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| **Abstract:** | Our goal is to create a state-of-the-art protocol for imaging Neurodegenerative Disease using 3T magnetic resonance imaging (MRI) scanners that will be capable of producing key clinical biomarkers for better diagnosing patients and following changes longitudinally. This will require collecting not only imaging data but also clinical data.  Our target is to collect 5,000 healthy controls and 5,000 Parkinson’s (PD) data sets using the state-of-the-art protocol and this normative data will be used as a public database that can be leveraged by AI and any other relevant software analysis tools to study the aging human brain.  Our proof of value will focus on using this protocol and data with a focus on Parkinson’s disease (PD) where we will develop AI algorithm to segment the deep gray matter, mapping iron in the substantia nigra and mapping neuromelanin in the midbrain and spine. The latter two measures can potentially predict who has PD and help discriminate different types of movement disorders. |

# 1 Overview

Evaluating any clinical biomarker is a difficult task best done with a standardization of a protocol, healthy controls and large amounts of data. We have developed a technology that allows for uniform data acquisition across multiple types of scanners and provides multiple contrast and quantitative data which produces a powerful new imaging biomarkers.

# 2 Relevance

Recently, there has been a major ongoing effort in the study of Parkinson’s disease (PD) in finding imaging biomarkers that can be used to reveal pathological changes. This is particularly important if these biomarkers could identify changes well before the serious onset of disease. In the case of PD, it is believed that up to 60% of the neuromelanin (NM) in the substantia nigra pars compacta (SNpc) has already depigmented by the time symptoms are recognized. To further promote the importance of measuring NM, the loss of NM has been correlated with the loss of dopaminergic neurons in both positron emission tomography (PET) and SPECT studies.

Having a clinically available biomarker would help to capture those patients in an early stage and perhaps allow for preventative treatment before the physical onset of the disease. One exciting new development in the field of magnetic resonance imaging (MRI) is the use of NM imaging along with quantification of iron content as a means to identify PD patients from healthy controls. The validation of NM as a biomarker offers the ability to use MRI in a clinical setting in just a few minutes, making it a practical, available and inexpensive means to monitor PD patients without using ionizing radiation.

# 3 Impact

There are a few ways AI solutions could help. The first is in automatically identifying the deep gray matter, specifically the substantia nigra from surrounding structures. The second is evaluating the iron content as a biomarker for identifying patients with PD. The third is finding the NM regions and their volumes. The fourth is evaluating the overlap between the SN iron containing regions and the NM as a marker for disease progression. The impact of this work would be a method to automatically diagnose PD and to discriminate different types of movement disorders. This affects treatment of the patients.

# 4 Existing work

To date, a number of papers have shown that volume loss of the SNpc and NM regions seen with MRI are associated with PD patients and with length of the disease. The receiver-operator-characteristic curves have yielded values as high as 90% for both sensitivity and specificity. Our hypothesis is by using both the overlap between the SN iron content and the NM measures as well as the SN and NM volume measures, the optimal discrimination between PD patients and HC subjects can be found.

A recent publication in NeuroImage journal by The MRI Institute for BMR “Cerebral microbleed detection using Susceptibility Weighted Imaging and deep learning” uses a deep learning model that was tested using 41 cases, including 13 hemodialysis cases, 9 traumatic brain injury cases, 9 stroke cases and 10 healthy controls. This model achieved similar performance to the most experienced human rater and outperform recently reported CMB detection methods.

One of OBI’s research programs is the Ontario Neurodegenerative Research Initiative (ONDRI), a prospective cohort study that is using a multimodal approach to predict the occurrence or progression of cognitive or neuropsychological impairment in a defined patient population. Patients are enrolled in the study with either (1) AD or amnestic single or multidomain mild cognitive impairment (MCI), (2) amyotrophic lateral sclerosis (ALS), (3) frontotemporal dementia (FTD), (4) Parkinson’s disease (PD), or (5) vascular cognitive impairment (VCI). Participants undergo evaluations across multiple assessment platforms, including extensive MRI data collection.

# 5 Feasibility

## 5i) Establishing international standards for neuroimaging

We have a history of developing and achieving wide adoption of state-of-the-art protocols for imaging neurodegenerative diseases. This includes a TBI protocol established in 2010 for traumatic brain injury still in use today and adopted by the US military for neuro-imaging; a protocol for multiple sclerosis and a protocol for Parkinson’s disease. The PD protocol has been tested at two major Chinese sites with the plans to expand to 7 or 8 next year in a major PD consortium effort.

## 5ii) Managing data sets

At the OBI, all imaging data is currently housed in an XNAT deployment on Brain-CODE. Several quality control pipelines are in place to ensure standardized naming conventions, as well as adherence to scan acquisition parameters. Additionally, on the Brain-CODE platform, we have adopted BIDS (Brain Imaging Data Structure) for data organization, as well as using both fBIRN and Lego MRI phantoms to ensure data quality assurance.

# 6 Data availability

At the MRI Institute for BMR, we have collected over 200 PD cases and 200 HC cases in collaboration with Ruijin Hospital in Shanghai and First Affiliated Hospital in Zhengzhou. (Data sharing is an issue still to be discussed.). However, as long as there is an agreement in place regarding publications and authorship, they are likely to agree to share their deidentified data. All data are in DICOM format and are 3D MRI data. From the Canadian side, we have current relationships with the University of Western Ontario and University of Saskatchewan.

At the Ontario Brain Institute we have open data sharing agreements in place with over 20 sites and host longitudinal MRI datasets from over 165 participants with Parkinson’s disease. These datasets are collected as part of the standardized Canadian Dementia Imaging Protocol (<https://www.cdip-pcid.ca/>). This protocol includes structural MRI, resting state fMRI, and diffusion-weighted MRI scans.

The Ontario Brain Institute is also actively involved in both national and international data sharing initiatives which could increase availability of data for this project. For example, OBI is a member of the Canadian Open Neuroscience Platform (CONP) which is designed to bring together existing Canadian neuroscience data platforms, initiatives and networks, and allow them to link, leverage, enhance and expand to form an integrated network. With enough data we could provide training, validation and finally testing data for evaluating any AI based program.

# 7 Data quality

Most datasets are collected at 3T with modern 32 or 64 channel head coils. The SNR is excellent and the resolution ranges from roughly 0.5 to 2mm3.

# 8 Annotation/label quality

All data are labeled with their appropriate imaging parameters. There are no anatomical labels.

# 9 Data provenance

All data has been collected with IRB approval and patients have signed consent forms. OBI has created [standardized informed consent](https://www.frontiersin.org/articles/10.3389/fgene.2019.00191/full#box5) language that is used across all research projects that plan to use Brain-CODE. The language is incorporated within existing study informed consent forms to describe in clear lay language how data will be transferred to Brain-CODE, in what form, and to explain the nature of open data initiatives. The standardized informed consent language has been widely adopted and has been well received by the research participants.

# 10 Benchmarking

There are many differences between the numerous neurodegenerative diseases that plague older (and even younger) people. For this reason, we need to know how the aging brain changes in its structure, vasculature, function and metabolic behaviour in order to train AI methods to understand what is abnormal against age matched healthy controls.

While our primary focus is PD, our overall aim and benchmark over time will be to have our dataset and protocol standards support the development of AI in other areas as well such as:

* ***Dementia***: Loss of brain function specifically in the hippocampus but also in the form of micro-strokes in the case or vascular dementia or cerebral amyloid angiopathy. Brain atrophy and oxidative stress may be part of the degenerative process.
* ***Multiple Sclerosis***: An auto-immune, inflammatory and demyelinating disease with some association with the venous system and usually attacking the periventricular white matter but with a gray matter component as well. The auto-immune aspect is thought to come from the acute phase of lesion development where the blood brain barrier becomes leaky.
* ***Parkinsons Disease***: A disease affecting the dopaminergic neurons in areas such as the substantia nigra and the locus cereleus. It is associated, as with many other movement disorders, with increases in iron content in the midbrain and basal ganglia.
* ***Stroke***: The vascular system and atherosclerosis are the key elements in understanding and treating stroke. Hence, a comprehensive vascular study is necessary to have in the healthy aging human brain project.
* ***Traumatic brain injury***: It is believed that diffuse axonal injury is the hallmark of this disease. Both structural and vascular damage are possible in many cases.

# 11 Organizer

The MRI Institute for BMR and Dr. Haacke have been doing extensive work in PD for the last few years and establishing MRI protocols for 30 years.

The Ontario Brain Institute (OBI) is a provincially funded, not-for-profit research center seeking to maximize the impact of neuroscience and establish Ontario as a world leader in brain research, commercialization, and care. OBI is an active partner in the funding, fielding and dissemination of research. Championing high impact research programs, OBI accelerates innovation with the goal of better patient outcomes. Through the development and use of a state-of-the-art informatics platform designed to store, manage and analyse findings, OBI’s Brain-CODE is a “shared brain” for researchers in Ontario and beyond.

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