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Machine Learning Classification of Schizophrenia Using Neuroanatomical and Functional Markers to Support Individualized Treatment: A Literature Review

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Abstract

Introduction: Heterogeneity in the clinical presentation and pathophysiology of schizophrenia presents challenges for effective diagnostic and therapeutic practices. Machine learning (ML) methods have emerged as a promising tool for addressing this, due to their ability to integrate neuroimaging and clinical data. This paper aims to review the literature on ML and its uses for identifying subtypes based on structural and functional brain features. Additionally, the paper will discuss how these insights can be used to target pathophysiological features and individualize treatment.

Methods: A literature search was conducted across various research databases for ML neuroimaging studies published in the past 10 years that included only schizophrenia samples. From this search, 38 were screened; 18 met criteria for full-text review and were included. Additionally, a secondary search was conducted to review potential clinical applications and individualized treatments. From this search, 6 articles were added, resulting in a total of 24 papers.

Results: Evidence supported the existence of distinct neurobiological profiles amongst patients with schizophrenia. Across 7 studies, two recurring neurobiological subtypes were identified: one defined by widespread cortical gray matter loss and greater cognitive and negative symptoms; and another marked by an intact cortical structure but subcortical enlargement, associated with positive symptoms. Results across the remaining 11 studies varied, ranging from 2 to 6 subgroups. Several of these neurobiological patterns corresponded to differences in symptom severity and cognitive performance. Further, predictive-modelling studies demonstrated moderate to high accuracy in forecasting treatment response.

Discussion: ML can be used to identify neurobiological subtypes of schizophrenia that align with differences in symptoms and potential treatment targets. Additional multimodal biomarkers further highlight substantial heterogeneity. While multimodal ML approaches may help integrate this variability, current methods face challenges. These findings suggest that ML can capture variability in schizophrenia, providing a basis for predicting treatment responses.

Conclusion: ML can be used to identify neurobiological subtypes of schizophrenia and additional multimodal biomarkers which further highlight substantial heterogeneity and treatment targets. Hence, ML approaches may help integrate this variability, but current methods face challenges which require further research.

Keywords: schizophrenia; machine learning; biomarkers; treatment; neuroimaging; functional connectivity; neuroanatomical heterogeneity; predictive modeling; subtyping

Introduction

Schizophrenia encompasses a broad spectrum of symptoms generally divided into three categories: positive symptoms, such as hallucinations; disorganized symptoms, including incoherent speech or behaviour; and negative symptoms, like diminished emotional expression or social engagement [1]. Furthermore, it is a highly heterogeneous disorder in terms of clinical presentation, treatment response, neurobiological factors, and degree of impairment [2–5]. Much of the literature trying to parse out this heterogeneity is consistent with Crow's conceptualization of schizophrenia as a "two-syndrome" disorder, where one type is marked by positive symptoms and greater response to antipsychotic treatment, and the other is characterized by negative symptoms, a higher degree of impairment and associated structural and functional brain changes [6]. In theory, the specificity of treatment and etiology can be increased by separating the disorder into two types, which may reveal distinct intervention targets and trajectories. However, evidence for the association between neurobiological features and clinical presentations has been mixed, and variability in structural features remains high across subtypes, which provides limited clinical utility for patient stratification beyond the existing diagnosis [7–10]. Additionally, the variability in treatment response to both biological and psychosocial interventions may reflect a lack of specificity and individualized treatment targets, given the heterogeneous etiological and pathological factors of the disorder [11].

However, novel machine learning (ML) methods that analyze and cluster Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI) and functional MRI (fMRI) data show promise for identifying neurobiologically distinct subtypes for a broad range of brain-related disorders, including schizophrenia [12]. Beyond identifying neurobiological subtypes, ML has become increasingly crucial for understanding and predicting treatment response in schizophrenia. Although antipsychotic medications remain the basis of care, they primarily improve positive symptoms and show limited effects on negative and cognitive symptoms, contributing to variability in individual outcomes [13, 14]. Approximately one-third of patients experience minimal benefit, highlighting the need for approaches that can predict response pre-treatment [15]. Recent research has suggested that ML-based predictive modelling has the potential to assist in personalizing interventions to improve treatment response. [16].

Together, these findings reveal a shifting landscape in which ML is increasingly used to organize heterogeneity, predict treatment outcomes, and inform individualized interventions. In addition, ML can integrate and process diverse forms and large amounts of clinical data to: a.) Find key neuroanatomical markers that differentiate certain groups of patients, b.) Make broad predictions across a range of outcomes, including treatment efficacy. Hence, this paper aims to provide an overview of the current literature on the utilization of ML to identify neurobiologically distinct schizophrenia subtypes and to link this to clinical applications for personalized interventions.

Methods

This study employed a narrative review approach. As such, a targeted literature search was conducted through various databases (ScienceDirect, PubMed and PsycInfo) using Boolean operators (Schizophrenia) AND (Machine Learning) AND (Functional) OR (Structural) AND (Subtype). In addition, secondary searches were conducted to broaden coverage. First, alternative search terms were included (Neuroanatomical) AND (Schizophrenia), (Machine Learning) (Clustering) AND (Schizophrenia). Moreover, a search was conducted to identify potential clinical applications of ML-based schizophrenia subtypes. The inclusion criteria consisted of studies published in or after 2015, written in English, clinical samples composed exclusively of patients with schizophrenia, papers that classified schizophrenia subtypes based on structural and/or functional differences, and neuroimaging methods including MRI, fMRI, and/or DTI. Meta-analyses and papers that did not discuss functional or structural differences among schizophrenia subtypes were excluded. The 2015 cutoff year was selected because of rapid advancements in the field of ML, where studies older than 10 years may be using outdated methods. The Schizophrenia-only sample was selected to reduce the heterogeneity found in psychotic disorders, increasing the interpretability of the results by isolating neurobiological features specific to schizophrenia. MRI and fMRI methods were selected for their high spatial resolution, which provides greater accuracy in displaying neuroanatomy; whereas DTI was selected for its use in mapping functional networks in the brain [20].

The primary search yielded 49,143 records. After removal of 12 duplicates, database limits reflecting the inclusion criteria (e.g., schizophrenia-only samples, English language) were applied prior to manual screening. This resulted in 38 records proceeding to title and abstract review. Full texts were obtained for all 38 reports, of which 20 were excluded for the following reasons: non-schizophrenia-only samples (n = 12), meta-analyses (n = 1), not using machine learning (n = 1), overlapping samples (n = 3), EEG methods (n = 2), and genetic markers only (n = 1). A total of 18 studies were included in the final review. Secondary searched resulted in the inclusion of 6 additional papers. In total, 24 papers were selected.

Results

Two Distinct Subgroups of Schizophrenia

A recurrent finding across the literature was the distinction between two groups of schizophrenia patients, where one group exhibits pronounced neuroanatomical abnormalities in the cortex and the other demonstrates primarily abnormalities in functional pathways and subcortical structures, with a largely intact cortical structure [7, 21–26]. Results from multiple studies indicate that the key marker for identifying the first neural signature (Signature 1), was widespread volumetric gray matter volume (GMV) loss in cortical and some subcortical regions, such as the hippocampus, thalamus, and nucleus accumbens [7, 21–26]. Here, a neural signature refers to a reproducible multivariate pattern of brain structure or function used to differentiate individuals. In contrast, the second subgroup (Signature 2) is characterized by structural enlargements in subcortical regions, most consistently involving the basal ganglia, all of which have been associated with the dopaminergic system [7, 21, 22, 25]. A pattern of abnormalities in functional connectivity was also found in one study with patients that presented similar subcortical enlargements, marked by heightened connectivity and white matter loss in the occipital lobe, affecting pathways between the somatomotor network (SMN), visuo-spatial network (VSN) and the default mode network (DMN); with changes to connectivity within the ventral attention network (VAN) [25]. Dysregulated network interactions in this subgroup are supported by evidence of enlargement in the internal capsule, a white matter tract that serves as a pathway between subcortical and cortical structures involved in sensory processing [21, 22, 25]. Findings on the causal factors underlying the enlargement of subcortical structures and the dysregulation of functional pathways are mixed. Some studies point to antipsychotic medications as a potential cause, where enlargement in the pallidum was associated

with antipsychotic dose [7, 25, 26]. However, a study demonstrated that striatal abnormalities are present in drug-naive First-Episode Schizophrenia patients, defined as individuals experiencing their first psychotic episode whose presentation meets diagnostic criteria for schizophrenia [27].

Multiple studies suggest that these subtypes are associated with distinct symptomatic profiles. Here, a subtype refers to the group of individuals characterized by a given signature. Signature 1 has been associated with marked cognitive deficits and neurodevelopmental impairments [7, 25, 26]. Further, there is evidence of an association between this pattern of atrophy and increased negative symptoms compared with Signature 2 [21, 25]. Alternatively, patients in Signature 2 had lower levels of cognitive deficits and negative symptoms, whilst presenting higher levels of positive symptoms, as well as increased associated improvements in positive symptoms with antipsychotic medication use compared to Signature 1 [7, 25]. However, conflicting results suggest that, whilst there are distinct neuroanatomical subtypes of schizophrenia, as well as subgroup membership based on symptom presentations, these are not associated [24, 28].

Structural and Functional Biomarkers of Distinct Subgroups of Schizophrenia

The literature employing ML to find subgroups in schizophrenia reflects a wide array of biomarkers that can be utilized to classify individuals based on structural and functional abnormalities, alternative to Signature 1 and 2. Across studies, evidence consistently supports the existence of distinct neurobiological profiles amongst patients with schizophrenia; however, the specific brain regions, networks and patterns of atrophy used to differentiate between these profiles vary considerably. In total, the studies in this section implicated 14 brain structures and 9 functional networks. Further, the number of data-driven subtypes identified ranged from 2 (the most common solution) to 6 [29–39]. The following tables provide an overview of alternative biomarkers used in the literature to identify subgroups of schizophrenia. Table 1 presents studies that focus solely on neuroanatomical differentiation by using structural and functional clustering. Table 2 summarizes research linking different subtypes of schizophrenia to clinical and cognitive features.

Table 1. Summary of alternative neurobiological markers.

Study	Method	Results
Chen et al., 2020 [29]	Resting state fMRI (rs-fFMRI); Multivariate classification analysis	Resting-state functional connectivity patterns in the right ventromedial prefrontal cortex reliably distinguished subtypes.
Gao et al., 2023 [30]	MRI; multivariate pattern analysis; Multivariate Relevance Vector Regression	Differences in abnormalities in the temporal lobe, inferior frontal gyrus and visual regions can distinguish between two symptomatic subtypes of schizophrenia: Deficit Schizophrenia (DS) and No-deficit schizophrenia (NDS).
Honnorat et al., 2019 [31]	fMRI; CHIMERA (Clustering of Heterogeneous Disease Effects) to cluster subtypes	Identified three subgroups: (a) Gray matter atrophy in thalamus, anterior cingulate and superior temporal gyrus (STG); (b) Frontal-Heavy Cerebral Spinal Fluid (CSF) expansion and reduced white matter; (c) A more heterogeneous group, with mild CSF volume expansion
Lalousis et al., 2023 [32]	MRI; blood samples analyzed for inflammation markers	Identified five subgroups defined by distinctive neuroanatomical profiles. Specific inflammatory profiles were associated with differential GMV loss. Whilst all groups showed GMV loss in the temporal lobe and hippocampus compared to healthy controls, Cluster 3 showed significantly greater atrophy in these regions.
Xiao et al., 2021 [33]	MRI; clustering using fast search and find of density peaks	Identified three distinct patterns of GMV loss: (a) Increased reduction of cortical and subcortical GMV, with substantial decreases in cortical surface area and thickness; (b) GMV loss localized to the left hippocampus only; (c) No marked alterations.

Note. Figure made using Microsoft Word

Table 2: Summary of alternative neurobiological markers linked to clinical features.

Jiang et al., 2024 [34]	MRI: Subtype and Stage Inference Algorithm (Clusters patients based on disease progression stage)	Early Broca's area GMV atrophy, compared with early hippocampal GMV loss, predicted distinct disease progression. Early Broca's GMV loss is associated with the progression of negative and depressive symptoms, with minimal change in positive symptoms.
Pan et al., 2020 [35]	MRI; Cognitive assessment (Verbal Fluency, N-back and Contour Integration Test), K-means clustering	Three subgroups were identified based on cortical thinning: (a) Higher degree of cortical thinning with marked cognitive deficits; (b) Reduced cortical thinning, illness duration, but increased positive symptoms; (c) Intermediate degree of cortical thickness loss.
Sugihara et al., 2017 [36]	MRI; Unsupervised K-means clustering and self-organizing map neural network analysis	Found six subgroups from cortical thickness patterns. Cluster 1 had the highest regional loss in prefrontal and temporal areas; Cluster 2 in the medial frontal area; Cluster 4 in the temporal lobe. Clusters 3,5, and 6 showed less cortical thinning. Differences in negative symptom severity were associated with high cortical thinning.
Talpalaru et al., 2019 [37]	MRI; hierarchical clustering and cluster stability analysis	Structural differences in the insula showed lateralized effects across subgroups: Right-sided alterations with higher symptom burden, bilateral abnormalities with higher positive symptoms, and left-sided alterations with mild burden. Differences in the left anterior cingulate and paracingulate gyrus were predictive of cognitive function.
Wei et al., 2025 [38]	Structural MRI (sMRI);Diffusivity MRI; rs-fMRI K-means clustering analysis	Subtypes were classified by MRI Composite Indicators (MRICIs), which were robust predictors of symptom presentation in both first-episode and schizophrenia patients. Subtype I presented milder symptoms, whereas Subtype II presented more severe symptoms and cognitive impairments, marked by elevated structural damage to the brain.
Sun et al., 2015 [39]	DTI; hierarchical clustering	Two white-matter abnormality patterns: (a) Reductions in fractional anisotropy with increases in mean diffusivity across fibre, associated with the presentation of negative symptoms; (b) Localized fractional anisotropy reduction in the superior longitudinal fasciculus pathway.

Note. Figure made using Microsoft Word

Treatment Prediction and Clinical Applications of Machine Learning

ML has achieved moderate to high predictive accuracy regarding treatment outcomes/efficacy, and several studies have demonstrated that baseline neuroimaging features can predict treatment response in schizophrenia. A study using rs-fMRI to identify superior temporal cortex (STC) connectivity patterns predicted risperidone response, achieving 78.6% diagnostic and 82.5% predictive accuracy [17]. Functional dysconnectivity in STC networks was associated with a reduction in positive symptoms following treatment. A similar study used rs-fMRI and multivariate pattern classification to examine treatment outcomes following electroconvulsive therapy (ECT) [40]. Classification scores derived from pre-treatment connectivity successfully predicted post-ECT symptom improvement, and ECT induced greater normalization of network connectivity than antipsychotics alone [40]. Additionally, a study reported that white matter integrity within superior longitudinal and cingulum fasciculi predicted 12-week treatment outcomes [41]. Furthermore, ML models were designed to predict treatment response in repetitive transcranial magnetic stimulation (rTMS) using sMRI. The findings from this paper showed that, when responders and non-responders were classified based on GM features, predictive patterns across brain regions were robust [42]. Jiang et al. (2023) utilized the subtype and stage inference algorithm to identify neurophysiological subtypes with distinct illness trajectories. Findings indicated that antipsychotic efficacy differed between subtypes [42]. In-practice studies have shown that structural MRI-derived grey matter patterns can reliably differentiate responders from non-responders to rTMS in schizophrenia [43]. Results show that accuracy ratings are around 76-81% with ML models identifying distributed prefrontal, temporal, and cerebellar features that contributed most strongly to treatment-response classification [43]. Importantly, most papers reviewed were retrospective or

cross-sectional in design, relying on previously collected neuroimaging datasets to train and validate ML models [17, 40–43]. While these approaches demonstrate promising predictive accuracy, retrospective analyses may overestimate performance due to sample-specific optimization and limited external validity. Few studies examined a prospective design in which models are tested in real-time clinical decision-making contexts.

Discussion

The results of this review provide evidence that ML can be used for classifying schizophrenia based on neuroanatomical and functional differences [7, 21–39]. In this case, novel methods have been used to demonstrate that distinct neurobiological subgroups with divergent progression characterize schizophrenia and that this has important clinical applications.

Structural and Functional Differences

The differences in neuroanatomy and functional pathways found in the literature have key implications in understanding the symptomology and potential treatment targets in schizophrenia. Signature 1 was found to have widespread and increased loss of GMV in cortical and subcortical regions [7, 21-26]. Further, this was found to be associated with greater cognitive deficits and prevalence of negative symptoms than Signature 2 [22, 25, 26]. The underlying pattern of neural atrophy found in this subset of patients appears to correspond to the symptom presentation. The volumetric alterations of gray matter in the prefrontal–thalamic–cerebellar network and temporo-frontal regions present in this Signature have been associated with impairments in executive functioning, working memory and language learning [44–46]. This may explain why there were pronounced cognitive deficits in Signature 1 compared to Signature 2, which has a more intact cortical structure. Treatments specifically targeting neural atrophy and cognitive impairments may benefit patients with more generalized GMV loss, whereas Signature 2 patients seem to have symptoms more related to dopaminergic structures and pathways. For example, therapies such as cognitive remediation have been shown to reduce cognitive impairment whilst having positive effects on structural changes, directly targeting the core deficits of this subtype [47, 48]. This may be a significant target considering that antipsychotic medication is ineffective in ameliorating cognitive deficits in psychosis, sometimes even having iatrogenic effects [13, 14].

The increased severity and presence of positive symptoms in Signature 2 are also associated with the subgroup's neurobiology. Abnormalities in connectivity between the occipital lobe, SMN, VSN, DMN and the VAN characterized this cluster [25]. Dysregulation in these circuits, particularly between the occipital lobe and higher-order attention networks, has been linked to increased sensitivity to external stimuli, which may in turn lead to increased hallucinations and delusions [25, 49]. Additionally, the volumetric increases in structures associated with dopaminergic activity in Signature 2 further implicate abnormal dopamine signalling as a core feature [7, 21, 22]. Dysfunctions in dopamine-regulated regions, such as the striatum and pallidum, have been associated with abnormal salience attribution, in which neutral or irrelevant stimuli are assigned exaggerated importance, and is implicated in the underlying pathology of positive symptoms [50].

However, long-term antipsychotic medication use has been associated with increased volumes in the basal ganglia [51–54]. Evidence supports that the characteristics of this subgroup arise as an effect of antipsychotic treatment [7]. This may suggest that the abnormalities found in this subgroup are due to medication effects. Alternatively, this could reflect differential brain response to antipsychotics across the subgroups. Whilst there is evidence to suggest individual differences in volumetric enlargement following antipsychotic exposure, this possibility requires further research [55]. Conversely, there is evidence suggesting that such volumetric increases predate medication exposure, as they have been observed in drug-naive schizophrenia patients [27, 56]. These differences may indicate neurobiological features are intrinsic to the specific patient subset. Dysfunction in dopamine-regulated structures reveals a potential treatment target, where dopamine-blocking antipsychotics may be beneficial due to their effects on functional connectivity and dopaminergic structures (e.g., increased responsiveness in patients with larger basal ganglia) [21, 57, 58]. Ultimately, these features should be interpreted with caution when considered as potential targets for individualized treatment. More studies are needed to disentangle medication effects from disease-related variation.

Collectively, these findings highlight that data-driven neurobiological subtypes of schizophrenia can exhibit distinct structural and functional profiles that map directly onto symptomatology, suggesting that treatment strategies may be optimized by tailoring interventions to the underlying neural characteristics of each subtype. However, this should be interpreted with caution, considering two studies suggest no differences in symptom profiles between the two Signatures [24, 28]. Notably, neither collected neurocognitive data, lacking information on cognitive impairments. This limits the extent to which the findings capture the patients' symptomatic profile beyond negative or positive symptoms, especially given that these deficits seem to be a differentiating feature between patients [26]. Accordingly, the findings may reflect a narrower symptom assessment rather than true equivalence between groups. Alternatively, abnormalities in specific structures, such as the thalamus, implicated in Signature 1 have previously been associated with positive symptoms; while certain regions within Signature 2, such as the striatum, have been linked to negative symptoms and cognitive deficits [27, 59, 60]. This suggests that, although there may be overlap in symptom presentations across subtypes, the underlying neural mechanisms driving those symptoms may differ.

Consequently, these subtype-specific neural alterations remain important potential treatment targets, highlighting the need for further research to clarify how interventions can be individualized.

Heterogeneity of Subtypes

In this review, 11 studies found alternative biomarkers to Signature 1 and 2 that can be used to differentiate between subsets of patients, reflecting the heterogeneity of neural alterations and overall pathophysiology in schizophrenia, as well as the challenge of linking this to specific symptom profiles [29–39]. Further, it reinforces the multidetermined nature of the disorder, implicating numerous structures and pathways, indicating there may not be a single dichotomous paradigm to use for subtyping schizophrenia based on neurobiological features. This variability could also reflect the wide range of clustering methods used across studies, as different algorithms, feature-selection approaches and preprocessing pipelines can generate distinct subgroup solutions, even when applied to similar neuroimaging data [61]. Consensus clustering, a method that aggregates multiple clustering solutions, can improve robustness to said differences [61]. Another option is using MRI Composite Indicators (MRICIs) generated from multimodal neuroimaging data that integrate structural, diffusivity, and functional data [38]. Using multiple imaging measures has been shown to improve classification performance and sensitivity, whilst accounting for the specific limitations of single neuroimaging techniques [62, 63]. This could be used to triangulate data to find clearer clustering solutions. However, multimodal fusion methods can fail to capture complex spatial-temporal relationships between imaging modalities [64]. Future research should apply consensus clustering or MRICIs to schizophrenia subtyping to clarify whether the identified neurobiological differences are between patients or a result of methodological differences.

At the same time, while these studies demonstrate distinct subtypes differentiated by specific biomarkers, some of the findings may reflect regional variations within a larger, interconnected neural system rather than fully independent markers. For example, rs-fMRI patterns in the right vmPFC were found to be a stable predictor of subgroup membership in schizophrenia patients, with another study finding thalamic, anterior cingulate, and STG atrophy as another potential marker for subtyping [29, 31]. The vmPFC has previously been implicated in affect regulation and modulation of subcortical limbic activity [66–67]. Similarly, the anterior cingulate, thalamus and STG have been jointly implicated in large-scale cortico-limbic regulatory networks involved in affective salience processing and emotion regulation [68–70]. Both studies implicate related circuitry central to affective modulation, yet define different subtype boundaries, suggesting that these subtyping frameworks may map regions of the same distributed regulatory network rather than isolate mutually exclusive biomarkers.

Treatment and Machine Learning

ML literature has demonstrated moderate to high accuracy in predicting response to antipsychotic and neuromodulator interventions [17, 40, 41]. Across modalities, predictive models consistently implicate distributed neurobiological features rather than symptom profiles alone, suggesting that treatment response reflects underlying neurobiological heterogeneity [38, 42, 43]. Structural and functional markers have been used to forecast outcomes for antipsychotic, ECT, and rTMS, supporting the presence of transdiagnostic predictive signatures that may inform individualized treatment selection. Despite these promising showcases of ML applications, most treatment-prediction studies were retrospective or cross-sectional, limiting generalizability and potentially inflating performance estimates. Sample sizes were often modest, with limited external validity across cohorts. In addition, substantial heterogeneity in preprocessing and feature selection methods reduces reproducibility and comparability across models. Finally, few studies have tested ML-guided treatment selection prospectively in real-world clinical settings. In the future prospective, longitudinal validation and standardization frameworks are necessary before ML tools can be reliably integrated into clinical treatment planning.

Conclusions

This review highlights the potential of ML to clarify the neurobiological heterogeneity of schizophrenia and its implications for individualized treatment. Evidence supports the existence of distinct structural and functional subtypes, each associated with different symptom patterns and potential therapeutic targets. Though promising, challenges remain, such as inconsistent ML models, which limits comparability across studies. Samples were cross-sectional or done retrospectively from previously collected datasets, which limits generalizability. Predictive models varied widely in their preprocessing, feature selection, and validation procedures, and often lacked clinical integration. Finally, clinical interpretability and implementation remain limited, highlighting the need for larger multimodal, longitudinal, and clinically integrated approaches. Though these are substantial limitations, ML is a tool for advancing treatment, and future research should continue developing clinically validated models that bridge the gap between computational advances and practical clinical treatment.

List of Abbreviations

CHIMERA: clustering of heterogeneous disease effects
CSF: cerebrospinal fluid
DMN:default mode network
dMRI: diffusion magnetic resonance imaging
DS: deficit schizophrenia

DTI: diffusion tensor imaging
ECT: electroconvulsive therapy
EEG: electroencephalography
fMRI: functional tensor imaging
GMV: gray matter volume
ML: machine learning
MRI: magnetic resonance imaging
MRICIs: magnetic resonance imaging composite indicators
NDS: no-deficit schizophrenia
rs-fMRI- resting state functional magnetic resonance imaging
SMN: somatomotor network
sMRI: structural resonance imaging
STC: superior temporal cortex
STG: superior temporal gyrus
VAN: ventral attention network
vmPFC: ventromedial prefrontal cortex
VSN: Visuo-spatial network

Conflicts of Interest
The authors declare that they have no conflicts of interest

Ethics Approval and/or Participant Consent
Because this was a literature review that involved no contact with participants, no ethical approval or consent needed to be considered.

Authors' Contributions
EA: made equal contributions to the conception and design of the work, drafting the manuscript as well as revising it critically and gave approval of the final version to be published.
RL: made equal contributions to the conception and design of the work, drafting the manuscript as well as revising it critically and gave approval of the final version to be published.

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References
[1] McCleery A, Nuechterlein KH. Cognitive impairment in psychotic illness: prevalence, profile of impairment, developmental course, and treatment considerations. Dialogues in clinical neuroscience. 2019;21(3): 239–48. https://doi.org/10.31887/DCNS.2019.21.3/amccleery
[2] Fang K, Wen B, Niu L, Wan B, Zhang W. Higher brain structural heterogeneity in schizophrenia. Frontiers in psychiatry. 2022;13:1017399. https://doi.org/10.3389/fpsyt.2022.1017399
[3] Ahmed AO, Strauss GP, Buchanan RW, Kirkpatrick B, Carpenter WT. Schizophrenia heterogeneity revisited: Clinical, cognitive, and psychosocial correlates of statistically-derived negative symptoms subgroups. Journal of psychiatric research. 2018;97:8–15. https://doi.org/10.1016/j.jpsychires.2017.11.004
[4] Alnæs D, Kaufmann T, van der Meer D, Córdova-Palomera A, Rokicki J, Moberget T, et al. Brain Heterogeneity in Schizophrenia and Its Association With Polygenic Risk. JAMA psychiatry (Chicago, Ill). 2019;76(7):739–48. https://doi.org/10.1001/jamapsychiatry.2019.0257
[5] Ruggeri M, Lasalvia A, Tansella M, Bonetto C, Abate M, Thorincroft G, et al. Heterogeneity of outcomes in schizophrenia: 3-year follow-up of treated prevalent cases. British journal of psychiatry. 2004;184(1):48–57. https://doi.org/10.1192/bjp.184.1.48
[6] Crow TJ. The Two-Syndrome Concept: Origins and Current Status. Schizophrenia bulletin. 1985;11(3):471–86. https://doi.org/10.1093/schbul/11.3.471
[7] du Plessis S, Chand GB, Erus G, Phahladira L, Luckhoff HK, Smit R, et al. Two Neuroanatomical Signatures in Schizophrenia: Expression Strengths Over the First 2 Years of Treatment and Their Relationships to Neurodevelopmental Compromise and Antipsychotic Treatment. Schizophrenia bulletin. 2023;49(4):1067–77. https://doi.org/10.1093/schbul/sbad040
[8] Mathalon DH, Ford JM. Neurobiology of Schizophrenia: Search for the Elusive Correlation with Symptoms. Frontiers in human neuroscience. 2012;6:136. https://doi.org/10.3389/fnhum.2012.00136
[9] Bombin I. Significance and Meaning of Neurological Signs in Schizophrenia: Two Decades Later. Schizophrenia bulletin. 2005;31(4):962–77. https://doi.org/10.1093/schbul/sbi028
[10] Brugger SP, Howes OD. Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis. JAMA psychiatry (Chicago, Ill). 2017;74(11):1104–11. https://doi.org/10.1001/jamapsychiatry.2017.2663
[11] Case M, Stauffer VL, Ascher-Svanum H, Conley R, Kapur S, Kane JM, et al. The heterogeneity of antipsychotic response in the treatment of schizophrenia. Psychological medicine. 2011;41(6):1291–300. https://doi.org/10.1017/S0033291710001893
[12] Varol E, Sotiras A, Davatzikos C. HYDRA: Revealing heterogeneity of imaging and genetic patterns through a multiple max-margin discriminative analysis framework. NeuroImage (Orlando, Fla). 2017;145(Pt B):346–64. https://doi.org/10.1016/j.neuroimage.2016.02.041
[13] Le Bail S, Mouden J, Gaillard M, Dupouy J. Clinical practical guide for the management of an acute psychiatric crisis in primary care: A meta-review of systematic literature. Presse Médicale Open. 2023;4. https://doi.org/10.1016/j.lpmope.2023.100043

[14] Allott K, Chopra S, Rogers J, Dauvermann MR, Clark SR. Advancing understanding of the mechanisms of antipsychotic-associated cognitive impairment to minimise harm: A call to action. Molecular psychiatry. 2024;29(8):2571–4. https://doi.org/10.1038/s41380-024-02503-x

[15] Samara MT, Leucht S, Leeflang MM, et al. Early improvement as a predictor of later response to antipsychotics in schizophrenia: A diagnostic test review. *Am J Psychiatry.* 2015;172(7):617–629. https://doi.org/10.1176/appi.ajp.2015.14101329

[16] Chen Y, Liu S, Zhang B, Zhao G, Zhang Z, Li S, et al. Baseline symptom-related white matter tracts predict individualized treatment response to 12-week antipsychotic monotherapies in first-episode schizophrenia. Translational psychiatry. 2024;14(1). https://doi.org/10.1038/s41398-023-02714-w

[17] Cao B, Cho RY, Chen D, Xiu M, Wang L, Soares JC, et al. Treatment response prediction and individualized identification of first-episode drug-naïve schizophrenia using brain functional connectivity. Molecular psychiatry. 2020;25(4):906–13. https://doi.org/10.1038/s41380-018-0106-5

[18] Kim EY, Kim J, Jeong JH, Jang J, Kang N, Seo J, et al. Machine learning prediction model of the treatment response in schizophrenia reveals the importance of metabolic and subjective characteristics. Schizophrenia research. 2025;275:146–55. https://doi.org/10.1016/j.schres.2024.12.018

[19] Wu CS, Luedtke AR, Sadikova E, Tsai HJ, Liao SC, Liu CC, et al. Development and Validation of a Machine Learning Individualized Treatment Rule in First-Episode Schizophrenia. JAMA network open. 2020;3(2):e1921660. https://doi.org/10.1001/jamanetworkopen.2019.21660

[20] Voineskos AN, Hawco C, Neufeld NH, Turner JA, Ameis SH, Anticevic A, et al. Functional magnetic resonance imaging in schizophrenia: current evidence, methodological advances, limitations and future directions. World psychiatry. 2024;23(1):26–51. https://doi.org/10.1002/wps.21159

[21] Chand GB, Dwyer DB, Erus G, Sotiras A, Varol E, Srinivasan D, et al. Two distinct neuroanatomical subtypes of schizophrenia revealed using machine learning. Brain. 2020;143(3):1027–38. https://doi.org/10.1093/brain/awaa025

[22] Chand GB, Singhal P, Dwyer DB, Wen J, Erus G, Doshi J, et al. Schizophrenia Imaging Signatures and Their Associations With Cognition, Psychopathology, and Genetics in the General Population. The American journal of psychiatry. 2022;179(9):650–60. https://doi.org/10.1176/appi.ajp.21070686

[23] Chew QH, Prakash KNB, Koh LY, Chilla G, Yeow LY, Sim K. Neuroanatomical subtypes of schizophrenia and relationship with illness duration and deficit status. Schizophrenia research. 2022;248:107–13. https://doi.org/10.1016/j.schres.2022.08.004

[24] Dwyer DB, Cabral C, Kambeitz-Ilankovic L, Sanfelici R, Kambeitz J, Calhoun V, et al. Brain Subtyping Enhances The Neuroanatomical Discrimination of Schizophrenia. Schizophrenia bulletin. 2018;44(5):1060–9. https://doi.org/10.1093/schbul/sby008

[25] Wang Y, Feng S, Huang Y, Peng R, Liang L, Wang W, et al. Revealing multiple biological subtypes of schizophrenia through a data-driven approach. Journal of translational medicine. 2025;23(1). https://doi.org/10.1186/s12967-025-06503-5

[26] Zhao Q, Cao H, Zhang W, Li S, Xiao Y, Tamminga CA, et al. A subtype of institutionalized patients with schizophrenia characterized by pronounced subcortical and cognitive deficits. Neuropsychopharmacology. 2022;47(12):2024–32. https://doi.org/10.1038/s41386-022-01300-w

[27] Yuchao Jiang, Cheng Luo, Jijun Wang, Lena Palaniyappan, Shitong Xiang, Jie Zhang, et al. Neurostructural subgroup in 4291 individuals with schizophrenia identified using the subtype and stage inference algorithm. Nature Communications. 2024;15. https://doi.org/10.1038/s41467-024-50267-3

[28] Chai C, Ding H, Du X, Xie Y, Man W, Zhang Y, et al. Dissociation between neuroanatomical and symptomatic subtypes in schizophrenia. European psychiatry. 2023;66(1). https://doi.org/10.1192/j.eurpsy.2023.2446

[29] Chen J, Patil KR, Weis S, Sim K, Nickl-Jockschat T, Zhou J, et al. Neurobiological divergence of the positive and negative schizophrenia subtypes identified on a new factor structure of psychopathology using non-negative factorization: An international machine learning study. Biological Psychiatry (2020). 2020;87(3):282–93. https://doi.org/10.1016/j.biopsych.2019.08.031

[30] Gao J, Jiang R, Tang X, Chen J, Yu M, Zhou C, et al. A neuromarker for deficit syndrome in schizophrenia from a combination of structural and functional magnetic resonance imaging. CNS Neuroscience & Therapeutics. 2023;29(12):3774–85. https://doi.org/10.1111/cns.14297

[31] Honnorat N, Dong A, Meisenzahl-Lechner E, Koutsouleris N, Davatzikos C. Neuroanatomical heterogeneity of schizophrenia revealed by semi-supervised machine learning methods. Schizophrenia Research. 2019;214:43–50. https://doi.org/10.1016/j.schres.2017.12.008

[32] Alexandros Lalousis P, Schmaal L, Wood SJ, L.E.P Reniers R, Cropley VL, Watson A, et al. Inflammatory subgroups of schizophrenia and their association with brain structure: A semi-supervised machine learning examination of heterogeneity. Brain, Behavior, and Immunity. 2023;113:166–75. https://doi.org/10.1016/j.bbi.2023.06.023

[33] Xiao Y, Liao W, Long Z, Tao B, Zhao Q, Luo C, et al. Subtyping Schizophrenia Patients Based on Patterns of Structural Brain Alterations. Schizophrenia Bulletin. 2022;48(1):241–50. https://doi.org/10.1093/schbul/sbab110

[34] Jiang Y, Luo C, Wang J, Palaniyappan L, Chang X, Xiang S, et al. Neurostructural subgroup in 4291 individuals with schizophrenia identified using the subtype and stage inference algorithm. Nature Communications. 2024;15(1). https://doi.org/10.1038/s41467-024-50267-3

[35] Pan Y, Pu W, Chen X, Huang X, Cai Y, Tao H, et al. Morphological profiling of schizophrenia: Cluster analysis of MRI-based cortical thickness data. Schizophrenia Bulletin. 2020;46(3):623–32. https://doi.org/10.1093/schbul/sbz112

[36] Sugihara G, Oishi N, Son S, Kubota M, Takahashi H, Murai T. Distinct patterns of cerebral cortical thinning in schizophrenia: A neuroimaging data-driven approach. Schizophrenia Bulletin. 2017;43(4):sbw176-906. https://doi.org/10.1093/schbul/sbw176

[37] Talpalaru A, Bhagwat N, Devenyi GA, Lepage M, Chakravarty MM. Identifying schizophrenia subgroups using clustering and supervised learning. Schizophrenia Research. 2019;214:51–9. https://doi.org/10.1016/j.schres.2019.05.044

[38] Wei L, Liu W, Li X, Zhang Y, Luo Y, Xie Y, et al. Deciphering the heterogeneity of schizophrenia: A multimodal and multivariate neuroimaging framework for unveiling brain-symptom relationships and underlying subtypes. Schizophrenia Bulletin. 2025. https://doi.org/10.1093/schbul/sbaf037

[39] Sun H, Lui S, Yao L, Deng W, Xiao Y, Zhang W, et al. Two patterns of white matter abnormalities in medication-naive patients with first-episode schizophrenia revealed by diffusion tensor imaging and cluster analysis. JAMA Psychiatry (Chicago, Ill). 2015;72(7):678. https://doi.org/10.1001/jamapsychiatry.2015.0505

[40] Li P, Jing RX, Zhao RJ, et al. Electroconvulsive therapy-induced brain functional connectivity predicts therapeutic efficacy in patients with schizophrenia: A multivariate pattern recognition study. NPJ Schizophr. 2017;3:21. https://doi.org/10.1038/s41537-017-0023-7

[41] Chen Y, Liu S, Zhang B, Zhao G, Zhang Z, Li S, et al. Baseline symptom-related white matter tracts predict individualized treatment response to 12-week antipsychotic monotherapies in first-episode schizophrenia. Transl Psychiatry. 2024;14(1):23. https://doi.org/10.1038/s41398-023-02714-w

[42] Jiang Y, Wang J, Zhou E, et al. Neuroimaging biomarkers define neurophysiological subtypes with distinct trajectories in schizophrenia. Nat Ment Health. 2023;1:186-199. \https://doi.org/10.1038/s44220-023-00024-0

[43] Koutsouleris N, Meisenzahl EM, Borgwardt S, et al. Predicting response to repetitive transcranial magnetic stimulation in patients with schizophrenia using structural magnetic resonance imaging: A multisite machine learning analysis. Schizophrenia Bulletin. 2018;44(5):1023–1033. https://doi.org/10.1093/schbul/sbx114

[44] Jirsaraie RJ, Sheffield JM, Barch DM. Neural correlates of global and specific cognitive deficits in schizophrenia. Schizophrenia Research. 2018; 201:237–42. https://doi.org/10.1016/j.schres.2018.06.017

[45] Guimond S, Chakravarty MM, Bergeron-Gagnon L, Patel R, Lepage M. Verbal memory impairments in schizophrenia associated with cortical thinning. NeuroImage clinical. 2016;11(C):20–9. https://doi.org/10.1016/j.nicl.2015.12.010

[46] Rüsch N, Spoletini I, Wilke M, Bria P, Di Paola M, Di Iulio F, et al. Prefrontal–thalamic–cerebellar gray matter networks and executive functioning in schizophrenia. Schizophrenia research. 2007; 93(1):79–89. https://doi.org/10.1016/j.schres.2007.01.029

[47] Penadés R, Pujol N, Catalán R, Massana G, Rametti G, García-Rizo C, et al. Brain effects of cognitive remediation therapy in schizophrenia: A structural and functional neuroimaging study. Biological Psychiatry. 2013;73(10):1015–23. https://doi.org/10.1016/j.biopsych.2013.01.017

[48] Fan F, Zou Y, Tan Y, Hong LE, Tan S. Computerized cognitive remediation therapy effects on resting state brain activity and cognition in schizophrenia. Scientific Reports. 2017;7(1) https://doi.org/10.1038/s41598-017-04829-9

[49] Weilnhammer V, Röd L, Eckert AL, Stuke H, Heinz A, Sterzer P. Psychotic experiences in schizophrenia and sensitivity to sensory evidence. Schizophrenia Bulletin. 2020;46(4):927–36. https://doi.org/10.1093/schbul/sbaa003

[50] Rössler J, Rössler W, Seifritz E, Unterrassner L, Wyss T, Haker H, et al. Dopamine-induced dysconnectivity between salience network and auditory cortex in subjects with psychotic-like experiences: A randomized double-blind placebo-controlled study.

Schizophrenia Bulletin. 2020;46(3):732–40. https://doi.org/10.1093/schbul/sbz110
[51] Di Sero A, Jørgensen KN, Nerland S, Melle I, Andreassen OA, Jovicich J, et al. Antipsychotic treatment and basal ganglia volumes: Exploring the role of receptor occupancy, dosage and remission status. Schizophrenia Research. 2019;208:114–23. https://doi.org/10.1016/j.schres.2019.04.002
[52] Andersen HG, Raghava JM, Svarer C, Wulff S, Johansen LB, Antonsen PK, et al. Striatal volume increase after six weeks of selective dopamine D2/3 receptor blockade in first-episode, antipsychotic-naive schizophrenia patients. Frontiers in Neuroscience. 2020;14:484. https://doi.org/10.3389/fnins.2020.00484
[53] Chopra S, Fornito A, Francey SM, O'Donoghue B, Cropley V, Nelson B, et al. Differentiating the effect of antipsychotic medication and illness on brain volume reductions in first-episode psychosis: A Longitudinal, Randomised, Triple-blind, Placebo-controlled MRI Study. Neuropsychopharmacology. 2021;46(8):1494–501. https://doi.org/10.1038/s41386-021-00980-0
[54] Tang Y, Li Y, Cao P, Dong Y, Xu G, Si Q, et al. Striatum and globus pallidus structural abnormalities in schizophrenia: A retrospective study of the different stages of the disease. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2024;133. https://doi.org/10.1016/j.pnpbp.2024.111022
[55] Yang C, Tang J, Liu N, Yao L, Xu M, Sun H, et al. Yang C, Tang J, Liu N, Yao L, Xu M, Sun H, Tao B, Gong Q, Cao H, Zhang W, Lui S. The effects of antipsychotic treatment on the brain of patients with first-episode schizophrenia: a selective review of longitudinal MRI studies. Frontiers in Psychiatry. 2021;12:593703. https://doi.org/10.3389/fpsyt.2021.593703
[56] Yesilkaya UH. Enlarged basal ganglia in drug-naïve patients with first-episode psychosis immediately upon symptom onset. Düşünen Adam. 2024;37(1):15–24. https://doi.org/10.14744/DAJPNS.2024.00233
[57] Sarpal DK, Robinson DG, Lencz T, Argyelan M, Ikuta T, Karlsgodt K, et al. Antipsychotic treatment and functional connectivity of the striatum in first-episode schizophrenia. JAMA psychiatry. 2015;72(1):5. https://doi.org/10.1001/jamapsychiatry.2014.1734
[58] Hutcheson NL, Clark DG, Bolding MS, White DM, Lahti AC. Basal ganglia volume in unmedicated patients with schizophrenia is associated with treatment response to antipsychotic medication. Psychiatry Research Neuroimaging. 2014;221(1):6–12. https://doi.org/10.1016/j.pscychresns.2013.10.002
[59] Ferri J, Ford JM, Roach BJ, Turner JA, van Erp TG, Voyvodic J, et al. Resting-state thalamic dysconnectivity in schizophrenia and relationships with symptoms. Psychological Medicine. 2018;48(15):2492–9. https://doi.org/10.1017/S003329171800003X
[60] Shukla DK, Chiappelli JJ, Sampath H, Kochunov P, Hare SM, Wisner K, Rowland LM, Hong LE. Aberrant frontostriatal connectivity in negative symptoms of schizophrenia. Schizophrenia bulletin. 2019 Sep 11;45(5):1051-9. https://doi.org/10.1093/schbul/sby165
[61] Nakuci J, Rahnev D. A practical guide to identifying robust clusters in neuroimaging data. Human Brain Mapping. 2025;46(13):e70330-n/a. https://doi.org/10.3389/fnhum.2025.1552178
[62] Lei D, Pinaya WHL, Young J, Amelsvoort T, Marcelis M, Donohoe G, et al. Integrating machining learning and multimodal neuroimaging to detect schizophrenia at the level of the individual. Human Brain Mapping. 2020;41(5):1119–35. https://doi.org/10.1002/hbm.24863
[63] Sui J, Yu Q, He H, Pearlson GD, Calhoun VD. A selective review of multimodal fusion methods in schizophrenia. Frontiers in Human Neuroscience. 2012;6:27. https://doi.org/10.3389/fnhum.2012.00027
[64] Bhattacharya S, Prusty S, Pande SP, Gulhane M, Lavate SH, Rakesh N, et al. Integration of multimodal imaging data with machine learning for improved diagnosis and prognosis in neuroimaging. Frontiers in Human Neuroscience. 2025;19:1552178. https://doi.org/10.3389/fnhum.2025.1552178
[65] Alexander L, Wood CM, Roberts AC. The ventromedial prefrontal cortex and emotion regulation: lost in translation? The Journal of Physiology. 2023;601(1):37–50. https://doi.org/10.1113/JP282627
[66] Gao K, Wong AB, Li S, Zhang Y, Zhang D. The ventromedial prefrontal cortex plays an important role in implicit emotion regulation: A focality-optimized multichannel tDCS study in anxiety individuals. Human Brain Mapping. 2024;45(13):e26812-n/a. https://doi.org/10.1002/hbm.26812
[67] Hiser J, Koenigs M. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. Biological Psychiatry. 2018;83(8):638–47. https://doi.org/10.1016/j.biopsych.2017.10.030
[68] Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in Cognitive Sciences. 2011;15(2):85–93. https://doi.org/10.1016/j.tics.2010.11.004
[69] Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends in Cognitive Sciences. 2011;15(10):483–506. https://doi.org/10.1016/j.tics.2011.08.003
[70] Palaniyappan L, Liddle PF. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. Journal of Psychiatry & Neuroscience. 2012;37(1):17–27. https://doi.org/10.1503/jpn.100176

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