Detecting Schizophrenia by Structural MRI using Deep Learning

Author

Ezzah Shahid

Reg. Number: 0000275584 MS - 18 (MTS)

Supervisor

Brig. Dr. Javaid Iqbal

DEPARTMENT OF MECHATRONICS ENGINEERING

COLLEGE OF ELECTRICAL & MECHANICAL ENGINEERING

NATIONAL UNIVERSITY OF SCIENCES AND TECHNOLOGY

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Author

Ezzah Shahid

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Thesis Supervisor:

Brig. Dr. Javaid Iqbal

Thesis Supervisor's Signature:

_____

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Declaration

I certify that I am the author of this research paper "*Detecting Schizophrenia by Structural MRI Using Deep Learning*". The work hasn't been submitted anywhere else for review. The information that was taken from other sources has been appropriately cited and acknowledged.

Signature of Student

Ezzah Shahid

Reg. Number 0000275584 MS – 18 (MTS)

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Signature of Student

Ezzah Shahid

Reg. Number 0000275584 MS – 18 (MTS)

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Abstract

Schizophrenia affects about 1% of the world population with a lifetime prevalence of 0.3-0.66% is among the frequently occurring psychotic disorders. Schizophrenia has been clinically identified, but there is no pathophysiology for diagnosing it. Despite the fact that much study has been done on volumetric MRI in Schizophrenia, detecting it using biological markers is difficult as most psychiatric diseases share the same symptoms.

The prefrontal and temporal lobes, particularly the medial and superior temporal lobes, have been found to have decreased volume in earlier research. Predictive analytics and clinical decision assistance both heavily rely on these findings. Analyzing enormous medical imaging data is time consuming for experts. Additionally, drawing inferences from these analyses may be erroneous or biased. While machine learning algorithms may aid specialists in automated analysis to some level, they might not be able to analyze such vast volumes of data and accurately resolve complex problems as these conventional methods often overlook important information. We suggest employing a deep learning approach based on the Convolutional Neural Networks (CNN) rather than the conventional machine learning approaches. Deeper networks can learn a new, more complex representation of the input data at each layer, allowing them to develop deep representations. Clinicians may find it easier to distinguish schizophrenia from other mental diseases using deep learning algorithms that have been trained on bigger data sets with a variety of illness stages and severity.

Key Words: *Schizophrenia, Medical Imaging sMRI, Detection, Deep Learning, CNN, Neuroimaging, neuropsychology, Early Detection, Psychiatric, Diagnosis, Neural Networks, Optimization.*

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1. Introduction

1.1. What is Schizophrenia?

Approximately 1 % of the total population of the world gets affected by Schizophrenia at some stage in their life, which makes Schizophrenia among one of the most commonly occurring psychotic disorders with a lifetime prevalence of approximately 0.3-0.66%. Criterion based diagnosis systems have been developed for accurate diagnosis of Schizophrenia. These include the International Classification of Diseases, tenth edition (ICD-11) and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-V) which describe characteristic symptoms of Schizophrenia. According to the diagnostic and statistical manual of mental disorders (DSM) criteria Identification of a group of symptoms connected to inadequate social or occupational performance is necessary for the diagnosis. People who have schizophrenia will vary substantially in most respects because it is a complex clinical disorder. Varying symptoms exhibited by Schizophrenic patients can be categorized into three categories: I) Positive II) Negative III) Cognitive [1][2]

Delusions and auditory hallucinations are among the positive symptoms. Lack of speech and disorderly thoughts and conduct are among the negative symptoms. Anhedonia and poor memory are among the cognitive symptoms. [3] Negative symptoms are crucial and may perhaps be the most fundamental signs of Schizophrenia. [4] These symptoms often manifest as a diverse combination of these three groups of clinical characteristics throughout the late second and early third decades of life.

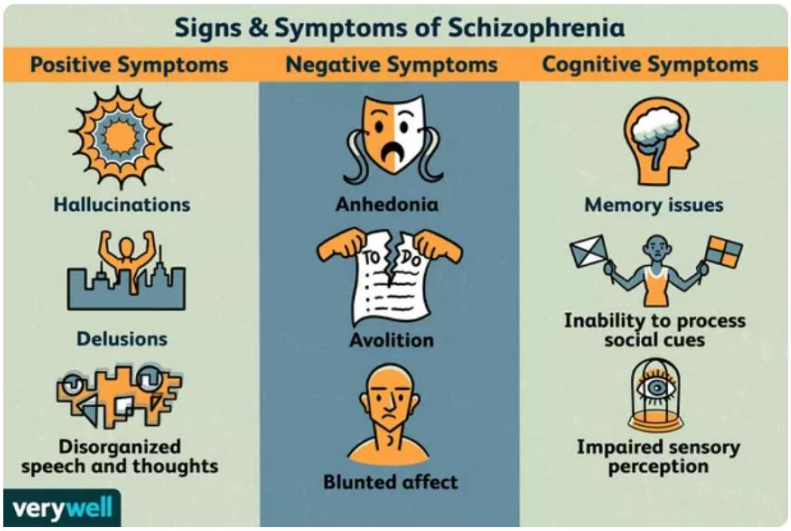


Fig 1 Signs and Symptoms of Schizophrenia

Modern biometric techniques for establishing diagnostic criteria are not fully utilised in the current DSM criteria. These criteria have not yet been developed using reliable symptoms that have a large enough base rate to adequately encompass the symptoms associated with Schizophrenia. There are many existing data sets that cover patients with both chronic and first-episode Schizophrenia. Using a more empirical and data-based approach, these data sets may be used to develop diagnostic criteria. Data sets with individuals who have schizophrenia as well as those who have other severe disorders will be needed for this strategy. To ascertain which symptoms are most useful in identifying patients, discriminant analysis may be used to analyse symptoms across independently obtained samples. [63] As these analyses are conducted, it may also be important to use different criteria for patients who have just experienced their first episode and for individuals who are more chronically ill. [5]

Individuals suffering from Schizophrenia frequently lose their ability to work or continue their education. They exhibit markedly reduced functionality in one or more key domains, such as work, interpersonal connections, or personal wellness. In the majority of cases, illness strikes young adults who are beginning a new job or a successful career. Apart from the personal toll, Schizophrenia places a significant financial strain on society.

4 stages of illness in Schizophrenia are: I) Premorbid, II) Prodromal, III) Progressive/ Syndromal, IV) Chronic/ Residual. The clinical and pathophysiologic progression of Schizophrenia in its many clinical stages is attempted to be integrated and schematically depicted in the figure. [6] In the Premorbid stage there are few to no symptoms. In the Prodromal stage, diminished symptoms appear which signal the onset of Schizophrenia. The prodromal symptoms include the attenuated positive symptoms like delusions, illusions, mood symptoms, cognitive symptoms. The patient exhibits signs of stress, depression, lability, irritability, sleeping problems, cognitive attention impairment, illusions, suspiciousness, drug usage, and social disengagement during the prodromal period. The Syndromal stage begins with the onset of psychosis and lasts until the progressive stage is reached. Patient shows severe psychotic symptoms the mental health of the patient begins to deteriorate. If the patient gets diagnosed at the Syndromal stage and preventive measures are started, this leads to the Chronic stage of Schizophrenia. In Chronic/ Residual stage of Schizophrenia the patients show fewer or less positive symptoms and more of negative and cognitive symptoms. [7]

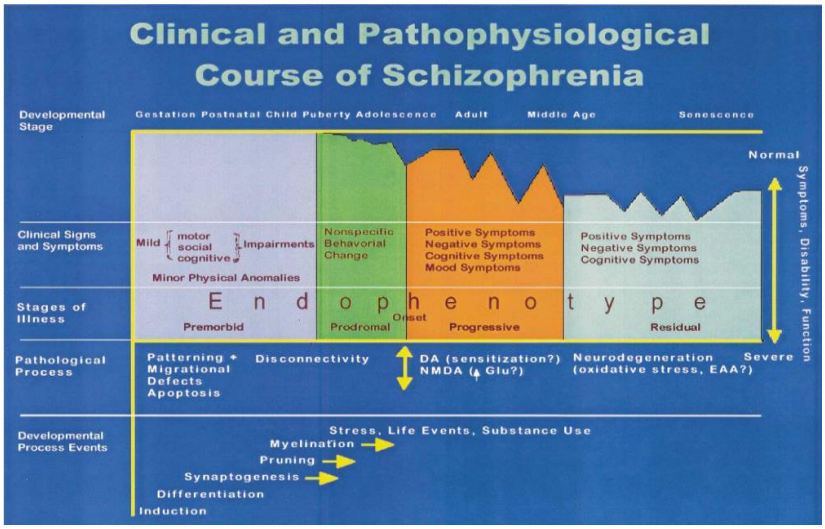


Fig 2 Clinical and Pathophysiological courses of Schizophrenia

Schizophrenia's psychotic symptoms normally appear between late adolescence and mid-adulthood. The men's early to mid-20s, and women's late 20s are the typical onset ages for the first psychotic episode. The majority of people exhibit a slow and steady development

of a range of clinically relevant signs and symptoms, while the start may be rapid or insidious in other cases. More than half of these people express depressed symptoms. Females who may have married are overrepresented in cases with late-onset (i.e., beyond age 40) onset. The course is frequently distinguished by a prominence of psychotic symptoms while retaining affect and social functioning.

There is also a high risk for suicides among Schizophrenic patients. About 5-6% of people with Schizophrenia commit suicide, about 20% make one or more attempts, and many more experience substantial suicidal thoughts. Sometimes hallucinations interpreted as orders to hurt oneself or others will cause suicidal conduct. Both males and females are at high risk of suicide throughout their lives, but young males who also use drugs or alcohol may be at a higher risk.

Although People with Schizophrenia require lifelong treatment, early detection and prevention, ideally close to the start of Syndromal stage, can reduce the number and duration of episodes of Schizophrenia, reduce the reoccurrences and also limit the progressive deterioration in the patients functionality. [8]

Table 1: Stages of Schizophrenia and symptoms

	Stage 1: Premorbid	**Stage 2: Prodromal**	**Stage 3: Progressive/ Syndromal**	**Stage 4: Chronic/ Residual**
Symptoms	Social Vulnerability	Mood swings, delusions, behavioural deficits, few cognitive deficits	Severe cognitive and psychotic symptoms	Chronic disability, negative symptoms.
Diagnosis	Clinical Assessment	Medical Imaging, Cognitive assessment	Medical treatment and rehabilitation	Medical treatment and rehabilitation

1.1.1. Importance of detecting Schizophrenia at an early stage?

About 28 million people suffer from Schizophrenia worldwide. Early diagnosis of Schizophrenia is important to protect these individuals from a long period of suffering, which can be done by taking preventive measures during the Premorbid stage or the Predromal stage when individuals are more vulnerable to Schizophrenia.

The Predromal phase not only indicates the onset of psychosis but the clinical deterioration also starts at this stage of Schizophrenia. But because these symptoms overlap with the symptoms of many other mental disorders, these Prodromal symptoms are cannot be considered diagnostic. Their non-specificity and their lack of validity makes them unreliable for early intervention.

In a study on mortality rates between Schizophrenia and bipolar disorders in comparison to general population, patients with a schizophrenia diagnosis had a standardized mortality rate (SMR) that was more than four times higher. [9]

Recent research indicates that individuals with brain volume loss definitely have a poorer prognosis for recovery than those with preserved brain volume. Patients are more likely to experience long-term functional impairments, such as the inability to maintain work, the longer antipsychotic medication is delayed. Psychopathology may also grow more chronic and treatment-resistant as a result of this delay.

The absence of reliable biomarkers that may be utilised for early diagnosis is the cause of the stagnation in the treatment of Schizophrenia. Schizophrenia diagnosis is made primarily based on clinical examination of the patient's and other informants' stated symptoms. This diagnostic criteria causes misdiagnosis and delays in the patient's treatment. Many psychotic disorders have almost similar symptoms, misdiagnosis of Schizophrenia with some other psychotic disorder can lead to severe repercussions and relapses. Neuroimaging studies show convincing brain structural and functional abnormalities to better understand the etiology of Schizophrenia.

Due to the fact that Schizophrenia usually manifests in early adulthood, those who suffer from it frequently benefit from early diagnosis and rehabilitation in order to improve their ability to manage their daily lives and maintain a proper employment.

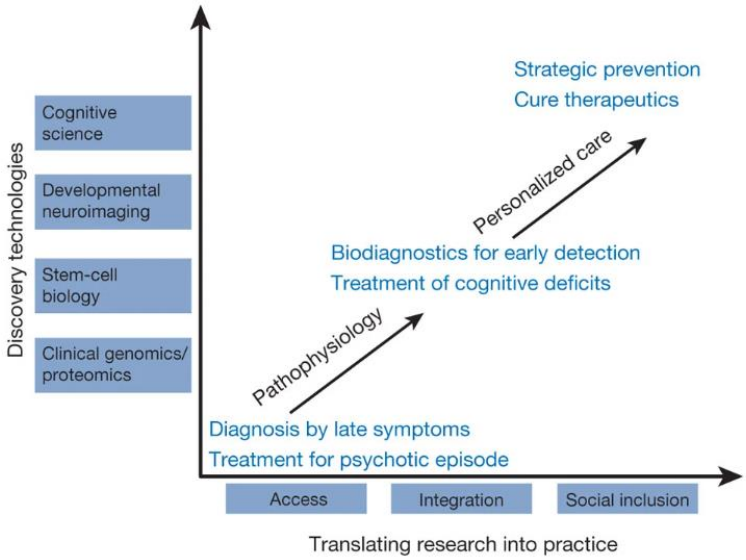


Fig 3 prediction for Schizophrenia in 2030

Insel[10] gave a vision for prognosis of Schizophrenia in the decades to come, which shows that our understanding of Schizophrenia can be changed by the use of discovery technologies, which have already revolutionized how many other medical disorders are understood and treated. This will allow for an earlier diagnosis (stages I or II) and more effective treatments that target the cognitive deficits that this disorder causes. However, the ultimate objective is the creation of tailored treatment that is based on an awareness of individual risk. In reality, this entails not only identifying risk factors and initiating preventive measures, but also ensuring that persons at any point of the Schizophrenia trajectory have access to these therapies, integrating care, and providing full social participation.

1.1.2. Neuroimaging in Schizophrenia

Recent research has found anomalies in late developmental processes around or before the onset of psychosis as well as early developmental abnormalities around or before birth. Given the reported decreases in cortical dendritic density [11, 12], it has been proposed that systematic pruning throughout adolescence may be excessive, causing the disorder to manifest. Degenerative processes that started after the disorder may also be involved. The predictions made by these seemingly disparate models might be examined using neuroimaging experiments. [13]

Table 2: Neuroimaging Modalities

Modality	**CT**	**MRI**	**MRS**	**fMRI**	**DTI**	**SPECT & PET**
Specialty	Brain Structure	Brain Structure	Brain Chemistry	Brain Functionality	Brain Structure and Functionality	Brain Chemistry
Measures	Detailed images of blood vessels, nerves, tissues in and around the brain	Gray matter, White matter, CSF	Metabolic changes in brain	Indirect neuronal activity by changes in blood flow and oxygen metabolism	In vivo study of white matter microstructure	Cerebral blood flow using radioacters

Schizophrenia diagnosis and treatment uses a variety of neuroimaging modalities:

1. Computed tomography (CT)
2. Magnetic Resonance Imaging (MRI)

3. Magnetic Resonance Spectroscopy (MRS)
4. Functional Magnetic Resonance Imaging (fMRI)
5. Diffusion Tensor Imaging (DTI)
6. Single Photon Emission Computed Tomography and Positron Emission Tomography (SPECT & PET)

Extensive in vivo and ex vivo research has been done on the human brain. With the advancement of imaging techniques the link between structural and functional aspects that underpins interest in brain structures as we can better understand the pathophysiology of schizophrenia by studying several characteristics of brain morphology.

Since then, imaging investigations in schizophrenia, particularly MRI scans, have offered significant new insights into the illness.

The grey matter and the white matter may clearly be distinguished by MRI and its advantage over other imaging techniques is that it is non-invasive and depends mostly on the magnetic characteristics of the water protons, which are present in large quantities in brain tissues.

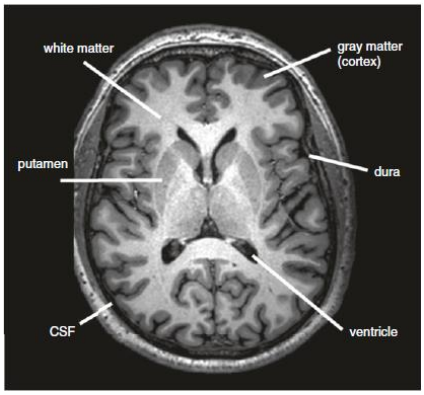


Fig 4: Transverse view of brain

1.1.3. Structural abnormalities found in the brain

Many studies have found some structural abnormalities in the brains of Schizophrenic patients. Some common abnormalities thought to be related to the causation of Schizophrenia are:

1) Shrinkage of the amount of grey matter overall

2) the bilateral medial temporal regions' volume decreased

3) deficiency in the left superior temporal region

Prior findings have been supported by structural magnetic resonance imaging (sMRI), which also shows further volume decreases in the prefrontal and temporal lobes, notably the medial and superior temporal lobes (STL). [14]

Volume of the thalamus has also been reported to be in deficit in many studies. [15] According to a study, first-episode patients with auditory hallucination symptoms had higher thalamic GM loss. Chronic and first-episode individuals with thalamic surface shape deformation may have structural changes in the thalamus's anterior, posterior, mediodorsal, and ventrolateral areas. [16]

More than 50 different brain areas have been shown to have grey and white matter impairments in brains of Schizophrenic patients as compared to healthy subjects and the most consistent findings were in the left superior temporal gyrus and the left medial temporal lobe. [17]

Gray matter loss in the lateral and medial prefrontal areas, insula, lateral temporal structures, medial temporal structures, and thalamus has been observed in schizophrenia patients and a gray matter increase has also been reported in the putamen and cerebellum. [18]

The structures that receive direct projection tracts from the cortex of the brain i.e. the thalamus, caudate nucleus, nucleus accumbens, and hippocampus show schizophrenia

patients' hippocampal-amygdala development and deep brain nuclei have been shown to alter over time as compared to healthy controls. [19]

The hippocampus is one of the brain regions that frequently displays abnormalities in structural and functional studies of patients with schizophrenia. According to Roeske et al, across subfields, hippocampal alterations seem to be fairly constant.. While overall neuron density does not appear to have altered in any location, the number of neurons is noticeably lower in the left hemisphere, indicating that volume loss may be related to a decline in the number of neurons. [20] As per Lieberman [11] this degenerative process causes an atrophic process in which the hippocampus neuropil is diminished and interneurons are destroyed as the condition worsens. It also spreads to other parts of the hippocampal circuit and projection fields in other anatomic sites, such as the frontal cortex.

2- Cluster analysis was applied on the MRI data of 79 Schizophrenic patients and 65 healthy controls and this algorithm separated near-normal and impaired groups appropriately based on the surface based cortical thickness mapping. A widespread cortical thinning pattern was observed in Schizophrenic patients. [21]

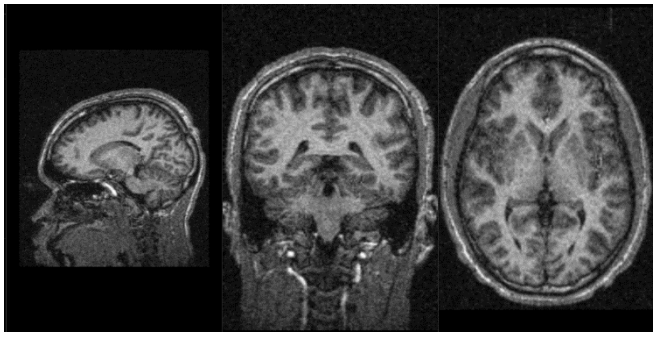


Fig 5 : Sagittal, coronal and transverse view of brain

The amount of grey matter, white matter, and overall brain volume is all diminishing, although the volume of the ventricles is increasing. The hippocampus, thalamus, left uncus/amygdala area, bilateral insula, and anterior cingulate all had lower volume at the

start of the disorder. More significant volume decreases in the brain are seen in chronic Schizophrenia, particularly in the left superior temporal gyrus and medial and dorsolateral prefrontal cortex. [22]

The corpus callosum (CC), which links the left and right hemispheres of the brain, is the biggest white matter tract in the body. Numerous investigations have documented structural abnormalities of the CC in first episode (FESZ) and chronic Schizophrenia, as well as in those who are at high risk of developing Schizophrenia. Volume loss in one or more of the CC subdivisions has also been recorded. [23]

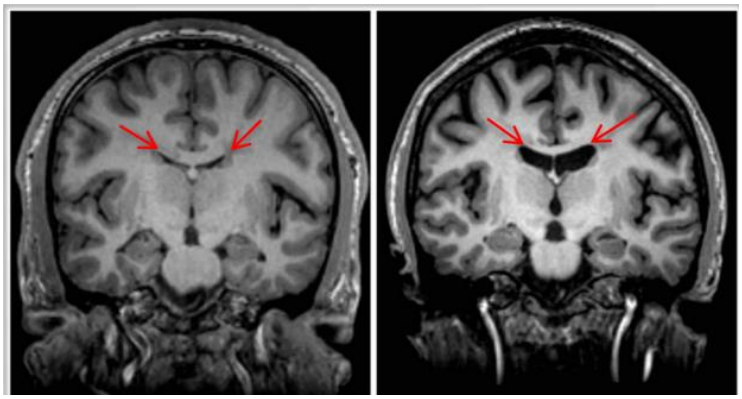
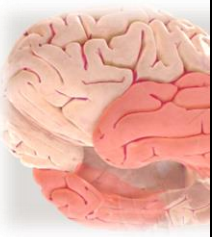
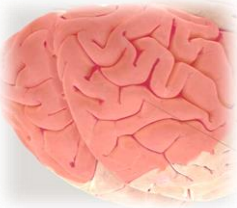
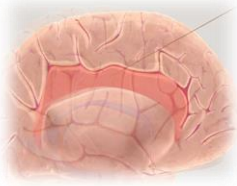


Fig 6: Arrows denote the lateral ventricles in this slice from a coronal T1-weighted MRI of a typical control subject and a patient with first-episode schizophrenia.

A research that identified extracellular matrix-glial interactions as a potential mechanism of Schizophrenia pathophysiology reported a significant reduction in perineuronal nets in the lateral nucleus of the amygdala [24]. In addition, one study found that Schizophrenia patients had more fibrous gliosis in their amygdala and other areas. [25]

Some studies also report the structural brain deficits to be replicable among siblings of the patients through voxel-based morphometry and source-based morphometry analysis. The patients and their healthy siblings, whether or not they had schizophrenia, revealed severe structural impairments in the medial frontal, insular, temporal, and posterior occipital lobes. [26]

Table 3: Brain region affected by Schizophrenia

Region	**Visual Representation**	**Functionality**	**Region**	**Visual Representation**	**Functionality**
Amygdala		Episodic memory, fear, aggression, anxiety	Temporal Lobe		Language Apprehension and recognition of objects , places and people
Prefrontal Cortex		Complex socially mindful decisions	Thalamus		Grand Central Station for sensory information
Cingulate Cortex		Emotions, distress	Ventricles		Produce and regulate CSF flow
Frontal Lobe		Behavioral traits, personality traits and decision making	Hippocampus		Long term memory

Middle Frontal Gyrus		Goal-directed behavior, reaction to external events			

1.2. Problem Statement

Schizophrenia diagnosis is made primarily based on clinical evaluations and is dependent on the signs and symptoms provided by patients and other informants. As a result, there are often missed diagnoses and treatment delays.

1.3. Motivation

Worldwide, there are at least 26 million people who have been diagnosed by schizophrenia. Schizophrenia is one of the top 10 causes of disability worldwide and has a negative impact on a person's health, and shortens life. Schizophrenia may benefit the patient in the long run from early and proper diagnosis and treatment; the longer it is left untreated, the more difficult it will be for the patient to heal and avoid recurrence. [27] Numerous research on the use of deep learning has been done to clinical decision support and predictive analytics. Deep learning could eventually prove to be an essential diagnostic ally in the inpatient setting, alerting medical personnel to changes in high-risk conditions like the need for urgent treatment.

1.4. Research Objectives

The primary goals of this research are:

- To study the pathophysiology of Schizophrenia and the regions of the brain affected the most by it.

- To study existing modes of diagnosing Schizophrenia using different classification techniques.
- To collect sMRI data of Schizophrenic patients and healthy controls.
- To develop an algorithm for the accurate and timely detection of Schizophrenia from structural MRI data by applying Deep Learning Algorithm for training and classification purposes.
- To assess how well the suggested categorization approaches work in contrast to the benchmark.

1.5. Classification of thesis

This research is organized into 5 chapters.

Chapter 1: Introduction

Chapter 1 comprises of a brief introduction of Schizophrenia, its symptoms and stages. The question of why Schizophrenia is important to diagnose at an early stage is also answered. State of the art neuroimaging modalities are also discussed briefly. Medical evidence of morphological changes in the brain has been provided and the motivation behind this research has been provided.

Chapter 2: Literature review of the different approaches used to detect Schizophrenia

In chapter 2, different approaches used in the past to detect Schizophrenia using sMRI data have been reviewed.

Chapter 3: Methodology

Chapter 3 discusses the methodology adopted for carrying out this research. From data acquisition protocols to image processing techniques have been thoroughly discussed. Algorithm development and a brief description of the performance metrics used to evaluate the algorithm have also been discussed.

Chapter 4: Results and Implementation

In chapter 4, the performance of the algorithm in detecting Schizophrenia has been evaluated and a comparison between the results obtained and the benchmark paper has been drawn.

Chapter 5: Conclusion and future work

Concluding remarks and future recommendations have been provided based on the limitations of this research in chapter 6.

2. Literature review of the different approaches used to detect Schizophrenia

To automatically categorize patients with schizophrenia, a local descriptor called scale invariance feature transform (SIFT) and a non-linear support vector machine (SVM) approach were employed with significant results with a dataset of 54 healthy controls, 54 Schizophrenia patients. [28]

74 anatomical brain MRI sub-regions were used together with the machine learning method Random Forest (RF), 98 patients with childhood onset schizophrenia (COS) and 99 healthy controls (of the same age, sex, and ethnicity) were discriminated from one another. RF was also used to assess the probability of Schizophrenia diagnosis based on MRI results. Next, the researchers examined the relationships among copy number variation (CNV) and the symptoms, premorbid development, and risk of schizophrenia based on brain structure. By comparing the cortical thickness of different brain areas, COS and control groups could be distinguished with an accuracy of 73.7%. [29]

Another study proposed a model using voxel-based morphometry (VBM), which extracts whole-brain grey matter densities from structural magnetic resonance imaging (MRI) images to classify Schizophrenia patients and healthy controls. 239 participants (128 sick and 111 healthy controls) were classified with a 71.4 % accuracy using a support vector machine SVM model. [30]

In another study a comparison between Schizophrenia patients and healthy individuals was made using structural neuroimaging data from two different field strengths. 3T and 7T. As the classifier, support vector machines have been used, and white matter and grey matter have been used as biomarker features. The accuracy of the 7-T classifier surpassed

the 3-T classifiers, reaching a maximum of 77 percent as opposed to 66.6 percent for the 3-T GM classifier. GM reduction at both 3 and 7 T in the bilateral insula, superior temporal cortex, thalamus, anterior cingulate cortex, and hippocampal gyrus. However, these variances were considerably clearer at 7 T than at 3 T. For WM impairments, similar patterns of more significant results at 7 T compared to 3 T were seen. [31]

Another study suggests that psychiatrists may be able to use an algorithm that may distinguish between these two disorders as a diagnostic tool. We scanned 66 patients with schizophrenia, 66 individuals with bipolar illness, and 66 healthy volunteers on a 1.5 T MRI scanner. Based on grey matter density images, three support vector machines were trained to separate schizophrenia patients from healthy people, bipolar disorder patients from healthy people, and schizophrenia patients from those with bipolar disorder, respectively. Cross-validation and an independent validation set of 46 Schizophrenia patients, 47 bipolar disorder patients, and 43 healthy participants imaged on a 3 T MRI scanner were used to assess the models' predictive potential. Patients with schizophrenia could be discriminated from healthy volunteers with an average accuracy of 90%. [32]

For a study, 163 patients with first episode Schizophrenia (FES) who were drug-naive and 163 demographically matched healthy controls were recruited. Each patient's high-resolution anatomical data was obtained, and the Freesurfer tool was used to determine the cortical thickness and surface area. The Support Vector Machine was then employed to see whether measurements of cortical thickness and surface area could be utilized to distinguish between patients and healthy controls (SVM). The accuracy of correctly classifying patients and controls was 85.0 % and 81.8 %, respectively, for cortical thickness and surface area. [33]

Another study also discriminated between Schizophrenic, Bipolar and healthy control with Schizophrenia vs. healthy 75%, bipolar disorder vs. healthy 63% and Schizophrenia vs. bipolar disorder 62% accuracy. [34]

Another research compared three machine learning algorithms (logistic regression (LR), support vector machines (SVMs), and linear discriminant analysis (LDA) on three

distinct datasets to assess the precision of machine learning approaches utilized in SZ/HC classifications investigations (435 subjects total). The best accuracies for a new feature set and validation approach were achieved by LR, SVMs, and LDA, however most accuracies were much lower than previously reported values, between 55 and 70 %. Using cortical thickness data and an SVM, the maximum accuracy was 73.5 %. [35]

Researchers used a deep learning model known as a deep belief network (DBN) to extract characteristics from brain morphometry data in another structural MRI investigation and tested its accuracy in distinguishing between healthy controls (N=83) and Schizophrenia patients (N=143). They also assessed at how well they classified patients with first-episode psychosis (N=32). The DBN performed noticeably better as a classifier than the support vector machine (accuracy=73.6 % vs. 68.1 %). Finally, the DBN had a 56.3 percent error rate in classifying first-episode patients, showing that these individuals could not be defined by the representations learnt from schizophrenia patients and healthy controls. These findings show that through improving neuro-morphometric analysis, deep learning could help us better understand psychiatric diseases like Schizophrenia. [36]

A deep auto encoder artificial neural network was used to create a normative model using sMRI data from 1,113 healthy individuals. Using two separate data sets, our model assessed global and local neuroanatomical deviation in individuals with schizophrenia and autism spectrum disorder and was able to identify distinct patterns of neuroanatomical aberrations in SCZ and ASD. [37]

Deep learning is a promising way to identify early stage risks and Predrome of Schizophrenia and many other disorders. [38] Deep neural networks, which can create a representation of data based only on the data they are given, have become a strong substitute to constructing graphics descriptors for pattern recognition applications in recent years. [39] [40]

In order to fully understand the extent to which first episode psychosis may be detected using ML applied to neuroanatomical data, a research was conducted (FEP). Using both

traditional ML and deep learning (DL), three feature sets of importance were explored. These feature sets included surface-based volumes and cortical thickness, voxel-based grey matter volume (GMV), and voxel-based cortical thickness. Cross-site and nested cross-validation (CV) were used to evaluate the performance. Accuracy ranged from 50% to 70% for surfaced-based features, from 50% to 63% for GMV, and from 51% to 68% for VBCT. When surface-based characteristics were used with DL, the highest accuracy rates (70%) were attained. [41]

Convolutional networks are the most common version of deep neural networks, a supervised learning method that is particularly well adapted to solving challenges of natural image classification and has recently been applied to some applications in chest CT analysis. [42] [43] Superior visual image recognition ability has improved their clinical value in several diagnostic tasks with the use of deep learning. [44]

In this study, we suggest utilizing a deep learning strategy based on CNNs rather than more traditional machine learning techniques. Conventional methods often overlook important information. In order to construct deep representations, deeper networks learn new, more abstract representations of the input at each layer. We also suggest adding more biomarker features to the research to achieve more accurate classification results (Lesser number features taken into account).

Table 4: Literature review table

	Research Paper	Year	Publication	Data Set	Classification technique	Parameters discussed
[1]	Multivariate voxel-based morphometry successfully differentiates Schizophrenia patients from healthy controls [18]	2007	Neuroimage	First group: 60 participants, including 30 people with schizophrenia and 30 healthy individuals. Group two: 16 people with schizophrenia and 16 healthy people.	Voxel Based Morphometry	Gray matter distribution
[2]	Progressive Deformation of Deep Brain Nuclei and Hippocampal-Amygdala Formation in Schizophrenia [19]	2008	Biological Psychiatry	56 Schizophrenia and 62 healthy subjects	Brain Mapping	Thalamus, caudate, hippocampus, putamen and amygdala.
[3]	Neuropsychological Near Normality and Brain Structure Abnormality in Schizophrenia [50]	2009	American Journal of Psychiatry	21 Neuropsychologically near normal schizophrenic patients 54 impaired schizophrenic patients and 30 healthy subjects.	Linear Mixed-Model multivariate analyses.	volumes of the cerebellum, thalamus, hippocampus, amygdala, and localised grey and white matter in the cortical regions.
[4]	Cortical thickness in neuropsychologically near-normal Schizophrenia [21]	2011	Schizophrenia Research	79 Schizophrenic and 65 Healthy participants.	2-cluster analysis Wards Method	Cortical thickness

[5]	Classification of Schizophrenia using feature-based morphometry [28]	2011	Journal of neural Transmission	54 healthy controls, 54 Schizophrenia patients	SVM	Volumetric changes
[6]	Heritability of Multivariate Gray Matter Measures in Schizophrenia [26]	2012	Twin Research and Human Genetics	209 schizophrenic and 228 healthy	Voxel Based Morphometry Source Based Morphometry.	Gray matter
[7]	Using multivariate machine learning methods and structural MRI to classify childhood onset Schizophrenia and healthy controls [29]	2012	Frontiers in Psychiatry	98 childhood onset Schizophrenia(COS) patients and 99 healthy controls	Random Forrest	Cortical thickness
[8]	Classification of Schizophrenia patients and healthy controls from structural MRI scans in two large independent samples [30]	2012	Neuroimage	Initial sample: 239 individuals (128 patients and 111 healthy controls) supplementary sample: 277 people (155 patients and 122 healthy controls)	VBM SVM	Gray matter density
[9]	Clinical utility of machine-learning approaches in	2013	Frontiers in Psychiatry	19 Schizophrenia patients 20 healthy controls	SVM	Gray matter volume White matter volume

	Schizophrenia : improving diagnostic confidence for translational neuroimaging [31]					
[10]	Can structural MRI aid in clinical classification? A machine learning study in two independent samples of patients with Schizophrenia , bipolar disorder and healthy subjects [34]	2014	Neuroimage	66 Schizophrenia patients, 66 patients with bipolar disorder and 66 healthy subjects	SVM	Gray Matter Density
[11]	The extent of diffusion MRI markers of neuroinflammation and white matter deterioration in chronic Schizophrenia [51]	2015	Schizophrenia Research	29 chronic Schizophrenia subjects and 25 matching controls	Free-water imaging maps	Neuroinflammation White matter density
[12]	Using deep belief network modelling to characterize differences in brain morphometry	2016	Scientific Reports	Healthy controls (N = 83) and patients with Schizophrenia (N = 143).	Deep neural networking deep belief network (DBN-DNN)	white matter ventricular volume

	in Schizophrenia [36]					
[13]	Discriminative analysis of Schizophrenia using support vector machine and recursive feature elimination on structural MRI images [52]	2016	Medicine	41 Schizophrenia patients and 42 controls	VBM and ROI SVM	Gray matter volume White matter volume
[14]	Evaluation of machine learning algorithms and structural features for optimal MRI-based diagnostic prediction in psychosis [32]	2017	PLoS One	Schizophrenia N = 128 Bipolar disorder N = 128 Controls N = 127	A Gaussian process classifier, a support vector classifier, regularised discriminant analysis, and random forests	Cortical thickness White and grey matter Volumetric measurements
[15]	Support vector machine-based classification of first episode drug-naïve Schizophrenia patients and healthy controls using structural MRI [33]	2017	Schizophrenia Research	163 treatment-naïve FES patients and 163 healthy controls	Two sample t-tests SVM	Cortical Thickness Surface area

[16]	Neuroanatomical heterogeneity of Schizophrenia revealed by semi-supervised machine learning methods [53]	2017	Schizophrenia Research	Schizophrenia was diagnosed in 157 individuals, whereas 169 people served as the control group.	Machine learning method called CHIMERA	gray matter, white matter CSF
[17]	Classification of Brain MRI Using SVM and KNN Classifier [54]	2017	2017 Third International Conference on Sensing, Signal Processing and Security (ICSSS). IEEE, 2017.	Clinical database from Sahyandri hospital, Pune. BRATS 2012 database	SVM KNN	malignant and benign type tumors
[18]	Association between structural and functional brain alterations in drug-free patients with Schizophrenia : a multimodal meta-analysis [55]	2018	Journal of Psychiatry and Neuroscience	16 functional MRI studies with 403 drug-free patients and 428 controls, as well as 15 structural MRI studies with 486 drug-free patients and 485 healthy controls	NIL	Gray matter
[19]	Reading the (functional) writing on the (structural) wall: multimodal fusion of brain	2018	NeuroImage	144 people with schizophrenia and 154 healthy people	Translation based Multimodal Fusion approach	static grey matter patterns from sMRI data and dynamic connectivity characteristics

	structure and function via a deep neural network based translation approach reveals novel impairments in Schizophrenia [56]					from fMRI data.
[20]	Using deep auto encoders to identify abnormal brain structural patterns in neuropsychiatric disorders: A large-scale multi-sample study [57]	2018	Human brain mapping	145 healthy controls 118 people with autism spectrum disorder and schizophrenia	deep auto encoder	Cortical thickness anatomical structural volume
[21]	Brain structure, cognition, and brain age in Schizophrenia, bipolar disorder, and healthy controls [58]	2018	Neuropsychopharmacology	53 euthymic BD, 81 schizophrenia, 91 healthy controls	general linear model	Cortical Thickness White matter
[22]	Investigating brain structural patterns in first episode psychosis and Schizophrenia using MRI and a machine learning approach [59]	2018		82 HC, 143 patients with chronic SCZ, and 32 FEP patients	Maximum Uncertainty Linear Discriminant Analysis (MLDA)	Volumetric changes

[23]	Integrating machining learning and multimodal neuroimaging to detect Schizophrenia at the level of the individual [41]	2019	Human Brain Mapping	452 healthy controls and 295 schizophrenia patients	SVM K-fold	White matter volume, grey matter volume, low-frequency fluctuation amplitude, and regional homogeneity
[24]	Identification of changes in grey matter volume using an evolutionary approach: an MRI study of Schizophrenia [60]	2020	Multimedia Systems	32 healthy controls and 28 Schizophrenia patients	VBM non-dominated sorting genetic algorithm	Gray matter changes and the relevant brain regions
[25]	Detecting Abnormal Brain Regions in Schizophrenia Using Structural MRI via Machine Learning [61]	2020	Computational intelligence and neuroscience	Dataset from the Centers for Biomedical Research Excellence (COBRE). 34 people with paranoid schizophrenia and 34 healthy controls.	T-tests Recursive feature elimination SVM	Gray Matter White matter

3. Methodology

3.1. Data Acquisition

Publically accessible neuroimaging data was obtained from NUSDAST, the Northwestern University Schizophrenia Data and Software Tool, which is funded by NIH as an effort for encouraging new research. One of the biggest single-site neuroimaging databases for schizophrenia, NUSDAST contains high-resolution sMRI datasets of a variety of individuals, all using the same scanners and sequence protocols along with their detailed clinical information, cognitive and genetic information as well.

Additionally, manual segmentation for the following brain regions is included in this dataset: Hippocampus, Amygdala, Thalamus, Basal Ganglia (Caudate Nucleus, Nucleus Accumbens, Putamen, Globus Pallidus), Cingulate Gyrus, including the anterior and posterior segments, Prefrontal cortex, including Superior, Middle, and Inferior Gyri, and Parahippocampal Gyrus (including entorhinal, perirhinal and parahipocampal cortices).

3.2. Subjects

Longitudinal data on 118 schizophrenia patients (m/f = 78/40, age = 33.8 12.5 years) and 102 controls (m/f = 91/29, age = 31.4 13.8 years) are provided.

3.3. Dataset Characteristics

Table 5: Dataset Characteristics

Characteristics	NUSDAST Dataset
No. of images	220
No. of normal images	102
No. of Schizophrenic images	118
Patient Demographics:	

Age, mean(SD), years	32.9(12.0)
Range of ages among subjects	14-66
Females/males	84/134
Image Quality	
Data Acquisition year	1998-2006
Scanner field strength	1.5 T
Number of images with too much noise	1
Number of erroneous images	2
Psychiatric Diagnosis of patients	
Schizophrenic	117
Schizoaffective	-

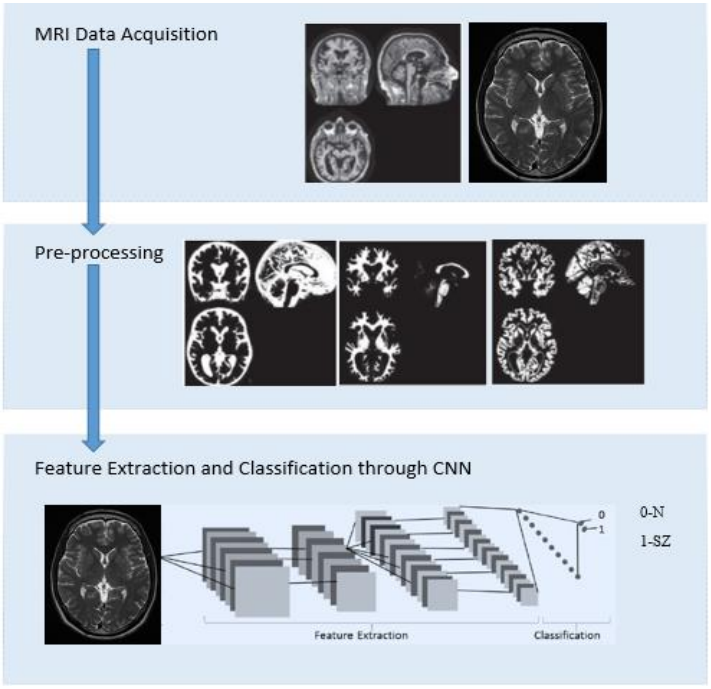


Fig 7: Flowchart of the methodology

3.4.Sequence protocol

The identical Siemens 1.5 T Vision scanner platform was used to gather all MR images.

The Vision scanner produces anatomical images with almost no distortion because to its dynamically protected gradients and exceptionally high gradient linearity (0.4 percent throughout a 22-cm diameter spherical volume compared to 2-5 percent over 22-cm for our other scanners) (0.4 percent voxel displacement). The same scanner delivered reliable longitudinal MR data during the whole data collecting period.

High quality T1 turbo-FLASH scans and several MPRAGE scans are generated throughout each scan session. The raw MR data was in Siemens VISION IMA format, which was afterwards converted into Analyze TM format. Since they may be laterally confusing, all analyze-format images are being changed to NIFTI format.

Table 6: Sequence Protocol

Sequence Name	**Geometry in mm (FOV@ reconstructed resolution)**	**Timing Parameters in ms**	**Slices**	**Scan Time in m:ss**	**Purpose**
3D turbo-FLASH	256 × 256 matrix, 1 × 1 mm in-plane resolution	TR = 9.7 ms, TE = 4 ms, flip = 10◦, ACQ = 1	180 slices, slice thickness 1 mm	13:30	With a very narrow excitation flip angle and short TR and TE, TurboFLASH is a special, ultrafast spoiled gradient echo method.
3D MPRAGE (2-4 repeats)	256 × 256 matrix, 1 × 1 mm in-plane resolution	TR = 9.7 ms, TE = 4 ms, flip = 10◦, ACQ = 1	128 slices, slice thickness 1.25 mm,	5:36	Produces great tissue contrast while collecting good spatial resolution and whole-brain coverage in a short scan duration. one of the most widely used structural brain imaging sequences in clinical and academic contexts.

3.5. Image Preprocessing

Almost all neuroimaging researches get a high-resolution T1-weighted anatomical scan, which has a high contrast between the white and grey matter. Cerebrospinal fluid is black, white matter is lighter, and grey matter is darker in these images. Before being fed to the algorithm, these T1-weighted images are then processed.

T1 weighted images were used as the input for FreeSurfer v6.0 to perform brain segmentation and cortical parcellation on the subjects. Additionally, hippocampus subfields were extracted [45]. Each individual brain received an approximate of 198 morphological assessments as a result of the FreeSurfer output. These include estimations of subcortical volumes, hippocampus subfields, cortical area, and cortical thickness using the Desikan-Killiany atlas [46]

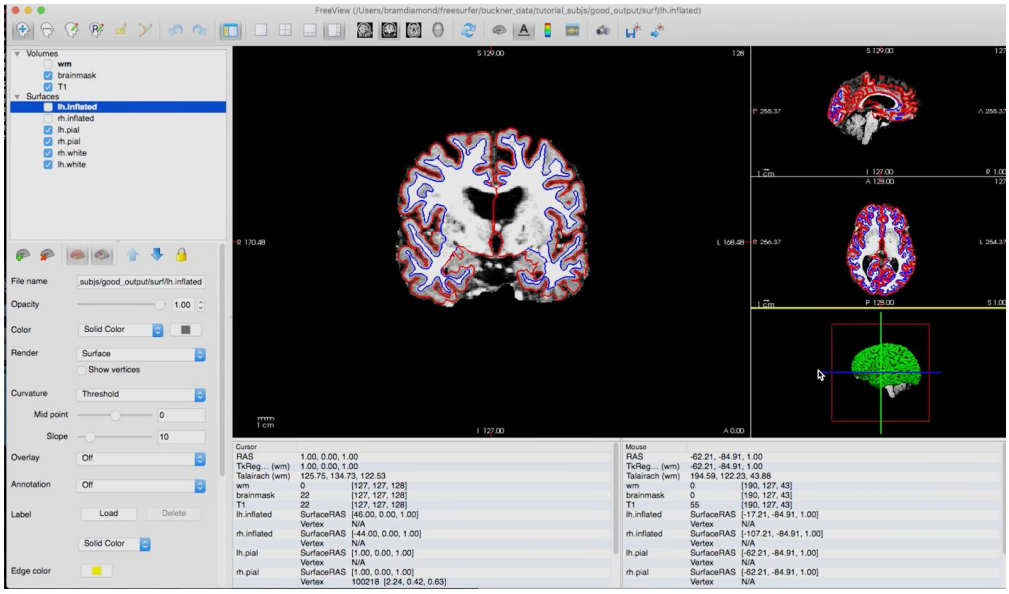


Fig 8: Desktop view of Freesurfer

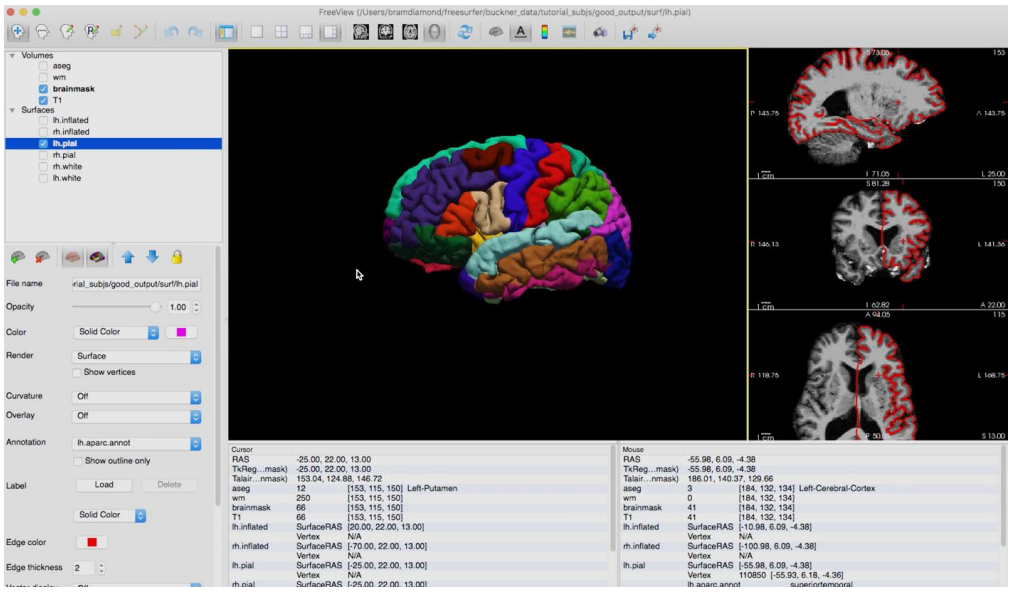


Fig 9: MRI Reconstruction using Freesurfer

For structural MRI data processing, FreeSurfer offers the following services:

- Motion Correction: This step will smooth out any minor movements across several source volumes before averaging them all together.
- Intensity Correction: This steps makes a few generalisations about the data as it corrects for intensity non-uniformity in MR data.
- Talairach: Using the FreeSurfer script talairach and the MINC programme mritotal, the affine transform from the original volume to the MNI305 atlas is calculated. [62] Many programs use the talairach coordinates as seed locations.
- Normalization: Carries out volume normalization of the original intensity.
- Skull Stripping: Strips the skull from normalized file.

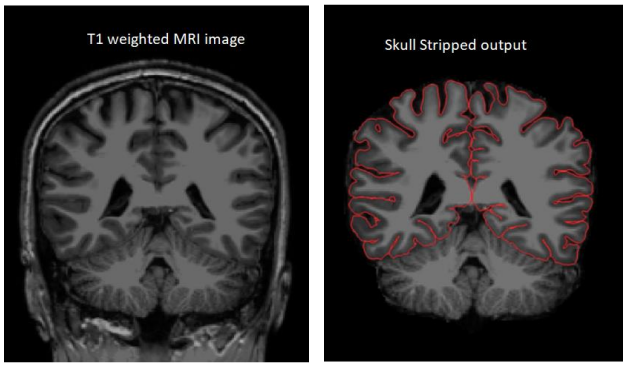


Fig 10: Skull stripping of MRI

- Gray-white matter segmentation.
- B1 bias field correction.
- Model reconstruction for the cortex (gray-white boundary surface and pial surface).

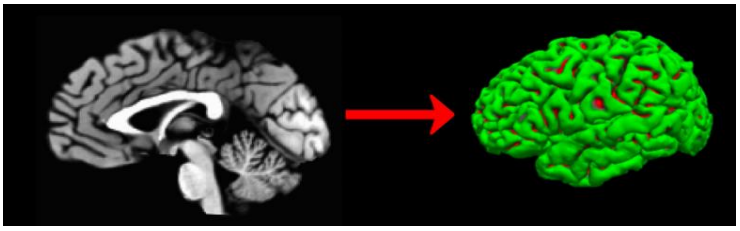


Fig 11: Reconstruction of MRI brain

- Automatic Subcortical Segmentation: FreeSurfer labels the cortical and subcortical regions using the surface reconstruction and knowledge of the normal architecture of the human brain based on the two atlases: The Desikan-Killiany atlas and the Destrieux atlas.

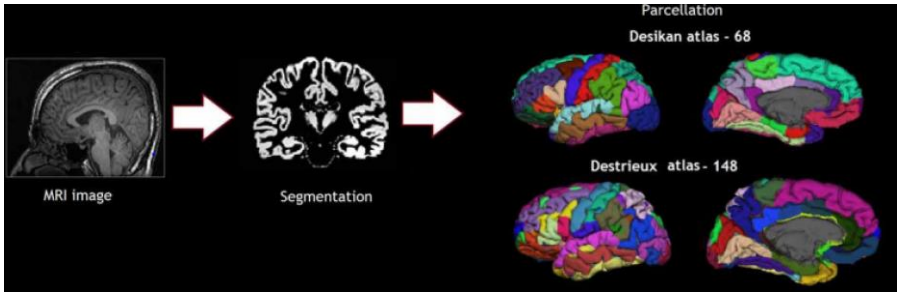


Fig 12: Segmentation based on Desikan-Killiany and the Destrieux atlases

- Parcellation: for labeling the cortex. The average of structural measures inside each parcellation is then calculated. These measurements can be used to compare individuals or to determine individual differences based on factors like sex, IQ, or age.
- Stereotaxic atlas and nonlinear registration of an individual's cortical surface.
- Comparisons in group morphometry statistically analyzed.

3.6. Algorithm development

Using a 3D convolutional neural network (CNN), schizophrenia patients and healthy controls are categorized.

The local connection and weight sharing approach used by Convolutional neural networks reduce the network's complexity and enables the network to take an image as input directly. Two key properties of the convolution neural network are that the features learnt from the image are translational and non-deformable, and that the features retrieved get more abstract and complicated the higher the convolution layer. The convolution layer, the pooling layer, and the fully connected layer make up the convolution neural network. Filters make up the convolution layer. Every filter is comparable to a little window. These tiny windows travel around the image to pick up details. In order to extract more representative features and increase the model's resilience and accuracy, the learnt features are then subsampled using a pooling technique. The prediction result is then output by the fully connected layer.

Processing RGB pictures often involves 2D CNNs (3 channels). A 3D CNN is essentially the 3D equivalent; it may learn representations for volumetric data using a 3D volume or a series of 2D frames, such as slices from an MRI scan.

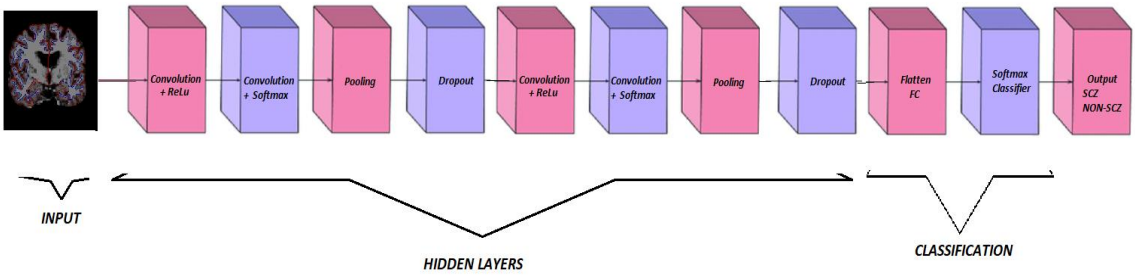


Fig 13: CNN Architecture

This architecture incorporates max-pooling-based down sampling in each of its four 3D convolutional layers. Activavtion is performed using Rectified linear unit (ReLU). If a negative value is sent to the function, it returns 0, but if a positive value is passed to the function, it returns the input value as follows: f(x) = max (0, x). An activation function has the ability to capture the variations in the dataset and the interactions. [47]

Keras library in Python was used, Sequential Model of CNN was used, training size was set as 0.80, test size as 0.20.

The pooling size matched the kernel size of 3 x 3 x 3. The 3 x 3 x 3 kernel size matches the Gaussian kernel size used for MRI post-processing in order to reduce motion artefacts [48]. A dropout rate of 0.25 is utilized in each of the convolutional layer in the architecture. After the convolutional layers, one highly connected layer with a dropout rate of 0.5 was added. 32 models were trained in a batch over a period of 50 epochs. [49]

To prevent overfitting that would affect the findings, Once convergence was attained (epochs = 50), the training was cut short. Previous research has demonstrated that terminating the training procedure early may enhance generalization.

3.7. A brief overview of the performance metrics for the classification problem:

Some of the performance metrics used to evaluate classification problems are:

3.7.1. Confusion Matrix

Four key elements that make up the confusion matrix, which is utilized to define the performance measures for the classifier. These are the four numbers:

Table 7: Confusion Matrix

		Actual Values: Positive (1)	Actual Values: Negative (0)
Predicted Values	Positive (1)	TP	FP
Predicted Values	Negative (0)	FN	TN

1. ***TP (True Positive):*** The number of patients who have been correctly diagnosed as having Schizophrenia.
2. ***TN (True Negative):*** TN denotes the proportion of correctly identified healthy controls.
3. ***FP (False Positive):*** FP refers to the number of people who were incorrectly diagnosed with Schizophrenia while, in reality, they were healthy. Another name for FP is a Type I error.

4. ***FN (False Negative):*** FN denotes the number of patients who were misdiagnosed as healthy while they actually had schizophrenia.

Different performance metrics e.g. Accuracy, Sensitivity, Specificity and Precision for an algorithm are derived from the confusion metrix.

3.7.2. Accuracy

The frequency that the classifier predicts correctly is how accuracy is calculated. Accuracy may be defined as the proportion of accurate predictions to all predictions.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

3.7.3. Area under the curve (AUC)

The area under the curve quantifies a classifier's ability to distinguish between classes (AUC). The performance of the model at various thresholds between positive and negative classes is improved by a higher AUC.

3.7.4. Precision

How many of the situations that were accurately predicted really came true is indicated by precision. The precision is calculated as the ratio of genuine positives to expected positives.

$$Precision = \frac{TruePositive}{TruePositive + FalsePositive}$$

3.7.5. Sensitivity/ Recall

Sensitivity/Recall is a metric that reveals what percentage of patients were really diagnosed with Schizophrenia by the algorithm actually had it.

$$Recall = \frac{TruePositive}{TruePositive + FalseNegative}$$

3.7.6. Specificity

Specificity indicates the percentage of individuals who did not have Schizophrenia who the model predicted to be either non-schizophrenic or normal.

$$\text{Specificity} = \frac{TN}{TN + FP}$$

4. Results and Implementation

4.1. Visualizing the model's performance

For the training and validation sets, the model's accuracy is displayed. Accuracy gives a fair assessment of the model's performance since the validation set is balanced across classes.

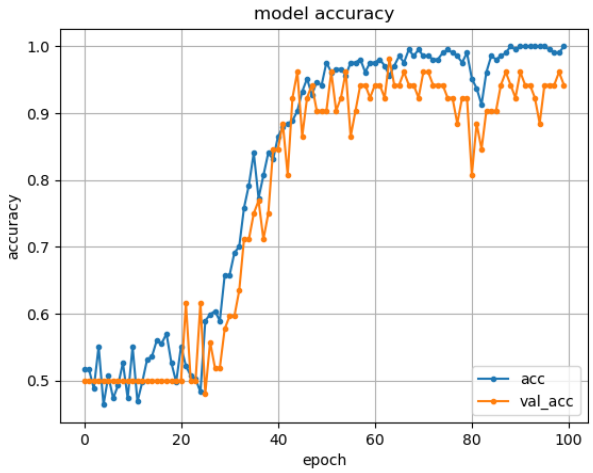


Fig 14: Model Accuracy Curve

With an accuracy rate of 71.0 % and an AUC of 0.72, the deep learning model effectively discriminated structural MRI data from patients with schizophrenia from those from healthy participants. Differences in the characteristics of the participants of the dataset can greatly affect the classifiers performance.

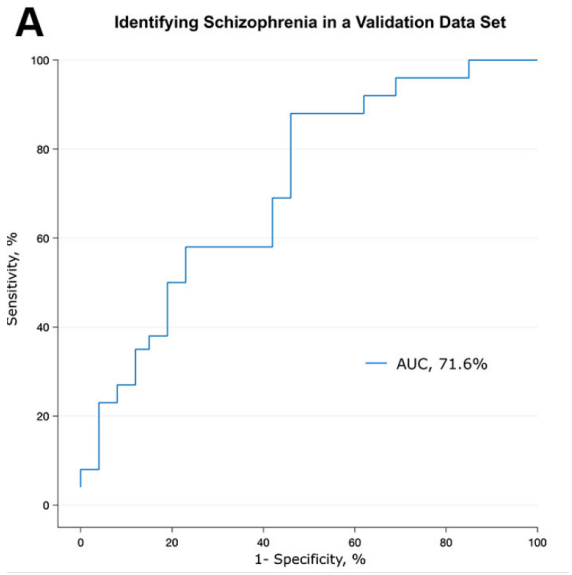


Fig 15: AUC Curve

4.2. Confusion matrix of proposed method

The output of the proposed classification algorithm is shown and summarized in the confusion matrix. The AUC-ROC curves, as well as recall, precision, specificity, and accuracy, may all be evaluated with the use of this confusion matrix.

Table 8: Confusion Matrix of proposed model

		TRUE	
		POSITIVE	NEGATIVE
PREDICTED	POSITIVE	83	35
	NEGATIVE	27	75

4.3. Conclusions derived from the confusion matrix:

The percentage of patients in a sample that test positively is referred to as the sensitivity. On a scale from 0 to 1, this true-positive rate is presented. 1 is the best rate (or 100 percent). Sensitivity is an estimate of the likelihood that an afflicted person would test positive when dealing with a single patient as opposed to a group of people. Sensitivity is essentially a test-quality attribute. The percentage of healthy people who test negative (a real negative result) or the predicted chance that an unaffected person would test negative are both examples of specificity.

A doctor would like to locate a test with high values for both specificity and sensitivity. This doesn't happen very often. The vast majority of tests have good specificity or sensitivity. When seeking to "rule in" a patient condition, therapists have historically been instructed to use a highly precise diagnostic test, and when trying to "rule out" a condition, a highly sensitive test. However, from the table the sensitivity comes out to be 0.75 and the specificity 0.68 which means that among all the person 75% of the patients will be classified as Schizophrenic correctly.

Table 9: Performance Metrics

Measure	Values	Derivation
Accuracy	0.7182	ACC= (TP + TN) / (P + N)
Sensitivity	0.7545	TRP= TP / (TP + FN)
Specificity	0.6818	SPC= TN / (FP + TN)
Precision/ Recall	0.7034	PR= TP/ (TP + FP)
False Positive Rate	0.3182	FPR= FP/ (FP + TN)
False Negative Rate	0.2455	FNR= FN/ (FN + TP)

A precision value of 0.70 is acceptable but can be improved. High precision is necessary for Schizophrenia prediction; in other words, you must also account for false negatives. A non-Schizophrenic individual being identified as Schizophrenic is somewhat acceptable, but a Schizophrenic patient shouldn't be given that designation. When using a deep neural network, the precision may be increased by choosing a loss function that is responsive to changes and doesn't round off data needlessly. The threshold value that you provide your final neural network layer is the crucial factor. When binary classification is involved, the threshold needs to be chosen to optimize recall or precision.

5. Conclusion and Future Recommendations

As a result of solely supervised learning, our results demonstrate that a deep CNN is capable of breaking records on a very difficult dataset. Notably, if just one convolutional layer is eliminated, our performance suffers. Because of this, the depth is crucial for reaching our goals.

We did not use any unsupervised pre-training in order to streamline our experiments, even though we anticipate that it will be beneficial, especially if we are able to obtain enough computational power to significantly increase the size of the network without obtaining a corresponding increase in the amount of labelled data. In contrast to normal machine learning, which depends on a programmer to determine if a conclusion is true or incorrect, deep learning's multi-layered structure allows it to independently judge the correctness of its responses.

Deep learning models use a cascade of layers to filter data, with each layer building on the findings of the one before it. As they analyze new data and essentially learn from previous findings, deep learning models can enhance their ability to recognize correlations and linkages. Deep learning models may complete classification tasks using this multi-layered technique, such as finding associations between symptoms and outcomes in huge amounts of unstructured data, spotting subtle variations in medical images, classifying patients into cohorts based on risk factors, etc.

Deep learning is an improvement over previous forms of machine learning since it also has the benefit of requiring far less input from human trainers. We want to use very large and deep convolutional networks in the future to analyze video sequences which has highly useful information that is either missing or much less visible in static images. Given that deep learning already has an advantage in many high-value applications on

the clinical side, image analytics is likely to remain the focus for the foreseeable future. The use of deep learning to predictive analytics and clinical decision support has been the subject of extensive research. With its ability to notify healthcare professionals of changes in high-risk conditions like the need for urgent treatment, deep learning may eventually prove to be an invaluable diagnostic ally in the inpatient environment.

Even when a patient requires urgent care, there may be significant delays between the time it takes to evaluate brain MRI images and the start of therapy due to the enormous volume of scans that medical personnel must review. These delays may potentially endanger the lives of patients if a severe emergency arises, such a brain hemorrhage. Deep learning allows for practically immediate diagnosis and ensures that patients receive high-quality care.

The limitations of this study are similar to those of other investigations. The deep learning method was trained using just binary-labeled MRI data (Schizophrenia or normal). Although this dualistic categorization is frequently employed in artificial intelligence investigations, it may make it difficult to deploy this approach in clinical settings. Multiple disorders can coexist in a patient, and the majority of mental conditions have a continuous spectrum of development. Our analysis lacked a clinical reference group, therefore more research involving conditions like bipolar spectrum disorder and neurodegenerative diseases is required. Due to the absence of clinical control groups, it is difficult to say with certainty that the medial temporal lobe abnormalities identified as being exclusive to schizophrenia.

Whether Schizophrenia can be diagnosed only by brain anatomical traits is another significant limitation. Structure and function impairments both accompany Schizophrenia as a disease. Combining structural and functional aspects of brain imaging would be expected to boost the possibility for therapeutic usage, since recent research has demonstrated that functional MRI data and artificial intelligence algorithms may also be used to reliably predict schizophrenia.

Apart from these bigger datasets are needed. Clinicians may be able to distinguish Schizophrenia from other disorders and describe the unique morphological and physiological features of the brain in schizophrenia patients with the aid of deep learning algorithms that have been trained on large data sets of illnesses in various stages and severity.

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