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Machine learning-based prediction of antipsychotic efficacy from brain gray matter structure in drug-naive first-episode schizophrenia

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Predicting patient response to antipsychotic medication is a major challenge in schizophrenia treatment. This study investigates the predictive role of gray matter (GM) in short- and long-term treatment outcomes in drug-naive patients with first-episode schizophrenia (FES). A cohort of 104 drug-naive FES was recruited. Before initiating treatment, T1-weighted anatomical images were captured. The Positive and Negative Syndrome Scale and the Personal and Social Performance Scale were adopted to assess clinical symptoms and social function. At the 3-month follow-up, patients were categorized into remission and non-remission groups. At 1-year follow-up, patients were categorized into the rehabilitation and non-rehabilitation groups. Machine learning algorithms were applied to predict treatment outcomes based on GM volume, cortical thickness, and gyrification index, and the model performance was evaluated. Widespread regions, such as the superior temporal gyrus, middle frontal gyrus, supramarginal gyrus, the posterior central gyrus, anterior cingulate gyrus, and parahippocampal gyrus showed substantial predictive value for 3-month treatment efficacy (74.32% accuracy). The inferior frontal gyrus, anterior cingulate gyrus, and inferior occipital gyrus demonstrated significant predictive power for treatment outcome at 1-year follow-up (70.31% accuracy). We developed a machine learning model to predict individual responses to antipsychotic treatments, which could positively impact clinical treatment protocols for schizophrenia.

INTRODUCTION

Schizophrenia is a severe mental disorder of unknown etiology, dramatically impacting multiple domains of patients' daily living, such as sustaining social relationships, holding employment, and living independently[1]. The current approach to treating schizophrenia with medication involves choosing drugs based on a patient's symptoms and adjusting them as needed depending on how well the patient responds. Since there are no reliable ways to predict how a person will react to a specific drug, it often takes several attempts to find the most effective treatment. Meanwhile, the effectiveness of initial treatment is critical to long-term compliance and therapeutic outcomes[2], and initial treatment response serves as a prognostic indicator of clinical outcomes and is a prerequisite for symptomatic remission and functional recovery[3]. However, a suboptimal initial medication selection can significantly compromise treatment efficacy[4]. Given the importance of early treatment response, recent research has increasingly aimed to identify biomarkers that can predict treatment outcomes in patients with schizophrenia. Such advancements would enhance the precision of medication selection and optimize treatment strategies.

Suffering from schizophrenia can lead to changes in the brain's structure similar to those caused by neurotoxicity[5], implicating the brain's gray matter configuration as a potential indicator of antipsychotic therapy efficacy. Traditional univariate analyses have identified and validated brain structure anomalies in individuals with schizophrenia[6]. However, these analyses often reflect inter-group differences and are not readily applicable to individualized treatment decisions. Machine learning approaches offer

substantial potential for individual-level feature integration and have shown promise in improving treatment and prognostic predictions for schizophrenia[7].

Using a machine learning approach, researchers classified remission and non-remission groups using the gray matter volume (GMV) of the parahippocampal gyrus, achieving an accuracy rate of 79%[8]. Besides, Koutsouleris et al. (2018) accurately predicted the treatment response of schizophrenia patients to rTMS based on gray matter structural characteristics, including changes in GMV across various brain regions, with an accuracy of 84.8%[9]. A relatively small sample study combined GMV and schizophrenia polygenic risk score features to predict the efficacy of a 6-week treatment, achieving an accuracy of 86%[10]. However, another study indicated that using baseline GMV from the dorsolateral prefrontal cortex, temporal lobe, and hippocampus to predict antipsychotic treatment outcomes showed limited predictive utility[11], highlighting the limitations of relying solely on single brain structure markers for forecasting treatment response.

Beyond GMV, both cortical thickness (Ct) and the gyrification index (GI) are pivotal in reflecting the brain's morphological properties and have been proven to predict treatment outcomes in schizophrenia patients effectively[12,13]. Ct refers to the shortest distance between the pial surface and the gray-white matter boundary at each vertex on the cortical surface, reflecting the size, density, and arrangement of neurons, glial cells, and neural fibers[14]. GI refers to the ratio between the cortex embedded within the sulci and the cortical surface exposed to the brain surface, which measures the degree of cortical folding[15]. A recent meta-analysis found reduced Ct in three regions of the default mode and salience networks in first-episode schizophrenia

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patients, including the right middle and superior temporal gyri, right insula, and right anterior cingulate gyrus[16]. Additionally, increased GI was observed in the right parahippocampal and lingual gyri[17], while reduced GI was noted in the prefrontal cortex and insula[18,19]. Incorporating metrics such as GMV, Ct, and GI can gain a more comprehensive understanding of brain gray matter morphology, enhancing the precision of detecting morphological changes[20], This approach allows for better identification of minor and often overlooked brain structures associated with disease pathophysiology and the efficacy of acute pharmacological interventions. Unfortunately, there has been limited research using these comprehensive indicators. Furthermore, antipsychotic treatment can contribute to progressive brain changes in patients with schizophrenia[21]. Therefore, research on patients with first-episode schizophrenia (FES), especially drug-naive patients, can eliminate potential confounding effects of antipsychotic drugs and secondary impacts that might alter the brain's longitudinal changes, such as social isolation, substance misuse, and weight gain, offering a better opportunity to study early-stage brain structural characteristics that relate to treatment efficacy[22-24].

Hence, this study proposed using machine learning techniques to combine various indicators, including GMV, Ct, and GI, to predict the treatment efficacy at the acute stage (3 months post-treatment initiation) and the maintenance phase (1-year follow-up) for drug-naive patients with FES. These findings could pave the way for establishing objective biological markers to better guide clinical treatment decisions, assist in selecting treatment plans, identify therapeutic targets, and offer insights into precise, personalized treatment strategies.

MATERIALS AND METHODS
Sample
This study was approved by the Ethics Committee of the Sixth Hospital of Peking University (2008-2). Based on a historical prospective cohort[25], 130 drug-naive patients with FES were recruited at baseline from the Peking University Sixth Hospital, the Beijing Huilongguan Hospital, and Capital Medical University Beijing Anding Hospital. Inclusion criteria for patients were as follows: (1) diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000)[26]; (2) aged 18–45 years; (3) experiencing their first episode of schizophrenia with a disease duration of <3 years; (4) not receiving any systemic treatment (continuous medication use for >4 weeks or intermittent medication use for >12 weeks)[27,28]; (5) meeting the magnetic resonance imaging (MRI) scanning requirements. Patients with a history of serious somatic disease, other mental or neurological disorders, or brain injury were excluded from participating.

Twenty-six patients' data were excluded due to the low-quality T1-weighted anatomical images. Subsequently, the remaining 104 patients participated in our 3-month follow-up assessments, with only 72 patients available for analysis at the 1-year follow-up.

Clinical assessments
The Positive and Negative Syndrome Scale (PANSS) assessed patients' positive, negative, and general symptoms[29,30]. The Personal and Social Performance Scale (PSP) assessed patients' social functions[31,32].

Research procedure
All participants underwent MRI scanning, and informed consent was obtained at the baseline. Clinical symptoms and social functioning were assessed using the PANSS and PSP at baseline, as well as the 3-month and 1-year follow-up measures, as outlined in Fig. 1.

MRI scanning and preprocessing
MRI data was collected on a GE Signa 3.0 T scanner equipped with an 8-channel head coil at the Peking University People's Hospital, Beijing, China. T1-weighted anatomical images were obtained with the following parameters: matrix size $= 288 \times 256$ mm, field of view (FOV) $= 240 \times 240$ mm, slice thickness $= 1$ mm, voxel size $= 1 \times 1 \times 1$ mm, repetition time (TR) $= 9.6$ ms, echo time (TE) $= 3.9$ ms, and flip angle $= 13°$.

Using the CAT toolbox (http://dbm.neuro.unijena.de/cat12/) based on SPM 12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), the T1-weighted images underwent processing as follows: (1) quality assessment and exclusion of low-quality images; (2) segmentation and spatial normalization to the Montreal Neurological Institute (MNI) template using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL); (3) modulation of volume using the Jacobian determinant to ensure GMV remained unchanged after registration; (4) smoothing of GMV images using an 8 mm full-width at half-maximum (FWHM) Gaussian kernel, Ct images using a 15 mm FWHM Gaussian kernel, and GI images using a 20 mm FWHM Gaussian kernel.

Pre-processed gray matter images were used for subsequent analyses, including calculation of GMV, Ct, and GI for each participant for subsequent analyses.

Therapeutic effect evaluation and analyses
The therapeutic efficacy for patients with FES at the 3-month acute phase was assessed using the "clinical symptom remission" criteria set forth by the Remission in Schizophrenia Working Group[33]. According to this criterion, remission is defined as scores of ≤3 on each of the eight specific symptom items of the PANSS: P1 "Delusions," P2 "Conceptual disorganization," P3 "Hallucinatory behavior," N1 "Blunted affect," N4 "Passive/apathetic social withdrawal," N6 "Lack of spontaneity and flow of conversation," G5 "Mannerisms and posturing," and G9 "Unusual thought content." Patients meeting this criterion were classified into the remission group, whereas others were categorized as non-remission.

After 1 year of treatment, patients were categorized into rehabilitation and non-rehabilitation groups based on whether they met the criteria for "clinical remission with good social functioning." The definition of clinical symptom remission remained consistent with the requirements set at the 3-month mark. Patients with a score >70 on the PSP scale, indicating only minor functional issues, were considered to have good social functioning. Conversely, those with a PSP score of ≤70, reflecting varying degrees of functional impairment, were classified as having poor social functioning.

For scores of PANSS and PSP, a series of repeated-measure analyses of variance (ANOVAs) were performed with a 2 (Treatment: Baseline vs. 3-month follow-up) × 2 (Group: Remission vs. Non-remission) design to examine the main effects of the 3-month Treatment and Group. Likewise, for the 1-year follow-up, a series of repeated-measure ANOVAs were performed with a 2 (Treatment: Baseline vs. one-year follow-up) × 2 (Group: Rehabilitation n vs. Non-rehabilitation) design to assess the main effects of the 1-year Treatment and Group. Subsequently, a set of post-hoc simple effects analysis with Bonferroni correction were used to compare group differences (remission vs. non-remission or rehabilitation vs. non-rehabilitation) at each time point (baseline & 3-month/12-month follow-up).

Machine learning algorithm modeling
In this phase, we explored the predictive value of brain MRI gray matter structural features in indicating the efficacy of second-generation antipsychotic drugs using machine learning. The main steps were as follows:
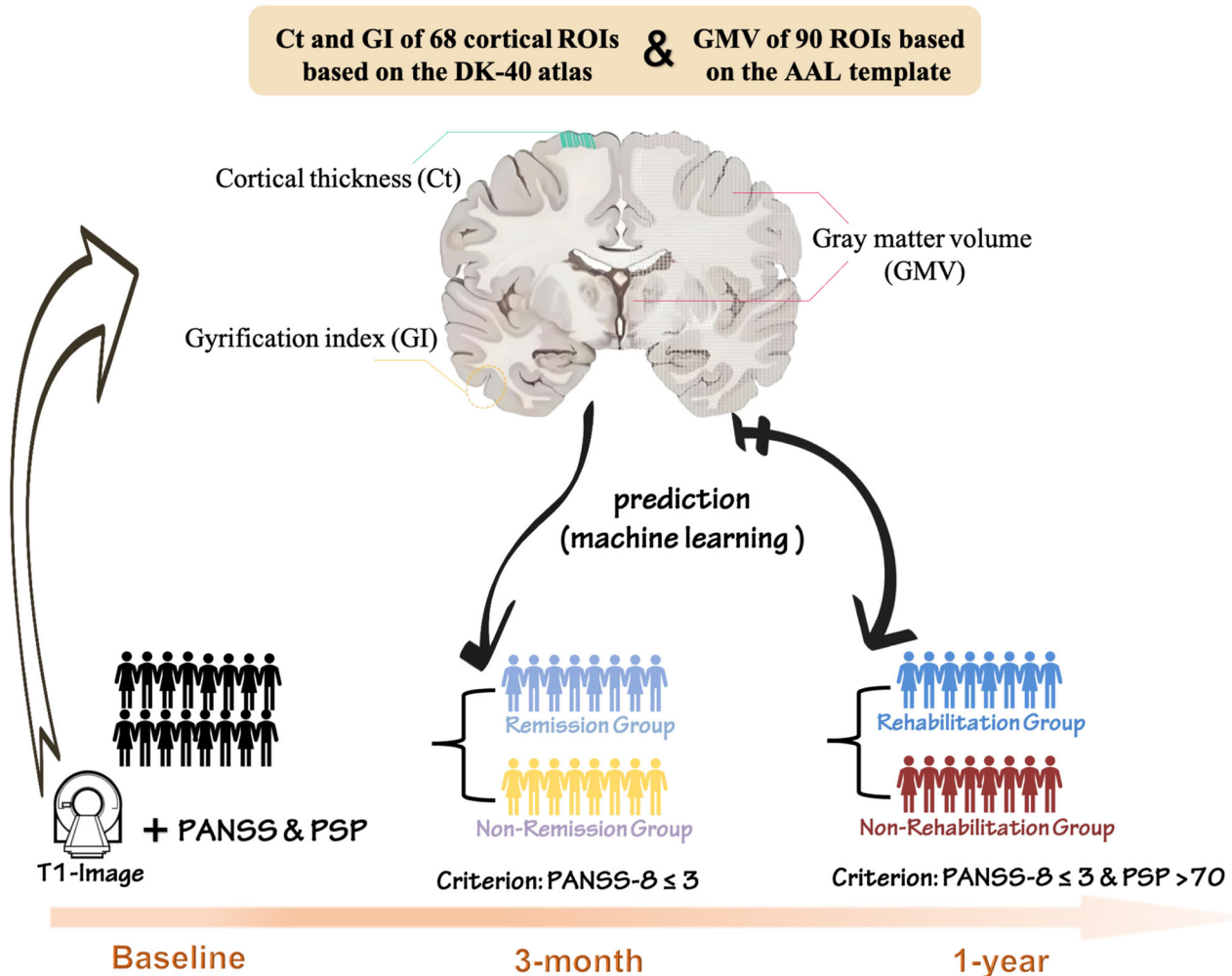
Fig. 1 The research procedure. All participants underwent MRI scanning at the baseline, clinical symptoms and social functioning were assessed using the PANSS (the Positive and Negative Syndrome Scale) and PSP (the Personal and Social Performance Scale) at baseline, as well as the 3-month and 1-year follow-up measures. Machine learning algorithms were applied to predict 3-month and 1-year treatment outcomes based on gray matter volume (GMV), cortical thickness (Ct), and gyrification index (GI).

1) Data cleaning and feature extraction: GMV of 90 ROIs based on the AAL template[34], and Ct and GI of 68 cortical ROIs based on the DK-40 atlas were extracted as feature values[35].

2) Feature selection: Recursive Feature Elimination was employed to a feature set most strongly correlated with the efficacy of antipsychotics, optimizing the predictive performance model based on the prediction accuracy of the Radial Basis Function Kernel (RBF) in the Support Vector Machine (SVM).

3) Machine learning modeling: MRI structural datasets were first normalized using the min-max method to eliminate dimensional influences on the model. The NearMiss method was applied for under-sampling to balance positive and negative class samples. Subsequently, classification prediction of the dataset was performed using various models, including SVM with linear function kernel and RBF, Decision Tree (DT), eXtreme Gradient Boosting (XGBoost), and Logistic Regression (LR), to predict the efficacy of second-generation antipsychotics. The final results were obtained through Leave-one-out Cross Validation (LOOCV).

4) Model predictive power evaluation: Models were assessed using *Accuracy*, *Sensitivity*, *Specificity*, and *AUC*.

5) Feature contribution quantification: The contribution of feature values to successful prediction efficacy was quantified by the absolute value of the brain MRI gray matter structural feature weights. Brain regions that significantly contributed to the short-

term effectiveness of the antipsychotics were identified. The significance of predictive power indicators (*Accuracy*, *Sensitivity*, *Specificity*, and *AUC*) was assessed using permutation testing with 10,000 permutations.

All SVM, LR, DT, and XGBoost models in this study were built and trained in a Python 3.10.8 environment on a Windows 11 platform. The significance threshold was set to $p < 0.05$ for all previously mentioned analyses.

RESULTS

Demographic and descriptive information at baseline

In this study, 45 male and 59 female patients with schizophrenia were included, with an average age of 20.87 ($SD = 3.27$) years and an average education level equivalent to 13.02 ($SD = 2.49$) years. The mean intracranial volume (ICV) of the patients was 1398.11 ($SD = 138.23$) cm^3, average gray matter volume (GMV) was 652.20 ($SD = 59.04$) cm^3, mean white matter volume (WMV) was 488.83 ($SD = 54.57$) cm^3, and average cerebrospinal fluid volume (CFV) was 256.29 ($SD = 49.97$) cm^3.

Results of ANOVAs

The results of ANOVAs and post-hoc tests indicated that 3 months of treatment significantly improved all clinical symptoms and
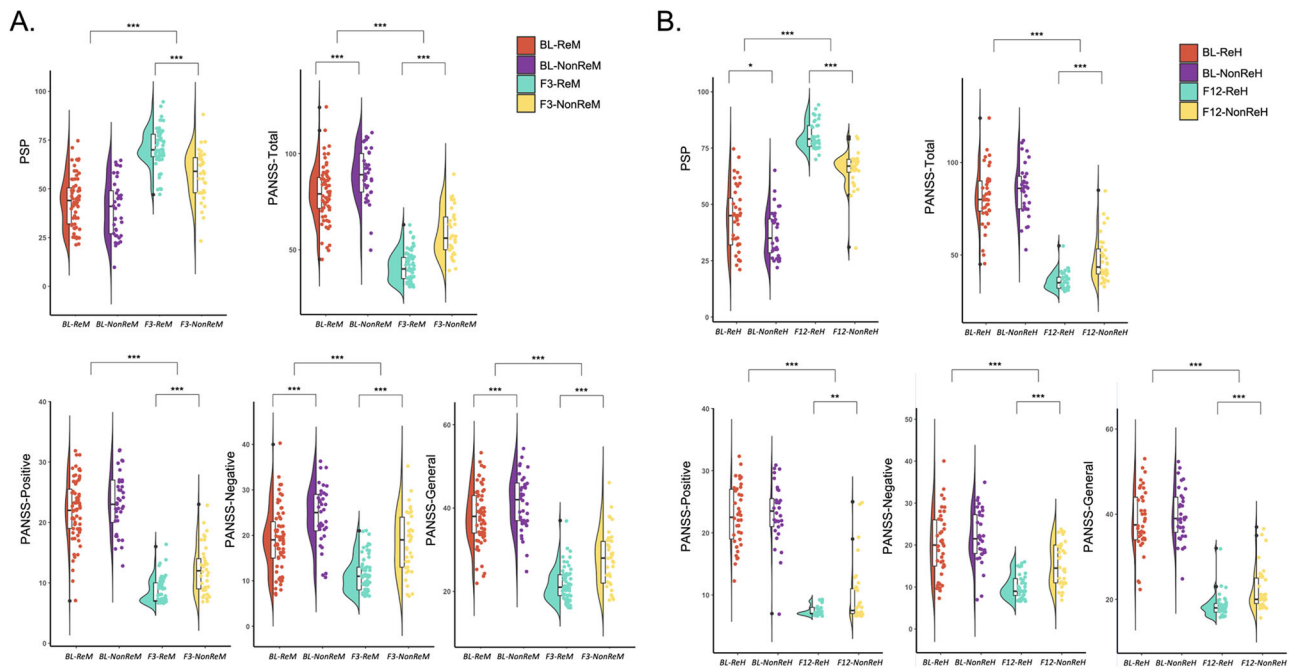
Fig. 2 Group differences of clinical symptoms and social functions. The violin scatter plot illustrates the group differences at baseline as well as the time point after 3-month (**A**) or 1-year efficacy (**B**). PSP: the Personal and Social Performance Scale; PANSS: the Positive and Negative Syndrome Scale; BL: Baseline; F3: three-month follow-up; ReM: the Remission group; NonReM: the Non-Remission group; F12: one-year follow-up; ReH: the Rehabilitation group; NonReH: the Non-Rehabilitation group. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 1. Differences of social functioning and clinical symptoms between the remission and non-remission group.

	Remission group ($n = 67$) M (SD)	Non-remission group ($n = 37$) M (SD)	p
Baseline			
PSP	43.04 (13.14)	40.14 (14.57)	0.301
PANSS-Positive	22.18 (5.16)	23.32 (4.74)	0.268
PANSS-Negative	19.15 (6.91)	24.41 (6.35)	**<0.001**
PANSS-Genernal	38.04 (6.86)	42.30 (9.19)	**0.009**
PANSS-Total	79.37 (14.70)	90.03 (15.68)	**0.001**
Three-month follow-up			
PSP	70.96 (9.58)	57.73 (12.66)	**<0.001**
PANSS-Positive	8.57 (2.05)	12.27 (4.07)	**<0.001**
PANSS-Negative	11.30 (3.83)	19.60 (11.57)	**<0.001**
PANSS-Genernal	21.52 (3.94)	28.16 (6.65)	**<0.001**
PANSS-Total	41.39 (7.65)	60.03 (16.29)	**<0.001**

M mean, SD standard deviation, PSP the personal and social performance scale; $PANSS$ the positive and negative syndrome scale. The p values in bold indicate significant group differences between the Remission and Non-remission groups.

social functions (main effects of Trentment: $Fs > 62.02$, $ps < 0.001$), with the remission group exhibiting even less severe symptoms and better social functions (main effects of Group: $Fs > 10.37$, $ps < 0.002$) (see Table S1). Notably, at baseline, the remission group exhibited significantly lower PANSS total scores than the non-remission group ($p < 0.001$), driven primarily by negative ($p < 0.001$) and general symptoms ($p = 0.008$). Conversely, no significant difference was observed in positive symptoms between the remission and non-remission groups ($p = 0.268$). However, the remission group exhibited significantly lower scores at the 3-month follow-up than the non-remission group ($ps < 0.001$). Regarding social functions, the remission group exhibited comparable scores on PSP at the baseline ($p = 0.301$) but lower scores at the 3-month follow-up ($p < 0.001$) compared with the

non-remission group. The results are shown in Fig. 2A and Table 1. More details can be found in Supplementary materials.

After 1 year of treatment, all clinical symptoms and social functions were improved (main effects of Trentment: $Fs > 78.50$, $ps < 0.001$), with the rehabilitation group, exhibiting less severe symptoms and better social functions (main effects of Group: $Fs > 4.49$, $ps < 0.038$) (see Table S2). Specifically, the rehabilitation group exhibited less severe clinical symptoms across all subscales of PANSS at 1-year follow-up than the non-rehabilitation group ($ps < 0.001$), whereas no significant symptom difference was observed between the two groups at the baseline ($ps > 0.3$). The rehabilitation group exhibited higher scores of PSP at baseline than the non-rehabilitation group ($p = 0.030$, Cohen's $d = 0.533$), and this group difference was further increased after 1 year of

Table 2. Differences of social functioning and clinical symptoms between the rehabilitation and non-rehabilitation group.

	Rehabilitation Group (n = 40) M (SD)	Non-rehabilitation Group (n = 32) M (SD)	p
Baseline			
PSP	43.82 (14.12)	37.19 (10.56)	0.030
PANSS-Positive	22.65 (4.85)	23.16 (4.94)	0.664
PANSS-Negative	20.15 (6.91)	21.94 (6.52)	0.301
PANSS-Gennernal	38.65 (7.14)	39.91 (6.24)	0.436
PANSS-Total	81.45 (15.75)	85.00 (14.23)	0.858
One-year follow-up			
PSP	80.28 (5.83)	65.34 (8.53)	**<0.001**
PANSS-Positive	7.43 (0.75)	10.06 (4.96)	**0.001**
PANSS-Negative	10.10 (2.81)	15.47 (5.16)	**<0.001**
PANSS-Gennernal	18.45 (2.82)	22.47 (5.28)	**<0.001**
PANSS-Total	35.98 (4.81)	47.75 (12.50)	**<0.001**

M mean, SD standard deviation, PSP the personal and social performance scale, PANSS the positive and negative syndrome scale. The p values in bold indicate significant group differences between the Rehabilitation and Non-rehabilitation groups.

Table 3. Contribution weights of gray matter structural features to the prediction of three-month treatment outcomes.

Contribution ranking	Features of gray matter structure	r
1	GI of the Right Superior Temporal Gyrus	0.891
2	Ct of the Right Rostral Middle Frontal Gyrus	0.769
3	Ct of the Left Supramarginal Gyrus	0.716
4	GI of the Left Post-central Gyrus	0.671
5	GI of the Left Pars Triangularis	0.666
6	Ct of the Right Parahippocampal Gyrus	0.609
7	GI of the Left Inferior Parietal Lobule	0.606
8	GMV of the Right Caudate Nucleus	-0.561
9	Ct of the Left Fusiform Gyrus	0.547
10	GI of the Right Anterior Cingulate Cortex	0.544
11	Ct of the Right Fusiform Gyrus	0.477
12	Ct of the Right Inferior Temporal Gyrus	0.475
13	Ct of the Left Lateral Orbitofrontal Cortex	0.467
14	GMV of the Right Rectus Gyrus	-0.466
15	GMV of the Left Caudate Nucleus	-0.461
16	Ct of the Left Rostral Middle Frontal Gyrus	0.404
17	Ct of the Right Cuneus	0.300
18	Ct of the Right Calcarine Sulcus	0.289
19	GMV of the Left Thalamus	0.287
20	Ct of the Left Lingual Gyrus	0.255
21	Ct of the Right Entorhinal Cortex	0.243
22	Ct of the Right Temporal Pole	0.217
23	Ct of the Left Parahippocampal Gyrus	0.196
24	Ct of the Left Cuneus	0.147

GI gyrification index, Ct cortical thickness, GMV gray matter volume.

treatment ($p < 0.001$, Cohen's $d = 2.050$). The results are shown in the Fig. 2B and Table 2. More details can be found in Supplementary materials.

The prediction of gray matter structural features on the 3-month efficacy of antipsychotics

In assessing the predictive capabilities of different models for the 3-month treatment efficacy, the LR classifier demonstrated optimal performance with an *accuracy* of 74.32% ($p = 0.0001$), *sensitivity* of 81.08% ($p < 0.0001$), *specificity* of 67.57% ($p = 0.0097$), and an *AUC* of 0.7845 ($p < 0.0001$). According to the regression coefficients, the 24 features that make the most significant contribution to the predictive value of the LR classifier, such as GI of the right superior temporal gyrus ($r = 0.891$), Ct of the right rostral middle frontal gyrus ($r = 0.769$), Ct of the left supramarginal gyrus ($r = -0.716$), GI of the left post-central gyrus ($r = 0.671$), as outlined in Table 3 and Fig. 3A. The results of other classifiers can be found in Table S3.

The prediction of gray matter structural features on the 1-year efficacy of antipsychotics

Upon evaluating the predictive capabilities of various models, the LR classifier emerged as the most effective model for predicting 1-year treatment efficacy. This model achieved a classification accuracy of 70.31% ($p = 0.0004$), a *sensitivity* of 71.88% ($p = 0.0011$), a *specificity* of 68.75% ($p = 0.0028$), and an *AUC* of 0.7617 ($p < 0.0001$). Based on the regression coefficients, the features contributing to the efficacy prediction, ranked from the most to the least significant, were: GI of the right pars triangularis ($r = 1.181$), GMV of the right inferior occipital gyrus ($r = -1.159$), Ct of the right caudal anterior cingulate ($r = -1.113$), and GI of the left inferior frontal gyrus ($r = 1.004$), as detailed in Table 4 and Fig. 3B. The results of other classifiers can be found in Table S4.

DISCUSSION

In our study, we categorized drug-naive patients with FES into different groups based on their responses to antipsychotics at the end of acute-phase (3-month) treatment, and the 1-year maintenance phase. We compared the baseline characteristics and follow-up data. The results indicated that patients with less severe negative and general symptoms at baseline were more likely to achieve remission after 3 months of acute-phase treatment, whereas patients with better social functions at the baseline were more likely to rehabilitate following 1 year of maintenance therapy. Importantly, our use of machine learning to predict drug efficacy revealed that widespread regions, such as the superior temporal gyrus, middle frontal gyrus, supramarginal gyrus, post-central gyrus, anterior cingulate gyrus, and parahippocampal gyrus, were significant predictors of 3-month treatment efficacy. For 1-year outcomes, the inferior frontal gyrus, anterior cingulate
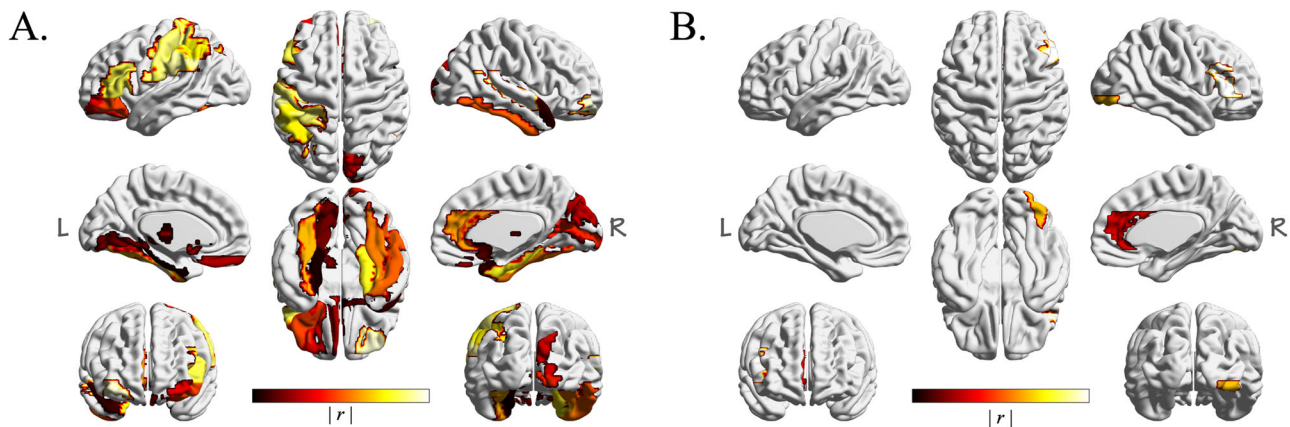
Fig. 3 The brain regions that can predict individuals' response to antipsychotics. Widespread regions, such as the superior temporal gyrus, middle frontal gyrus, supramarginal gyrus, post-central gyrus, anterior cingulate gyrus, and parahippocampal gyrus, were significant predictors of 3-month treatment efficacy (**A**). The inferior frontal gyrus, anterior cingulate gyrus, and inferior occipital gyrus demonstrated substantial predictive power for 1-year outcomes (**B**).

Table 4. Contribution weights of gray matter structural features to the prediction of one-year treatment outcomes.

Contribution ranking	Features of gray matter structure	r
1	GI of the Pars Triangularis	1.181
2	GMV of the Right Inferior Occipital Gyrus	−1.159
3	Ct of the Right Caudal Anterior Cingulate Gyrus	−1.113
4	GI of the Left Inferior Frontal Gyrus	1.004

GI gyrification index, *Ct* cortical thickness, *GMV* gray matter volume.

gyrus, and inferior occipital gyrus demonstrated substantial predictive power.

There is significant variability in individual responses to antipsychotic treatments, a long-standing concern for clinical psychiatrists and researchers. This study leveraged machine learning models to explore predictors of an individual's response to antipsychotics. By merging conventional statistical analysis with machine learning algorithms, our study revealed intricate correlations between brain structure features and treatment outcomes, a feat that previous research often found challenging[36]. We utilized various machine learning algorithms and validated their predictive accuracy through cross-validation techniques, ensuring the findings' robustness and reliability. Furthermore, by quantifying the predictive contribution of each feature, we highlighted the potential role of machine learning to elucidate the underlying pathophysiological mechanisms of schizophrenia.

Patients who had less severe negative and general symptoms at baseline were more likely to achieve remission after 3 months of acute-phase treatment, whereas the severity of positive symptoms at baseline had no predictive effect on the 3-month efficacy. It's probably because second-generation antipsychotic drugs were most effective in managing positive symptoms[37], therefore more severe positive symptoms at baseline can hardly affect patients' remission. Furthermore, our results suggested that responses to antipsychotics could potentially be predicted by examining brain structures before medication. The critical predictive brain regions included the superior temporal gyrus, middle frontal gyrus, supramarginal gyrus, post-central gyrus, anterior cingulate gyrus, and parahippocampal gyrus, which have been consistently found to associate with negative symptoms[38–43]. Moreover, compared with assessing symptoms directly, using gray matter indicators not

only provides a more stable, objective measure of brain structure but also enables us to investigate the neurobiological mechanisms of negative symptoms in a way that complements clinical assessment. Given most antipsychotics are poorly effective against negative symptoms[44], it's reasonable that the abnormalities in these brain regions associated with negative symptoms will have a significant impact on the treatment outcomes of patients.

Interestingly, the 24 regions that could predict 3-month efficacy predominantly linked to the sensorimotor network (SMN) and the salience network (SN). As early as the 1990s, Gray et al. proposed that patients with schizophrenia cannot merge previously stored memories of perceptual input patterns with current motor programs that govern perception[45], a core function of SMN. Studies using dynamic causal modeling showed that the SN regulates the activity of the default mode network and central-executive networks, a function that is impaired in patients with schizophrenia[46]. The structural abnormalities in the SN were also related to positive schizophrenia symptoms, such as reality distortion[47]. Therefore, our findings highlighted that brain structures related to perceptual and mediating abnormalities could predict the efficacy of acute treatment. Abnormalities in the SN in schizophrenia may lead patients to assign inappropriate significance to irrelevant stimuli, contributing to positive symptoms such as delusions and hallucinations. The predictive value of brain regions associated with the SMN and SN for 3-month treatment outcomes likely stems from the fact that treatments during the acute phase target aberrant sensory processing. Both networks play a key role in sensory perception and attention, which are central to the treatment of early-stage symptoms. Thus, improvements in these networks may reflect the reduction of perceptual disturbances, explaining their relevance for short-term treatment efficacy.

Traditionally, the emphasis has been on the short-term response to antipsychotic treatment, with limited focus on long-term efficacy predictions. The current research indicated that it was social functioning, rather than symptom severity prior to medication, could predict rehabilitation outcomes after one year of treatment. More importantly, specific brain structural changes in regions such as the inferior frontal gyrus, anterior cingulate gyrus, and inferior occipital gyrus were reliable indicators of long-term treatment response. Consistently, previous research has documented a decrease in the GMV of the inferior frontal gyrus among treatment-naive schizophrenia patients, a structural abnormality correlated with positive symptoms[48]. The cingulate gyrus, a critical pathological area in schizophrenia, plays a vital role in conflict monitoring, motivation adjustment, emotion

regulation[49], executive, and cognitive functions[50]. Autopsy studies revealed a reduction in non-pyramidal neuron density in the anterior cingulate of patients with schizophrenia, potentially leading to cortical thinning[51]. Glutamatergic neurotransmitter dysfunction was associated with both positive and negative symptoms of schizophrenia[52]. Magnetic resonance spectroscopy studies suggested increased glutamate concentration in the anterior cingulate in patients with treatment-resistant schizophrenia (TRS) compared to responders[53]. Because high glutamate concentration could cause excitotoxicity related to brain structural changes, the elevated glutamate levels in TRS patients might contribute to their abnormal anterior cingulate gray matter structure. Additionally, Anderson et al. have noted reduced occipital GMV in patients with TRS compared to responders[54]. These findings collectively suggest that abnormalities in certain regions of the frontal cortex, anterior cingulate, and occipital cortex are significant in the pathophysiology of schizophrenia and its various biological subtypes.

The brain gray matter abnormalities identified in this study may provide crucial insights into the pathophysiology of schizophrenia, offering a potential pathophysiological basis for the disorder and its biological subtypes. For instance, a previous study[55] we contributed to identified two distinct subtypes of schizophrenia, with differing patterns of brain atrophy in the Broca's area and hippocampus. These subtypes were associated with different symptom profiles and treatment responses, highlighting the potential for more personalized treatment approaches. By predicting both short- and long-term treatment outcomes, our findings clarify the relationship between brain structure and the efficacy of second-generation antipsychotics during the early stages of first-episode schizophrenia. These insights have the potential to refine patient classification, inform clinical decision-making, and identify biomarkers for treatment response, ultimately paving the way for more personalized treatment strategies and novel therapeutic targets.

This study faced several limitations. First, a significant dropout rate was observed during the 1-year follow-up, and the relatively small sample size hindered our ability to validate our findings with an independent sample set. Consequently, the results should be interpreted cautiously, and a clear need exists for more extensive future studies to confirm these findings. Moreover, although widely used in neuroimaging, our reliance on AAL90 and DK-40 templates for feature extraction in machine learning analysis might have led to the omission of crucial information, as full-brain voxel-level analysis was not performed.

CONCLUSION

The study employed machine learning methods and discovered that widespread brain regions, such as the post-central gyrus, anterior cingulate gyrus, and parahippocampal gyrus, significantly predicted 3-month treatment efficacy during the acute phase of the illness, with an accuracy of 74.32%. Furthermore, specific brain areas such as the inferior frontal gyrus, anterior cingulate gyrus, and inferior occipital gyrus displayed significant predictive power for long-term (1-year) treatment outcomes, with an accuracy of 70.31%. Overall, our study offers valuable insights into the neurobiological underpinnings of schizophrenia, particularly in treatment-naive patients, and highlights potential targets for future therapeutic interventions.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, Xin Yu, Peking University Sixth Hospital, upon reasonable request.

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AUTHOR CONTRIBUTIONS
The study was conceptualized, designed, and supervised by Xin Yu and Cheng-cheng Pu. The first author was responsible for data organization, analysis, and manuscript drafting. The other co-authors assisted with data collection, processing, and analysis, contributed to manuscript revisions, and provided technical support. All authors contributed to the preparation of the manuscript, critically reviewed its content, and approved the final version for submission.

COMPETING INTERESTS
The authors declare no competing interest.

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