Research Plan/Post Summary

1. ***a) Rationale***

Schizophrenia is a psychotic disorder that is characterized by disruptions in thought processes, perceptions, emotional responsiveness, and social interactions. Schizophrenic patients experience hallucinations, delusions, and have difficulty in differentiating between reality and what they have imagined. This disorder is one of the top 15 leading causes of disability in world[1,8,11] . However, due to the complexities that come with diagnosing schizophrenia, it is difficult to say exactly how many people are affected by the disorder. Current estimates based on clinical research, surveys, and medical records indicate that approximately 1.06% of Americans and 1.10% of people worldwide are afflicted[1,8,11].

People are generally diagnosed with schizophrenia and similar ailments late in their teenage years or in early adulthood. However, with advancements in technology, doctors have been able to offer diagnoses at earlier ages[10,13]. This allows for earlier interventional treatment to occur and prepare patients for dealing with the disorders.

The issue with this is that diagnosing adult patients with psychotic disorders is a very complex process that involves waiting for symptoms to be exhibited by the patient at a typical age to onset and an analysis of their medical history to ensure that no outside variables could be at play to see if their development matches what a typical patient's development would be[8,10,13]. When applying this to a pediatric patient, many issues arise, the most prevalent being the difficulty to differentiate between a child with an active imagination and a child suffering from hallucinations and delusions[3,10].

Additionally, the symptoms attributed to individuals affected by a specific psychotic disorder often overlap with those of another one[2,3,7,13]. For example, schizophrenia and

psychosis patients generally experience hallucinations and delusions. For the past century, they have been classified according to the Kraepelinian system. This dichotomy of psychoses is the division of endogenous psychotic disorders into conceptual categories that focus largely on schizophrenia and bipolar disorder[13,14]. Recent debate has risen regarding this classification because of the magnitude of similarities the disorders share[13,14]. Moreover, when a patient is diagnosed with one of these disorders, it is probable that they will be affected by other mental disorders[10,18]. This explains why doctors can have difficulty in diagnosing patients with psychoses, which is only magnified when working with pediatric patients due to the complexities involved in interpreting their symptoms.

A gray area in the diagnostic process of schizophrenia and other psychoses is that there are no concrete anatomical indicators that are present in a majority of affected individuals[10,18]. This factor often causes physical indicators, such as volumetric brain measurements from magnetic resonance imaging (MRI) data, to be overlooked[10,18]. However, these types of measurements can be used to find significant trends in patients with schizophrenia, specifically in pediatric patients.

In conjunction with trends being pinpointed in pediatric schizophrenic patients, the analysis of prevalent anatomical trends in brain development in pediatric patients with family history of other disorders will aid doctors in differential diagnoses of schizophrenia. If significant trends are known, then diagnoses can be supported by information of the patients' development in comparison to that of similar disorders. Based on those trends, doctors will also have a better understanding of a patient's prognosis due to a comparison of brain development in patients with a family history of similar psychotic disorders.

These volumetric measurements include gray matter volume (GMV), white matter volume (WMV), global cortical thickness (GCT), cerebrospinal fluid (CSF), and total-intracranial volume (TIV) and are derived from the MRI data of patients through a three-dimensional segmentation procedure.

Gray and white matter volumes are measures of how much space each respective tissue takes up in the brain and spinal cord[12,16,17,18]. Gray matter is the 'living; tissue of the brain since it is responsible for chemical signals being sent and received due to it hosting the entirety of brain's dendrites, axon terminals of neurons, and synaspes[16,17]. White matter is tissue that is primarily composed of axons to connect the gray matter[12,18].

Global cortical thickness refers to the morphometric analyzation used to examine the breadth of the cerebral cortex's layers[4,9,12]. Measurements of cerebrospinal fluid refer to the amount of fluid in the space between the arachnoid membrane and the pia mater of the spine[12]. Total intracranial volume is the measure of how much space is in the cranial cavity of a subject[5].

These measurements have been utilized as tentative physical indicators in previous studies on schizophrenia but were used on large groups that varied in ages[2,6,7,9,12]. These results allowed researchers to hypothesize how schizophrenics' brains would develop over time. Although, volumetric measurements have not been adequately studied as a means of physical markers to support a diagnosis of schizophrenia.

The two other psychotic disorders were selected to be involved in this experiment due to their high correlations and similarities to schizophrenia; bipolar disorder and psychosis[2,7,13,14]. Bipolar disorder is characterized by extreme mood swings. Although it is far complex than what

the general population may believe; those affected experience manic and depressive episodes that can last from hours tomonths[7]. Psychosis is a broader type of diagnosis as it is defined as a mental state where patients often lose touch with reality and have difficultly conducting mundane thought processes. They are also subject to a myriad of symptoms, including spacing out, bouts of agitation and confusion, and extreme delusions[8].

b) Hypothesis

The goal of this investigation was to pinpoint significant trends in volumetric brain measurements in subjects with schizophrenia, family history of bipolar disorder, and family history of psychosis to act as support for differential diagnoses of schizophrenia in pediatric patients. Statistical analysis was conducted on the aforementioned measurements to locate prevalent trends. The hypothesis was that volumetric brain measurements can be utilized as a differential diagnostic tool of schizophrenia in pediatric patients.

c) Methods

Subjects

All subjects are to be collected from the Child Mind Institute's Healthy Brain Network, a database of over 1000 participants from the New York metropolitan area. The experiment will include female and male subjects ranging from ages of 5 to 20 years old that were diagnosed with schizophrenia, had a family history of bipolar disorder or psychosis. These subjects along with their respective age and gender matched controls are to be analyzed.

Each schizophrenic subject analyzed will solely be diagnosed with schizophrenia while the subjects with a family history of the latter disorders were not diagnosed with any psychotic disorder. All the patient data is de-identified prior to being obtained since the source is an open

database. Additionally, each control subject will have no diagnoses and be age and sex-matched to subjects to each disorder group.

Segmentation Procedure

All subjects' T1-weighted files will undergo the same segmentation procedure via three-dimensional imaging software Matlab (R2017b, MathWorks, Natick, MA), Cat12 (2016, CAT, Jena, Germany) and SPM12 (2017, London, UK). Before the segmentation process, each image will be orientated to normalize them. This will be accomplished by navigating the crosshairs on the T1-weighted images to intersect the anterior commissure.

In Cat12, voxel size for the normalized images will be specified as 1.0-millimeter, deformation fields will be specified to be outputted in the inverse orientation, and surface and thickness estimation, as well as native space for gray and white matter, are to be selected as outputs.

Intracranial Volume Estimation

XML files of each subject group will be inputted into the 'Estimate TIV' facet of Cat12's statistical analysis tools in the order they are to be used for comparison (schizophrenia group, family history of bipolar disorder, and family history of psychosis). For all comparisons after this point, the same order will be employed.

Smoothing Gray Matter

In SPM12, a neuroimaging analysis software, gray matter files resulting from the segmentations will undergo smoothing. This will yield SPM files which subsequently undergo estimation.

Cortical Thickness Extraction Process

Surface data of each subject will be resampled and smoothed in Cat12. The smoothing filter will be 12.0x12.0x12.0 millimeters. Additional surfaces will be extracted from the newly smoothed images, specifically the centralized left hemisphere surfaces. These resulting surfaces will then subject to the previous smoothing procedure and the creation of their respective SPM files.

Statistical Models

The basic models function in Cat12 will be used to format the statistical model for each outputted volumetric measurement. Two-sample *t*-tests with *p*-values of 0.05 will be used to compare each subject's group's volumetric measurements to one another, including controls, with a threshold of 0.1 for the gray matter analysis and no threshold masking for all other measurements. Each *t*-test will have uniform contrasts: Group 1 > Group 2, and Group 2 > Group 1.

d) Bibliography

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2. Subject Specific Guidelines:

Non-applicable as this project did not include human participants, vertebrate animals, PHBAs or hazardous chemicals, activities and devices.

3. ***Addendum:***

No changes were made to the original research plan.