz. Table A.3 shows the attenuation difference between the left and right inserts.

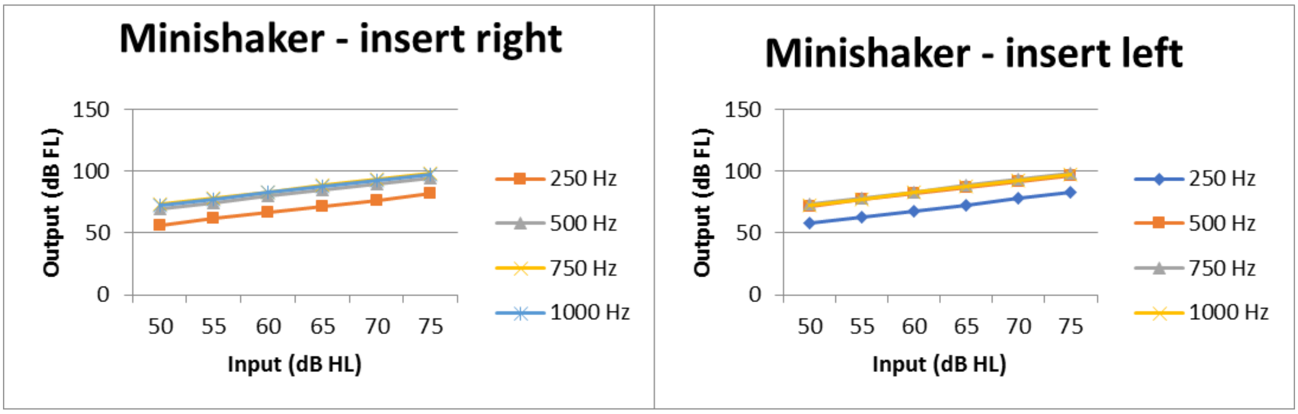


Figure A.1 Calibration curve for the right and left insert sockets for each frequency

Table A.3 Output (in dB FL) to an attenuator level of 95 dB input for the right and left sockets. There is a small discrepancy in calibration between the sockets at 250 and 500 Hz.

Frequency (Hz)	Output right (dB FL)	Output left (dB FL)	Difference (dB FL)
250	121	122	1
500	134	136	2
750	137,4	137,4	0
1000	136,4	136,4	0

A.3 Limitations and Implications

To compensate for small variation in location and angle of the Mini-shaker, measurements were repeated at least twice, and these values proved reproducible with a standard deviation of <0.5 dB. The same variability in intensity applies for clinical measurements, therefore only an approximate stimulus intensity may be reported.

The output of the setup is linear to the input and contains a frequency specific attenuation. Due to the high attenuation at 250 Hz, it is unlikely that ocular VEMP responses can be evoked using this frequency. For the other frequencies, stimulus intensity should be sufficient to evoke responses and provide reproducible measurements. At 250 and 500 Hz, the output of the left and right input sockets differs 1 respectively 2 dB SPL (Table A.3). Therefore, a separate correction factor for left- and right sided measurements is necessary at these frequencies.

Appendix B: preliminary study

B.1 Methods

Vibratory stimuli were administered with the 4810 “minishaker” connected to a type 2718 amplifier (both Bruel & Kjær, Denmark). The minishaker was fitted with a hard plastic cap. The responses were acquired with Ag-AgCl electrodes and recorded by the VEMP modality of an Eclipse EP 25 system (Interacoustics, Denmark). Electrodes were placed according to the belly-tendon montage with a common reference on the nasion, in an adaptation of the belly-tendon montage described by Sandhu et al., which used separate reference electrodes on each medial canthus [Sandhu et al., 2013]. The ground electrode was placed on the chin and electrical impedances were maintained below 5 kΩ. The minishaker was placed at a right angle to the forehead at Fz and held in place by the examiner. Measurements were repeated at least twice for reproducibility with 60 stimuli per recording. Short breaks were instituted regularly to minimize discomfort and prevent gaze fatigue.

Several protocol parameters were investigated in a small number of subjects. These parameters included the stimulus rate (5.1 or 8 Hz), stimulus polarity (initial positive or negative deflection or alternating), stimulus length for 500 Hz stimuli and the level of gaze elevation (neutral or upwards), as well as threshold measurements at different frequencies, an overview is given in Table . No statistical analysis was performed due to the limited number of subjects, instead, a qualitative analysis of the results is given.

B.2 Results

Subjects

Of the six subjects (3 male, mean age 24), five had a clear otological history. The remaining subject had a history of cholesteatoma and a corresponding unilateral conductive hearing loss. Responses could be elicited binaurally in all subjects for at least some test conditions.

Polarity

Figure B.1 shows an example of condensation, rarefaction and alternating polarity curves from a single subject. This shows that the n1 latency is dependent on the polarity, which leads to a double peak complex when alternating polarity is used.

Stimulus rate

A higher stimulus rate shortens the total measurement time slightly. However, all subjects in which this condition was tested reported that the 8 Hz stimulus was less comfortable. There seemed no qualitative difference between the responses, although this was not statistically verified due to the low number of subjects.

Frequency and thresholds

Threshold measurements were performed for various frequencies. Except at 2 kHz, at which level no EMG response was found, all stimuli had some level of response. Responses were largest for 500 Hz stimuli, an example of which is shown in Figure B.2 (Left).

Table B.1 Preliminary study parameters. The conditions tested in the preliminary study and the number of subjects for each test condition are shown here. Default values are printed in bold, this is the setting used when another parameter was investigated. Cycle length: each cycle is a sine wave of 2 ms duration. So the duration of the 500 Hz TB stimuli used in this preliminary study is between 6 and 16 ms.

Parameter	Value	subjects
polarity (initial deflection)	**Rarefaction** condensation alternating	2
Stimulus rate (Hz)	**5.1** 8	3
Gaze angle	Neutral **maximal**	3
Stimulus frequency (Hz)	250	4
	500	6
	750	1
	1000	3
	2000	1
Stimulus length 500 Hz (ms; rise/plateau/fall cycles)	6; 1/1/1	6
	8; 1/2/1	3
	12; 2/2/2	3
	16; 2/4/2	1

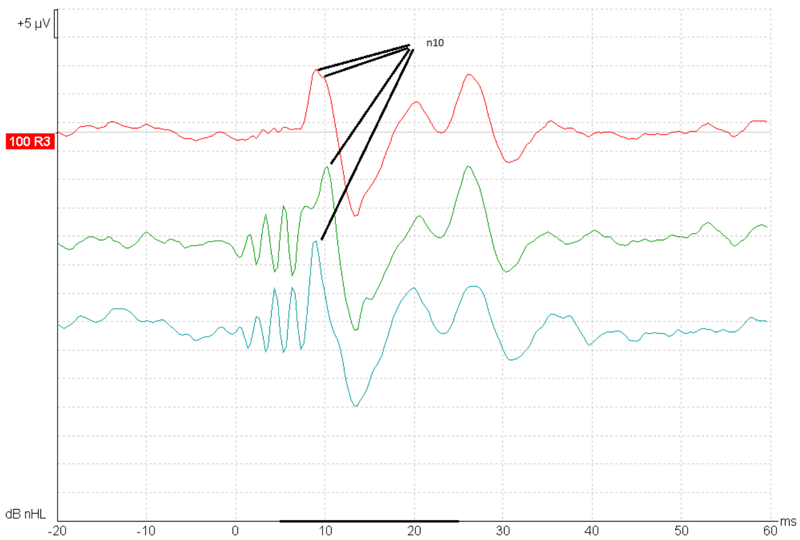


Figure B.1 A comparison of alternate (red trace), rarefaction (green trace) and condensation (blue trace) polarities for a 500 Hz Tone Burst. This graph shows that responses to rarefaction and condensation stimuli have distinct peaks, which leads to a double peak when the polarity alternates. Note that in this condition, the stimulus artifact is masked through summation of the rarefaction and condensation curves.

Stimulus length

Due to the prominent stimulus artefacts in bone conduction measurements, long stimuli interfere with the EMG response, leading to an unreliable measurement. This phenomenon is shown in Figure B.2 (right, upper trace). Tone burst stimuli of 6 to 8 ms gave no or little interference with the EMG response, as the response is typically found around 10 ms.

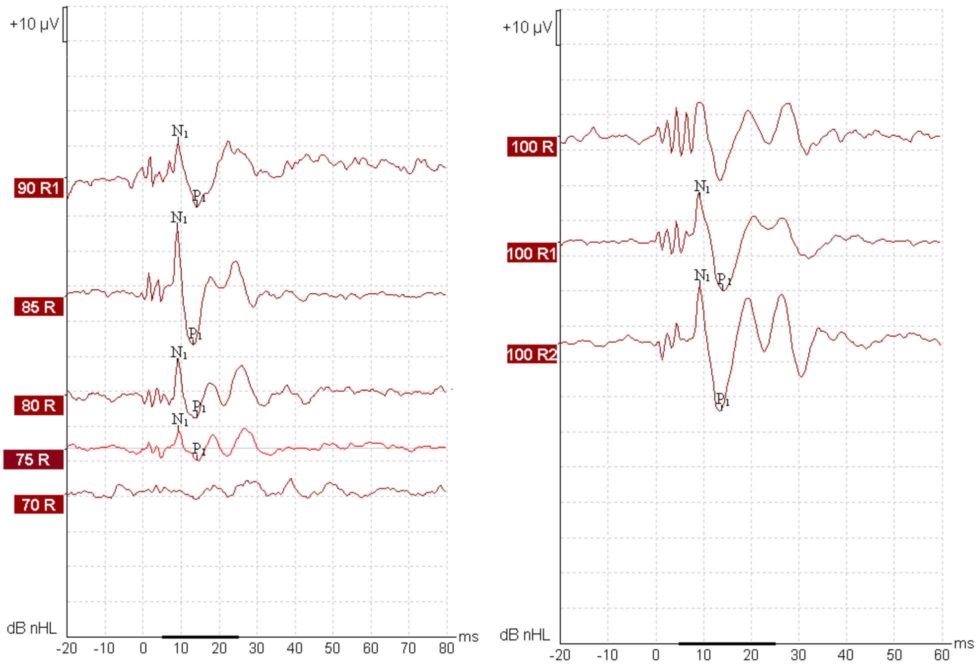


Figure B.2 Two examples of oVEMP measurements. Left: a threshold measurement performed with a 500 Hz Tone Burst. The stimulus intensity is decreased in steps of 5 dB until a threshold is found. Right: the oVEMP response to different stimulus lengths at 500 Hz to the same stimulus intensity. The uppermost trace has a total stimulus length of 12 ms and shows interference of the stimulus artifact with the oVEMP response. Stimuli of 8 and 6 ms (middle and lower trace) show no interference. Legend: N1 – initial response peak. P1 – subsequent trough.

Upwards gaze

All subjects showed higher amplitudes with gaze elevation compared to a neutral eye position, this difference can also affect the threshold determination as shown in Figure B.3.

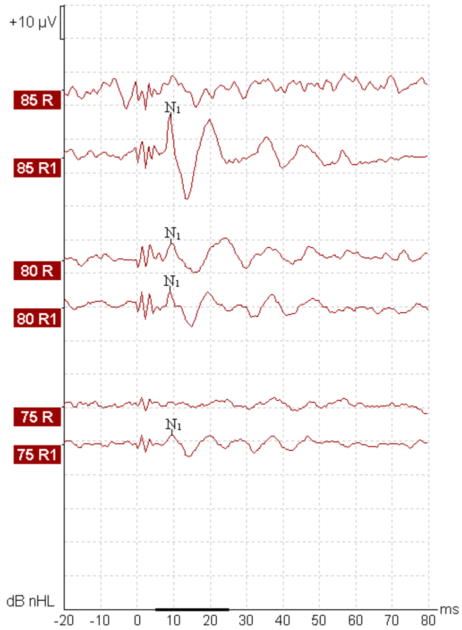


Figure B.3 oVEMP response to 500 Hz tone bursts to three different intensities. At each intensity, the upper trace represents a neutral gaze and the lower trace represents an upward gaze condition. Note that the level of gaze elevation affects the response amplitudes and also has an effect on the threshold, as no response is visible at the lowest intensity with the eyes in neutral position, whereas a response can be found in the upwards gaze condition.

Appendix C: Measurement protocol (Dutch)

v2.1 9-1-2017

Voor de meting

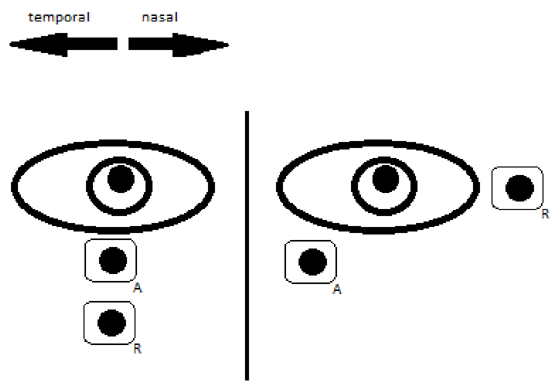
Zorg dat alle apparatuur (PC, Eclipse en amplifier) aan staat en goed is aangesloten. De gain van de amplifier staat op 20 dB. Controleer ook of de cap goed op de minishaker zit. Controleer of alle materialen aanwezig zijn (voldoende elektrodes, tube scrubgel, geleidende gel, ontsmettingsalcohol). Controleer of de computertafel en de lakens op de onderzoeksbank schoon zijn.

Voorbereiding

Alcohol en (licht) scrubben op de plaatsen waar de elektrodes worden aangebracht. Gebruik een beetje geleidende gel op de elektroden bij het aanbrengen op de huid. Controleer de impedanties, houd deze < 5 kΩ.

Bij elektrode plaatsing volgens de belly-tendon montage: actieve elektrodes op linker en rechter laterale oogkas (zie figuur C.1), en een gemeenschappelijke referentie op het nasion. Bij elektrode plaatsing volgens de standaard montage: actieve elektrodes midden op de onderste zijde van de oogkas en referenties ~1 cm direct onder de actieve elektrode. Bij deze opzet moet je dus de referentie verwisselen afhankelijk van of je links of rechts meet. Plaats bij beide montages de aardelektrode op het sternum. Gezien de respons contralateraal is, **sluit de linker en rechter elektroden andersom aan** in de collector box. Hiermee is de respons die je meet van het rechter oor dus een indicatie van de linker utriculusfunctie en vice versa.

Laat de patiënt eerst de impuls even voelen op bijvoorbeeld de onderarm en daarna op het voorhoofd, om een schrikreactie te voorkomen.



Figuur C.1 Schematische voorstelling van beide montages. Rechts de standaardmontage, met de actieve elektrode recht onder het oog en een referentie ~1 cm direct onder de actieve elektrode. Links de belly-tendon montage, met (gemeenschappelijke) referentie-elektrode op het nasion. De actieve elektrodes op de spierbuik van de inferior oblique oogspier, aan de inferio-laterale zijde van de oogkas. De grondelektrode (niet afgebeeld) ligt op het sternum. A: actieve elektrode; R: referentie elektrode.

Uitvoeren meting

Laat de patiënt liggen op de onderzoeksbank en geef de instructie om te ontspannen en tijdens het meten de ogen open en omhoog gericht houdt. Plaats de minishaker mediaal op het voorhoofd van de patiënt (EEG positie Fz). Tijdens de meting ondersteunen vanaf de zijkant om gepositioneerd te houden, maar niet drukken. Let erop dat de shaker niet verschuift!

Een serie van 60 stimuli duurt 12 seconden. Doe niet meer dan 4-6 series achter elkaar en geef de patiënt zo nodig een korte pauze tussendoor, om de belasting zo laag mogelijk te houden. Stop onmiddellijk als de patiënt klachten meld, zoals hoofdpijn of duizeligheid.

Na de meting

Koppel de elektrodes af en verwijder de elektrodes en de gel van de patiënt. Ruim gebruikte materialen op en maak de opstelling klaar voor een volgende meting. Reinig ook gebruikte oppervlakten, inclusief de cap van de minishaker

Instellingen

Gebruik het oVEMP protocol. De belangrijkste instellingen staan in tabel C.1. Deze instellingen zijn allemaal al standaard ingebouwd, en hoeven dus niet aangepast te worden. Alleen bij meten op een andere frequentie dan 500 Hz, moet deze worden aangepast in de tijdelijke setup.

Tabel C.1 Overzicht van de parameters van het oVEMP protocol, zoals geimplementeerd in Eclipse.

Parameter	**Value**
Stimulus methode	Beengeleiding (minishaker 4810)
Stimulus locatie	Fz
Stimulus type	500Hz TB (standard)
Intensiteit	Start op ’95 dB HL’
EMG RMS	Off
Rise/fall tijd	2 ms
Plateau tijd	2 ms
# Sweeps	60
Stimulus rate	5.1Hz
Low pass filter	5-30Hz
High pass filter	1000-3000Hz
Gain	2500-5000x

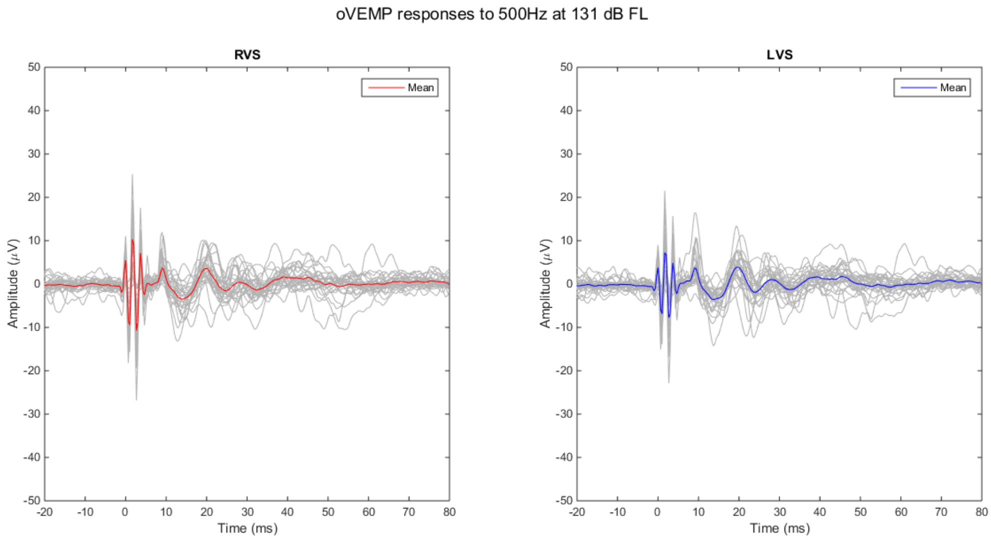
Appendix D. Table of cVEMP characteristics in CI studies

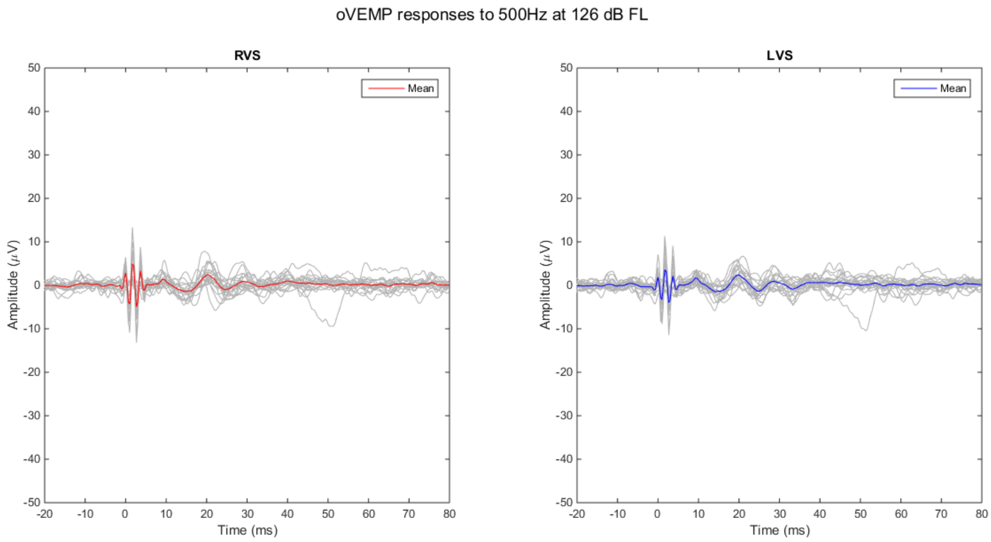
Table D.1 Characteristics of cVEMP studies on CI recipients. All studies performed both pre- and postoperative evaluations. AC: air conduction, BC: bone conduction; TB: tone burst, HL: Hearing Level, SPL: Sound Pressure Level

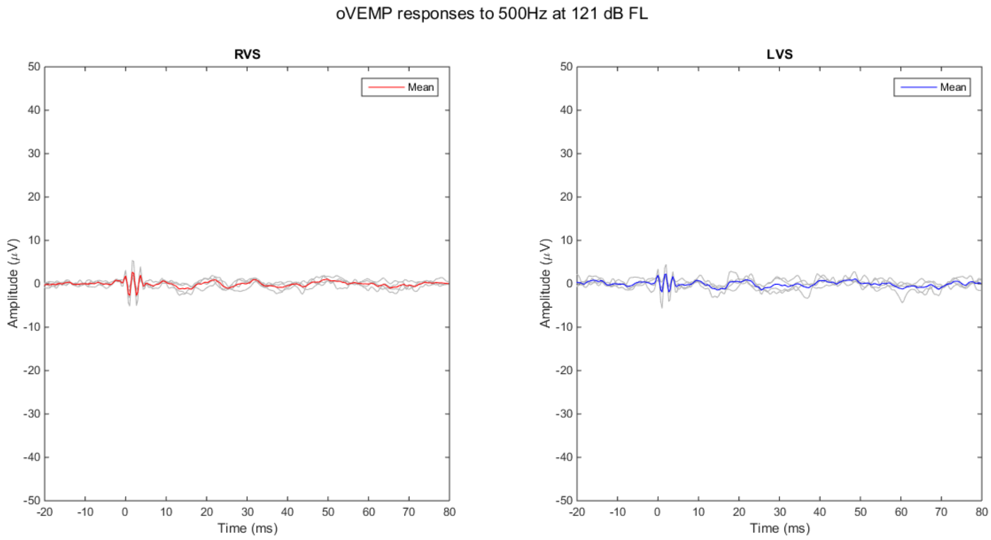
Study	***Population*** *(number of subjects, composition)*	***Contraction method***	***Conduction mode***	***Stimulus type*** *(length, rate)*	***Sound intensity***	***Outcomes***
Basta et al., (2008)	19; adult and pediatric	Contralateral turning	AC (inserts) and BC	TB 500 Hz, 7ms, 5/s	115 dB SPL	Absence
Katsiari et al., (2013	20; adult and pediatric	Contralateral turning	AC (headphones)	TB 500 Hz, no plateau 5.1/s	95 dB HL	Absence
Licameli et al., (2009)	61; pediatric	Not reported	AC (inserts)	TB 500 Hz, no plateau; Clicks 0.1 ms	Threshold	Absence, threshold, amplitude/latency at 90 dB nHL
Louza et al., (2015)	41; adult	Contralateral turning	AC (headphones)	TB 500 Hz, 7ms, 5/s	115 dB SPL	Interpeak amplitude (P1/N1)
Meli et al., 2016	25; adult	Contralateral turning	AC (headphones)	TB 500 Hz	95 dB HL	Latency and amplitude
Melvin et al., (2009)	35; adult	Contralateral turning	AC (headphones)	Click 0.1 ms	Threshold (reported in dB nHL)	Absence or worsening of threshold of >10 dB nHL
Robard et al., (2014)	34; adult and pediatric	Not reported	AC (N=30, mode not reported); BC (N=4)	logon 750 Hz, 6.65 ms	Not reported	AC:Absence BC: not reported
Todt et al., (2008)	62; adult	Contralateral turning	AC (mode not reported) BC when AC absent	TB 500 Hz, 7ms, 5/s	AC: 95 dB HL BC: 37 dB HL	Absence
Wagner et al., (2010)	20; adult and pediatric	Contralateral turning	AC (mode not reported) BC when AC not successful	TB 500 Hz, 7 ms, 5/s	AC: 95 dB HL BC: not reported	Absence
Xu et al., (2015)	13; pediatric	Supine head raising	AC (inserts)	TB 500 Hz, 4 ms, rate not reported	131 dB SPL; threshold	Threshold; latency and amplitude at 131 dB SPL;

Appendix E: Grand average oVEMPs

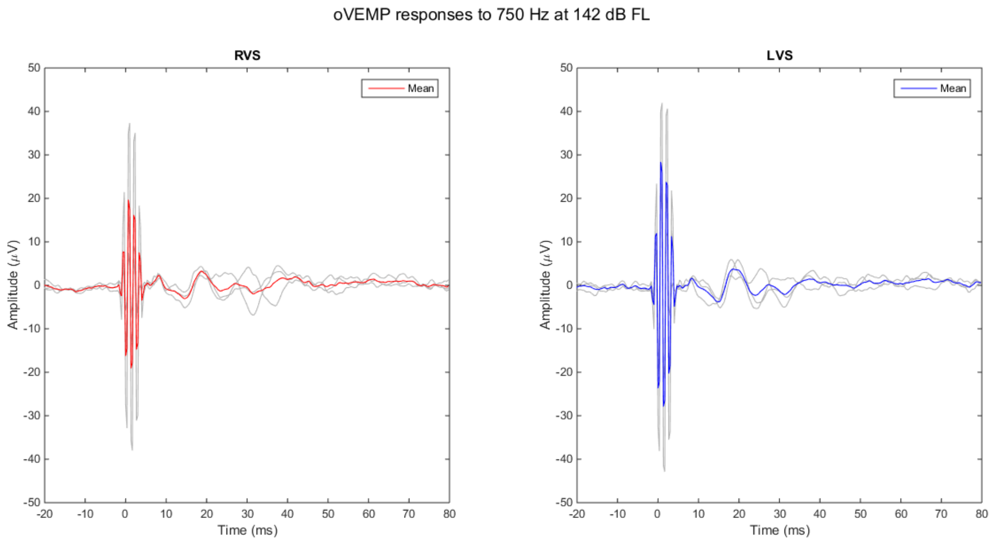
D1. oVEMPs to 500 Hz stimuli

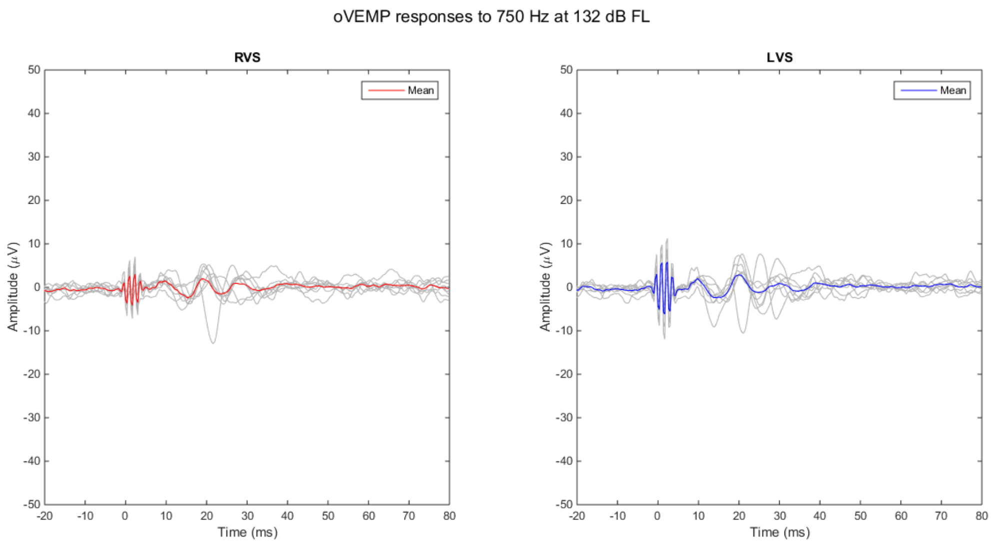


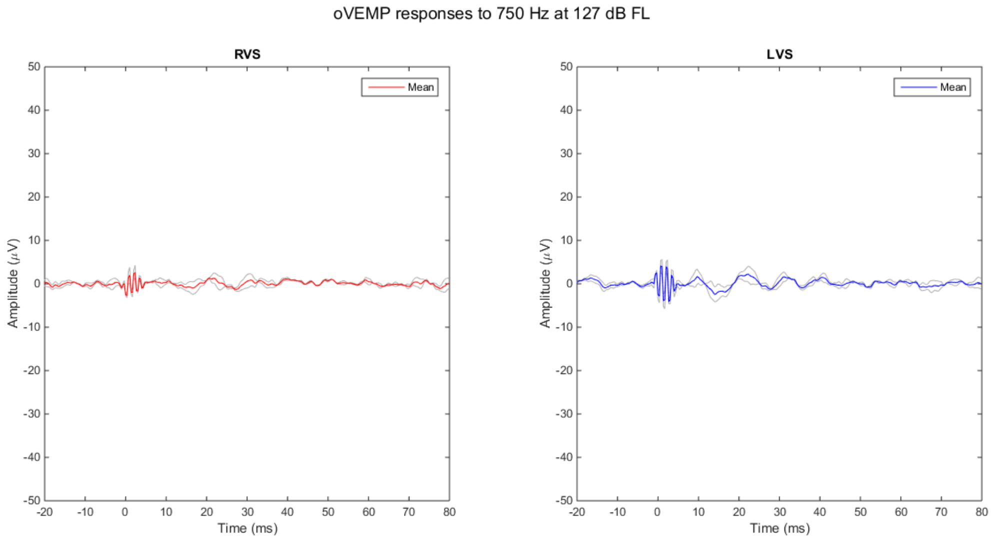




D2. oVEMPs to 750 Hz stimuli







D3. oVEMPs to 1000 Hz stimuli