


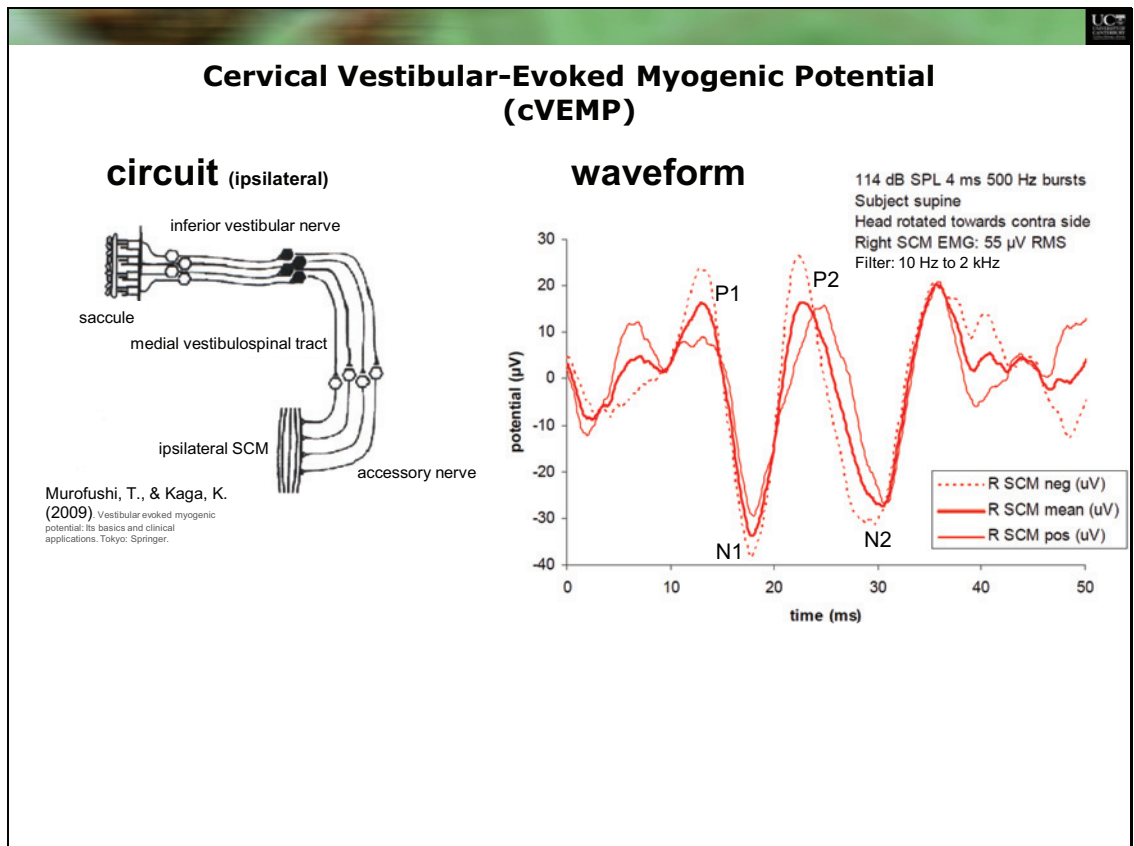
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A close-up photograph of a fiddlehead, a tightly coiled, spiral-shaped bud of a fern frond, showing intricate patterns and textures. It is set against a blurred green background of other ferns.

oVEMPs and cVEMPs in patients with "clinically certain" Ménière's Disease

Sarah-Anne McElhinney, Greg A. O'Beirne,
Emily Lin, and Jeremy Hornibrook

Department of Communication Disorders
University of Canterbury
Christchurch, New Zealand



As you're all aware, interest in the cervical VEMPs was revived by Colebatch and Halmagyi in the early 1990s.

Stimulation of the saccule with a loud acoustic stimulus causes a transient inhibition of the ipsilateral sternocleidomastoid muscle via this pathway creating a waveform that looks like this. It's an incredibly useful objective test of otolith function that has found many uses.

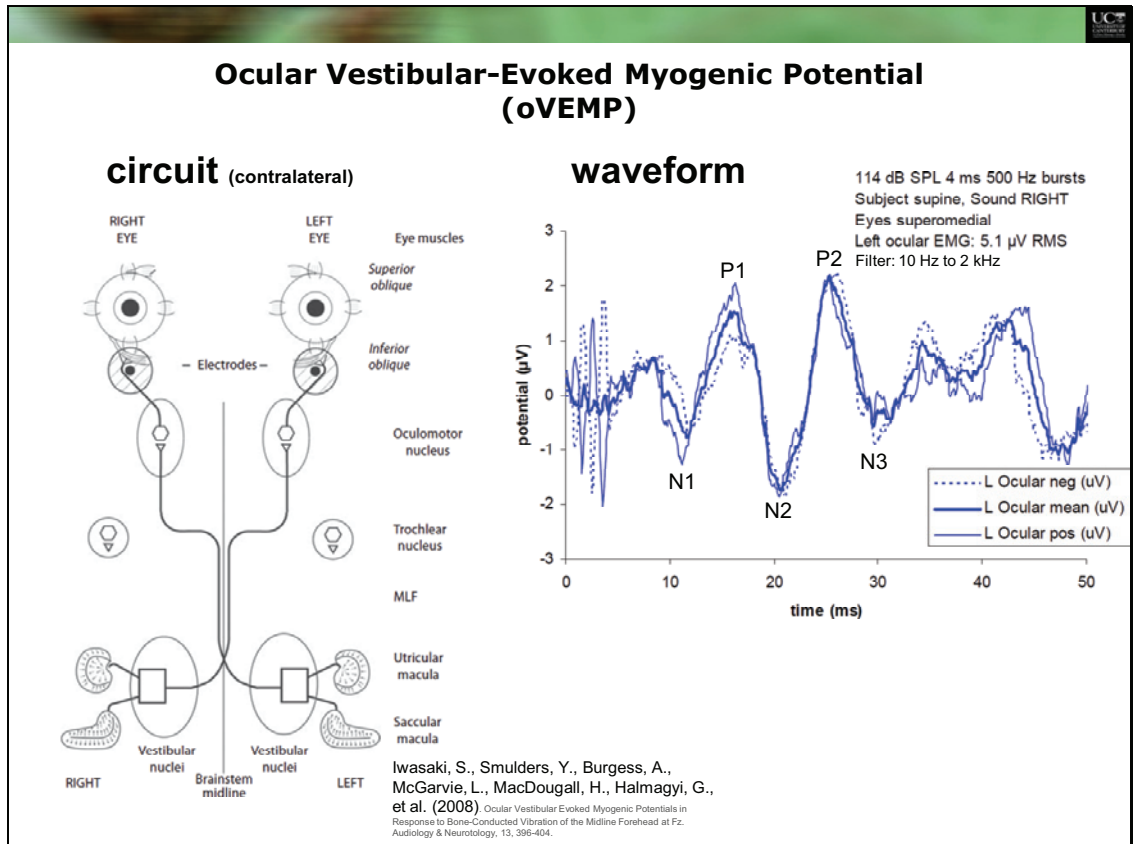
Ménière's Disease and cVEMPs

- Cervical VEMPs (cVEMPs) have been used as part of the test battery for Ménière's disease (Colebatch et al., 1994; Bath et al., 1998; Rauch et al., 2004b), primarily showing amplitude and threshold differences compared to controls.
 - cVEMP abnormalities seen more than half of all participants with Ménière's disease (Ribeiro et al. 2005 - 50%, de Waele et al. 1999 - 54%, and Kuo et al. 2005 - 67%).
 - Amplitude changes found by Rauch et al. (2004b), Rauch et al. (2004b), Ohki, Matsuzaki, Sugawara, & Murofushi, (2002), Akkuzu et al. (2006) and Murofushi et al. (2001), Chen & Young (2006).
 - Threshold changes found by Lin, Timmer, Oriel, Zhou, Guinan, Kujawa, Herrmann, Merchant, & Rauch (2006) and Rauch et al. (2004b).
 - However, a lack of statistically-significant differences in threshold reported by Osei-Lah et al. (2008).

Not surprisingly, it's been investigated by many researchers as part of a test-battery approach for the diagnosis of Ménière's disease.

The main findings have been abnormalities in the cVEMP waveform in 50 to 67% of participants with Ménière's disease mainly in the peak amplitudes.

Changes in the threshold of the response in Ménière's has also been found by some researchers but not by others.



More recently, the cervical VEMP has been supplemented by the ocular VEMP, discovered by Rosengren and colleagues about five years ago.

The oVEMP is an excitatory response recorded from the muscles below the eye contralateral to the stimulated otolith organs, most likely via this pathway and results in a waveform that looks like this.

Research into the affect of Ménière's on the oVEMP response has been much more limited.

Outline of the present study

- Bilateral measurements of both cVEMPs and oVEMPs
- All Ménière's participants had transtympanic electrocochleography in months prior to testing
- Use of the term “clinically-certain” is somewhat provocative, but is there to signify “AAOHNS definite Ménière's Disease *plus* electrocochleographic indicators of endolymphatic hydrops”

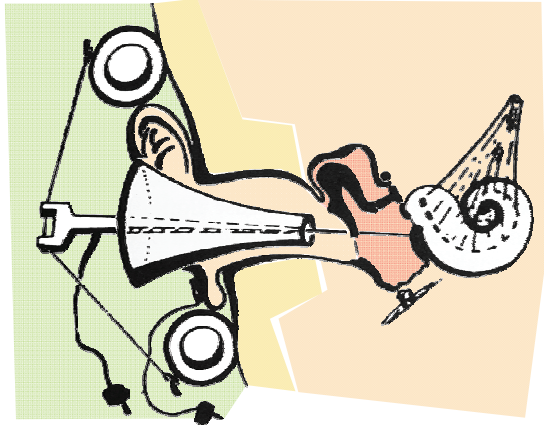
In this study, we carried out bilateral measurements of both cVEMPs and oVEMPs in control participants and in patients with Ménière's disease.

Unlike many of the other studies I mentioned, all of our Ménière's participants had transtympanic electrocochleography in months prior to testing.

The use of the term “clinically-certain” is somewhat provocative, but is there to signify “AAOHNS definite Ménière's Disease *plus* electrocochleographic indicators of endolymphatic hydrops”

Transtympanic electrocochleography (ECoChG)

- ECoChG carried out on all Ménière's patients by J. Hornibrook at Christchurch Hospital (using Amplaid MK 15, Milan, Italy).
- Electrode configuration: Active electrode on promontory, ground electrode on forehead, reference electrode on ipsilateral earlobe.
- Air conduction click and tone burst stimuli delivered via supra-aural headphone positioned on ring over the test ear.
- 100 μ s alt. clicks (10/s, 90 dB HL)
 - Response filtered 0.5 - 2.5 kHz
 - 256 averages/waveform
- 0.5, 1, 2, 4 kHz tonebursts (16 ms, 1 ms rise/fall, 90 dB HL except 4 kHz at 100 dB HL)
 - Response filtered 0.5 - 3 kHz
 - 1024 averages/waveform



Transtympanic ECoChG

The electrocochleographic recordings were performed at Christchurch Hospital using a promontory electrode referenced to the ipsilateral earlobe.

We used both clicks and tone-bursts and I'll describe the analysis of these waveforms in a moment.

Participants

- Participants were divided into two groups:
 - Control group of 22 participants (9 male, 13 female) with no known vestibular pathologies
 - Mean age of 34 ± 13 years (range: 22 to 63 years)
 - Patient group with “clinically certain” Ménière’s disease (14 male, 4 female), with positive ECoHG signs of endolymphatic hydrops
 - Mean age of 60 ± 8 years (range: 52 to 77 years)
- Participants were excluded if they had conductive hearing loss or problems maintaining head or eye position.
- Study approved by the Health and Disability Upper Regional A Ethics Committee (ref: URA/08/04/030) and the University of Canterbury Human Ethics Committee (ref: HEC 2008/61 and HEC 2009/LR/05).

We had two groups of participants:

22 in the control group and 18 in the Ménière’s group. You’ll notice that the age range of the two groups differs somewhat – this may be a problem, given that a several studies have found decreasing VEMP amplitude with age [*Ochi and Ohashi (2003), Welgampola and Colebatch (2001) and Su, Huang, and Cheng (2004)*]. In addition, while some studies have found no effect of age on VEMP latencies [*Basta et al. (2005) and Su et al. (2004)*], others have [*Lee, Cha, Jung, Park, & Yeo, (2008)*].

Participants were excluded if they had conductive hearing loss or problems maintaining the head or eye position required to activate the muscles we were recording from. And, of course, the study was fully approved by the relevant Ethics committees.

Ménière's participant characteristics

- Tone-burst ECoG results judged by Gibson's (1992) normative data shown below.

Tone burst Frequency	Hearing level dB HL	Abnormal if SP >
.5 kHz (75 dB HL)	Under 25	-2 μ V
	20 – 35	-2 μ V
	40 – 55	-2 μ V
	60 – 75	-1 μ V
1 kHz (90 dB HL)	Under 25	-6 μ V
	20 – 35	-6 μ V
	40 – 55	-6 μ V
	60 – 75	-3 μ V
2 kHz (100 dB HL)	Under 25	-9 μ V
	20 – 35	-7 μ V
	40 – 55	-5 μ V
	60 – 75	-5 μ V
4 kHz (75 dB HL)	Under 25	-9 μ V
	20 – 35	-5 μ V
	40 – 55	-5 μ V
	60 – 75	-5 μ V

Patient	Affected ear	AAOHNS criteria	Ménière's stage	Gibson score	ECoG results	
					SP/AP click stimulus (> 33% = abnormal SP/AP ratio)	Positive result for tone burst stimuli (0.5 – 4 kHz)
P1	Left	D	3	10	73%	1, 2, & 4
P2	Left	D	2	9	50%	1, 2, & 4
P3	Right	D	3	9	-	1, & 2
P4	Left	D	3	10	51%	1
P5	Left	D	2	10	56%	0.5, 1, & 2
P6	Right	D	4	10	-	0.5, 1, 2, & 4
P7	Right	D	3	7	-	1, & 2
P8	Left	D	3	8	-	1, 2
P9	Left	D	3	10	61%	0.5, & 1
P10	Right	D	4	7	-	0.5, 1, & 2
P11	Left	D	3	10	80%	0, 5, 1, & 2
P12	Right	D	1	10	-	0.5, 1, & 2
P14	Right	D	1	8	53%	0.5, 1, & 2
P15	Right	D	1	10	-	0.5, 1, & 2
P16	Left	D	3	8	56%	2, & 4
P17	Right	D	3	10	-	0.5, 1, & 4
P18	Right	D	1	10	-	0.5, 1, & 2

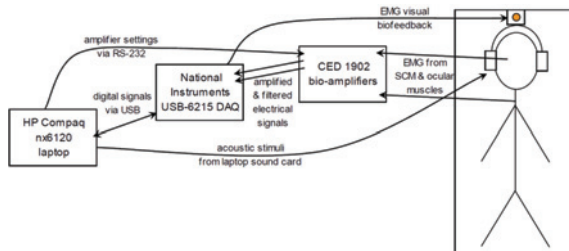
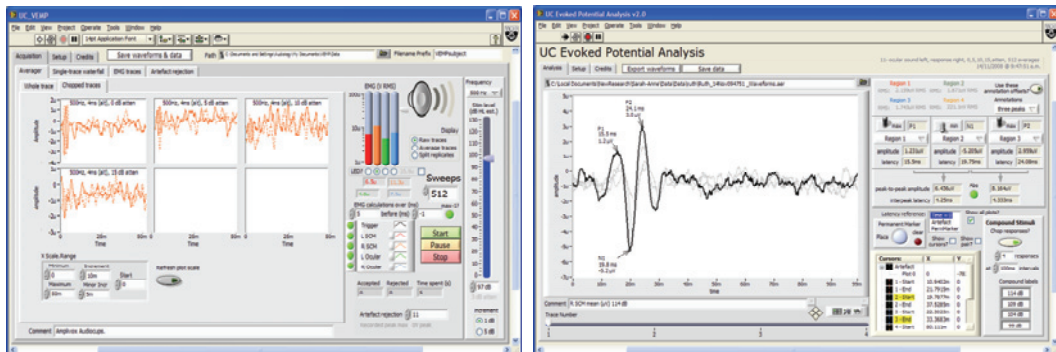
The Ménière's patients in our study were roughly split 50:50 right:left in terms of the ear that was affected. All had "Definite Ménière's Disease" according to the AAOHNS criteria.

The patients had their hearing check on the day of the VEMP test, and we had a range of stages of Ménière's from stage 1 through to Stage 4.

The patients had Gibson scores of between 7 and 10 and the patients all tested positive for hydrops in their ECoG results, according to Bill Gibson's 1992 criteria, shown here.

Data acquisition

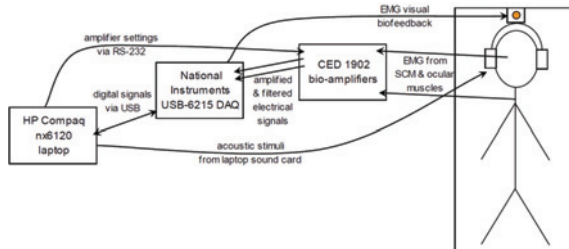
- Custom-written evoked potential averaging and analysis software.



To record the VEMP responses we developed our own measurement system that was capable of recording from both the left and right ocular muscles and neck muscles simultaneously. In practice, however, we found it better to have the participants focus on tensing these muscles separately.

Data acquisition

- Custom-written evoked potential averaging and analysis software.
- cVEMP recordings:
 - Active electrode on middle of SCM body, indifferent on upper sternum, ground on forehead.
- oVEMP recordings:
 - Active electrode on orbital margin below eye, indifferent on cheek, ground on forehead.
- Electrical signals band pass filtered between 10 – 2000 Hz and amplified (gain 3000x) using a CED 1902 bio-amplifier (Cambridge Electronic Design, Cambridge, UK), and digitized by a NI USB-6215 DAQ card (National Instruments, TX, USA).

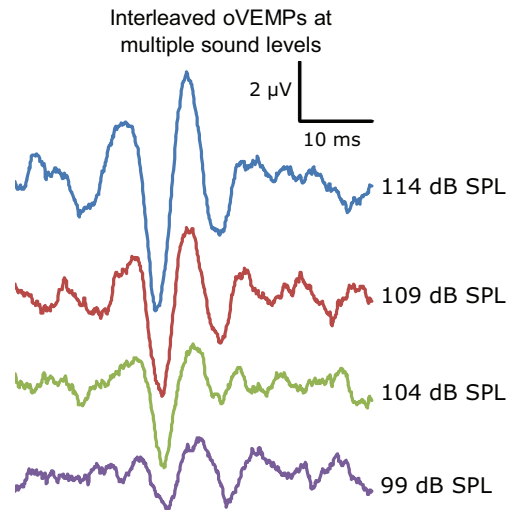
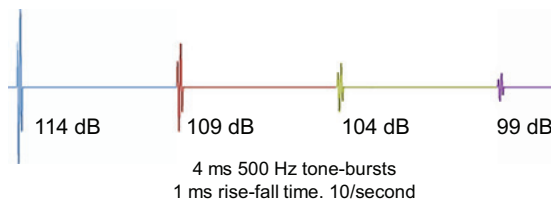


We used standard electrode placements for the cVEMP and the oVEMP.

Details of the filtering and amplification are shown here.

Measurement

- VEMP response amplitude is dependent on EMG level during testing (Zhou & Cox, 2004; Akin, Murnane, Panus, Caruthers, Wilkinson, & Proffitt, 2004).
- EMG levels recorded to file during testing. Visual feedback regarding EMG level from target muscle presented to subject via LED indicators.
- Simultaneous measurement of VEMPs from multiple locations and using multiple interleaved stimuli
 - e.g. VEMP thresholds were determined from waveforms evoked by stimuli at up to six different sound levels, reducing chance of EMG fluctuation during recording.







Threshold not found, so present at 94 dB SPL, 89 dB SPL etc.

Being a myogenic response, it's vital to maintain a consistent level of muscle tone throughout testing. We used an LED feedback system to indicate to the participant when they had contracted their muscles sufficiently.

When hunting for thresholds we interleaved multiple sound levels to ensure they were all recorded under the same conditions. Our stimuli were 4 millisecond 500 Hz tonebursts presented at a rate of 10 per second.

We also measured the EMG continuously during the recordings and normalized the amplitudes of the waveforms by the EMG level.

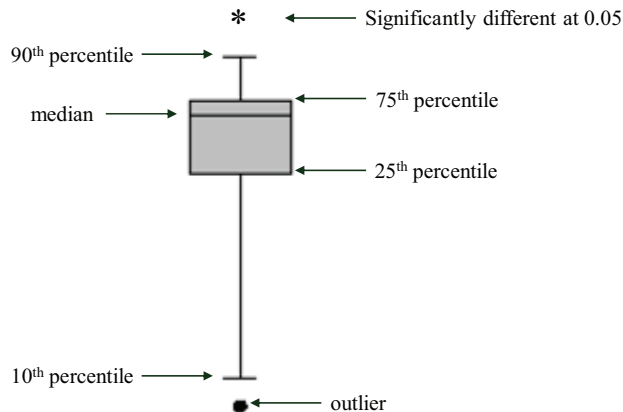
*Note:
Statistical analysis*

- One independent variable: Group, with 4 levels, including
 -  Control, left ear
 -  Control, right ear
 -  Ménière's, affected ear
 -  Ménière's, unaffected ear
- Seven dependent variables:
 - cVEMP: Threshold, and P1N1 and N1P2 peak-to-peak amplitudes
 - oVEMP: Threshold, and N1P1, P1N2 and N2P2 peak-to-peak amplitudes
- A series of Kruskal-Wallis one-way ANOVAs on Ranks, followed up with post-hoc tests with Dunn's method if a significant group effect was detected.
- Significance level set at 0.05

In our analysis, we looked at the waveforms evoked by sound presented to the left and right ears of the control participants, and to the affected and un-affected ears of the Ménière's participants.

We measured the VEMP thresholds and a number of peak amplitudes and latencies, and performed statistical analysis on the resulting data.

Refresher: Box & whisker plots



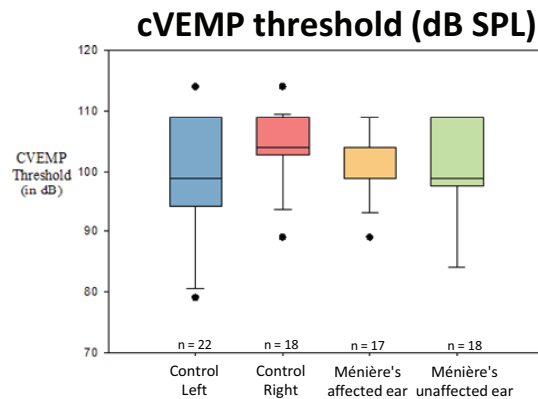
Just a quick refresher for those of you who haven't seen box & whisker plots in a while. They give much more information than simple means and standard deviations.

The median is the line at the centre of the box, with the various percentiles giving the spread of data as shown.

In the following plots, the significant differences are indicated with an asterisk.

Results: cVEMP threshold

- No significant difference between Ménière's ears and controls.



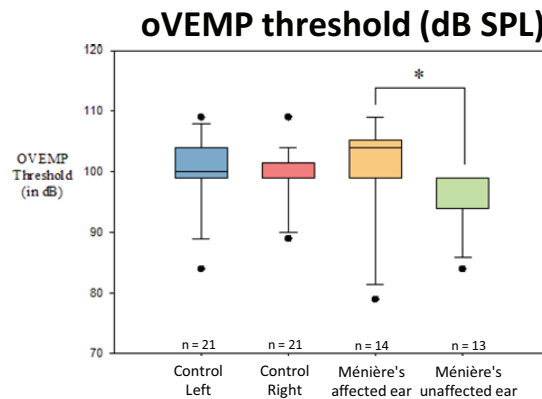
No significant group effect
($H = 4.513$, $df = 3$, $p = 0.211$)

Control, left ear Control, right ear Ménière's, affected ear Ménière's, non-affected ear

Firstly, we found no significant difference in the threshold of the cervical VEMPs between our normal participants and our Ménière's participants, or between the ears of the Ménière's participants.

Results: oVEMP threshold

- oVEMP threshold significantly elevated in affected ears of Ménière's participants compared to their unaffected ears.



However, Ménière's oVEMP thresholds not significantly different from control subjects

Significant group effect
($H = 11.1$, $df = 3$, $p = 0.011$)

Control, left ear Control, right ear Ménière's, affected ear Ménière's, non-affected ear

For the oVEMPs, the Ménière's participants did show a difference in threshold between their affected and unaffected ears, but they weren't significantly different from the results of the control participants.

Results:
Measures of peak-to-peak amplitude

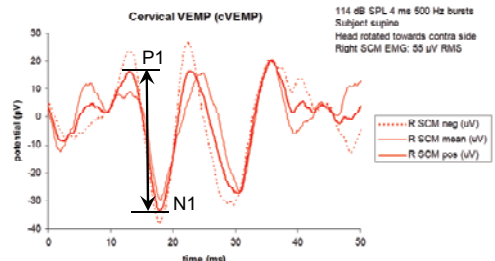
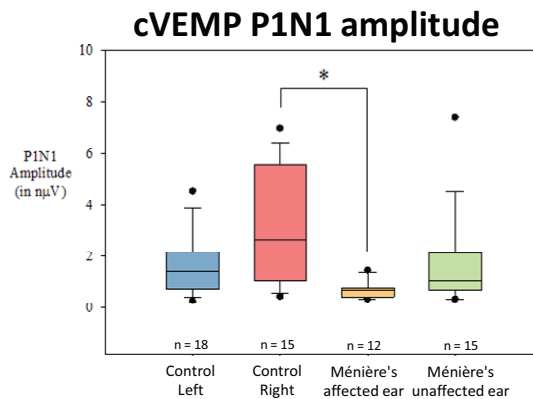
- Each peak-to-peak amplitude measure presented here was divided by the mean RMS amplitude of the EMG level during that recording.
- $\mu\text{V pp} / \mu\text{V RMS} = \text{"normalised microvolts (n}\mu\text{V)"}$
- Difference in VEMP response amplitudes measured on left and right sides of control participants made it necessary to analyse each side separately.

As I mentioned earlier, the peak-to-peak amplitudes I'm about to show you are all normalized by the EMG in that muscle at the time of recording.

We did run into a complication that our control subjects showed quite different peak amplitudes between their right and left sides, which was very interesting. The differences weren't statistically significant, but they were enough to make us analyze them separately.

Results: cVEMP P1-N1 amplitude

- Significant reduction in cVEMP P1-N1 amplitude for affected Ménière's ears compared to right ear of the control group



Significant group effect
($H = 14.092$, $df = 3$, $p = 0.003$)

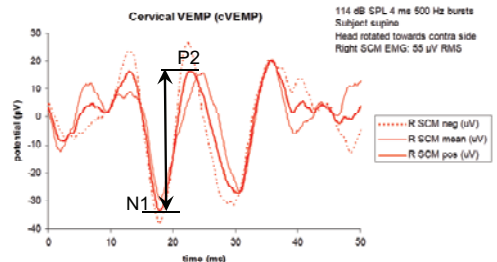
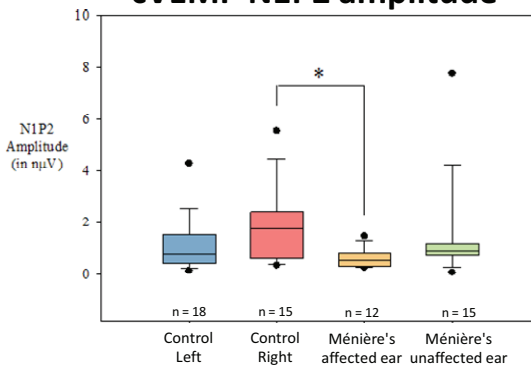
Control, left ear Control, right ear Ménière's, affected ear Ménière's, non-affected ear

Looking at the cervical VEMPs first, we found that the P1N1 amplitude was significantly reduced in Ménière's subjects compared to the right ear of the controls...

Results: cVEMP N1-P2 amplitude

- Significant reduction in cVEMP N1-P2 amplitude for affected Ménière's ears compared to right ear of the control group

cVEMP N1P2 amplitude

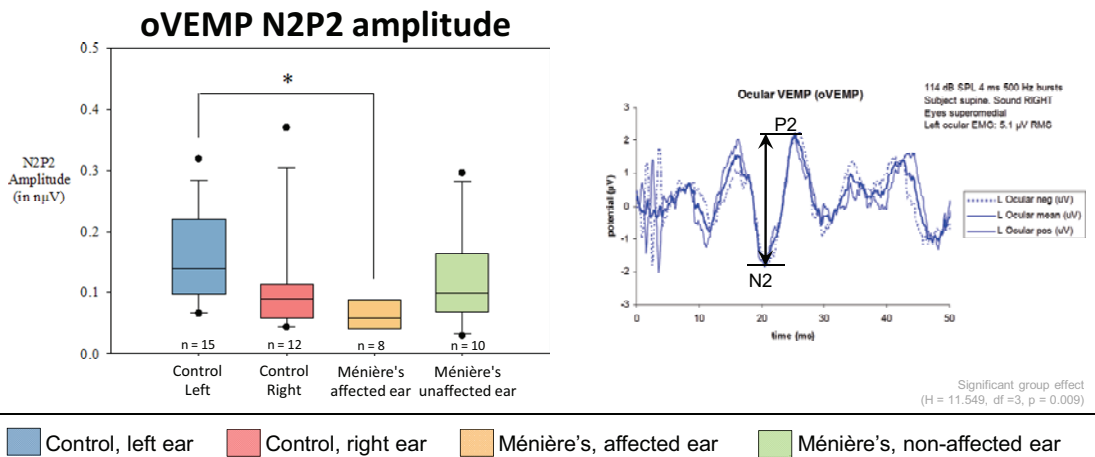


Control, left ear Control, right ear Ménière's, affected ear Ménière's, non-affected ear

...as was the next peak along – the N1P2 peak. None of the other peaks for the cVEMP showed significant differences.

Results: oVEMP N2-P2 amplitude

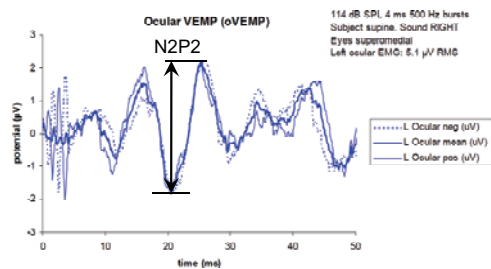
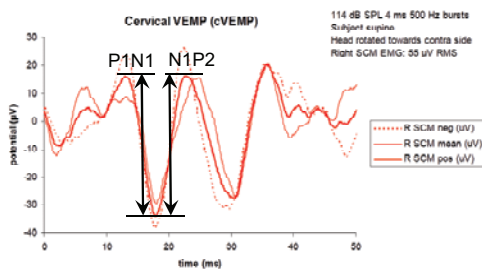
- Significant reduction in oVEMP N2-P2 amplitude for affected Ménière's ears compared to left ear of the control group



For the oVEMPs, the only peak that showed a significant difference was the N2P2 peak, shown here, which was significantly smaller than those evoked by the left ear of the control subjects.

Results summary: Amplitude measures

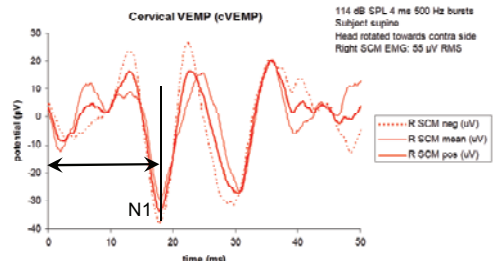
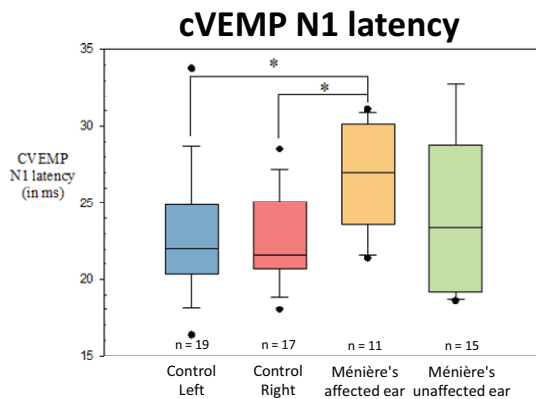
- The following peak-to-peak amplitudes were significantly reduced in the Ménière's ears compared to control ears (either right or left):
 - cVEMP: P1N1 and N1P2
 - oVEMP: N2P2



So, those peaks that showed differences are summarized here.
Now let's take a look at the peak latencies.

Results: cVEMP N1 latency

- Latency of cVEMP N1 peak of affected Ménière's ear significantly prolonged compared to both right and left ears of control group



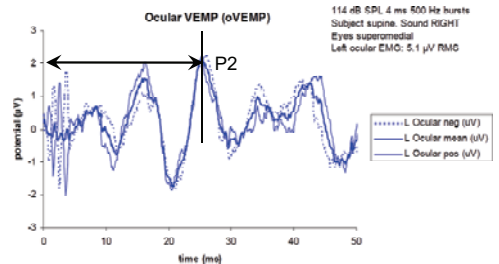
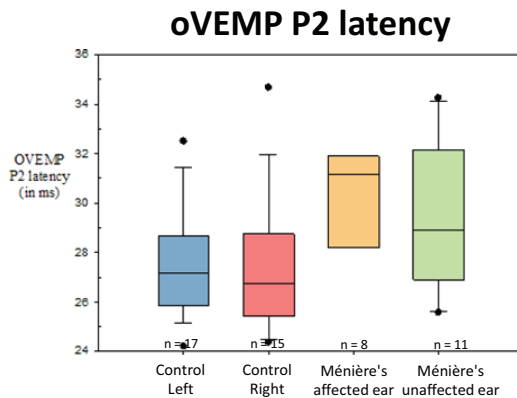
Significant group effect
($H = 9.09$, $df = 3$, $p = 0.028$)

Control, left ear Control, right ear Ménière's, affected ear Ménière's, non-affected ear

For the cVEMPs, the only peak latency which was significantly different between controls and Ménière's was the N1 peak, shown here. This was delayed by about 5 ms compared to both ears of the control participants.

Results: oVEMP latencies

- No statistically-significant difference in any of the oVEMP latencies among groups.



No significant group effect
($H = 10.53$, $df = 3$, $p = 0.015$)

Control, left ear Control, right ear Ménière's, affected ear Ménière's, non-affected ear

None of the oVEMP peaks showed any latency differences between the controls and Ménière's participants. The closest was the P2, which was delayed but not significantly.

Results: Questionnaire – ease of each procedure

2. Indicate on the scale the degree of difficulty you found the cervical vestibular evoked myogenic test where you had to lift your head up from a supine position.



3. Indicate on the scale the degree of difficulty you found the ocular vestibular evoked myogenic test where you had to maintain your gaze upward.



oVEMP significantly easier than cVEMP ($p = 0.001$)

For those of you who have had their VEMPs measured, you'll know that it can be quite uncomfortable and requires a lot of effort, particularly for elderly participants.

We had our participants activate their SCM muscles for the cVEMP by turning their head and lifting it from a supine position, which, not surprisingly, they found quite difficult.

The oVEMP, on the other hand, required them to look upwards and toward the midline. Our participants found this significantly easier.

Summary

- Threshold measures:
 - No significant difference between VEMP thresholds of Ménière's patients and controls participants (either cVEMP or oVEMP)
- Amplitude measures:
 - P1N1 and N1P2 of cVEMP and N2P2 of oVEMP significantly reduced in affected ears of Ménière's patients
- Latency measures:
 - cVEMP N1 peak latency significantly prolonged in affected ears of Ménière's patients
- Ease of procedure:
 - oVEMP significantly easier than cVEMP, and preferred by 67% of participants
- Large overlap between results of Ménière's patients and controls limits ability to reliably distinguish them on the basis of VEMP results alone.

To sum up...

Thank you!



*Thanks to our participants, and to
Assoc. Prof. Owen Murnane
for valuable comments.*

Thanks very much.