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Neuroimaging in schizophrenia

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INTRODUCTION:

Psychotic disorders are mental illnesses characterized by difficulties in reality testing¹. Schizophrenia is a severe and chronic psychotic disorder with a life time prevalence of about 1%. Onset is typically in adolescence or early adulthood; characteristic symptoms include abnormally held beliefs (delusions), altered perceptions (hallucinations), disordered thinking, disorganized behavior (collectively positive symptoms) and deficits in motivation, affect, and socialization (negative symptoms). Diagnosis of schizophrenia, by the Diagnostic and Statistical Manual of mental disorders (DSM), 5th edition² requires the presence of at least 2 of these symptoms, along with a decline in functioning, lasting at least six months, and ensuring that these symptoms cannot be better explained by another medical disease, substance use or another psychiatric disorder. Impairments in cognition in recent years have emerged as central features underlying the disability in schizophrenia³.

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DISCLOSURE STATEMENT

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WHAT IS CURRENTLY KNOWN ABOUT THE NEUROBIOLOGY OF SCHIZOPHRENIA

Schizophrenia has been increasingly viewed as a disorder of brain development^{4–6}. Abnormalities in *early brain development*, around or before birth, as well as *late developmental* derailments around or prior to the onset of psychosis have been proposed. It has been suggested that programmed pruning during adolescence may be excessive leading to the emergence of the illness, consistent with observed reductions in cortical dendrite density⁷. *Post-illness onset* degenerative processes may also be involved⁸. Neuroimaging studies have the potential to examine predictions generated by these seemingly contrasting models. We will review the current status of the burgeoning imaging literature across several imaging modalities (structural, functional and neurochemical), which has accumulated during recent years to illuminate the putative causal mechanisms, which may help improve our approaches to diagnosis, outcome prediction, and treatment selection.

IMAGING BRAIN STRUCTURE AND WHITE MATTER CONNECTIONS

Brain structural abnormalities are widely reported in schizophrenia with large-scale meta-analyses detecting a smaller hippocampal volume in patients compared to controls, followed by smaller amygdala, thalamus, nucleus accumbens, and intracranial volumes, as well as larger pallidum and lateral ventricle volumes⁹. Individuals with schizophrenia also have widespread cortical thinning and smaller cortical surface area, with the largest effects observed in frontal and temporal lobe regions¹⁰. Differences in cortical thickness are found to be more regionally specific, whereas differences in cortical surface area are more global¹⁰. Cortical thickness reductions are also larger in individuals receiving antipsychotic medication and negatively correlate with medication dose, symptom severity, and duration of illness¹⁰. Advances in neuroimaging methods have also led to a dysconnectivity hypothesis of schizophrenia—whereby the disorder may involve abnormal or inefficient communication between functional brain regions¹¹ contributed by abnormalities in the underlying white matter connections. Notably Psychoradiology, a subspecialty of radiology pioneered by Gong et al, is showing promise in guiding clinical management of the psychiatric disorders^{12–14}. As one of most important tools for psychoradiology, diffusion tensor imaging (DTI) allows for the *in vivo* study of white matter microstructure. DTI studies of schizophrenia typically report significantly lower fractional anisotropy (FA, a value ranging from 0 to one which reflects the degree of freedom for water molecules to diffuse in all directions) in patients compared with controls, typically in the fiber tracts connecting prefrontal and temporal lobes^{15, 16}. However, recent meta-analytic findings suggest that FA decreases are more widespread in schizophrenia, affecting almost all major white matter regions with largest effects observed for cortical-thalamic and interhemispheric tracts, including the corona radiata and corpus callosum⁵.

Although structural and diffusion imaging studies have shed light on the underlying neurobiology of schizophrenia^{17–20}, the majority of these studies examine chronic patients and individuals taking anti-psychotic medications²¹. Therefore, it is difficult to identify the timing of brain changes and the effects of medication exposure. Additional studies

examining populations before illness onset, as well as longitudinal studies throughout the course of the illness, are warranted. Furthermore, advanced neuroimaging methodologies such as DTI are also limited in their ability to identify the type of underlying pathology. For example, lower FA may reflect abnormal fiber coherence or packing, or alterations of axonal integrity and/or myelination. Future studies using more advanced diffusion MRI methods, such as free-water imaging, may offer increased sensitivity to subtle brain abnormalities, as well as improved specificity to pathologies such as neuroinflammation or demyelination²².

IMAGING BRAIN FUNCTION AND PERFUSION

It is well established that brain function parallels changes in brain structure, which can be assessed using functional neuroimaging studies. Because cerebral blood flow is tightly coupled to brain metabolism, early neuroimaging studies measured cerebral blood flow using ¹³³Xenon inhalation²³ or various radiotracers in single photon emission tomography (SPECT)²⁴, while Positron Emission Tomography (PET) techniques were used to measure metabolism (¹¹C-glucose and fluorine-18 fluorodeoxyglucose tracers)²⁵ and blood flow (oxygen-15 tracer)²⁶. Advances in neuroscientific methods which improved on cost, time and patient burden have favored the use of two *in vivo* techniques; Blood Oxygenation Level Dependent (BOLD) functional MRI (fMRI) and Arterial Spin Labeled (ASL) perfusion MRI. These techniques provide robust, balanced (spatial and temporal resolution), and clinically relevant correlates of neural activity and microvascular function in schizophrenia. While fMRI can robustly measure neuronal activity indirectly through changes in blood flow and oxygen metabolism²⁷, ASL measures cerebral blood flow (CBF) directly by inverting the magnetization of the arterial blood water using radiofrequency (RF) pulses to create an endogenous diffusible tracer²⁸. Unlike PET or SPECT, fMRI and ASL are non-invasive and do not require ionizing radiation, relying rather on the magnetic properties of the brain's natural elements.

Alterations in brain metabolism and blood flow have been demonstrated in a meta-analysis of ¹³³Xenon, SPECT and PET studies, where Hill et al. (2014) identified evidence for a resting hypofrontality with small-to-medium effect sizes in patients with schizophrenia, with chronic patients showing the largest effects²⁹. Hill et al. (2004) also demonstrated evidence for task-activated hypofrontality, with medium effect size differences in executive, vigilance and memory tasks, and showed that poorer performance was associated with greater hypofrontality²⁹. In a meta-analysis of PET and fMRI studies of working memory in schizophrenia, Glahn et al. (2005) found that in addition to hypofrontality there is also increased activation in the anterior cingulate and left frontal pole regions³⁰. Abnormal resting state brain activity has also been reported in a meta-analysis of studies using PET, fMRI and ASL and the authors identified hypoactivation in the ventromedial prefrontal cortex, left hippocampus, posterior cingulate cortex, precuneus, and hyperactivation in bilateral lingual gyrus of schizophrenic patients compared to controls³¹. Lastly, in a systematic review of ASL imaging in schizophrenia, the authors identified convergent reductions in cerebral blood flow in the frontal lobe, left middle frontal gyrus, inferior frontal gyrus, lingual gyrus, cuneus, middle occipital gyrus, fusiform gyrus, anterior cingulate and parietal lobe, with the putamen as the only region showing increased CBF in schizophrenia³². The same study also found inconsistent results for middle temporal,

parahippocampal, precuneus and thalamic regions³². Taken together, functional imaging studies point towards altered metabolic or hemodynamic activity in frontal, cingulate, parietal and occipital brain regions with a few areas of hyperactivity, such as the putamen and sensorimotor regions, but more work is needed to determine the clinical implications of these observations.

IMAGING BRAIN CHEMISTRY

PET, SPECT and magnetic resonance spectroscopy (MRS) have been extensively employed to investigate chemical changes in the brain. PET imaging studies have examined the receptors of interest to schizophrenia, primarily dopamine, serotonin, GABA and glutamate. PET studies have provided direct evidence of D₂/D₃ receptors as the primary site of action of most antipsychotic drugs³³. Dopamine D₂ receptor density and occupancy of D₂ receptors by dopamine has been shown to be increased in schizophrenia patients³⁴ along with increased dopamine transmission³⁵. Although increased in patients, D₂ receptor density is not a consistent marker discriminating schizophrenia patients and controls³⁶. Striatal dopamine transporter availability is also not different between healthy controls and medication-naïve schizophrenia patients³⁷. By contrast, several studies have shown that schizophrenia patients show a modest but significant increase in dopamine synthesis capacity compared to controls³⁸.

Examinations of other neurotransmitter receptors have provided important leads in understanding the pathophysiology of schizophrenia. A meta-analysis of PET studies reported reduced 5-HT₁ receptors in the midbrain and pons, and reduced 5HT₂ receptors in the neocortex with no changes in serotonin transporter relative to controls³⁹. The glutamate system has also been investigated using PET and proton magnetic resonance spectroscopy (¹H MRS). A review of these studies suggested hypofunction of N-methyl-D-aspartate (NMDA) receptors in schizophrenia⁴⁰. Similarly, a meta-analysis of ¹H MRS GABA studies did not show significant differences in GABA levels between patients and controls⁴¹. Even PET/SPECT studies do not show replicable differences⁴², although findings that GABA dynamics may be different in medicated and non-medicated patients⁴³ could contribute to the inconsistent results observed in case-control studies. Similarly, meta-analyses of ¹H MRS studies on glutamate alterations in schizophrenia have resulted in inconsistent results. One meta-analysis reported decreased glutamate and increased glutamine in the medial frontal region in patients with schizophrenia⁴⁴. A later meta-analysis reported elevation of glutamate in basal ganglia, glutamine in the thalamus, and glutamate + glutamine in the thalamus and medial temporal lobe⁴⁵, but no specific brain region showing decreased glutamate levels in schizophrenia.

In all, these findings suggest that the evidence for dopamine dysfunction is more replicable than that for other neurotransmitter systems. However, these neurotransmitters do not work in isolation, and changes in these systems may vary with the course of the illness. For example, feedback neural circuitry involving glutamate, GABA and dopamine is essential for regulating dopamine transmission in the striatum. Furthermore, GABA (an inhibitory neurotransmitter) modulates dopamine release in the frontal cortex and striatum is regulated by glutamate (an excitatory neurotransmitter) through NMDA receptors. A

hypoglutamatergic state can lead to reduced inhibition of dopamine, which in turn could lead to increased dopamine secretion/synthesis. Thus, the excitation/inhibition balance between GABA and glutamate is proposed to be central to the regulation of dopamine.

MRS studies have examined the brain biology of schizophrenia apart from neurotransmitter alterations. N-acetyl aspartate (NAA), a marker of neuronal viability, has been found to be reduced in different regions of the brain, including the prefrontal cortex, temporal lobe and the thalamus. Phosphorus magnetic resonance spectroscopy (^{31}P MRS) studies, which assess differences in membrane expansion/contraction of cellular components by quantifying precursors (phosphomonoesters) and catabolites (phosphodiester) of membrane phospholipids (MPL), have demonstrated regionally specific imbalances in MPL metabolism related to neuropil in schizophrenia compared to controls reflecting neuropil contraction. In addition, decreased phosphomonoester levels in frontal regions, and elevated phosphodiester levels in temporal regions provide evidence of decreased synthesis and increased degradation of neuropil membrane, respectively⁴⁶. Another method called phosphorus magnetization transfer MRS (^{31}P MT MRS) has been applied to examine cerebral bioenergetics. Using this method, reduced creatine kinase forward reaction constant has been observed in the frontal lobes of schizophrenia patients, suggesting an altered regeneration of adenosine triphosphate, a high energy metabolite⁴⁷.

DIAGNOSTIC VALUE OF IMAGING IN SCHIZOPHRENIA

The diagnosis of schizophrenia is currently primarily dependent on clinical assessments based on psychiatric history and mental status examination. Laboratory tests and imaging procedures have so far been used mainly to “rule out” disorders that cause secondary psychosis such as medical illnesses and substance abuse. Lubman et al (2002) observed that nearly 30% of all brain scans of schizophrenia patients are reported as abnormal by radiologists, but the majority were seen as not clinically significant⁴⁸. Only a small proportion (4/340) of scan findings lead to the discovery of a previously unsuspected pathology. This suggests that the routine use of brain scans to “rule out” neuropathology in psychotic patients may not be cost-effective⁴⁹.

Current classificatory systems such as the DSM and the international classification of diseases (ICD) do not include any biomarkers as part of the diagnostic schemes for psychotic disorders. However, there has been an increasing interest in developing reliable objective biomarkers including those involving neuroimaging data to “rule in” a diagnosis by supplementing clinical approaches to diagnosis. Literature showed the potential of neuroimaging data for single subject prediction of diagnosis across various neuropsychiatric disorders, including schizophrenia⁵⁰. However, limitations across these studies include limited sample sizes, feature selection bias, lack of external validation, incomplete reporting of results, and unfair comparison across studies. Furthermore, very few single observations have emerged that have sufficient effect sizes to effectively discriminate between psychiatric disorders, though imaging findings show robust, but non-specific differences between patients with psychotic disorders and healthy subjects⁵¹. Single imaging features are limited by their inability to capture the heterogeneity and complexity of multifactorial brain disorders, such as schizophrenia, which are likely not related to discrete “lesions” but are

likely disorders of distributed brain circuits⁵². Precisely for this reason, machine learning approaches using multivariate imaging data for diagnosis in psychiatric disorders have shown promise. Modern data sharing models and data-intensive machine learning methodologies such as deep learning should be encouraged⁵³.

The challenge in developing reliable diagnostic neuroimaging biomarkers for psychotic disorders may at least in part be related to current limitations in psychiatric nosology, with the disorders being distinguished based on symptom clusters rather than based on the underlying neurobiology. In a way, testing the diagnostic value of neuroimaging in psychiatric disorders is akin to comparing chest X-rays across groups defined by symptoms such as cough and breathlessness, rather than laboratory data (such as sputum microscopy). Testing the diagnostic value of imaging data may be more valuable across biologically defined subtypes than across symptom-based categories of psychotic disorders^{54,55}. Notably, the work by Sun et al. has been groundbreaking as it is the first time to parse the psychiatric disorders based on Magnetic Resonance imaging in conjunction with the unsupervised machine learning technique/algorithm⁵⁵.

OUTCOME PREDICTION IN CLINICAL HIGH RISK INDIVIDUALS

Most individuals who develop psychosis (i.e., 80–90%) first experience a prodromal phase characterized by subthreshold symptoms, cognitive difficulties, and functional decline⁵⁶. Identifying individuals at risk for psychosis at this early stage opens up opportunities for early intervention, which may ameliorate outcome in youth prone to psychosis. The prodromal or high-risk stage is known with slight variations in clinical features as the Clinical High Risk, Ultra-High Risk or At-Risk Mental State. The syndrome is diagnosed using clinical interviews that have been shown to have a prognostic accuracy comparable to other tests in preventive medicine⁵⁷. However, their accuracy is mediated mainly by their ability to rule out psychosis, rather than their ability to differentiate among high-risk individuals in terms of outcome. Given these drawbacks and the limitations of current treatments for psychosis, there is a need for improved outcome prediction in high-risk youth.

Neuroimaging data, on its own or in addition to clinical data, may contribute to improved prediction of psychosis in high-risk individuals⁵⁸. There are two broad types of studies examining imaging biomarkers for psychosis in at-risk cohorts. The first type are cross-sectional studies of baseline imaging data in high-risk individuals who subsequently develop psychosis (i.e. converters) as compared to those that do not (nonconverters). These studies suggest that converters show a number of structural and functional brain abnormalities as compared to nonconverters and controls, including grey matter changes in frontal, temporal, and cingulate cortices^{59,60}, reduced integrity of striatal and (medial) temporal white matter⁶¹, aberrant language-related activation in frontal, temporal, and striatal regions⁶², and changes in functional connectivity and network organization^{63,64}. The second type are machine-learning studies that use a prediction model to separate converters from nonconverters and combine this with some type of cross-validation to estimate how the results of the model would generalize to an independent sample. For example, leave-one-out cross-validation leaves out one subject per run and classifies that individual subject using a model created from all other participants. As this type of analysis facilitates outcome

prediction based on individual patient data, it may in the future become useful in a clinical setting. Machine learning studies have shown considerable accuracy (i.e. exceeding 80%) in separating converters from nonconverters, with classifiers relying mostly on grey and white matter changes in cingulate, frontal, and temporal cortex^{65,66}, subcortical volumes of thalamus, amygdala, striatum, and cerebellum⁶⁷, as well as surface area changes involving mainly frontal, temporal, and parietal cortices^{67,68}.

There is clearly a need for improved prediction of psychosis in clinical as well as familial high-risk youth, which may be achieved through the application of neuroimaging and machine-learning methods. Recent studies using these methods in high-risk cohorts suggest that neuroimaging predictors of psychosis include measures of brain structure, functional activation, and connectivity of predominantly frontal, temporal, and cingulate cortex.

PREDICTION OF TREATMENT RESPONSE AND OUTCOME IN SCHIZOPHRENIA

Imaging technology can highlight observable differences in brain structure and function associated with treatment response. Hence, various factors at the molecular, functional and structural level may provide clues to predict treatment response in schizophrenia. Predictors of response to antipsychotic medication have been mostly studied using PET and MRI.

Pharmacological treatments of first-episode psychosis or schizophrenia mainly target the dopamine synthesis pathway in the brain. At the molecular level, evidence suggests that individuals experiencing a first episode of psychosis or with a diagnosis of schizophrenia exhibit elevated striatal dopamine synthesis, and that individuals with greater striatal dopamine synthesis are more responsive to antipsychotic treatments^{69,70}. At the functional level, greater response to antipsychotic medication in schizophrenia has also been associated with greater brain activation at baseline in the anterior cingulate cortex, temporal-parietal junction, and superior temporal gyrus⁷¹. Patients who respond to antipsychotic treatment also exhibit increased baseline amplitude of low-frequency fluctuations in the left postcentral gyrus/inferior parietal lobule relative to non-responders⁷².

In addition to the suggested functional biomarkers of treatment response, spatial distribution information from brain tissue data acquired using structural MRI scans can also distinguish first-episode psychosis patients who respond to treatment from those who do not⁷³. Furthermore, there is evidence that reduced gray matter volume as well as an abnormal reduction in gyrification (hypogyria) across multiple brain regions are associated with poor antipsychotic treatment response^{74,75}. In contrast, studies investigating whether white matter connectivity in schizophrenia patients is predictive of antipsychotic treatment response have shown inconsistent results. For instance, studies have reported higher FA in frontal regions to be associated with greater response to antipsychotic treatment, but some report a positive association⁷⁶ while others report a negative association⁷⁷.

In search of potential predictors for non-pharmacological treatment response in individuals with schizophrenia, structural brain markers have been identified as potential predictors of treatment response regarding cognitive remediation therapy and cognitive behavioural

therapy. Keshavan et al. (2011) investigated the impact of cortical reserve as a structural brain predictor of cognitive improvement after cognitive remediation therapy⁷⁸. Baseline cortical surface area and gray matter volume predicted greater improvements in social cognition one year following cognitive remediation therapy. Similarly, Guimond and colleagues observed a positive association between greater cortical reserve in the left prefrontal cortex at baseline and improved use of memory strategies after cognitive remediation therapy⁷⁹. Interestingly, greater gray matter volume in the prefrontal cortex, observed pre-therapy, is also associated with a considerable amelioration of positive symptoms following cognitive behavioral therapy in individuals with schizophrenia⁸⁰. Cortical reserve thus appears to predict cognitive and clinical outcomes following cognitive remediation therapy and behavioral therapy. This cortical reserve could reflect the level of neuroplasticity available in individuals with schizophrenia, thereby predisposing them to benefit from these types of therapies. If these findings are replicated, the results could provide further justification for combining cognitive remediation therapy or cognitive behavioral therapy with other approaches (i.e., physical activity or brain stimulation) that could enhance brain plasticity.

Studies show that greater striatal dopamine synthesis, enlarged gray matter volume, normal gyrfication as well as increased brain activity in fronto-parietal regions are potential markers of an individual's positive response to pharmacological treatment in schizophrenia. There is less consistent evidence on brain markers associated with non-pharmacological treatment response in schizophrenia, but greater gray matter volume and thickness in the prefrontal cortex could be predictive of a better response to non-pharmacological treatment. Nonetheless, more research in this area is essential. A better understanding of neuroimaging biomarkers of treatment response could assist the development of more personalized treatments for people with schizophrenia. Hence, such biomarkers of treatment response may eventually guide targeted clinical decisions based on neuroimaging data.

CHALLENGES AND WAYS FORWARD.

In summary, neuroimaging literature accumulated over the last four decades has shed considerable light on the pathophysiology of schizophrenia. As it may be seen in table 1, several observations are emerging from a variety of imaging techniques that provide a composite picture of the pathophysiological substrate of the heterogeneous syndrome we call schizophrenia. However, many large gaps in knowledge exist. There are numerous reasons for this, including the study of variable populations, methodological limitations, and small sample sizes. The limitations of our current neuroimaging approaches should also be considered as they still offer only a hazy view of the complex pathophysiology of this illness. Several novel imaging techniques are becoming available. One example is the use of synaptic vesicles glycoprotein (SV2A) as a ligand for PET imaging in a variety of psychiatric disorders⁸¹. Given the proposed synaptic abnormalities in schizophrenia this might become a powerful tool to investigate the pathophysiology of schizophrenia in the near future. In addition, neuromelanin MRI imaging is now being used to examine dopamine release and has been found to show excessive dopamine in the substantia nigra of patients with schizophrenia⁸². While recently Cassidy and colleagues (2019) did not observe significant group differences between schizophrenia patients and controls, they observed

correlation with neuromelanin concentration, dopamine levels, and severity of psychosis in schizophrenia^{83,84}. Another novel technique is neurite orientation dispersion and density imaging (NODDI), which has shown altered gray matter microstructure in schizophrenia⁸⁵.

A new area of investigation involving the integration of imaging data with genetic variations has been informative in revealing the association of genetic variations with structural, chemical and functional brain changes observed in a given illness. Since these are data driven and hypothesis free, large samples with adequate power are desirable along with corrections for multiple testing⁸⁶. Large scale imaging data can be used to generate target phenotypes for discovery-based genetic associations, e.g. databases such as the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) showed common variants associated with hippocampal structural abnormalities⁸⁷. Such efforts provide hints into the pathophysiological mechanisms and quantitative trait loci while controlling for false positives. This approach is being extended to study other genetic mechanisms such as epigenetics, gene-gene interactions and gene-environment interactions⁸⁸.

While all these approaches will clearly shed considerable light on our understanding of schizophrenia, progress will also depend on a better elucidation of our current diagnostic system, which is still symptom-based⁵⁴. It is also critical that researchers pay careful attention to issues of reproducibility, effect sizes, specificity and sensitivity. Multisite consortia for large-scale data collection, open data sharing approach, as well as rigorous methodology are likely to contribute to progress in the field.

At this time, the clinical value of imaging tools for diagnosis is limited apart from identifying organic brain pathologies in a small proportion of individuals with secondary psychoses. Nonetheless, there may be some value for imaging techniques to provide prediction of outcome. Imaging approaches may allow enhanced prediction or monitoring of therapeutic outcomes of treatments such as pharmacological agents, cognitive remediation and neuromodulation. Similar to neurological disorders, psychiatric disorders are more likely to be related to distributed neural network dysfunctions than discrete lesions⁸⁹. For this reason, multivariate analysis of multimodal imaging data sets using machine learning approaches may offer better diagnostic and predictive value in schizophrenia and other psychiatric disorders at the individual level. Notably with the technical advancement, psychoradiology is showing promise from this perspective^{12,13,90}.

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KEY POINTS

1. Neuroimaging studies have shown substantive evidence of brain structural, functional and neurochemical alterations in schizophrenia, consistent with the neurodevelopmental and neurodegenerative models of this illness.
2. The observed alterations are not regionally specific, but are more pronounced in the association cortex (pre-frontal, parietal and temporal) and subcortical (limbic, striatal) brain regions.
3. At this time, the individually observed abnormalities across psychiatric disorders are not sufficiently specific to be of diagnostic value. Neuroimaging studies have the potential to be used for the prediction of outcome and treatment response across several domains of treatment.
4. Future research should pay attention to multivariate machine learning approaches, multi-site consortia for large sample sizes, prospective studies and novel approaches to address emerging models of genetic, synaptic and neurochemical models of schizophrenia pathophysiology.

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Table 1.

Summary of the proposed pathophysiological domains, imaging modalities, main findings and emerging approaches in the schizophrenia literature.

	Hypothesized measures	Imaging modality	Frequently replicated findings in schizophrenia	Emerging approaches
Brain structure	Gray matter White matter tracts Synapse and neurite integrity	Structural MRI DTI	Widespread gray and white matter deficits, in particular in prefrontal and temporal regions, larger ventricles	Machine learning analyses NODDI, synaptic vesicle imaging High field MRI (7T) Shape analyses
Brain function	Cerebral blood flow Resting-state brain function Task-related brain function Neuroinflammation	PET, SPECT, Resting state fMRI, ASL, Task-fMRI	Prefrontal hypoperfusion Altered function of default mode networks Altered task-related activation of prefrontal and temporal regions	Pseudo-continuous ASL Free water DTI
Brain connectivity	Long and short range connectivity, Connectome organization	fMRI, DTI	Decreased long and short range connectivity Reduced connectome efficiency and altered modularity	Graph theory approaches
Brain chemistry	Dopamine Serotonin Glutamate GABA Neuropil integrity Neuropil synthesis and metabolism	PET PET, MRS ¹ H MRS ¹ H MRS, PET ¹ H MRS ³¹ P MRS	Increased presynaptic dopamine Variable alterations in regional glutamate and GABA levels Reductions in N-acetyl aspartate Alterations in membrane phospholipid metabolites	High field MRS (7T) Neuromelanin MRI to investigate dopamine
Genetics	Multi-factorial, polygenic	Structural MRI, DTI,	Common variants associated with human hippocampal and intracranial volumes	Imaging genomics

MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; PET: Positron emission tomography; fMRI: Functional Magnetic resonance Imaging; DTI: Diffusion tensor imaging; ASL: Arterial spin labelling; NODDI: Neurite orientation dispersion and density imaging; GABA: Gamma aminobutyric acid