PROCEEDINGS of the
23rd International Congress on Acoustics

9 to 13 September 2019 in Aachen, Germany

Phenotyping and computational modeling of diverse forms of genetic hearing loss

Ian C. BRUCE[1,a]; Michael R. WIRTZFELD[1]; Anne GRIFFIN[2]; Amanda K. MORGAN[3]; Matthew B. LUCAS[3], Jill LOWTHER[2]; Terry-Lynn YOUNG[2]; Susan G. STANTON[3]

[1] McMaster University, Canada

[2] Memorial University Newfoundland, Canada

[3] Western University, Canada

EXTENDED ABSTRACT

Computational models of auditory processing that can incorporate pathology (1, 2, 3) may be helpful in understanding the effects of hearing impairment (4, 5, 6) and in the development of improved devices for those with hearing loss (7), such as hearing aids and cochlear implants. However, incorporating pathology into computational models to explain a human subject's experimental data is typically problematic due to a lack of definitive knowledge about the pathology that they have.

A number of diverse forms of genetic hearing impairment have been molecularly characterized from the genetically isolated human population of Newfoundland, Canada. Affected members of these families form a useful pool of subjects to target for computational modeling, as within each extended family the specific genetic mutation leads to a similar pattern of pathology and resulting pathophysiology and perceptual deficits, but the types of hearing loss are very different between families due to different gene mutations.

A CLDN14 autosomal recessive mutation, affecting the protein Claudin14 that regulates the formation of tight cellular junctions, produces precipitous mid/high frequency hearing loss at around 4–6 years of age in 15 affected family members (8). A FOXL1 autosomal dominant mutation, affecting the signaling protein FOXL1, gives rise to otosclerosis in 11 individuals (9). A KCNQ4 autosomal dominant mutation affecting the Kv7.4 ion channel leads to progressive high frequency hearing loss in approximately 13 affected family members (10). A WFS1 autosomal dominant mutation, affecting the protein Wolframin that is involved in intracellular Ca^{2+} regulation, gives rise to a nonsyndromic low-frequency hearing loss in 28 affected individuals (11).

We are developing computational models incorporating the suspected cochlear pathology for each affected relative with a specific mutation, based on psychophysical tuning curves (12) and distortion-product otoacoustic emission (DPOAE) growth functions (13), in addition to routine audiometric measures. The model for each research subject will be validated via quantitative predictions of advanced electrophysiological recordings, specifically auditory brainstem responses (ABRs) and electrocochleograms (ECochGs), and word perception in quiet and noise (14) for that subject. The electrophysiological measurements were collected at a range of click rates using continuous loop averaging deconvolution (CLAD) sequences, in order to take into consideration neural adaptation at high click rates (15). Model predictions of the ABRs and ECochG will use the unitary response function approach of (16), while word perception predictions will make use of physiologically-based speech intelligibility predictors (17).

Keywords: Auditory modeling; genetic hearing loss; human electrophysiology

[a] ibruce@ieee.org

ACKNOWLEDGEMENTS

Supported by Atlantic Canada Opportunities Agency- Innovative Communities Fund Project # 204210 and Business Development Program Project # 205595, the Government of Newfoundland and Labrador Regional Development Fund Ref # 30-11044-003, Excite Corporation, and NSERC Discovery Grant 261736.

REFERENCES

1. Bruce IC, Erfani Y, Zilany MSA. A phenomenological model of the synapse between the inner hair cell and auditory nerve: Implications of limited neurotransmitter release sites. Hear Res. 2018; 360: 40–54.
2. Verhulst S, Altoè A, Vasilkov. Computational modeling of the human auditory periphery: Auditory-nerve responses, evoked potentials and hearing loss. Hear Res. 2018; 360: 55–75.
3. Sumner CJ, O'Mard LP, Lopez-Poveda EA, Meddis R. A nonlinear filter-bank model of the guinea-pig cochlear nerve: rate responses. J Acoust Soc Am. 2003; 113(6): 3264–3274.
4. Zilany MSA, Bruce IC. Predictions of speech intelligibility with a model of the normal and impaired auditory-periphery. Proc 3rd International IEEE/EMBS Conference on Neural Engineering; May 2–5, 2007; Kohala Coast, HI, USA 2007. pp. 481–485.
5. Verhulst S, Jagadeesh A, Mauermann M, Ernst F. Individual differences in auditory brainstem response wave characteristics: relations to different aspects of peripheral hearing loss. Trends Hear. 2016; 20:1–20.
6. Meddis R, Lecluyse W, Clark NR, Jürgens T, Tan CM, Panda MR, Brown GJ. A computer model of the auditory periphery and its application to the study of hearing. In: Moore BCJ, Patterson RD, Winter IM, Carlyon RP, Gockel HE, editors. Basic Aspects of Hearing. Advances in Experimental Medicine and Biology, vol 787. New York, NY: Springer; 2013. p. 11–20.
7. Sachs MB, Bruce IC, Miller RL, Young ED. Biological basis of hearing-aid design. Ann Biomed Eng. 2002; 30(2):157–168.
8. Pater JA, Benteau T, Griffin A, Penney C, Stanton SG, Predham S, Kielley B, Squires J, Zhou J, Li Q, Abdelfatah N, O'Rielly DD, Young T-L. A common variant in CLDN14 causes precipitous, prelingual sensorineural hearing loss in multiple families due to founder effect. Hum Genet. 2017; 136(1):107–118.
9. Abdelfatah N. The Genetic Aetiology of Otosclerosis in the Population of Newfoundland and Labrador. PhD Thesis, Memorial University Newfoundland 2014.
10. Abdelfatah N, McComiskey DA, Doucette L, Griffin A, Moore SJ, Negrijn C, Hodgkinson KA, King JJ, Larijani M, Houston J, Stanton SG, Young TL. Identification of a novel in-frame deletion in KCNQ4 (DFNA2A) and evidence of multiple phenocopies of unknown origin in a family with ADSNHL. Eur J Hum Genet. 2013;21(10):1112–1119.
11. Young TL, Ives E, Lynch E, Person R, Snook S, MacLaren L, Cator T, Griffin A, Fernandez B, Lee MK, King MC. Non-syndromic progressive hearing loss DFNA38 is caused by heterozygous missense mutation in the Wolfram syndrome gene WFS1. Hum Mol Gen. 2001; 10(22): 2509–2514.
12. Sek A, Moore BCJ. Implementation of a fast method for measuring psychophysical tuning curves. Int J Audiol. 2011; 50:237–242.
13. Kummer P, Janssen T, Arnold W. The level and growth behavior of the 2f1-f2 distortion product otoacoustic emission and its relationship to auditory sensitivity in normal hearing and cochlear hearing loss. J Acoust Soc Am. 1998; 103(6):3431–3444.
14. Tillman TW, Carhart R. An expanded test for speech discrimination utilizing CNC monosyllabic words. Northwestern University Auditory Test No. 6, USAF School of Aerospace Medicine Technical Report, Brooks Air Force Base, TX; 1966. p. 1–12
15. Delgado RE, Ozdamar O. Deconvolution of evoked responses obtained at stimulus rates. J Acoust Soc Am. 2004; 115(3):1242–1251.
16. Rønne FM, Dau T. Modeling auditory evoked brainstem responses to transient stimuli. J Acoust Soc Am. 2012; 131(5):3903–3913.
17. Wirtzfeld MR, Ibrahim RA, Bruce IC. Predictions of speech chimaera intelligibility using auditory nerve mean-rate and spike-timing neural cues. JARO. 2017; 18(5):687–710.