Letter of Transmittal

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March 28, 2022

Dr. Yagna Pathak
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Dear Dr. Pathak,

We would like to thank you and Abbott Neuromodulation for the opportunity to work on this project. The following report contains our current design and prototype description for finding correlations between MRI scans and the progression of Parkinson's disease.

We are implementing a convolutional neural network, for which the implementation is described more in the Design Description section. This project will be completed using our own resources, which are free for the University of Texas at Austin students, and thus our estimated cost is $0.00.

We worked on this project under the mentorship and guidance of our professors, teaching assistants, and advisors. If you have any questions on this matter or concerning any information contained in the following report, please contact Jonathan Mathews at jonmat04@gmail.com.

Sincerely,

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Spring 2021

Predicting the Presence of Parkinson's Disease in T2 FLAIR MRIs

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Executive Summary

Parkinson’s disease is a neurodegenerative disorder that affects more than 10 million people worldwide and is predicted to affect more than 4 million additional people in the next two decades alone. Although Parkinson’s has a high prevalence, especially among the elderly, the causes of the disease are largely unknown, and no cure currently exists. As such, there has long been an urgent need to develop solutions to assess, monitor, and make predictions about a patient affected by Parkinson’s disease. Most prior studies and solutions have sought to measure a patient’s current disease state, predict their likelihood of developing Parkinson’s or existing symptoms worsening, or monitor their day-to-day symptoms and wellbeing. However, no major study or solution has yet been devised in which the progression of the disease has been analyzed to determine which measurement source most strongly correlates with the apparent progression of the disease. This project aims to create a machine-learning-based model that accurately predicts whether a patient has Parkinson’s disease based on anatomical MRI images.

The model uses an input of medical image data to try and classify each image as healthy or Parkinson’s. The data used is a selection of anatomical MRI images of both healthy and Parkinson’s patients from the Parkinson’s Progression Markers Initiative (PPMI). The model extracts and analyzes the pixel data of the analyzed MRI images. The images are then processed to reduce their size when inputted to the model. Only 28 two-dimensional slices were extracted from each three-dimensional MRI scan, reduced from the original 192 two-dimensional slices per MRI, so that only slices containing the subthalamic nucleus were inputted. A five-layer convolutional network is built, predicting the classification of the inputted data and comparing its results with the actual classification of the data. The model is successful, resulting in an accuracy of 98%, a sensitivity of 97%, and a specificity of 99%. In addition to the 2D model, a 3D model was developed that extracts and analyzes voxel data directly from the three-dimensional MRI scans. This model faced memory allocation issues, long queues for the supercomputer, as well as other runtime issues that resulted in no results being collected. However, the framework for a proper 3D image analysis has been built and can be further developed into a working model.

Problem Description

Problem Background

There is a plethora of data available showing the progression of Parkinson's disease in patients; however, there is currently no analysis determining which data streams are most effective at predicting or diagnosing the disease. This project will attempt to address the lack of research by correlating publicly available imaging results with biomarker data from various data streams, including sensors, screens, and clinical sources, to determine which data streams most accurately indicate Parkinson's disease progression. Ultimately, this project needs to attempt to analyze and correlate different types of biomarker data with the progression of Parkinson's disease.

Physiological Basis

Epidemiology Parkinson's disease is a neurodegenerative disease that affects about 10 million people worldwide and is expected to affect almost 14.2 million people by 2040. While Parkinson's disease can affect people of any age, it is most prevalent in older people, with the prevalence percentage increasing from 1% at 65 years to almost 5% at 85 years.[1] While the causes are largely unknown, monogenic (mutations in a single gene) forms of the disease, which account for less than 5% of cases, have been mapped to three dominant genes (*SNCA*, *LRRK2*, *VPS35*) and three recessive genes (*Parkin*, *PINK1*, *DJ-1*).[2] However, all other idiopathic forms of the disease are assumed to be caused by a mix of genetic and environmental risk factors (e.g. family history of Parkinson's disease, history of head trauma).[2,3] In addition to the causes being unknown, a widely accepted mechanism for the progression of Parkinson's disease is just as elusive.

Anatomy and Physiology In those unaffected by Parkinson's disease, the nervous system functions without abnormalities. The concentration of dopamine throughout the brain is at normal levels. Within the ventral tegmental area, where dopamine production takes place, the dopamine concentration will be 4.8 ± 1.5 nM, and in the striatum, the dopamine concentration will be 1.7 ± 0.2 nM.[4] With normal dopamine levels throughout the brain, the dopaminergic neurons will stimulate bodily movement via motor cortex excitation through the nigrostriatal pathway.[5] The direct pathway of movement produces an excitatory effect on the motor cortex. In the presence of dopamine, striatal neurons that make up the direct pathway depolarize due to the D1 Dopamine receptors along the cell's surface. This depolarization excites the direct pathway of movement, exciting the motor cortex. Alternatively, the indirect pathway of movement produces an inhibitory effect on the motor cortex. In the presence of dopamine, the indirect pathway striatal neurons hyperpolarize due to the D2 Dopamine receptors along their surface. This hyperpolarization inhibits the indirect pathway of movement, exciting the motor cortex.[5-6]

Pathophysiology Parkinson's disease is linked with the degradation of dopaminergic neurons in the brain, causing widespread dopamine deficiency. While an unaffected individual will exhibit some degradation of dopaminergic neurons as they age, those affected by Parkinson's have an accelerated loss.[1] Dopamine loss in the peripheral autonomic and olfactory bulb contributes to the early non-motor symptoms. The decrease in dopamine in these areas of the brain results in hyposmia, constipation, and rapid eye movement sleep disorders.[6] These non-motor symptoms precede the motor symptoms by decades. Once the decreased dopamine levels are widespread throughout the brain, the person affected starts to show motor symptoms.[6] The loss of dopaminergic neurons within the basal ganglia, specifically in the substantia nigra, is responsible for many of the symptoms associated with Parkinson's disease, such as tremors and bradykinesia. The loss of neurons in the nigrostriatal pathway results in decreased stimulation within the motor cortex. The lack of dopamine decreases the direct pathway excitation, decreasing stimulation of the motor cortex. Similarly, the lower dopamine levels lead to the failure to inhibit the indirect pathway, further decreasing stimulation.[5] Protein aggregates, called Lewy bodies, start to form within those affected by Parkinson's disease. Lewy bodies are present in the brain areas with the most neuron loss, usually in the substantia nigra; however, Lewy bodies have been observed throughout the nervous system.[7]

Clinical Presentation Parkinson's disease is most commonly characterized by degeneracies in simple motor skills. Currently, there is not a clinical exam that is able to diagnose Parkinson's disease.[8] Instead, physicians look for the presence of the four cardinal features using the acronym TRAP:[3]

1. Tremors at rest
2. Rigidity
3. Akinesia or bradykinesia
4. Postural instability

A variety of cognitive scales are used to evaluate these four motor impairments along with other symptoms, risk factors, and family history; the two most widely used scales are the Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr scale.[9] Patients who score high enough on either of these scales are diagnosed with Parkinson's disease and should seek treatment.

Clinical Outcomes Patients with Parkinson's disease most commonly face motor symptoms causing issues with their daily activities. Due to tremors primarily, people with Parkinson's disease have impaired fine motor skills.[10] Simple motor tasks become more time-intensive for those affected and, in some cases, necessitate aid from caretakers. Those exhibiting akinesia would have a reduced ability to display emotions through facial expressions and body language.[11-12] Body language plays an important part in social interactions, meaning the social interactions of those with Parkinson's disease may be negatively affected, as others may perceive the patients as non-engaged.

Current Solutions

Currently, there is no existing cure for Parkinson's disease (PD). Medications are primarily utilized to alleviate symptoms in patients with PD to help provide a better quality of life. Carbidopa-levodopa is administered in a number of ways (orally, inhalation, infusion) and is the main drug utilized for treatment as it allows for dopamine to reach the brain.[15] Other drugs used for treatment include dopamine agonists, MAO B inhibitors, Catechol O-methyltransferase (COMT) inhibitors, Anticholinergics, and Amantadine.[15] Medications would not be something that competes with our deliverable for this specific project but should be accounted for as we monitor the progression of the disease state.

Another effective treatment for PD is Deep Brain Stimulation (DBS). DBS involves the implantation of electrodes to further control electrical pulses in the brain. DBS is only recommended for Parkinson's patients with advanced cases and is used to control adverse reactions to certain medications.[15] DBS requires surgery to implant the devices used in the treatment. DBS devices are not something that competes with our deliverable for this specific project.

Additionally, there are many wearable devices that utilize accelerometers and gyroscopes to help monitor and track the movements of PD patients to help track the progression of motor symptoms.[16] This is not something that competes with our deliverable, but it merited mention as these devices provide long-term information on the progression of the disease.

As far as tools that are comparable to the deliverable expected from our group, there is a study by independent researchers of an algorithm that seeks similar results to that of the goals of our device. This one, in particular, focused on the diagnosis of early-stage PD with the use of numerical analysis, machine learning tools, and statistical methods. This algorithm made sure to account for the age range of patients since PD progression is age-dependent. The study utilized similar data to that of what we will be working with.[13]

It is important to note that this study's results mainly focused on the diagnosis of PD[13] while our goal is to use similar methods to monitor the progression of PD and possibly understand the molecular biology of it to further understand the progression of the disease state. Based on the research done by our team, there is not another device or study that seeks goals similar to this or our project. Other studies similar to this seek primarily to

determine the early diagnosis of PD or to determine a decision making progress for the treatment of a specific PD patient.

An algorithm for the comparison of Parkinson's patients to healthy patients was developed by The Lancet Neurology. This study aimed to focus on data without using motor control information, which is the most obvious identifier.[14] This information would be helpful in the production of our own algorithm even though the study does not utilize the open dataset with multiple imaging modalities.

Another study reported the utilization of a Deep Belief Network and Self-Organizing Map to predict the progression of the disease state (not to track it).[17] This method was used and evaluated based on a PD dataset similar to the one our group will be used to develop our own algorithm. This study is fairly dissimilar to our project but will be useful to develop our ideas.

All other proposals and studies seek to help determine treatment plans based on symptoms by using decision making algorithms. Other than the specific study listed above, there were none comparable enough to our device to be mentioned in this report.

Market Analysis

Market Size Currently, there is a large potential market for this type of model with no current competitors aside from the previously mentioned algorithms that only scratch the surface of what the targeted goal is. Because of this, there is huge potential for customers in the healthcare industry across the nation and the world. A model that correctly diagnoses, predicts progression, and gives the current disease state of Parkinson's disease would be monumental for the healthcare industry and would likely lead to further breakthroughs in other similar neurodegenerative diseases. There are currently over 10 million people worldwide living with PD.[3] This statistic alone shows the impact a successful model will have.

Market Cost Living with PD has cost individuals a total of 51.9 billion dollars total between healthcare treatments and non-medical losses in the United States alone.[18] This economic cost further shows the need for the more efficient treatment and monitoring provided by the model. This product would likely be marketed to private and public hospitals as a diagnostic test device. The cost for these types of tests cost anywhere from roughly 100 to 4000 dollars.[19] However, it would be hard to compare this device to the cost of current diagnostics since it will be extremely niche.

Stakeholder Analysis

Stakeholder	Role	Benefits	Costs	Net Impact
Payers	Decision maker	*Expansion of Technology*: The model would be further developed after being put to use in the market. These resources would allow for the model to grow to be more precise.	*Risky Investment*: The market is very small and would require very little issues with the model developed.	Neutral
Physicians	Influencer	*Provide Safer Options:* Physicians would be given the option to provide patients with a device designed specifically for PD. This	*Technology Adoption:* Physicians may prove to be slow or less willing to adopt	Positive

		would further allow for a more precise diagnosis and treatment plan to be developed. *Further Understanding of PD*: The diagnostic could provide areas of extrapolation to further understand the disease state development. *Decrease Time*: Physicians would not have to spend time writing medication orders for the patients.	the new technology.	
Facilities	Influencer	*Attract More Business*: The device may draw additional patients that have relied on other forms of diagnostic testing.	*Need For More Resources*: No facilities currently exist specifically for PD testing and diagnostics. Production would take resources and would be reliant on current neurological centers/hospitals for use.	Negative
Patients	Decision maker	*More Precise Diagnostic:* Patients would be given a treatment option that would allow them to avoid potential side effects corresponding to the current PD treatments. The disease state of patients could further be predicted for monitoring.	*Inconvenience*: The patient would likely need multiple scans for diagnostics; this inconvenience is likely minimal considering the current treatment practices.	Positive

Needs Statement

A way to further diagnose, model, and predict the disease state of Parkison's disease in an individual to provide more adequate treatment options.

Needs Criteria

Must Haves	**Nice to Haves**
Correlate data from clinical, imaging, and sensor sources	Framework for easier prediction based on a patient's test results

Consider differences in resolutions of different imaging modalities	Graphical or visual representation of analysis
Integrate different datasets into one larger data frame	
Analysis must determine which data streams correlate most directly with imaging results	

The task of analyzing Parkinson's data to correlate longitudinal imaging and digital sensor data has some specific needs that must be addressed in order for the project to be a success. This project must include data from clinical, imaging, and sensor sources that are available to the team for analysis. Analysis must consider the differences in resolution of the available imaging data and determine a way to standardize the data despite resolution differences. The data from all the sources should be compiled into one larger data frame for ease of analysis and transparency. The last thing that must be done in this project is to determine which data streams correlate most strongly with imaging results, this way one could recommend certain tests or screens based on what is most relevant to determining the state of Parkinson's progression.

One thing that would be really nice to have upon completion of this project is a framework for analyzing an individual's Parkinson progression by relating it to the dataset automatically. This could be done by machine learning, and if machine learning is already in use this could be a nice touch to the project. Another thing that would be nice to have is a visual representation of the analysis to assist in outlining our findings. This would most likely be in the form of graphical analysis but could also be done in other ways such as comparing specific images to emphasize what considerations were made in the analysis of the dataset.

Design Targets

The data for this project comes from an open source database created by the Parkinson's Progression Markers Initiative. This database contains biomarker data that includes both anatomical and functional imaging and digital sensor data. For labeled and unlabeled data, that is data given with the target values and without the target values, our engineering requirements are different.

For labeled data:

- Accuracy > 80%
    - This allows us to check how accurately our labeled data was predicted by our algorithm. A cutoff of 80% allows us to create a robust and working model, but also does not limit us to highly accurate and efficient solutions.
- Specificity > 75%
    - This measure, also called the true negative rate, is a metric of how well our algorithm performs at classifying negative data as negative. By keeping the value at 75%, we allow for some false negatives and keep a healthy margin of error for our primary model design.
- Sensitivity > 75%
    - This measure, also called the true positive rate, is a metric of how well our algorithm performs at classifying positive data as positive. By keeping the value at 75%, we allow for some false positives and keep a healthy margin of error for our primary model design.

For unlabeled data, there are no specific requirements that can be tested and provide us with feedback on our model. Instead, we simply cluster our data together and observe the number, size, and shape of the different clusters. However, for both labeled and unlabeled data, we will be using cross-validation, which essentially trains and tests our model on some of the data, while keeping the rest of the data for a testing round with data unseen by our model. This is meant to reduce biases and overfitting of our model. While this is not testable nor does it act as strong feedback on our model, cross-validation allows our model to train on multiple different folds of our data, and gives our model a more robust look at the biases that could be in the data.

Design Description

Overview

Presently, our prototype model relies on a machine learning technique that learns patterns from features extracted from images fed to the model. This technique is a neural network, specifically a convolutional neural network. Since the PPMI dataset itself contains large sets of data with multiple variables from different modalities, the developed model would potentially greatly benefit from the use of neural networks, as neural networks are ideal for solving complex computation problems involving large datasets and multiple variables. Neural networks also benefit from utilizing an activation function, which allows the network to learn complex and nonlinear relationships between inputs and outputs. Convolutional neural networks are ideal for image and video data, and as such would be of great use for the vast amount of imaging data present in the PPMI dataset. Convolutional neural networks use filters at each layer of the network to extract various meaningful features from the input image or video via convolution and build a feature map for each layer. This type of neural network is also able to automatically learn the filters without manually specifying them, allowing the algorithm to make the best choices in terms of which features to extract from the input data to produce the expected result. Convolutional neural networks are ideal for image and video data also because they can capture and learn the spatial features of an image or video; they can learn from visual patterns and relationships between arrangements of pixels in an image to infer features that help in detecting or identifying an object or its location in an image and its relation to other objects in the image as well. Primarily imaging and non-text, non-sensor data from the PPMI dataset should be analyzed using a convolutional neural network. Convolutional neural networks also benefit from parameter sharing, just as recurrent neural networks do, as convolutional neural networks, at each layer, can apply the filter at that layer to different parts of the input image to produce a feature map consisting of the multiple features learned in the network.

When images are fed to the model, various open-source python libraries (NumPy, Nilearn) are used to convert the images to arrays of pixel intensity values, creating a numerical representation of the images. From there, the same libraries handle feature extraction by looking at the numerical intensity values for each pixel in an image, determining which regions of an image have certain predetermined features, as determined by the creators of the open-source libraries, and storing those features in some data structure. Our model then passes the features and image data, as well as class labels, through a convolutional neural network as described in the previous paragraph, which determines probabilities that certain features are patterns across images of the same class, i.e., images from Parkinson's patients share specific patterns that, on average, are not found in the images from healthy patients. The probabilities and patterns determined from the convolutional neural network can then be used to make predictions on unlabeled imaging data of a similar nature to the labeled imaging data used to train the model, and the predictions are compared against the ground truth for the testing data, as the testing data is labeled data from the PPMI dataset, to determine accuracy and errors of the model.

Design Solution

Figure 1 in the appendix gives a visual overview of the major steps taken by the model from start to finish. The current model works by first obtaining anatomical images from the PPMI dataset of both classes, healthy and diseased, reading and extracting a matrix of pixel intensities from each image, and splitting the three-dimensional scan into 192 two-dimensional slices. Before processing the pixel values of the two-dimensional images, the images are loaded into FSL[20], a neuroimaging processing software, which helps to identify which slices include the subthalamic nucleus (STN). The STN usually shows itself within 3 mm to 17 mm on either side of the midline, utilizing sagittal slices.[21] From the FSL analysis, it was confirmed that the STN was included in the specific slices mentioned previously, and those slices were extracted for input to the model. That data is then standardized by calculating the z-score for each pixel value to reduce unintended feature bias, and the image feature data and class labels from images of both classes are combined into data and label arrays. Once this is done, the data is randomly split into training and testing sets, based on a 70/30 training/testing split. The convolution neural network is then built by five alternating layers (convolutional, max

pooling, convolutional, max pooling, convolutional) and trained on the training data. From there, the resulting tensors from the convolutional neural network are fed to a classification layer for binary classification of healthy or diseased. Once training and testing are completed, the model reports its accuracy and other evaluation metrics, such as loss, sensitivity, and specificity, based on how the model performed when making predictions as compared against the testing data.

Alternative Designs

While the current model analyzes 2-dimensional slices of the medical scans as input, we also built a model that can analyze the full 3-dimensional scan as input and can extract voxel (3-dimensional representation of a pixel) features to analyze. The voxel values are also standardized by calculating the z-score for each pixel value. The 3D design will use 3D convolutional layers and 3D max pooling layers in the same basic structure of five alternating layers that the current model uses. In addition, the 3D design includes some normalization layers, such as dropout layers that randomly delete neurons from the neural network, and a few dimensionality reduction layers prior in an attempt to mitigate the computational and storage costs of the model. This alternative design will follow the same evaluation as the current model.

Evaluation

Prototype

The prototype first preprocesses the images by extracting the pixel data from each of the MRI scans, and storing them in 2-dimensional arrays to simulate a 2D slice of an MRI scan. As stated earlier, the number of 2D slices is decreased from 192 slices to 28 slices per MRI, using only slices between 3 mm and 17 mm on either side of the midline in sagittal slices, in an attempt to reduce overfitting and mitigate computational costs of the model. The pixel data is then standardized using the z-score to avoid giving some features greater weights in the model due to their higher value in the original image. After standardizing the pixel data, it is properly labeled as Parkinson's or healthy, and randomly split into training and testing sets, which make up 70% and 30% of the original dataset, respectively. After the training and testing sets were finalized, the actual deep learning model was built and tested.

The model is made up of five layers: three 2D convolutional layers and two 2D max pooling layers, alternating between the two types. The convolutional layers perform the spatial feature extraction on the 2D images, while the max pooling layers help to downsample the input and keep only the most important features. After passing through these five layers, the input then enters a classification layer where the selected features are used to calculate class probabilities, from which the greater of the two calculated probabilities indicate the predicted class of the image.

This prototype was tested using a small subset of the MRI scans available to our team: 23 healthy MRI scans and 23 Parkinson's MRI scans, which keeps a balanced dataset to reduce bias. Using this data, the model was able to perform successfully, as shown in the following section.

Testing Results

After running the model with the subset of data, the predicted class labels of the test data were compared to the actual labels. From this comparison, a confusion matrix was created, where the positive label was Parkinson's and the negative label was healthy. The confusion matrix was used to calculate accuracy, sensitivity, specificity, and plot an ROC curve.

The preliminary results collected from the model were as follows: accuracy = 98%, sensitivity = 97%, specificity = 99%. In addition the ROC curve (**Fig.2**) had an area under the curve of 0.98, which indicates that the model was successful in classifying 2D slices of MRI scans as Parkinson's or healthy. All of the requirements specified before testing were met, thus resulting in a successful prototype.

Non-Technical Considerations

As long as the specificity, sensitivity, and accuracy of the code are not each 100%, the code will have some errors. Any false negatives will cause missed diagnoses. A false negative will entail potential patients with Parkinson's disease not receiving the proper treatment for their disease. Thus, the disease will progress in these patients while going unnoticed until symptoms severely worsen. On the contrary, any false positives will cause misdiagnoses. False positives will entail a healthy individual incorrectly receiving Parkinson's disease treatment. These healthy individuals may receive medication or undergo surgical procedures to treat their nonexistent condition, which could cause stress and anxiety.

When training our machine learning algorithm with the provided data streams, we must take into consideration the demographics of said data. Ideally, the demographics of the data provided will accurately represent the greater population of patients with Parkinson's disease and those at risk for the condition. However, if the demographics of the data are skewed in comparison to the complete patient population, the algorithm may not be able to detect Parkison's disease equally in all groups of people.

Shortcomings and Improvement

While this design shows a prototype that can classify MRIs as Parkinson's or healthy, issues such as overfitting and feature loss slightly overshadow the success. While the number of 2D slices per MRI were reduced in an attempt to mitigate overfitting issues, the lack of input data proves a bane to the attempt. As stated earlier, only 28 slices from each MRI (46 total MRIs) were used in the model, between training and testing. Usually, deep neural networks, especially for image analysis, require many more inputs to allow the model to properly learn the underlying distribution behind the image sets and separate them into different classes. Due to this lack of input data, the model might be finding patterns within the training data that do not exist when accounting for the whole dataset. This can be tested by running the model using the entire MRI dataset available on the PPMI source.

In addition, the current model is trained on 2-dimensional slices of MRI scans, and as a result could be losing voxel features that can correlate across different slices of the original scan (across volumes). This is the reason why an alternative model that handles 3-dimensional input was developed. The 3-dimensional convolutional neural network could help mitigate the single-class classification issue by providing more specific and important features from the MRI scans to the model. However, the 3D model faced numerous runtime, and memory allocation errors, as well as long queues before being allowed to run. While these issues stopped any results from the 3D model, the framework for the model is finished and can be optimized for work with GPUs (higher processing power) in future work.

Future Work

Currently, our 2D model performs well and can successfully predict whether a patient has Parkinson's disease or not based on MRI scans. While more testing with larger datasets is required to validate the results, we are confident that the 2D model is robust enough to find patterns across the whole dataset. The 3D model is yet to yield any results; however, the framework for the model is built and is ready to be optimized for better computing efficiency.

Another avenue for expansion of our prototype that we would like to explore in the future is including more diverse subjections of our data, and including more data types in our model. The PPMI dataset is a multi-modal dataset with massive amounts of data available in many formats, including anatomical and functional imaging, MRI and CT scans, sensor readings, and clinical assessments. Presently, we are using only anatomical MRI scans, and by including functional images, sensor data, and clinical assessments in our prototype, our model should be able to finally learn and analyze progression of the disease and not just classification, as these other data types are mostly time-series or sequential.

References

1. Wood-Kaczmar, A., Gandhi, S., & Wood, N. W. (2006). Understanding the molecular causes of parkinson's disease. *Trends in Molecular Medicine*, 12(11), 521–528. https://doi.org/10.1016/j.molmed.2006.09.007

2. Noyce, A. J., Bestwick, J. P., Silveira‐Moriyama, L., Hawkes, C. H., Giovannoni, G., Lees, A. J., & Schrag, A. (2012). Meta‐analysis of early nonmotor features and risk factors for parkinson disease. *Annals of Neurology*, 72(6), 893–901. https://doi.org/10.1002/ana.23687

3. Lang, A. E. (2019). Parkinson's Disease at 200 Years: Progress, New Faces, and Unmet Needs. *University of Toronto Medical Journal: Neuroscience*, 93(2), 6–8.

4. Slaney, T. R., Mabrouk, O. S., Porter-Stransky, K. A., Aragona, B. J., & Kennedy, R. T. (2013). Chemical gradients within brain extracellular space measured using low flow push-pull perfusion sampling in vivo. *ACS chemical neuroscience*, 4(2), 321–329. https://doi.org/10.1021/cn300158p

5. Galvan, A., & Wichmann, T. (2008). Pathophysiology of parkinsonism. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, 119(7), 1459–1474. https://doi.org/10.1016/j.clinph.2008.03.017

6. Kouli, A., Torsney K. M., & Kuan W.L. (2018). Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In: Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects [Internet]. *Brisbane (AU): Codon Publications*. Chapter 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536722/ doi: 10.15586/codonpublications.parkinsonsdisease.2018.ch1

7. Zigmond, M. J., & Burke, R. E. (2002). Pathophysiology of Parkinson's Disease. In *Neuropsychopharmacology: The Fifth Generation of Progress* (Section *123*, pp. 1781–1794). Philadelphia, PA: Lippincott Williams & Wilkins

8. Tosin, M. H. S., Mecone, C. A. C., Oliveira, E. F. M., Tsui, D. S., Tan, S.-B., Irene, S., Oliveira, B. C., & de Oliveira, B. G. R. B. (2021). Nursing and Parkinson's Disease: A Scoping Review of Worldwide Studies. *Clinical Nursing Research*. https://doi.org/10.1177/10547738211044047

9. Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. , 79(4), 368–376. doi:10.1136/jnnp.2007.131045

10. Iakovakis, D., Chaudhuri, K. R., Klingelhoefer, L., Bostantjopoulou, S., Katsarou, Z., Trivedi, D., Reichmann, H., Hadjidimitriou, S., Charisis, V., & Hadjileontiadis, L. J. (2020). Screening of parkinsonian subtle fine-motor impairment from touchscreen typing via Deep Learning. *Scientific Reports*, 10(1). https://doi.org/10.1038/s41598-020-69369-1

11. Prenger, M. T., Madray, R., Van Hedger, K., Anello, M., & MacDonald, P. A. (2020). Social Symptoms of Parkinson's Disease. *Parkinson's Disease*, 1–10. https://doi.org/10.1155/2020/8846544

12. Yang, G., Schmiel, L., Zhou, M., Cintina, I., Spencer, D., & Hogan, P. (2019). Economic Burden and Future Impact of Parkinson's Disease Final Report. *Lewin Group*.

13. Singh, G., & Samavedham, L. (2015). Algorithm for image-based biomarker detection for differential diagnosis of parkinson's disease. *IFAC-PapersOnLine*, *48*(8), 918–923. https://doi.org/10.1016/j.ifacol.2015.09.087

14. Goldman, S. M. (2015). A diagnostic algorithm for Parkinson's disease: what next? *The Lancet Neurology*, *14*(10), 971-973. The Lancet Neurology. https://doi.org/10.1016/S1474-4422(15)00192-1

15. Mayo Clinic. (2018). Parkinson’s disease - Diagnosis and treatment - Mayo Clinic. Mayoclinic.org. https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/diagnosis-treatment/drc-20376062

16. Channa, A., Popescu, N., & Ciobanu, V. (2020). Wearable Solutions for Patients with Parkinson's Disease and Neurocognitive Disorder: A Systematic Review. Sensors (Basel, Switzerland), 20(9), 2713. https://doi.org/10.3390/s20092713

17. Nilashi, M., Ahmadi, H., Sheikhtaheri, A., Naemi, R., Alotaibi, R., Abdulsalam Alarood, A., Munshi, A., Rashid, T.A., & Zhao, J. (2020) Remote Tracking of Parkinson's Disease Progression Using Ensembles of Deep Belief Network and Self-Organizing Map, Expert Systems with Applications. https://doi.org/10.1016/j.eswa.2020.113562

18. “Parkinson's Disease Economic Burden on Patients, Families and the Federal Government Is $52 Billion, Doubling Previous Estimates | Parkinson's Disease.” *The Michael J. Fox Foundation for Parkinson's Research*, 13 June 2019, https://www.michaeljfox.org/publication/parkinsons-disease-economic-burden-patients-families-and-federal-government-52-billion. Accessed 25 March 2022.

19. “Diagnostic Tests.” *True Cost of Healthcare*, https://truecostofhealthcare.org/diagnostic-tests/. Accessed 25 March 2022.

20. Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. NeuroImage, 62(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

21. Nakano, N., Taneda, M., Watanabe, A., & Kato, A. (2012). Computed three-dimensional atlas of subthalamic nucleus and its adjacent structures for deep brain stimulation in Parkinson's disease. *ISRN neurology*, 2012, 592678.

Appendix

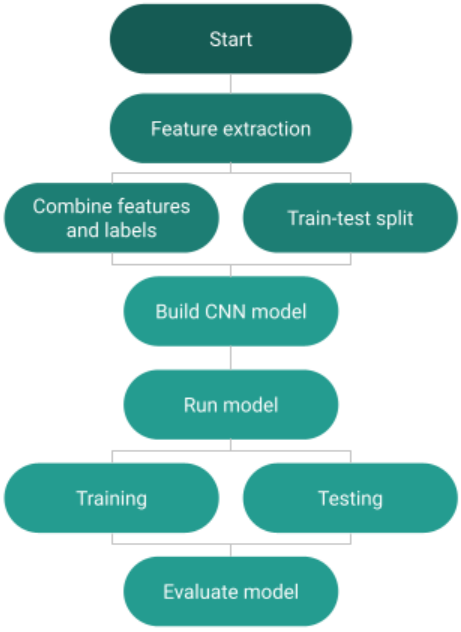

Figure 1 *Flow chart showing major steps of the prototype model*

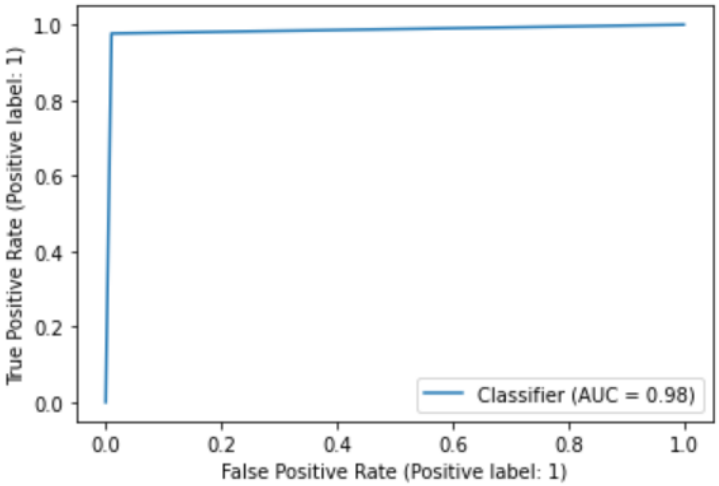

Figure 2 *ROC curve for the preliminary run of the model. AUC = 0.98 shows that the model performed well and correctly classified a majority of positive and negative class MRI images.*