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ADVANCES IN NEURODEGENERATIVE AND PSYCHIATRIC IMAGING SPECIAL FEATURE: REVIEW ARTICLE

Progress in psychoradiology, the clinical application of psychiatric neuroimaging

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ABSTRACT:

Psychoradiology is an emerging field that applies radiological imaging technologies to psychiatric conditions. In the past three decades, brain imaging techniques have rapidly advanced understanding of illness and treatment effects in psychiatry. Based on these advances, radiologists have become increasingly interested in applying these advances for differential diagnosis and individualized patient care selection for common psychiatric illnesses. This shift from research to clinical practice represents the beginning evolution of psychoradiology. In this review, we provide a summary of recent progress relevant to this field based on their clinical functions, namely the (1) classification and subtyping; (2) prediction and monitoring of treatment outcomes; and (3) treatment selection. In addition, we provide guidelines for the practice of psychoradiology in clinical settings and suggestions for future research to validate broader clinical applications. Given the high prevalence of psychiatric disorders and the importance of increased participation of radiologists in this field, a guide regarding advances in this field and a description of relevant clinical work flow patterns help radiologists contribute to this fast-evolving field.

INTRODUCTION

Psychoradiology is an emerging field that applies radiological imaging technologies to psychiatric conditions, and Gong et al have been its pioneers.[1] In a recent editorial published on JMRI which is the official journal of ISMRM, psychoradiology was recognized as a new subfield where the value of MRI for psychiatric applications had been emphasized.[2] The term was selected to parallel that of the field of neuroradiology, and to reflect the evolution of the research field of psychiatric neuroimaging to a new medical practice discipline. The broad aim of this field in some ways builds upon advances in the RDoC initiative from the NIMH in the USA which was structured to advance systematic objective behavioral and neurophysiological measurement of features related to psychiatric illness. It is also an effort aiming to advance precision medicine in psychiatry by using radiological examinations to guide more individualized treatment planning than is now possible using only traditional psychiatric evaluation.

The potential clinical utility of using brain structural and functional imaging to investigate cerebral alterations in psychiatric disorders has been demonstrated in hundreds of MRI studies of major psychiatric disorders[3] including schizophrenia[4] and depression.[5,6] Based on these advances in psychiatric neuroimaging research, there has been growing interest in developing clinical applications for diagnosis, prognosis and treatment planning. These

developments have led to the emergence of psychoradiology as a new subfield in radiology. Psychoradiology has developed to utilize radiological imaging approaches for differential diagnosis and individualized patient care for psychiatric illnesses. Given the high prevalence of psychiatric disorders, this is particularly important, where the development of the multimodal MRI has allowed quantification of brain characteristics at the structural, functional and molecular levels.

In the current review, we provide a summary of the progress in psychoradiology research in relation to clinical functions: (1) classification and subtyping heterogeneous psychiatric syndromes; (2) monitoring and predicting treatment response, and (3) guiding treatment selection. We then discuss issues related to implementing neuroimaging into clinical psychiatric practice with a suggested work flow for confirming diagnosis and guiding minimally invasive and optimally therapeutic interventions such as psychiatric medications, transcranial magnetic stimulation (TMS) and other procedures in the evolving subfield of interventional psychoradiology. While these clinical uses remain to be qualified for particular uses and validated as useful biomarkers, progress proceeds at a rapid pace and planning for the clinical emergence of psychoradiology is timely.

Rather than giving a systematic review regarding this rapid developing and large field, we will emphasize areas of research where promising new findings are now available and the path forward for the field. The potential real-world utility of these techniques as clinical tools will likely be based on the fusion of information from different imaging modalities and the selection of the most informative markers for particular clinical purposes. This work in many ways represents a translational step leveraging the extensive existing psychiatric brain imaging literature for developing the applied field of psychoradiology. We hope that by providing an overview of recent developments, this review will serve as a guide for the practice of psychoradiology in clinical settings as radiologists more actively engage and advance this fast-evolving field.

CLINICAL FUNCTIONS OF PSYCHORADIOLOGY

Classification and subtyping

Diagnostic practice in psychiatry has long been criticized for subjective diagnosis of ill-defined and overlapping clinical syndromes. Subtyping of common complex syndromes based on clinical symptoms has not successfully reduced the heterogeneity of these syndromes with robust clinical or research utility. As a result, current syndromal diagnoses, as in the early phase of most areas of medicine, are to a degree placeholders, or general descriptions for clinical description, necessary until neurobiologically discrete subgroups and related nosological distinctions can be established. These features of diagnostic practice in psychiatry differ from most areas of medicine that define diseases based on biological measures and pathophysiological models.

As a result, several investigators have proposed that new strategies and nosologies are needed to guide diagnosis and syndrome subtyping based on objective biomarkers. Pattern recognition or machine learning techniques have shown promise for detecting biomarkers from neuroimaging data and making diagnostic predictions in clinically defined psychiatric disorders.[7] Subtyping patients with syndromal diagnoses using statistical cluster analysis or related approaches to group individuals according to shared signatures of brain abnormalities has been a common focus of studies.[8] This latter approach has the potential to identify biologically homogeneous groups within and across current diagnoses, for which novel treatments may be applied or developed based on identifiable shared biological abnormalities rather than symptom profiles that do not robustly separate syndromes into meaningful patient subgroups in the current psychiatric nosology. Ongoing psychoradiology research may provide diagnostic biomarkers for known disorders, but also actually define new biologically distinct disorders to jumpstart neuroscience drug development that has been stalled for decades.

Use of support vector machine (SVM), a popular machine learning technique, has been widely applied in various psychiatric disorders to overcome univariate analysis at the patient group level. It has revealed patterns of brain abnormalities that differentiate patient groups, but to date it has limited clinical translation particularly for single patients.[9] This method had been applied to both structural or functional imaging in a number of psychiatric disorders including schizophrenia,[10] depression,[11] and obsessive compulsive disorder (OCD).[12,13] In recent years, more advanced algorithms such as deep learning (DL) have been increasingly used to investigate the neuroimaging features of psychiatric and neurological disorders. DL methods differ from conventional machine learning methods by virtue of their ability to learn the optimal representation from raw data through consecutive nonlinear transformations. DL can achieve increasingly higher levels of abstraction and complexity to detect patterns of subtle and diffuse alterations. In this way, DL represents a powerful tool in the search for clinically useful biomarkers of psychiatric disorders[14] and its utility in psychoradiology is becoming widely recognized.

By using rs-fMRI in a large multisite sample of 1188 subjects, Drysdale et al[15] showed that patients with depression can be subdivided into four neurophysiological subtypes ("biotypes") defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. In addition, clustering patients on this basis enabled the development of diagnostic classifiers with high sensitivity and specificity validated by out-of-sample replication analysis. These biotypes could not be readily or robustly differentiated based on psychiatric clinical evaluation, and show promise in predicting responsiveness to transcranial magnetic stimulation therapy. More recent work from Sun et al[16] based on structural and diffusion MRI had selected features representing the shape properties of gray matter and diffusion properties of white matter to identify significant discriminative power for diagnosis and subtyping of attention-deficit/hyperactivity disorder (ADHD). With comprehensive analysis and robust validation methods, those studies illustrate the potential utility of radiomics and added value of psychoradiology approaches for clinical practice in psychiatry.[17]

This biomarker approach contrasts with most psychiatric studies that stratified patients based on symptom clusters within a single diagnostic category (*e.g.* schizophrenia[18–20] psychotic disorders,[8,21] depression,[22–26] ADHD,[27–29] and autism.[30–32] One recent study[33] applied a data-driven framework for identifying robust subtypes across major depression, panic disorder, and post-traumatic stress disorder. By recruiting 420 individuals with the above diagnoses, they identified transdiagnostic subtypes coherent across symptom, behavioral, and neural levels. This kind of approach can help disentangle the symptom-level overlap in conventional psychiatric diagnoses with the ultimate goal of developing nosological categories based on biological rather than behavioral characteristics, and targeting treatment options to more homogeneous and differentiated subgroups than is not achieved using behavioral symptoms alone.

Predicting and monitoring

Clinical syndromal diagnosis can be reliably accomplished using psychiatric evaluations in the large majority of patients. For this reason, developing diagnostic biomarkers represents more of a step to show clinical utility of MRI rather than a primary aim in itself. What is more appealing to the clinical psychiatric field is the potential of radiological imaging markers not to assist with differential diagnosis, but to help with subgroup identification, prediction of treatment outcomes, and early detection of outcomes to make treatment modifications earlier than is now possible. There is also interest in objective markers to help predict onset or relapse of a syndrome, and risk for adverse events that cannot be well predicted by psychiatric examination such as suicide risk and adverse drug responses.

Predictions of illness onset, relapse and long-term prognosis

The prediction of psychosis onset in, at risk individuals (based on familial background or subclinical behavioral difficulties) has been actively studied based on clinical symptoms including attenuated or brief psychotic symptoms and a marked decline in functioning.[34] It has been found that about one-third of individuals presenting with these prodromal features develop a psychotic disorder within 3 years. However, predicting which individual is at increased risk to develop psychosis has been a challenge for clinical management because clinical/behavioral and family background on their own are weak predictors of transition to a psychotic disorder. With advances in image acquisition and analysis, it has been suggested that the structure, function, and biochemistry of the brain in high-risk individuals who will become psychotic differ from those in individuals who do not become psychotic.[35] Thus, the development of techniques that allow clinicians to tailor interventions to the level of risk is a major translational goal for research in this field.[36]

Using structural MRI, Das et al[37] performed graph-based gyrification connectome analysis in the early stages of psychosis and tested the accuracy of this systems-based approach to predict a transition to psychosis among clinical high-risk (CHR) individuals. They found that gyrification-based connectomes provided a promising means to improve individual prediction of a transition to psychosis in CHR individuals.

Mario et al[38] examined functional connectivity (FC) in the reward network at baseline to predict depressive disorder in a community sample of adolescents. They found that ventral striatum FC related to reward sensitivity predicted future risk for depressive disorder. This striatal node FC strength did not predict other common adolescent psychopathology, such as anxiety, attention deficit hyperactivity, and substance use disorders.

Relapse prediction is especially important in psychiatry given the risks of relapse such as suicide and unemployment, and the relatively long time often needed to fully benefit from psychiatric drug therapy. Zaremba et al[39] examined whole-brain and region-of-interest changes in gray matter volume (GMV) and cortical thickness over 2 years in 60 patients with acute major depressive disorder (MDD) and 54 healthy controls. They found that patients with relapse showed a significant decline of insular volume and dorsolateral prefrontal volume which are crucial for regulation of emotions from baseline to follow-up. Early identification of these changes may allow for early intervention to reduce risk for relapse, which would represent a use of neuroimaging studies for guiding maintenance treatment in patients with recurrent MDD.

With the development of imaging data algorithm, Gifford et al[40] used machine learning methods to predict onset of psychosis in individuals at high risk by incorporating multiple imaging modalities in the predictive model and found that ML methods predicted clinical outcomes. Other researchers[41] have developed multicenter MRI prediction models and performed multimodal fusion of MRI data to enhance prediction accuracy to enable individualized prediction regarding multiple clinical measures and outcomes.[42]

The cutting-edge of using ML to predict onset of psychiatric disorders is now combining neuroimaging markers with psychiatric clinical profiles in prediction models. For example, Lebedeva et al[43] has shown that adding the baseline Mini-Mental State Examination (MMSE) scores to imaging data can improve the accuracy/sensitivity/specificity beyond what is possible for either measure alone for predicting mild cognitive impairment (MCI) and dementia 1 year prior to diagnosis in late life depression (LLD) patients.

A recent study by Koutsouleris et al[44] established machine-learning prediction models trained on clinical, imaging-based, and combined information to determine social-functioning outcomes at 1 year for patients in CHR states and with recent-onset depression across geographically distinct populations. They found that lower functioning before study entry was a transdiagnostic predictor of outcome. Medial prefrontal and temporo-parieto-occipital GMV reductions and cerebellar and dorsolateral prefrontal GMV increments had predictive value regarding psychosis onset in the CHR group; reduced medio-temporal and increased prefrontal-perisylvian GMV had predictive value in patients with recent-onset depression. This study demonstrated that psychoradiology has potential as a tool in precision medicine for predicting future clinical outcomes and events. With such information, psychiatrists might augment and

individualize therapeutic interventions aiming to improve social functioning and clinical outcomes.

These studies document potential clinical utility for psychoradiology, and indicate that future efforts may need to combine psychiatric and psychoradiological data in prediction models to achieve optimal clinical utility. With such advances, replication studies and ongoing optimization of imaging parameters for various clinical applications, psychoradiology offers potential for a quantum leap forward in diagnostic and treatment planning practice in clinical psychiatry.

Predicting and monitoring treatment response

The ability to predict an individual patient's response to treatment would permit clinicians to more prudently plan and modify treatment to improve patient outcomes and ultimately better allocate patient care resources. Psychoradiological biomarkers of abnormal brain function have proven utility in the prediction of treatment response[45–49] in depression and outcome of global functioning of patients with CHR for psychosis.[50,51]

MDD is the second leading cause of disability worldwide.[52] Important problems such as the low rate of remission after first treatment[53] and the high relapse rate[54] both contribute to the high level of disability associated with this illness. For this reason, the prediction of treatment response and relapse has profound clinical significance. Identifying neural mechanisms underlying those issues has been a central aim in previous correlational neuroimaging studies.[55–59]

One recent study[60] used measurements of hippocampal subfield volumes to predict early response to antidepressant treatment in drug-naïve patients with MDD. This study found that pre-treatment volumes of specific hippocampal subfields were associated with antidepressant treatment response. Another study related increased hippocampal tail volume to remission following antidepressant medication treatment in patients with major depression.[61] Smaller hippocampal volume has previously been associated with poorer outcomes following antidepressant medication treatment.[62] All those studies aim to predict treatment response with available imaging analysis techniques. Clinically, this is important because slow acting standard treatments for psychosis and depression means medication trials often continue for 4–6 weeks to evaluate clinical benefit, and new ways to guide earlier decisions about changing treatments or dose could greatly improve standard clinical care and improve clinical outcomes.

Reggente et al[63] used machine learning with cross-validation to assess the utility of FC patterns for predicting individual patient posttreatment symptom severity in OCD patients after 4 weeks of daily cognitive behavioral therapy (CBT). They found that pretreatment FC patterns within the default mode network and visual network significantly predicted post-treatment OCD severity, and did so more robustly than pretreatment clinical psychiatric ratings.

Treatment selection

Selecting specific drugs and even drug classes is a challenge in clinical psychiatry. It is particularly important because of the slow gradual onset of action of many widely used psychiatric medications. Imaging biomarkers of abnormal brain function appear to have some utility in treatment selection for psychiatric disorders.

In a recent study by Zhang et al[64] of pediatric bipolar disorder, the authors began with a cluster analysis of cortical thickness data and identified two patient groups, one with regional decreases in cortical thickness and one with increased regional thickness. After scans, patients were enrolled in a randomized clinical trial (RCT) to either lithium or quetiapine therapy. Patients with increased cortical thickness responded better to quetiapine than the group with decreased thickness, but the groups did not differ in lithium response. This approach of doing cluster analysis with pre-treatment data before a RCT has considerable appeal, as it allows for identifying discrete heterogeneity in complex syndromes and then an evaluation of treatment outcome prediction in the identified subgroups.

To date, many of the studies have predicted response to a single-intervention, which has the limitation that they do not provide information about whether an alternative treatment would have been more or less effective than the evaluated one. This makes it difficult to determine whether the imaging marker of interest indicates response regardless of treatment, or is specific to the intervention in the study.[65] Thus, treatment outcome-based studies are more valuable if they precede a RCT comparing different treatments, especially when those approaches work via differing mechanisms (*e.g.* medication *vs* psychotherapy *vs* TMS).

The studies from Mayberg et al were performed with such aims. They had two RCTs to identify neuroimaging patterns that could differentially predict outcomes to treatment with an antidepressant medication or CBT. Their first study used fluorodeoxyglucose-PET to establish that resting metabolism of the right anterior insula could distinguish remitters from non-responders to treatment with the antidepressant escitalopram and CBT.[66] Their later resting state fMRI study identified FC patterns in the subcallosal cingulate cortex and three other brain regions that distinguished responders and non-responders to antidepressant medication (escitalopram or duloxetine) and to CBT.[67]

These treatment outcome prediction studies establish the promise of clinical psychoradiology. Imaging studies appear to have potential for predicting failure to standard first line treatments for depression even before treatment initiation. In this event, application of interventions usually reserved for treatment-resistant depression, such as TMS, electroconvulsive therapy, or ketamine might be initiated earlier to avoid months of ineffective treatment.

GUIDELINES FOR THE PRACTICE OF PSYCHORADIOLOGY IN CLINICAL SETTINGS

Current studies[4,20,58] provide support for the potential clinical value of psychoradiology in clinical diagnosis, prediction and treatment evaluation of patients with psychiatric disorders. In this context, it seems prudent to begin to think through appropriate clinical guidelines for this emerging field at the interface of radiology and psychiatry. Recently, the MR group in the Chinese Society of Radiology published the first expert consensus report on the clinical psychoradiological MR examination of patients with schizophrenia in China[68] . This consensus paper proposed that patients with suspected diagnosis of schizophrenia should have MR examination including high spatial (1 mm at least) resolution structural imaging besides traditional clinical MR scans with higher slice thickness. Quantitative analysis of GMV and cortical thickness are recommended to identify patterns of regional gray matter changes.[4] Besides the scanning sequences and data analysis, the consensus also suggested additional requirements for the safety of patients and additional environmental considerations before and during MR examinations that are of special importance for psychiatric patients.

INTERVENTIONAL PSYCHORADIOLOGY

One potential future role of psychoradiology may be to guide minimally invasive or non-invasive procedures for psychiatric patients under radiological imaging guidance. This is a component of "interventional psychoradiology," which is a new subfield of interventional radiology. A similar role might be considered for neuromodulation therapies. Its ultimate goal is to precisely localize the optimal brain regions for the targeted neurostimulation treatment under imaging guidance to improve therapeutic efficacy for psychiatric patients.

Helen Mayberg et al have been pioneers in interventional psychoradiology, performing the deep brain stimulation (DBS) for patients with major depression.[69–72] DBS has been approved by the FDA in the USA for movement disorders and for humanitarian use in severe treatment-nonresponsive OCD, with different target areas in brain. For example, the striatum, subthalamic nucleus or internal capsule have been selected as a targets of DBS, but the response rate and side-effects vary among different patient groups.[73] In the case of depressive disorder, subcallosal cingulate cortex is the target for many studies, while the medial forebrain bundle has been another target. However, the results of clinical trials to date have not been positive.[74] Current imaging-guided placement of electrodes using conventional radiological facilities may not be sufficiently accurate, and greater precision for the targeted intervention might be achievable using MRI to advance research and practice in this area. One would see this as a potential future area for psychoradiology research.

CHALLENGES TO THE CLINICAL APPLICATION OF PSYCHORADIOLOGY

In the past two decades, radiological imaging methods and image analysis techniques have rapidly evolved to provide powerful quantitative tools in studying the human brain. These methods, which are more precise and sophisticated, have made possible the identification of the subtle structural and functional brain changes associated with psychiatric disorders. While methodological issues continue to be addressed and resolved, progress may not have been sufficient to warrant enthusiasm and the initiation of large multisite validation studies to establish the clinical utility of MRI in psychiatry. There are multiple practical challenges on the path to developing MRI measures as diagnostic and predictive biomarkers in psychiatry.

First, because neuroimaging findings were rarely replicated (using identical settings) in psychiatric samples in the past, the optimal acquisition parameters and analytical methods to extract pertinent clinically useful information for individual patient care planning will need to be determined. In addition, with the development of technologies and the availabilities of a large number of complimentary imaging methods, the approaches for combining and using the multimodal information provided using MRI examination needs to be established.

In addition, recent scientific and methods development will require reexamination of some previous observations. For example, most prior resting fMRI studies investigating different frequency focused on the traditional low-frequency band (0.01–0.1 Hz). However, recent studies have demonstrated the presence of resting state FC patterns at frequency bands higher than 0.1 Hz.[75,76] Gohel et al[77] investigated the amplitude of frequency fluctuations within discrete frequency bands and higher than 0.1 Hz in patients with psychosis at different illness stages. Moreover, study of dynamic as well as static FC, and explorations of clinical significance of connectivity in specific frequency bands may provide additional clinically useful information.[78]

Second, as in any field, there can be considerable discrepancies across studies. Some of this may be due to differences in patient recruitment strategies, demographic considerations or MR protocols, but some variations may be true within disorder inconsistency. The way forward to address this issue is the need to conduct larger-scale consortia multisite studies that collect sufficiently large samples that within disorder heterogeneity can be leveraged to identify more biologically homogeneous subgroups of patients than comprise the original syndromal diagnosis. Ideally, advances along these lines will identify groups with differential optimal treatments, so that MRI data can be used to guide personalized care for patient subgroups who meet criteria for a particular syndrome but whose psychiatric presentation may not differ significantly. These data collection could be further enhanced using statistical methods to harmonize these data collected across multiple data sites.

FUTURE DIRECTIONS

Although numerous clinical studies have identified imaging biomarkers for mental disorders and clarified their pathological mechanisms, their capacity to identify the unique structural and functional architecture of an individual's brain is a critical step towards individual-specific brain analysis for psychoradiology. Wang et al[79] have developed a novel cortical parcellation approach to accurately map functional organization at the individual subject level using resting-state fMRI. More work will be needed in this field to validate and determine optimal

parcellation approaches and other optimal applications for new imaging methods.

Moreover, diagnostic biomarkers need to demonstrate utility in the differential diagnostic challenges most frequently encountered in psychiatry, such as schizophrenia *vs* bipolar disorder, bipolar disorder *vs* major depression, and ADHD *vs* high functioning autism *vs* bipolar disorder in pediatric patients. Additionally, clinical samples will need to be examined, not the relatively confound-free samples used in mechanistic research, but maybe more complex sample with comorbidity which is the real clinical situation.

Improvements in quantitative analyses makes MRI an indispensable tool to elucidate the neurobiological substrates that underlie psychiatric illnesses.[80] While longitudinal clinical trials are needed to solidify those findings before final clinical implementation, we already stand at the cross-road with new paths for radiologists to play an important role in diagnosis and treatment of psychiatric disorders.

Finally, pharmacological MRI based on the principle that neurotransmitter-specific drug challenges evoke regional changes in neurovascular coupling and resultant changes in brain hemodynamics, such as the CBF, will be another type of marker worth more notification for the psychoradiology practice. In a recent RCT, by using noninvasive pharmacological MRI, Schrantee et al demonstrate age-dependent effects of methylphenidate treatment on human extracellular dopamine striatal–thalamic circuitry in young *vs* adult patients with ADHD.[81]

CONCLUSION

In summary, using high-field MRI (*i.e.,* 3.0 Tesla and higher field MRI), the structural and functional correlates of a number of psychiatric disorders have been identified. These results provide the basis for a major step forward towards the translational use of psychiatric imaging for diagnosis, prediction of treatment response, and monitoring therapeutic interventions. For success of this field, we note that interdisciplinary teams involving radiologists, psychiatrists, psychologists, and physicists, biochemists, mathematicians and engineers with computer science skills are needed to develop optimal measurements for the examination of psychiatric patients.

Radiologists need to take an active role in carrying out clinical trials to establish and validate the utility of imaging markers and the use of quantitative imaging measures that can be readily used in clinical settings. They also need to become familiar with the quantitative procedures required to detect the relatively subtle brain changes typically associated with neuropsychiatric disorders, and the functional brain system conceptualizations of psychiatric disorders. We hope that more clinically orientated validation studies will be carried out in the near future to achieve this end given the urgent need for improving clinical outcomes of psychiatric patients.

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