Volumetric Measurements Provide a Differential Diagnosis of Schizophrenia from Related Disorders

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Introduction

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].

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.

Methods

Subjects

All subjects were collected from the Child Mind Institute's Healthy Brain Network, a database of over 1000 participants from the New York metropolitan area. The experiment included 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. Specifically, data from 14 subjects with schizophrenia, 14 with a family history of bipolar disorder, and 31 with a family history of psychosis, and their respective age and gender matched controls were analyzed.

Table 1: Demographic Information

Subject Group	Number of Subjects	Number of Controls	Average Age (Years)	Gender
Schizophrenia	14	14	13.13	6 Females 8 Males
Family History of Bipolar Disorder	14	14	10.90	6 Females 8 Males
Family History of Psychosis	31	31	11.17	15 Females 16 Males

(Created by Researcher)

Each schizophrenic patient selected was solely diagnosed with schizophrenia while the subjects with a family history of the latter disorders were not diagnosed with any. All the patient data were de-identified prior to being obtained. Additionally, each control subject had no diagnoses and was age and sex-matched to subjects from each disorder group.

Segmentation Procedure

All subjects' T1-weighted files underwent 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 was orientated to normalize them. This was accomplished by navigating the crosshairs on the T1-weighted images to intersect the anterior commissure.

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

Intracranial Volume Estimation

XML files of each subject group were inputted into the 'Estimate TIV' facet of Cat12's statistical analysis tools in the order they were 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 was employed.

Smoothing Gray Matter

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

Cortical Thickness Extraction Process

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

Statistical Models

The basic models function in Cat12 was used to format the statistical model for each outputted volumetric measurement. Two-sample *t*-tests with *p*-values of 0.05 were 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 had uniform contrasts: Group 1 is greater than Group 2, and Group 2 is greater than Group 1.

Analysis

The two-sample *t*-tests resulted in significant differences in the volumetric measurements of each subject pool to be identified. This information was then evaluated through SPSS (2009,

IBM Stanford, CA), a statistical software. The tests also calculated *T*-values that indicate whether there was an increase or decrease in the volumetric measurements for a specific group.

Then, a multivariate ANOVA encompassing every variable was conducted to assess how each yielded variable compared to each other and produced an f-value. Several one-directional ANOVAs were conducted for each volumetric measurement as well.

The covariates accounted for were age and gender as they are known to impact brain development. The dependent variables, volumetric brain measurements, also underwent a full factorial analysis with an alpha of 0.05.

Additionally, a receiver operating curve (ROC) analysis was performed through Matlab to assess the performance of all recorded volumetric brain measurements as predictive tools, including calculations of the area under the curve (AUC), specificity, sensitivity, and accuracy.

Results

Two-Sample t-Tests

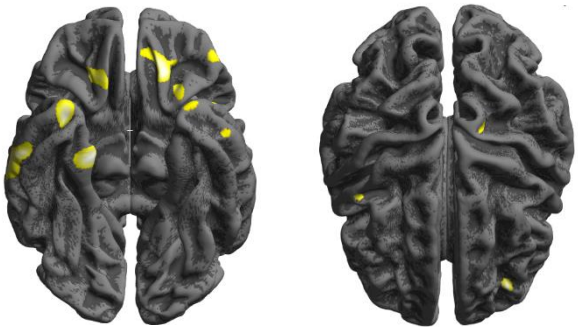
The two-sample *t*-tests revealed significant increases in cortical thickness and brain gyrification when comparing the schizophrenic subjects to subjects with a family history of bipolar disorder with a family history of psychosis.

Table 2: Two-Sample t-Test Results Schizophrenia Compared to Fam. Hx. Bipolar Disorder (Cortical Thickness)

	p-value	Voxel Size	*T*-Value	Coordinates (x y z)
Region 1	0.002	4771	6.42	-20 15 -36
Region 2	0.002	4143	5.82	13 03 -21

(Created by researcher)

Figure 1: Visual Representation of Two-Sample t-Test Results Schizophrenia Compared to Fam. Hx. Bipolar Disorder (Cortical Thickness)
(Created by researcher)



According to Table 2 and Figure 1, schizophrenic patients showed statistically significant ($p < 0.05$) differences in cortical thickness when compared to the cortical thickness of subjects with a family history of bipolar disorder. The coordinates and positive *T*-values of 6.42 and 5.82 show that these discrepancies were increases in cortical thickness in region one, the left temporal pole, and region two, the right amygdala respectively.

Table 3: Two-Sample *t*-Test Results Schizophrenia Compared to Fam. Hx. Psychosis (Cortical Thickness)

	p-value	Voxel Size	*T*-Value	Coordinates (x y z)
Region 1	0.054	566	5.06	-37 17 8

(Created by researcher)

Figure 2: Visual Representation of Two-Sample t-Test Results Schizophrenia Compared to Fam. Hx. Psychosis (Cortical Thickness)
(Created by researcher)

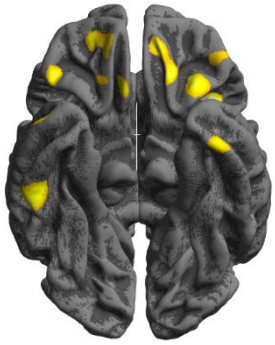


Table 3 and Figure 2 show the differences in cortical thickness in schizophrenic subjects when compared to subjects with a family history of psychosis. The *T*-value of 5.06 indicates a significant increase in the left inferior frontal gyrus at a *p*-value of 0.054.

Table 4: Two-Sample *t*-Test Results Schizophrenia Compared to Fam. Hx. Psychosis (Brain Gyrification)

	p-value	Voxel Size	*T*-Value	Region (x y z)
Region 1	0.000	557	4.71	31 7 -42

(Created by researcher)

Figure 3: Visual Representation of Two-Sample *t*-Test Results Schizophrenia Compared to Fam. Hx. Psychosis (Brain Gyrification)
(Created by researcher)

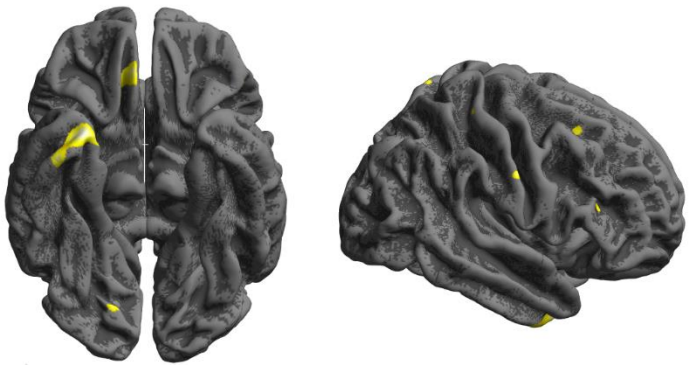


Table 4 and Figure 3 demonstrate that schizophrenic subjects also showed a substantial increase in gyrification in the right temporal pole when compared to subjects with a family history of psychosis at a *T*-value of 4.71 and *p*-value of 0.000.

General Linear Model

Table 5: General Linear Model Statistics on Effect of Schizophrenia on Volumetric Measurements

Volume	F-statistic	*p*-value
TIV	1.365	0.243
GMV	1.731	0.134
WMV	2.410	0.041
CSF	15.074	<0.001
GCT	4.524	0.001

(Created by researcher)

The general linear model statistics shown in Table 5 express significant variation in the WMV, CSF, and GCT measurements in subjects with schizophrenia in comparison to both other subject groups (family history of bipolar disorder and family history of psychosis). It also shows that the TIV and GMV differences in schizophrenic subjects are not statistically significant ($p > 0.05$) when compared to both groups. This is unlike the two-sample *t*-tests as those were comparisons of the schizophrenic subject pool to one other subject pool at a time; the general linear model compares all three groups at once. Thus, signifying that specific variations in

volumetric brain measurements in schizophrenic subjects are statistically significant when compared to both other groups.

ANOVAs

Table 6: Multivariate ANOVA Statistics – Schizophrenia Group Compared to Fam. Hx. of Bipolar Disorder and Psychosis Groups

Volumetric Measurement (V)	Comparison Subject Group (S)	Mean Difference (V-S)	Std. Error	*p*-Value
TIV	Fam. Hx. Bipolar Disorder	-77.4176	12.45365	0.000
	Fam. Hx. Psychosis	-59.5714	10.41147	0.001
GMV	Fam. Hx. Bipolar Disorder	-36.6099	11.10557	0.103
	Fam. Hx. Psychosis	-8.6843	9.28445	0.969
WMV	Fam. Hx. Bipolar Disorder	-37.2692	2.69615	0.000
	Fam. Hx. Psychosis	-23.0484	2.25403	0.000
CSF	Fam. Hx. Bipolar Disorder	-20.3956	1.41227	0.000
	Fam. Hx. Psychosis	-43.3088	1.18068	0.000
GCT	Fam. Hx. Bipolar Disorder	-0.1059	0.01384	0.000
	Fam. Hx. Psychosis	-0.1167	0.01127	0.000

(Created by researcher)

According to Table 6, schizophrenic subjects showed statically significant differences in four out of the five tested volumetric measurements. Since the *p*-values for GMV are above an alpha of 0.05, this means that the differences in gray matter volumes would not be a reliable physical indicator for schizophrenia in this population.

In addition, when a one-way ANOVA was conducted on the data in Table 6, the results showed that TIV, WMV, CSF, and GCT were all significantly different in schizophrenic patients. It also indicated that GMV was approaching statistical significance.

ROC Analysis

Tables 7-9: ROC Analyses' Coefficients and Predictors
(Created by researcher)

Table 7: Schizophrenia

Row	Coef2
Intercept	-0.400020069
Age	492307825
CSF	1.068063352
GMV	1.26078359
WMV	-1.793900342
GCT	0.955836949

Table 8: Fam. Hx. Bipolar Disorder

Row	Coef2
Intercept	-0.46692985
Gender	-0.402185377
CSF	1.649140832
GMV	0.343587109
WMV	-0.802878295
GCT	1.870428121

Table 9: Fam. Hx Psychosis

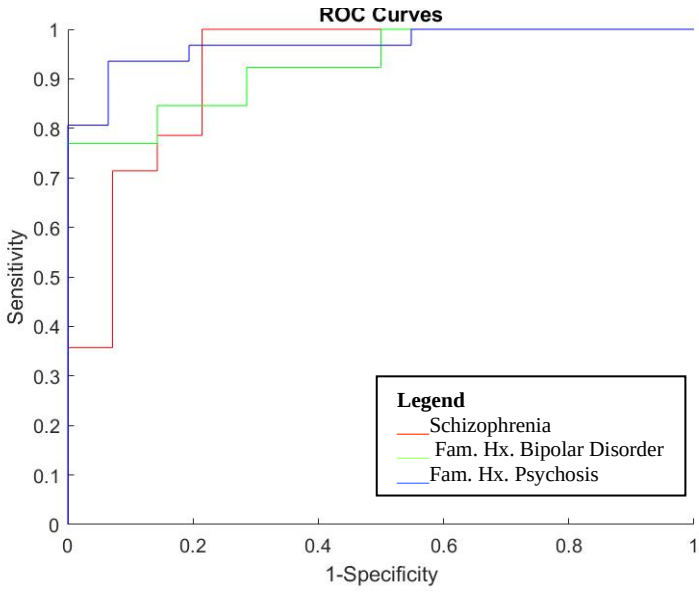
Row	Coef2
Intercept	-0.437596302
Gender	-0.064064904
CSF	2.727077635
GMV	-0.281838194
WMV	-0.29906052
GCT	2.590068269

Table 10: AUC Analysis Results

Predicted for Variables	AUC	Sensitivity	Specificity	Accuracy
Schizophrenia	0.92	100%	79%	89%
Family History of Bipolar Disorder	0.93	77%	100%	89%
Family History of Psychosis	0.97	94%	94%	94%

(Created by researcher)

Figure 4: ROC Curves for Subject Groups



(Created by researcher)

As a diagnostic test, the ROC analysis demonstrates the accuracy of the model's ability to use volumetric measurements to differentiate between the three disorders. Tables 7-9 indicate that CSF, GMV, WMV, and GCT are the most reliable in predicting which disorder the subject has. Table 10 specifically cites the AUC values that were depicted in Figure 4. The range for the AUC values, 0.92-0.97, demonstrates that the volumetric measurements are very accurate in determining what disorder a subject has in this population. Figure 4 offers a visual representation of the data in Tables 7-10 to further clarify how accurate the volumetric measurements are as tools to determine which disorder a subject has.

Discussion

Through the use of three-dimensional imaging software, specific trends of volumetric measurements in pediatric schizophrenia subjects were able to be determined. Thus supporting the hypothesis that volumetric measurements can offer a differential diagnosis of schizophrenia from related disorders. As the two-sample *t*-tests outputted the regions that were significantly different in the schizophrenic subjects per volumetric measurement, physicians can now utilize this knowledge to further support their diagnoses of schizophrenia in pediatric patients. Due to the sample size used, further research can be done by focusing on the development of these locations in pediatric schizophrenic patients, but with a larger subject pool to fortify the results and further specify how brain development is affected in these regions.

Furthermore, the results of the general linear model and multivariate ANOVA show that the disorder of a subject does influence their WMV, CSF, and GCT measurements. This test also corroborates the findings of the *t*-tests, which showed statistically significant increases in GCT and brain gyrification in schizophrenic patients. These findings suggest that the volumetric

measurements used in this experiment can be used as differential diagnostic tools for schizophrenia due to their significance in variation in this population.

Additionally, the use of multiple statistical analyses allowed for specification of the variations found in pediatric schizophrenic patients. While the general linear model showed that TIV differences in the schizophrenia group were not statistically significant when compared to both groups of subjects with family history of other psychotic disorders, the multivariate ANOVA analysis showed that when the TIV values of each subject pool are individually compared, the differences shown by the schizophrenic group are statistically significant. The one-way ANOVA indicated that GMV was approaching statistical significance as well, indicating that if the experiment was run on a larger sample size, it may also be a significant finding. These types of distinctions would be a great aid in a clinical application as it will allow physicians to use these types of trends as physical indicators for these psychotic disorders in their diagnostic processes.

The AUC values, all in the range of 0.92 to 0.97, specifically indicate that the model created using the volumetric brain measurements as tools to distinguish between disorders was very accurate. Since the average sensitivity value, 90.3, and average specificity value, 91.0, are relatively close to each other and high, they show that the model can accurately differentiate among the three disorders in this subject pool. Moreover, this suggests that the model has the potential to be of aid on a clinical level due to its overall strength.

An interesting aspect of the statistical analyses' results was that differences in WMV for schizophrenic patients in the multivariate and one-way ANOVA were distinctly different from the measurements found in the other groups. This was an unexpected result because neural operations largely take place in the gray matter of the brain. This would lend itself to further

research as this may be an indicator that WMV does influence mental capabilities and processes. While the findings of the one-way ANOVA are promising, it should be acknowledged that the statistical test does not account for covariates such as age and gender, two variables that are known to affect brain development and precaution should be taken while interpreting them.

Furthermore, it must be noted that the results of this experiment do not prove that specific levels of volumetric measurements are concrete indicators to diagnose pediatric patients with schizophrenia. The purpose of this experiment was to pinpoint trends within this subject population that could be used as support for diagnoses, which it did accomplish. Nevertheless, it is important to understand the limitations of this experiment.

Due to the sample sizes of each disorder group, the results may be misconstrued. Therefore, while specific volumetric brain measurements may be indicated to be reliable physical indicators to differentiate between psychotic disorders in this population, further research should be done to corroborate this. For this reason, the next step for continuing this strain of research would be to conduct this experiment again with a larger sample size to get a better idea as to how the volumetric measurements differ per subject group. This will also further fortify the strong ROC model created from the results of this experiment and allow for more accurate diagnoses of pediatric schizophrenia.

Conclusion

Overall, volumetric brain measurements can be used as a differential diagnostic tool of schizophrenia in pediatric patients from related disorders. By analyzing three-dimensional brain segmentations of diagnosed patients and patients with a family history of a related disorder, specific regions of the brain were pinpointed the locations where substantial differences in

volumetric measurements were prevalent and indicated whether there was an increase or decrease in that specific measurement in that region.

Based on the overall statistical significance of the results from the multiple analytical tests and ROC analysis, using volumetric brain measurements as support for diagnoses of psychotic disorders may be a novel way for doctors to increase the accuracy of their diagnoses in pediatric patients. Due to the limitations of this experiment, it should be conducted again with a larger number of subjects to further reinforce the results founded. Furthermore, future research should include an in-depth analysis should be run on how white matter volume affects mental capabilities and processes based on the novel finding in the results of the one-way ANOVA analysis.

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`References

1. About Schizophrenia. (n.d.). Retrieved from https://sardaa.org/resources/about-schizophrenia/.
2. Cao, B., Mwangi, B., Passos, I. C., Wu, M.-J., Keser, Z., Zunta-Soares, G. B., … Soares, J. C. (2017). Lifespan Gyrification Trajectories of Human Brain in Healthy Individuals and Patients with Major Psychiatric Disorders. *Scientific Reports*, *7*(1). doi: 10.1038/s41598-017-00582-1
3. Freudenreich, O. (2012, December 3). Differential Diagnosis of Psychotic Symptoms: Medical "Mimics". Retrieved from https://www.psychiatrictimes.com/forensic-psychiatry/differential-diagnosis-psychotic-symptoms-medical-mimics.
4. Lerch, J. (n.d.). Measuring Cortical Thickness - McGill University. Retrieved from http://www.bic.mni.mcgill.ca/users/jason/masters_proposal.pdf.
5. Malone, I. B., Leung, K. K., Clegg, S., Barnes, J., Whitwell, J. L., Ashburner, J., … Ridgway, G. R. (2015). Accurate automatic estimation of total intracranial volume: A nuisance variable with less nuisance. *NeuroImage*, *104*, 366–372. doi: 10.1016/j.neuroimage.2014.09.034
6. Mcintosh, A. M., Moorhead, T. W. J., Mckirdy, J., Hall, J., Sussmann, J. E. D., Stanfield, A. C., … Lawrie, S. M. (2009). Prefrontal gyral folding and its cognitive correlates in bipolar disorder and schizophrenia. *Acta Psychiatrica Scandinavica*, *119*(3), 192–198. doi: 10.1111/j.1600-0447.2008.01286.x
7. Nenadic, I., Maitra, R., Dietzek, M., Langbein, K., Smesny, S., Sauer, H., & Gaser, C. (2015). Prefrontal gyrification in psychotic bipolar I disorder vs. schizophrenia. *Journal of Affective Disorders*, *185*, 104–107. doi: 10.1016/j.jad.2015.06.014

8. Psychosis (Schizophrenia) in Children and Youth: Mental Health America. (n.d.). Retrieved from https://www.mhanational.org/psychosis-schizophrenia-children-and-youth.
9. Rapoport, J. L. (1999, July 1). Progressive Cortical Change During Adolescence in Childhood-Onset Schizophrenia. Retrieved November 6, 2019, from https://jamanetwork.com/journals/jamapsychiatry/fullarticle/205131.
10. Read "Improving Diagnosis in Health Care" at NAP.edu. (n.d.). Retrieved from https://www.nap.edu/read/21794/chapter/7.
11. Schizophrenia. (n.d.). Retrieved from https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml#part_154881.
12. Silveri, M. M., Tzilos, G. K., & Yurgelun-Todd, D. A. (2008). Relationship between white matter volume and cognitive performance during adolescence: effects of age, sex and risk for drug use. *Addiction*, *103*(9), 1509–1520. doi: 10.1111/j.1360-0443.2008.02272.x
13. Staff, N. B. I. C. (n.d.). Psychotic Disorders in Children and Adolescents: A Primer ... Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4116281/.
14. The Editors of Encyclopaedia Britannica. (2019, October 3). Emil Kraepelin. Retrieved November 6, 2019, from https://www.britannica.com/biography/Emil-Kraepelin.
15. Tietz, T. (2018, October 12). Emil Kraepelin's classification system for Mental Illness. Retrieved November 6, 2019, from http://scihi.org/emil-kraepelin-mental-illness/.
16. V, C., & RM, M. (n.d.). Institute of Psychiatry, Denmark Hill, London, UK. Retrieved from https://europepmc.org/abstract/med/12570067.

17. Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., … Glahn, D. C. (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *NeuroImage*, *53*(3), 1135–1146. doi: 10.1016/j.neuroimage.2009.12.028

18. Yurgelun-Todd, D. A., Killgore, W. D. S., & Young, A. D. (2002). Sex Differences in Cerebral Tissue Volume and Cognitive Performance during Adolescence. *Psychological Reports*, *91*(3), 743–757. doi: 10.2466/pr0.2002.91.3.743