Review

Neuroimaging in Psychiatry: An Overview

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Neuroimaging in Psychiatry: An Overview

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Abstract

Psychiatric diagnoses remain largely reliant on clinical observation and self-report, lacking validated biological markers to ensure reliability and specificity. Neuroimaging has emerged as a critical tool to bridge this gap by enabling in vivo assessment of brain structure, connectivity, and neurochemistry. Structural modalities such as MRI and diffusion tensor imaging (DTI) have illuminated consistent alterations in cortical and white-matter networks across schizophrenia, obsessive-compulsive disorder, bipolar disorder, and major depressive disorder, offering insights into shared and disorder-specific pathophysiology. Functional imaging techniques—including fMRI, PET, and SPECT—have further delineated dysconnectivity in key circuits and neurotransmitter abnormalities, reinforcing a network-based model of mental illness. While neuroimaging currently lacks diagnostic specificity for individual patients, its integration with machine learning, genetics, and multimodal biomarkers holds promise for precision psychiatry. Future directions emphasize large-scale harmonized datasets, multimodal fusion, and AI-assisted analysis to develop clinically meaningful biomarkers that can guide diagnosis, predict treatment response, and inform targeted neuromodulation strategies. Neuroimaging thus represents a transformative frontier linking neuroscience and psychiatric practice.

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1. Introduction

Psychiatric disorders continue to be diagnosed primarily through clinical interviews and observation of behaviour, emotions, and subjective experiences. In the absence of validated biological markers, our diagnostic systems struggle with issues of reliability, stability, and specificity, leading to heterogeneity within disorders and overlap across them. This diagnostic uncertainty not only limits individualized treatment decisions but also poses challenges for psychiatric research, risk stratification, and prognostication. [1]

Neuroimaging has become a key tool in addressing these limitations by enabling direct study of the living human brain. It allows measurement of brain structure, network dynamics, and neurochemical processes and offers a framework to connect clinical symptoms with underlying neural mechanisms. Although neuroimaging has transformed research in psychiatry, current evidence does not yet support its independent diagnostic use in clinical practice as highlighted by the APA in the DSM 5. [2]

Ongoing progress in magnetic resonance imaging, diffusion imaging, functional imaging, molecular and spectroscopic techniques, and multimodal data integration is moving psychiatry toward a more biologically informed discipline. This seminar will examine the role of neuroimaging in psychiatry in two major parts. The first section focuses on structural imaging techniques that map morphology and white matter pathways. The second discusses functional imaging approaches that assess brain activity and physiological processes. Together these perspectives illustrate how imaging can advance the future development of clinically meaningful biomarkers.

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2. Structural Neuroimaging

Structural neuroimaging serves as the foundational tool for evaluating the brain in psychiatric practice. CT and MRI are widely accessible modalities that support clinical decision-making by detecting conditions that may mimic or contribute to psychiatric presentations. They are particularly valuable in scenarios such as late-onset psychosis, rapidly progressive cognitive or behavioural change, suspected neurodegeneration, seizure-related behavioural alterations, traumatic brain injury (TBI) etc., In these contexts, imaging helps identify focal lesions, vascular pathology, white-matter disease, developmental abnormalities, or neurodegenerative processes, ensuring that treatable organic causes are not overlooked. [3]

MRI has extended well beyond conventional anatomical imaging to include sequences that assess multiple aspects of brain structure and tissue integrity. Fluid-attenuated inversion recovery (FLAIR) improves visualization of demyelination and gliotic changes, diffusion-weighted imaging (DWI) detects acute ischemia and cellular injury, and MR angiography assesses vascular abnormalities. Among the most significant advances is diffusion tensor imaging (DTI), which measures the directional diffusion of water molecules along axonal pathways. Through metrics such as fractional anisotropy and mean diffusivity, DTI provides a noninvasive assessment of white-matter microstructure and connectivity that is not apparent on routine scans, enabling detection of subtle injuries such as diffuse axonal injury in traumatic brain injury, as well as alterations associated with psychiatric disorders. [4]

Beyond its clinical applications, structural neuroimaging has played a central role in shaping modern understanding of the neurobiology of mental illness. By quantifying cortical thickness, grey-matter volumes, and white-matter connectivity, it has identified reproducible alterations in key brain circuits relevant to symptom domains across disorders. To illustrate the insights gained, we will focus on four psychiatric conditions with the strongest structural imaging evidence base - schizophrenia, obsessive-compulsive disorder, bipolar disorder, and major depressive disorder, where advances in structural MRI and DTI have been particularly informative.

2.1. Understanding the Neurobiological Basis of Psychiatric Disorders

2.1.1. Schizophrenia

The most consistent and replicated structural abnormality reported in schizophrenia is enlargement of the lateral and third ventricles. Meta analytic data in early onset schizophrenia further demonstrate robust grey matter volume reductions in the right superior temporal gyrus, the middle temporal gyrus, and the temporal pole which are regions critically involved in auditory processing, language integration, and socio emotional perception. [5]

Within the superior temporal gyrus, subregions such as Heschl's gyrus and the planum temporale show significant volume loss and this finding has been repeatedly associated with the occurrence of auditory verbal hallucinations and related perceptual disturbances. Involvement extending into the rolandic operculum suggests altered auditory feedback mechanisms that may contribute to the persistence of hallucinatory experiences.

The middle temporal gyrus supports semantic processing, language comprehension, and aspects of social cognition and its atrophy correlates with communication difficulties and broader cognitive impairments in schizophrenia. Reduction in the temporal pole which is important for the integration of emotional and social information aligns with impaired social functioning that is commonly observed in the disorder. Several studies have also demonstrated reduced grey matter volume in mesial temporal and limbic structures. With progression of illness, grey matter loss has been noted in frontal regions particularly the prefrontal cortex which has been linked to the emergence of negative symptoms and cognitive decline. [6]

Taken together, the convergence of these structural alterations in temporal associative and limbic regions helps explain key clinical features of schizophrenia including auditory hallucinations, disorganization, and socio emotional deficits. [7]

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The ENIGMA Schizophrenia DTI Working Group has demonstrated pronounced reductions in fractional anisotropy involving major association and projection fiber pathways including the anterior corona radiata, corpus callosum, and cingulum bundle. These findings remain consistent across international cohorts which supports the concept of schizophrenia as a disorder characterized by diffuse impairment of white matter connectivity rather than isolated tract involvement. Such "dysconnectivity" provides a neural basis for the cognitive and clinical symptoms seen in the disorder including deficits in information integration, executive functioning, and overall functional outcomes. [8]

2.1.2. Obsessive Compulsive Disorder

Meta analytic studies in obsessive compulsive disorder consistently demonstrate a pattern of increased grey matter volume in the thalamus, striatum, and cerebellum, along with reductions in medial prefrontal cortex, anterior cingulate cortex, insula, orbitofrontal cortex, and precentral gyrus. These findings reflect an imbalance between overactive habit and salience circuits and reduced capacity of control networks. The involvement of medial prefrontal cortex and anterior cingulate cortex suggests impaired top down regulation and reduced cognitive flexibility. Volume reductions in the insula, a region essential for integrating emotional and interoceptive signals, may contribute to heightened internal distress and intrusive urges. Importantly, anterior cingulate cortex volume loss correlates with illness duration which suggests progressive disruption in conflict monitoring and cognitive control mechanisms. Together, these structural abnormalities align with the core clinical picture of obsessive compulsive disorder including excessive internal salience, compulsive repetition, and difficulty inhibiting maladaptive responses. [9]

The ENIGMA OCD Working Group has identified distinct neuroanatomical features among adult patients. These include subcortical volume abnormalities such as smaller hippocampal volumes and relatively larger pallidal volumes. Cortical involvement includes thinning in the bilateral inferior parietal cortex and reduced surface area in the left transverse temporal region. Diffusion based measures show reduced fractional anisotropy and increased radial diffusivity in the sagittal stratum and posterior thalamic radiation along with increased mean diffusivity in the sagittal stratum. [10]

In pediatric obsessive compulsive disorder, the structural alterations partially overlap with those seen in adults but with additional regions affected. Children with obsessive compulsive disorder demonstrate cortical thinning in the left inferior parietal cortex, both superior parietal cortices, and the left lateral occipital cortex which are not observed in adult cohorts. This indicates developmental variability in the involvement of associative cortices and suggests that structural brain alterations may follow age specific trajectories in this disorder. [11]

DTI studies in obsessive compulsive disorder also report subtle and widespread disruptions of white matter microstructure involving major commissural and projection fibers including the corpus callosum, internal capsule, and posterior thalamic radiation. These findings support the notion of diffuse dysconnectivity among cortical subcortical networks although site and medication effects require cautious interpretation and the results are not yet sufficiently robust to allow diagnostic level prediction. [12]

2.1.3. Bipolar Disorder

Structural neuroimaging studies in bipolar disorder consistently demonstrate grey matter volume reductions in the hippocampus and prefrontal cortical regions which are areas critically involved in emotional regulation, memory processing, and cognitive control. These alterations may reflect the effects of neuroinflammation and microglial activation in some patients although medication exposure has also been implicated which highlights the complex interplay between underlying disease biology and treatment influences. The variability in hippocampal findings across individuals along with associations reported with sex specific mood and cognitive profiles indicates considerable heterogeneity in the disorder. Together, these structural changes within limbic and

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prefrontal circuits align with the affective instability and executive dysfunction that characterise bipolar disorder. [13]

Findings from the ENIGMA Bipolar Disorder Working Group show localised and progressive cortical thinning that is most evident in frontal and temporal regions. In parallel, lithium treatment has been associated with relative preservation of cortical thickness which suggests a potential neuroprotective effect. These observations support a model in which bipolar disorder involves selective vulnerability in interconnected networks rather than diffuse and global atrophy. [14]

DTI studies have reported widespread disruptions in white matter microstructure affecting all major classes of tracts with the most consistent reductions in fractional anisotropy observed in long association pathways particularly in right posterior white matter and anterior cingulate regions. [15]

Further evidence of dysconnectivity comes from reductions in fractional anisotropy within fronto limbic pathways including the anterior cingulum, corpus callosum, and prefrontal white matter tracts which may contribute to impaired modulation of emotional responses and difficulties in maintaining cognitive control during mood episodes. [16]

2.1.4. Major Depressive Disorder

Recent meta-analytic studies show that major depressive disorder is associated with grey matter reductions in the anterior cingulate cortex, medial prefrontal cortex, hippocampus, amygdala, and insula. These regions play key roles in emotion regulation, stress responsivity, and self-related processing. Atrophy of the anterior cingulate cortex and medial prefrontal cortex has been associated with increased rumination and reduced capacity to regulate negative affect. Hippocampal volume loss is linked to the effects of chronic stress and correlates with memory disturbances. Reductions in amygdala and insula volumes reflect disruptions in emotional salience processing and altered perception of bodily and internal states. Together, these findings indicate that major depressive disorder involves impaired integration between cognitive control regions and limbic emotional circuits which aligns with the characteristic experiences of persistent negative mood and diminished self-regulation in depression. [17]

Results from the ENIGMA Major Depressive Disorder Working Group demonstrate consistent hippocampal and fronto-limbic abnormalities that correlate with illness burden which supports the conceptualisation of depression as a network level disorder involving disrupted communication within emotion regulation systems. [18]

Some studies have proposed that antidepressant treatment may promote recovery of hippocampal structure which raises important questions about neuroplasticity in the course of depression. [19]

White matter studies in depression have found that the regions that most strongly contributed to the global effect of lower FA were regions of the corona radiata and corpus callosum and anterior limb of internal capsule, suggesting interhemispheric and fronto-subcortical network disruption. [20]

2.2. Application Beyond Understanding Neurobiology

In psychiatric research neuroimaging has moved beyond merely elucidating the pathophysiology of psychiatric disorders to informing prognosis and guiding interventions and treatments. Structural imaging allows for the identification of biomarkers that predict treatment response and recovery trajectories, offering a window into individualized outcomes. Importantly, these insights are shaping the application of targeted neuromodulation techniques, such as rTMS, tDCS, and DBS- by precisely localizing cortical and subcortical nodes within mood, obsessional, and psychotic circuits.

2.2.1. Prediction of High Risk

Structural MRI is being explored as a tool to predict which individuals at clinical high risk may progress to psychosis. Reductions in grey matter volume within the hippocampus, medial prefrontal

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cortex, and temporal cortices have been associated with a higher likelihood of later conversion. Machine learning models that incorporate these imaging features along with clinical and cognitive data have demonstrated improved accuracy in identifying those at greatest risk. [21]

2.2.2. Guiding Interventions

Structural magnetic resonance imaging (sMRI) plays an increasingly important role in neuromodulation treatments including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and Gamma Knife radiosurgery (GKRS) in psychiatry. It provides anatomical information needed for accurate targeting of relevant brain circuits with the goal of enhancing therapeutic outcomes.

sMRI-guided neuronavigation is used to localize stimulation sites in disorders such as major depressive disorder. For example, sMRI guided repetitive transcranial magnetic stimulation has been shown to modulate neural activity in the angular gyrus and superior frontal gyrus which are regions involved in emotion regulation and cognitive control. This approach was associated with symptom improvement in patients with major depressive disorder. [22] Despite the widespread use of sMRI for neuronavigated TMS, there is currently no evidence demonstrating clear clinical superiority over standard TMS, and no MRI-guided TMS protocol has received FDA approval.

In DBS, sMRI helps ensure accurate electrode placement within circuits related to mood regulation and compulsive behavior. Beyond its role in targeting the subcallosal cingulate cortex for treatment resistant depression where encouraging therapeutic effects have been reported, sMRI is also used to guide stimulation in obsessive compulsive disorder. In OCD, targets such as the anterior limb of the internal capsule, subthalamic nucleus and the ventral striatum are selected based on their involvement in the cortico-striato-thalamo-cortical circuit which is central to compulsivity and impaired inhibitory control. [23]

GKRS is a non-invasive technique employed in treating refractory psychiatric disorders. sMRI aids in delineating target regions such as the anterior limb of the internal capsule (ALIC) in treatment of refractory OCD, ensuring precise lesioning. This underscores the importance of sMRI in enhancing the efficacy of GKRS in psychiatric applications. [24]

2.3. Limitations of Structural Neuroimaging

Despite its significant contributions, structural neuroimaging continues to face limitations that prevent it from functioning as a definitive diagnostic or predictive tool in psychiatry.

A primary barrier is limited diagnostic specificity. Similar patterns of grey and white matter change are observed across multiple disorders. Prefrontal and limbic volume reductions, for example, are reported in schizophrenia, bipolar disorder, and major depressive disorder. Such overlaps likely reflect shared neural vulnerabilities rather than distinct disease signatures, underscoring that psychiatric disorders often do not conform to clearly separable biological categories.

Heterogeneity within diagnostic groups further complicates interpretation. Psychiatric diagnoses are based on symptoms rather than underlying biology, and patients classified under the same label frequently differ in illness duration, treatment exposure, comorbidities, and developmental factors. These sources of variability influence brain structure and reduce the clarity of disorder-specific findings. [25]

Additionally, the magnitude of detected structural differences is modest. Cortical thinning or volumetric reductions are often subtle and require large sample sizes to achieve statistical reliability. Variations in scanners, acquisition protocols, and analysis pipelines introduce further noise, challenging reproducibility even in large consortia studies. Moreover, structural imaging provides only a static snapshot of the brain. Even though imaging resolution is improving, it also reveals how different every brain is in its structure. This natural variability makes it harder to separate true disease-related changes from normal differences between individuals.

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Ultimately, structural neuroimaging identifies where the brain may be altered but not how neural circuits operate, when changes emerge, or why dysfunction occurs. It delineates anatomy without capturing the dynamic flow of information that underlies cognition and emotion. Without concurrent biological and functional context, structural findings alone offer an incomplete understanding of the mechanisms that drive mental illness. [26]

2.4. Future Directions

Despite its current limitations, structural neuroimaging is entering an important phase of advancement. The focus is shifting from static description of brain anatomy to more precise and informative markers that may hold clinical meaning. Progress is being driven by improvements in imaging resolution, analytical techniques, and large scale collaborations.

International initiatives such as ENIGMA, the UK Biobank, and the Human Connectome Project are integrating data across thousands of individuals and research sites. These harmonized datasets reduce the impact of site level variability and support the identification of reliable, generalizable patterns of brain alterations across psychiatric disorders. They allow researchers to move beyond isolated findings toward a broader understanding of how brain structure relates to illness course, genetics, development, and environmental influences. [27]

At the same time, advances in ultra-high-field MRI and precision morphometry are sharpening our view to near-microscopic detail, tracing cortical layers, subfields, and microstructural gradients once invisible. [28] Diffusion based imaging continues to refine the mapping of white matter pathways and their role in communication between brain regions. The integration of machine learning methods with imaging data is enabling the detection of subtle multivariate signatures that may improve risk prediction and treatment stratification.

Looking forward, progress will rely on combining structural imaging with complementary approaches such as functional MRI, PET, electrophysiology, and genetics. These multimodal strategies have the potential to connect anatomical findings directly to neural activity and behavior which may support the development of biomarkers with true clinical relevance.

Although significant challenges remain including variability across individuals and the need for strong biological grounding of diagnoses, continuing advances hold promise for more personalized and mechanistically informed care. With this foundation established, we now shift from the anatomical features of the brain to its dynamic activity. The next section will focus on functional neuroimaging which examines how brain networks operate in real time and how these patterns relate to psychiatric symptoms and treatment.

3. Functional Neuroimaging

Having explored the structural architecture of the brain, we now turn our focus to how the brain functions in real time. Functional neuroimaging techniques provide insight into neural activity, network interactions, and neurotransmitter dynamics that underlie psychiatric symptoms. Unlike structural imaging which reflects anatomy, functional imaging captures changes in metabolism, blood flow, and electrophysiology, allowing us to understand how circuits become dysregulated in mental illness.

These modalities have helped identify consistent abnormalities in large scale brain networks such as the default mode network, salience network, and frontoparietal control network which supports the growing view that psychiatric disorders are disorders of connectivity rather than isolated regional dysfunction.

Although primarily used in research, functional imaging continues to expand its clinical relevance by contributing to early risk detection, differentiation between overlapping syndromes, monitoring treatment response, and the development of targeted neuromodulation strategies.

- **Key Modalities**

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Functional neuroimaging examines how the brain operates in real time by measuring neural activity, connectivity, and neurotransmitter function. It complements structural imaging by revealing circuit level abnormalities that underlie psychiatric symptoms. Various functional imaging modalities include -

- **Functional Magnetic Resonance Imaging** (fMRI)

fMRI measures brain activity by detecting blood-oxygen-level dependent (BOLD) signal changes, reflecting local neuronal metabolism and hemodynamic responses within active neural circuits.

Functional MRI can broadly be categorized into **task-based fMRI**, which measures brain activation during specific cognitive, emotional, or perceptual tasks, and **resting-state fMRI**, which assesses spontaneous neural fluctuations to map intrinsic functional connectivity when no task is performed.

- **Positron Emission Tomography** (PET)

Uses radiotracers to quantify glucose metabolism and neurotransmitter systems, providing direct insight into in vivo neurochemistry.

- **Single Photon Emission Computed Tomography** (SPECT)

Assesses regional cerebral blood flow and receptor binding with greater availability in clinical settings, especially useful in movement and cognitive disorders.

- **Magnetic Resonance Spectroscopy** (MRS)

Estimates neurochemical concentrations including glutamate, GABA, and N acetyl aspartate, reflecting neuronal metabolic status.

- **Magnetoencephalography (MEG) and Electroencephalography** (EEG)

Record electrical activity with high temporal resolution to assess neural oscillations and network synchronization.

- **Functional Near Infrared Spectroscopy** (fNIRS)

Portable technique measuring cortical blood oxygenation, suitable for pediatric and bedside psychiatric applications.

In this seminar, discussion will primarily focus on **fMRI, PET, and SPECT and its role in psychiatry**, as these modalities currently have the most established relevance for understanding neural circuitry and informing research and treatment in psychiatry.

3.1. Understanding the Neurobiology of Psychiatric Disorders and Phenomenology

A major contribution of functional neuroimaging in psychiatry has been clarifying abnormal neural circuits and neurotransmitter systems underlying psychiatric illnesses. Schizophrenia has served as a prototype because it has been extensively studied using functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT).

fMRI

Functional MRI reveals consistent abnormalities in brain activity and connectivity in schizophrenia. One of the most replicated findings is **hypofrontality**, referring to reduced activation in the dorsolateral prefrontal cortex during working memory and executive tasks, which correlates with cognitive and negative symptoms. [29,30] Resting-state studies demonstrate **default mode network hyperconnectivity**, impaired prefrontal connectivity, and altered cortical–subcortical interactions linked to impaired self-monitoring and psychotic experiences. [31,32] Some connectivity changes are also found in unaffected relatives, suggesting potential endophenotypes associated with genetic risk. [31,32] A recent review by Voineskos et al. (2024) confirmed that these circuits are consistently implicated across multiple methodologies and populations worldwide. [30]

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PET

PET has been instrumental in substantiating the dopamine hypothesis of schizophrenia. Radioligands such as [18F] DOPA have been used to measure presynaptic dopamine synthesis capacity. In [^{18}F]-DOPA PET imaging, the patient receives an intravenous injection of [^{18}F]-DOPA, a radiolabeled precursor of dopamine. The [^{18}F]-DOPA molecule crosses the blood-brain barrier (BBB) via the L-type amino acid transporter (LAT1) and is taken up by dopaminergic neurons in the striatum (caudate and putamen), where it is converted into [^{18}F]-dopamine by Aromatic L-Amino Acid Decarboxylase (AADC) and stored in synaptic vesicles. As [^{18}F] undergoes radioactive decay, it emits positrons (β^+ particles), which interact with electrons, leading to annihilation and the release of two gamma photons (511 keV) in opposite directions. The PET scanner detects these coincident gamma rays, generating an image of dopamine synthesis and storage activity. The uptake of [^{18}F]-DOPA is quantified using the influx constant (Ki), which reflects dopamine synthesis capacity—higher uptake indicates increased dopamine activity, while lower uptake suggests dopaminergic deficits. [33] [^{18}F]-DOPA PET studies confirm hyperactive dopamine synthesis in the striatum, particularly in the dorsal caudate and putamen, which correlates with hallucinations and delusions. [34] Amphetamine-induced dopamine release PET (using [11C] raclopride specific binding over D2/3) studies further demonstrate excessive striatal dopamine transmission, reinforcing the dopamine hypothesis of schizophrenia. [35] Moreover, PET imaging with D2/D3 receptor ligands has shown elevated receptor availability in unmedicated patients, and the extent of this elevation often correlates with symptom severity and response to antipsychotics. [36]

SPECT

SPECT imaging offers similar molecular insights to Schizophrenia, particularly in dopaminergic and GABAergic systems SPECT studies have primarily utilized dopaminergic radiotracers like [123I] IBZM (targeting D2/D3 receptors in the striatum), [123I] epidepride (for extrastriatal regions), and DAT tracers such as [123I] β-CIT and [99mTc]-TRODAT. While post-synaptic D2/D3 receptor availability is only slightly elevated in treated patients, increased amphetamine-induced dopamine release has been observed in unmedicated individuals, suggesting presynaptic dysregulation. Notably, the BG/FC (basal ganglia/frontal cortex) binding ratio of IBZM correlates with treatment response and the presence of extrapyramidal side effects. Explorations into the GABAergic system using [123I] iomazenil have shown mixed findings, with some studies linking negative symptoms to decreased GABA-A binding in the medial frontal cortex and positive symptoms to changes in the medial temporal lobe. Glutamatergic involvement has also been studied using [123I] CNS-1261, an NMDA receptor ligand, which shows reduced binding in patients on clozapine and a negative correlation between NMDA binding and residual symptom severity in patients on typical antipsychotics. [37]

Together, findings from fMRI, PET, and SPECT converge on a model of schizophrenia characterized by **network-level dysconnectivity and neurochemical imbalance** across frontal, temporal, and subcortical circuits. Similar functional neuroimaging discoveries are now being reported in major depressive disorder, bipolar disorder, obsessive compulsive disorder, and other psychiatric conditions, reinforcing the role of circuit-based pathology across diagnostic categories.

3.2. Functional Neuroimaging in Diagnosis and Differential Diagnosis

Although functional neuroimaging is not yet used as a standalone diagnostic tool in psychiatry, it provides valuable supplementary information that can enhance diagnostic clarity, particularly in complex or ambiguous cases. The APA stated that brain imaging currently "has no clinical value in psychiatry" as a stand-alone diagnostic method. Nonetheless, functional imaging can identify distinct neurophysiological signatures associated with psychiatric disorders and assist in distinguishing overlapping conditions.

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A prime clinical indication is the SPECT-TRODAT scan, which uses the radiopharmaceutical technetium-99m labelled TRODAT-1 to select for dopamine transporters (DAT) on presynaptic nigrostriatal terminals. After intravenous administration, the tracer crosses the blood–brain barrier and accumulates in the striatum (caudate and putamen). In healthy individuals, uptake is symmetrical, while in idiopathic Parkinson's disease (iPD) the binding is reduced and asymmetric, typically in the posterior putamen contralateral to the symptomatic side. [38,39] This allows differentiation between iPD and drug-induced parkinsonism (DIP): in DIP striatal DAT binding remains normal and symmetrical, whereas in iPD it is reduced. [38,39]

Functional imaging also plays a critical role in dementia sub-typing. In Alzheimer's disease (AD), ^18F-FDG-PET shows bilateral temporoparietal hypometabolism extending to the posterior cingulate and precuneus, correlating with memory and visuospatial deficits. [40] In Frontotemporal dementia (FTD) the pattern is predominantly frontal and anterior temporal hypometabolism/ hypoperfusion, aligning with executive and behavioural dysfunction. [40] Lewy body dementia (LBD) often retains posterior cingulate metabolism with occipital hypometabolism (the "cingulate island sign") on FDG-PET. [40] SPECT perfusion scans, albeit with lower resolution, echo these patterns and provide pragmatic support in resource-limited settings. In vascular dementia PET and SPECT demonstrate patchy or asymmetric perfusion/metabolism deficits aligned with infarcts or chronic ischaemia rather than typical AD regions. [40–42]

Henderson et al. (2020) present compelling case studies illustrating how functional neuroimaging can unmask organic etiologies that mimic psychiatric disorders. In one case, a patient initially diagnosed with major depressive disorder demonstrated diffuse frontal and parietal hypoperfusion consistent with traumatic brain injury rather than primary depression. [2] In another, a patient with presumed ADHD exhibited anterior cingulate gyrus and thalamic hyperperfusion on SPECT which pointed instead to an obsessive-compulsive spectrum disorder, leading to modified treatment and improved outcomes. [2] Beyond differentiation of psychiatric conditions, functional imaging also aids in identifying underlying biological contributors to symptoms including infections (e.g., Lyme disease, Herpes simplex encephalitis), inflammatory states, neurodegenerative conditions, toxin exposure etc., [2]

In summary, while functional neuroimaging is not diagnostic on its own, it significantly enriches clinical understanding by revealing hidden brain abnormalities. It supports diagnostic clarification, reduces misdiagnosis, detects comorbid organic pathology, and identifies biologically meaningful subtypes that inform personalized treatment. This insight forms the foundation of precision psychiatry, where treatment is driven not only by symptoms but by the individual's underlying brain biology, moving toward an integrated clinical-biological paradigm.

3.3. Aiding in Treatment

Beyond characterizing disease mechanisms, functional neuroimaging increasingly informs and individualizes treatment strategies in psychiatry. Because schizophrenia has a large body of functional neuroimaging research, it is again used as a prototype here, with similar principles now being applied to other psychiatric disorders.

fMRI-Guided Transcranial Magnetic Stimulation (TMS)

Functional MRI has been used to guide repetitive TMS (rTMS) targeting in treatment-resistant auditory verbal hallucinations. Stimulation of the left temporoparietal junction is standard, but fMRI connectivity mapping can identify the most aberrant network nodes on an individual basis. Baliga and Mehta (2021) highlight that patients with stronger temporoparietal–default mode network connectivity may respond better to fMRI-guided stimulation than to conventional scalp-based targeting. However, the authors also note that there is **currently no conclusive evidence** that fMRI-guided TMS is superior to conventional TMS for auditory hallucinations in schizophrenia, although early findings remain promising and warrant further controlled trials. [43] The same principles have informed targeting in major depressive disorder, where individualized stimulation of the

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dorsolateral prefrontal cortex most anticorrelated with the subgenual anterior cingulate cortex is associated with improved outcomes.

One example is the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol, where resting-state functional connectivity MRI is used to personalize high-dose intermittent theta burst stimulation. In the trial by Cole et al. (2020), SAINT achieved remission in 86.4 percent of patients with treatment-resistant depression, demonstrating the clinical potential of functional imaging-guided neuromodulation. [44]

fMRI-Guided Neurofeedback

Real-time fMRI neurofeedback allows patients to learn voluntary control over aberrant neural activity. In schizophrenia, down-regulation of superior temporal gyrus and anterior cingulate cortex activity has been shown to reduce hallucination severity. [45] Neurofeedback approaches have also demonstrated potential benefit in anxiety disorders, depression, attention-deficit hyperactivity disorder, obsessive-compulsive disorder and substance use disorders by enabling self-modulation of pathological network dynamics. [46] While still experimental, this strategy represents a meaningful step toward self-directed, circuit-specific treatment.

Neuroimaging-Guided Pharmacotherapy

Functional neuroimaging contributes increasingly to medication optimization. Task-based and resting-state fMRI studies have shown that antipsychotic treatment can normalize dorsolateral prefrontal cortex and anterior cingulate cortex activity, and such changes may precede observable clinical improvement, offering a potential early biomarker of treatment response. [30]

PET and SPECT have been essential in determining dopamine D2 receptor occupancy, guiding dose selection to maximize antipsychotic efficacy while minimizing extrapyramidal side effects. [36] Higher presynaptic dopamine synthesis on [18F]-DOPA PET predicts better response to antipsychotic medication, particularly in first-episode psychosis, while individuals with normal or low synthesis may require alternative therapeutic approaches. [34,47] SPECT also demonstrates longitudinal changes in receptor binding, supporting its role in monitoring pharmacotherapy effectiveness. [48]

Although not yet routine in clinical psychiatry, these findings illustrate the potential of functional neuroimaging as a biological readout of treatment efficacy. This is especially useful in cases of treatment resistance or partial response, where neuroimaging can help assess whether the brain is biologically responsive despite limited clinical improvement. Moreover, it offers a non-invasive avenue to detect early signs of relapse before symptoms worsen. [47]

3.4. Biomarkers, Classification, and Precision Psychiatry

Functional neuroimaging is increasingly driving a fundamental transformation in psychiatry—from symptom-based diagnosis to biologically grounded, precision-guided care. For decades, psychiatric classification systems such as the DSM and ICD have been criticized for relying on clusters of subjective symptoms that often poorly align with underlying neurobiology. Functional neuroimaging provides objective measures of neural circuit dysfunction, neurotransmitter abnormalities, and network-level signatures that support biomarker development for diagnosis, prognosis, treatment selection, and subtype identification. [30]

Toward Predictive and Theranostic Biomarkers

In schizophrenia, elevated presynaptic dopamine synthesis measured using [18F]-DOPA PET predicts favourable antipsychotic response, while individuals with normal synthesis capacity show poor dopamine-blocking response and may require alternative strategies such as glutamatergic modulation. [34,47] Functional MRI studies similarly show that early normalization of dorsolateral prefrontal cortex and anterior cingulate cortex activity can precede clinical improvement, offering an

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early response biomarker. [30] In depression, resting-state connectivity between the dorsolateral prefrontal cortex and subgenual anterior cingulate cortex predicts response to TMS, enabling personalized stimulation targeting. [44] PET and SPECT metrics of dopamine D2 receptor availability support dose optimization and treatment monitoring, reducing side-effect risk like discussed. [36,48]

Endophenotypes and Risk Biomarkers

Functional imaging has identified heritable neural signatures—endophenotypes—that bridge genetic liability and symptom emergence. These include: Default mode network hyperconnectivity, Working-memory related hypofrontality, and Error-processing ACC abnormalities seen in both schizophrenia patients and unaffected relatives. [31,32,49] In clinical high-risk states, resting-state fMRI identifies network disruptions (e.g., reduced DMN coherence or salience hyperconnectivity) before symptomatic conversion, improving prediction when combined with clinical features. [31]

Biological Subtyping and Transdiagnostic Classification

Machine-learning applied to multimodal datasets (fMRI, PET, SPECT, genomics, behaviour) is revealing neurobiologically distinct subgroups within and across disorders. [30] For example, Drysdale et al. (2017) identified four depression subtypes (biotypes) based on fronto-amygdala and DMN connectivity, each demonstrating different neuromodulation response patterns. [50] In psychosis, connectivity-based clustering identifies biotypes spanning schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis, defined by thalamo-cortical dysconnectivity, hypofrontality, or altered salience network recruitment. [51,52] These data-driven categories better map to treatment response and clinical prognosis than DSM diagnoses alone.

RDoC and Dimensional Circuit-Based Models

The NIMH Research Domain Criteria (RDoC) initiative promotes a dimensional framework, studying mental illness through core functions such as reward learning, cognitive control, and emotional regulation, each tethered to specific neural circuits. [53] Functional neuroimaging is central to operationalizing RDoC, linking circuit dysfunction to behavior across diagnostic boundaries. This approach allows identification of cross-diagnostic biomarkers relevant to constructs (e.g., threat responsivity, working memory) rather than syndromes.

3.5. Multimodal Integration of Functional Neuroimaging in Psychiatry

Functional neuroimaging has become central to translational and computational psychiatry, providing biologically grounded phenotypes that bridge the gap between basic neuroscience and clinical practice. By offering measurable proxies for neural activity, fMRI enables validation of circuitry models across species. For example, abnormalities in prefrontal–striatal–thalamic pathways observed in animal models of schizophrenia have been confirmed in humans using functional MRI. [54]

In early-phase drug development, resting-state and task-based fMRI are increasingly used to assess target engagement and neural response before clinical improvement becomes detectable. For instance, modulation of connectivity between the subgenual anterior cingulate cortex and the default mode network has served as a mechanistic biomarker across both pharmacological and neuromodulatory trials. [44,55]

Computational psychiatry employs mathematical modeling and artificial intelligence to quantify neural processes. When combined with multimodal imaging, these methods enhance disease classification and trajectory prediction. Machine learning approaches such as multivariate pattern analysis have differentiated schizophrenia from bipolar disorder with notable accuracy by leveraging distributed connectivity patterns. [56] Generative computational models further simulate how perturbations in neural circuits produce symptoms, enabling hypothesis-driven mechanistic research. [57]

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Emerging integration with Large Language Models (LLMs) offers additional potential. By fusing imaging features with clinical notes, genomics, and behavioral metrics, LLMs can support clinical decision-making, stratify patient populations, and reveal latent brain–behavior associations. With neuroimaging repositories such as the UK Biobank and Human Connectome Project expanding rapidly, LLM-driven analytics are poised to significantly advance interpretability and precision care in psychiatry.

Neuroimaging also interfaces synergistically with genetics. Imaging-genetics studies have linked variants in COMT, DRD2 and GRM3 with alterations in cortical activation and fronto-striatal processing. [58] Incorporating polygenic risk scores into imaging models enhances prediction of disease liability, particularly in disorders like schizophrenia. [58]

Connectomics integrates functional MRI with diffusion tensor imaging to map whole-brain network structure and dynamics. Large-scale initiatives like the Human Connectome Project have elucidated network architecture supporting cognitive and affective functions, establishing normative connectivity benchmarks [59,60]. Comparing psychiatric populations to these connectome standards has identified reproducible network alterations across diagnostic boundaries, contributing to transdiagnostic biomarker discovery and refined classification systems.

3.6. Limitations of Functional Neuroimaging

Despite significant advancements and promising translational potential, functional neuroimaging continues to face challenges that limit its routine use in clinical psychiatry:

- **Diagnostic specificity remains limited**, as many imaging abnormalities overlap across disorders, complicating individual-level interpretation.
- **Most findings are based on group-level statistics**, and robust individualized biomarkers have yet to be fully validated for clinical decision-making.
- **Variability in imaging protocols, scanners, and analytic pipelines** affects reproducibility and generalizability of results across populations and centers
- **High operational and maintenance costs**, along with the requirement for specialized infrastructure and trained personnel, restrict access in many regions.
- Modalities like SPECT and fNIRS are limited by **lower spatial resolution and signal-to-noise ratio** compared to other techniques.
- **Radiation exposure** in PET and SPECT raises considerations for repeated imaging and vulnerable populations.
- Clinical interpretation requires **multidisciplinary expertise**, slowing scalability outside tertiary care and research settings.

Overall, while functional neuroimaging provides powerful research insights, several technological, methodological, and practical hurdles must be addressed before it can be widely integrated into standard psychiatric care.

3.7. Future Directions of Functional Neuroimaging

As the field rapidly evolves, multiple priorities are expected to shape clinical translation of functional neuroimaging in psychiatry:

- **Protocol standardization and harmonization** of acquisition and analytic techniques across centers to improve reproducibility and comparability.
- **Development of affordable and portable imaging systems** to improve accessibility in low-resource and community settings.
- **Integration with AI, machine learning, and large language models (LLMs)** to enhance pattern recognition, automate interpretation, and support clinical decision-making.
- **Multimodal data fusion** with genomics, digital phenotyping (e.g., smartphones, wearables), electrophysiology, and connectomics to enable precise patient stratification.

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- **Biomarker-based adaptive clinical trials**, employing imaging-derived predictors to guide treatment selection and monitor response in real time.
- **Longitudinal functional imaging tools** capable of tracking dynamic circuit changes across illness onset, relapse, and recovery.
- Addressing **insufficient sample sizes** that currently limit robust population-level inference; major research consortiums such as **ENIGMA, UK Biobank, and the Human Connectome Project** are rapidly closing this gap by enabling large-scale, harmonized datasets and high-power analyses.

As imaging technologies become more accessible and analytical approaches advance, functional neuroimaging is positioned to play a transformative role in psychiatry. By shifting away from purely symptom-based frameworks toward **objective, biology-informed evaluation**, neuroimaging will help bridge neuroscience and clinical practice—enhancing prediction, prevention, and precision treatment across mental health disorders.

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