Tuning of the ocular vestibular evoked myogenic potential (oVEMP) to air and bone conducted sound stimulation in superior canal dehiscence

Author:
Zhang, Alex; Govender, Sendhil; Colebatch, James

Publication details:
Experimental Brain Research
v. 223
Chapter No. 1
pp. 51-64
0014-4819 (ISSN)

Publication Date:
2012

Publisher DOI:
http://dx.doi.org/10.1007/s00221-012-3240-3

Tuning of the ocular vestibular evoked myogenic potential (oVEMP) to air and bone conducted sound stimulation in superior canal dehiscence

Authors:

Alexander S Zhang[1], Sendhil Govender[1,2], James G Colebatch[1,2]

1. Prince of Wales Clinical School and 2. Neuroscience Research Australia, University of New South Wales, Randwick, Sydney, NSW 2031, Australia.

Corresponding Author:
Prof J.G. Colebatch
Institute of Neurological Sciences
Prince of Wales Hospital
Randwick, Sydney
NSW 2031
Australia
Tel +612 9382 2407
Fax +612 9382 2428
Email: j.colebatch@unsw.edu.au

Keywords: oVEMP, vestibular, tuning, superior canal dehiscence, SCD

ABSTRACT

Recent studies have demonstrated the frequency selectivity of air-conducted (AC) and bone-conducted (BC) stimuli in eliciting ocular vestibular evoked myogenic potentials (oVEMPs). In this study frequency tuning of the oVEMP was assessed in patients with superior canal dehiscence (SCD) and compared to responses previously reported for healthy subjects. Six (five unilateral) SCD patients were stimulated using AC sound (50 – 1200 Hz) and BC transmastoid vibration (50 – 1000 Hz). Stimuli were delivered at two standardized intensities: one the same as previously used for healthy controls and the other at 10 dB above vestibular threshold (a similar relative intensity to that used in controls). For AC stimulation, SCD patients had larger oVEMP amplitudes across all frequencies tested for both stimulus intensities. Normalized tuning curves demonstrated greater high frequency responses with the stronger stimulus. For BC stimulation, larger oVEMP amplitudes were produced at frequencies at and above 100 Hz using standard intensity stimuli. For the matched intensity above vestibular threshold, enhancement of the oVEMP response was present in SCD patients for 500 – 800 Hz only. We conclude that SCD causes greater facilitation for AC than BC stimuli. The high frequency response is likely to originate from the superior (anterior) canal and is consistent with models of inner ear changes occurring in SCD.

1. INTRODUCTION

The recognition of vestibular-evoked myogenic responses, short latency reflexes related to vestibulo-collic (cervical vestibular evoked myogenic potential or cVEMP) and vestibulo-ocular (ocular vestibular evoked myogenic potential or oVEMP) projections, has allowed investigation of the frequency responses of human vestibular end organs. The otoliths (saccule and utricle), consisting of a mass on a compliant base, have long been recognised as having the potential for showing resonance. Goldberg and Fernandez (1975) estimated resonant frequencies of about 400 Hz for human otolith organs. Indeed a response peak from 400 – 1000 Hz has been demonstrated for air-conducted (AC) sound when used to evoke cVEMPs (Akin et al. 2003; Murofushi et al. 1999; Park et al. 2010; Todd et al. 2000; Todd et al. 2009; Welgampola and Colebatch 2001) and oVEMPs (Chihara et al. 2009; Lewis et al. 2010; Park et al. 2010; Todd et al. 2009; Zhang et al. 2011a). When bone-conducted (BC) sound is used the resonant frequency is lower, with a peak around 100 Hz (Todd et al. 2008; Zhang et al. 2012) or 400 Hz (using a B71 bone conductor: Donnellan et al., 2010). It has been suggested that these two peaks correspond to the resonances of the saccule and utricle respectively (Todd et al. 2009).

Superior canal dehiscence (SCD: Minor et al. 1998) is a condition in which the vestibular response to sound is profoundly altered. This condition arises from a fenestration of the temporal bone overlying the superior semicircular canal (SSC). The bony labyrinth defect is believed to cause changes in the flow dynamics of the endolymph, resulting in symptoms such as sound and pressure-induced vertigo or oscillopsia, and chronic disequilibrium (Minor et al. 1998). Patients affected by SCD display pathologically enlarged vestibular-evoked potentials and lowered response thresholds (Brantberg et al. 1999; Colebatch et al. 1998). Ocular VEMP testing has

been recently proposed as a sensitive diagnostic marker of the condition (Rosengren et al. 2008; Welgampola et al. 2008). The question then arises whether the pathology in SCD merely increases vestibular sound sensitivity overall, with preservation of the usual pattern of tuning or whether there are specific features of the response to both AC and BC sound that are characteristic of this condition.

This study was designed to investigate the patterns of vestibular activation in SCD, using both AC and BC stimulation. SCD has differing effects on AC and BC stimuli at least for the hearing changes at low frequencies where one is attenuated and the other enhanced ("conductive hyperacusis": Watson et al. 2000). We have previously reported the findings of one subject included in this report, who demonstrated profound alterations in the pattern of tuning to BC stimulation which were corrected by definitive surgery (Zhang et al. 2011b).

2. METHODS

2.1 Patients and healthy subjects

Six patients with SCD were recruited for the study (3 male, 3 female; aged 22 to 69 years: Table 1). One had bilateral dehiscences (P3) and her results for BC stimulation are presented separately. Dehiscence of the superior canal had been previously confirmed in all patients using high resolution CT imaging of the temporal bone. The 5 unilateral patients all underwent formal audiometry. Three had evidence of low frequency reduction in BC thresholds on the affected side, an accepted feature of SCD (e.g. Minor et al. 2003) but none had any other evidence of conductive hearing changes. Patient results were compared to those of normal healthy subjects reported previously (6 male, 4 female; range: 19 to 34 years: Zhang et al. 2011a; Zhang et al. 2012). The control group was significantly younger than the patient group ($t_{(5.4)} = 3.6$,

P = 0.013) but we do not regard this as relevant our findings (Taylor et al., 2012). Both patients and healthy subjects recruited for the study gave informed consent according to the Declaration of Helsinki.

Table 1 here

2.2 Stimulation techniques

Stimuli were generated using custom software and a CED laboratory interface (1401plus, Cambridge Electronic Design, Cambridge, UK). Signal amplification was achieved using a custom amplifier for AC sound and a model 2718 Brüel and Kjær amplifier for BC sound. For AC stimulation, patients were presented with sinusoidal tone bursts for 30-250 repetitions at a rate of ~ 5 Hz at 50, 80, 100, 150, 200, 400, 500, 600, 800, 1000 and 1200 Hz. AC stimuli were delivered using calibrated headphones (TDH 49, Telephonics Corp., Farmingdale, USA) with an A-weighted equivalent sound intensity level of 120 dB re 20 μPa. A-weighting was used to account for frequency-filtering by the ear. The stimulus polarity was alternated to reduce artefact in the AC oVEMP recordings. BC sound was delivered using a hand-held mini-shaker with an attached perspex rod (model 4810, Brüel and Kjær, Denmark). Driving frequencies used were 50, 80, 100, 125, 150, 200, 400, 500, 600, 800 and 1000 Hz. A constant peak force output of 134dB re 1μN was maintained across all frequencies of BC sound. The initial polarity of the stimulus was in the positive direction (i.e. movement of the rod away from the motor) for all frequencies tested.

For both modalities, a 10 ms stimulus duration (rise/hold/fall: 2ms/6ms/2ms) was used for all frequencies at and above 100 Hz. An increased stimulus duration was used for 80 Hz (2ms/6ms/ 4.5ms) and 50 Hz (2ms/6ms/12ms) to ensure the delivery of a complete cycle of sound. Fourier analysis of the waveforms showed that the peak

frequency was consistent with the applied frequency. Frequency tuning was assessed in the affected ear of SCD patients using AC sound (n=6) and BC stimulation at the mastoid process (n=5). Patients were assessed at the same intensities as normal subjects (120 dB re 20 μPa for AC and 134 dB peak FL re 1 μN for BC) and at a second, lower intensity adjusted to be 10 dB above each patient's oVEMP threshold.

2.3 oVEMP recordings

Surface recordings were made using standard EMG electrodes (Cleartrace 1700-030, Conmed Corp., NY, USA). The active electrode was located over the inferior orbital margin and a reference electrode was placed immediately below it. An earth electrode was placed near the suprasternal notch. Subjects were seated upright and directed their gaze approximately 30° above horizontal for the duration of the recording. The recorded EMG was amplified using D150 amplifiers (Digitimer Co, Welwyn Garden City, UK), bandpass filtered (5 to 1000 Hz) and sampled using a second CED Power1401 laboratory interface at 10 kHz from 10 ms before to 60 ms after stimulus onset. Data collection was performed using SIGNAL software (version 2.15, Cambridge Electronic Design, Cambridge, UK). Three amplitude parameters were measured; the initial negative peak (n1), the initial negative-positive peaks (n1-p1) and the largest peak-to-peak (P-P) amplitude over the entire oVEMP response. Measurements were taken following stimulation of the affected ear and recorded from the contralesional eye for AC stimulation and from both the contralesional and ipsilesional eyes following BC stimulation.

2.4 Thresholds

Both healthy subjects and SCD patients were tested in order to compare groups at matched intensities above their vestibular threshold. Ocular VEMP thresholds for AC and BC stimulation were determined by systematically reducing the stimulus intensity at 500Hz in 5 dB increments. Threshold was defined as the lowest intensity at which an n1 response (from the eye contralateral to the stimulated ear) was present in two consecutive trials for both modalities. For healthy subjects, mean oVEMP thresholds were 113 ± 5 dB SPL and 128 ± 5 dB FL for AC and BC stimuli respectively (Zhang et al. 2011a; Zhang et al. 2012). In SCD patients, mean oVEMP thresholds were 95 ± 8 dB SPL for AC stimuli and 110 ± 4 dB FL for BC stimuli. Thresholds were significantly lowered in SCD patients compared to healthy subjects for both stimulus modalities ($t_{(11-14)} = 5.7$ and 7.4, $P < 0.001$ in both cases).

2.5 Statistical analysis

Statistical analysis was performed using SPSS (version 18.0.0, SPSS Inc., Chicago, IL, USA). Analysis of oVEMP amplitudes was performed using both raw and normalized (N) values. Ocular VEMP amplitudes were normalized by expressing responses at each frequency (f) as a ratio of the largest measured amplitude (at f_{max} Hz) prior to averaging (i.e. $N(f) = Amplitude(f)/Amplitude(f_{max})$). Absent responses were assigned a 0 µV value. Two-way within-subjects ANOVA (eye and frequency as factors) were used for analysis of tuning effects using BC mastoid stimulation. Tuning effects following unilateral AC stimulation were assessed using one-way within-subjects ANOVA (frequency as a factor). The initial n1 and p1 peaks were considered for analysis of latency values. Student's paired and unpaired t-tests were used for post hoc testing. Wilcoxon's nonparametric tests were used to compare responses between SCD patients and healthy subjects. For AC stimulation, responses were compared for

the eye contralateral to the stimulated ear (i.e. the contralesional eye in SCD patients and the contralateral eye in healthy subjects). Responses for BC stimulation were compared for the eye ipsilateral and contralateral to the stimulated ear. Grand mean illustrations were constructed using custom scripts written using MATLAB software (Version 6.5.1, Mathworks Inc., Massachusetts, USA). Values are reported in the text as means ± standard deviation (S.D) and are displayed in figures as means ± standard error of the mean (S.E.M).

3. RESULTS

3.1 AC stimulation

Standard intensity

AC evoked oVEMPs recorded in SCD patients using standard intensity stimuli showed large amplitude responses with broad high frequency tuning (Fig. 1). The largest mean amplitudes were recorded at 600 Hz (n1: 15.5 ± 8.8 μV) and 800 Hz (n1-p1 and largest P-P: 35.0 ± 19.0 μV). There was a significant main effect of frequency on oVEMP n1, n1-p1 and largest P-P amplitudes ($F_{(10,50)}$ = 7.4 to 10.6 , $P < 0.001$ for all cases). For the n1-p1 measurements, amplitudes at 800 Hz were larger than amplitudes at and above 1000 Hz ($t_{(5)}$ = 3.3 and 3.7, $P < 0.02$ in both cases). Similarly, larger amplitudes were recorded at 800 Hz when compared to amplitudes at and below 200 Hz ($t_{(5)}$ = 3.9 to 5.9, $P < 0.02$ in all cases). There was no significant difference in n1-p1 amplitudes between 400 - 800 Hz or for 50 – 200 Hz ($t_{(5)}$ = 0.3 to 1.8, $P > 0.05$ in all cases).

There was a significant main effect of frequency on both n1 and p1 latencies ($F_{10,50}$ = 5.5 & 12.6, $P < 0.001$ for both cases; Fig. 2A). The longest latency values were recorded at 800 Hz (n1: 11.2 ± 0.6 ms; p1: 19.7 ± 0.8 ms). Shortest latency

values were recorded at 200 Hz (n1: 10.2 ± 0.4 ms) and 150 Hz (p1: 14.9 ± 0.6 ms). For n1 latencies, responses appeared later at 800 Hz compared to responses at 1000 Hz and frequencies at and below 400 Hz ($t_{(5)}$ = 3.3 to 6.1, P < 0.02 in all cases). For p1 latencies, responses at 800 Hz were later than at 1200 Hz and frequencies at and below 150 Hz ($t_{(5)}$ = 3.5 to 15.4, P < 0.02 in all cases).

FIGURE 1 and 2 HERE

Lowered intensity

When SCD patients were stimulated at 10 dB above their AC oVEMP threshold the responses showed similar tuning to the standard intensity (Fig. 3). Mean amplitudes were largest at 600 Hz (n1-p1: 10.4 ± 2.6 μV; n1: 4.8 ± 1.0 μV; largest P-P: 11.1 ± 3.5 μV). For all three measurements, there was a significant main effect of frequency on oVEMP amplitudes ($F_{(10,50)}$ = 4.4 to 5.3 , P < 0.001 for all cases). For the higher frequencies, n1-p1 amplitudes at 600 Hz were significantly larger than amplitudes at 500 and 1200 Hz ($t_{(5)}$ = 3.1 and 4.0, P < 0.03 in both cases). In the lower frequency range, n1-p1 amplitudes at 600 Hz were significantly larger than amplitudes at 50, 80, 150 and 200 Hz ($t_{(5)}$ = 3.0 - 4.2, P < 0.03 in all cases). At 100 Hz, n1-p1 amplitudes were larger than amplitudes at 50, 80, 150 and 200 Hz ($t_{(5)}$ = 3.3 - 6.1, P < 0.02 in all cases), suggesting the presence of a secondary tuning peak..

In contrast to standard intensity stimuli, there was a main effect of frequency only on p1 latencies ($F_{(10,50)}$ = 4.1, P < 0.001). Latencies for the p1 peak appeared later at 800 Hz when compared to either 50 or 100 Hz ($t_{(5)}$ = 3.1 & 3.4, P < 0.03 in both cases).

FIGURE 3 HERE

Standard vs lowered intensity (AC stimulation)

For n1-p1 amplitudes, responses were larger for standard intensity stimuli compared to lowered intensity stimuli at all frequencies tested ($t_{(5)} = 2.7 - 3.8$, $P < 0.045$ in all cases).

For latency values, n1 peaks appeared slightly earlier at 600 Hz when using the lowered intensity stimulus ($t_{(5)} = 2.7 - 3.8$, $P < 0.045$). For p1 peaks, latencies at 400 – 1000 Hz appeared earlier when using the lowered intensity stimulus ($t_{(5)} = 3.5 - 6.1$, $P < 0.018$ in all cases)

3.2 BC stimulation

Standard intensity

SCD patients with unilateral lesions showed a broad peak of oVEMP tuning following BC mastoid stimulation of the affected ear, with a difference between the normalized responses from the two eyes for frequencies of 400 Hz and above (Fig. 4). Overall, largest mean amplitudes occurred at 125 Hz (n1-p1: 30.7 ± 14.0 μV) and 150 Hz (n1: 15.7 ± 7.4 μV; largest P-P: 35.6 ± 16.2 μV) in the contralesional eye. For the ipsilesional eye, mean amplitudes were largest at 125 (n1-p1: 13.6 ± 6.3 μV; largest P-P: 16.1 ± 11.1 μV) and 200 Hz (n1: 5.1 ± 3.0 μV).

There were significant main effects of frequency ($F_{(10,40)} = 2.5$ to 3.9 , $P < 0.02$ for all cases) and eye ($F_{(1,4)} = 17.5$ to 22.4 , $P < 0.01$ for all cases) on n1, n1-p1 and largest P-P oVEMP amplitudes ($F_{(10,40)} = 2.5$ to 3.9 , $P < 0.02$ for all cases). ANOVA also revealed a significant interaction between eye and frequency for all three measurements ($F_{(10,40)} = 2.7$ to 5.7 , $P < 0.01$ for all cases). For n1-p1 raw amplitudes, responses at all frequencies tested were significantly larger for the contralesional eye than the ipsilesional eye ($t_{(4)} = 3.0$ to 4.8, $P < 0.04$ in all cases). However, when comparing normalized n1-p1 amplitudes the response with increasing frequency was

more pronounced for the contralesional eye (Fig. 4A). For the contralesional eye, n1-p1 normalized amplitudes were larger at 400, 600 and 800 Hz when compared to the ipsilesional eye ($t_{(4)} = 3.4$ to 4.8, $P < 0.03$ in all cases). At 50 Hz, n1-p1 normalized amplitudes were smaller for the contralesional eye ($t_{(4)} = 3.7$, $P = 0.02$).

There were significant main effects of eye ($F_{(1,85)} = 37.8$ and 104.5, $P < 0.001$) and frequency ($F_{(10,85)} = 3.4$ and 6.7, $P < 0.002$) on the latencies of both n1 and p1 peaks. The n1 contralesional latencies were generally shorter than for the ipsilesional n1 latencies (Fig. 2B, Fig. 4). Responses for the n1 peak occurred significantly earlier in the contralesional eye than the ipsilesional eye at 80 – 200 Hz and at the 500 – 800 Hz ($t_{(4-7)} = 2.9 – 4.0$, $P < 0.044$ in all cases). For p1 responses, peaks occurred earlier in the contralateral eye than the ipsilateral eye at frequencies between 80 – 150 Hz ($t_{(4)} = 4.4$ to 8.6, $P < 0.011$ in all cases).

The longest latency values were recorded at 50 Hz for both the contralesional (n1: 13.6 ± 2.6 ms; p1: 19.1 ± 3.4 ms) and ipsilesional (n1: 16.6 ± 1.0 ms; p1: 22.4 ± 1.2 ms) eyes. Shortest latencies were recorded at 1000 Hz (n1: 10.0 ± 0.7 ms) and 200 Hz (p1: 15.1 ± 1.1 ms) for the contralesional eye, and at 1000 Hz (n1: 11.7 ± 1.6 ms; p1: 16.7 ± 2.2 ms) for the ipsilesional eye. At 50 Hz, n1 responses for the contralesional eye tended to occur later than at 400 and 1000 Hz ($t_{(4)} = 2.9$ and 3.9, $P = 0.043$ and 0.017 in both cases). For p1 peaks, responses at 50 Hz occurred later than at 125 - 200 Hz for the contralesional eye ($t_{(4)} = 2.8$ to 3.6, $P < 0.048$ in all three cases). For the ipsilesional eye, n1 peaks at 50 Hz occurred later than at 80 – 400 Hz and 1000 Hz ($t_{(4-7)} = 3.8$ to 6.5, $P < 0.019$ in all cases), whereas p1 peaks at 50 Hz occurred later than at all frequencies excluding 600 Hz ($t_{(4-7)} = 3.1$ to 8.5, $P < 0.027$ in all cases).

FIGURE 4 HERE

Lowered intensity

Responses were smaller overall but still showed a peak around 100-200 Hz with greater high frequency responses for the contralesional eye and a relatively smaller response at 50 Hz (Fig. 5). The largest mean amplitudes were recorded at 150 Hz (n1-p1: 13.0 ± 7.5 μV; largest P-P: 13.2 ± 7.9 μV) and 200 Hz (n1: 6.4 ± 3.6 μV) for the contralesional eye. Responses were largest for the ipsilesional eye at 100 (n1: 1.8 ± 0.7 μV) and 200 Hz (n1-p1: 5.0 ± 3.6 μV; largest P-P: 7.2 ± 4.3 μV). For raw n1-p1 amplitudes, responses tended to be larger for the contralesional eye at frequencies at and above 80 Hz ($t_{(4)}$ = 2.9 to 4.3, $P < 0.043$ in all cases). Normalized n1-p1 amplitudes were significantly larger for the contralesional eye at 600 Hz ($t_{(4)}$ = 4.2, $P = 0.013$). For the ipsilesional eye, larger normalized n1-p1 amplitudes were recorded at 50 Hz ($t_{(4)}$ = 3.3, $P = 0.03$).

For the n1 peak, responses occurred earlier in the contralesional eye than the ipsilesional at 50 – 200 Hz and at 600 – 800 Hz ($t_{(4-7)}$ = 3.6 to 8.2, $P < 0.023$ in all cases). For the p1 peak, responses occurred earlier in the contralesional eye at 50 – 100 Hz, 150 Hz, 200 Hz and 600 Hz ($t_{(4-7)}$ = 3.3 to 4.8, $P < 0.031$ in all cases).

FIGURE 5 HERE

Standard vs lowered intensity (BC stimulation)

For the contralesional eye, n1-p1 amplitudes at all frequencies tested were larger using standard intensity stimuli than with lower intensity stimuli ($t_{(4)}$ = 3.2 to 4.8, $P < 0.032$ in all cases). For the ipsilesional eye, standard intensity stimuli produced larger n1-p1 amplitudes at 50 – 200 Hz and at 600 Hz ($t_{(4)}$ = 3.1 to 4.8, $P < 0.035$ in all cases).

For both intensities of stimulation, similar patterns of latency changes were seen for n1 and p1 peaks across the majority of frequencies tested (Fig. 2B). Standard

intensity stimuli produced earlier responses for the p1 peak at 80 Hz for the ipsilesional eye ($t_{(4)} = 5.9$, $P = 0.004$) and at 125 Hz for the contralesional eye ($t_{(4)} = 2.8$, $P = 0.049$).

Bilateral SCD

The pattern of evoked responses to BC mastoid stimulation in the bilateral SCD patient (P3) differed somewhat from those seen in the unilateral patients and was therefore analysed separately (Fig. 6). For standard intensity stimulation, there was no clearly observable tuning peak at all following stimulation of the affected mastoid but rather responses that continued to 1 kHz with little attenuation. The largest n1-p1 response for the right and left eyes occurred at 200 (10.4 μV) and 400 Hz (14.3 μV) respectively. In contrast, lower intensity stimuli produced a double peak tuning curve with maxima occurring at 150 and 800 Hz. Responses in the bilateral SCD patient occurred earlier in the left eye (i.e the eye ipsilateral to the stimulated mastoid) and this was more pronounced in the lower frequency range (50 Hz: left eye = 12.6 ms, right eye = 15.5 ms; 1000 Hz: left eye = 11.6, right eye = 12.9 ms).

FIGURE 6 HERE

3.3 SCD vs NORMALS

AC stimulation

For both stimulus intensities, raw n1-p1 amplitudes at all frequencies tested were larger in SCD patients compared to healthy subjects ($z = 2.2$ to 3.3, $P < 0.03$ for all cases: healthy subjects; 50 Hz = 1.0 ± 0.8 μV, 80 Hz = 1.6 ± 1.2 μV, 100 Hz = 1.9 ± 1.7 μV, 150 Hz = 1.8 ± 1.8 μV, 200 Hz = 1.6 ± 1.3 μV, 400 Hz = 2.7 ± 1.8 μV, 500 Hz = 3.3 ± 1.8 μV, 600 Hz = 3.5 ± 2.5 μV, 800 Hz = 2.9 ± 2.2 μV, 1000 Hz = 1.7 ± 1.6 μV, 1200 Hz = 1.0 ± 1.1 μV: Zhang et al. 2011a). However, normalized n1-p1 amplitudes demonstrated broadly similar tuning curves for both groups (Fig. 7A).

Standard intensity stimuli produced larger normalized n1-p1 amplitudes in SCD patients when compared to healthy subjects at 50, 800, 1000 and 1200 Hz ($z = 2.1$ to 2.8, $P < 0.036$ for all cases). There was no significant difference in normalized n1-p1 amplitudes between SCD patients when using the lowered intensity stimuli and healthy subjects ($z = 0.2$ to 1.4, $P > 0.05$ for all cases). There was no significant difference in tuning maxima between groups for both AC stimulus intensities (HS: 615 ± 226 Hz vs SCD: 667 ± 151 Hz (standard intensity) and 550 ± 266 Hz (lowered intensity); $z = 0.3$ for both comparisons, $P > 0.05$ for both cases).

BC stimulation (contralesional eye)

For standard intensity stimuli, raw n1-p1 amplitudes for frequencies at and above 100 Hz were larger in SCD patients compared to healthy subjects ($z = 2.1$ to 2.9, $P < 0.04$ for all cases) (healthy subjects; 50 Hz = 10.1 ± 6.7 μV, 80 Hz = 13.1 ± 7.9 μV, 100 Hz = 12.8 ± 8.6 μV, 125 Hz = 12.0 ± 7.8 μV, 150 Hz = 11.0 ± 6.6 μV, 200 Hz = 7.2 ± 5.2 μV, 400 Hz = 6.1 ± 3.3 μV, 500 Hz = 3.6 ± 3.9 μV, 600 Hz = 3.2 ± 2.7 μV, 800 Hz = 1.7 ± 1.5 μV, 1000 Hz = 1.9 ± 1.2 μV: Zhang et al. 2012). When stimulated at similar intensities above threshold both groups showed a low frequency peak in tuning. At 500, 600 and 800 Hz, n1-p1 amplitudes were significantly larger in SCD patients when compared to healthy subjects ($z = 2.1$ to 2.4, $P < 0.037$ in all cases).

After normalization, SCD patients showed larger responses to high frequency BC stimulation for both stimulus intensities (Fig. 7B). For standard intensity stimuli, normalized n1-p1 amplitudes were larger in SCD patients than in healthy subjects at frequencies at and above 500 Hz ($z = 2.4$ to 3.1, $P < 0.014$ in all cases). At 50 and 80 Hz, normalized n1-p1 amplitudes were significantly smaller than for healthy subjects ($z = 2.2$ & 2.3, $P < 0.027$ in both cases) For lowered intensity stimuli, normalized n1-

p1 amplitudes were larger in SCD patients than in healthy subjects at 200 Hz and between 500 – 800 Hz (z = 2.3 to 2.7, P < 0.02 in all cases). Normalized n1-p1 amplitudes were smaller than in healthy subjects at 50 and 80 Hz (z = 2.7 to 2.8, P < 0.005 in both cases). Tuning maxima were significantly higher in SCD patients compared to healthy subjects for both stimulus intensities (HS: 104 ± 35 Hz vs SCD: 325 ± 218 Hz (standard intensity) and 310 ± 225 Hz (lowered intensity); z = 2.5 and 2.8, P < 0.011 in both cases).

BC stimulation (ipsilesional eye)

Raw n1-p1 amplitudes for standard intensity stimuli were larger from the ipsilesional eye in SCD patients compared to the ipsilateral eye in healthy subjects at 600 and 1000 Hz (z = 2.1 & 2.2, P < 0.04 for both cases; healthy subjects; 50 Hz = 9.0 ± 4.4 μV, 80 Hz = 12.7 ± 5.6 μV, 100 Hz = 13.6 ± 4.7 μV, 125 Hz = 13.4 ± 5.0 μV, 150 Hz = 14.0 ± 5.2 μV, 200 Hz = 11.7 ± 2.7 μV, 400 Hz = 4.3 ± 2.2 μV, 500 Hz = 2.5 ± 2.2 μV, 600 Hz = 1.6 ± 1.6 μV, 800 Hz = 0.6 ± 0.6 μV, 1000 Hz = 0.8 ± 0.9 μV: Zhang et al. 2012). For the lower intensity stimuli, raw n1-p1 amplitudes were smaller than in healthy subjects at and below 400 Hz (z = 2.3 and 3.1, P < 0.023 in all cases). Normalized n1-p1 amplitudes for standard intensity stimuli were larger in SCD patients than for healthy control subjects at 600 and 1000 Hz (z = 2.2, P < 0.03 for both cases). At 800 Hz, lowered intensity stimuli produced greater normalized n1-p1 amplitudes in SCD patients (z = 2.0, P = 0.041: Fig. 7B).

FIGURE 7 HERE

4. DISCUSSION

SCD is a consequence of a defect in the normal bony covering of the superior (or anterior) semicircular canal (Minor et al. 1998). The consequences include the characteristic increase in vestibular sensitivity to AC sound. This can be

demonstrated as sound induced nystagmus or by changes in cVEMPs or oVEMPs. Both these reflexes show an increase in amplitude and reduced threshold. The reduction in AC threshold is highly characteristic and is present even when the patients do not complain of sound-induced vertigo (Mikulec et al. 2004). VEMP threshold testing has a sensitivity and specificity of over 90% in detecting SCD (Zhou et al. 2007).

Our SCD patients had significantly larger amplitude oVEMP responses for AC stimulation when compared to healthy subjects, consistent with previous reports (Rosengren et al. 2008; Welgampola et al. 2008). For the same intensity of stimulation, responses in the SCD patients were larger than those of normals similarly tested by Zhang et al. (2011a) at all the frequencies tested (Fig. 7A). Even when the stimulus was only 10 dB above threshold, and therefore the same relative intensity as for normals, responses in the SCD patients were still larger at all frequencies. This observation indicates that the changes in SCD are not simply a consequence of a lowered threshold for vestibular activation but rather that there is an overall facilitation of vestibular activation. This in turn is likely to be due to a greater proportion of acoustic energy being available to excite vestibular afferents more intensely. After normalization of the AC tuning curves to allow for the larger overall amplitudes, the morphology of the tuning curve for SCD patients showed two peaks of tuning, similar to those reported in normal subjects (Zhang et al. 2011a). In SCD patients however, the dominant peak in amplitudes occurred at higher frequencies (600 to 800 Hz) with responses at 800 Hz, 1000 Hz and 1200 Hz being relatively larger than in normals. A smaller, low frequency peak in amplitudes occurred from 80 to 150Hz, with a relatively larger response at 50 Hz than in normals. Taylor et al. (2012) also reported a higher likelihood of an optimal oVEMP response at higher

frequencies in SCD patients compared to normals. The relative increase at 50 Hz reflects the diversion of low frequency sound towards the dehiscence and away from the cochlea (Mikulec et al. 2004).

BC stimulation inevitably affects both sides but, as the projection underlying the normal oVEMP is crossed (Iwasaki et al. 2007), for unilateral pathology the ipsilesional oVEMP should reflect the function of the unaffected vestibular apparatus while the contralesional oVEMP indicates the effects of the pathological one. BC tuning in SCD patients showed very clear differences when compared to that observed for normal subjects. We have previously reported that these changes are reversible with closure of the defect (Zhang et al. 2011b). In absolute terms, the responses in SCD for the contralesional side were larger at frequencies at and above 100 Hz than for normals when using the same stimulus intensity. For the lower intensity, the amplitude difference was still significantly greater for 500 – 800 Hz, indicating that this was not simply due to the lower vestibular threshold in SCD but rather a selective enhancement. While the normal low frequency peak around 100 Hz was still present, the contralesional oVEMP showed almost the same response amplitude up to 1000 Hz. After normalization, significantly greater responses were present for 500 Hz and above compared to normals. This relative increase in high frequency responses in BC oVEMP tuning has been previously observed by Welgampola et al. (2009) who reported wide variation of the optimal stimulus frequency from 500 to 2000 Hz in SCD patients. Responses at low frequencies (50 Hz) were, in contrast, relatively smaller for SCD patients, the converse of AC, indicating a preferential shunting of these frequencies to the cochlea partition (Mikulec et al. 2004).

Current evidence favours both AC and BC stimuli mainly exciting irregularly discharging otolith afferents (Curthoys et al. 2006; McCue and Guinan, 1994;

Murofushi and Curthoys, 1997), although some canal afferents may also be excited (Zhu et al. 2011). Todd et al. (2009) proposed that the tuning properties of the oVEMP and cVEMP primarily reflected the resonant properties of the otolith organs, with a resonance around 100 Hz for the utricle and around 500 Hz for the saccule. Both AC and BC tuning curves show two effects. One is a facilitation of responses, as indicated by the difference for the lower intensity stimulation from normal. For AC this applied to all frequencies while for BC this was for frequencies of 500 Hz and above. The presence of a defect in the normal bony covering of the SSC will lead to a greater proportion of AC acoustic energy being diverted away from the cochlea-round window pathway towards the defect and the overall facilitation of AC responses is consistent with this. In addition, particularly for BC stimulation, there was selective facilitation of high frequency responses. An increase of inner ear compliance would be expected, if anything, to lower the resonant frequency of the otoliths. A dominant 100 Hz peak was still present suggesting the low frequency (utricular) resonance was unchanged. Saccular ocular pathways are relatively weak and we and others (Rosengren et al. 2008; Taylor et al. 2012) have concluded that there must be a contribution from superior canal afferents to the enlarged amplitudes of oVEMPs seen in this condition. The high frequency response is therefore likely to originate from afferents arising from the SSC and experimentally these afferents become highly responsive to acoustic stimulation when a third window into the SSC is made (Carey et al. 2004; Hirvonen et al. 2001). This also implies that the n1 peak is not unique to a single afferent type but may originate from SSC afferent activity. The enhancement of the response for the eye ipsilateral to the dehiscent canal that we have shown for higher frequencies indicates that there are bilateral abnormalities for these frequencies (Fig. 7B) and this is likely to be due to the projections of superior canal afferents to

the ipsilateral inferior rectus. Activity in this muscle can be recorded from the surface (Weber et al. 2012) and this is also consistent with the delay we found for the initial negative peak on the ipsilesional side.

The presence of a dehiscence in the SSC not only affects vestibular function but also has profound effects upon hearing. In some patients this is the main or sole symptom (Mikulec et al. 2004). There is loss of sensitivity to low frequency AC sound but enhancement of BC sound at the same frequencies. Rosowski et al. (2004) noted that the dehiscence means that the pressure at the two ends of the superior canal are no longer equal and that this in turn allows motion of the stapes to produce flow of lymph (endolymph and perilymph) through the bony canal. They modelled the changes induced by the dehiscence and also recorded the sound-induced velocity of lymph within the SSC of experimentally dehiscent inner ears. They showed a broad tuning response with a peak around 1-2 kHz, falling off below 400 Hz and above 4 kHz. This response in turn was mainly determined by a tuned circuit consisting of the effective middle ear capacitance with the acoustic mass of the fluid in each arm of the SSC remnant, equivalent to a series inductive element (Olson, 1966). Middle ear effects remained important for BC stimulation where it acts as a load. The main source of the high frequency tuning effects we have shown for both AC and, more markedly, BC stimulation, is therefore likely to be the excitation of SSC afferents due to sound energy causing flow within the dehiscent canal, shown experimentally to have a resonant frequency around 1-2 kHz. The effective capacitance of the dehiscence itself is substantially larger than that of the middle ear and thus would be expected to have little effect on the tuning frequency (Rosowski et al. 2004, Table 1).

AC cVEMPs thresholds are a sensitive method for diagnosing SCD (Brantberg et al. 1999; Colebatch et al. 1998). In contrast, BC evoked cVEMPs do not always

show a clear reduction in the normal threshold in SCD (Welgampola et al. 2003). More recently AC oVEMPS have been proposed as simple test for SCD, based upon amplitude changes alone (Rosengren et al. 2008; Welgampola et al. 2008). Welgampola et al. (2008) showed that the separation of patients from normals was better using AC stimuli than BC stimulation at 500 Hz. Our findings indicate that a dehiscence facilitates the response to AC sound in addition to any change in threshold, by causing more AC sound energy to be shunted towards the otolith organs rather than to the cochlear partition. This enhances the normal saccular and utricular responses to sound and leads to a lowered threshold. For BC stimulation, the main effect of the dehiscence is to facilitate a different type of BC-induced excitation of SSC afferents while otolith excitation appears to be less affected. The changes we have shown for oVEMP tuning in SCD patients using low intensity stimulation do however suggest that high frequency BC stimulation, around 600 - 1000Hz, may be a more effective means of SCD detection than using lower frequencies.

Conclusion

SCD causes significant changes to the patterns of vestibular excitation evoked by both AC and BC stimulation. For both, afferents arising from the superior canal are likely to be activated, particularly for higher frequencies. For AC there is an overall facilitation of the normal vestibular response to sound while for BC this applies mainly to higher frequencies. These changes can be understood using models of inner ear function.

Acknowledgments:

This work was supported by the Garnett Passe and Rodney Williams Memorial Foundation and the National Health and Medical Research Council of Australia. We thank Prof. G.M. Halmagyi and Dr. Tom Kertesz for referring several of the patients studied.

5. REFERENCES

Akin FW, Murnane OD, Proffitt TM (2003) The effects of click and tone-burst stimulus parameters on the vestibular evoked myogenic potential (VEMP). J Am Acad Audiol 14:500-509.

Brantberg K, Bergenius J, Tribukait A (1999) Vestibular-evoked myogenic potentials in patients with dehiscence of the superior semicircular canal. Acta Otolaryngol 119: 633-640.

Carey JP, Hirvonen TP, Hullar TE, Minor LB (2004) Acoustic responses of vestibular afferents in a model of superior canal dehiscence. Otol Neurotol 25: 345-352.

Chihara Y, Iwasaki S, Fujimoto C, Ushio M, Yamasoba T, Murofushi T (2009) Frequency tuning properties of ocular vestibular evoked myogenic potentials. Neuroreport 20:1491-1495.

Colebatch JG, Day BL, Bronstein AM, Davies RA, Gresty MA, Luxon LM, Rothwell JC (1998) Vestibular hypersensitivity to clicks is characteristic of the Tullio phenomenon. J Neurol Neurosurg Psychiatry 65:670-678.

Curthoys IS, Kim J, McPhedran SK, Camp AJ (2006) Bone conducted vibration selectively activates irregular primary otolithic vestibular neurons in the guinea pig. Exp Brain Res 175:256-267.

Donnellan K, Wei W, Jeffcoat B, Mustain W, Xu Y, Eby T, Zhou W (2010) Frequency tuning of bone conducted tone burst-evoked myogenic potential in extraocular muscles (BOVEMP) in normal human subjects. Laryngoscope 120:2555-2560.

Goldberg JM, Fernández C (1975) Vestibular mechanisms. Ann Rev Physiol 37:129-162.

Hirvonen TP, Carey JP, Liang CJ, Minor LB (2001) Superior canal dehiscence: mechanisms of pressure sensitivity in a chinchilla model. Arch Otolaryngol Head Neck Surg 127: 1331-1336.

Iwasaki S, McGarvie LA, Halmagyi GA, Burgess AM, Kim J, Colebatch JG, Curthoys IS (2007) Head taps evoke a crossed vestibulo-ocular reflex. Neurology 68: 1227-1229.

Lewis A, Mustain W, Xu Y, Eby T, Zhou W (2010) Frequency tuning in the tone burst-evoked myogenic potentials in extraocular muscles in normal human subjects. J Otolaryngol Head Neck Surg 39:491-497.

McCue MP, Guinan JJ (1994) Acoustically responsive fibers in the vestibular nerve of the cat. J Neurosci 14:6058-6070.

Mikulec AA, McKenna MJ, Ramsey MJ, Rosowski JJ, Herrmann BS, Rauch SD, Curtin HD, Merchant SN (2004) Superior semicircular canal dehiscence presenting as conductive hearing loss without vertigo. Otol Neurotol 25:121-129.

Minor LB, Carey JP, Cremer PD, Lustig LR, Streubel SO (2003) Dehiscence of bone overlying the superior canal as a cause of apparent conductive hearing loss. Otol Neurotol 24:270-278.

Minor LB, Solomon D, Zinreich JS, Zee DS (1998) Sound- and/or pressure-induced vertigo due to bone dehiscence of the superior semicircular canal. Arch Otolaryngol Head Neck Surg 124:249-258.

Murofushi T, Curthoys IS (1997) Physiological and anatomical study of click-sensitive primary vestibular afferents in the guinea pig. Acta Otolaryngol (Stockh) 117:66-72.

Murofushi T, Matsuzaki M, Wu CH (1999) Short tone burst-evoked myogenic potentials on the sternocleidomastoid muscle. Are these potentials also of vestibular origin? Arch Otolaryngol Head Neck Surg 125:660–664.

Olson HF. Solutions of Engineering Problems by Dynamical Analogies, 2nd ed. Van Nostrand: New Jersey, 1966.

Park HJ, Lee I-S, Shin JE, Lee YJ, Park MS (2010) Frequency-tuning characteristics of cervical and ocular vestibular evoked myogenic potentials induced by air-conducted tone bursts. Clin Neurophysiol 121:85-89.

Rosengren SM, Aw ST, Halmagyi GM, Todd NP, Colebatch JG (2008) Ocular vestibular evoked myogenic potentials in superior canal dehiscence. J Neurol Neurosurg Psychiatry 79: 559-568.

Rosowski JJ, Songer JE, Nakajima HH, Brinsko KM, Merchant SN (2004) Clinical, experimental, and theoretical investigations of the effect of superior semicircular canal dehiscence on hearing mechanisms. Otol Neurotol 25:323-332.

Taylor RL, Bradshaw AP, Halmagyi GM, Welgampola MS (2012) Tuning characteristics of ocular and cervical vestibular evoked myogenic potentials in intact and dehiscent ears. Audiol Neurotol 17:207-218.

Todd NPM, Cody FWJ, Banks JR (2000) A saccular origin of frequency tuning in myogenic vestibular evoked potentials: implications for human responses to loud sounds. Hear Res 141:180-188.

Todd NM, Rosengren SM, Colebatch JG (2008) Tuning and sensitivity of the human vestibular system to low-frequency vibration. Neurosci Lett 444:36-41.

Todd NPM, Rosengren SM, Colebatch JG (2009) A utricular origin of frequency tuning to low-frequency vibration in the human vestibular system? Neurosci Lett 451:175-180.

Watson SR, Halmagyi GM, Colebatch JG (2000) Vestibular hypersensitivity to sound (Tullio phenomenon): structural and functional assessment. Neurology 54:722-728.

Weber KP, Rosengren SM, Michels R, Sturm V, Straumann D, Landau K (2012) Single motor unit activity in human extraocular muscles during the vestibulo-ocualr reflex. J Physiol. 590(13): 3091-3101.

Welgampola MS, Colebatch JG (2001) Characteristics of tone burst-evoked myogenic potentials in sternocleidomastoid muscles. Otol Neurotol 22: 796-802.

Welgampola MS, Migliaccio AA, Myrie OA, Minor LB, Carey JP (2009) The human sound-evoked vestibulo-ocular reflex and its electromyographic correlate. Clin Neurophysiol 120:158-166.

Welgampola MS, Myrie OA, Minor LB, Carey JP (2008) Vestibular-evoked myogenic potential thresholds normalize on plugging superior canal dehiscence. Neurology 70:464-472.

Welgampola MS, Rosengren SM, Halmagyi GM, Colebatch JG (2003) Vestibular activation by bone conducted sound. J Neurol Neurosurg Psychiatry 74: 771-778.

Zhang AS, Govender S, Colebatch JG (2011a) Tuning of the ocular vestibular evoked myogenic potential (oVEMP) to AC sound shows two separate peaks. Exp Brain Res 213:111-116.

Zhang AS, Govender S, Colebatch JG (2011b) Superior canal dehiscence causes abnormal vestibular bone-conducted tuning. Neurology 77:911-913.

Zhang AS, Govender S, Colebatch JG (2012) Tuning of the ocular vestibular evoked myogenic potential to bone-conducted sound stimulation. J Appl Physiol 112:1279-1290.

Zhou G, Gopen Q, Poe DS (2007) Clinical and diagnostic characterization of canal dehiscence syndrome: a great otologic mimicker. Otol Neurotol 28:920-926.

Zhu H, Tang X, Wei W, Mustain W, Xu Y, Zhou W. Click-evoked responses in vestibular afferents in rats. J Neurophysiol 2011 106:754-763.

6. FIGURE LEGENDS

Figure 1: Normalised tuning curves (left column) and grand means (right column) for AC evoked oVEMPs for the SCD patients elicited using standard intensity stimuli following stimulation of the affected ear (n = 6). Tuning curves are shown for the n1-p1 (A), n1 peak (B), and largest peak to peak measurements (C). AC evoked oVEMPs demonstrated two peaks with responses to stimuli up to 1200 Hz.

Figure 2: Mean latencies for the initial n1 and p1 peaks following AC (A, n=6) and BC (B, n=5) stimulation for both stimulus intensities. For BC the results for the ipsilesional eye (grey) are shown separately from those for the contralesional eye (black).

Figure 3: Normalised tuning curves (left column) and grand means (right column) for AC evoked oVEMPs for SCD patients elicited using intensities 10 dB above threshold following stimulation of the affected ear (n = 6). The n1-p1 (A), n1 peak (B) and largest peak to peak measurements (C) showed responses up to 1200 Hz.. A second tuning maximum was present around 100 Hz.

Figure 4: Normalised tuning curves (left column) and grand means (right column) for BC evoked oVEMPs elicited using standard intensity stimuli delivered to the affected mastoid process for the unilateral SCD patients (n = 5). Amplitudes measured from the ipsilesional (grey) and contralesional (black) eyes were averaged and showed differential effects on n1-p1 (A), n1 peak (B) and largest peak to peak measurements (C) at the higher frequencies tested. * indicates significantly different normalised response amplitudes ($P < 0.05$). † indicates statistical trend ($P = 0.06 – 0.09$).

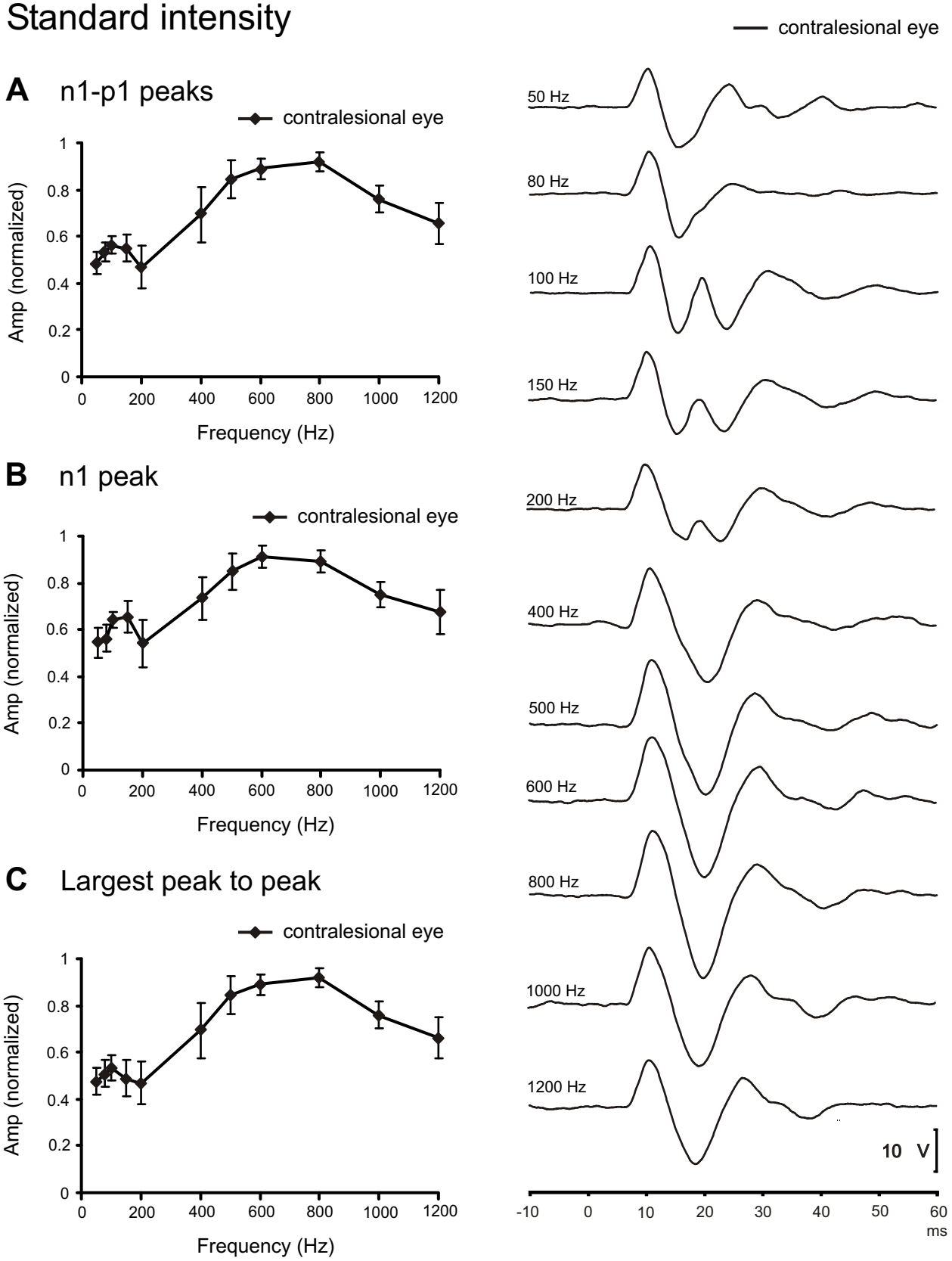
Figure 5: Normalised tuning curves (left column) and grand means (right column) for BC evoked oVEMPs elicited using intensities 10 dB above threshold delivered at the affected mastoid process for the unilateral SCD patients (n = 5). Tuning curves are shown for the n1-p1 (A), n1 peak (B), and largest peak to peak measurements (C). The contralesional and ipsilesional eyes are shown in black and grey respectively. * indicates significantly different normalised response amplitudes ($P < 0.05$). † indicates statistical trend ($P = 0.06 – 0.09$).

Figure 6: BC evoked oVEMP following stimulation of the left mastoid in the patient with bilateral SCD. The upper half shows the responses for both eyes to the standard intensity stimulus (left) and for the lower intensity stimulus (right). The lower half shows the n1-p1 amplitudes normalised to the largest value, for both conditions.

Figure 7: Comparison of tuning effects using n1-p1 raw (left column) and normalised (right column) amplitudes following AC (A) and BC (B) stimulation in the unilateral SCD patients and healthy subjects (HS). For BC stimulation, amplitudes were compared between the contralesional eye in the SCD patients and the contralateral eye following mastoid stimulation for the healthy subjects (contra eye). Similarly, amplitudes were also compared between the ipsilesional eye in SCD patients and the ipsilateral eye following mastoid stimulation in healthy subjects (ipsi eye). * Statistically significant differences between SCD responses (either high or lowered intensity) and those recorded in healthy subjects.

AC oVEMP tuning (SCD)

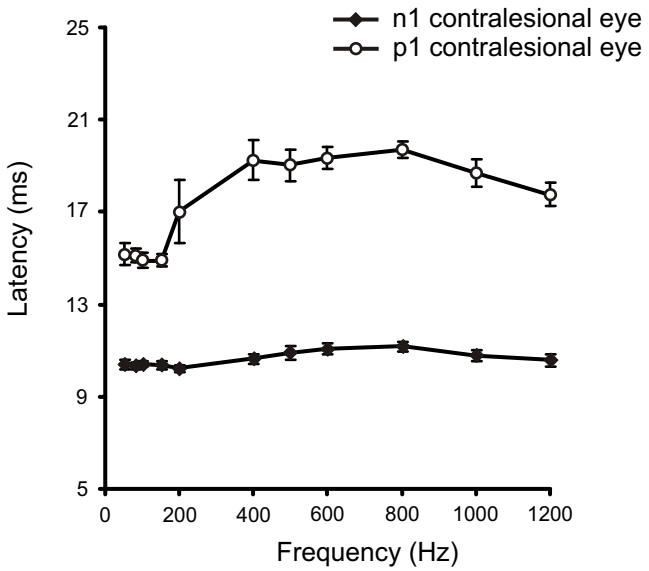
Standard intensity



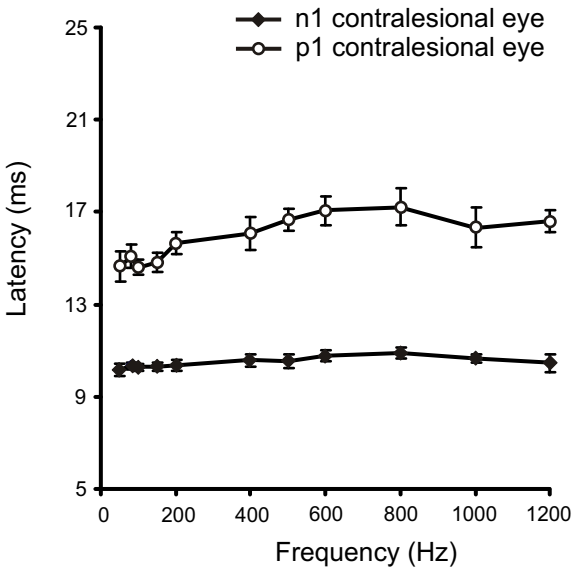
oVEMP latencies (SCD)

A AC stimulation

Standard intensity

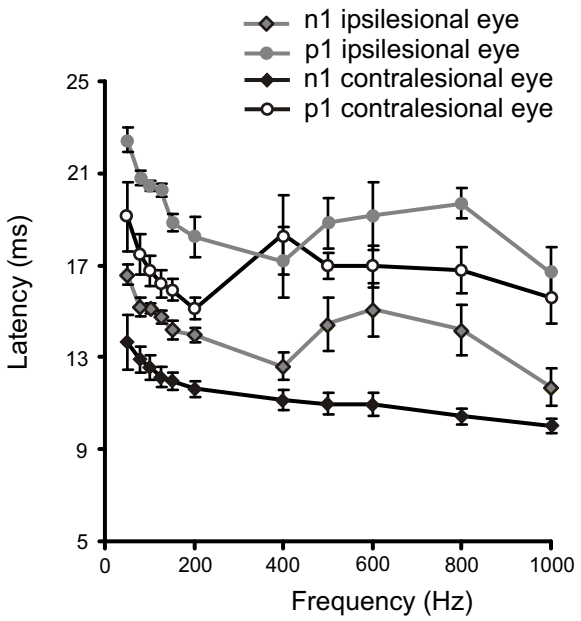


Lowered Intensity

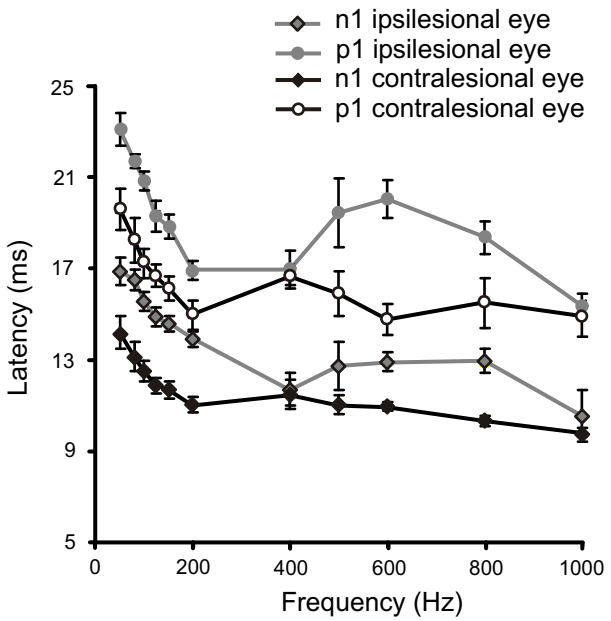


B BC mastoid stimulation

Standard intensity

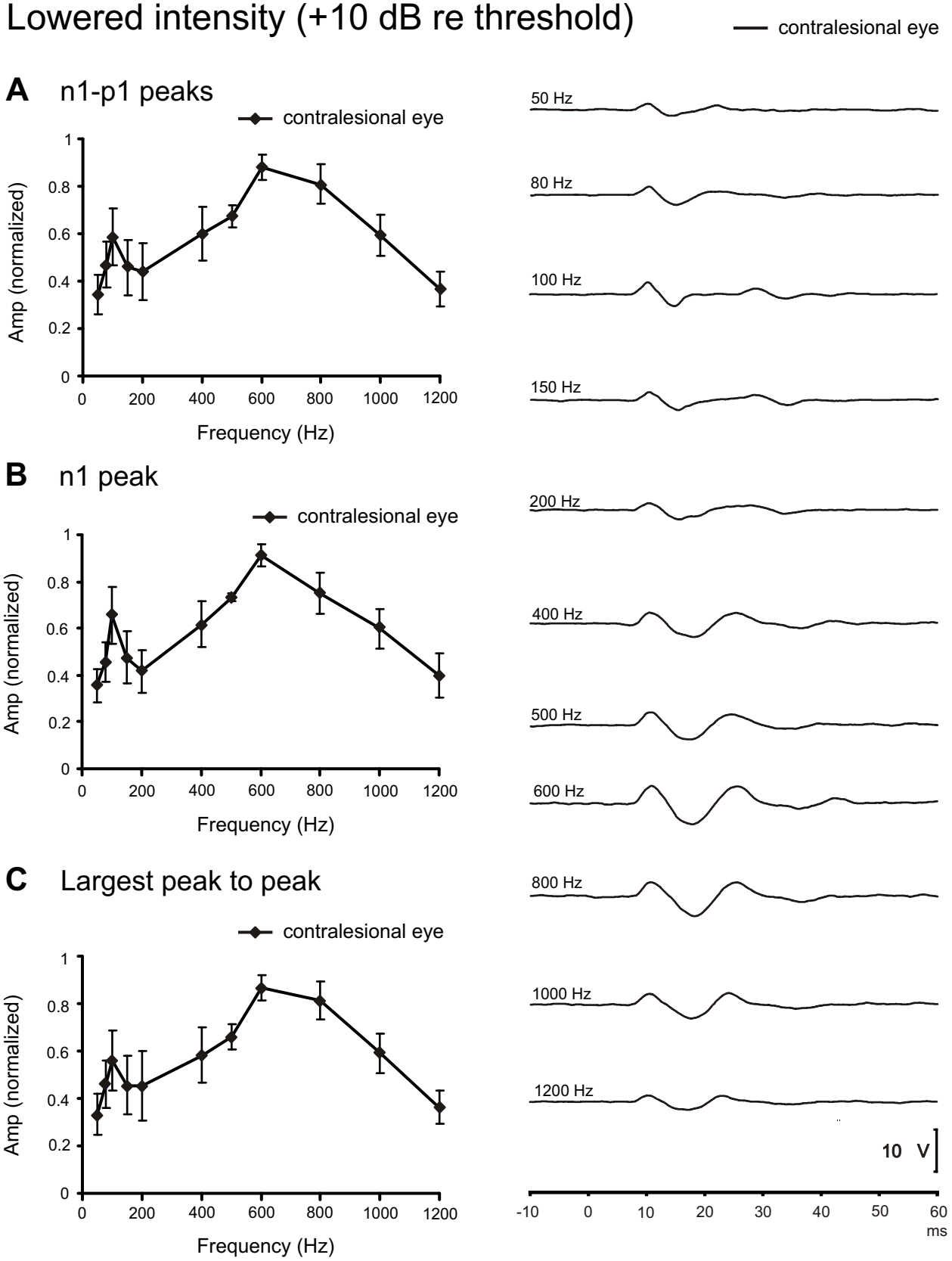


Lowered Intensity



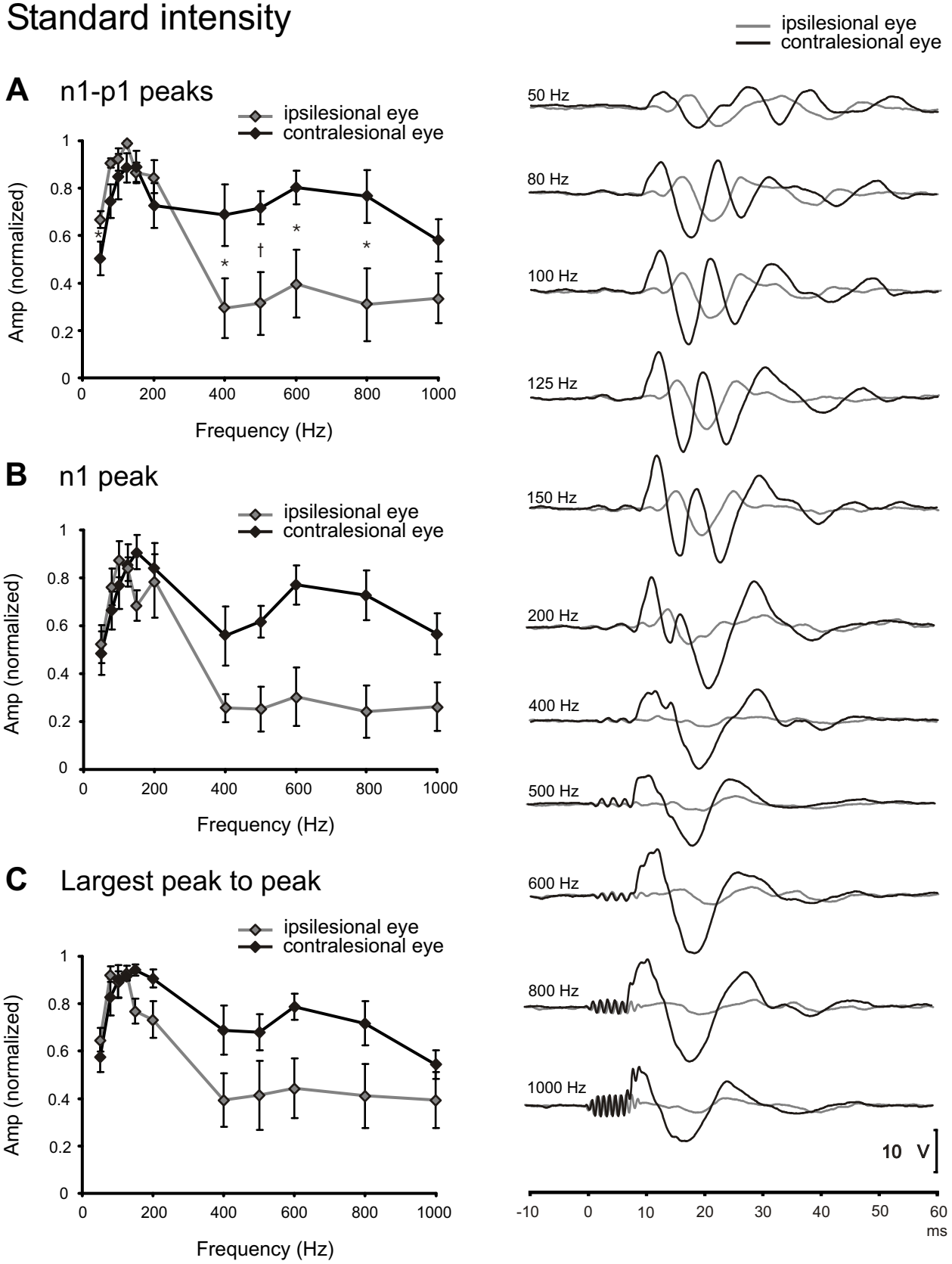
AC oVEMP tuning (SCD)

Lowered intensity (+10 dB re threshold)



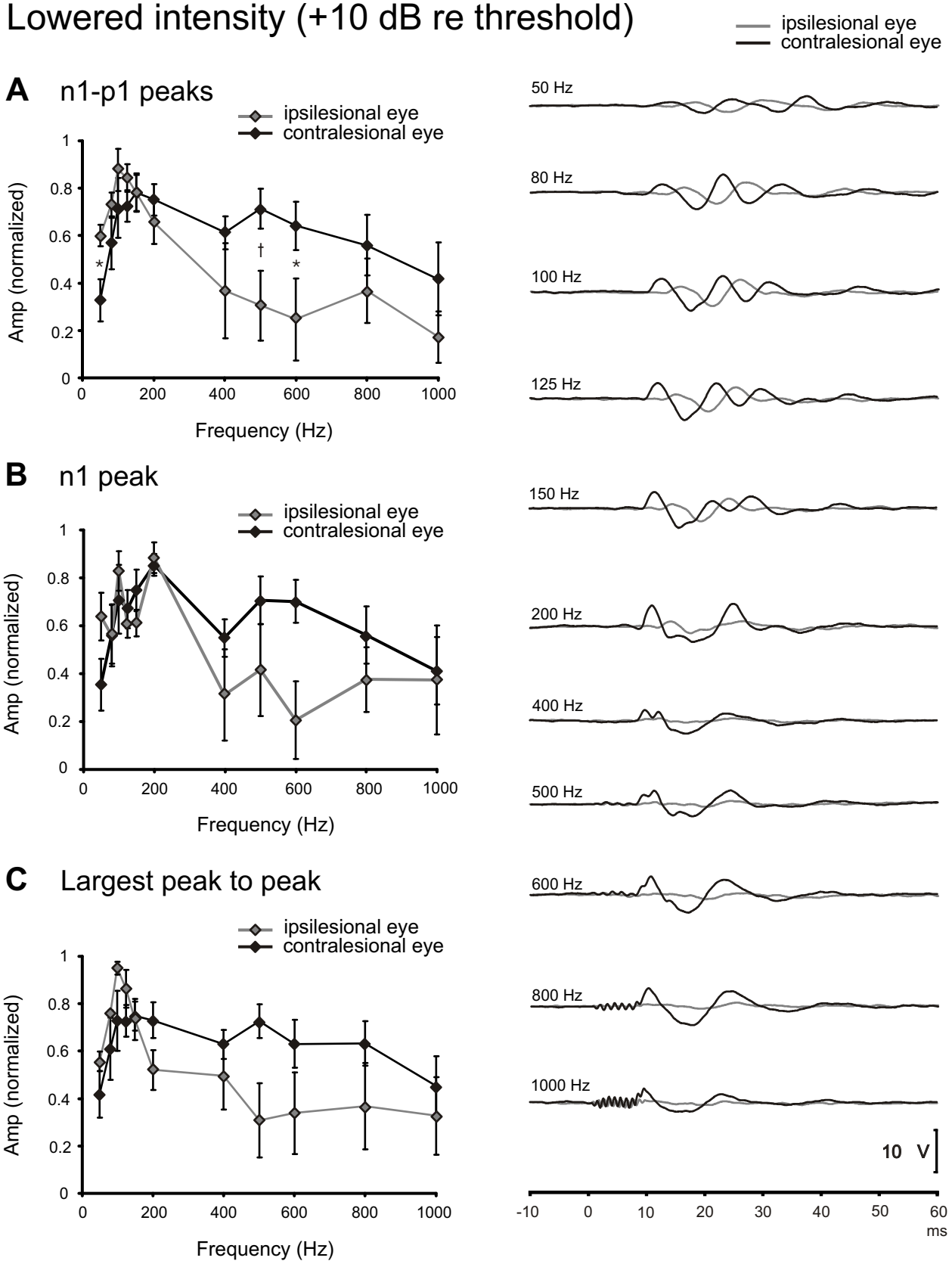
BC oVEMP tuning (SCD)

Standard intensity



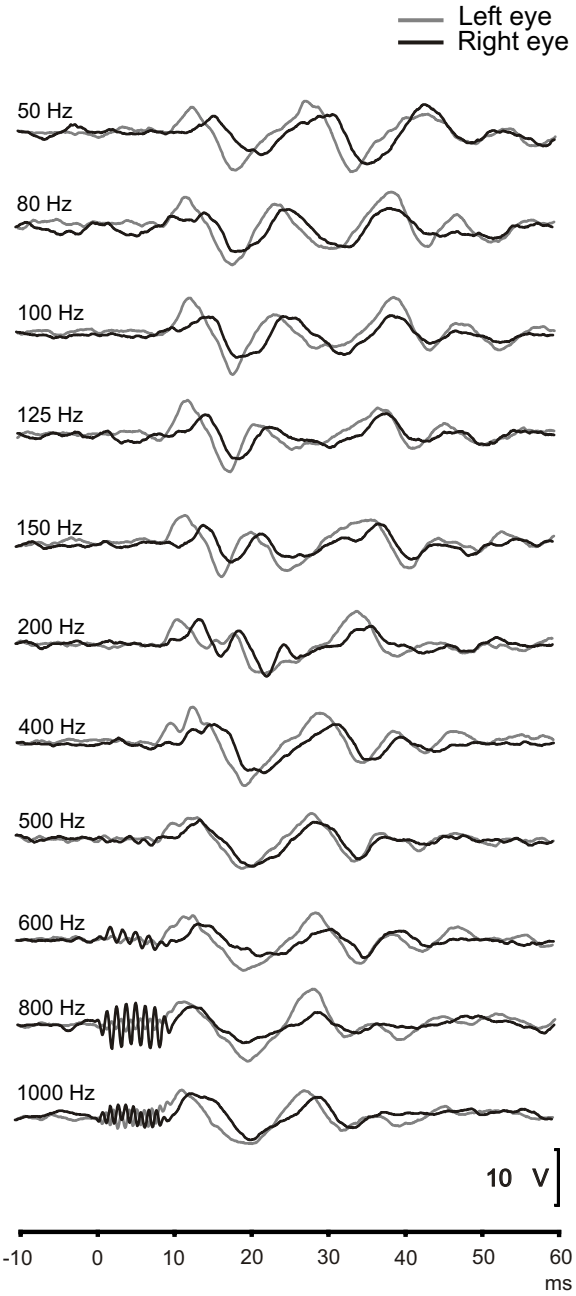
BC oVEMP tuning (SCD)

Lowered intensity (+10 dB re threshold)

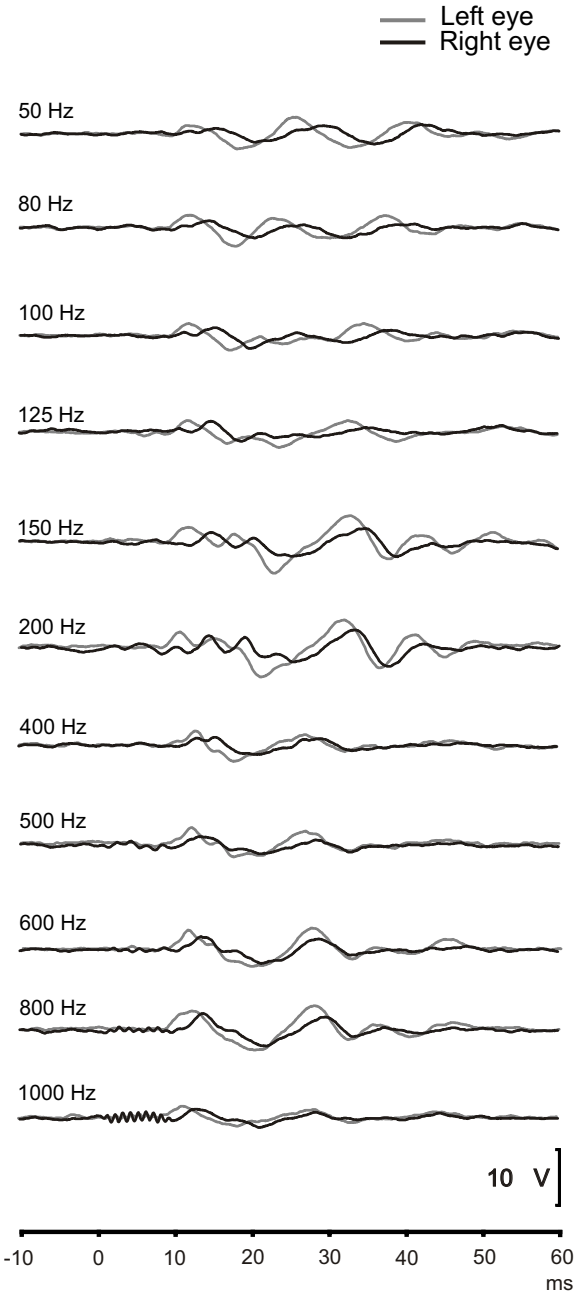


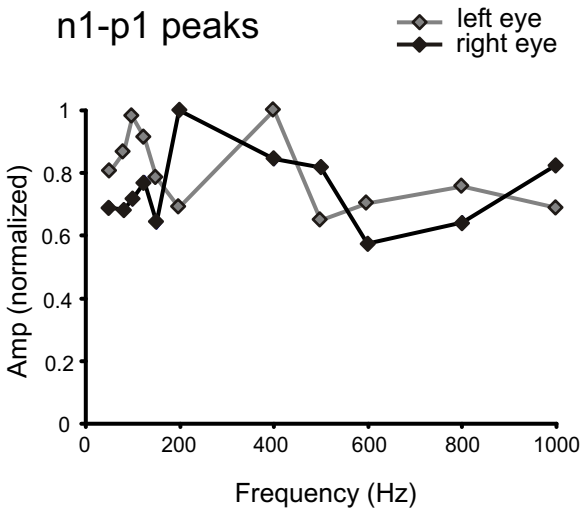
BC oVEMP tuning (Bilateral SCD)

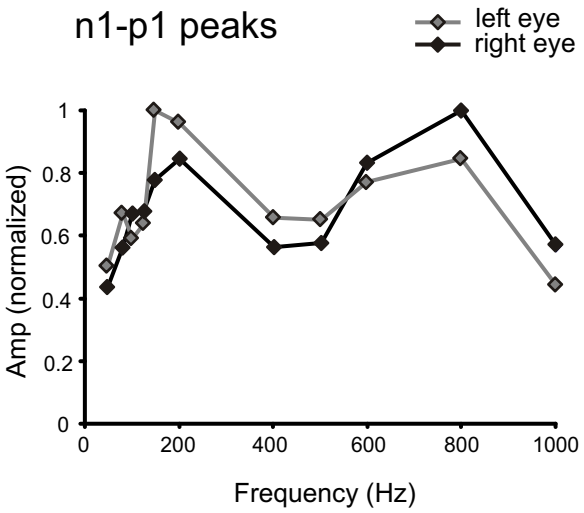
Standard intensity



Lowered Intensity

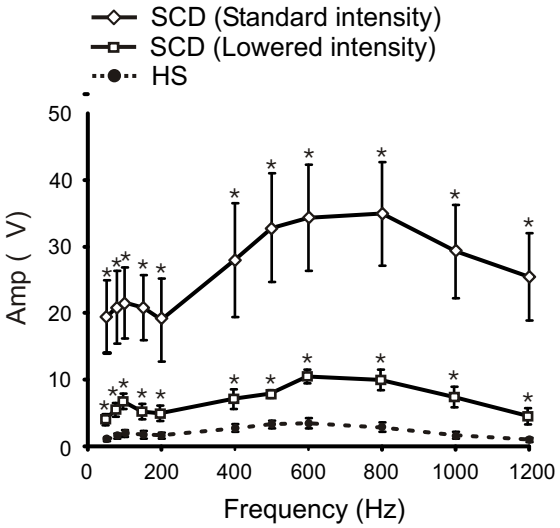


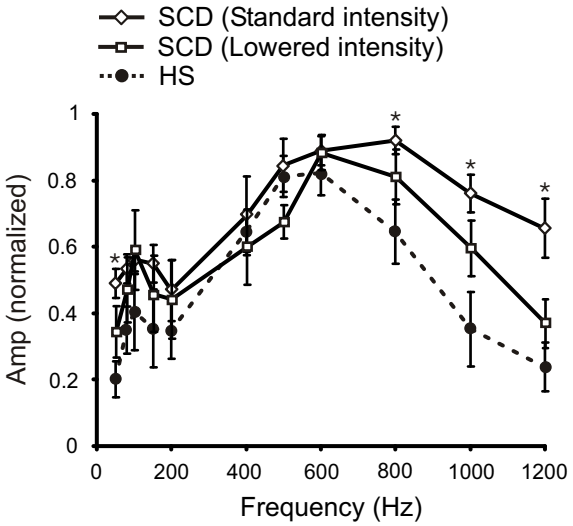




oVEMP tuning (SCD vs healthy subjects)

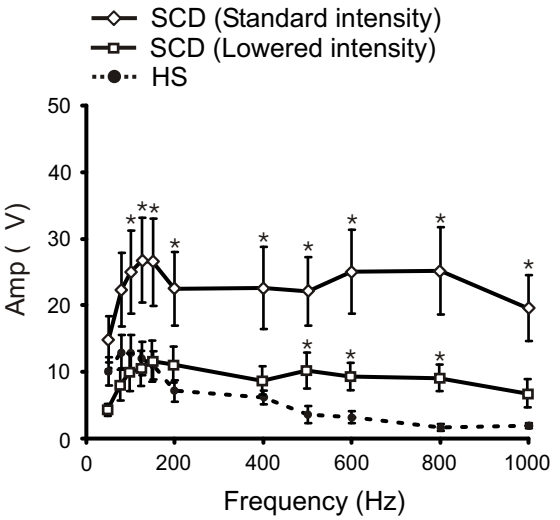
A AC stimulation

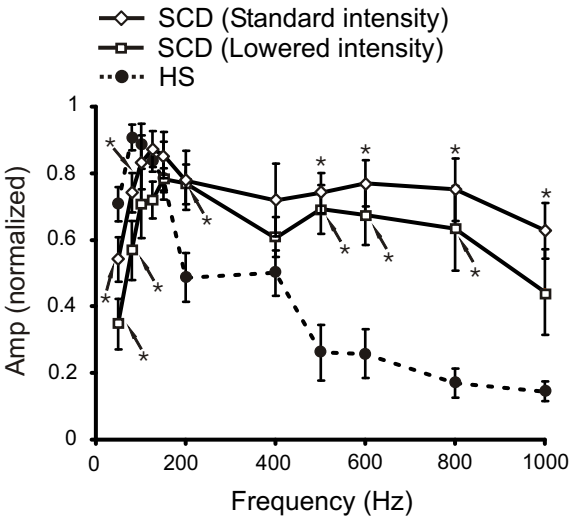




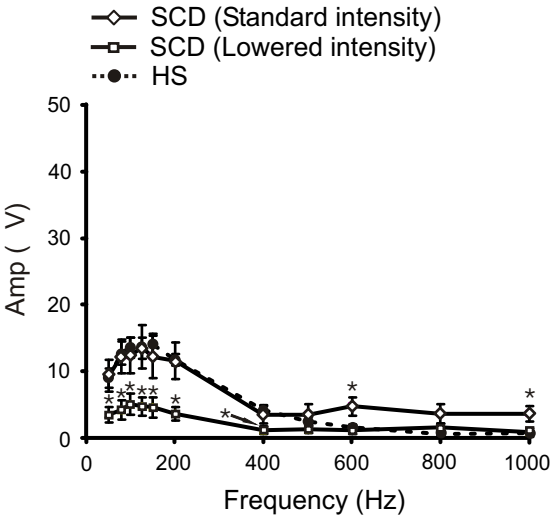
B BC mastoid stimulation

Contra eye





Ipsi eye



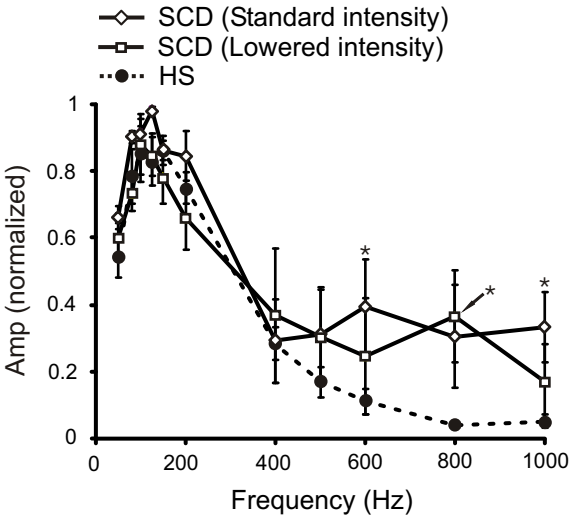


Table 1: Clinical characteristics

Patient	Gender	Age	Dehiscence	Weber's test	Rinne's test	Symptoms	PTA	
							R ear	L ear
P1	M	22	R	Localised to R ear	AC>BC for both ears	Vertigo triggered by loud sounds and pressure changes; Autophony	6.7	11.7
P2*	M	39	L	Localised to L ear	AC>BC for both ears	Vertigo triggered by loud sounds and pressure changes; Autophony; Tinnitus	11.7	20
P3	F	46	Bilateral (L tested)	NA	NA	Vertigo triggered by loud sounds; Autophony	NT	NT
P4	F	49	L	Localised to L ear	AC>BC for both ears	Vertigo triggered by loud sounds and pressure changes; Autophony	8.3	15
P5	F	59	L	Localised to L ear	AC>BC for both ears	Vertigo triggered by loud sounds; Tinnitus	36.7	16.7
P6	M	69	R	Localised to R ear	AC > BC for L ear AC < BC for R ear	Autophony	23.3	18.3

Pure tone audiometry (PTA) results are averaged thresholds from 250 Hz, 500 Hz, and 1000 Hz. NT = not tested. *Preoperative results for this patient have been reported previously (Zhang et al. 2011b)