Clinical Strategies and Technical Challenges in Psychoradiology

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INTRODUCTION

Psychoradiology is an emerging discipline at the intersection between radiology and psychiatry. It applies radiological technologies to unveil patterns of anatomic and functional brain changes in patients with psychiatric disorders in vivo. It holds promise for playing a key role in clinical diagnosis, evaluation of treatment response, prediction of prognosis, and illness risk prediction for patients with psychiatric disorders.\textsuperscript{1} Although psychoradiology was formally described by Lui and colleagues in 2016,\textsuperscript{1} the idea of developing imaging biomarkers for psychiatric disorders dates back to 1976, when the first study revealed an enlarged ventricular size in patients with schizophrenia.\textsuperscript{2}

Gong and colleagues and other investigators have since developed the psychoradiological hypothesis of mental disorders, theorizing that brain structural and functional connectivity alterations lead to clinical symptoms and syndromes.\textsuperscript{1,3–5} Well-replicated radiological observations\textsuperscript{6} have played a major role in the shift from seeing serious mental illnesses in psychological terms as problems of adaptation to life circumstances to the current view that they represent brain disorders.\textsuperscript{7–9}

This effort has accelerated to a great degree within the past 20 years due to the rapid and extensive development of magnetic resonance imaging (MRI), molecular imaging, and other diagnostic imaging techniques. In particular, new MRI
technologies, such as high-resolution structural MRI, perfusion mapping, magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and blood oxygenation level–dependent (BOLD) functional MRI (fMRI), have given rise to an increasing body of scientific literature that elucidates how various psychiatric syndromes are associated with alterations in brain structures and function across time and with treatment.

Multiple imaging biomarkers have been identified in different psychiatric disorders, among which some have shown potential clinical utility for subtyping, prediction, and evaluation. Although the clinical use of psychoradiology is already in sight, there are still issues and challenges that need to be addressed before wide-scale clinical application. In particular, the clinical strategies for examining patients, analyzing images, and using findings to help clinical work need to be better validated and optimized.

**STRATEGY FOR EXAMINATIONS**

Like other imaging examinations, the first step of psychoradiology is to choose proper techniques for managing patients. Unlike tumor, stroke, and most neurologic diseases, brain abnormalities in psychiatric disorders are subtle and often involve functional alterations that contribute to cognitive and emotional disturbances. As a result, psychoradiology approaches require multimodal imaging techniques, especially high spatial resolution structural MRI, DTI, fMRI, perfusion-weighted imaging, MRS, electroencephalography, and positron emission tomography (PET). Multimodal imaging techniques require clinical balance between the number of the techniques needed for particular patients or disorders and their cost. As in neurologic disorders, high-resolution T1-weighted imaging (T1WI) is used for detecting anatomic gray matter abnormality, DTI for white matter deficits, resting-state fMRI (rs-fMRI) for brain dysfunction identification, and MRS for neurometabolic information.

A second question pertains to which patients need psychoradiological examination. Given the current state of knowledge, anyone with a suspected serious mental illness may benefit from an imaging examination, not only for ruling out other diseases, such as inflammation or tumor, but also as a baseline for subtyping and following treatment response. The clinical high-risk population, individuals with strong familial liability or prodromal manifestations of illness, also may benefit from an imaging examination to objectively assess risk and guide initiation of preventive interventions. Another issue is whether sedation or even anesthesia is needed for evaluating patients. A large majority of patients can cooperate with examination, sometimes with the help of mental health staff and relatives. In cases of some children or acutely ill manic patients, however, sedation may be needed, although sedating medications can affect imaging features, especially fMRI. The safety of the patient needs to be an important consideration as in other imaging examinations. To reduce patient distress and increase cooperation, it can be advantageous to have a psychiatrist, psychologist, or relative accompany patients to scan sessions and, if needed, be with patients during an examination. A quiet ready room is helpful for preparing patients for examination and a mock scanner may be helpful to prepare patients. Magnetic resonance (MR)-compatible monitoring devices, such as an eye tracking system, are useful not only for monitoring patient safety but also for monitoring head position and collecting data about eye movements that have an impact on fMRI data. Usually, the time for 1 MR examination is best limited to 40 minutes to 60 to maintain patient comfort and safety and optimize acquired image quality.

Image quality control in psychoradiology is stricter than in other radiology disciplines because both structural and functional quantitative analyses are needed. In addition to general quality control, the control of the signal-to-noise ratio (SNR), the contrast-to-noise ratio (CNR), and image uniformity are required. For example, when acquiring T1WI, the image interpolation function should be turned off, the acceleration factor should not exceed 2, and T2-weighted images with the same resolution should be acquired for better accuracy of brain surface reconstruction. For DTI, the acceleration factors of 2 to 3 might be optimal, and the use of cardiac gating would be helpful in minimizing the tissue pulsation secondary to the cardiac cycle. In rs-fMRI acquisition, an electrocardiogram needs to be acquired simultaneously for the correction of cardiac cycle effects on BOLD signals. The incorporation of a gradient-echo acquisition also can be useful in generating phase and magnitude images simultaneously that can be used for correcting or visualizing distortions caused by susceptibility and inhomogeneous fields. The acquisition of MRS data requires precise anatomic location of regions of interest (ROIs). For psychoradiology, the main focus shifts from visual inspection of images to quantitative analysis, leading to many of these requirements for image acquisition.
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STRATEGY FOR IMAGE ANALYSIS

Unlike traditional qualitative diagnostic procedures in clinical radiology, psychoradiology is performed in a quantitative way. Thus, postprocessing is necessary after image acquisition. Although tools for such analysis are rapidly evolving, there is no guideline for the integrated analysis of multimodel imaging, which remains a challenge for the clinical application of psychoradiology. In this issue, some detailed strategies for data analysis are presented in the following chapters.

In brief, for T1WI, there are 2 common methods for structural MRI postprocessing, voxel-based analysis (VBA) and surface-based morphologic (SBM) analysis. Voxel-based morphometry (VBM) analysis can be conducted via Statistical Parametric Mapping (SPM) (http://www.fil.ion.ucl.ac.uk/spm/), and the most commonly used method is diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL).20–22 Basic procedures include segmentation of gray/white matter and cerebrospinal fluid, creation of DARTEL templates (6 templates through an 18 iteration process), registration of all individual deformations to the DARTEL template (the sixth template is the clearest for standard Montreal Neurological Institute space), and smoothing (usually with a full-width at half-maximum [FWHM] gaussian kernel of 8 mm to 12 mm).23 The smoothed image allows for intergroup comparisons of gray matter density and gray matter volume; the image after modulation represents gray matter volume, and the unmodulated image represents gray matter density. In subsequent statistical analyses, the whole-brain volume of each subject is acquired as a covariate for comparison between groups to eliminate the effects of individual differences in total brain volume, and for comparison of individual patient values with normative data. SBM analysis is usually performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) or CIVET (developed by the McConnell Brain Imaging Centre). The standard procedures of image postprocessing with FreeSurfer include head motion correction, removal of nonbrain tissue,24–26 automated transformation to standard Talairach space, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization,27 tessellation of gray matter and white matter boundary, automated topology correction,26,28 and surface deformation following intensity gradients to optimally place the gray/white matter and gray matter/cerebrospinal fluid borders where the greatest shift in intensity defines the transition to the other tissue class.29

FreeSurfer automatically applies different FWHM (ie, 10 mm, 15 mm, 20 mm, or 25 mm) gaussian smoothing kernels for later statistical analysis. In statistical analysis, between-group comparisons have been performed with the general linear model method, which can include features, such as sex and age, as covariates.30 Cortical thickness, surface area, sulcal features (the number, depth, and frequency) and brain asymmetry can also be quantified.

In DTI, by using tract-based spatial statistics (TBSS) and VBA, parameters, including fractional anisotropy (FA), mean diffusivity, packing density, myelination, and axon diameter, can be quantified to assess changes of the physical properties of white matter bundles. VBA registers all data of the subject (including gray matter and cerebrospinal fluid) into a standard space and performs statistical analyses on each voxel of the brain; then, it locates brain regions with altered parameters. The image data preprocessing and statistical analysis of VBA can be achieved by SPM version 2 and above. TBSS examines the whole brain without prespecifying tracts of interest for estimating localized change in FA by constructing average FA fiber skeleton maps of all subjects first and then registering all FA images of from patients on it to identify altered white matter tracts. TBSS combines the strengths of both VBAs with those of tractography-based analyses, thus avoiding the problem of inaccurate positioning caused by inaccurate image registration and smoothing. It can quantitatively and objectively evaluate white matter structure. Additionally, by using tractography, graph theory analyses can be performed to comprehensively evaluate white matter connectivity in the brain.31–33

Rs-fMRI focuses on spontaneous changes in the BOLD signal in a resting state or task-negative state. In addition to regular data preprocessing, slice time correction, motion correction, spatial normalization, and spatial smoothing are required. The time series needs to be bandpass filtered to assess a particular frequency band of interest (eg, 0.01–0.08 Hz) to eliminate influences of low-frequency signal drift and high-frequency noise caused by respiration and heartbeat and to extract low-frequency signal oscillations that reflect spontaneous activity of the brain.34 Post-processing typically is carried out in 1 of 2 ways: (1) the synchronization analysis of low-frequency oscillations between different brain regions for functional connectivity analyses,35 which is used to identify connectivity alterations in neural networks, such as in the default mode network,33,36 and (2) the regional characteristic analysis of the low-frequency oscillations. The amplitude of
low-frequency fluctuation, fractional amplitude of low-frequency fluctuation, and regional homogeneity are commonly used as indicators to investigate the characteristics of low frequency oscillations in local brain regions.

MRS noninvasively detects and quantifies neurometabolites, such as N-acetylaspartate (NAA) (a putative marker of neuronal viability), choline (Cho) (a marker for membrane integrity and phospholipid metabolism), creatine (Cr) (a marker for energy metabolism), myoinositol (mI) (an astroglial marker), γ-aminobutyric acid (an inhibitory neurotransmitter in mammalian brain), and glutamate or/and glutamine (related to excitatory neurotransmission). One common finding in depression is the reduction of NAA in temporal and hippocampal regions. Other findings included reductions in NAA/Cr, NAA/Cho, and NAA/(Cr plus Cho). For example, the NAA/Cr ratio in prefrontal cortex of individuals with depression has been shown to be significantly lower than that of healthy individuals, with this deficit being greater in moderate than mild depression. Detailed information is provided in John D. Port’s article, “Magnetic Resonance Spectroscopy for Psychiatry: Progress in the Last Decade,” in this issue. These quantitative results may be useful for clinical work.

STRATEGY FOR CLINICAL APPLICATION

Although traditional MRI is widely used to detect tumors or inflammation in patients with psychiatric disorders, the subtle brain abnormalities associated with psychiatric disorders have been noninvasively identified with advanced radiological technologies. Numerous basic, preclinical, and clinical studies have revealed a series of imaging biomarkers of brain structural and functional abnormalities. These studies have greatly promoted understanding of the pathologic mechanisms of abnormal brain structure and function in psychiatric disorders. The clinical value of imaging biomarkers for the most common psychiatric disorders, such as major depressive disorder, schizophrenia, posttraumatic stress disorder, and autism spectrum disorder, are presented in the later chapters of Section Three. In this article, strategies for clinical use are summarized. Generally, psychoradiological biomarkers considered in isolation have not yet been validated for making patient care decisions for individual patients; however, they can visually show psychiatrists and patients subtle structural and functional changes and in the near future help assist doctors in differential diagnosis, treatment planning, and prediction of illness course.

Diagnosis and Subtyping

Psychiatric disorders traditionally have been diagnosed and classified on the basis of broad syndromes defined by patients’ and parents’ reports and behavioral observations rather than on the basis of their underlying neurobiological substrates. As a result, psychiatric syndromes are heterogeneous and they biologically overlap, limiting the success of developing imaging and other biological biomarkers. Because this situation limits feasibility of identifying imaging biomarkers for different psychiatric syndromes, the field has moved in different directions, primarily toward developing objective psychoradiological biomarkers, such as structural features (alterations in gray matter/white matter volume, cortical morphometric features including thickness and surface area, and diffusion properties of white matter tracts) and functional features (activity and connectivity), which can facilitate early diagnosis and subtype patients into more biologically homogeneous groups. The US National Institute of Mental Health proposed the Research Domain Criteria project, with the aim to in part develop psychoradiological biomarkers for psychiatric disorders based on different dimensions of observable behaviors and neurobiological measures that are correlated to specific cognitive constructs across different brain systems.

For example, Sun and colleagues made 1 of the first efforts to subtype psychiatric disorders based on imaging features, and 2 distinct schizophrenia subtypes were identified using DTI. Using fMRI in a multisite sample, it was shown that patients with major depressive disorder can be divided into 4 neurophysiological subtypes (biotypes) by distinct patterns of dysfunctional connectivity in limbic and frontotemporal networks. Clustering patients on this basis led to high sensitivity and specificity (82%–93%) in the development of diagnostic classifiers for depression subtypes with multisite validation and out-of-sample replication data sets. Similar studies have revealed new biotypes in schizophrenia, attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, and other psychiatric disorders, which highlights the potential application for psychoradiology to help subtype patients with psychiatric disorders based on objective imaging markers rather than observation of behavior and symptom profiles and for using these classifications to better individualize patient care in parallel with development of optimal treatment strategies for the identified subgroups.
Psychoradiological biomarkers can be of importance in guiding treatment of patients with psychiatric disorders by helping clinicians make difficult differential diagnoses and select optimal treatment procedures and targets for subgroups of patients with particular neurobiological abnormalities. Psychoradiological biomarkers also may help predict psychiatric disorders in at-risk individuals so that primary prevention approaches can be implemented for those who most need them, so patients likely to be refractory to first-line treatments can be identified before beginning treatment, and so that the fundamental understanding of causal neural mechanisms of illness can be identified to spur development of novel treatments.43–47

For example, studies have identified a distributed pattern of brain activity reflected in fMRI responses during fear conditioning, which can discriminate patients with panic disorder who responded to cognitive behavioral therapy from those who did not with 82% accuracy.45 Using resting-state functional connectivity analyses, other studies discovered that disrupted functional connectivity mainly in thalamocortical circuits is correlated to refractory depression, whereas connectivity mainly in thalamocortical circuits is correlated to refractory depression, whereas connectivity mainly in thalamocortical circuits is correlated to refractory depression, whereas connectivity mainly in thalamocortical circuits is correlated to refractory depression, whereas connectivity mainly in thalamocortical circuits is correlated to refractory depression, whereas connectivity mainly in thalamocortical circuits is correlated to refractory depression, whereas connectivity mainly in thalamocortical circuits is associated with nonrefractory depression.43 Imaging biomarkers also could provide valuable information about treatment targets.3,48 For example, regions including prefrontal cortex and striatum receive robust dopaminergic projections, which are believed to be implicated in the pathogenesis of schizophrenia. Hypofunction of the medial prefrontal cortex as well as hyperactivity of the hippocampus and striatum, in patients with schizophrenia may in time provide psychoradiological biomarkers for the targets of treatment.3

These findings demonstrate promising new evidence that psychoradiological biomarkers may provide valuable information in monitoring and predicting treatment response, which could be of great importance in detecting patients at an early stage who require adjunctive medical and psychosocial therapies, because they may not respond to first-line treatments, and those likely to recover without any intervention, by optimizing timing, intensity, and form of therapeutic intervention.

**Prediction of Illness Onset**

Predicting the onset of illness for a high-risk person is another important role of psychoradiology. Psychoradiological studies have suggested that the brain’s structure and function are different between high-risk individuals who subsequently develop psychosis and individuals who do not.49–52 For example, using multiparadigm fMRI data to investigate network-level changes in functional connectome of the human brain, Cao and colleagues found an individual-specific “trait” abnormality in brain architecture characterized as increased connectivity in the cerebello-thalamocortical circuitry in individuals at clinical high risk for psychosis. This is a pattern that is significantly more pronounced among those who develop psychosis than those who do not among high-risk individuals. This abnormality is significantly associated with thought disorder and predictive of time to conversion.

These findings highlight the potential for psychoradiology to help identify those at high risk for developing psychosis to predict who will later convert to a disease state in advance of its onset. This knowledge can indicate a need for those at greatest risk for early preventive pharmacologic and psychological interventions, while sparing those with lower conversion risk of unnecessary exposure to treatment side effects. These advances could help optimize allocation of clinical resources in mental health care systems.

The workflow pipeline of psychoradiology in clinical practice is summarized in Fig. 1.

**FUTURE CHALLENGES**

Although psychoradiology has great promise as a clinical discipline aiding in the diagnosis and treatment of psychiatric patients, there are still many issues and challenges in this growing field that need to be addressed before routine clinical application.

**Problems in Clinical Translation**

First, MRI-based brain volume measurements can be influenced by various technical parameters, especially when reliability and reproducibility are critical for clinical translation in psychoradiology. For instance, the number of head coil channels, inconsistent subject positioning, inconsistent image contrast, and differences in MR scanner vendors, and field strength can have an impact on interpretation of quantitative image characteristics. Heterogeneity of MRI scanning parameters across studies and sites in voxel size, number of diffusion directions, and slice thickness may have resulted in decreased reliability of functional and structural MRI studies in psychiatric disorders.56–58 These differences are difficult to eliminate by statistical means. Homogenization of technical considerations becomes more crucial with the introduction of multiple MRI scanners, in a
situation where multicenter trials or cross-site application of a diagnostic or predictive algorithm are used. Kruggel and colleagues compared different scanner platforms of 1.5T and 3.0T and found that different levels of image quality, regarding SNR, CNR, and combined information of the joint histogram limited the consistency of brain volume measurements. Hence, data from different scanning protocols and platforms must be carefully considered to avoid confounding the true effects of interest with variability among scanning platforms. Also, this issue highlights the need to establish optimal acquisition parameters for specific clinical applications.

Fig. 1. Workflow pipeline of psychoradiology in clinical practice. AFNI, analyses of functional neuroimages; DPABI, data processing and analysis for brain imaging; EEG, electroencephalography; FSL, FMRIB software library; GRE, gradient echo; PWI, perfusion-weighted imaging; REST, resting-state fMRI data analysis toolkit.
An early study in schizophrenia with fMRI suggested that factors of variation (both artifactual and intrinsic) could be controlled to improve test-retest reliability. Zhao and colleagues analyzed data from 21 subjects who underwent 2 scans within 2 weeks on a 3T MRI scanner from General Electric (Milwaukee, United States) and the third visit on a 3T MRI scanner from Siemens approximately 8 months later for assessment of intrascanner and interscanner reliability of rs-fMRI based on voxelwise whole-brain analytical metrics. The rs-fMRI results indicated that the data were reliable within the same scanner, whereas inter-scanner reliability was a more significant factor when data were compared across platforms and field strength. Data, including MRI-derived measurements in a longitudinal morphometric study of human brains were trustworthy at a single 1.5T site, even with different sequences or after upgrading systems; nevertheless, the reliability should be carefully considered when images are collected across vendors and/or field strength. Changes in scanner hardware can lead to the introduction of different bias effects in the brain analyses, whereas intervendor changes generally exerted greater effects compared with intravendor scanner changes. In the context of quantitative analysis to detect relatively subtle brain alterations, consideration of the impact of technical factors in multisite research and in developing widely useful normative data are particularly important.

The acquisition of structural MRI and fMRI data is costly, especially regarding the time involved in postprocessing. Furthermore, the quality of MRI data is affected by many factors, including head motion, and physiologic factors, such as heart beating and breathing, are critical biological confounds. This is especially with fMRI, where cardiovascular function, age and sex effects, and anatomic variability have an impact on data interpretation. Thus, individual patient variability and protocol/scanner factors are critical for clinical application.

Therefore, it is imperative to establish standardized data acquisition and image quality control solutions. To address heterogeneity between different centers/sequences, a standardized MRI sequence is needed that can generate images with similar properties concerning SNR, CNR, voxel size, and slice thickness, regardless of the scanner platform and manufacturer. Homogeneous data acquisition and analysis can be provided by a specific protocol across sites, like that developed by the Alzheimer’s Disease Neuroimaging Initiative consortium. Even with these efforts, heterogeneities based on site still exist for complicated reasons. Multitask learning has been deployed to simultaneously learn the features of site-shared and site-specific features extracted from multicenter MRI data of brain morphology. Neuroimaging studies have demonstrated the advantages of multitask learning to decode brain alterations and for classifying disease.

Second, it is necessary to develop stable and efficient semiautomated computational approaches for image analysis. Studies of brain morphometry initially used morphometric measurements obtained from brain regions with manual delineation of ROIs. This ROI-based method sometimes encountered difficulties under certain conditions for the delineation of unambiguous structures, such as the hippocampi or the ventricles. VBAs and surface-based analyses can be used to identify whole-brain changes; these analyses are automated, relatively easy-to-use, time-efficient tools and have been widely used in psychiatric research. Such approaches can also shorten the duration of the evaluation pipeline to speed availability of feedback to referring physicians. The recent development of psychoradiological tools to detect the individual-specific biomarkers in patients with psychotic disorders has been extremely exciting. Although reliable, fully automated, standardized methods can improve implementation across different sites with a unified software platform, an individualized approach can be implemented as suited for specific purposes. Standardized pipelines for preprocessing MRI data are becoming increasingly sophisticated, such as improved sequences linked to the Human Connectome Project.

Third, the development of fast multimodal imaging facilities is important. To discover robust neuroimaging biomarkers for diagnosis and patient stratification, multicenter and multimodal studies are becoming popular, thereby increasing sample size and providing detailed imaging features of psychosis patients. Multimodal imaging, which can combine structural MRI, DTI, fMRI, and even PET data together, can scan subjects with a variety of sequences to acquire structural, functional, and metabolic data of the brain in a single session. It is a challenge for psychoradiologists to interpret these combined data sets acquired from variable combinations of different imaging modalities and methodologies, but machine learning approaches offer promise for usefully organizing multimodal data.

A method was specifically developed to analyze multimodal imaging data by Radua and colleagues. This technique is a voxel-wise multimodal meta-analysis applied to anatomic and
fMRI examinations in first-episode psychosis patients. This meta-analysis identified both structural and functional abnormalities in the brain as well as heterogeneity between studies. To speed up the reconstruction of images, Xiang and colleagues\(^83\) fused multimodal MR acquisitions through deep learning. This deep learning approach reconstructed a 3-dimensional T2WI volume from the T1WI data and undersampled T2WI images. This approach was applied to data sets acquired by different MR vendors, and it showed excellent transferring capability. These approaches open the way for faster and more efficient multimodal image acquisition in clinical settings.

**Pathophysiology of Imaging Signs**

In addition to the challenges of particular imaging techniques, the unclear pathophysiology of imaging biomarkers is another challenge when explaining the meaning of brain imaging findings. Until this is resolved, psychoradiology will remain an empirical or actuarial field.

For example, in vivo neuroimaging studies\(^84,85\) have supported the hypotheses that cortical glutamate dysfunction has an impact on subcortical dopamine synthesis capacity, which is a leading theory of the pathogenesis of schizophrenia. It is unclear, however, how alterations in in vivo cortical glutamate and dopamine levels and function result in the pathophysiology of psychosis. PET studies have shown that multiple neurochemical systems and molecular mechanisms can play roles in the pathophysiology of psychosis in the early course of the syndrome.\(^86,87\) In terms of correlations between brain activation and behavior using task-based fMRI (studying brain activity as a particular cognitive, motor or emotion task is performed) to study individual differences, it is crucial that behavioral paradigms be optimized for clinical application. These studies can be effective in challenging brain circuitry of clinical interest and relating brain alterations to clinical features of interest, but add an additional layer of methods validation.

Region-specific structural changes in the rat cortex\(^88,89\) after chronic antipsychotic treatment raise the issue that psychopharmacological treatments themselves can alter brain anatomy and function and thus have an impact on the use of algorithms for diagnosis and prediction. Postmortem structural studies in schizophrenia\(^90\) found volume and cell number reduction in the pulvinar with stereological studies of the thalamus. This finding is in accordance with the view that thalamocortical dysfunction might play a role in schizophrenia because of the function of the thalamus as a key node in whole-brain neuronal circuits. This type of finding highlights the importance of network-level analysis of brain systems in studies of psychiatric illness. Structural imaging studies\(^91,92\) provide evidence of volume reductions in bilateral thalami in schizophrenia that support the thalamocortical dysfunction hypothesis in patients with schizophrenia. Although understanding of the pathogenesis of psychiatric illness remains limited, these initial results highlight the potential value of psychoradiology in better understanding the pathogenesis of serious mental illness and the translation of these findings into clinical practice.

**Heterogeneity of Psychiatric Disorders**

Psychiatric disorders are now diagnostically classified as broad syndromes defined based on patient complaints and behavioral observations.\(^1\) The overlap of these syndromes in terms of illness presentation, genetics, neurobiology, and treatment response profiles remains large. This highlights the importance of psychoradiology not only for patient care but also as an important field working toward nosologic reorganization for diagnosis of serious mental illnesses based on biological features. In this latter effort, in vivo brain imaging can play a crucial role, to the great advantage of efforts to identify biologically discrete patient subgroups requiring specific therapies based on the nature of their brain disturbances.

Individuals with symptoms indicating that they are at risk for serious mental illness based on psychological assessment may share a phenotypic expression but one that results from different underlying brain abnormalities as suggested by recent large-scale multisite collaborative studies. For instance, autism spectrum disorder and schizophrenia share clinical features, including social withdrawal, theory of mind deficits, and sensory abnormalities.\(^93-95\) It is not uncommon that several mental disorders show similar anatomic and functional deficits in brain networks including schizophrenia and bipolar disorder.\(^96\) Psychiatric disorders share similar neurocognitive deficits\(^97\) and overlapping features of emotional disorders.\(^1\) Wang and colleagues\(^98\) analyzed the multisite data set of patients with ADHD (ie, data from the ADHD-200\(^99\)) with rs-fMRI based on 3 whole-brain VBA methods. Abnormal activity was found in some brain regions with the pooled data set; however, these results were highly heterogeneous across cohorts and within the same research center. The results from the study of multisite functional connectivity classification of autism\(^100\) also
indicated a poorer degree of accuracy of whole-brain functional connectivity in favor of heterogeneous features of connectivity disturbances with a particular spatial distribution in specific brain regions.

The clinical and imaging heterogeneity of psychiatric syndromes resulted in compromised specificity when assigning psychiatric disorders using machine learning approaches with MRI data. This has led many in psychiatric research to step back and conclude that the next step forward needs to be collecting large samples in multisite projects with dense phenotyping (including but not restricted to MRI) to identify biologically discrete patient groups, which can then be studied separately or stratified in clinical trials and genetic research. In this way, the clinical relevance of novel patient subgrouping approaches developed using MRI data can be evaluated. This is especially important as decades of patient subgrouping efforts based on psychological and behavioral features has produced limited gains. Until this issue of within diagnosis heterogeneity is resolved, the ability to identify MR biomarkers for diagnosis or guiding treatment decisions remains limited. The best way for psychoradiology to address this issue is to use psychoradiology and machine learning with prolonged imaging times, standardized acquisition strategies, advanced classification methodology, and large sample sizes to identify distinct patterns of brain abnormalities that run across and are not specific to particular psychiatric syndromes, and to define patterns of brain alterations and their relation to cognitive, affective, and behavioral clinical manifestations.1

This effort will require considerable interdisciplinary collaboration, from radiologists and physicists optimizing acquisition protocols, to statisticians and programmers developing rapid and automated measurement of brain features of interest, and to clinicians, psychiatrists, and psychologists working to translate new approaches into clinically useful contributions for improving psychiatric patient care.

SUMMARY

Psychoradiology is a young and evolving field. Research to date is already showing the utility of MRI data in psychiatry for facilitating clinical diagnosis, evaluation of treatment response and prognosis, identifying patient subgroups, and illness risk prediction. Further advances to translate these observations into clinical practice will require proper examination and validation of image acquisition and processing methods, rigorous image quality control, and standardized semiautomated image analysis. Addressing complex issues, such as the biological heterogeneity of psychiatric syndromes and unclear neurobiological mechanisms underpinning radiological abnormalities, is a challenge that needs to be resolved but one for which psychoradiology can make important contributions. With the advance of multimodal imaging and more efforts in standardization of image acquisition and analysis, psychoradiology has become a promising tool for the future of the clinical care of patients with psychiatric disorders.

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