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**Systematic Review**

# Impact of neuroanatomical alterations identified by advanced imaging on the diagnosis and management of schizophrenia: a systematic review of psychosocial interventions and pharmacological therapies

**Rebeca Rosas Hernández[1]*, Luisana Darionara Maldonado De Santiago[2], Dario Javier Caguate Miranda[3], Melanie Betsabe Orellana Velasco[3], Juan David Alzate Maldonado[3], Dianna Mishell Loor Arroba[4], Saltos Hernández Milton Diego[5]**

[1]School of Health Sciences, Universidad del Valle de México campus, San Luis Potosí, México
[2]Medical Department, Hospital de lota, Chile
[3]Medical Department, Universidad de las Américas, Quito, Ecuador
[4]Independent Investigator, Ecuador
[5]Medical Department, Ministerio De Salud Pública, Ecuador

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***Correspondence:**
Dr. Rebeca Rosas Hernández,
E-mail: rebeca.rosas@uvmnet.edu



## ABSTRACT

We aim to systematically evaluate neuroanatomical alterations identified through advanced imaging on the diagnosis and management of schizophrenia. Neuroimaging advancements of magnetic resonance imaging (MRI), positron emission tomography (PET) and diffusion tensor imaging have made it possible to reveal in-depth structural and functional abnormalities such as reduced grey matter in the prefrontal cortex and hippocampus or ventricular enlargement and disrupted white matter tracts such as in schizophrenia case. Key symptoms such as disordered behaviour, hallucinations, and cognitive deficiencies are correlated with these alterations. Morphological features are also associated with neurotransmitter dysregulation specifically about dopamine and glutamate. The review also looks at pharmacological treatments like antipsychotics and psychosocial methods like cognitive behavioural therapy emphasising their varying effectiveness in treating the complex symptomatology of schizophrenia. Although there is potential for individualized treatment when neuroimaging results are integrated with clinical techniques but there are still obstacles to putting these insights into practice, especially in areas with low resources.

**Keywords:** Impact of neuroimaging advancements, Structural and functional brain alterations, Neurotransmitter dysregulation, Schizophrenia symptoms correlation, Pharmacological therapies, Psychosocial interventions

## INTRODUCTION

Schizophrenia is a psychiatric disorder, and is marked by hallucinations delusions, and cognitive dysfunction which is seen to impact approximately 21 million people worldwide. It is counted among the top 10 causes of disability, disproportionately affecting individuals in their most productive years between the ages of 25 and 54. Economic burden is staggering with United States reporting an annual cost of $281.6 billion in 2020 encompassing direct medical expenses and indirect costs such as lost productivity.[1] For individuals diagnosed at 25 lifetime costs are estimated at $3.8 million per person. Aetiology of schizophrenia involves a complex interplay of genetic and neurobiological along with environmental factors. It comes with estimated heritability of 79% specific genetic variations including disruptions in the DISC1 and NRG1 genes, are strongly implicated. Neurodevelopmental disruptions, such as obstetric complications leading to fatal hypoxia which increase susceptibility.[2] Environmental triggers including prenatal infections (e.g., *Toxoplasma gondii*) and early-life

stressors which further elevate risk. Sociocultural factors like urban living, social isolation and migration also contribute. Neurobiological studies show dopamine dysregulation, glutamate abnormalities, and structural changes such as reduced grey matter in key brain regions which points toward multifactorial origin for this debilitating disorder. Advancements in neuroimaging show structural and functional brain abnormalities in individuals with schizophrenia. Reductions in gray matter in regions like the prefrontal cortex and hippocampus are linked to cognitive impairments while hyperactivity in the mesolimbic dopamine system drives positive symptoms such as delusions and hallucinations. Treatment outcomes remain inconsistent with high rates of relapse and treatment resistance.[3]

## METHODS

### *Search strategy*

We searched on PubMed and Google scholar to cover pertinent literature. In conjunction with Boolean operators AND, OR NOT, our major key terms were schizophrenia," "neuroimaging," "functional magnetic resonance imaging (MRI)," "psychosocial interventions," and "pharmacological treatments" were employed.

**Table 1: Designed search string designed by primary and secondary key terms.**

| Primary key terms | Secondary key terms | String Mesh |
|---|---|---|
| **Schizophrenia** | Cognitive impairments | "Schizophrenia AND neuroanatomy", "Schizophrenia AND cortical gray matter", "Schizophrenia AND hippocampus shrinkage", "Schizophrenia AND ventricular enlargement" |
| **Ventricular enlargement** | Temporal lobe | "Schizophrenia AND ventricular enlargement", "Schizophrenia AND temporal lobe", "Schizophrenia AND executive functions", "Hippocampus AND emotional regulation" |
| **Cortical gray matter** | Prefrontal cortex | "Cognitive deficits AND schizophrenia", "Schizophrenia AND prefrontal cortex", "White matter tracts AND schizophrenia", "Synaptic dysfunction AND glutamate" |
| **Prefrontal cortex** | Hippocampal circuits | "Prefrontal cortex AND executive dysfunction", "Hippocampal shrinkage AND schizophrenia", "Structural MRI AND schizophrenia", "Neurodevelopmental changes AND schizophrenia" |
| **Hippocampus** | Arcuate fasciculus | "Schizophrenia AND arcuate fasciculus", "White matter abnormalities AND schizophrenia", "Neurotransmitter dysregulation AND dopamine", "DTI AND fractional anisotropy" |
| **Amygdala** | Default mode network (DMN) | "Amygdala AND emotional regulation", "DMN connectivity AND schizophrenia", "Synaptic pruning AND schizophrenia", "PANSS scale AND symptom severity" |
| **White matter tracts** | Synaptic pruning | "White matter pathways AND schizophrenia", "Schizophrenia AND cognitive symptoms", "Schizophrenia AND neuroinflammation", "Dopamine signaling AND positive symptoms" |
| **Dopamine dysregulation** | Neurotransmitter function | "Schizophrenia AND glutamate signaling", "Schizophrenia AND dopamine hypoactivity", "MRS AND neuronal dysfunction", "Neurocognitive testing AND schizophrenia" |
| **Glutamate signaling** | Executive functions | "Executive dysfunction AND schizophrenia", "Cortical thinning AND schizophrenia", "AI in schizophrenia diagnosis", "PET imaging AND dopamine dysregulation" |
| **Diffusion tensor imaging (DTI)** | Fractional anisotropy | "DTI AND schizophrenia", "Fractional anisotropy AND schizophrenia", "Neuroimaging AND schizophrenia biomarkers", "Schizophrenia AND neural connectivity" |
| **Neuroimaging** | Cognitive flexibility | "fMRI AND schizophrenia", "PET AND metabolic activity in schizophrenia", "Neuroimaging AND default mode network", "Schizophrenia AND Wisconsin Card Sorting Test (WCST)" |
| **Magnetic resonance imaging (MRI)** | Neural connectivity | "MRI AND schizophrenia progression", "Schizophrenia AND brain volume loss", "Cognitive impairment AND schizophrenia biomarkers", "CSF biomarkers AND inflammation" |
| **Functional MRI (fMRI)** | Wisconsin card sorting test (WCST) | "Schizophrenia AND clinical interviews", "PANSS AND symptom clusters", "AI tools AND neuroimaging", "22q11.2 deletion syndrome AND schizophrenia risk" |
| **Positron emission tomography (PET)** | Neurodevelopmental theories | "PET AND schizophrenia dopamine", "Schizophrenia AND neurodevelopmental abnormalities", "Excessive synaptic pruning AND schizophrenia", "Neuroleptic medications AND atrophy" |

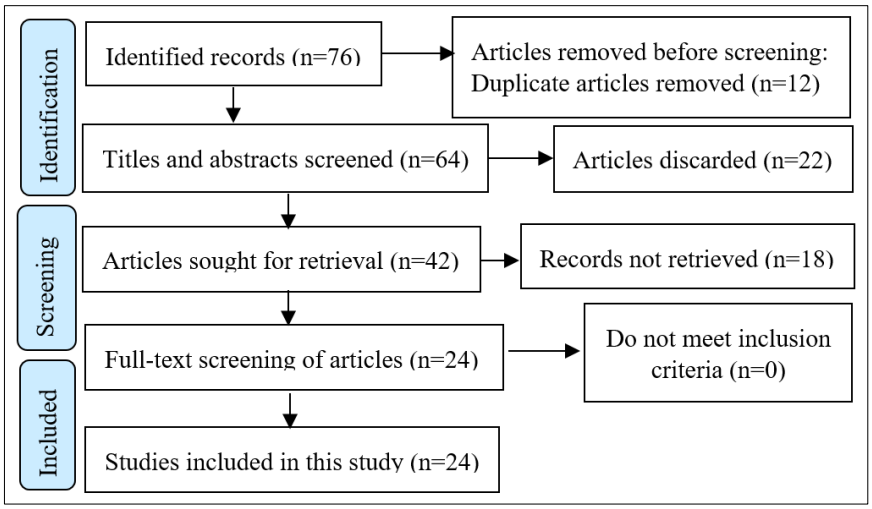


**Figure 1: PRISMA flow diagram.**

***Data extraction***

To capture a variety of studies we included Medical Subject Headings (MeSH) terminology. Filters for language (English) and publication date (last 10 years) were applied.

***Inclusion and exclusion criteria***

Studies that assessed pharmaceutical or psychosocial therapies, had well-defined outcomes and concentrated on imaging abnormalities associated with schizophrenia were included. We gave priority to studies that used cutting-edge imaging techniques like positron emission tomography (PET), diffusion tensor imaging (DTI), or functional magnetic resonance imaging (fMRI). We did not consider case reports, unpublished papers, grey literature or unauthentic papers. These standards were created to guarantee that the analysis was pertinent to the goals of the study and to narrow its scope. Qualitative data was extracted for this paper.

***Quality assessment***

Validated instruments were used to assess the quality of the included studies. To keep the review process transparent, we followed PRISMA guidelines. ROBINS-I was used to analyze potential biases in non-randomized research while imaging-specific criteria were used for studies that primarily focused on diagnostic or therapeutic imaging. The validity and dependability of the conclusions derived from the review were guaranteed by quality assessment.

## RESULTS

***Neuroanatomical alterations in schizophrenia***

Schizophrenia is closely associated with distinct anatomical alterations in both gray and white matter, contributing to the disorder's complex symptomatology. One of the most consistent and clinically significant findings is the enlargement of the ventricles in chronic cases which reflects substantial brain volume loss. Structural MRI studies showed reduction of cortical gray matter within the frontal and temporal lobes which is often accompanied by an overall decrease in total hemispheric volume. Reduction is most prominent in areas like the superior temporal gyrus which is a region important for auditory processing and language.[4] Hippocampus and amygdala have a role of memory and emotional regulation which also consistently show shrinkage correlating with cognitive and affective disturbances commonly seen in schizophrenia. Abnormalities of white matter are particularly evident in tracts that connect essential brain regions and white matter disruptions further show profound structural and functional brain alterations in schizophrenia which profoundly impact cognitive, emotional, and behavioral functions. Prefrontal cortex and hippocampus show reductions in gray matter with the prefrontal cortex vital for executive functions such as decision-making and impulse control undergoing marked atrophy. Atrophy is linked with deficits in planning problem-solving and other executive functions. Hippocampal shrinkage impairs memory formation and emotional regulation while exacerbating the disorder's cognitive and emotional symptoms.[5]

Progressive ventricular enlargement indicates global brain shrinkage or disturbed neural development which is frequently the defining feature of structural alterations associated with schizophrenia. People with more severe clinical presentations including noticeable negative symptoms including apathy, less emotional expression and decreased social interaction are more likely to exhibit this trait. Schizophrenia is characterized by notable abnormalities in neural connections in important brain networks while including the default mode network (DMN), which controls social cognition and self-referential thought.[6,7] Disorder is characterized by disorganized thinking and perception because of impaired

communication between the prefrontal cortex and thalamus which hinders the brain's capacity to integrate sensory and cognitive information.[8]

The pathophysiology of schizophrenia is influenced by neurotransmitter imbalance. Positive symptoms such as hallucinations and delusions are supported by dopamine hyperactivity in mesolimbic pathways whereas negative symptoms and cognitive deficiencies are caused by dopamine hypoactivity in prefrontal regions. Glutamate signalling anomalies intensify synaptic dysfunction, exacerbating emotional and cognitive disorders. Structural alterations seen in the brain are closely related to these neurochemical disturbances. While negative symptoms stem from cortical and subcortical atrophy, positive symptoms, such hallucinations which are linked to increased activity in sensory and associative regions. Disruptions in the prefrontal-thalamic and hippocampus circuits are closely associated with cognitive impairments, which include executive function, memory, and attention deficiencies.[9,10]

Structural changes of white matter pathways, further complicate the disorder. Disruptions in critical tracts such as the arcuate fasciculus, uncinate fasciculus, and fornix impair connectivity between the frontal, temporal, and limbic regions, which are essential for cognition, emotion, and behaviour regulation. Diffusion tensor imaging studies have identified reduced fractional anisotropy in these tracts, indicating compromised myelination or axonal integrity, which likely contributes to the cognitive deficits and disorganization seen in schizophrenia.

Longitudinal studies tracking first-episode patients reveal progressive cortical thinning and ventricular expansion over 5–10 years. This progression is more pronounced in severely ill individuals and it correlates with a decline in cognitive and functional capacities. During the prodromal phase abnormalities are concentrated in regions such as the temporal lobe, anterior cingulate cortex and parahippocampal gyrus. These regions continue to atrophy as the illness progresses which is indicative of the ongoing neurodegenerative process.[11,12]

The extensive brain shrinkage seen in schizophrenia cannot be entirely explained by the use of neuroleptic drugs even if they do contribute to some anatomical alterations such as the loss of caudate volume. According to neurodevelopmental theories, these structural alterations may be primarily caused by processes such excessive synaptic pruning, aberrant myelination, and neuroinflammation. In particular, executive failure and negative symptoms that are typical of schizophrenia are linked to cortical atrophy in regions such as the prefrontal cortex.

***Psychosocial interventions***

Neurobiological insights can help in advanced psychosocial therapies for schizophrenia to improve treatment results. Through processes shown by functional MRI studies which show increased prefrontal brain activity and prefrontal-limbic connectivity and both of which are essential for emotional regulation. Cognitive behavioural therapy (CBT) has been developed to target resistant symptoms. Even though symptoms severity has decreased but result variability still calls for stratified treatments that are in line with each person's unique neurobiological profile. Focus on enhancing functional connectivity within the metalizing network including the temporoparietal junction and medial prefrontal cortex, social skills training (SST) now includes neuro feedback and augmented reality. Family therapy and structured peer support programs have shown efficacy in reducing stress-induced neuroinflammation as demonstrated by neuroimaging evidence of decreased amygdala hyperactivity and improved anterior cingulate connectivity.[18] Such interventions also correlate with hippocampal neurogenesis which aim to foster resilience but it works effectively when initiated early. Emerging digital therapies including virtual reality (VR) and digital CBT are also emerged as cutting-edge solutions. VR therapies with real-time neuro feedback target social brain hypoactivity are seen in improving social interaction and paranoia desensitization while digital CBT integrated with EEG-guided neuro feedback enhances anterior cingulate and insular modulation while improving cognitive and emotional stability. Despite their potential, many strategies have issues with adherence and accessibility and when it comes to managing schizophrenia, these cutting-edge psychosocial techniques place a higher priority on neuronal plasticity, functional recovery, and improved quality of life.[19]

**Table 2: Neuroimaging advancements.**

| Tool/technique | Description | Examples |
|---|---|---|
| **Functional MRI (fMRI)** | Measures brain activity by detecting blood flow changes. It is critical in mapping brain functions, particularly in regions implicated in schizophrenia. | Example: Studies using fMRI show altered connectivity in the default mode network (DMN) and frontal lobe in patients with schizophrenia, impacting cognitive functions. |
| **Positron emission tomography (PET)** | Detects metabolic activity and neurotransmitter function, identifying dopamine dysregulation common in schizophrenia. | Example: PET imaging of dopamine receptors has been used to show altered dopaminergic signalling in schizophrenia, particularly in the striatum. |

Continued.

| Tool/technique | Description | Examples |
|---|---|---|
| **Diffusion tensor imaging (DTI)** | Visualizes white matter tracts, crucial for assessing brain connectivity, which is disrupted in schizophrenia. | Example: DTI studies show decreased fractional anisotropy in the prefrontal cortex and corpus callosum, correlating with cognitive dysfunction in schizophrenia. |
| **Magnetic resonance spectroscopy (MRS)** | Measures the concentration of metabolites, such as N-acetyl aspartate (NAA) and glutamate, which are often altered in schizophrenia. | Example: MRS has demonstrated decreased NAA levels in the frontal lobe of schizophrenia patients, reflecting neuronal dysfunction.[13] |

**Table 3: Diagnosis strategies.**

| Strategy | Description | Example |
|---|---|---|
| **Clinical interviews and symptom scales** | Structured diagnostic tools like the positive and negative syndrome scale (PANSS) assess symptom severity. | Example: A study used PANSS to differentiate between positive, negative, and cognitive symptoms in schizophrenia, helping to tailor treatment approaches. |
| **Genetic testing** | Identifying genetic risk factors, including copy number variations (CNVs) and single nucleotide polymorphisms (SNPs). | Example: Studies have linked the 22q11.2 deletion syndrome to a significantly higher risk of developing schizophrenia. |
| **Neurocognitive testing** | Assesses cognitive impairments (e.g., attention, executive function), which are central to schizophrenia pathology. | Example: Cognitive assessment tools like the Wisconsin card sorting test (WCST) are used to evaluate cognitive flexibility deficits in schizophrenia.[14] |
| **Biomarker research** | Investigates blood or cerebrospinal fluid (CSF) markers associated with schizophrenia. | Example: Studies have shown altered levels of immune markers such as interleukin-6 (IL-6) in CSF, suggesting an inflammatory component in schizophrenia.[15] |

**Table 4: AI and machine learning tools.**

| Tool/algorithm | Description | Example |
|---|---|---|
| **Convolutional neural networks (CNNs)** | Used to analyse complex neuroimaging data like fMRI, identifying patterns that correlate with schizophrenia diagnosis. | Example: A CNN model analysing structural MRI scans identified structural changes in the hippocampus and thalamus of schizophrenia patients, with 85% accuracy in classification. |
| **Support vector machines (SVMs)** | A machine learning algorithm used to classify neuroimaging data and clinical features to predict schizophrenia onset. | Example: SVM has been used with structural MRI data to predict conversion from at-risk states to schizophrenia with high sensitivity and specificity. |
| **Random forests** | A robust ensemble machine learning method used to classify patients based on neuroimaging and genetic data. | Example: Random forest models applied to genetic data identified key SNPs linked to schizophrenia, achieving predictive accuracies of up to 90%. |
| **Deep learning for multimodal data** | Integrates neuroimaging data with clinical information for more accurate diagnosis and prediction of schizophrenia. | Example: A deep learning model integrating MRI and clinical features identified early biomarkers of schizophrenia with 92% accuracy in a cohort of high-risk patients.[16] |

**Table 5: Biopsy and other diagnostic methods.**

| Test | Description | Example |
|---|---|---|
| **Brain biopsy** | Invasive procedure to exclude other pathologies when diagnosis is unclear. Rarely used in schizophrenia. | Example: Brain biopsy has been used in cases where neurodegenerative diseases were suspected, but it's not a standard procedure for schizophrenia diagnosis. |
| **Cerebrospinal fluid (CSF) analysis** | Detects inflammatory or immune markers that could indicate an autoimmune or neuroinflammatory component. | Example: Elevated levels of interleukin-1β (IL-1β) in CSF have been found in schizophrenia, suggesting an inflammatory response. |

Continued.

| Test | Description | Example |
|---|---|---|
| **Electroencephalogram (EEG)** | Records electrical activity in the brain; can help identify abnormal neural oscillations often seen in schizophrenia. | Example: EEG studies have shown altered theta and gamma waves in schizophrenia, linked to impaired cognition and perception.[17] |

***Treatment of schizophrenia***

Schizophrenia complex psychiatric disorder and it require individualized and long-term treatment plans cantered on pharmacological interventions. Primary therapeutic approach includes antipsychotic medications which modulate neurotransmitter pathways implicated in the disorder. Its medications are categorized into first-generation (typical) and second- or third-generation (atypical) antipsychotics and each with distinct mechanisms of action (MOA), efficacy profiles and adverse effect risks. Treatment is guided by the nature of symptoms—positive, negative, or cognitive deficits—and the patient's response to previous interventions.

*First-generation antipsychotics (typical antipsychotics)*

Typical antipsychotics primarily target dopaminergic hyperactivity in the mesolimbic pathway through potent D2 receptor antagonism. Examples include haloperidol, chlorpromazine, and fluphenazine. These therapeutic interventions are seen to effectively reduce positive symptoms such as hallucinations and delusions but have limited efficacy for negative or cognitive symptoms. The strong D2 blockade disrupts dopamine function in other brain regions of a nigrostriatal pathway which lead to significant extrapyramidal side effects (EPS), including dystonia, akathisia and tardive dyskinesia. Trade-off between therapeutic benefit and risk of motor side effects often limits their use in long-term management and continued utility lies in acute psychotic episodes or in situations where newer agents are contraindicated.[20]

*Second-generation antipsychotics (atypical anti-psychotics)*

Atypical antipsychotics have become the cornerstone of schizophrenia treatment due to their dual action on D2 dopamine and 5-HT2A serotonin receptors. In addition to addressing positive symptoms, pharmacodynamic profile provides better treatment of negative symptoms as flattened affect and social disengagement. Olanzapine, risperidone, quetiapine, and clozapine are a few examples. Clozapine is mostly used among these for treating treatment-resistant schizophrenia and lowering suicidality but because of the risk of agranulocytosis which needs to be closely monitored. Even while atypical antipsychotics are more effective but they might still cause problems such as weight gain, dyslipidaemia and insulin resistance are examples of metabolic side effects that are serious concerns, while using medications like quetiapine and olanzapine. Because of the increased cardiovascular morbidity caused by these metabolic hazards, lifestyle modifications and routine monitoring are required. Despite having lesser metabolic hazards, lurasidone and risperidone can nevertheless result in mild EPS at larger dosages, demonstrating the variation in tolerance within this class.[21]

*Third-generation antipsychotics*

Emerging third-generation antipsychotics, including aripiprazole, brexpiprazole, and cariprazine, offer a more nuanced approach to dopamine modulation. These agents act as partial agonists at D2 receptors, allowing for stabilization of dopaminergic activity. Unlike full antagonists, they reduce hyperactivity in the mesolimbic pathway while simultaneously enhancing dopamine transmission in the mesocortical pathway, addressing both positive and negative symptoms with improved tolerability. Additionally, their 5-HT1A agonism and 5-HT2A antagonism contribute to their efficacy in managing cognitive symptoms and mood stabilization. These medications exhibit a lower incidence of metabolic and motor side effects, making them a preferred choice for long-term therapy, particularly in younger patients or those with a high risk of side effects.

*Adjunctive therapies and challenges*

Adjunctive medications are critical in addressing comorbid conditions often seen in schizophrenia. Mood stabilizers such as lithium and valproate are used for co-occurring bipolar features, while SSRIs like fluoxetine manage depressive symptoms. Short-term use of benzodiazepines for instance lorazepam is employed for acute agitation although their addictive potential limits long-term use. Several issues regarding pharmacological treatment remain for instance side effects, stigma, and cognitive dysfunction affecting patients' recognition of the disease and therefore compliance with treatment. Consequently, there are such approaches as the formulation of long-acting injectable antipsychotics such as paliperidone palmitate or aripiprazole detachment that can contribute to the improvement of compliance.

***Critical considerations and future directions***

While current therapies provide substantial relief from psychotic symptoms, the management of cognitive and negative symptoms remains an unmet need. Neurotransmitters beyond dopamine such as glutamate and GABA are being explored to address these domains. Pharmacogenomics offers the potential for personalized medicine; tailoring treatments based on genetic markers to optimize efficacy and minimize side effects. Emerging therapies such as neuromodulation techniques which

include transcranial magnetic stimulation (TMS) in combination with psychopharmacology may further expand the therapeutic landscape to provide effective management.[22]

## CONCLUSION

Advanced neuroimaging has enhanced our understanding of schizophrenia's neuroanatomical underpinnings while providing critical information about this disease's diagnosis and management. Despite progress, integrating these findings into clinical practice remains challenging while continued research is necessary to bridge gaps between neuroimaging advancements and therapeutic applications to improve personalised treatment and patient outcomes.

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