# Effect of Multi-site Variabilities on Electrovestibulography: Environmental and Physical Factors

## Invited article

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**Abstract:**

***Background*: There are physiological changes in pathologies such as Alzheimer's Disease (AD) within the lower vestibulo-acoustic system, which may be potentially useful when used as neurodegeneration features. We hypothesize two Electrovestibulography feature types (Field Potential (FP) shape and the Firing pattern of detected FP's) may have utility as Neurodegeneration features. Our long term objective is to use a population of Parkinson's Disease (PD), AD, Post-Concussion Syndrome (PCS), Bipolar Disorder (BD) and Major Depressive Disorder (MDD) patients together with individual pathology-wise age and gender matched control cohorts to determine the degree to which each of these pathologies varies from controls and in proportion to the level of Neurodegeneration often associated (either temporarily or permanently) with each pathology. However, before such a comparison can be made it is necessary to ensure the various populations recorded across different countries are comparable. This paper determines which populations are comparable.**

***Methods*: An initial comparison of AD (with N = 16) and a best matched healthy control population (with specific age/gender/recording site/electrode matched controls) from a pool of 112 controls produced two EVestG features (FP shape and FP firing pattern). These features were examined for their variability with respect to electrode type, age, gender, powerline frequency and environmental factors.**

***Results*: Age and gender did not have a significant impact on the features. Powerline and environmental artefacts could be accounted for by filtering; thus, they did not significantly affect the features measured. However, electrode type had a significant effect on the extracted features.**

***Conclusions*: For the two EVestG features tested only electrode type had a significant effect on the recordings, and hence the extracted features. Thus, only populations with the same electrode type can be compared.**

**Keywords:** *Multi-site recording variability, electrodes, powerline frequency, gender, age, Electrovestibulography, biological markers, vestibular.*

## GLOSSARY

| | |
|---|---|
| **AD** | Alzheimer's Disease |
| **Background phase** | 1.5sec EVestG recording immediately prior to motion |
| **EVestG** | Electrovestibulography |
| **EVS** | Efferent Vestibular System |
| **FP** | Field Potential |
| **$IH_{33}1$** | EVestG long window interval firing pattern feature recorded during static (no motion) time |
| **LDA** | Linear Discriminant Analysis |
| **N1, N2** | Negative peaks of compound Action potential |
| **NEER** | Neural Event Extraction Routine |
| **PCS** | Post-Concussion Syndrome |
| **ROC** | Region of Convergence |
| **Sh1** | Background (no motion) shape feature |
| **VN** | Vestibular Nucleus |

## I. INTRODUCTION

In studies care is taken to match age, gender, recording methodology and environmental factors (e.g. powerline frequency). This is even more important when comparing populations recorded in multi-site studies, wherein there are differences that can be potentially very difficult to control for such as powerline frequency (artefacts). Electrovestibulography (EVestG) is a non-invasive measure from the vestibulo-acoustic system in both background (no motion)

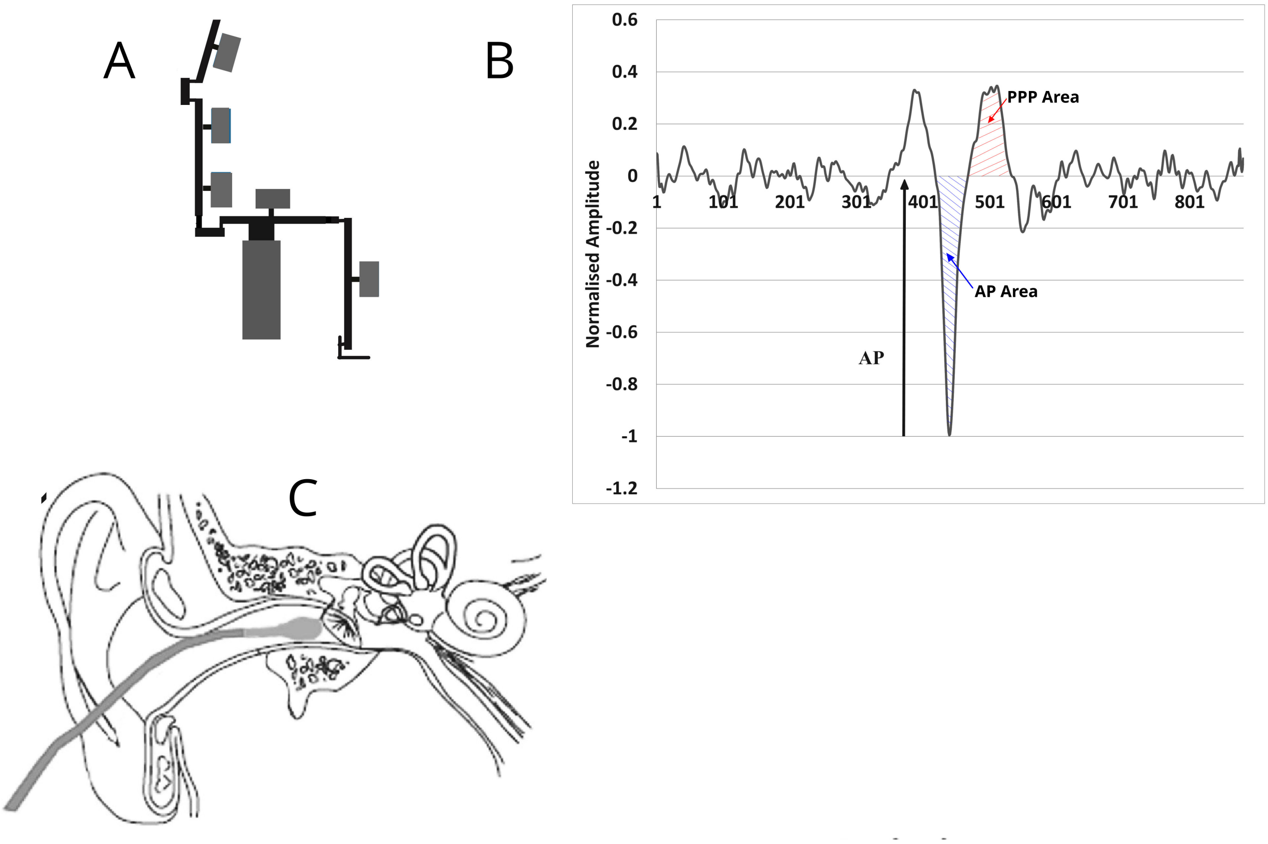


Figure 1: EVestG Methodology: (A) EVestG chair; (B) Example averaged field potential (FP) showing the AP and PPP areas (horizontal scale is in samples (41.67 kHz)); (C) Ear canal electrode placement, a reference is placed on the earlobe or outer ear canal, a common ground silver/silver chloride electrode is placed on the forehead.

and/or in response to passive whole-body tilt [1–3] stimuli. There is evidence that the EVestG responses are vestibulo-acoustic and predominantly vestibular [1–5]. EVestG assessment has been applied to the detection of a number of pathologies including Alzheimer's Disease (AD) [5], Parkinson's Disease (PD) [6], Post-Concussion Syndrome (PCS [7–9], Vertiginous disorders [10–12], Major Depressive Disorder (MDD) [2], non-manic Bipolar Disorder [1] and the separation of Bipolar and MDD [13]. In previous studies we have collected Electrovestibulography recording data from Parkinson's Disease (PD), Alzheimer Disease (AD), Post-Concussion Syndrome (PCS), Major Depression and Bipolar Depression populations as well as a pool of healthy controls ($N$ = 117). These were recorded across two sites (Australia and Canada), each with different powerline frequencies, slightly different equipment setups, different age groups and gender ratios, and also quite different recording electrodes (BiopacTM versus soft cotton-wool electrodes). In this study, we aim to determine which populations are or can be made directly comparable for the two EVestG main feature types that we commonly measure and apply in neurodegeneration studies.

In our recent neurodegeneration studies (i.e. Parkinsons, PCS, AD) we have commonly used two feature types. Those features types are the average extracted field potential shape and the pattern of occurrence of the detected field potentials. The results have been quite promising with accuracies above 80%. These feature types have been hypothesized to be representatives of channelopathies and neurotransmitter changes.

**Alzheimer's Disease (AD) and EVestG**: In a recent study [7], one feature of the EVestG response used to identify post-concussion syndrome (PCS) individuals from age-and-gender-matched healthy individuals with an 84% leave-one-out cross-validated test accuracy (ROC = 84%) was the shape of the average Field Potential (FP) signal. This feature was hypothesized to be linked to channelopathies. A recent study suggests the existence of a time- and dose-dependent risk of developing dementia more than 30 years after Traumatic Brain Injury (TBI); the risk being higher for more severe and multiple TBIs than for single mild TBI [14]. These ideas were carried forward in a pilot AD study using EVestG [5]. In that AD study the EVestG features used were developed based on:

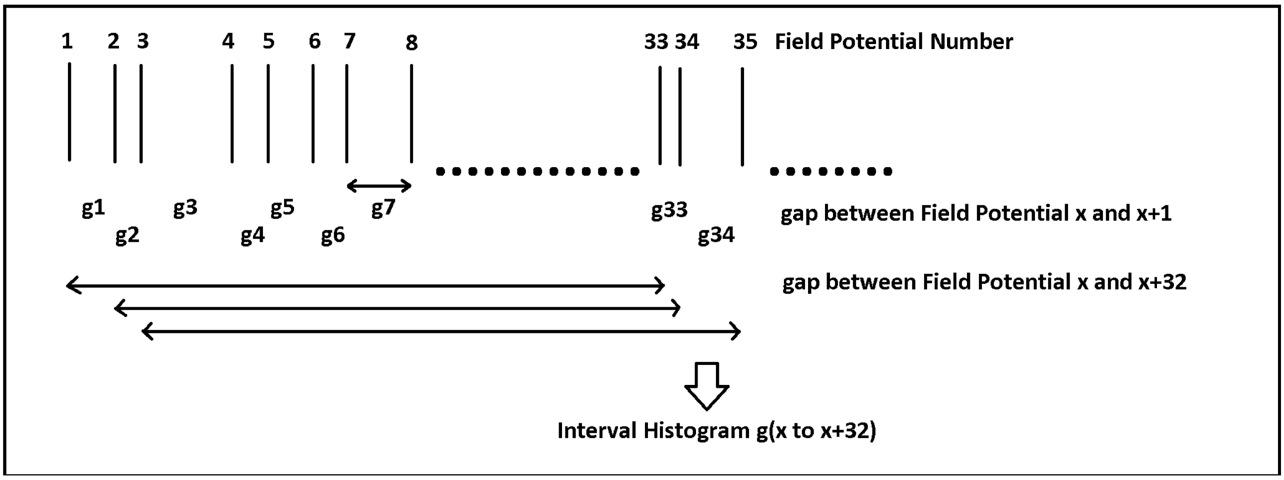


Figure 2: $IH_{33}$ formation.

1) A link between the amyloid precursor protein and an increase in the surface expression of some voltage dependent Na+ channels [15]. Thus, one AD classification/detection feature should search for FP shape changes relevant to an increase in the number of Na+ channels; this was hypothesized to be and then shown to appear as a steeper descending arm in the average EVestG AP part (Figure 1B) of the recorded FP in AD patients.
2) The contribution of GABAergic dysfunction to AD is known or suspected [16, 17]. Cortes, 2013 suggests GABA could act as a facilitator in the spontaneous discharge of the vestibular afferents by altering intracellular Ca++ concentration [18, 19]. Reduced GABA then may lead to a de-facilitation in spontaneous (and driven) discharge. Thus, a feature sensitive to firing pattern changes was hypothesized and then shown to be a sensitive second AD biomarker [5].

Thus, there are physiological changes in AD within the lower vestibulo-acoustic system [5], which might be potentially useful as Neurodegeneration features. We have hypothesized the two EVestG feature types (FP shape and FP firing pattern) may have utility as neurodegeneration features. Our focus herein is to use these two features initially derived from a comparison of an AD patient population with its best matched healthy control population and examine those features for age/gender/recording site/electrode type variability using best matched healthy subgroups from our pool of 112 controls. This will allow us to determine which previously recorded neurodegenerative populations are directly comparable for the two EVestG feature types that have been commonly measured and applied to neurodegeneration detection studies.

## II. Methods

The detailed methodology for EVestG recordings is given in [1–3, 9]. Briefly, EVestG recordings are made inside an electromagnetically shielded and sound attenuated (greater than 30dB) chamber. To minimize movement artefacts subjects are positioned in a sitting position on a hydraulic chair. During EVestG recordings participants have their eyes closed and are in a relaxed state with their neck supported. A gelled wick electrode is positioned close to the tympanic membrane (Figure 1C). Recordings analyzed herein were made with each subject stationary. Each trial is repeated twice, the first trial is for subject familiarization and data from the second trial recorded. The subject remains passive with closed eyes, and is not required to interact cognitively during the measurement. A background recording of spontaneous activity 1.5sec immediately prior to any potential chair's movement is considered as the static phase response. Only static recordings were used in this study.

The Neural Event Extraction Routine (NEER-V4) [3] averages the detected spontaneous field potentials (FPs) to produce an average FP plot (e.g. Fig. 1B) and generate a firing pattern interval histogram ($IH_{33}$) of the FP occurrence times. These intervals were calculated as shown in Figure 2. The $IH_{33}$ plot represents low frequency ( 10Hz) modulations of detected spontaneous FP interval activity, as hypothesized [2] to occur in response to efferent and or EEG (potentially $\alpha$ band) activity. Spontaneous vestibular efferent activity is seen at 10 – 50 spikes/sec [20] and the $\alpha$ band is 8 – 13 Hz. Average interval histograms were generated based on every $33^{rd}$ FP gap ($IH_{33}$). A 33 FP gap corresponds to about 100ms (10Hz) and the lower range of any hypothesized potential efferent/$\alpha$ band modulatory

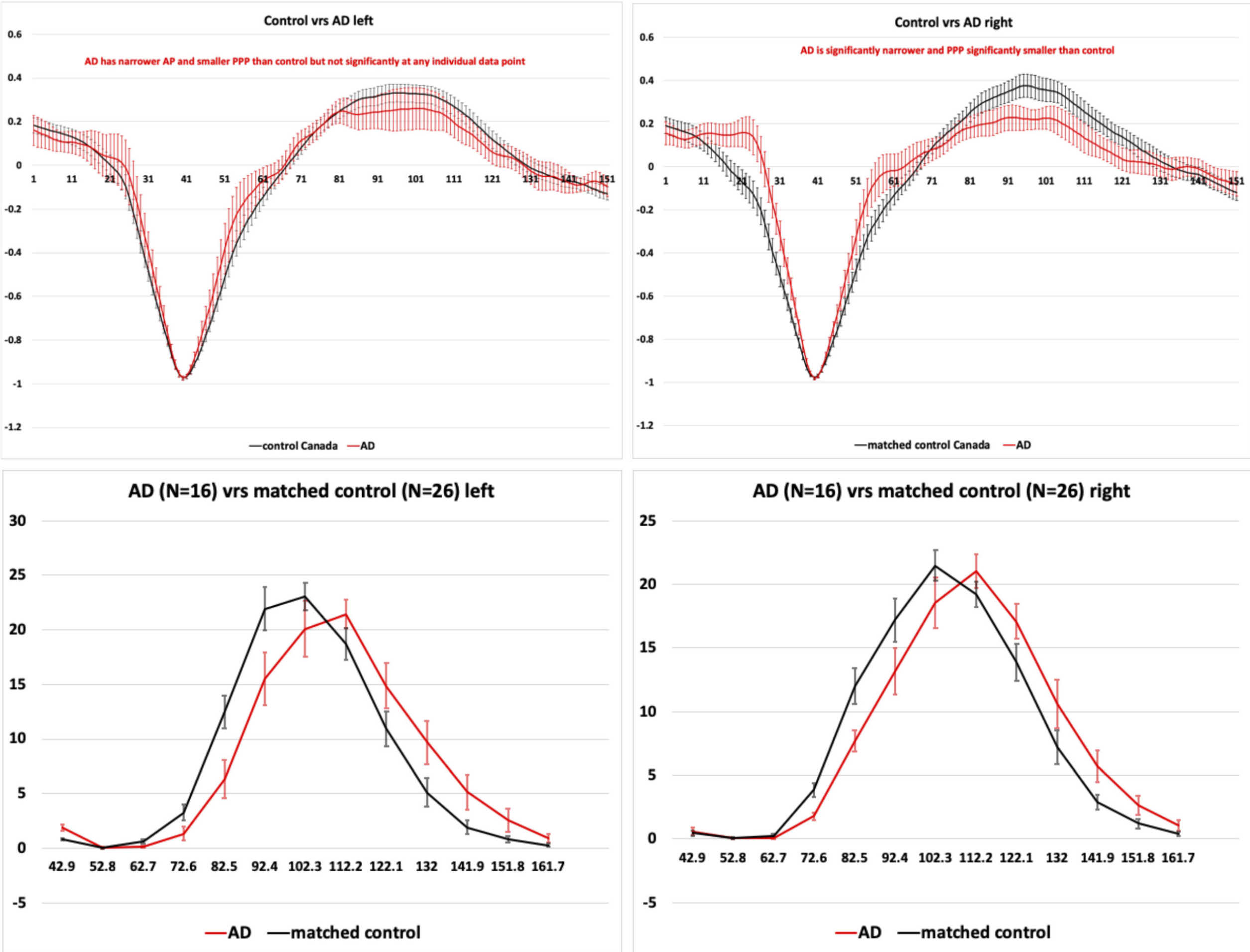


Figure 3: AD versus matched control data (95% error bars). Upper plots are average FP responses for left and right sides. Lower plots are $IH_{33}$1 responses for left and right sides. Best match means matched electrodes, age, gender, site frequency etc.

burst firing effect as the average experimentally detected gap measured with NEER was 3.3ms. Figure 3 shows an example $IH_{33}$ plot. SPSS Version 24 software (IBM, New York, NY, USA) was used for statistical analysis. Statistical significance ($p$-value) was set at 0.05 unless specified.

**Study cross-compatibility**

The data recorded in Australia was with a powerline frequency of 50Hz and hydraulic jitter frequency (HJF) of 940 or 1024 Hz. HJF is the frequency at which the hydraulic controller used in controlled tilts of the chair is applied to prevent "sticking" of the piston between and during motion. Comparatively, the data recorded in Canada was with a powerline frequency of 60Hz and HJF of 980Hz. Within NEER-V4 notch filtering was applied at all odd powerline harmonics and at multiples of the HJF up to 4500Hz. This ensured best match of responses across sites. The AD population were all recorded in Canada, and included 16 individuals (with 9 females, age: 66.7 ± 10.1 (SD), MOCA = 13.4 ± 5.7). The control population demographics were: Australia, $N$ = 57, Age = 46.7 ± 15.5yrs (SD), 29 Females; Canada, $N$ = 54, Age = 53.0 ± 18.2yrs (SD), 29 Females. The Australian site used Sanibel$^{TM}$ in the ear recording electrodes (Figure 4), had multiple of 50Hz powerline notch filters and a hydraulic artefact frequency of 1024 or 940 Hz (selected automatically). The Canada site used both Sanibel$^{TM}$ and cotton wool (in house) in the ear recording electrodes (Figure 4), had multiple of 60Hz powerline notch filters and a hydraulic artefact frequency of 980 Hz.

## III. Results

### 1. AD versus Control Feature formation

It was hypothesized that the AD response relative to the other neurodegenerative pathologies would be most different from best matched controls if the features used

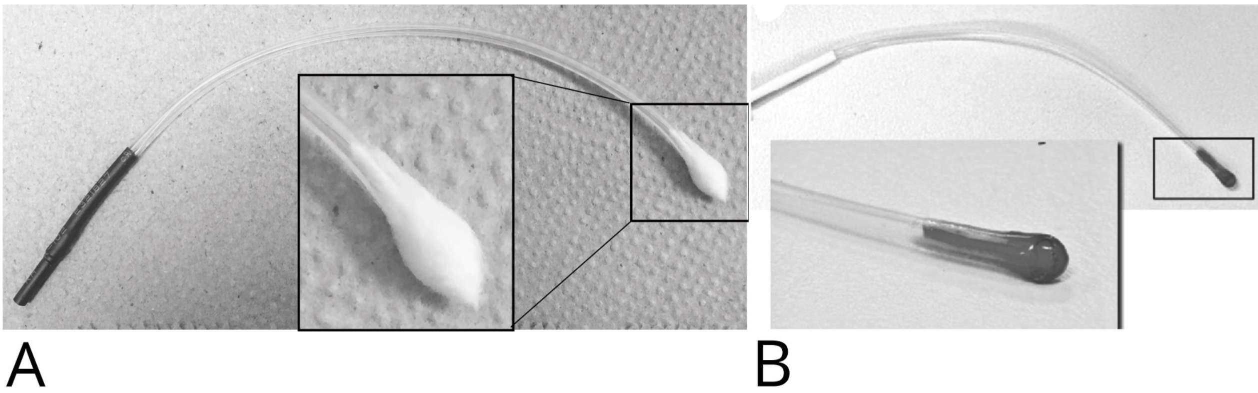


Figure 4: Electrode Types: (left) In-house Cotton-wool tipped soaked in saline and conductive Gel; (right) TM ECochG Electrode, Sanibel.

were neurodegenerative in nature. Examination of the FP response for AD ($N = 16$) and best matched controls ($N = 26$) (Figure 3A) showed not only the Action potential (AP) area as significantly smaller (narrower) but also the Post-Potential Peak (PPP see Figure 1B) area. Accordingly, these combined areas were chosen as a feature Sh1. Arguing similarly, the AD $IH_{33}$ should be most different from matched controls. Examination of the AD $IH_{33}$ plot shows a marked shift to the right (Figure 3B) relative to matched controls. This shift was chosen as feature $IH_{33}1$.

**Shape (Sh1)**- Average Sh1 data for AD versus control groups were found to have significantly ($p < 0.05$) smaller AP and PPP areas on both the left and right sides useful in characterizing populations (Figure 3A). The area of the AP plus PPP was calculated as the area between the baseline ($y = 0$) and the AP plus the area between the baseline and PPP (Figure 1B). For AD the Figure 3 upper plots show a narrowing in the AP and PPP areas on both the left and right sides with the right side displaying significant pointwise differences. The Figure 3 lower plots show a significant rightward shift for the right and left sides for AD relative to matched controls.

For AD versus matched control classification accuracy using the 2 right side features Sh1 and $IH_{33}1$, the one-way MANOVA revealed a significant multivariate main effect (Wilkes $\lambda = 0.687$, $F(2,39) = 8.869$, $p = 0.001$, partial $\eta^2 = 0.313$, power= 0.961). The hypothesis that the interaction of features Sh1 and $IH_{33}1$ has a significant effect on the classification of AD from matched controls is confirmed. The Boxes M test for homogeneity of covariances ($p = 0.206$) and the Levene's test for equality of variances ($p = 0.601$_Sh1, $p = 0.526$_$IH_{33}1$) were not significant. Given the significance of the overall test, the univariate main effects were examined. Significant univariate main effects were obtained supporting features Sh1 and $IH_{33}1$ being applied to AD versus matched control classification: feature Sh1 $F(1,40) = 13.393$, $p = 0.001$, $\eta^2 = 0.259$, power = 0.954; and feature $IH_{33}$ $F(1,40) = 16.853$, $p < 0.001$, $\eta^2 = 0.296$, power = 0.980.

**2. Site Comparability Using Best Matched Controls**

*1) Comparison of electrode types:* At the Canada site, it was determined the signal to noise ratio of the EVestG recording was markedly improved by using impedance matched electrodes [21]. For this reason, in-house made cotton wool (active in the ear and reference earlobe/outer ear canal) electrodes (Figure 4) replaced the previously used higher impedance and impedance mismatched Sanibel/Biopac electrode combinations for recording. The in-house ear electrodes were silastic wrapped silver wire with the tip covered in cotton wool soaked in a mixture of saline and conductive gel to reduce interface impedance. Biopac electrodes (in the ear-TM ECochG Electrode, Sanibel (Figure 4) earlobe reference Biopac silver-silver chloride 4mm, EL254) were exclusively used at the Australian site as these, date wise, were the first EVestG recordings. At the Canada site we could compare the responses of the two electrode types.

Figure 5 clearly shows the response of the cottonwool electrodes ($N = 17$ left, $N = 17$ right) is narrower in the AP and PPP than that of the Sanibel electrodes ($N = 17$ left, $N = 17$ right) for the Canada site. The narrowing was significant ($p < 0.05$) on the right in both the AP and PPP areas. The yellow ellipses mark regions of significant difference. The populations were age (Sanibel, $58.7 \pm 4.3$ (SD), cotton wool, $54.7 \pm 12.6$yrs ) and gender (11F, 10F) matched. Accordingly, comparisons should be made only between common electrode types.

Figure 6 shows the Cottonwool ($54.7 \pm 4.3$yrs, $N = 17$, and 10F) compared to the Sanibel ($58.7 \pm 12.7$yrs, $N = 17$, and 11F) age and gender matched responses from the same

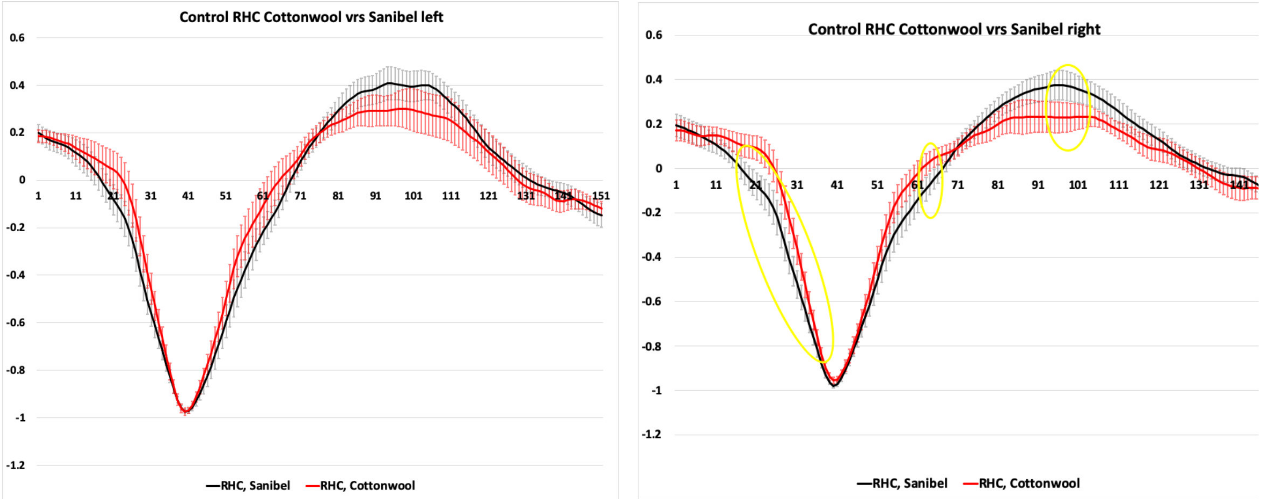


Figure 5: FP response: AP plus PPP area shape response at the Canada site comparing the Sanibel and in-house cottonwool electrodes. 95% Confidence bars are overlaid. Sample number is on the horizontal axis (44.1 samples/ms). Vertical axis is the normalised magnitude.

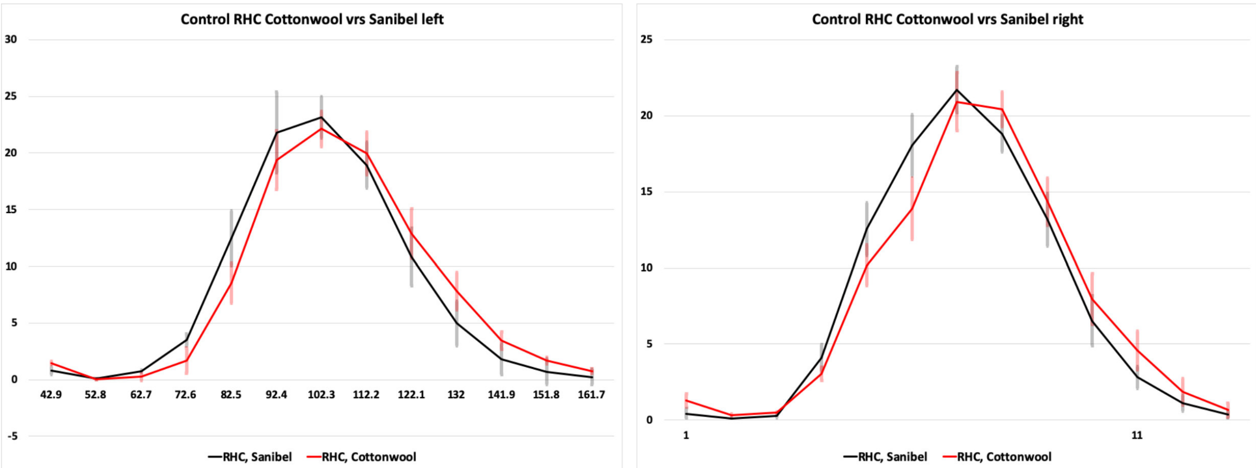


Figure 6: IH33 response at the Canada site comparing Cottonwool ($N$ = 17) and Biopac ($N$ = 17) age and gender matched responses. 95% Confidence bars are overlaid. The horizontal axis is in ms. Vertical axis is population percentage.

(Canada) site on the left or right side are right shifted. A yellow ellipse marks a bin of significant difference. Accordingly, comparisons should be made only between populations with matched electrode types.

*2) Gender matching:* Figure 7 shows the female response ($N$ = 24 female left and right) is marginally but not significantly narrower than that of the comparable male ($N$ = 24 male left and right) response at the same (Australian) site. The populations were age and electrode type matched. Ideally, comparisons should be made only between male or female types but as the difference is not significant gender is considered not a major factor for AP area herein. However, gender matching for combined male/female populations should be applied when possible.

Figure 8 shows the age matched male and female responses at the same Australian site and with same electrode type on the left side are very similar ($N$ = 24). The right response shows the female population with a slightly broader response, a small right shift and lower peak value however, these differences are not significant. Ideally, comparisons should be made only between gender matched types but as the difference is not significant gender is considered not a major factor for the $IH_{33}$ plots herein. However, gender matching should be applied when possible.

*3) Age matching:* Figure 9 shows the older (greater than 51 years old) and younger responses at the same site with the same electrode type on the left and right side are very similar ($N$ = 23, 11F). The age division was determined

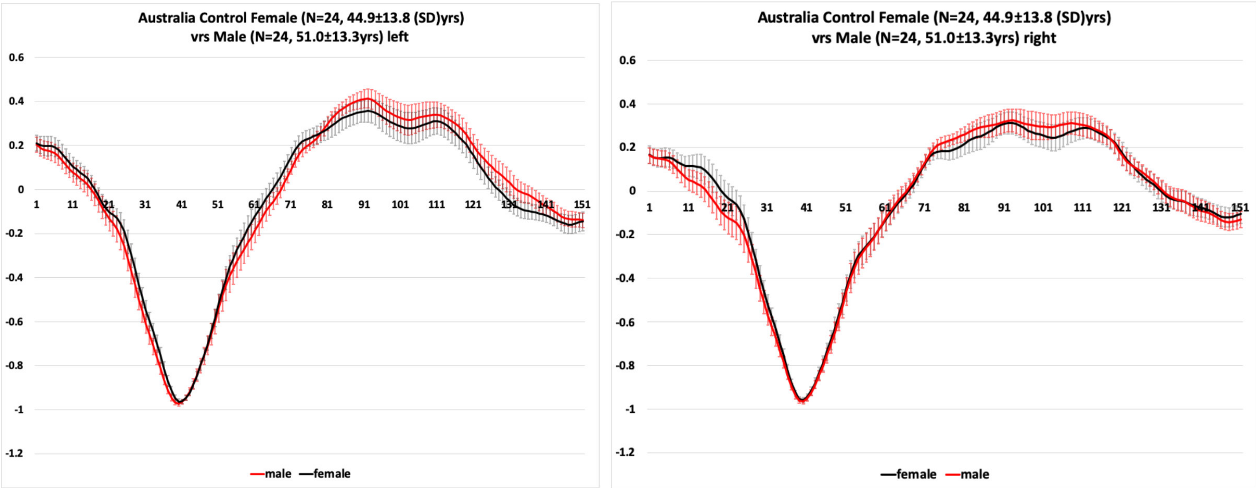


Figure 7: AP plus PPP shape response at the Australia site comparing male and female responses. 95% Confidence bars are overlaid. Sample number is on the horizontal axis (44.1 samples/ms). Vertical axis is normalised magnitude.

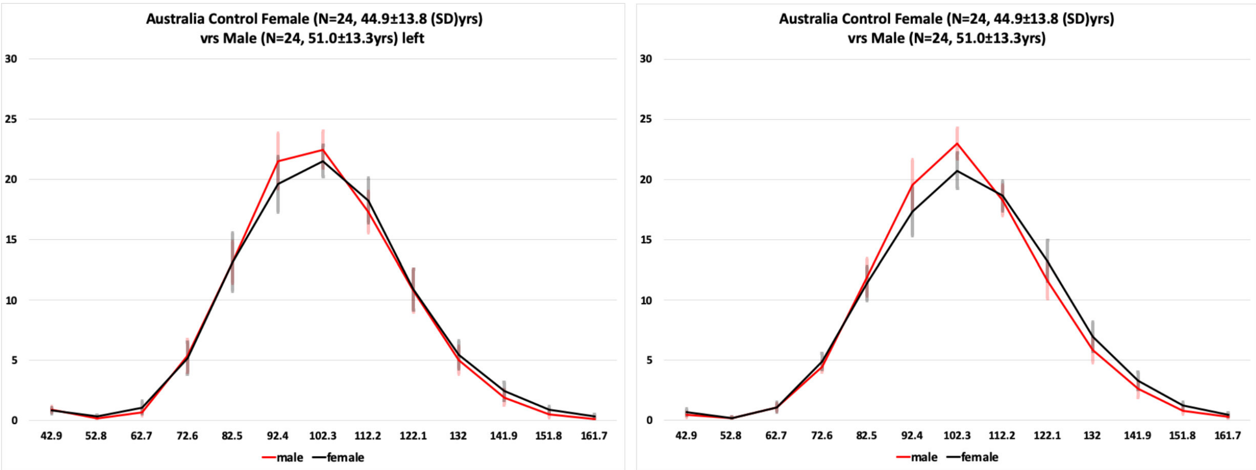


Figure 8: IH33 response at the Australia site comparing male ($N$ = 24) and female ($N$ = 24) responses. 95% Confidence bars are overlaid. The horizontal axis is in ms. Vertical axis is population percentage.

by the available population and approximate halving of that population. The right response shows the older population with a slightly narrower (smaller AP and PPP area) response but this is not significant. Ideally, comparisons should be made only between age matched types but as the difference is not significant age is considered not a major factor for AP area herein. However, age matching should be applied when possible.

Figure 10 shows the older and younger responses at the same site and with same electrode type on the right side are very similar ($N$ = 24, 11F). The left response shows the older population with a slightly broader response and lower peak value however, these differences are not significant. The older responses are very marginally right shifted. Ideally, comparisons should be made only between age matched types but as the difference is not significant age is considered not a major factor for the IH33 plots herein. However, age matching should be applied when possible.

*4) Site comparison (50 versus 60 Hz and 940/1024 versus 940Hz hydraulic artefact removal):* Figure 11 shows the Australian ($N$ = 36, 22F) and Canadian ($N$ = 20, 13F) site responses for a control population that is age, electrode type (Sanibel) and gender matched are, on the left side and right side similar. The right response shows the Australian site with a marginally narrower (smaller AP and PPP area) response but this is not significant. Ideally, comparisons should be made only between populations from the same site but when comparing studies this is not possible. Site differences for age and gender matched populations recorded with the same electrode type appear minor.

Figure 12 shows the Australian and Canadian age and gender matched responses with same electrode type (Sani-

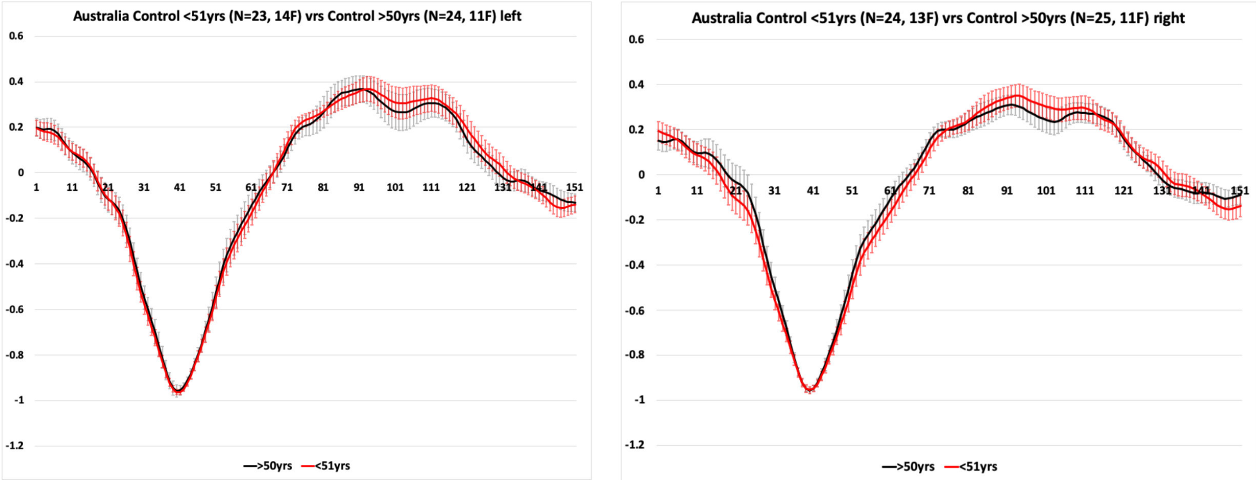


Figure 9: AP plus PPP shape response at the Australia site comparing older (greater than 50yrs) and younger (less than 51yrs) responses. 95% Confidence bars are overlaid. Sample number is on the horizontal axis (44.1 samples/ms). Vertical axis is normalised magnitude.

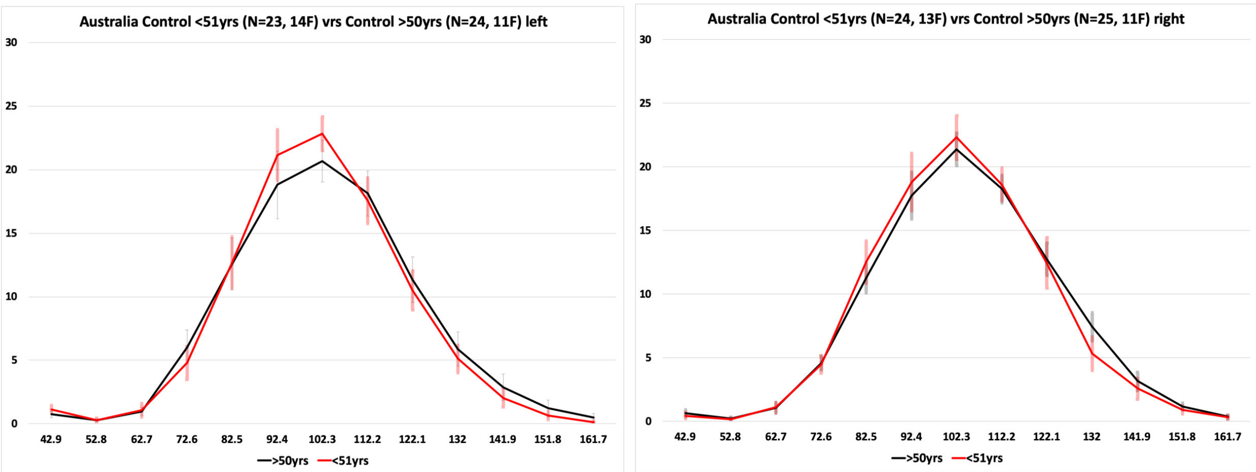


Figure 10: IH33 response at the Australia site comparing older (greater than 50yrs) and younger (less than 51yrs) responses. 95% Confidence bars are overlaid. The horizontal axis is in ms. Vertical axis is population percentage.

bel) on the right side are very similar. The left response shows the Australian population with a slightly broader response and lower peak value however, these differences are not significant. There is no rightward shift of populations. Ideally, comparisons should be made only between age and gender matched types from the same site but as the difference is not significant site is considered not a major factor for the $IH_{33}$ plots herein. However, within site comparisons should be applied when possible.

## IV. Discussion

Figure 3 shows significant features can be derived; thus, it is possible to distinguish AD population from best matched healthy controls. On the other hand, Figure 5 and Figure 6 show the comparative effects on healthy controls of using different electrode types at the same site (Canada) can be significant; hence, the need for any subsequent comparisons only to be between the recordings with the same electrode types. The Sanibel™ FP response (Figure 5) has more low frequency content relative to that of the in-house cotton-wool electrode on both right and left sides. The Sanibel™ $IH_{33}$ response (Figure 6) is left shifted relative to that of the in-house cotton wool electrode on both right (significant different bin marked with a yellow ellipse) and left sides.

It is interesting to ask why the electrode type should affect IH detection. Perhaps there is more noise detected with the Sanibel electrode configuration; that is likely as the SNR was improved significantly with matched cotton wool electrode configuration [21]. Figures 7-12 show the effect

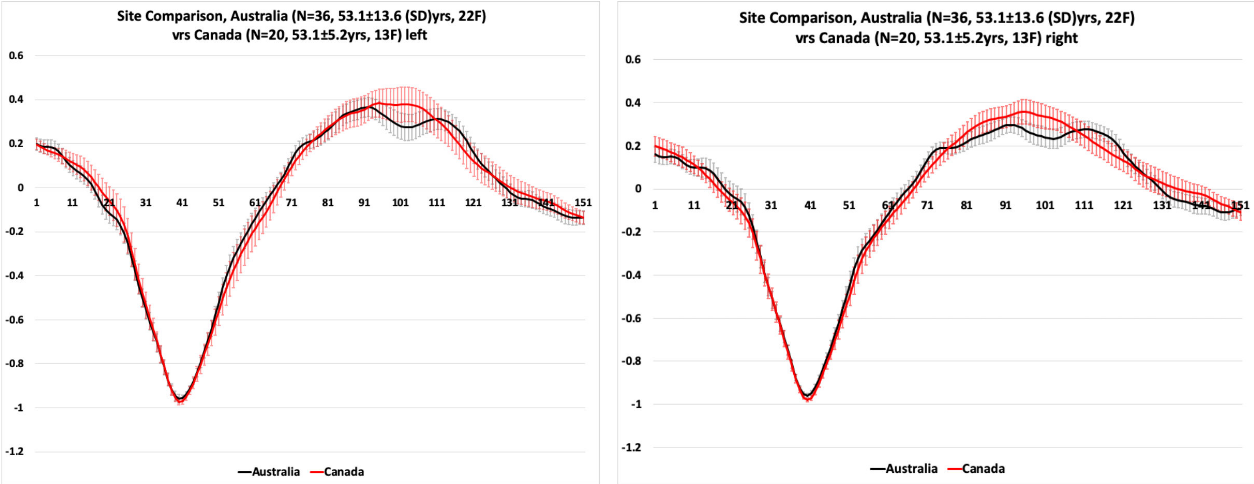


Figure 11: Left and Rightside AP plus PPP shape response at the Australia site compared with the Canada site. 95% Confidence bars are overlaid. Sample number on the horizontal axis (44.1 samples/ms). Vertical axis is normalised magnitude.

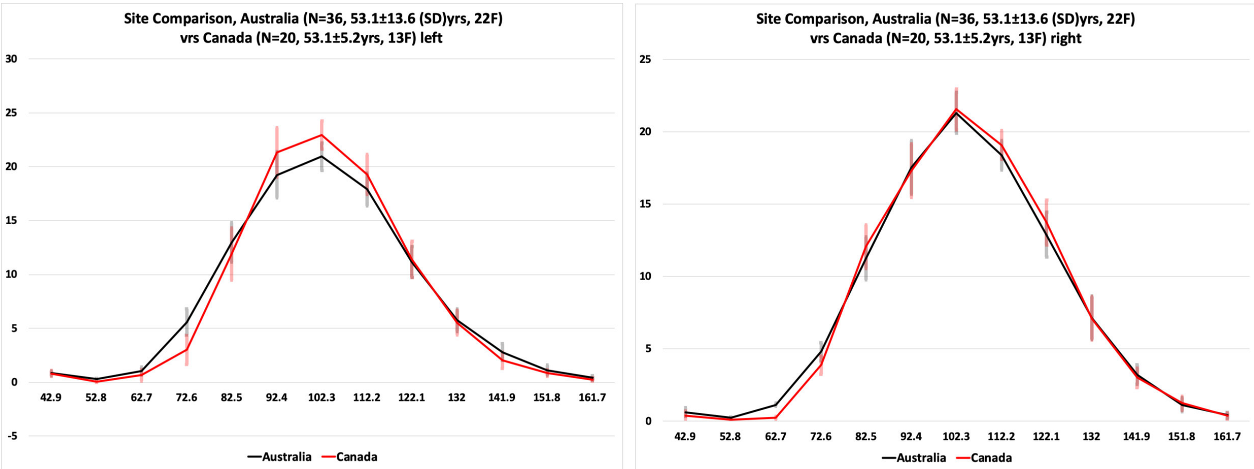


Figure 12: IH33 response comparing the age and gender matched Australian ($N = 36$) and Canadian ($N = 20$) responses. 95% Confidence bars are overlaid. The horizontal axis is in ms. Vertical axis is population percentage.

of gender, age and site (powerline frequency/hydraulic artefact) on FP shape and $IH_{33}$ plot response were not significant; however, gender, age and site matching for all populations should best applied where possible. However, there is a need for comparisons only to be made for comparable electrode types and where possible only within sites.

## V. Conclusion

It is possible to discern AD from best matched healthy controls using EVestG given the comparison recordings are matched in terms of electrode type. Age and gender did not have a significant factor on the main EVestG feature types. Powerline and environmental artefacts could be accounted for adequately; implying they did not significantly affect the features measured. For the two EVestG features tested only electrode type had a significant effect on recordings. Therefore, only populations with the same electrode type can be compared.

## References


[1] B. J. Lithgow, Z. Moussavi, C. Gurvich, J. Kulkarni, J. J. Maller, and P. B. Fitzgerald, "Bipolar disorder in the balance," *European archives of psychiatry and clinical neuroscience*, pp. 1–15, 2018.

[2] B. J. Lithgow, A. L. Garrett, Z. M. Moussavi, C. Gurvich, J. Kulkarni, J. J. Maller, and P. B. Fitzgerald, "Major depression and electrovestibulography," *The world journal of biological psychiatry*, vol. 16, no. 5, pp. 334–350, 2015.

[3] B. Lithgow, "A methodology for detecting field potentials from the external ear canal: NEER and EVestG," *Annals of biomedical engineering*, vol. 40, no. 8, pp. 1835–1850, 2012.

[4] B. Blakley, A. Suleiman, G. Rutherford, Z. Moussavi, and B. Lithgow, "EVestG recordings are vestibuloacoustic

signals," *Journal of Medical and Biological Engineering*, vol. 39, no. 2, pp. 213–217, 2019.

[5] B. J. Lithgow and et al., "Electrovestibulography identifies Alzheimer's Disease from Mixed Dementia and from Healthy Controls," *Journal of Alzheimer's Disease*, 2019, submitted.

[6] B. J. Lithgow and M. Shoushtarian, "Parkinson's disease: disturbed vestibular function and levodopa," *Journal of the neurological sciences*, vol. 353, no. 1-2, pp. 49–58, 2015.

[7] A. Suleiman, B. Lithgow, Z. Dastghieb, B. Mansouri, and Z. Moussavi, "Quantitative measurement of post-concussion syndrome using Electrovestibulography," *Scientific reports*, vol. 7, no. 1, p. 16371, 2017.

[8] A. Suleiman, B. Lithgow, B. Mansouri, and Z. Moussavi, "Investigating the validity and reliability of Electrovestibulography (EVestG) for detecting post-concussion syndrome (PCS) with and without comorbid depression," *Scientific reports*, vol. 8, no. 1, p. 14495, 2018.

[9] Z. Moussavi, A. Suleiman, G. Rutherford, O. R. Pouya, Z. Dastgheib, W. Zhang, J. Salter, X. Wang, B. Mansouri, and B. Lithgow, "A pilot randomised double-blind study of the tolerability and efficacy of repetitive transcranial magnetic stimulation on persistent post-concussion syndrome," *Scientific reports*, vol. 9, no. 1, p. 5498, 2019.

[10] Z. A. Dastgheib, B. Lithgow, B. Blakely, and Z. Moussavi, "Application of vestibular spontaneous response as a diagnostic aid for Meniere's disease," *Annals of biomedical engineering*, vol. 44, no. 5, pp. 1672–1684, 2016.

[11] Z. A. Dastgheib, B. Lithgow, B. Blakley, and Z. Moussavi, "A new diagnostic vestibular evoked response," *Journal of Otolaryngology-Head and Neck Surgery*, vol. 44, no. 1, p. 14, Apr. 2015.

[12] B. Blakley, Z. A. Dastgheib, B. Lithgow, and Z. Moussavi, "Preliminary report: neural firing patterns specific for Meniere's disease," *Journal of Otolaryngology-Head & Neck Surgery*, vol. 43, no. 1, p. 52, 2014.

[13] B. J. Lithgow, Z. Moussavi, and P. B. Fitzgerald, "Quantitative separation of the depressive phase of bipolar disorder and major depressive disorder using electrovestibulography," *The World Journal of Biological Psychiatry*, pp. 1–14, 2019.

[14] A. Nordström and P. Nordström, "Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study," *PLoS medicine*, vol. 15, no. 1, p. e1002496, 2018.

[15] C. Liu, F. C. K. Tan, Z.-C. Xiao, and G. S. Dawe, "Amyloid precursor protein enhances Nav1. 6 sodium channel cell surface expression," *Journal of Biological Chemistry*, vol. 290, no. 19, pp. 12 048–12 057, 2015.

[16] R. A. Rissman, A. L. De Blas, and D. M. Armstrong, "GABAA receptors in aging and Alzheimer's disease," *Journal of neurochemistry*, vol. 103, no. 4, pp. 1285–1292, 2007.

[17] T. J. Marczynski, "GABAergic deafferentation hypothesis of brain aging and Alzheimer's disease revisited," *Brain research bulletin*, vol. 45, no. 4, pp. 341–379, 1998.

[18] P. Theofilas, A. J. Ehrenberg, S. Dunlop, A. T. D. L. Alho, A. Nguy, R. E. P. Leite, R. D. Rodriguez, M. B. Mejia, C. K. Suemoto, R. E. D. L. Ferretti-Rebustini *et al.*, "Locus coeruleus volume and cell population changes during Alzheimer's disease progression: A stereological study in human postmortem brains with potential implication for early-stage biomarker discovery," *Alzheimer's & Dementia*, vol. 13, no. 3, pp. 236–246, 2017.

[19] C. Cortes, F. Galindo, S. Galicia, J. Cebada, and A. Flores, "Excitatory actions of GABA in developing chick vestibular afferents: effects on resting electrical activity," *Synapse*, vol. 67, no. 7, pp. 374–381, 2013.

[20] V. Marlinsky, "The effect of somatosensory stimulation on second-order and efferent vestibular neurons in the decerebrate decerebellate guinea-pig," *Neuroscience*, vol. 69, no. 2, pp. 661–669, 1995.

[21] C. Kumaragamage, B. Lithgow, and Z. Moussavi, "A new low-noise signal acquisition protocol and electrode placement for electrocochleography (ECOG) recordings," *Medical & biological engineering & computing*, vol. 53, no. 6, pp. 499–509, 2015.

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