

Neuro-Otology and Auditory Science

Auditory Science Lab

Robert V. Harrison

The Auditory Science Laboratory has been a part of the university Department of Otolaryngology-Head & Neck Surgery for well over three decades. Over that period we have enjoyed continuous funding from CIHR, as well as supplementary grants, large and small, from other agencies. Our mission has been to increase knowledge about the complex biological mechanisms that allow us to hear and to understand the exact nature of hearing deficits. This new knowledge may lead to improved strategies for prevention, diagnosis and remediation of hearing disorders.

We use a wide range of research tools to explore the structure and function of the normal and pathological inner ear, as well as the developmental plasticity of the central auditory brain pathways. Our electrophysiological techniques include measurement of single neuron response properties in auditory midbrain and cortex. We also use evoked potential and otoacoustic emission research in human subjects and in animal models.

In our anatomical studies, we make histological evaluations of the inner ear with light and electron microscopy. In recent years we have mastered corrosion cast studies of vascular structures in the inner ear. Some of our recent research was on the capillary network of the stria vascularis in an animal model of cytomegalovirus (CMV) infection. This work was part of PhD thesis research by Mattia Carraro and was in collaboration with Dr. Albert Park and colleagues at the University of Utah. Our work to date has been published in *Hearing Research* and in the *Journal of the Association for Research in Otolaryngology (JARO)*. This research was supported, in part, by a Barberian scholarship award. This collaborative work continues with new studies on the link between damaged capillaries in the cochlea and impaired haircell function.

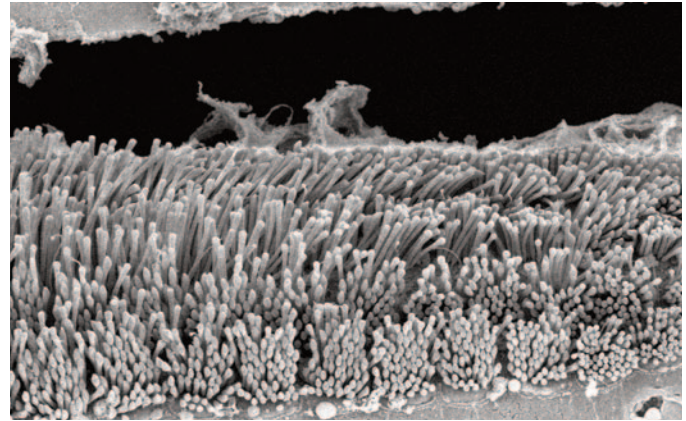


Figure: Haircells lined up in the hearing organ of the lizard.

This past year has also been productive for our project manager Jaina Negandhi. She has been working on projects ranging from recording ABRs in mouse models of hearing loss, as well as studying auditory midbrain activity patterns with c-fos labeling. She has also made extensive use of immuno-labeling techniques to assess neural activity (excitatory and inhibitory) in central auditory pathways. This project has been supported by a Barberian scholarship grant.

Another ongoing research topic relates to otoacoustic emissions (OAEs). For these studies we are using a species of lizard. The lizard has very robust otoacoustic emissions, and we are attempting to see what structural features of the hearing organ (basilar papilla) could account for otoacoustic emission waveforms. The scanning electron micrograph here shows the haircells lined up in the hearing organ (equivalent to a mammalian cochlea) of the lizard. This project is a collaboration with Chris Bergevin at York University. The project is very exciting, and is wholly supported by Barberian scholarship funding.

In addition to the projects outlined above we have finalized and published other work relating to auditory neuropathy in children (with Adrian James) and in relation to auditory midbrain plasticity (with

Lisa d'Alessandro). This has been a very productive year, and thanks to all those who have collaborated with us in the Auditory Science Laboratory.

For more information check out our website:
<https://lab.research.sickkids.ca/harrison>

Neurotology and Vestibular Research

John Rutka, David Pothier and Sharon Cushing

Clinical based research pertaining to the vestibular system and its disorders continues in conjunction with the Hertz Multidisciplinary Neurotology Clinic and the Centre for Advanced Hearing and Balance Testing at the University Health Network. Staff physicians involved in clinical vestibular research include Drs. John Rutka, Paul Ranalli and Philip Gerretsen. Ms. Carolyn Falls is responsible for the collaborative laboratory vestibular testing in our clinical studies. Ms. Shaleen Sulway and Ms. Wanda Dillon are responsible for our vestibular rehabilitation therapy and vestibular nursing projects. Dr. Fatemeh Hassan Nia continues as our clinical research co-ordinator.

Continued collaborative research projects include:

- a) Investigation of posttraumatic dizziness from our large prospective WSIB data base (>4,000 patients) research and outcomes following head injury.
- b) Assessment and prevention of systemic aminoglycoside ototoxicity with major focus on the efficacy of monitoring.
- c) The development of a validated catastrophization scale in the management of dizzy patients.

New research projects include:

- a) Correlation between multifrequency VEMP studies, ECoG and multifrequency tympanometry for the diagnosis of Meniere's disease.
- b) Investigation of high velocity/acceleration VOR impairments in patients with vestibular schwannomas.

- c) The investigation of the role of Vitamin D deficiency in benign positional paroxysmal vertigo (BPPV).
- d) Further investigation of patients with elevated oVEMP amplitudes but normal intracranial temporal bone studies.

Multidisciplinary research projects are also currently being undertaken to assess the role of vestibular rehabilitation therapy in falls' prevention with the Division of Neurology (Principal Investigator: Dr. Tartaglia).

It is not without considerable sadness that we lost the many talents of Dr. David Pothier due to medical illness this year. David was a profound thinker who influenced many of us to reconsider how we viewed the vestibular system by placing a greater emphasis on the role of the otolithic system and by appreciating how an individual's psychology affects their clinical presentation. A brilliant mind, he was instrumental in developing an effective monitoring system to minimize aminoglycoside vestibulotoxicity with a specially crafted balance workshop performance and computerized dynamic visual acuity testing. His vestibular input/output (VESTIO) device innovation utilizing an auditory signal synchronized to a head mounted gyroscope has been commercialized and is currently being studied in children receiving cochlear implantation. In a final hurrah his textbook on Vestibular Disorders written in conjunction with Jane Lea will soon be available in print. David left us before his time but his contributions as an academic researcher in clinical vestibular disorders will not be forgotten. Travel well dear friend.

Cochlear Implant Research

Vincent Lin, Trung Le, Joseph Chen, and Andrew Dimitrijevic

The vision to create three separate platforms of research at Sunnybrook HSC dedicated to the inner ear continues to expand. During the past year, the Sonja Koerner Regeneration laboratory and the G. Mason Cochlear Implant Electrophysiology Laboratory have realized growth and exciting new

discoveries. Drs. Dabdoub, Le, and Dimitrijevic report on highlights and accomplishments in their respective domains in this section. It is important to note that both laboratories have found sustainable solutions to funding research through philanthropy and grants. Both labs are scheduled to grow with additional PI's and further investment.

On the clinical research side, our main foci revolve around technology and how they help our patients, vis-a-vis cochlear implants and other implantable devices. Performance, QOL measures, aging, and expanded criteria driven by one of the largest CI database serve as our core interest in research. Our strength in clinical and research resources and infrastructures bode extremely well for industry support and sponsored trials. A critical mass is coming together to make Sunnybrook a major hub of research in North America.

Linkages to both labs allow us to delve into brain activities of auditory plasticity that figures critically in clinical performance. How drugs interact with the inner ear during injuries and regeneration can help translate research ideas into clinical applications, including how drugs are best delivered into the inner ear. Novel MRI imaging techniques of the inner ear and of the skull base are already making a difference in our understanding of the anatomy, leading to changes in clinical care. They include electrode selection based on customized measurements, better visualization of the inner ear compartments through high tesla MRI and contrast enhancement, and localizing the facial nerve course in acoustic neuroma surgery.

Administratively, the Sunnybrook CI program remains the provincial lead in forecasting needs and matching resources to demands in Ontario. Recent applications in expanded indications to implantation that included several Health Technology Assessments (HTA) led by Sunnybrook in collaboration with Health Quality Ontario (HQO) and Ontario Health Technology Advisory Committee (OHTAC) gave us a glimpse into how they can help us drive funding shortfalls with an eye on both clinical and cost effectiveness. Soon, we will have more coherent strategies in funding bilateral implantations, single

sided deafness, conductive hearing loss, etc. Ontario is certainly taking a leadership role in this regard in Canada. An important aspect of clinical research is to develop appropriate tools to measure outcome, to that end, Peter Dixon (PGY3 resident) has taken two years from his training toward a masters degree with the IHPME-University of Toronto; his thesis is to develop a more discriminating disease-specific utility instrument by modifying the Health Utility Index (HUI-3). This is a major undertaking and a potentially very impactful tool for cost-effectiveness analyses of hearing related interventions.

Advocacy for better awareness in the treatment of hearing loss and calling attention to missed opportunities of limited public investment at the government level continues to be an important mandate for us. A recent fund-raising campaign in this regard through a very successful Docs-on-Ice hockey tournament chaired by Dr. Vincent Lin in Toronto will help promote awareness in hearing loss.

Cochlear Implant Lab

Andrew Dimitrijevic

The Cochlear Implant Laboratory at Sunnybrook has a mandate to conduct research that ultimately benefits our patients. The role of cognition and hearing is a major focus of the program with a number of projects currently underway.

Lightening the cognitive load. People with hearing loss need to exert more mental effort in order to follow a conversation. This may be related to the higher rate of dementia in this population. To this end we have found, across three separate studies, that effortful listening in people with cochlear implants engage specific executive function centres in the brain. The goal of this research is to use this neural activation pattern in a precision-medicine manner to tailor optimal rehabilitation strategies.

How plastic are you? Neural plasticity is thought to be a factor in how a patient is able to adapt to a cochlear implantation. Studies are underway to relate how the visual and auditory systems interact and whether we can use this to predict and guide optimal rehabilitation.

Our team consists of a postdoctoral fellow Dr. Brandon Paul who joined the lab in November 2017. His previous work examined electrophysiological measures of tinnitus. His current project in the lab involves brain modelling of neural markers of listening effort. Dr. David Low is a fellow who has developed a Cantonese version of the Digit Triplet test. This is an important project that involves developing a diagnostic test of speech perception in cochlear implant patients that does not depend on language ability, only knowledge of English digits. His projects opens the door to more reliable diagnostic testing in a multicultural city such as Toronto. We have three undergraduate students: Ayden Malekjahani who developed a lip-reading/brain activation paradigm which is now being used preoperatively as a cochlear implant success predictor; Jordan Chan who developed a working memory paradigm that is now being used pre-operatively; Mila Uzelac who is working on a speech spatial attention task to test bilateral hearing in cochlear implant users. Varia Sajeniouk is our research coordinator and also coordinates ongoing clinical research activities.

We have established active collaborations with the SickKids cochlear implant program and the Rotman Research Institute at Baycrest Hospital. This collaboration has culminated in a multicentre CIHR grant proposal involving hearing and cognition in cochlear implant recipients across the life span. Other active collaborations include the Department of Music, University of Toronto. We are currently exploring the neural basis of music therapy in adults with cochlear implants.

The research program is supported by a generous donation from a private donor and an industry grant.

This year the lab has had invited lectures to Auditory EEG Signal Processing symposium and Dr. Dimitrijevic was one of the organizers of this symposium. Three presentations were made at the Association for Research in Otolaryngology.

Neurotology & Otology Research

Joseph Chen, Trung Le, Vincent Lin

Ageing and Dementia: We continue to collaborate with our neurology colleagues to collect data to finish our validation of the Hearing Impaired MoCA (HI-MoCA). We are nearing the numbers required for our study and interim data analysis look promising. We are also continuing our partnership with Med-EL with the development of the HI-MoCA app which will be ready for pilot testing within the next few months. Once the app has been vetted and beta tested, we can also develop language modules so it can be translated into different languages and validated as well. There is also a tremendous opportunity for collaboration with international centres of excellence and also the potential for mass data collection with other centres that use our app.

Otoprotection Trial: Our work with the Canadian Society of Otolaryngology – Head & Neck Surgery Collaborative Research Initiative has allowed our group to be the lead centre for a potentially ground breaking intratympanic N-acetylcysteine otoprotective trial in patients undergoing cisplatin chemotherapy. We are spear heading the development of the research protocol and hope to recruit other centres across Canada to participate. We anticipate applying for funding so we can partake in collection of pilot data.

CI-CROS: This product is now available for commercial purchase through Advanced Bionics and Oticon. Our centre has been recognized as the core development group in its inception, design and validation.

Post-op Narcotics Trial: We have partnered with Dr. Eric Monteiro to be part of a trial looking at the use of post-operative narcotics in ambulatory care otology procedures. Phase I of the work has been performed and initial data being collated and prepared for publication.

TTC Noise Study: Our group also published a high profile article looking at the surprising levels of subway noise in the Toronto Transit Commission (TTC). The article generated a lot of publicity and

increased public awareness of the dangers of chronic high level noise exposure (J Otolaryngol Head Neck Surg. 2017 Nov 23;46(1):62. doi: 10.1186/s40463-017-0239-6). The authors were featured in a number of radio, internet and television interviews.

Auditory Development, Protection & Regeneration

Alain Dabdoub & Trung Le

Our lab had an excellent year advancing basic research in inner ear biology and translational medicine discovering novel molecular insights and potential new therapies for the treatment of inner ear disorders focusing on hearing loss and balance disorders. Two graduate students successfully defended their theses and published their work in addition to several other impactful publications from the lab. We presented our research at national and international meetings including the Canadian Developmental Biology Meeting, the Canadian Neuroscience Meeting, the Hearing and Structure Preservation Workshop, and the International Cochlear Implants Meeting.

We continue to advance our research program building on a solid foundation expanding and exploring new projects and discoveries for our central goal of a biological solution for hearing and balance disorders. I continue to be an active member in Hearing Health Foundation's Hearing Restoration Project, the international scientific consortium dedicated to identifying better treatments for hearing loss.

Our lab is supported by grants from the Canadian Foundation for Innovation; Canada First Research Excellence Fund; Medicine by Design; the International Hearing Restoration Project – Hearing Health Foundation and the Koerner Foundation.

Pediatric Cochlear Implant Research Lab

Karen Gordon, Blake Papsin, Adrian James, Sharon Cushing

The Cochlear Implant Laboratory at the Hospital for Sick Children continues to investigate auditory and vestibular development and plasticity. We ask: 1)

What aspects of auditory and vestibular development are arrested in children with hearing loss; 2) What changes in the auditory and vestibular system occur during the period of deafness; and 3) To what extent can auditory and vestibular plasticity and development be promoted by cochlear implant use? We are also interested in innovations in cochlear implant design and programming which seek to improve the resilience of the device as well as to preserve residual hearing and binaural cues. Our work is supported by research funding from the Canadian Institutes of Health Research along with the Cochlear Americas Chair in Auditory Development and generous donations. Specific hypotheses which stem from these questions are tested through a number of studies currently underway.

Our team includes Carmen McKnight, our Research Project Manager, and we welcomed Jaina Neghandi, our Research Project Co-ordinator, in May 2018. We are also expecting to welcome Al Blakeman as a Research Project Co-ordinator in July 2018.

In September 2017, we were joined by Claire McSweeney who is in the M.Sc. program at the Institute for Medical Science. She is working on a new project in which we are exploring the effects of impaired binaural hearing and vestibular deficits on spatial awareness, memory, and navigation. We are also interested in implications of these spatial problems on physical activity and academics (reading and mathematics). We were also joined by Dr. Hillary Ganek who is a PhD speech-language pathologist. She is working on language outcomes in children who use cochlear implants with a specific emphasis, in collaboration with Dr. Adrian James, on children with auditory neuropathy spectrum disorder. She is also interested in the language exposure that children with cochlear implants receive in their everyday environments and how that impacts their auditory abilities in spoken language. She is comparing data recorded with a Language ENvironment Analysis (LENA) device and scene categorization provided by data logging functions in the cochlear implant processors.

We have several other wonderful members of our research team. Dr. Homira Osman is a post-doctoral fellow who graduated with her PhD and AuD (clinical audiology) from University of Washington. She is working on delays that children with hearing loss have when responding to speech and this has been funded by the Integrative Research Training Fellowship Award, Centre for Brain and Mental Health, The Hospital for Sick Children. She presented preliminary findings at the 2017 Conference on Implantable Auditory Prostheses). She has also been measuring distortions in binaural cues created by bilateral hearing aids (presentation at American Auditory Society 2018) and at perception of emotion in speech by children using unilateral cochlear implants (presentation at Scientific Day, Collaborative Program in Neuroscience 2018). Daniel Smieja and Ashley Deonarain are both engineers in the MHS program in the Institute of Biomaterials and Biomedical Engineering. Daniel is working on novel ways to process electrophysiological responses to sound (presentations at the 2017 Conference on Implantable Auditory Prostheses and the 2018 Acoustical Society of America). Ashley is exploring effects of hearing aid technology on binaural cues. Melissa Polonenko, a clinical audiologist, continues to make great gains in her PhD thesis work. She is studying the use of bimodal hearing (acoustic hearing in one ear and electrical hearing through a cochlear implant in the other). She has received an impressive 16 major studentship awards including the Ontario Student Graduate Award, the prestigious SickKids Scientist-Training Program Award, and most recently, the Exceptional Trainee Award from the Neuroscience and Mental Health program at the SickKids Research Institute. In July 2017, she gave an invited keynote presentation at the Conference for Implantable Auditory Prostheses. She will be defending her PhD thesis in late July 2018.

We have enjoyed the opportunity to work with a number of summer students over the past 2 summers: Jonah Gorodensky, Robel Alemu, and Simrat Gill (binaural hearing in children with hearing loss); Joshua Baitz (innovative recording of vestibular myogenic responses); Leanne Ruderman (vocational and social outcomes of implantation),

Meera Mehta (balance improvement using electrical stimulation through cochlear implants), and Jacob McLennan (genetic variants in children with hearing loss). We continue to have important collaborations both locally (Robert Harrison, Sharon Cushing, Adrian James, Ben Dunkley, James Rutka, Sandra Trehub, Susan Blaser, and Frank Russo, Jenny Campos), nationally (Sam Doesburg) and internationally, with Robert Cowan. Some new collaborations have begun. We will examine language processing in children with autism spectrum disorder with Dr. Elizabeth Pang and auditory streaming in individuals who have hearing loss with Dr. Andrew Dimitrijevic and Dr. Claude Alain.

The past year has been very productive: 18 publications came out or are in the press. Between this summer and last, we collectively presented over 14 abstracts at international meetings and gave more than two dozen invited talks internationally.

Some highlights from the past year include: 15 student awards, Melissa Polonenko, Exceptional Trainee Award, Neuroscience and Mental Health program, SickKids Research Institute, Melissa Polonenko, Don Henderson Award and first place award, Poster Blitz trainee presentations, Annual Meeting of the Association for Research in Otolaryngology (Melissa Polonenko); Fellow Travel Award for outstanding abstract, The Annual meeting of the American Audiological Society (Homira Osman); Trainee Award for outstanding abstract, Annual Meeting of the Acoustical Society of America (Daniel Smieja).

OtoSim™ Lab

Paolo Campisi and Vito Forte

OtoSim™ has enjoyed another successful year thanks to the ongoing efforts of team members and collaborators.

Dr. Vito Forte is still full-time CEO and CTO of OtoSim Inc and he also leads the 'Hammers and Nails' Program at the Hospital for Sick Children and IBBME. This has resulted in a successful collaborative team involving engineering students from UofT as well as other programs across Canada.

This activity has stimulated 4 students from the lab and program to pursue masters studies, 2 successfully completed their masters and 1 has gone on to pursue a PhD.

Product development remains a key component at OtoSim Inc. We have introduced advanced self-learning software and remote teaching capabilities.

OtoSim Mobile™, a novel simulator that can be used with any smart phones has now been developed and was piloted in pre-clerkship medical students at UofT in an education study funded by a Harry Barberian Scholarship. The study was co-supervised by Dr. Paolo Campisi, Dr. Brydges and Dr. Allan Vescan and undertaken by Dr. Josie Xu PGY3, Armin Rahmani, Ragavan Ganeshathasan and Stephen Szeto, 3rd year medical students at UofT. Dr. Xu won an award at the CSOHNS Poliquin Competition in Quebec City. Further studies conducted on residents and physicians assistants are planned in the near future.

The OtoSim Mobile™ and the Educators Portal™ were launched commercially to the North American market in May 2018 and have already been purchased by several sim centers in the US.

Development is well underway for OphthoSim Mobile™. We continue to get engineering and computer science students involved in design and development through MITACS, NSERC and USRP (Undergraduate Summer Student Program). Both smart-phone based mobile simulators will bring another dimension to teaching otoscopy and direct ophthalmoscopy applying effective, efficient and affordable simulation to hopefully achieve a global impact.