Modeling Neurodegeneration and Regeneration in Parkinson's Disease

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The diagnosis and prevention of neurodegenerative diseases is a heavily examined topic in the neuroscience discipline. Whether it be from the anatomical and biological perspectives or the psychological and sociological perspectives, the ultimate goal is to discover strategies to pinpoint the infection as soon as possible. This article begins with reviewing the small-world network structure and then combines the sociological and anatomical perspectives to explain the progression of neuronal death within the brain by using rsfMRI data and the Hegselmann-Krause Model of Opinion Dynamics to illustrate critical interactions between brain regions, and to predict the ultimate behavior of the neural network after initial degeneration.

Following experimentation–in which critical regions related to Parkinson's Disease were studied–thresholds were identified in specific regions which exhibited consistent converging behavior of the neural network toward either degenerative or regenerative directions. Furthermore, a simple graphical model is proposed to demonstrate the ranges of values in which current brain health could be of concern. We concluded that neuron death in one brain region can lead to further infection in the resulting system; however, some regions can also directly/indirectly compensate for the system's decreased function. In future research endeavors, this could provide insight into developing more accurate predictive models for the goal of early detection of a diseased brain and its recovery.

Keywords
Neurodegeneration; Dopamine; Connectome; Graph theory; Small-World; Hegselmann-Krause; Parkinson's disease

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INTRODUCTION

The progressive loss of neurons can lead to various issues and deficiencies within the brain such as tremors in Parkinson's disease (PD). As one of many neurodegenerative brain diseases that affect the majority of the elderly population, Parkinson's disease (PD) affects approximately one million people currently in the U.S., and 50,000 to 60,000 new cases are diagnosed each year. Parkinson's disease develops from the death of dopaminergic neurons in the substantia nigra pars compacta.[1] Not only is dopamine – a critical excitatory neurotransmitter involved in learning, memory, and motor movement – underutilized in PD patients, but entire systems that involve the substantia nigra as a key component of information exchange are compromised. For example, dopaminergic signaling spans other brain regions including the basal ganglia, nucleus accumbens, and outer cortex. With the deficient function of the substantia nigra, the mesostriatal pathway that controls common behaviors such as reinforcement learning, and voluntary movement are also disrupted.

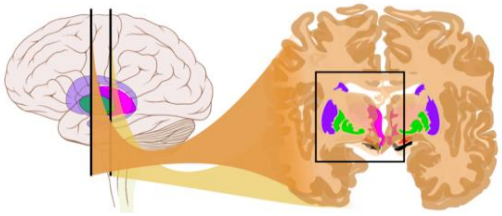

Figure 1: The location of the Basal Ganglia within the human brain. A coronal section of the brain is cut out from this image to show the multiple structures of the basal ganglia.

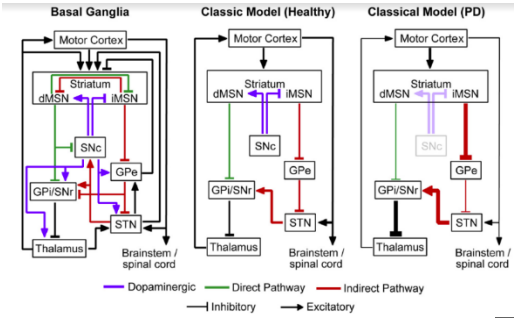

Figure 2: Direct and indirect pathways of multiple types of neurons (including dopaminergic ones) between healthy and PD patients. Lack of signaling from regions of the brain can be identified in PD patients

Efforts toward early diagnosis and prevention of the infection has been initiated from multiple ends of the neuroscience discipline such as deactivating an enzyme involved in apoptosis in order to halt neurodegeneration or controlling the overexcitement of glial cells by inhibiting ion channels.[2,3] While these methods are largely centered around clinical applications, other efforts have focused on predictive models of neurodegeneration to serve the purpose of projecting the long-term results of an individual's condition.[4]

One emerging idea – the connectome – is the main interest of this study. Defined as a visual representation of the neural networks within the brain, it is capable of displaying both static and dynamic changes of cross communication between brain regions. Structural and functional MRI data is compatible with this mode of brain visualization as it can provide a real-life reference to compare predictive results from a model. Therefore, this study utilized the rsfMRI data from The 1000 Functional Connectomes Project to serve as data for the experiments. Benefits of using MRI data in tandem with connectomes include being able to investigate brain networks that vary in scale – from between neurons at the synapse to ones that involve collections of nuclei – to explore major changes within the network due to neuroplasticity, and also reflect the unique aspects of brain

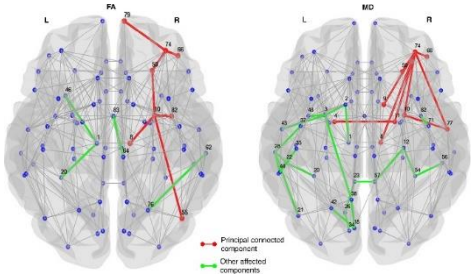

Figure 3: This figure shows a simple connectome of an individual's brain with Parkinson's Disease and the connections that are affected.

structure and function in different individuals. In this case, the goal is to simulate neurodegeneration in a model brain similar to Parkinson's Disease in order to observe negative and positive changes within the entire brain system. [5, 6]

Taking a more sociological perspective on the issue of neurodegenerative diseases, the neural networks within the brain serve functions similar to those of a society. Neurons are analogous to individuals, and the synapses in which they exchange electrochemical signals are analogous to how individuals exchange information through conversation . Graph theory complies with this concept by nodes (the neurons) and edges (their dynamic linkages). Trends within the many nodes and edges in a neural network can be simplified to three distinct parameters on a graph: Segregation, Integration, and Influence. Segregation is defined as the extent to which nodes tend to cluster together, similar to how students in a college may naturally gravitate to specific groups (this value is measured by the clustering coefficient). Integration is defined as how easy communication may occur within the given network, similar to how maybe musically inspired students and artistically inspired students may find many things in common and communicate with each other much more smoothly compared to interactions between the theatre cluster and the math cluster of students (this value is measured by the path length and sometimes closeness). Finally, influence is defined as the "importance" of the nodes, similar to how the president of the club/group may exert an overwhelming impact and reveal the group's vulnerability to collapse if removed. The elements of graph theory are applied to the connectome to study the inner mechanisms of the brain network. [6, 9]

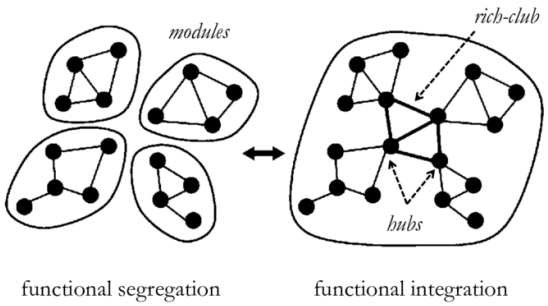

Figure 4: Examples of how segregation and integration engage in simple network analysis.

The novelty of this study resides in the application of opinion dynamics, specifically with respect to the Hegselmann-Krause Model – which again, taps into the sociological perspective of this issue of neurodegenerative disease. Opinion dynamics refers to the study of how opinions evolve and spread through social networks over time – its significance lies in its ability to explain real-world phenomena as common as the psychology of group behavior.[7, 8, 10] In this study, opinions are analogous to the infection of neurons (the nodes), and the evolution and ultimate changes of social structure are analogous to the end state of the neural network. The Hegselmann-Krause Model specifically focuses on assigning values to the bulk behavior of a social – or in this case – neural network. The model involves dynamic agent-based simulations which can allow for predictive assumptions on various populations. It also considers the weight of "opinions" therefore influencing nodes' receptivity and the eventual polarization of clusters. This model flawlessly incorporates all of the concepts above – the connectome, graph theory, and rsfMRI data sets since they are all built upon a similar foundation: the characteristics of agent interaction.

$$x_i(t+1) = \frac{\sum_{j \in \Gamma_\epsilon} x_j(t)}{\#\Gamma_\epsilon}$$

Figure 5: This figure shows the Hegselmann-Krause model equation. On the left, for each additional time increment, a node's state is the average of all of the node states around it.

As a result, the purpose of this study is also to gather and identify similar concepts from sociology, psychology, neuroscience, and computer science in order to propose a novel way of viewing the progression of neurodegenerative diseases. Specifically, rsfMRI data sets will be

analyzed over time using the Hegselmann-Krause Model and the parameters of Graph Theory in order to predict brain states after initial infection/neuronal death. Furthermore, this study seeks to explore and improve the strategies of early diagnosis and prevention in order to provide patients and families with accurate information and assistance.

RESULTS AND DISCUSSION

Static Modeling of the Brain Network

In this section of the experiment, we wanted to review the existence of a small-world network within the brain. Implementing both the rsfMRI data from the 1000 Functional Connectomes Repository and the Network X Python Toolbox, a heat map was generated – where darker colors denoted stronger connections and vice versa – in order to visually represent the linkages between brain regions at a particular instant.

A small-world network is a type of graph in graph theory as having both high segregation (as measured by the clustering coefficient) and high integration (as measured by path length and sometimes closeness). When viewing the generated heat map, the model did in fact display distinct groups of brain regions with significantly stronger linkages compared to others surrounding them and also an off-diagonal path that allows easy exchange of information between clusters. We also referenced a similar generated graph of connections representing the U.S. Power Grid network.[11, 14] Both models exhibit multiple similarities in terms of clustering and path trends. The most probable explanation for these similarities is that a small-world network maximizes efficiency and minimizes energy costs within a given system, therefore providing the system with efficient communication, coordination, and robustness. As nature-made systems like the brain and manmade systems like the power grid continue to pursue efficiency, they naturally gravitate towards a small-world structure.[12]

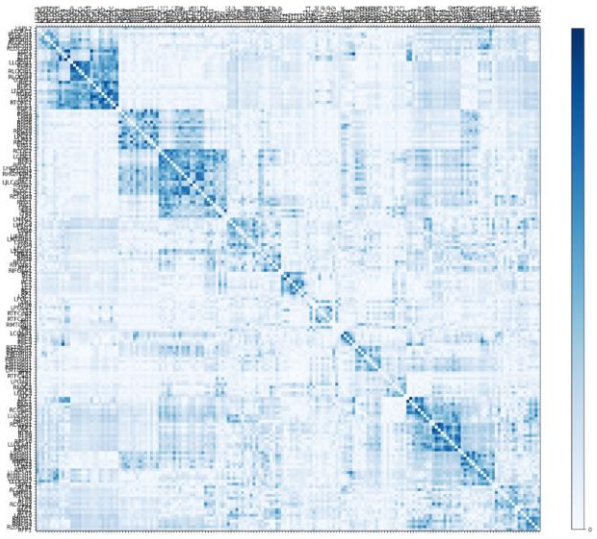

Figure 6: Static heat map representing connections between 180 different brain regions provided by the 1000 Functional Connectomes Repository and Network X Python Toolbox

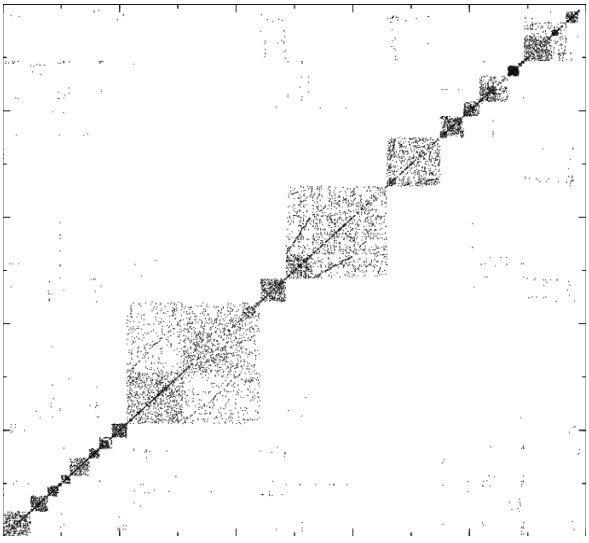

Figure 7: A related image representing the U.S. Power Grid network [11, 14]; both models show similar trends in shape and connectivity strength (dark color versus light color)

Following this, we decided to narrow down the brain regions to those related to Parkinson's disease in order to study their unique connections and influences on the entire brain system. Fifty nodes (regions) were selected and placed on a separate heat map as they were either directly involved with controlling voluntary movement (something PD patients lack) or indirectly collaborating with said regions. The heat map was then used to find regions with the most influence on the 50-node network along with clustering coefficient and closeness calculations (closeness is the inverse of path length).[13] The purpose for this was to find regions that aligned with the Small-World characteristics but also showed a significant impact on the network as a whole. Two regions on both the left/right hemispheres of the brain became the ultimate focus of the second section of the study: the putamen and the thalamus.

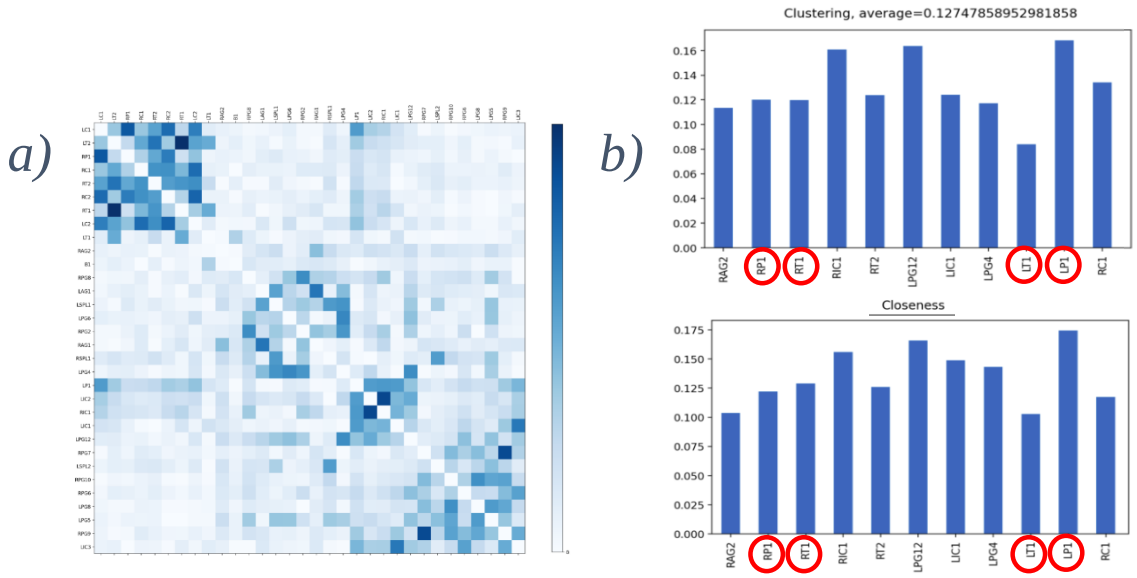

Figure 8: a) The generated 50-node heat map for selected regions related to Parkinson's Disease; small world characteristics are consistent with the previous heat map containing high clustering and short path length b) Clustering Coefficient and Closeness measurements of various high impact regions within the 50-node network (Closeness is the inverse of Path Length); the left/right putamen and thalamus were chosen for the second part of the experiment

The putamen loses its critical role in the deficient brain system of a Parkinson's patient since the region is located within the basal ganglia and heavily depends on intact dopamine communication to function. This region also receives direct input from the substantia nigra pars compacta – the source of neurodegeneration in Parkinson's. With reduced dopamine input due to neurodegeneration in the substantia nigra pars compacta, this results in abnormal firing patterns and abnormal synchronization between the two structures and leads to dysregulation of cortico-striatal-thalamic loops involved in motor programs.

The thalamus loses its critical role in the deficient brain system of a Parkinson's patient since the region directly facilitates communication between subcortical structures such as the basal ganglia and the cortex using the dopamine neurotransmitter. The dopamine loss upstream in the substantia nigra pars compacta and putamen causes downstream structures like the thalamus to change as well – specifically in altering activation thresholds of said neurons as a result of abnormal firing patterns. The incorrect information sent from the substantia nigra, and other structures further exacerbates the cardinal symptoms of Parkinson's Disease. From this evidence,

it is clear that the putamen and thalamus play integral roles in regulating and initiating motor movement and weaken the bulk of the brain system when removed.

Dynamic Modeling of the Brain Network

In this section of the experiment, we wanted to simulate the progression of neurodegenerative diseases such as Parkinson's disease through a dynamic examination of the rsfMRI data from the 1000 Functional Connectomes Repository. The DyNET Python Toolbox and Hegselmann-Krause Model were employed to generate a visual representation of the changes in brain states over one hundred time iterations. Specifically, we wanted to observe the occurrence of a threshold when the initial states of particular brain regions were manipulated (healthy versus infected).

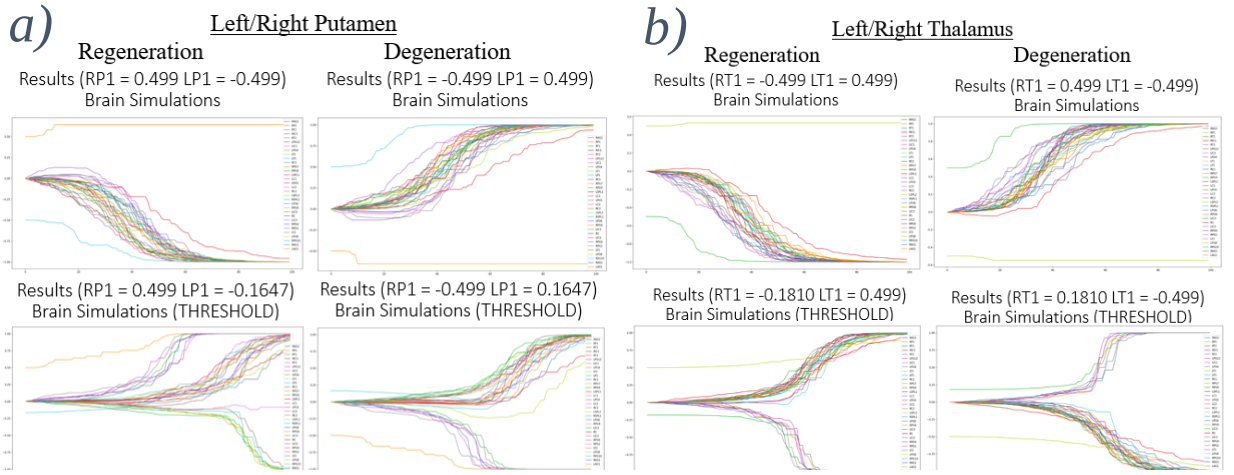

Figure 9: a) Simulations on the Left/Right Putamen where initial states range from -0.5000< x <0.5000; one side (RP1) stayed constant at the highest positive or highest negative value as also to test the compensative ability of brain regions when one side is infected and the other is healthy; a threshold was observed at LP1 = ± 0.1647; all other nodes' initial states stayed constant at zero b) Simulations on the Left/Right Thalamus where initial states range from -0.5000< x<0.5000; one side (LT1) stayed constant at the highest positive or highest negative value as also to test the compensative ability of brain regions when one side is infected and the other is fully healthy; a threshold was observed at RT1 = ± 0.1810; all other nodes' initial state stayed constant at zero

The graphs are formatted so that the x-axis represents time (t) from 1 to 100, the y-axis represents brain states ranging from -1 to 1. In the original Hegselmann-Krause Model, opinions were expressed on a range from 0 to 1 where y = 0 symbolizes one extreme of the spectrum (i.e., absolute certainty, fully trust, etc.) while y = 1 symbolizes the other extreme (i.e., absolute uncertainty, fully opposed etc.) However, we decided on a range from -1 to 1 to symbolize "absolute degeneration" and "absolute regeneration" of the brain system, respectively. Each line on the graph represented one node of the 50-node network chosen from the heat map, and all but the putamen and thalamus nodes' initial states were manipulated in order to control other variables. Therefore, the results from the simulations would only be an effect of the manipulated initial states.

Out of all the simulations executed, the extreme positive, extreme negative, and threshold are displayed. Additionally, one of either the left or right putamen/thalamus remained constant at 0.499 or -0.499 as to assess the compensative ability of the contralateral region when the other was in an infected initial state. Ultimately, the simulation results were compiled into a proposed phase

diagram of neurodegeneration and regeneration progression based on the manipulated initial states of the putamen and thalamus.

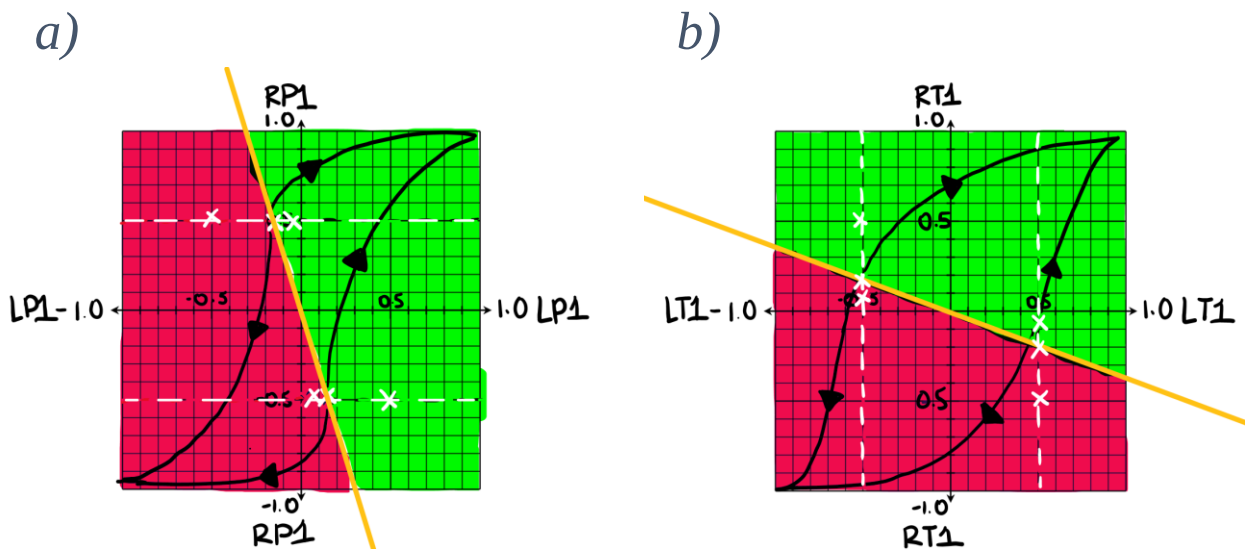

Figure 10: a) Phase diagram of neurodegeneration/regeneration due to healthy/infected brain states of the left and right putamen; a line connects the threshold values (± 0.1647) to separate behaviors that converge on major infection from behaviors that converge on major recovery based on the nature of the Hegselmann-Krause model b) Phase diagram of neurodegeneration/regeneration due to healthy/infected brain states of the left and right thalamus; a line connects the threshold values (± 0.1810) to separate behaviors that converge on major infection from behaviors that converge on major recovery based on the nature of the Hegselmann-Krause model

From these phase diagrams, it can be observed that there is an approximate divide between when initial brain region states lead to major infection or major recovery – denoted by the line connecting the threshold values. Not only that, but in a myriad of other simulations between the extremes and the threshold values, the regions on either side of the brain could compensate for minorly infected initial states of its counterpart – the rates of "degeneration" of all regions of the system were minimal up to a point where they all dropped to full infection. Of course, this aligns with the fact that regions on the opposite side of the brain may be capable of accepting partial responsibility of the functions of its counterpart only for a short amount of time before the progression of neuron loss leads to decreased brain function. From this dynamic modelling of neurodegeneration in a simulated neural network, we were able to distinguish between bulk network behaviors that signified infection or recovery of the brain system and also reviewed the short-term compensative ability of opposite hemisphere structures during the onset of infection.

CONCLUSION

The goal of this study is to gather and identify similar concepts from sociology, psychology, neuroscience, and computer science in order to propose a novel way of viewing the progression of neurodegenerative diseases. Following experimentation, a static and dynamic modelling of brain degeneration and regeneration was proposed. Using the rsfMRI data sets, the concepts of Connectomics, parameters of Graph Theory, and the Network X Python toolbox gave way to a detailed examination of particular brain regions that not only had a significant influence on global brain communication, but also were lacking function and efficiency in Parkinson's Disease.

The Hegselmann-Krause Model and the DyNET Python Toolbox were then applied to the rsfMRI data sets from the 1000 Functional Connectomes Project in order to display and predict bulk behaviors of a simulated neural network after initial infection/neuronal death. This yielded thresholds that divided initial states that would lead to further infection or recovery of the neural network, but also exhibited the short-term compensative behavior of brain regions in opposite hemispheres to replace partial functions in the deficient side during the onset of infection.

This experiment is the first step in examining the progression of neurodegeneration within a simulated brain. Of course, this model is purely predictive, and as a result is currently used with old data references within the 1000 Functional Connectomes Project repository. The model also attempts to dynamically represent (string together) static brain scan images into a comprehensive display of brain region state transitions between infected and healthy. In this case, this study is limited by data type.

In future research, though, once real-time brain scan data can be recorded from patients with neurodegenerative diseases such as Parkinson's Disease, this proposed model will have the capability of predicting unique results in terms of disease progression to accurately diagnose the severity of the brain disease based on the current brain's initial states and predict the progression of the disease against time in order to assist in providing the best treatments possible.

METHODS

Materials Included:

- Network X Python Toolbox for Static Graph
- DyNET Python Toolbox for Dynamic Graph
- 1000 Functional Connectome rsfMRI Brain Scan Repository for General Data Collection
- Hegselmann-Krause Model Equation to Simulate Dynamic Brain Activity Over Time
  Human participants were not involved in the experiment. Only the 1000 Functional

Connectomes rsfMRI Brain Scan Repository was used for data collection. Due to the fact that this repository was publicly available, ethical considerations were not applicable.

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