Project Proposal

Project Title: Modeling T1 Resting-State MRI Variants Using Convolutional Neural Networks in Diagnosis of OCD

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Project Description:

This project serves to find a method to create a more defined and measured system to demonstrate if a patient is suffering from obsessive-compulsive disorder (OCD). Building on the premise that glutamic dysfunction is a primary contributor to the clinical diagnosis of OCD, this project looks at metabotropic glutamate receptor 5 (mGlru5) in particular. Activation levels between healthy and diagnosed patients are expected to deviate and result in a neurological impact on the patient. Therefore, using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the activation level will be modeled against one's Y-BOCS score. These data points can be re-normalized to an appropriate scale that fits the receptor activation values, and then compared against the scores with an analysis to determine this system as a clinical mean of diagnosis. There is expected to be a clear association with higher activation values for mGlru5 and more extreme severity of OCD that also have significant deviation from the Y-BOCS score.

Background:

How does the level of activation in the glutamate receptor mGlru5 influence neurological responses in patients suffering with obsessive compulsive disorder (OCD)? As the levels of the neurotransmitter glutamate's mGlru5 activation level deviates from an empirical mean level, communication between the frontal cortex and thalamus decreases, leading to abnormalities that correlate to and worsen the symptoms of OCD, a pattern which may deviate from the Y-BOCS scale.

Topic Overview: Defining Obsessive Compulsive Disorder

Over the past decade, OCD has been ranked ~~as~~ one of the ten most disabling disorders (Murray and Lopez, 1996). A patient suffering from OCD will often experience a variety of symptoms. These symptoms end up falling into two main categories: obsessions and compulsions. Obsessions refer to being overly focused on a specific issue, involving overthinking that comes in the form of impulsions. Furthermore, compulsions reflect specific actions taken to settle the obsessive piece. These can include checking and mental compulsions, though the list of specific compulsions varies by case (International OCD Foundation, 2010). These symptoms on their own are not a largely concerning issue. The main concern arises when analyzing the impact of these symptoms as a function of time. The fear that comes with failing to complete an impulse is the major component in the factors that push a diagnosed patient to follow their obsession. As a result, a sufferer of OCD will typically spend an hour each day fixated on these obsessions and compulsions (NIMH, 2019). ~~Though~~, an hour a day defines the more common observations of an OCD sufferer. Those facing extreme cases of

OCD can often face further disruptions to their life such as being unable to attend school or work (Medication, Therapy and Now Surgery Offer Hope for OCD, n.d.).

The Systematic Inadequacies

Though OCD has been established as a severely disabling condition, treatments and knowledge of the disorder are still developing. For instance, current treatments involve utilizing selective serotonin reuptake inhibitors (SSRIs). Researchers previously hypothesized that serotonin was an area of target for effectively curing OCD. However, when this solution was tested, 40% - 60% of patients noticed no or partial improvements to their symptoms (Kellner, 2010). Low success rates with SSRIs demonstrate a lack of understanding in targeting the source of OCD. Thus, rather than focusing on serotonin-based solutions, glutamate has risen as a new area of study in understanding the triggers for OCD. Though, glutamate serves in various aspects of learning and memory, meaning that expanding a correlation from glutamate to OCD would not be specific enough. However, drawing correlations between specific aspects of glutamate and obsessive-compulsive disorder is not possible without defining and understanding the core concepts of the neurotransmitter glutamate.

Glutamate

Prior to glutamate, the neurotransmitters of the target were serotonin and dopamine. However, as evidenced by the low remission rate, these targets proved to be an ineffective choice. As a result, the neurotransmitter glutamate was instead looked at. Glutamate is an excitatory neurotransmitter, meaning that it stimulates a nerve cell that sends a chemical message from a nerve cell to another nerve cell. Glutamate itself is made from glial cells in the brain and is recycled as the older glutamate is simply refreshed with new glutamate naturally. Beyond serving the different trigger actions, glutamate also helps to process gamma-aminobutyric acid, which is another neurotransmitter to calm the brain. In the body, glutamate serves to enhance learning and memory, energy sources for brain cells, chemical messengers, sleep-wake cycles, and pain signaling. Therefore, in the scope of OCD where obsessive behaviors such as constant checking are prevalent, the involvement of glutamate becomes a potential. Furthering this notion is the past work done with glutamate. At Ruhr University in Germany, researchers were able to determine that glutamate led to a higher cerebrospinal fluid level in OCD patients compared to non-OCD patients. High levels of glutamate were also observed in OCD patients based on a magnetic resonance spectroscopy scan at Wayne State University (International OCD Foundation, 2010). However, concluding that glutamate is a cause for OCD would be an extrapolation. With anxiety disorders, changes observed in the brain may be a consequence of the disorder rather than a cause. Therefore, in the case of OCD, patients with the disorder may experience higher levels of glutamate as a result of being diagnosed with OCD rather than the glutamate being a casual factor. Determining which side of the spectrum glutamate falls on presents itself as a major knowledge gap in OCD research. Creating medication oriented towards glutamate before confirming its function would assume a correlation drawn between the two would result in a drug that creates unanticipated consequences. As previously stated, glutamate is responsible for providing a plethora of functions to the brain, meaning that incorrect modifications to the function of glutamate could lead to devastating impacts. Therefore, past literature has begun to examine specific receptors that show excessive signaling. Specific receptors are more accurate to study

because they depict the behavior of the neurotransmitter. In the case of glutamate and OCD, this receptor was mGluR5.

Metabotropic Glutamate Receptor 5

Furthermore, with mGluR5 as a specified receptor, further methods have been investigated. Levels of mGluR5 can be measured by the distribution volume ratio (DVR) — a linear function that expresses a receptor's availability. mGluR5 is commonly associated with mood disorders and addiction, making it a primary receptor of study in the scope of OCD. A recent study confirmed the importance of mGluR5, not specifically in terms of OCD, but more broadly in the view of mental disorders. Researchers from the United Kingdom found that intervention of mGluR5 led to anxiolytic effects. By definition, because OCD is an anxiety disorder, an anxiolytic effect would be of interest in finding a target for medications. Furthermore, these researchers found that this receptor also has influenced social functions and responses to social stress— important factors of OCD (Terbeck, 2015). Therefore, at face value, mGluR5 appears to be a potential receptor for studying OCD. Observing previous evidence and findings helps to confirm or alter this notion.

Evidence and Issues with Metabotropic Glutamate Receptor 5

Previously, researchers at Duke University conducted a study using mice. Their main goal was to examine the significance of mGluR5 in this organism in terms of any abnormalities that occurred with the mice. As a result, they discovered that mGluR5 signaling in excessive amounts was demonstrated by the mice. In their literature, they state that the findings prove at least a causal relation for mGluR5 and OCD (Ade et al., 2016). Other studies in the field have also supported these findings. However, the issue arrives with counter examples or studies involving confounding variables. Researchers in Switzerland conducted a similar study involving mice where they attempted to find mGluR5 binding in OCD patients. The distribution volume ratio (DVR) of the receptor was measured as a response on a group of 10 individuals put through a PET scan. No significant difference between receptors in healthy versus OCD diagnosed patients. However, this study was unable to account for patients that had previously also suffered from OCD (a major component of the participant sample). This experiment was invalidated because many of the OCD patients had depression in the past which reduces their DVR (Akkus et al., 2014). As a result, studies such as this one, lead to highly unclear results about mGluR5 and its potential role in OCD. Therefore, there is a need for understanding how the level of activation in the glutamate receptor mGlru5 influences neurological responses in patients suffering with OCD.

Experimental Design/Research Plan Goals:

Model 1 IDV: T1 resting-state scans provided for OCD, anxiety, depression, and healthy patients.

Model 2 IDV: Dataset and values provided with the data alongside the number of datasets available and data within each.

Model 1 DV: Vector of the inputted MRI scan images per disorder

Model 2 DV: Accuracy based off gene expression/other available datasets

Controls: The languages used to perform analysis as well as applications used in analysis as they have no impact in the results.

Iterations: iterations will involve changing the algorithm used in determining results in order to achieve more accurate or more efficiently produced results

Materials List:

- 13-inch 2022 MacBook Pro with M2 silicon chip
- Remote development server via SSH
- Jupyter Notebook
- iTerm
- Visual Studio Code
- Pandas
- TensorFlow
- Python 3
- CSV files
- JavaScript
- Java

Procedure:

1. Download gene expression data for OCD from NIH as well as from Nature
2. Download T1 resting-state datasets from OpenNeuro and from Nature
3. Pre-process T1 resting-state scan images to standardized images for model
4. Create diagrams to display the distribution/demographics of scan data in use (i.e. charts)
5. Create model for patterns based on convolutional neural networks using tensorflow/pre-trained machine learning algorithms
6. Divide up data with roughly one quarter being left for testing data and the other three quarters being used for training the model
7. Repeat steps 5 and 6 for each disorder (OCD, depression, anxiety)
8. Train the models with the selected model from step 2 using the test data set aside from step 7
9. Feed the remaining quarter of test data back into the model and receive metrics for accuracy for each model
10. Improve the dataset via modifications to the existing algorithm
11. Determine areas of high signaling/activity in the T1 resting-state vector resultants

12. Correlate gene expression results from T1 resting-state to expected and preform analysis

Future Extensions:

In order to make these results more accessible to those that would require them, an application could be developed in order for a user to input either their Y-BOCS score or gene data. Because Y-BOCS test score would more likely be accessible to a user, inputting this value would allow them to view a variety of stats and analytics for their gene expression data, specifically with mGlru5. However, this potential extension would need to take into consideration security of data in order to ensure that patients are able to securely send and receive information.

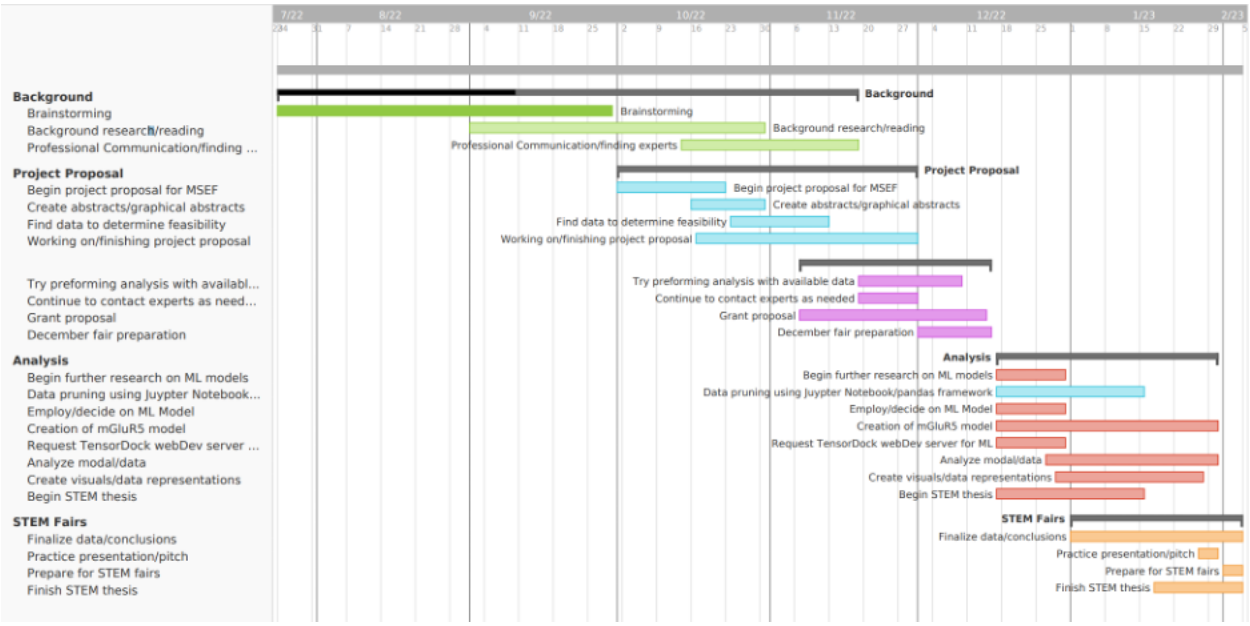
Risk/Safety Concerns:

This project is centered around using AI, therefore there are no risks to humans/animals.

Data Analysis:

Once the procedure is completed, the recognition of different gene expressions can be compared with another for significance using statistical analysis. It is expected that ANOVA will be used to find variation across 2+ genes from the dataset. Furthermore, the data used in this project will be made accessible at the conclusion. In addition, correlation between the target gene—mGlur5— and Y-BOCS scores will be conducted. Because Y-BOCS values may not be included as part of the original dataset, Y-BOCS and gene pattern values will be normalized to a normal model and the compared against the other to deter the feasibility of correlation. If determined as feasible, a paired t-test will be utilized.

Timeline:



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