



THE UNIVERSITY  
OF BRITISH COLUMBIA

## Impact Report

### ACCELERATING THE DEVELOPMENT OF NON-INVASIVE BRAIN STIMULATION

2017-2018 IMPACT REPORT

Prepared for the Pacific Parkinson's Research Institute and  
Ian and Rosemary Mottershead of the Charros Foundation

October 2018

Your support is advancing  
real solutions for people  
living with Parkinson's  
disease.

### Thank you.

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The UBC Faculty of Medicine and the Pacific Parkinson's Research Centre (PPRC) are sincerely grateful to the Pacific Parkinson's Research Institute (PPRI) and Ian and Rosemary Mottershead of the Charros Foundation for supporting a three-year project to conduct research to develop non-invasive brain stimulation as a treatment option for patients with Parkinson's disease and to establish a comprehensive database to inform other innovative treatment options.

Led by Dr. Martin McKeown, Professor of Neurology, Head of PPRC, and the UBC-PPRI Chair in Parkinson's Research, this project has been a huge success. After three years of remarkable scientific productivity, we are proud to have launched a new area of research into the role of vestibular stimulation in Parkinson's disease, while training numerous young clinicians and scientists in this emerging field. Now at the forefront of this research internationally, PPRC is attracting collaborators from other provinces and countries, leveraging your support into new funding to continue this work, and acting on opportunities for commercialization. In addition, a comprehensive, web-based clinical database was established and the data are being mined to answer key questions in the treatment of Parkinson's disease.

We are pleased to share the following summary of our accomplishments since 2015, none of which would be possible without your generous support.

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# Non-Invasive Brain Stimulation Research

## SUMMARY OF KEY FINDINGS

The potential of non-invasive brain stimulation as a treatment option for Parkinson's patients is a new area of research. This project included several studies to determine whether vestibular stimulation would work in Parkinson's. We found this technique does not suppress resting tremor in Parkinson's disease, but we are confident it is a useful technique for improving motor symptoms. Our key findings include:

- A deeper understanding of the fundamental mechanisms of brain stimulation in Parkinson's disease - it appears to exert its effects by modulating brain rhythms
- Vestibular stimulation in Parkinson's disease:
  - Can non-invasively "disrupt" abnormal brain oscillations in Parkinson's
  - Improves interaction between different subnetworks of the brain
  - Augments deficient connectivity from the PPN, an important brainstem structure associated with balance
  - Has complex effects on effects on standing in Parkinson's, which might lead to improved balance treatments
- Identification of a biomarker for Parkinson's disease
- Electroencephalogram (EEG), or brain wave patterns, can be used to estimate disease severity in Parkinson's

## UNIVERSITY OF NEW MEXICO COLLABORATION

A research collaboration with Meeko Oishi, Associate Professor of Electrical and Computer Engineering at the University of New Mexico, focused on determining the optimal type of non-invasive brain stimulation to minimize Parkinson's. Dr. Oishi is a control theorist who uses mathematics to calculate the specific input required to achieve the desired output. In this study, she evaluated two models of low-level vestibular stimulation to select the best model to minimize symptoms of Parkinson's disease identified for gait and postural perturbation tasks. Her team found that stimulation at high frequencies was more effective at disrupting the abnormal brain waves of Parkinson's shown on EEG.

Research by our collaborators is ongoing. A new PhD student, Ms. Harini Sridhar, was recruited in January 2018 to work on this project. She is applying inverse reinforcement learning to estimate cost functions and characterize significant differences across groups. The University of Notre Dame collaborators, Dr. Vijay Gupta and Ms. Nayara Aguiar (PhD student), are investigating model based methods, in contrast to reinforcement learning approaches, to estimate cost functions.

### Presentations

Probabilistic safety via stochastic reachability: Application to autonomous systems and to physiological systems. Electrical Engineering, University of Michigan at Ann Arbor, September 22, 2017.

Collaborative control of human-in-the-loop systems: Optimal interface design and reachability-based collaborative navigation. Electrical Engineering and Computer Science, University of California at Berkeley, September 26, 2016.

Towards design of human-in-the-loop cyber-physical systems. Electrical and Computer Engineering, University of California at Santa Barbara, February 26, 2016.

Gonzalez C, Svenkeson D, Kim DJ, McKeown MJ, and Oishi M. Detection of manual tracking submovements in Parkinson's disease through hybrid optimization. IFAC Conference on Analysis and Design of Hybrid Systems, Atlanta, GA, October 2015.

### Theses

Mr. Gabriel Parras, UNM, MSc/MBA, August 2014-May 2017. A frequency domain based approach to evaluating manual tracking behavior in Parkinson's disease. Upon graduation, Laboratory Manager at Central New Mexico Community College.

Mr. Carlos Gonzalez, UNM, MSc, January 2015-August 2016. Hybrid system identification of manual tracking submovements in Parkinson's disease. Upon graduation, a doctoral student at New York University, Electrical Engineering.

# Non-Invasive Brain Stimulation Research

## TRAINEES

Since 2015, this donation has created invaluable training opportunities for 17 students and early career researchers – two of whom went on medical school, and another is pursuing a PhD in one of top brain stimulation labs in world.

## Postdoctoral Fellows

Azadeh Haji Hosseini  
Aiping Liu

## Research Associate

Saurabh Garg

## Graduate Students

Four graduate students will have completed theses as part of the non-invasive brain stimulation project. Each student expressed gratitude to PPRI and Ian and Rosemary Mottershead of the Charros Foundation in the acknowledgements at the beginning of their thesis.

Marcus Cheun, MSc 2017

- Personalized stimuli as treatment for resting tremor in Parkinson's disease.

Soojin Lee, PhD 2019 (expected)

- Galvanic Vestibular Stimulation for Parkinson's disease treatment.

Stephanie Tran, MSc 2018

- Galvanic vestibular stimulation: The effects on postural instability in Parkinson's disease.

Maria Zhu, MSc 2017

- Neurophysiological characteristics of apathy in Parkinson's disease.

## Research Assistants/Coordinators

Christina Jones, Clinical Research Coordinator

Joo-Hyun Kang, Clinical Coordinator

Daniel Kliger, Database project

Ryan Leung, Database project

Kristen Sundvick, Database project

Adam Yu, Database project

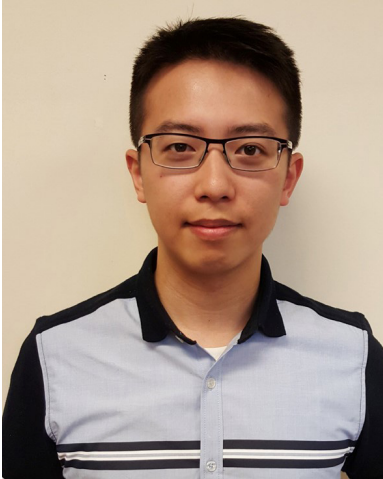
## Undergraduate Students

Adam Book

Suhana Kamakari

Jowon Kim

Jonathan Schmok



## PROJECT UPDATES

### Marcus Cheung, Master's student, School of Biomedical Engineering

Marcus completed a pilot study investigating the use of transcranial alternative current stimulation (tACS) on tremor in Parkinson's. Through multiple forms of modelling, his findings indicate that an individually tailored stimulus may be crucial for lessening tremor in Parkinson's, and the timing of this stimulus is highly important and needs further investigation. Alongside this research, Marcus was developing a portable stimulation device that would allow for multiple stimulation patterns (to ensure the best and most accurate outcomes for patients). His device improves upon commercially available devices, which provide limited input types. Marcus successfully defended his Master's thesis in biomedical engineering and was accepted into medical school at the Chinese University of Hong Kong. He remains involved in Dr. McKeown's lab and the portable stimulator project, remotely and during his medical school research placements.

### Presentation

Marcus Cheung and Martin J. McKeown. A non-invasive and non-pharmacological treatment for Parkinson's resting tremor. 2017 Faculty of Medicine Graduate Student Research Day, Vancouver, BC, May 26, 2017.

## Non-Invasive Brain Stimulation Research



### Stephanie Tran, Master's student, Neuroscience

Stephanie completed two experiments studying the effect of different types of galvanic vestibular stimulation (GVS) on the static balance and gait of Parkinson's patients. Her presentation of this study at the International Neuromodulation Society 13th World Congress was selected as one of six winners from more than 460 abstracts in the best abstract competition. Her work was published in *Brain Stimulation*, a scientific journal with a focus on neuromodulation research. After completing her Master's, Stephanie began her PhD at the University of Toronto.

### Presentations

Tran S, et al. Galvanic vestibular stimulation: Effects on postural instability in Parkinson's disease. International Neuromodulation Society 13th World Congress, Edinburgh, Scotland, May 27-June 1, 2017.

Tran S, et al. Effects of galvanic vestibular stimulation on postural instability in Parkinson's disease. 2017 Faculty of Medicine Graduate Student Research Day, Vancouver, BC, May 26, 2017.

Tran S et al. Galvanic vestibular stimulation as a potential treatment for Parkinson's disease postural instability and gait disorders. Innovation in Health Research and Technologies: Strategies for Successful Partnerships, Vancouver, BC, May 27, 2016.



### **Maria Zhu, Master's student, Neuroscience**

Maria studied the effects of GVS on motivational and emotional apathy in Parkinson's disease. She collected data from Parkinson's patients with and without apathy and healthy control subjects and measured emotional and motivational apathy through skin conductance response, physical effort, and oscillatory components of EEG. She found significant differences in EEG patterns and responses to reward among these groups, thus providing a potential biomarker for diagnosing apathy in Parkinson's. Maria successfully defended her Master's thesis.

### **Presentations**

Zhu M, HajiHosseini A, Schmok J, Garg S, Lee S, McKeown MJ. Impaired frontal beta desynchronization during an incentive motivation task in apathetic patients with Parkinson's disease. 11th Annual CAN Meeting Canadian Association for Neuroscience, Montreal, QC, May 28-31, 2017.

Zhu M, HajiHosseini A, Garg S, McKeown MJ. Altered beta desynchronization during an incentive motivation task in apathetic patients with Parkinson's disease. 2017 Faculty of Medicine Graduate Student Research Day, Vancouver, BC, May 26, 2017.

Zhu M, HajiHosseini, A, Garg S, McKeown MJ. Impaired frontal beta desynchronization during an incentive motivation task in apathetic patients with Parkinson's disease. Neurology Resident Research Day, Vancouver, BC, May 10, 2017.

Zhu M and McKeown MJ. GVS: A prospective treatment for apathy in Parkinson's disease. Innovation in Health Research and Technologies: Strategies for Successful Partnerships, Vancouver, BC, May 27, 2016.

## Non-Invasive Brain Stimulation Research



### Soojin Lee, PhD candidate, School of Biomedical Engineering

Soojin is studying GVS for the treatment of Parkinson's. Specifically, she has been investigating the effects of a range of stimuli on brain oscillations and motor performance in Parkinson's, as well as the interconnection between the two. She conducted a study where Parkinson's and healthy subjects performed a motor task in two conditions (sham vs. GVS). They were instructed to squeeze a rubber ball as fast as they could after receiving a visual cue to start. GVS was found to improve motor performance, including grip strength, reaction time, and movement time in Parkinson's patients. Faster reaction time and movement time was associated with stronger beta desynchronization in the motor area, and GVS augmented the beta desynchronization.

This was the first study to demonstrate a causal relationship between augmented beta desynchronization and improved motor performance induced by GVS. It suggests through neuromodulation, GVS may provide a new way to ameliorate some of the motor symptoms of Parkinson's, as a complement to current pharmacotherapy. Soojin's presentation at the Canadian Student Health Research Forum in June 2018 received a gold award.

### Presentations

Lee S, Wang ZJ, McKeown MJ. Non-invasive galvanic vestibular stimulation augments beta desynchronization and improves motor performance in Parkinson's disease. International Brain Stimulation Conference, Vancouver, BC, February 24-27, 2019.

Lee S, McKeown MJ. Engineering approaches to non-invasive electrical stimulation of the brain: Application to Parkinson's disease. Emerging Technologies 2018, Whistler, BC May 9-11, 2018.

Lee S, Wang ZJ, McKeown MJ. Removal of high-voltage brain stimulation artifacts from simultaneous EEG recordings. 2nd International Brain Stimulation Conference, Barcelona: Spain, March 5-8, 2017.

Lee S, Cai J, Kim DJ, Wang ZJ, McKeown MJ. Stimulation dependent, wide spread cortical effects of galvanic vestibular stimulation in Parkinson's disease. 4th World Parkinson Congress, Portland, OR, September 20-23, 2016.

Lee S, Cai J, Kim DJ, Wang ZJ, McKeown MJ. Differential effects of noisy and sinusoidal galvanic vestibular stimulation on resting-state functional connectivity. 4th Annual Minnesota Neuromodulation Symposium, Minneapolis, MN, April 14-15, 2016.

Lee S, Kim DJ, Svenkeson D, Oishi MMK, McKeown MJ. Synergistic effects of noisy galvanic vestibular stimulation and oral L-dopa in improving manual tracking performance in Parkinson's disease. 1st International Brain Stimulation Conference, Singapore, March 2-4, 2015.





### Aiping Liu, Postdoctoral Fellow

Traditionally, dopaminergic treatments benefit all Parkinson's patients, yet the non-dopaminergic and non-motor disabilities are not satisfactorily controlled with current medication. Alternative techniques such as non-invasive electrical brain stimulations have shown to be potential avenues for Parkinson's treatments. GVS is capable of activating vestibular afferents to thalamus and basal ganglia, potentially improving the motor deficits in Parkinson's disease.

This project is a comprehensive evaluation of the effects of various GVS stimulations on brain functions and provides the biomarkers associated with GVS effects for Parkinson's, thus promoting non-invasive stimulations as potential treatments for Parkinson's patients.

In preliminary work, functional Magnetic Resonance Imaging (fMRI) was used to explore the modulation of Pedunculopontine Nucleus (PPN) connectivity by GVS in Parkinson's disease. The results suggest GVS can enhance deficient PPN connectivity seen in Parkinson's, in a stimulus-dependent manner. This work was published in the scientific journal *Frontiers in Neuroscience* in February 2018. In addition to studying the regional interactions, this research also explores the effects of GVS on sub-network interactions to estimate the impacts of various stimulations on the neural systems.

### Presentations and other academic activity

Liu A. Effects of galvanic vestibular stimulation on brain activity. 12th Annual UBC MRI Research Center Researcher's Retreat, Vancouver, BC, May 7, 2018.

Publicity Chair, 20th IEEE International Workshop on Multimedia Signal Processing, Vancouver, BC, August 2018.

Guest Associate Editor, *Frontiers in Aging Neuroscience*.

## Non-Invasive Brain Stimulation Research

### PEER REVIEWED JOURNAL ARTICLES

#### Published

Liu A, Lin SJ, Mi T, Chen X, PChan, Z J Wang, M J McKeown. (in press) Decreased Subregional Specificity of the Putamen in Parkinson's Disease Revealed by Dynamic Connectivity-derived Parcellation. *NeuroImage: Clinical*.

Tran S, Shafiee M, Jones C, Garg S, Lee S, Pasman E, Carpenter M, McKeown MJ. (2018) Subthreshold Stochastic Vestibular Stimulation Induces Complex Multi-planar Effects during Standing in Parkinson's Disease. *Brain Stimulation*.

Lee S, McKeown MJ, Wang ZJ, Chen X. (2018) Removal of High-voltage Brain Stimulation Artifacts from Simultaneous EEG Recordings. *IEEE Transactions on Biomedical Engineering*.

Cai J, Lee S, Ba F, Garg S, Kim LJ, Liu A, Kim D, Wang ZJ, McKeown MJ. (2018) Galvanic Vestibular Stimulation (GVS) Augments Deficient Pedunculo-pontine Nucleus (PPN) Connectivity in Mild Parkinson's Disease: fMRI Effects of Different Stimuli. *Frontiers in Neuroscience* 12: 101.

Kamakari S, Lee S, McKeown MJ. (2016) Non-invasive Electrical Brain Modulation: A New Avenue for Treatment? *University of Toronto Medical Journal* 93:2.

#### Under Review

Lee S, Wang ZJ, McKeown MJ. High-frequency Vestibular Stimulation Jointly Affects Motor Performance and Beta Rhythms in Parkinson's Disease.

Liu A, Lee S, Mi T, Cai J, Garg S, Kim LJ, Zhu M, Chen X, Wang ZJ, McKeown MJ. Galvanic Vestibular Stimulation Improves Subnetwork Interactions in Parkinson's Disease.

## Database Project

### PROJECT UPDATE

iCAPTURE PD (integrated Comprehensive Assessment of Parkinson's disease to Treat, Understand, Research, and Educate) integrates multi-disciplinary, comprehensive, and standardized clinical assessments, education for trainees and patients, treatment and quality assurance tools, and research applications. The tools and assessments are embedded into the electronic medical record, and the electronically captured, quantified data can be de-identified and automatically exported to the PPRC Registry, previously referred to as the clinical research database. The PPRC Registry currently contains longitudinal clinical and demographic data for more than 1,900 participants, more than 1,300 of whom have Parkinson's disease.

iCAPTURE transforms patient care in our provincial movement disorder clinic by providing individualized handouts for patients to summarize their consultation, including action points, updated treatment plans, clinical team contact details, education, and patient support resources. It also facilitates the semi-automated generation of consult notes to other physicians, thus reducing potential for error and turn-around time for communication. It serves as a quality assurance tool.

The PPRC Registry is an invaluable resource for research, which has been used to answer questions such as: Are there gender differences in depression and Parkinson's? Are there changes in the coping strategies or personalities of people dealing with Parkinson's? It is also helpful in the microbiome projects for longitudinal clinical data and for identifying potential research participants.

### PRESENTATIONS

Surathi P, Mirian M, Sundvick K, Appel-Cresswell S, McKeown M. A bayesian network approach for prediction of future dementia in Parkinson's disease. Abstract accepted by the 22nd International Congress of Parkinson's disease and Movement Disorders, Hong Kong, October 2018.

Influences of gender, depression and disease severity on MoCA subscores in Parkinson's disease. Poster presentation 21st International Congress of Parkinson's Disease and Movement Disorders, Vancouver, BC, June 2017.

Learning effect plays a significant role in performance on the Montreal Cognitive Assessment in patients with Parkinson's disease. Poster presentation and oral presentation at the Poster Tour at the 19th International Congress of Parkinson's Disease and Movement Disorders, San Diego, CA, June 2015.

## Next Steps

This project used bulky, lab-based stimulators to determine that vestibular stimulation is an effective treatment option for Parkinson's disease. We are now exploring an exciting opportunity for commercialization—the manufacture of a portable stimulator in collaboration with a medical company. A portable device would enable clinicians and scientists to monitor patients beyond the lab, opening new doors for research and future improvements to clinical care.

We also plan to pursue a new study to determine whether GVS delivered during walking may be able to improve stability during the gait cycle. We are interested in three main ideas:

1. Whether GVS is specific to each individual with Parkinson's disease and, if we can determine an optimal intensity for GVS, whether this may show improvements in mobility;
2. Whether GVS has immediate and/or lasting effects such that any improvements seen may still be present even after the stimulation has stopped;
3. Whether GVS can be delivered and gait recorded outside the lab using a semi-portable stimulator and portable sensors for remote data collection.

In addition to this ongoing work, two proposals have been submitted to leverage this funding into new grants:

- "Postural instability and falls in Parkinson's disease" is under review by the Canadian Institutes of Health Research. This grant would specifically investigate if brain stimulation will improve balance problems in Parkinson's disease, in collaboration with Mark Carpenter, Professor in the School of Kinesiology at UBC, and Dr. Fang Ba, Assistant Professor in the Division of Neurology at the University of Alberta.
- A second grant proposal to investigate GVS for prevention of falls in Parkinson's disease is under review by the Vancouver Coastal Health Innovator's Challenge.

## Thank You

The UBC Faculty of Medicine and the Pacific Parkinson's Research Centre are honoured by the commitment of support from the Pacific Parkinson's Research Institute and the generosity of your philanthropic community, including Ian and Rosemary Mottershead of the Charros Foundation. Thank you for investing in the development of non-invasive brain stimulation, which we are demonstrating has great potential as an effective treatment option to improve the lives of patients with Parkinson's disease.