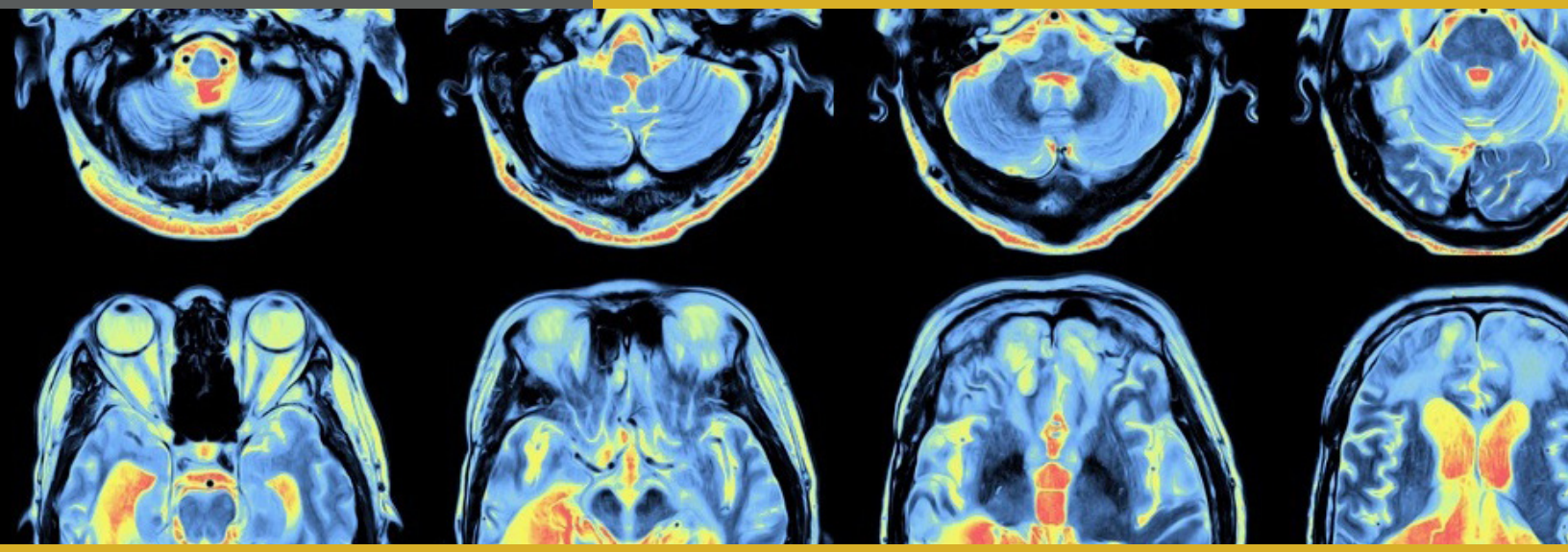
Pacific Parkinson's
RESEARCH INSTITUTE

2023 IMPACT REPORT

Brain Energetics in Parkinson's Disease



The Pacific Parkinson's Research Institute (PPRI) partners with the UBC Faculty of Medicine to fund the strategic research priorities of the Pacific Parkinson's Research Centre (PPRC), a Canadian Centre for Excellence for the diagnosis and management of Parkinson's disease and related disorders.

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UBC Faculty of Medicine and the Pacific Parkinson's Research Centre (PPRC) gratefully acknowledges the invaluable support provided by the Pacific Parkinson's Research Institute (PPRI) in the critical area of brain energetics – exploring energy production and usage in the brain – and its impact of exercise individuals with Parkinson's disease (PD). This project is led by Connor Bevington, PhD, under the supervision of Principal Investigator Dr. Vesna Sossi.

Previous research on Parkinson's has hinted at the involvement of mitochondrial dysfunction in the disease's initiation and progression, but confirming this in a living organism has remained elusive. Mitochondrial dysfunction is characterized by the brain producing energy anaerobically, without oxygen, leading to a decrease in cerebral oxygen consumption (CMRO2) and cerebral glucose consumption (CMRglu).

Project Overview

This research project aims to delve into the impact of exercise on brain energetics, encompassing the production and utilization of energy in the brains of individuals living with PD. Brain energetics can be precisely quantified by assessing the ratio of the cerebral metabolic rate of CMRO2 CMRglu. While earlier research suggests that mitochondrial dysfunction might be involved in the initiation and progression of PD, such a phenomenon has yet to be validated. Additionally, exercise has shown promise in mitigating the progression of PD as assessed by clinical symptoms, but the underlying neurophysiological mechanism responsible for this effect remains enigmatic. We hypothesize that exercise could enhance brain energetics, manifesting in changes in CMRO2, CMRglu, or both.

The assessment of both CMRO2 and CMRglu is feasible through neuroimaging techniques: CMRglu can be evaluated using [18F]FDG positron emission tomography (PET), while advanced functional magnetic resonance imaging (fMRI) facilitates the measurement of CMRO2. Given the significant fluctuations in CMRO2 and CMRglu throughout the day, it becomes imperative to measure them simultaneously, and we are fortunate to possess a cutting-edge GE SIGNA PET/MRI scanner at our center, enabling us to acquire PET and MRI images simultaneously. In collaboration with Professor Bruce Pike, the Campus Alberta Innovates Program (CAIP) Chair in Healthy Brain Aging and Head of the Departments of Radiology and Clinical Neurosciences at the University of Calgary, we have successfully implemented advanced fMRI methodologies that facilitate the precise measurement of CMRO2.

Recruitment

As of July 2023, we have successfully recruited:

- 15 subjects as healthy controls
- Six exercising PD participants
- Seven non-exercising PD participants that have completed the cycling intervention and follow-up scans and assessments
- Five non-exercising PD participants for the control group

Challenges in finding sedentary PD subjects locally were influenced by the active lifestyle of BC and the frequent exercise recommendations given by neurologists at diagnosis and follow-up appointments. Nonetheless, we are optimistic about recruiting and scanning two more participants by the end of the year. This would allow us to complete all cohort follow-up imaging and assessments by mid-2024.

Furthermore, we are excited about our collaboration with the upcoming IMPACT 360 study, which will investigate the effects of lifestyle choices on PD progression and provide an opportunity for data pooling and potentially increase the number of subjects in our study.

Data Analysis - Preliminary Results

We applied pattern analysis to CMRglu and CMRO2 data from PD and healthy controls, allowing us to identify altered brain metabolism patterns due to disease and patterns influenced by the intervention. By grouping data from all PD subjects and healthy controls, we have observed variance in the data due to disease and exercise levels. Comparing these patterns for CMRglu (fig. 1) and CMRO2 (fig. 2) reveals a significant spatial overlap, indicating that exercise positively modulates brain metabolism alterations caused by PD. This finding provides a neurophysiological basis for exercise's observed clinical effect of slowing disease progression. Additionally, changes in pattern expression appear to correlate with improvements in aerobic fitness, suggesting a possible dose-response effect where the more an individual exercises, the greater the impact on brain metabolism modulation. Validation of these patterns will be possible once more subjects from the PD non-exerciser control group complete the study.

We have also made significant progress in developing techniques for joint analysis of CMRglu and CMRO2 data, enabling us to measure changes in brain energetics due to disease and exercise. Initial results suggest increased aerobic glycolysis in the more affected side of the posterior putamen (a structure located at the base of the forebrain) in PD subjects compared to healthy controls. While we have yet to observe significant changes in aerobic glycolysis due to exercise with our preliminary analysis, ongoing and more advanced analyses, along with additional subject data, may reveal subtle signal changes not currently apparent in the dataset.

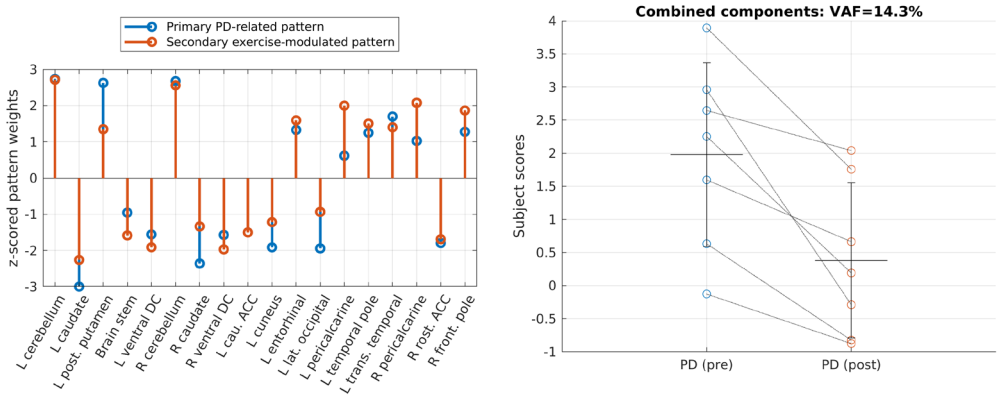

Figure 1. Stem plots of the spatial patterns that characterize changes to CMRglu metabolism due to disease (blue) and modulated by exercise (red). The patterns are sets of regional weights, where positive weights indicate relative hypermetabolism of CMRglu and negative weights indicate relative hypometabolism. Right: subject scores for the exercise-modulated pattern, which indicate how strongly the pattern is expressed in each subject's data, before and after the exercise intervention. Since the expression is significantly reduced after exercise, the overlap of the disease-related and exercise-modulated patterns signifies that exercise is modulating metabolism in the opposite direction of disease—agreeing with clinical observations of exercise slowing down disease progression.

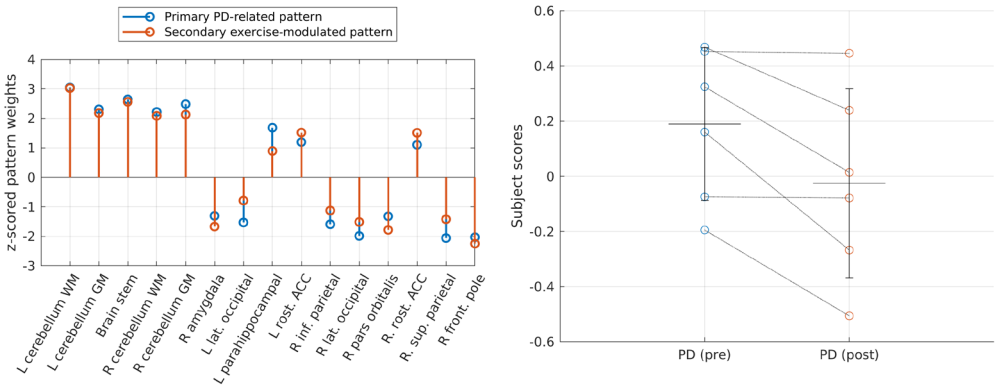

Figure 2. Stem plots of the spatial patterns that characterize changes to CMRO2 metabolism due to disease (blue) and modulated by exercise (red). As with above, the patterns are sets of regional weights, where positive weights indicate relative hypermetabolism of CMRO2 and negative weights indicate relative hypometabolism. Right: subject scores for the exercise-modulated pattern before and after the exercise intervention.

Broader Impact

These preliminary results indicate detectable and quantifiable effects of exercise on neuroimaging measures of PD-induced alterations in brain energetics, potentially offering new insights into the positive impact of exercise on disease progression. Based on these promising findings, we plan to extend these techniques to evaluate the effects of other lifestyle interventions, such as diet and mindfulness, on brain energetics in relation to PD progression, as part of the Impact 360 study. Additionally, this pilot study has paved the way for exploring brain energetics in the context of other potential disease-modifying treatments.

A Personal Message from Dr. Vesna Sossi

Dr. Vesna Sossi

Through your generosity, the UBC Neuroimaging Community can conduct groundbreaking research, and the scientific community throughout Canada recognizes UBC as a leading institution in brain imaging.

This project has been characterized by substantial technical development and the need to overcome early logistical challenges imposed by the COVID-19 pandemic. Nonetheless, the preliminary results show promise, and we eagerly anticipate the completion of the study and analysis. Our deep gratitude extends to all our volunteer subjects, whose generous contributions of time and effort have been indispensable to the progress of this research. With their participation, advancing our scientific pursuits was possible.

Your support is making a significant impact on Parkinson's disease research. It links ongoing scientific advancements with enhancing health outcomes for patients not only in British Columbia but also throughout Canada. The opportunity to uncover new knowledge and positively influence patients, their families, and communities fills my colleagues and I with genuine gratefulness. Thank you for your support.

Thank You

The UBC Faculty of Medicine and Dr. Sossi are sincerely grateful for your transformational support, which will drive breakthroughs in unlocking the mysteries of the human brain. Your ongoing generosity has positioned UBC at the forefront of Parkinson's disease study, and together we can change the future for patients, their families and communities through healthy lifestyle interventions.