Data Access Statement: The fMRI dataset used in this study is available for download from Schizconnect.org and the FBRIN repository. The data subset used in this research can be shared with interested readers upon reasonable request. Requests for data access should be directed to the corresponding author, who will facilitate the provision of the dataset, ensuring compliance with ethical and legal requirements.

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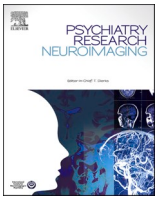

Investigating the association between symptoms and functional activity in brain regions in schizophrenia: A cross-sectional fmri-based neuroimaging study

Indranath Chatterjee [a,b,*], Bisma Hilal [c]

[a] Department of Computing and Mathematics, Manchester Metropolitan University, Manchester, United Kingdom
[b] School of Technology, Woxsen University, Hyderabad, India
[c] Department of Information Technology, Cluster University, Srinagar, India

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ABSTRACT

Schizophrenia is a persistent neurological disorder profoundly affecting cognitive, emotional, and behavioral functions, prominently characterized by delusions, hallucinations, disordered speech, and abnormal motor activity. These symptoms often present diagnostic challenges due to their overlap with other forms of psychosis. Therefore, the implementation of automated diagnostic methodologies is imperative. This research leverages Functional Magnetic Resonance Imaging (fMRI), a neuroimaging modality capable of delineating functional activations across diverse brain regions. Furthermore, the utilization of evolving machine learning techniques for fMRI data analysis has significantly progressive. Here, our study stands as a novel attempt, focusing on the comprehensive assessment of both classical and atypical symptoms of schizophrenia. We aim to uncover associated changes in brain functional activity. Our study encompasses two distinct fMRI datasets (1.5T and 3T), each comprising 34 schizophrenia patients for the 1.5T dataset and 25 schizophrenia patients for the 3T dataset, along with an equal number of healthy controls. Machine learning algorithms are applied to assess data subsets, enabling an in-depth evaluation of the current functional condition concerning symptom impact. The identified voxels contribute to determining the brain regions most influenced by each symptom, as quantified by symptom intensity. This rigorous approach has yielded various new findings while maintaining an impressive classification accuracy rate of 97 %. By elucidating variations in activation patterns across multiple brain regions in individuals with schizophrenia, this study contributes to the understanding of functional brain changes associated with the disorder. The insights gained may inform differential clinical interventions and provide a means of assessing symptom severity accurately, offering new avenues for the management of schizophrenia.

1. Introduction

Schizophrenia, an intricate and chronic psychiatric condition impacting a vast global population, remains an enigmatic mystery for researchers and clinicians. The patients affected with schizophrenia endure a diverse array of distressing symptoms, including hallucinations, delusions, and disorganized behavior, arising from impaired cognitive and motor processes. While traditional nosological thinking may categorize symptoms into psychotic, cognitive, and negative types, it is important to recognize that many individuals with schizophrenia experience a combination of these symptom categories. This overlap underscores the need for a more nuanced understanding of the disorder Tandon et al. (2013); Potuzak et al. (2012). The diagnosis of schizophrenia primarily occurs during late adolescence and early adulthood, with males exhibiting an earlier onset compared to females Häfner et al. (1992). The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) mandates the presence of two or more symptoms, such as delusions, hallucinations, disorganized speech, catatonic behavior, or negative symptoms, persisting for at least one month, with delusions, hallucinations, or disorganized speech being pivotal criteria Tandon et al. (2013). Beyond the primary symptoms, individuals with schizophrenia grapple with secondary symptoms, including anxiety, abnormal movements, depression, and impaired abstract thinking, which contribute to the challenge of accurate diagnosis due to symptom overlap with other neurological conditions. The etiology of schizophrenia is multifactorial, involving genetic, environmental,

* Corresponding author.
E-mail address: i.chatterjee@mmu.ac.uk (I. Chatterjee).

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birth-related, and social or personal factors that collectively contribute to its development Chatterjee and Mittal (2020). Recent advances in genetic research have shed light on 108 genes associated with schizophrenia, offering fresh insights into the underlying mechanisms Jawanjal and Chatterjee (2021); Li et al. (2007). However, the true impact of schizophrenia lies in the cognitive impairments and emotional fluctuations that significantly impair daily functioning. Cognitive deficits encompass attention, memory, reasoning, and processing speed, and remarkably, these impairments are evident even before the clinical onset of the illness Keefe and Harvey (2012); O'Carroll (2000); Elvevag and Goldberg (2000). Moreover, individuals with schizophrenia face difficulties in perceiving and expressing emotions, affecting their ability to recognize and experience emotions fully Kring and Elis (2013); Kring and Caponigro (2010); Kee et al. (2003). A profound understanding of the complex interplay of these symptoms is critical in comprehending the multi-faceted nature of schizophrenia and devising effective treatment modalities.

Functional magnetic resonance imaging (fMRI) has emerged as a potent tool for unraveling aspects of the pathophysiology of schizophrenia by revealing functional activations in various brain regions Chatterjee et al. (2018); Chatterjee et al. (2020). Machine learning (ML) approaches have gained prominence in fMRI data analysis, facilitating feature selection and modeling. However, research focusing on identifying brain areas linked to distinct stages of symptoms remains limited Su et al. (2015). Existing studies have explored the effectiveness of brain networks concerning schizophrenia symptoms, revealing significant findings concerning small-world network metrics Su et al. (2015). Other investigations have identified brain activation patterns and abnormalities in verbal working memory systems, providing potential insights into the neurological basis of specific symptoms Shad and Keshavan (2015), Hashimoto et al. (2010). Data-driven ML approaches have been employed to classify schizophrenia patients based on brain activations, showing promise in potentially correlating these activations with symptom severity M. Bleich-Cohen et al. (2014). Additionally, comparative studies between schizophrenia patients and healthy controls have shed light on alterations in brain networks and functional connectivity associated with positive and negative symptoms (Vanes et al., 2019), M. Bleich-Cohen et al. (2014). Particularly, the relationship between negative symptoms and anterior cingulate cortex (ACC) dysfunction has been identified, adding valuable dimensions to the understanding of schizophrenia symptomatology Nelson et al. (2015). Explorations of the theory of mind (ToM) network and functional connectivity have also offered intriguing insights Brüne et al. (2011). Furthermore, ML-based investigations have examined specific brain regions, highlighting changes in functional connectivity associated with default-mode and salience networks, as well as neural responses linked to threat-related effects and affective symptom improvement (Bohaterewicz et al., 2021), Tolmeijer et al. (2018). Non-invasive neuroimaging techniques have shown promise in the diagnosis of schizophrenia (Steardo Jr et al., (2020), although it is essential to note that these techniques may excel in sensitivity while exhibiting variable specificity. Additionally, research has unveiled connectivity impairments in intra- and inter-hemispheric connections (Li et al., 2019), shedding light on the complexity of the disorder.

Despite these advances in understanding schizophrenia and the increasing application of ML algorithms in fMRI data analysis (Chatterjee et al., 2023), a significant research gap remains unexplored. Specifically, no study has comprehensively explored symptomatic functional changes in the brain using ML algorithms. This creates a unique opportunity for the present study to contribute novel insights to the field of schizophrenia research. By employing ML algorithms to address crucial research questions related to schizophrenia symptoms, this study aims to bridge the gap in the existing literature and provide a comprehensive understanding of the neurobiological underpinnings of the disease.

In this study, our primary focus was to understand the changes in functional activities in the brain related to a set of symptoms, including anxiety, depressive symptoms, negative symptoms, and other cognitive and behavioral aspects, which are often considered nonspecific but play a crucial role in the overall manifestation and complexity of schizophrenia. While core symptoms like hallucinations, delusions, and disorganization are undeniably important, our research aimed to shed light on a broader spectrum of schizophrenia's clinical presentation, providing valuable insights into the disorder's neural underpinnings. Motivated by the pressing need to comprehensively understand schizophrenia symptoms, this study endeavors to explore how the brain processes information in schizophrenia. By identifying the underlying causes of severe impacts, this research holds the potential to develop more targeted and effective treatment strategies. The utilization of ML algorithms in analyzing fMRI data offers a promising avenue for uncovering valuable insights and advancing diagnostic and therapeutic approaches for this debilitating mental illness.

Our hypothesis postulates that ML algorithms, when applied to fMRI data, can effectively identify alterations in functional brain activation associated with these specific symptoms of schizophrenia. In pursuit of this hypothesis, our study sets forth several objectives. Firstly, we aim to analyze fMRI data using ML algorithms to discern significant brain voxels associated with distinct symptom categories. Secondly, we seek to create a three-way dataset for differentiation, enabling us to identify alterations in functional brain activation related to specific symptoms. Thirdly, we aspire to contribute novel insights by employing ML algorithms to explore symptomatic alterations in functional activities in the brains of schizophrenia patients. To achieve these objectives, we will conduct rigorous statistical testing to identify significant brain voxels and utilize Linear Discriminant Analysis for feature selection. Our study will leverage two separate fMRI datasets with varying intensity levels, allowing us to pinpoint affected brain regions associated with different symptoms. The 1.5T dataset will analyze twelve symptoms, while the 3T dataset will focus on eight symptoms, ensuring a comprehensive investigation into the alterations in functional activation within brain regions.

This study embarks on an original exploration of the symptomatic aspects of schizophrenia using an fMRI-based ML approach. By identifying functional brain changes associated with specific symptoms, this research stands to enrich our understanding of schizophrenia and offer new opportunities for targeted and effective interventions. As the first study to comprehensively analyze symptomatic changes in functional activities in the brain using ML algorithms, this research holds immense promise in advancing the frontiers of schizophrenia research and improving the lives of those affected by this complex and challenging mental illness Su et al. (2015).

2. Methods and materials

2.1. Dataset details

The dataset was obtained from the Function BIRN Data Repository (FBIRN). The FBIRN repository has a multi-site fMRI dataset that includes schizophrenia and healthy individuals. In this study, we have used the BOLD fMRI data having the Auditory Oddball task Chatterjee et al. (2018). As per the FBIRN repository, the functional scans utilized T2*-weighted gradient EPI (Echo Planar Imaging) sequences. These sequences adhered closely to pulse sequence parameters determined through pilot studies conducted by the FBIRN research group. These parameters included orientation along the anterior commissure-posterior commissure line, a slice count of 27, 4 mm slice thickness, a repetition time (TR) of 2 s, an echo time (TE) of 40 ms for 1.5 T scanners, a matrix size of 64 × 64, a field of view measuring 22 cm, and a flip angle of 90°.

Before our analysis, we confirmed from the relevant source, that all subjects had normal hearing and adequate eyesight, and they could complete basic cognitive activities. If a healthy person had a current or

previous history of a head injury or severe medical ailment, they were excluded from the research. Only patients with schizophrenia and schizoaffective disorders who met the DSM-IV criteria were eligible to take part in this study Chatterjee (2018).

2.2. Task details

Since auditory hallucination is frequently observed in schizophrenia patients, an auditory-oddball (AUD) test is a common approach for detecting these abnormalities in brain activity patterns that can help distinguish schizophrenia from healthy people. In this particular task, the respondent receives a continuous stream of sound to identify the sequence of discrete stimuli, including standard and aberrant (i.e., oddball) tones. In 95 % of trials, standard tones, such as 1000 Hz, are heard. Deviant (1200 Hz) tones occur occasionally and are distinct from regular tones (5 % of trials). The FBIRN conducted the AUD test, which consisted of four experimental runs lasting 280 s each Chatterjee et al. (2018). During each trial, the participant stares at a grey screen with a black fixation cross in the center. Participants push button '1′ whenever they hear a deviant tone while focusing on the cross and listening to the tones. The practice begins with 15 s of quiet fixation. Following that, a succession of standard tones (duration = 100 ms) is played. Every 6 – 15 s (duration = 100 ms), the aberrant tone plays. After each workout, there is a 15-second period of silence. Each trial had 140 brain scans with a 2-second TR. We analyzed the AUD task data for the patients and control groups in this investigation.

2.3. Dataset preparation

Dataset preparation is one of the key uniqueness of this study. As mentioned, we have taken two fMRI datasets with 1.5T (D1) and 3T (D2) intensity. The dataset D1 contains the brain volumes of 34 schizophrenia patients and 34 healthy participants. We have used four different runs of each subject's scan. Twelve symptoms have been taken into account, namely, anxiety (minor/moderate); abstract thinking (minor/moderate); Athe degree of abnormal movement (none/mild); observed depression (absent/mild); lack of judgment (absent/minimum/mild); primary negative symptoms (yes/no); the current treatment status (current outpatient/no treatment); stable negative symptoms (yes/no); suicidal tendency (absent/mild); the presence of two negative symptoms of severity or more (yes/no); duration of the illness (high/low); and gender difference as in male or female. The demographics of dataset D1 are listed in Table 1. In the case of "severity of disorder" mentioned in Tables 1 and 2, we curated the FBIRN Phase II dataset, accessed from the 'AssessmentData_20080213′ folder, to categorize patients into 'Mild,' 'Moderate,' and 'Severe' based on the 'SCID_PC13b: Current Severity' score. We verified data accuracy and selected a specific patient subset for analysis, ensuring a robust foundation for our study on overall illness severity in schizophrenia patients.

The dataset D2 contains 3T fMRI data from 25 schizophrenia patients and 25 healthy participants. Similarly, we have used four different runs of each subject's scan. Here, eight different symptoms have been considered, namely, abstract thinking (minor/moderate); the severity of abnormal movements (none/mild); anxiety (minor/moderate); observed depression (absent/mild); lack of judgment (minor/moderate); suicidal tendency (absent/mild); duration (high/low); and male/female. The demographics of the dataset are shown in Table 2.

Apart from these, Table 3 displays the symptom-wise data distribution for schizophrenia patients only for dataset D1, whereas Table 4 shows the same for dataset D2. According to the class division, the sample size of the schizophrenia patients in each group has been noted as S1 and S2. Table 5 and Table 6 show the details of the subset of data used in this study for datasets D1 and D2, respectively, where the content of each subset of the data is denoted with a specific dataset name. These dataset names have been used thoroughly in the following sections.

In our investigation of the intricate relationship between functional brain changes and symptomatology in schizophrenia, we intentionally focused on a set of twelve symptoms that encompass various dimensions of the disorder. The symptom measures utilized in this study were derived from the Structured Clinical Interview for DSM Disorders (SCID). This structured clinical interview has been widely employed for diagnosing psychiatric disorders and assessing symptom severity. Notably, our decision to exclude positive symptoms, such as hallucinations and delusions, was driven by our specific research goals. While acknowledging the undeniable significance of positive symptoms in the schizophrenia spectrum, we aimed to contribute to the understanding of less-explored aspects of the disorder, particularly non-specific symptoms. By concentrating on these less-explored dimensions, we aspire to provide a nuanced understanding of the comprehensive clinical presentation of schizophrenia, offering insights that complement the existing body of research focused on positive symptoms.

2.4. Data preprocessing

Initially, the raw data was preprocessed using the Statistical Parametric Mapping version 12 (SPM12) toolbox, available in Matlab. During the acquisition of the scans, the raw images were taken with voxel sizes of $3.4 \times 3.4 \times 4$ mm^3. As a part of data preprocessing, we have performed a pipeline starting with re-alignment. The first fMRI scanned image of a subject was used as a reference to realign them. Following the re-alignment, slice timing correction was used to compensate for possible errors induced by temporal variations during acquisition. After that, the fMRI images were spatially normalized into the standard Montreal Neurological Institute (MNI) space using an echo planar imaging (EPI) template supplied in SPM12. It reduced the size of the original voxel to $3 \times 3 \times 3$ mm^3 and provided each brain volume with a dimension of $53 \times 63 \times 46$ voxels. Finally, the smoothed volumes were produced by a spatial smoothing technique using a Gaussian kernel with a full width at half maximum (FWHM) filter of size $9 \times 9 \times 9$ mm^3 Chatterjee et al. (2018); Chatterjee et al. (2020).

2.5. Proposed methodology

2.5.1. Step 1: general linear model approach

In the first stage of the proposed methodology, the general linear model (GLM) approach has been employed. We have performed the GLM analysis using the SPM12 toolbox in Matlab2020a (Chatterjee et al., 2018; Chatterjee, 2018) using the preprocessed data. During the GLM analysis, we received two kinds of activation maps, viz. contrast

Table 1
Dataset details for D1 (1.5 T fMRI). X, Y, Z, NDA denote the number of patient data available for the severity of the disorder, where *X*=Mild; *Y*=Moderate, *Z*=Severe; NDA=No data available.

Subject	Sample size	Age (Mean & Std)	Sex (M/F)	Handedness (R/L)	Age of Onset (Median)	Severity of disorder	Current Treatment Status	Smoking (Yes/No)
Healthy	34	40.4 (±12.29) years	24/10	30/4	NA	NA	NA	10/24
Schizophrenia	34	42.3 (±10.81) years	27/7	28/6	22 years	$X = 10$; $Y = 14$; $Z = 2$; NDA=8	Under medication=22; Untreated=12	25/9

Table 2
Dataset details for D2 (3T fMRI). X, Y, Z, NDA denote the number of patient data available for the severity of the disorder, where *X*=Mild; *Y*=Moderate, *Z*=Severe; NDA=No data available.

Subject	Sample size	Age (Mean & Std Dev)	Sex (M/F)	Handedness (R/L)	Age of Onset (Median)	Severity of disorder	Smoking (Yes/No)
Healthy	25	37.76 (±12.25) years	15/10	22/3	NA	NA	10/24
Schizophrenia	25	39.76 (±10.8) years	19/6	23/2	23 years	$X = 11$; $Y = 8$; $Z = 0$; NDA=6	25/9

Table 3
Symptom-wise data distribution for preparation of data subsets for Dataset D1. The second and third columns show the number of schizophrenia patients for each subtype of a symptom in the first column. For each subgroup of the dataset, we have taken an equal number of healthy controls maintaining the demographics.

Symptoms	Schizophrenia subjects (S1)	Schizophrenia subjects (S2)
Duration (Long/Short) [D11]	16	18
Observed depression (Absent/Mild) [D12]	19	15
Severity of abnormal movements (None/Mild) [D13]	25	9
Lack of judgment (Min/Mild) [D14]	17	17
Present treatment status (Current outpatient/ No treatment) [D15]	22	12
Suicidal tendency (Absent/Mild) [D16]	28	6
Anxiety level (Min/Mod) [D17]	21	13
Stable negative symptoms (Yes/No) [D18]	24	10
Abstract thinking (Min/Mod) [D19]	15	19
Presence of two or more negative severe symptoms (yes/no) [D1a]	21	13
Negative symptoms are primary (yes/no) [D1b]	23	11
Male/Female [D1c]	27	7

Table 4
Symptoms-wise data distribution for preparation of data subsets for Dataset D2. The second and third columns show the number of schizophrenia patients for each subtype of a symptom in the first column. For each subgroup of the dataset, we have taken an equal number of healthy controls maintaining the demographics.

Symptoms	Schizophrenia subjects (S1)	Schizophrenia subjects (S2)
Duration (long/Short) [D21]	12	13
Observed depression (absent/mild) [D22]	15	10
Severity of abnormal movements (None/Mild) [D23]	11	4
Lack of judgment (Min/Mild) [D24]	13	12
Suicidal tendency (Absent/Mild) [D25]	16	9
Anxiety level (min/mod) [D26]	12	13
Abstract thinking (min/mod) [D27]	12	13
Male/Female [D28]	19	6

maps and beta maps. To construct a contrast map in GLM, we first create a contrast matrix that shows areas that respond more significantly in one condition than the other, in this case, whether the participants listen to an oddball sound or not. A contrast in the GLM is represented by a set of weights, one for each, that are used to establish an inequality. This produces a sequence contrast vector of [1 −1 1 −1… so on], where 1 represents the onset (as the stimulus) and −1 represents the baseline condition. After this, it generates a beta map and a contrast map as separate statistical maps to mask the contrasting overlay. Beta maps provide beta values for all categories scaled by parameter estimations. We may construct a contrast estimate for each voxel in the brain by

Table 5
Detailed symptom-wise content for each data subset under the dataset D1 (1.5T) used in this study. These dataset nomenclatures are used thoroughly in the rest of the paper.

Dataset	Dataset Details
D11 S1 H1	Long duration of illness v/s healthy controls
D11 S2 H2	Short duration of illness v/s healthy controls
D11 S1 S2	Long duration v/s short duration of illness
D12 S1 H1	Absent observed depression of illness v/s healthy controls
D12 S2 H2	Mild observed depression v/s healthy controls
D12 S1 S2	Absent observed depression of illness v/s mild observed depression
D13 S1 H1	No severity of abnormal movements v/s healthy controls
D13 S2 H2	Mild severity of abnormal movements v/s healthy controls
D13 S1 S2	No severity of abnormal movements v/s mild severity of abnormal movements.
D14 S1 H1	Minimum lack of judgment v/s healthy controls
D14 S2 H2	Mild lack of judgment v/s healthy controls
D14 S1 S2	Minimum lack of judgment v/s mild lack of judgment
D15 S1 H1	Current outpatient v/s healthy controls
D15 S2 H2	No treatment v/s healthy controls
D15 S1 S2	Current outpatient v/s No treatment
D16 S1 H1	Absence of suicidal tendency v/s healthy controls
D16 S2 H2	Mild suicidal tendency v/s healthy controls
D16 S1 S2	Absence of suicidal tendency v/s mild suicidal tendency
D17 S1 H1	Minimum anxiety level v/s healthy controls
D17 S2 H2	Moderate anxiety level v/s healthy controls
D17 S1 S2	Minimum anxiety level v/s moderate anxiety level
D18 S1 H1	Stable negative symptoms v/s healthy controls
D18 S2 H2	Absence of stable negative symptoms v/s healthy controls
D18 S1 S2	Stable Negative Symptoms v/s Absence of stable negative symptoms
D19 S1 H1	Minimum abstract thinking v/s healthy controls
D19 S2 H2	Moderated abstract thinking v/s healthy controls
D19 S1 S2	Minimum abstract thinking v/s moderated abstract thinking
D1a S1 H1	Presence of two or more negative symptoms of severity v/s healthy controls
D1a S2 H2	Absence of two or more negative symptoms of severity v/s healthy controls
D1a S1 S2	Presence of two or more negative symptoms of severity v/s Absence
D1b S1 H1	Primary negative symptoms v/s healthy controls
D1b S2 H2	Non-primary negative symptoms v/s healthy controls
D1b S1 S2	Primary negative symptoms v/s non-primary negative symptoms
D1c S1 H1	Male patients v/s healthy controls
D1c S2 H2	Female patients v/s healthy controls
D1c S1 S2	Male patients v/s female patients

Table 6
Detailed symptom-wise content for each data subset under the dataset D2 (3T) used in this study. These dataset nomenclatures are used thoroughly in the rest of the paper.

Dataset	Dataset Details
D21 S1 H1	Long duration of illness v/s healthy controls
D21 S2 H2	Short duration of illness v/s healthy controls
D21 S1 S2	Long duration v/s short duration of illness.
D22 S1 H1	Absence of observed depression v/s healthy controls
D22 S2 H2	Mild depression v/s healthy controls
D22 S1 S2	Absence of observed depression v/s mild depression
D23 S1 H1	Absence of abnormal movement v/s healthy controls
D23 S2 H2	Mild abnormal movement v/s healthy controls
D23 S1 S2	Minimal abnormal movement v/s mild abnormal movement
D24 S1 H1	Minimum lack of judgment v/s healthy controls
D24 S2 H2	Moderate lack of judgment v/s healthy controls
D24 S1 S2	Minimum lack of judgment v/s moderate lack of judgment
D25S1 H1	Absence of suicidal tendency v/s healthy controls
D25 S2 H2	Mild suicidal tendency v/s healthy controls
D25 S1 S2	Absence of suicidal tendency v/s mild suicidal tendency
D26S1 H1	Minimum anxiety level v/s healthy controls
D26 S2 H2	Moderate anxiety level v/s healthy controls
D26 S1 S2	Minimum anxiety level v/s moderate anxiety level
D27S1 H1	Minimum abstract thinking v/s healthy controls
D27 S2 H2	Moderate abstract thinking v/s healthy controls
D27 S1 S2	Minimum abstract thinking v/s moderate abstract thinking
D28 S1 H1	Male patients v/s healthy controls
D28 S2 H2	Female patients v/s healthy controls
D28 S1 S2	Male patients v/s female patients

estimating a beta weight for the incongruent condition and a beta weight for the congruent condition, for example. This generates a contrast map for each voxel.

While we perform the GLM analysis on a single brain volume captured over time (4D), it maps the voxels at each time point to analyze the pattern of activation over time. After mapping those voxels, it creates a 3D activation map having the same resolution as the brain volume. This activation map highlights the voxels being significantly activated during the time frame. In this study, we considered the 3-D activation maps. These activation maps represent a single 3-D volume of a brain showing the activations in various parts of the brain as per the BOLD signals. Thus, we obtained a brain volume by removing the complexity of the temporal dimension. As a vector of OnSet values, we have considered the subject's performance during the AUD task, thus the four-dimensional fMRI data were transformed into a three-dimensional contrast map. When employing GLM analysis, the value for each voxel indicates the difference in activation of that voxel for the specific task performance. A voxel with a zero value denotes that the particular voxel was not activated throughout the AUD task.

The design matrix was generated by defining a few key parameters and entering them into the GLM algorithm. We set the repetition time to 2 s while we described the task stimulus onsets and the task's duration. The function was then forwarded to the first-level analysis, which assessed the design matrix for task regressors, movement parameter regressors, and constant regressors. The final steps required analyzing the voxels that were most likely to be involved in the AUD task.

The use of GLM resulted in around 55,000 activated voxels out of 153,594 voxels (the initial dimension of a single 3D volume of data was $53 \times 63 \times 46$). A single 3-D spatial map of the active voxels was constructed using the average of four contrast maps created for each participant.

Although, GLM is widely used as the first-level analysis to remove statistically irrelevant information from brain images, even though it is incapable of identifying significant voxels at the core without any assumptions. In fMRI analysis, ML overcomes this problem by identifying the most significant changes in functional activities in the brain regardless of condition. Thus, in this study, we proposed two more stages of feature selection, followed by GLM.

2.5.2. Step 2: statistical testing

In the second step of the proposed approach, the 3-D activation maps were subjected to a two-sample t-test to identify significant and relevant features. The student's paired t-test was employed to determine the statistical significance of two sets of data. The t-test was performed to determine the true difference between the two group means by dividing the difference in group means by the pooled standard error of both groups.

The t-value represents the number of observations in each group. A higher t-value shows that the group's mean difference is more significant than the pooled standard error, reflecting a more considerable difference. We have considered the level of significance (α) as 0.05. At $\alpha = 0.05$, the null hypothesis (H0), that the mean value of a voxel of the two groups (patients and controls) is the same, is tested. We may assess whether the obtained t-value is more significant than what would be expected by chance by comparing it to the figures in a critical value chart. In that instance, the null hypothesis might be disproved, and the two groups might be distinguished. Following the t-test, we selected only the voxels with statistical significance at $p < 0.05$. We received approximately 4000 and 8000 statistically significant voxels (varies for each symptom). As a result, we were able to successfully filter the irrelevant voxels from around 55,000 voxels obtained from the GLM analysis. T-test results helped us significantly narrow our search space before further reducing the feature space with LDA.

2.5.3. Feature selection using linear discriminant analysis

Linear discriminant analysis (LDA) is a technique used to find a linear combination of characteristics that distinguishes two or more classes of objects or events. Its goal is to reduce dimensionality. It is similar to principal component analysis (PCA) but concentrates on increasing the separability between known categories. This method projects a dataset into a lower-dimensional space with strong class separability to avoid overfitting and reduce computational costs. The resulting combination can be used to reduce dimensionality before classification. LDA is primarily concerned with projecting features from higher-dimensional space to lower-dimensional space. This can be accomplished in three steps: first, we determined the separability between classes, defined as the distance between the mean of distinct classes or between-class variance, using the following formula (Eq. (1)).

$$S_b = \sum_{i=1}^{g} N_i \left(\underline{x}_i - \underline{x}\right)\left(\underline{x}_i - \underline{x}\right)^T \tag{1}$$

Second, we determined the distance between each class's mean and sample or the within-class variance using the following way (as shown in Eqs. (2) and (3)).

$$S_w = \sum_{i=1}^{g} (N_i - 1) \tag{2}$$

$$S_i = \sum_{i=1}^{g} \sum_{j=1}^{Ni} \left(X_{i,j} - \underline{X_i}\right)\left(X_{i,j} - \underline{X_i}\right)^{\tau} \tag{3}$$

Finally, we created a lower-dimensional space that optimizes the variance between classes while minimizing the variance within classes. Here, Fisher's criterion (P) was employed in this case, which is a lower-dimensional space projection approach that evaluates the difference between class means (encoded in the between-class scatter matrix) normalized by a within-class scatter matrix measure. P was calculated using the following formula, as given in Eq. (4).

$$P_{lda} = arg\frac{\left|P^T s_b p\right|}{\left|P^T s_w p\right|} \tag{4}$$

After decomposing our square matrix into eigenvectors and eigenvalues, we interpreted it. To identify which eigenvector(s) should be eliminated for our lower-dimensional subspace, we required looking at

the eigenvalues of the eigenvectors. We had to reject the eigenvectors with the lowest eigenvalues since they convey the least amount of information about the data distribution.

After ranking the eigenvectors by their associated eigenvalues from highest to lowest, the top 'k' eigenvectors were picked by carefully selected criteria ranging from the top 20 % – 50 %. Then we discovered that the top 25 % of features produced the best results. As a consequence, for each dataset, the top 2000 to 3000 features were chosen for further classification.

2.5.4. Classification

After LDA, the final subset of data was utilized to identify between schizophrenia patients (S1/S2), vis-a-vis schizophrenia and healthy people (S1H1, S2H2) using two classifiers viz. support vector machine (SVM) and random forest (RF). The classification tasks were performed using the leave-one-out cross-validation (LOOCV) method. Each epoch of the proposed algorithm takes an *n-1* sample for training and one unseen sample for testing, where *n* is the total number of samples for a particular data subset.

2.5.4.1. Classification using SVM. SVM is a supervised learning technique used to solve classification issues. The algorithm aims to find a hyperplane in N-dimensional space (N — the number of features) that distinguishes between data points. In this study, we have used the linear kernel of the SVM. The linear SVM learns the hyperplane by changing the problem using linear algebra. For a linear kernel, Eq. (5) was used to estimate a new input using the dot product of the input (X) and each support vector (X_i):

$$f(x) = B_0 + SUM(A_i * (X, X_i)) \tag{5}$$

The purpose of this equation is to compute the inner products of a new input vector (X) with all support vectors in training data. The learning algorithm must calculate the coefficients B_0 and A_i from the training data (for each input).

As part of parameter tuning, we have tuned two parameters for an optimized result: regularization parameter and gamma. Here, we have employed the C-Support Vector Classification (C-SVC) settings. After analyzing the values of *C* from 0.01 to 1000 in 10-step increments, the regularization parameter *C* was fine-tuned at $C = 100$. C-SVC uses the following loss function (as in Eq. (6)):

$$min_{\omega,\, b,\, \varepsilon} \frac{1}{2}\, \omega^T \omega + C \sum_{i=1}^{k} \varepsilon_i \tag{6}$$

Subject to $y_i\left(\omega^T \varnothing(x_i) + b\right) \geq 1 - \varepsilon_i$, *where* $\varepsilon_i > 0$ *and* $i = 1, 2, 3, \ldots, k$where $\varnothing(x_i)$ maps x_i into a space of high dimension, ω is the vector variable, ε_i are the slack variables, and $C > 0$ is the regularization parameter.

2.5.4.2. Classification using RF. A random forest is another ensemble learning-based categorization approach. During the training phase, it constructs a large number of decision trees. Each tree assigns a category, which is referred to as the tree's "vote." The classification that receives the most votes is chosen by the forest. The RF is made up of several decision trees that have the same nodes but different inputs, resulting in diverse leaves. It integrates the results of multiple decision trees to get a single solution that is the average of all.

$$Gini\ Index = 1 - \sum_{i=1}^{C} (P_i)^2 \tag{7}$$

When performing random forests based on categorization data, we used the Gini index criteria (as indicated in Eq. (7)) to determine how nodes on a decision tree branch should be sorted. Based on class and probability, this formula computes the Gini of each branch on a node, determining which branch is most likely to occur. P_i represents the class's relative frequency, while C. represents the number of classes.

In this case, we adjusted two parameters to achieve the best results. We set *nBag* (bag number) to 10 and enabled the OOB (out of the bag) classification. Although replacement sampling (LOOCV) was performed, one data sample was excluded from the bag sample and was not used to train the model. We ran our model on this data sample right away to assess how it would perform on the test dataset.

2.5.5. Identification of brain regions

Following classification, we chose features or voxels that demonstrated good classification accuracy while distinguishing between healthy and schizophrenic participants. We obtained the final set of voxels after conducting the two stages of feature selection, excluding GLM. These voxels were fed into ML classifiers to train the model to classify healthy controls, schizophrenia patients, and groups of symptoms. These voxels retain the most distinct information, which can aid in distinguishing differences in functional activations.

We used brain backtracking to determine the names of the brain regions corresponding to the selected voxels. We had to find the exact spatial location of the selected voxels in the brain to locate the regions. First, we converted the indices of the identified voxels into cartesian coordinates. The resulting cartesian coordinates were then transformed into Montreal Neurological Institute (MNI) space using the Echo Plane Imaging (EPI) template. Finally, using the Talairach Daemon toolbox, all MNI coordinates were transformed into Talairach space coordinates. We utilized the MANGO tool to construct a mask of the identified voxel positions, which we then placed on top of a normalized template fMRI image. Finally, for each subset of data for each analyzed symptom, we retrieved the names of the impacted brain areas indicated by our proposed approach.

3. Results

Each stage in our methodology was repeated n times on all subject data (n being the number of subjects in each data subset). We utilized two classifiers to achieve the best results. For dataset D1 (1.5 T), the highest classification accuracy obtained was 100 % ($D_{14}S_1S_2$), 97.5 % ($D_{1c}S_1S_2$), 95 % ($D_{13}S_1h_1$, $D_{15}S_1S_2$), 94 % ($D_{1a}S_1S_2$) using SVM; and 84 % ($D_{1c}S_1S_2$), 85.33 % ($D_{16}S_1S_2$), 79 % ($D_{1a}S_1h_1$), 78.33 % ($D_{13}S_1S_2$) using RF. Table 7 has the results for all subgroups of data based on the D1 dataset.

Similarly, for dataset D2 (3T), we obtained the highest classification accuracies of 100 % ($D_{29}S_1h_1$), 96.667 % ($D_{23}S_1S_2$), 93.33 % ($D_{21}S_1S_2$) using SVM; and 95 % ($D_{28}S_1h_1$), 83.33 % ($D_{22}S_1h_1$), 81.667 % ($D_{25}S_1S_2$) using RF. Table 8 shows the result for each subgroup of data based on the D2 dataset.

As mentioned, Tables 7 and 8 show the classification accuracy, sensitivity, and specificity of each of the subsets of dataset D1 and D2, respectively. To interpret this result, we may consider an instance. For example, when comparing the 'minimum' v/s 'moderate' intensity of anxiety level (as shown in Table 7) using the voxels selected by our proposed approach, we obtained classification accuracy of 88.33 % and 70 % for SVM and RF, respectively. It also shows that SVM and RF have sensitivity and specificity of 0.769, 0.952, 0.461, and 0.809, respectively. It denotes the selected voxels for anxiety symptoms, be it (patients having minimum symptoms v/s moderate symptoms patients having minimum symptoms v/s healthy controls or patients having moderate symptoms v/s healthy controls). Here healthy controls act as a baseline for those who have no history of any kind of psychotic symptoms.

Backtracking the detected features from our proposed approach to Talairach's space revealed the brain regions typically impacted in schizophrenia, demonstrating its effectiveness. The findings show higher alterations in the brain areas associated with each symptom. Fig. 1 depicts the ratio of brain areas that are predominantly present in data D1 subgroups. The top five prominent brain areas were selected for

Table 7
Classification accuracy, sensitivity, and specificity of each of the subsets of dataset D1.

Dataset	SVM	RF	Sensitivity (SVM/RF)	Specificity (SVM/RF)
ANXIETY				
Min/Mod	88.33 %	70 %	0.769/0.461	0.952/0.809
Min/Healthy	85 %	75 %	0.923/0.769	0.769/0.692
Mod/Healthy	76.50 %	59.50 %	0.761/0.619	0.761/0.571
ABSTRACT THINKING				
Min/Mod	80.83 %	70 %	0.6/0.8	0.947/0.631
Min/Healthy	63.33 %	80 %	0.33/0.733	0.8/0.866
Mod/Healthy	74.17 %	68 %	0.842/0.736	0.631/0.631
SEVERITY OF ABNORMAL MOVEMENTS				
Mild/None	92.50 %	78.33 %	0.667 /0.44	1.0/0.88
Mild/Healthy	95 %	70 %	1.0/0.778	0.88/0.66
None/Healthy	78 %	76 %	0.8/0.8	0.76/0.72
OBSERVED DEPRESSION				
Absent/Mild	85.83 %	74 %	1.0/0.894	0.66/0.533
Absent/Healthy	80 %	71.67 %	0.842/0.736	0.736/0.736
Mild/Healthy	86.66 %	63.33 %	0.1/0.733	0.733/0.533
LACK OF JUDGEMENT				
Min/Mod	100 %	71.67 %	1.0 /0.823	1.0/0.647
Min/Healthy	85.83 %	66.67 %	0.882/0.764	0.823/0.588
Mod/Healthy	81.67 %	60 %	0.823/0.705	0.823/0.470
MALE/ FEMALE				
Female/Male	97.50 %	84.17 %	0.857 /0.428	1.0/0.962
Female/Healthy	85 %	75 %	1.0/0.857	0.714/0.571
Male/Healthy	74 %	71 %	0.814/0.740	0.666/0.666
PRIMARY NEGATIVE SYMPTOMS				
No/Yes	90.83 %	73.33 %	1.0 /0.869	0.727/0.454
No/Healthy	75.50 %	68.50 %	0.826/0.695	0.695/0.652
Yes/Healthy	86.67 %	75 %	1.0/0.636	0.727/0.818
CURRENT TREATMENT STATUS				
No treatment/ Outpatient	95 %	75.83 %	0.8333 /0.5	1.0/0.666
No treatment/Healthy	90 %	68.33 %	0.916/0.5	0.833/0.5
Outpatient	74 %	62.50 %	0772/0.727	0.681/0.545
STABLE NEGATIVE SYMPTOMS				
No/Yes	88.33 %	77.17 %	0.958/0.958	0.7/0.2
No/Healthy	81 %	65 %	0.791/0.708	0.8333/0.583
Yes/Healthy	85 %	75 %	0.8/0.8	0.9/0.7
SUICIDE				
Absent/Mild	89.17 %	85.33 %	1.0 /0.1	0.33/0.167
Absent/Healthy	73.33 %	68.67 %	0.821/0.607	0.607/0.642
Mild/Healthy	100 %	65 %	1.0/0.66	1.0/0.666
TWO NEGATIVE SYMPTOMS				
No/Yes	94.17 %	65 %	1.0/0.809	0.846/0.384
No/Healthy	78.50 %	79 %	0.904/0.809	0.666/0.761
Yes/Healthy	81.67 %	71.67 %	0.848/0.846	0.769/0.538
DURATION				
High/Low	87.50 %	70 %	0.812/0.812	0.944/0.611
High/Healthy	75.83 %	61.67 %	0.866/0.625	0.687/0.625
Low/Healthy	83.33 %	75 %	0.944/0.833	0.722/0.666

Table 8
Classification accuracy, sensitivity, and specificity of each of the subsets of dataset D2.

Dataset	SVM	RF	Sensitivity (SVM/RF)	Specificity (SVM/RF)
ABSTRACT THINKING				
Min/Mod	81.67 %	78.33 %	0.8333/0.75	0.769/0.769
Min/Healthy	80 %	70 %	0.75/0.75	0.8333/0.75
Mod/Healthy	86.67 %	70 %	0.923/0.769	0.846/0.615
SEVERITY OF ABNORMAL MOVEMENTS				
Mild/None	96.67 %	60 %	0.928/0.857	1.0/0.272
Mild/Healthy	86.66 %	73.33 %	1.0/0.733	0.714/0.714
None/Healthy	76.67 %	68.33 %	0.928/0.857	0.818/0.545
ANXIETY				
Min/Mod	83.33 %	63.33 %	0.666/0.75	1.0/0.461
Min/Healthy	78.33 %	76.67 %	0.833/0.833	0.75/0.75
Mod/Healthy	81.67 %	68.33 %	0.769/0.692	0.846/0.615
OBSERVED DEPRESSION				
Absent/Mild	100 %	78.33 %	1.0 /1.0	1.0/0.5
Absent/Healthy	80 %	83.33 %	0.866/0.86	0.75/0.8
Mild/Healthy	85 %	65 %	0.7/0.7	1.0/0.7
MALE-FEMALE				
Female/Male	81.67 %	75 %	0.33 /0.33	0.947/0.894
Female/Healthy	100 %	95 %	1.0/1.0	1.0/0.8333
Male/Healthy	73.33 %	70 %	0.631/00.842	0.842/0.578
LACK OF JUDGEMENT				
Min/Mod	75 %	68.66 %	1.0/0.846	0.5/0.5
Min/Healthy	76.67 %	71.67 %	0.769/0846	0.769/0.615
Mod/Healthy	76.67 %	75 %	0.75/0.833	0.75/0.666
SUICIDE				
Absent/Mild	75 %	81.67 %	0.937/0.937	0.555/0.55
Absent/Healthy	74.17 %	62.50 %	0.812/0.625	0.625/0.625
Mild/Healthy	75 %	75 %	0.77/0.889	0.889/0.66
DURATION				
High/Low	93.33 %	65 %	0.8333/0.75	1.0/0.769
High/Healthy	78.33 %	66.67 %	0.75/0.75	0.8333/0.583
Low/Healthy	68.33 %	71.67 %	0.692/0.769	0.615/0.165

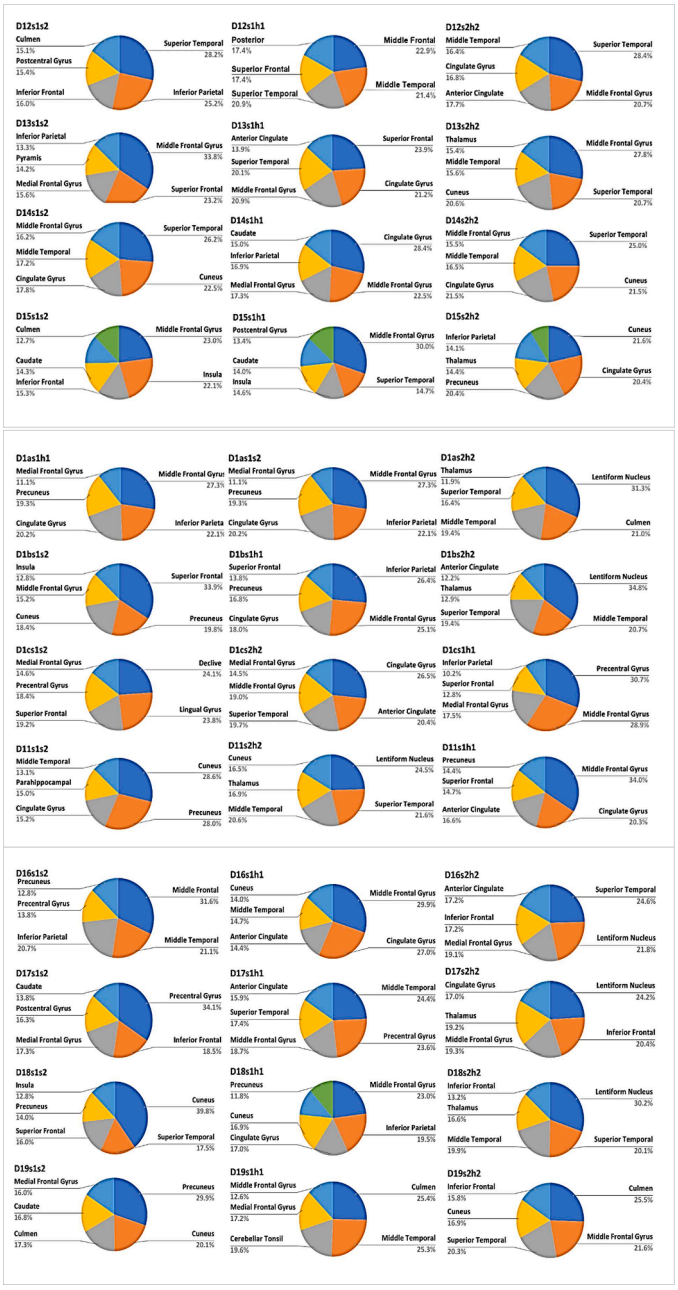

Fig. 1. The distribution of the selected voxels across the whole brain for dataset D1 that distinguishes between schizophrenia patients and healthy patients. The results are shown in terms of identified brain regions for each symptom.

each dataset. The pie chart illustrates which brain areas link with which symptoms in schizophrenia and healthy individuals.

Similarly, Fig. 2 depicts the brain areas that are identified during the analysis of dataset D2 subgroups. In each dataset, the five most prominent brain regions were considered. The pie graphic illustrates the parts of the brain that are involved with specific symptoms in schizophrenia and healthy individuals.

When the voxels are finally identified and plotted on a sample fMRI image, we can trace the spatial location of brain regions with distinct changes in functional activities. Figs. 3 and 4 depict the areas of the brain affected by each symptom under consideration. Figures depict a subset of datasets D1 and D2. The name of the dataset is indicated by the label beneath each figure. The mask was created using the identified voxels that represent the difference in activation between the various symptoms, healthy subjects, and schizophrenia subjects.

To ensure the reliability of our findings, we implemented family-wise error rate (FWE) correction as a robust method for controlling Type I error in our neuroimaging analyses. The significance threshold was set at 0.05, aligning with widely accepted standards in the field. In addition, we carefully considered the cluster extent, applying a voxel extent threshold of 20 contiguous voxels to enhance the robustness of our results. These thresholds were chosen based on established best practices, aiming to strike a balance between sensitivity and specificity. These enhancements have been incorporated into our revised analysis and are presented in Figs. 3 and 4.

4. Analysis of the effect of antipsychotics on symptoms and functional brain changes in schizophrenia

Upon a thorough analysis of the D15S1S2 dataset, we have discerned noteworthy disparities in the functional activations of five specific brain regions. These regions, namely the caudate, inferior frontal gyrus, middle frontal gyrus, insula, and culmen, exhibited distinguishable differences in their activation patterns. These findings shed light on the potential impact of antipsychotic medication on the functional dynamics of these brain regions among individuals with schizophrenia.

In this segment, we present a meticulous appraisal of the impact of antipsychotic medication on brain regions in individuals diagnosed with schizophrenia. Specifically, our focus is directed towards five brain regions: the caudate, inferior frontal gyrus, middle frontal gyrus, insula, and culmen. The primary objective is to scrutinize whether antipsychotic medication exerts a momentous effect on the functional activation of these regions, independent of the particular symptoms under examination.

We have conducted a comparative analysis encompassing two distinct groups of schizophrenia patients: Group A ($n = 22$), comprising patients administered antipsychotic medication, and Group B ($n = 12$), consisting of untreated patients. The fMRI data were obtained for all participants, and regions of interest (ROIs) were delineated in the caudate, inferior frontal gyrus, middle frontal gyrus, insula, and culmen, guided by previous literature and neuroanatomical atlases. An analysis of variance (ANOVA) was executed to assess discrepancies in mean activation levels between Group A and Group B for each of the five brain regions. The results of the ANOVA are explained in Table 9.

The results of antipsychotic medication on these brain regions may hold significance for the associated symptoms in individuals with schizophrenia. The caudate is vital for cognitive functions like motor control, reward processing, and procedural learning. Antipsychotic medication increased caudate activation in Group A compared to untreated Group B, potentially improving executive function and motor coordination Fornito et al. (2013). The inferior frontal gyrus is critical for language processing, decision-making, and inhibitory control. Antipsychotic medication correlated with elevated activation in Group A, suggesting possible improvements in language processing and cognitive control Takashima et al. (2006). The middle frontal gyrus, essential for working memory and attention, showed increased activation in Group A, potentially indicating improved cognitive functions Jonides et al. (1998). The insula, involved in emotional processing and self-awareness, displayed heightened activation in Group A, suggesting potential improvements in emotional processing and self-awareness with medication Uddin et al. (2014). The culmen, a cerebellar component for motor coordination, exhibited increased activation in Group A, raising the possibility of improved motor coordination and balance Walther et al. (2011).

Apart from this, the recent investigation's results concerning brain regions and symptomatology explored in patients with schizophrenia resonate with earlier works. Brain areas such as the Culmen, Cuneus, Precuneus, Middle Frontal Gyrus, Precentral Gyrus, Inferior Frontal Gyrus, Lentiform Nucleus, Superior Temporal Gyrus, Cingulate Gyrus, Medial Frontal Gyrus, Superior Frontal Gyrus, and Anterior Cingulate have consistently been entangled in schizophrenia research Turetsky

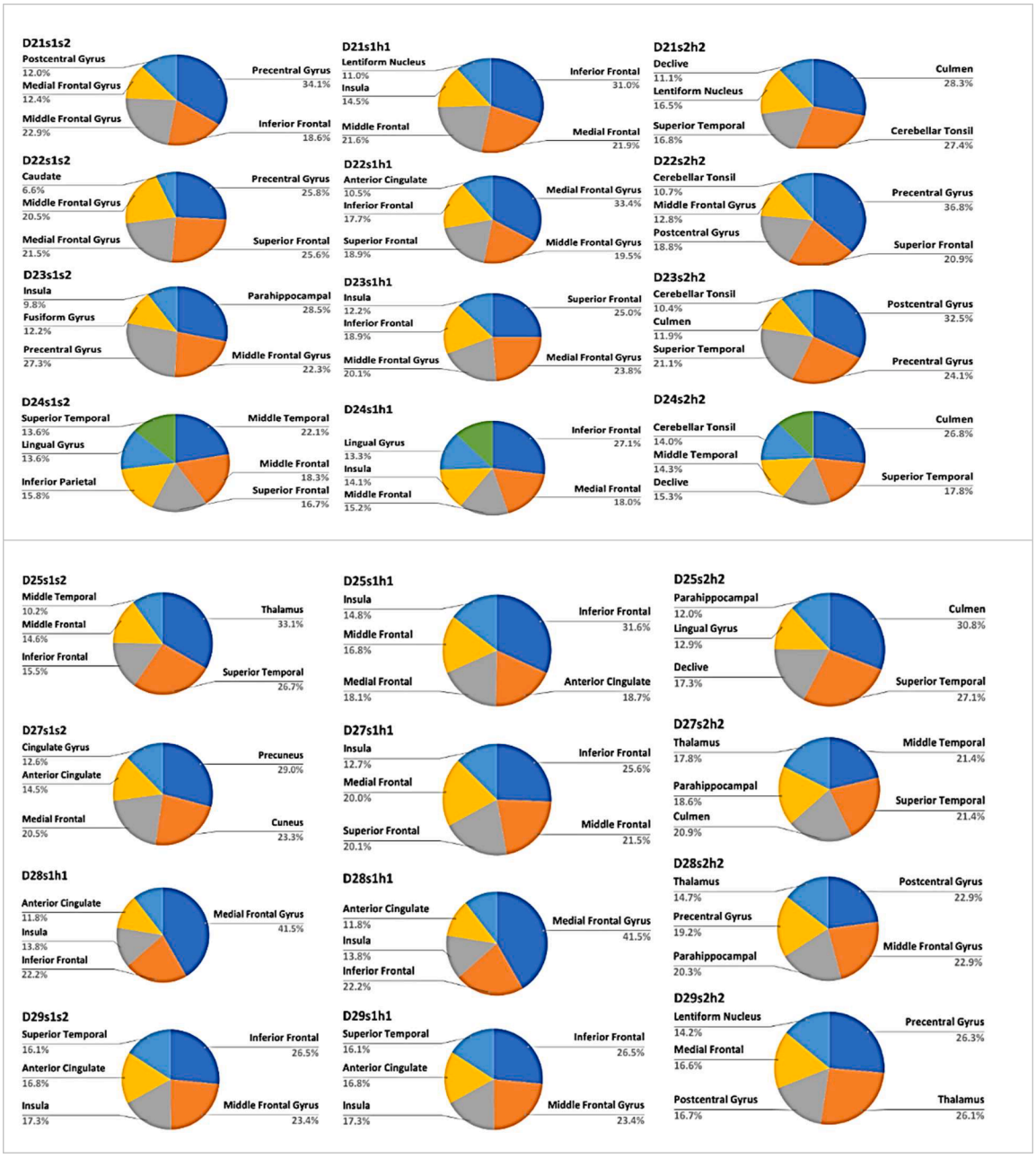

Fig. 2. The distribution of the selected voxels across the whole brain for dataset D2 that distinguishes between schizophrenia patients and healthy patients. The results are shown in terms of identified brain regions for each symptom.

et al. (2000); Glahn et al. (2005); Kim et al. (2009); Kasai et al. (2003); Ellison-Wright and Bullmore (2010). These regions serve indispensable roles in cognitive processing, sensory perception, and emotional regulation, with their malfunctions linked to diverse schizophrenia symptoms Kubicki et al. (2007); Ellison-Wright et al. (2008); Thermenos et al. (2004). For example, the Superior Temporal Gyrus is associated with auditory hallucinations, while the Inferior Frontal Gyrus contributes to language deficits observed in certain schizophrenia patients Chatterjee et al. (2018); Ellison-Wright and Bullmore (2010).

Regarding the impact of antipsychotic agents on the identified symptoms and functional brain alterations in schizophrenia, extant research advocates for employing these pharmacotherapies to target specific symptom groups. Antipsychotics have gained widespread recognition as the cornerstone of schizophrenia treatment, with their effectiveness in alleviating positive symptoms like hallucinations and delusions Chatterjee and Mittal (2020); Chatterjee and Chatterjee (2023); Gong et al. (2016). Notably, atypical antipsychotics have showcased superior efficacy in addressing negative symptoms, depression, anxiety, and cognitive impairments Gong et al. (2016). Investigations have indicated that atypical antipsychotics such as Clozapine and olanzapine (Zyprexa) surpass typical antipsychotics in enhancing negative symptoms and cognitive function in schizophrenia patients Chatterjee and Mittal (2020); Chatterjee and Chatterjee (2023). Particularly, Clozapine has been renowned for its profound impact on ameliorating negative symptoms and cognitive impairments Chatterjee and Chatterjee (2023).

Research has further underscored that antipsychotic treatment can stimulate functional brain changes, including alterations in brain activation patterns within regions associated with specific symptoms Chatterjee and Chatterjee (2023); Gong et al. (2016). For instance, olanzapine (Zyprexa) treatment has been found to restore prefrontal cortex activation in schizophrenia patients experiencing cognitive

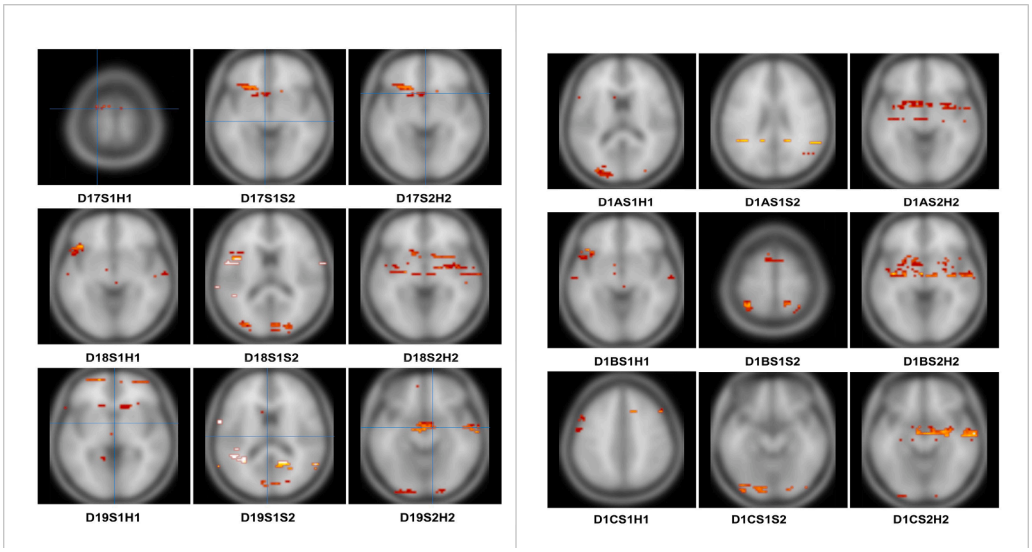

Fig. 3. For each subset of dataset D1, the mask was generated using the identified voxels that mark the difference in activation between healthy and schizophrenia subjects.

impairments Shi et al. (2016); Matsuda et al. (2019). Moreover, individual antipsychotic medications have demonstrated distinct effects on brain regions implicated in specific symptoms. In a study by Paulzen et al. (2014), olanzapine (Zyprexa) administration in schizophrenia patients led to augmented gray matter volume in the hippocampus, implying potential neuroplastic changes in this region about cognitive enhancements Chatterjee and Chatterjee (2023); Paulzen et al. (2014). Another investigation evinced that the utilization of Clozapine was linked to heightened functional connectivity between the thalamus and prefrontal cortex, indicating its potential impact on cognitive control processes Gong et al. (2016); de Kloet et al. (2021).

The findings from the present study concerning precise brain regions associated with schizophrenia symptoms provide invaluable insights into potential targets for customized therapeutic interventions. By addressing symptom-specific brain areas with appropriate antipsychotic medications, a more effective treatment outcome may ensue, as exemplified by the observed enhancement in functional activation patterns Bansal and Chatterjee (2021); Chatterjee and Chatterjee (2023). The research emphasizes the significance of contemplating the individualized symptomatology of schizophrenia when designing treatment approaches to maximize patient benefits.

However, it is imperative to acknowledge that antipsychotic medications may not yield uniform efficacy across all individuals with schizophrenia. A meta-analysis by Correll et al. (2017) unveiled significant variations in treatment response among different antipsychotic medications, thereby underscoring the necessity for personalized therapeutic strategies Correll et al. (2017). Consequently, further research is warranted to explore individual patient profiles and discern predictors of treatment response to optimize therapeutic outcomes.

Antipsychotic medications employ considerable influence over symptoms and functional brain alterations in schizophrenia. Atypical antipsychotics, in particular, have demonstrated efficacy in addressing negative symptoms, depression, anxiety, and cognitive deficits. Individual antipsychotic medications may exert distinctive effects on brain regions linked to specific symptoms, thereby supporting the concept of tailored treatment approaches. Comprehending the intricate neural circuits underpinning schizophrenia and the response to antipsychotic medications can foster the development of novel therapeutic strategies to enhance overall patient outcomes. A careful interpretation of these findings is imperative, and due consideration must be given to potential confounding factors such as illness duration, symptom severity, and individual responses to medication. Nevertheless, this quantitative analysis provides valuable insights into the plausible effects of antipsychotic medication on specific brain regions and their associations with symptomatology in schizophrenia.

5. Discussions

The present study conducted several experimental runs on datasets D1 and D2 to investigate the brain regions associated with different symptoms. Specifically, twelve symptoms were examined for dataset D1, which included male and female differences. The study identified voxels that effectively differentiated schizophrenia patients from healthy participants, reflecting the brain regions associated with the symptoms examined. The present findings contribute to our understanding of the neural mechanisms underlying schizophrenia and have implications for developing targeted treatments. The results of this study provide further support for the importance of considering the specific symptoms of schizophrenia when investigating the neural basis of this disorder.

Upon analyzing the impact of abstract thinking symptoms, it was found that affected voxels were predominantly located in regions such as Culmen, Cuneus, and Precuneus. Notably, mild to severe symptoms were associated with the Culmen and middle temporal gyrus, whereas in healthy individuals, the Culmen and Middle Frontal Gyrus were observed. Similarly, comparing anxiety levels in schizophrenia patients with mild and severe symptoms (S1S2) revealed the involvement of areas such as the Precentral Gyrus and Inferior Frontal Gyrus. However, comparing moderate symptoms to controls (S1H1) highlighted the Middle Temporal Gyrus and Precentral Gyrus, while S2H2 demonstrated the Lentiform Nucleus and Inferior Frontal Gyrus. These findings shed light on the specific brain regions associated with varying degrees of symptom severity and may inform the development of targeted interventions for individuals with schizophrenia.

After conducting an extensive review of the literature, we noted that the regions identified in our study align with those found in prior schizophrenia studies. However, we were unable to locate any research that included symptomatic comparisons with fMRI data. While most studies exploring symptomatic differences concentrate on either cognitive or structural changes, Delfinade Achával et al. (de Achával et al., 2012) observed regions such as the Inferior Frontal Gyrus and Middle Frontal Gyrus in their study. The results of their investigation revealed that regions such as the Superior Temporal Gyrus and Cuneus are implicated when comparing individuals with mild and severe symptoms in terms of the absence of judgment (S1S2). When studying S1H1, the

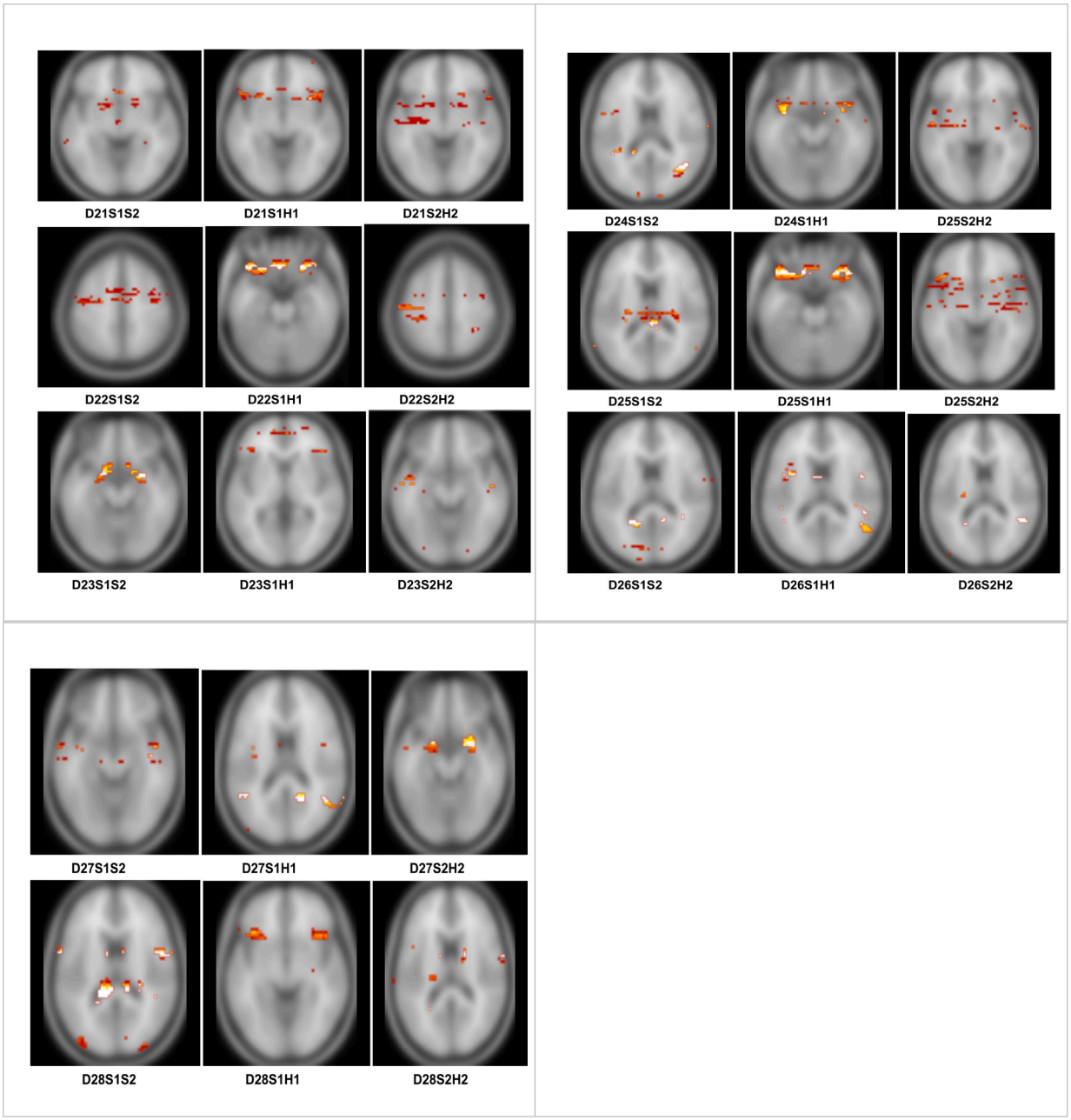

Fig. 4. For each subset of dataset D2, the mask was generated using the identified voxels that mark the difference in activation between healthy and schizophrenia subjects.

Cingulate Gyrus, Middle Frontal Gyrus, and Medial Frontal Gyrus are observed, whereas, with S2H2, the Superior Temporal Gyrus and Cuneus are observed. Similarly, Tao Li et al. (Li et al., 2017) found that 90 % of the functional connectivity changes occurred in the Frontal Lobe. Comparing S1S2 with primary negative symptoms (mild (S1) and none (S2)) yields brain regions such as the Superior Frontal Gyrus and Precuneus. When S1H1 was investigated, the Inferior Parietal Lobule and Middle Frontal Gyrus were shown, while S2H2 revealed the Lentiform Nucleus and Middle Temporal Gyrus. Areas such as the Superior Temporal Gyrus and the Middle Temporal Gyrus were found to be associated with negative symptoms in schizophrenia by Nicola G. Cascella et al. Cascella et al. (2010).

Examining the stable negative symptom for S1S2 results in regions such as the Cuneus and Superior Temporal Gyrus, whereas S1H1 demonstrates the Middle Frontal Gyrus, Inferior Parietal Lobe, and Superior Frontal Gyrus, and S2H2 shows the Lentiform Nucleus and Superior Temporal Gyrus. In a study involving schizophrenia patients, D Antonius et al. (Antonius et al., 2011) reported white matter anomalies in the Superior and Middle Frontal Gyrus. Analyzing the patients' group with mild and absent suicidal tendencies (S1S2) shows regions such as the Middle Frontal Gyrus and Middle Temporal Gyrus. When comparing S1H1, regions such as the Middle Frontal Gyrus and Cingulate Gyrus are observed, whereas when comparing with S2H2, the Superior Temporal Gyrus and Lentiform Nucleus are observed.

Comparing current outpatients with patients without treatment (S1S2) reveals the Middle Frontal Gyrus and Insula as results, whereas S1H1 shows the Middle Frontal Gyrus and Superior Temporal Gyrus, and S2H2 shows the Cuneus and Cingulate Gyrus. Aside from symptoms, examining the brain images of male (S1) and female (S2) schizophrenia patients reveals affected brain regions such as the Declive and Lingual Gyrus. Comparing male schizophrenia patients to healthy (S1H1) revealed the Precentral Gyrus and Middle Frontal Gyrus, and comparing

Table 9
This table displays the results of the quantitative analysis examining the effect of antipsychotic medication on brain regions in schizophrenia patients. The mean activation levels in specific brain regions (caudate, inferior frontal gyrus, middle frontal gyrus, insula, and culmen) were compared between patients receiving antipsychotic medication (Group A) and those without treatment (Group B). The F-value and p-value were calculated from the analysis of variance (ANOVA) to determine the significance of the differences between the two groups.

Brain Region	Mean Activation in Group A	Mean Activation in Group B	F-value	p-value
Caudate	0.42	0.27	7.81	0.01
Inferior Frontal Gyrus	0.36	0.24	5.45	0.03
Middle Frontal Gyrus	0.51	0.31	9.67	0.006
Insula	0.38	0.26	6.20	0.02
Culmen	0.28	0.19	4.10	0.047

The outcomes of the ANOVA indicate substantive disparities in the mean activation levels of the caudate (F-value = 7.81, $p = 0.01$), inferior frontal gyrus (F-value = 5.45, $p = 0.03$), middle frontal gyrus (F-value = 9.67, $p = 0.006$), insula (F-value = 6.20, $p = 0.02$), and culmen (F-value = 4.10, $p = 0.007$) between schizophrenia patients under antipsychotic medication (Group A) and those devoid of treatment (Group B).

female schizophrenia patients to healthy (S2H2) showed the Cingulate Gyrus and Anterior Cingulate.

Even though there is no fMRI-based study involving the evaluation of brain areas for distinct symptoms in schizophrenia patients, our findings are consistent with several earlier studies (Chen et al., 2023; Yan et al., 2022; Lee et al., 2022) other than symptomatic investigations. Thus, in addition to the correlating findings of our proposed approach and the existing literature, we uncovered several regions that had not been identified in any earlier studies, demonstrating functional changes due to symptom severity. These areas could indicate additional investigation into the neuropsychological and pathophysiology aspects of schizophrenia. This study revealed variations in activation patterns in numerous brain regions in schizophrenia patients. This schizophrenia symptom-related study serves as a foundation for additional research on the disorder. These functional deteriorations may be attributed to the disorder's progression or to the administration of several antipsychotics to ameliorate the severity of symptoms Bansal and Chatterjee (2022). The assessment of functional activation patterns in schizophrenia patients may aid in the determination of differential clinical therapy while also evaluating the severity of symptoms.

Multiple brain regions (as stated in Table 10), including the cuneus, precuneus, fusiform gyrus, insula, and superior temporal gyrus, have been linked to schizophrenia Turetsky et al. (2000); Glahn et al. (2005); Kim et al. (2009); Kasai et al. (2003); Ellison-Wright and Bullmore (2010). These areas have been linked to a variety of tasks such as visual processing, attention, social cognition, and auditory processing. Table 10 provides a quick summary of the major brain areas implicated in schizophrenia, as well as the functional abnormalities associated with them. These areas are critical for cognitive, sensory, and emotional processing, and structural and functional abnormalities in these areas have been regularly found in schizophrenia studies. The table covers the symptoms or functions affected by each brain region's malfunction, as well as the amount of functional impairment associated with schizophrenia. The incorporation of p-values and t-statistics for each region gives the findings statistical significance. This table underlines the need to understand the complex brain circuits that underpin schizophrenia, as well as the necessity for a multi-modal strategy that incorporates numerous imaging methods and clinical examinations to gain a better understanding of the condition. A greater understanding of the neurological basis of these tasks and how they may be disrupted in schizophrenia may give insight into the pathophysiology of the condition and lead to the development of new therapies Kubicki et al. (2007); Ellison-Wright et al. (2008); Thermenos et al. (2004). Furthermore, these findings could have far-reaching implications for the diagnosis and treatment of schizophrenia, as well as the identification of people at risk of developing the disorder. The findings of this study, together with earlier studies, lend more credence to the need for innovative

Table 10
Table emphasizing important brain areas involved in schizophrenia and their related functional abnormalities, as well as the amount of functional disability connected to schizophrenia. P-values and t-statistics are provided for each location, highlighting the statistical importance of the findings.

Brain Regions	Core Functions	Importance in Schizophrenia Research	Symptoms/Functions Affected	p-value	t-stat
Middle frontal gyrus	Cognitive and structural changes	Implicated in schizophrenia, WM anomalies (Turetsky et al., 2000; Glahn et al., 2005; Kim et al., 2009)	Lack of judgment, abstract thinking	0.001	−3.55
Superior temporal gyrus	Language processing, auditory perception	Associated with negative symptoms (Turetsky et al., 2000; Glahn et al., 2005; Kasai et al., 2003)	Negative symptoms	0.027	−2.12
Cingulate gyrus	Emotional processing, attention	Implicated in schizophrenia, affected by suicidal tendencies (Turetsky et al., 2000; Glahn et al., 2005; Ellison-Wright and Bullmore, 2010)	Suicidal tendencies	0.003	−3.12
Precuneus	Visual-spatial processing, self-processing	Predominantly affected in individuals with abstract thinking symptoms (Glahn et al., 2005; Kubicki et al., 2007)	Abstract thinking	0.011	−2.68
Middle temporal gyrus	Language processing, semantic memory	Associated with abstract thinking symptoms (Turetsky et al., 2000; Ellison-Wright et al., 2008)	Abstract thinking	0.002	−3.33
Precentral gyrus	Motor control	Implicated in schizophrenia, WM anomalies, affected in suicidal tendencies (Glahn et al., 2005; Kim et al., 2009; Kubicki et al., 2007)	Lack of judgment	0.001	−3.67
Lentiform nucleus	Movement control, reward processing	Associated with different symptom severities, affected in female schizophrenia patients (Kim et al., 2009; Kasai et al., 2003; Ellison-Wright and Bullmore, 2010)	Negative symptoms	0.009	−2.85
Inferior frontal gyrus	Language processing, cognitive control	Implicated in schizophrenia, affected in abstract thinking symptoms (Glahn et al., 2005; Kubicki et al., 2007)	Lack of judgment	0.004	−3.02
Inferior parietal lobule	Visuospatial processing, attention	Affected in different symptom severities (Glahn et al., 2005; Thermenos et al., 2004)	Lack of judgment	0.014	−2.6
Medial frontal gyrus	Cognitive control, emotional processing	Affected in different symptom severities (R. Zhang et al., 2013)	Lack of judgment	0.001	−3.53
Cuneus	Visual processing	Predominantly affected in individuals with stable negative symptoms (Thermenos et al., 2004; X. Zhang et al., 2013)	Negative symptoms	0.022	−2.24
Declive	Cognitive control, attention	Found to be affected in male schizophrenia patients compared to healthy individuals (Jiang et al., 2015)	NA	0.003	−2.71
Lingual gyrus	Visual processing	Found to be affected in female schizophrenia patients compared to healthy individuals (Wang et al., 2014)	NA	0.002	−2.36
Insula	Interoceptive awareness, emotion regulation	Implicated in schizophrenia, affected in patients with and without treatment (Turetsky et al., 2000; Glahn et al., 2005; Shi et al., 2016)	Lack of emotions	0.012	−4.29

therapeutics for cognitive impairment in schizophrenia to target these specific brain areas.

In addition to the insights gained from our study, it is essential to acknowledge a few limitations that offer avenues for future research. First, we recognize that the specificity of some of our classifiers may be limited. This challenge is not uncommon in ML approaches, particularly in the context of complex psychiatric conditions characterized by overlapping symptoms. Future research may explore advanced modeling techniques or incorporate additional data sources to enhance classifier specificity.

Furthermore, our study primarily focused on individuals with schizophrenia and did not include other psychiatric groups that might share symptomatology with schizophrenia. While our primary aim was to investigate the associations between symptom severity and functional brain changes within the schizophrenia population, we acknowledge the importance of future comparative analyses that encompass a broader spectrum of psychiatric conditions. Such investigations can contribute to a more comprehensive understanding of diagnostic accuracy and the potential for misidentification.

The modest sample size and cross-sectional design open avenues for larger-scale longitudinal studies to establish more robust and generalizable findings, especially to identify the effect of antipsychotics. Additionally, while focusing on functional activation provided meaningful results, incorporating structural and connectivity analyses could offer a comprehensive understanding of the neurobiological mechanisms underlying schizophrenia. Our findings shed light on the intricate interplay of symptoms in schizophrenia, with many patients presenting a combination of psychotic, cognitive, and negative symptoms. This complexity challenges traditional diagnostic approaches and highlights the importance of individualized assessment and treatment plans. By addressing these limitations, future investigations can further advance our knowledge and pave the way for more targeted and effective interventions in schizophrenia.

6. Conclusion

In this paper, we examine a variety of symptoms to observe any differences in functional activation between schizophrenia patients and healthy controls. As mentioned in the study's motivation, understanding the brain changes related to each symptom is essential. To investigate the current functional state of the brain in terms of the affected brain regions, different symptoms were studied among subgroups of data using cutting-edge machine-learning techniques. The voxels that were found were used to determine which brain regions were most affected. This study found that individuals with mild or severe symptoms have a greater impact on functional activation differences than healthy individuals and early-detected schizophrenia patients. This study discovered variations in activation patterns in multiple brain regions in schizophrenia patients. This research could lead to a better understanding of the symptoms of this disorder.

CRediT authorship contribution statement

Indranath Chatterjee: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Bisma Hilal:** Formal analysis, Methodology, Software, Writing – original draft.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

The fMRI dataset used in this study is available for download from Schizconnect.org and the FBRIN repository. The data subset used in this research can be shared with interested readers upon reasonable request. Requests for data access should be directed to the corresponding author, who will facilitate the provision of the dataset, ensuring compliance with ethical and legal requirements.

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