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REVIEW

Translational application of neuroimaging in major depressive disorder: a review of psychoradiological studies

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Abstract **Major depressive disorder (MDD) causes great decrements in health and quality of life with increments in healthcare costs, but the causes and pathogenesis of depression remain largely unknown, which greatly prevent its early detection and effective treatment. With the advancement of neuroimaging approaches, numerous functional and structural alterations in the brain have been detected in MDD and more recently attempts have been made to apply these findings to clinical practice. In this review, we provide an updated summary of the progress in translational application of psychoradiological findings in MDD with a specified focus on potential clinical usage. The foreseeable clinical applications for different MRI modalities were introduced according to their role in disorder classification, subtyping, and prediction. While evidence of cerebral structural and functional changes associated with MDD classification and subtyping was heterogeneous and/or sparse, the ACC and hippocampus have been consistently suggested to be important biomarkers in predicting treatment selection and treatment response. These findings underlined the potential utility of brain biomarkers for clinical practice.**

Keywords psychoradiology; major depressive disorder; MRI; biomarker

Introduction

Characterized by a persistent low mood and a feeling of sadness and loss of interest, major depressive disorder (MDD) causes great decrements in health and quality of life and increments in healthcare costs [1]. The causes of MDD may be associated with several risk factors, such as a family history of mood disorders, gender, major life events or stress, trauma, and low socioeconomic status [2]. However, the causes and pathogenesis of depression remain largely unknown. Furthermore, there are several issues needed to be solved in the clinical practice in MDD.

First of all, the clinical diagnosis of psychiatric disorders has been criticized for years due to its symptom-based diagnostic pattern. The clinicians make a diagnosis of MDD depending on the appearance of a number of symptoms that greatly affect the emotional, cognitive, and social functioning in patients for a period lasting at least two weeks [3]. Detection of subtle clinical abnormalities in the early phase of this disorder requires skilled doctors who are highly specialized in mental health services. MDD and other mood disorders, share several symptoms and treatment responses similarities that could be explained by a common etiology [4–6]. Moreover, MDD is a heterogeneous clinical syndrome that has multiple integrations of alterations in emotion, appetite, sleep, cognition, motor activity, and social function [7]. This complexity has increased the challenges in delivering accurate diagnosis and effective treatment of MDD. As a result, new strategies and nosologies are required to guide the classification and subtyping using objective biomarkers with high sensitivity and specificity.

Second, despite advances in pharmacology, approximately 50% of MDD patients will not have full remission of symptoms despite first-line treatments [8,9]. For the patients who do not respond to standard antidepressant treatment, i.e., refractory depression [10], selecting the

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most effective treatment or combination of several kinds of treatments will shorten the duration and reduce the number of ineffective treatment trials [11]. To develop personalized treatments and improve patient outcomes, there is an urgent need of discovering biomarkers for the assessment of treatment outcome and the selection of subjects who are most likely to benefit from treatment.

With the development of neuroimaging techniques, there is an emerging research field, i.e., psychoradiology which results from the integration between the fields of psychiatry and radiology [12]. Psychoradiology has been recognized as a new research subfield of radiology where the traditional neuroimaging techniques, such as magnetic resonance imaging (MRI) combined with new computational science to play important roles in the research and clinical practice of psychiatric disorders [13]. The term, psychoradiology was selected to parallel that of the field of neuroradiology and there were main discrepancies between these two fields (Table 1). Neuroradiology mainly focuses on diagnosis and characterization of abnormalities in central and peripheral nervous system using traditional imaging methods, and the abnormalities are usually visible to the naked eye. Nevertheless, psychoradiology focuses on the emotion, behavior, and advanced cognitive function of subjects. The abnormalities are usually invisible using traditional imaging methods which needed to be further analyzed with the help of computer science. Psychoradiology also aims to explore the association or causal relationship between the cerebral changes and alterations in emotion, behavior, and advanced cognitive function. Psychoradiological researches on MDD had revealed both cerebral structural and functional alterations at cortical and subcortical level [14–17].

In recent years, there is a move toward the translational application of psychoradiology in clinical practice, which means applying psychoradiological findings with a specified focus on its translational potentiality such as selecting the most informative biomarkers or predictors that could be used in disorder classification, subtyping, prediction, and treatment monitoring [18]. In this review, we provide an updated summary of the progress in this foreseeable translational applications achieved for different MRI modalities in disorder classification, subtyping, and prediction in MDD. We emphasize the importance of clinical validation of those results with some suggestions on how future studies could help to shift the research findings from bench to bed.

Structural findings and potential clinical utility in MDD

MRI can provide structural information of brain, including gray matter volume and cortical thickness, white matter integrity and density. Gray matter volume can be measured using voxel-based morphometry (VBM), which involves a voxel-by-voxel comparison of gray matter partitions in the brain [18,19]. Many neuroimaging studies have reported group level anatomical brain volume changes in MDD patients in the frontal lobe, parietal lobe, thalamus, caudate, pallidum, putamen, temporal lobe, hippocampus, and amygdala [20–22]. Recently, a meta-analysis reported thinning of cortical thickness in the bilateral orbitofrontal gyrus, left pars opercularis, and left calcarine fissure/lingual gyrus, as well as thickened cortical thickness in the left supramarginal gyrus in the MDD patients compared to healthy subjects [23]. The white matter integrity can be evaluated with diffusion tensor imaging (DTI) by either directly assessing the fractional anisotropy (FA) of water molecule diffusion along axonal fibers, or measuring connectivity using multiple forms of white matter tractography [24,25]. Previous meta-analysis had found that MDD patients showed reduced FA in right inferior longitudinal fasciculus, right inferior fronto-occipital fasciculus, right posterior thalamic radiation, and inter-hemispheric fibers running through the genu and body of the corpus callosum [26].

Structural biomarker for MDD classification

To identify useful structural biomarkers for the classification of MDD, many studies have utilized the machine learning methods [27,28], such as the support vector machine (SVM) and the relevance vector machine (RVM) which train classifiers that can distinguish patients group from healthy controls group at an individual subject level [29–31].

Mwangi *et al*. [32] combined machine learning with features selection and description, to differentiate between MDD patients and controls based on a multi-center data set of T1-weighted structural scans. The RVM analysis showed a good performance with 90.3% accuracy, 87.5% specificity, and 93.3% sensitivity. The SVM analysis achieved almost as good performance as the RVM analysis. Similarly, Qiu *et al*. [33] reported that first-episode, medication-naïve MDD patients and healthy

Table 1 Difference between research by psychoradiology and traditional neuroradiology

	Psychoradiology	Neuroradiology
Aim	Association or causal relationship	Diagnosis
Subject	Behavior and cognitive function	Central nerve system and neural function
Methodology	Objective results from algorithm computation	Subjective decision with naked eyes

subjects could be distinguished by both volumetric and geometric parameters, in which the cortical thickness in the right hemisphere showed the best performance with 78% accuracy. This classification was achieved by a bilateral network mainly comprising the frontal, temporal, and parietal regions. However, more recent work by Yang *et al*. [34] based on a multicenter, multimodal imaging data set of diffusion and structural MRI reported that the binary classification achieved 87.95% sensitivity and 32.00% specificity in the validation analysis of 83 MDD patients and 25 healthy controls. The mean FA in the left medial orbitofrontal cortex and right cuneus highly contributed to the prediction of MDD. The classification performance was not sufficiently good for clinical application, and the poor accuracy of the results may reflect the current equivocal findings. Future studies could utilize the study features (large sample size, multimodality, robust methods, and additional validation analyses) and other potential neurobiomarkers from additional imaging modalities or behavioral data to identify more clinically relevant MDD biomarker.

Structural biomarker for MDD subtyping

Due to the heterogeneous clinical symptoms of MDD and the increasing need for personalized medicines, there is a tendency toward subtyping and expanding the psychiatric nosology in this disorder. In early days, researchers have proposed vascular depression (VD) as a unique subtype of late-life depression [35–37]. The hallmark of MRI findings of VD is the white matter hyperintensities (WMHs) identified in T2-weighted or fluid attenuated inversion recovery sequences. MRI hyperintensities were found to be over-represented in the late-life depression patients [38–41]. Increased WMHs severity may serve as a risk factor for future depression and it may reach as high as 8.1 times greater risk [42]. WMHs have also been associated with poor response to antidepressant treatment [43–47]. Except for the white matter lesions, structural abnormalities in vascular depression mainly included gray matter reduction within the fronto–striato–limbic network and orbitomedial prefrontal limbic network [48]. However, the causal relationship between brain structural alterations, cerebral vascular diseases, and depression in advanced age remains controversial.

Structural biomarker for prognosis prediction

Using SVM, Foland-Ross *et al*. [49] tested whether the baseline cortical thickness could reliably predict the onset of depression at the individual level. Using the cortical thickness data from 33 never-disordered adolescents, the authors found that the baseline cortical thickness of the participants predicted the future onset of depression with an overall accuracy of 70% (69% sensitivity, 70% specificity). Compared to those participants who did not develop depression, the participants who subsequently developed depression exhibited decreased cortical thickness in the right medial orbitofrontal, right precentral, left anterior cingulate, and bilateral insular cortex, therefore mostly contributing to this classification. Consistently, in a prospective study the authors conducted two MRI scans on 38 MDD patients, at base line and 3 years later [50]. They found that adult participants who developed at least one episode of depression, during the three-year follow-up, showed more gray matter decrease between the baseline and the follow-up scans when compared to the adults who remitted from depression.

More than half of all MDD patients develop a relapse within 2 years after recovery [51]. It is important to investigate the correlation between relapse and brain changes during the course of MDD. Soriano-Mas *et al*. [52] examined the cerebral structural changes in MDD patients with melancholic features and healthy controls lasting for over a 7-year period. The results showed that the number of relapses between scans were correlated with reductions in gray matter volume in the right middle occipital gyrus and the bilateral insular cortex. The number of relapses were also positively associated with the white matter volume in the arcuate fasciculus. However, most MDD patients were on medication during two MRI scans, which may have affected the interpretations of the results. In a longitudinal study, Zaremba *et al*. [53] assessed the whole-brain gray matter volume, the cortical thickness of the anterior cingulate cortex, orbitofrontal cortex, middle frontal gyrus, and insula in 60 MDD patients and 54 healthy controls over 2 years. The MDD patients with relapse exhibited significant decreases in the insular and dorsolateral prefrontal volumes, which are important for the emotional regulation from baseline to follow-up. Furthermore, these volume changes did not correlate with medication or symptom severity at the follow-up stage. These cerebral structural findings are preliminary potential biomarkers which showed promising utility in predicting the onset and relapse of depression. However, more studies are needed to validate these findings in a different large sample and elucidate the pathophysiological processes by which these structural anomalies increase the risk of developing MDD.

Structural biomarker for treatment response prediction

It has been suggested that decreased volume in the hippocampus was a highly repetitive finding in MDD patients compared to healthy controls [54,55]. This was particularly prominent in recurrent MDD patients and patients with more severe symptoms or chronic depression [56,57]. One study reported that larger hippocampal tail volume was positively correlated to clinical remission

following antidepressant medication treatment of MDD patients, independent of total hippocampal volume, total brain volume, and age [58]. Smaller hippocampal volume was also correlated with poorer treatment outcomes that was measured by a follow-up to 2 or 3 years [59,60]. Similarly, a neuroimaging meta-analysis found that smaller hippocampal volumes were related to lower response/remission rates in depressed patients that were treated with antidepressant drugs [61]. One recent study used measurements of the hippocampal subfield volumes to predict an early response to first-time use of antidepressants in drug-naïve MDD patients [62]. Inconsistent with the previous results, this study showed that nonresponding patients had significantly increased volumes than early responding patients and healthy controls in specific hippocampal subfields. These included the bilateral subiculum, cornu ammonis (CA) 1 and left CA2/3, CA4/dentate gyrus. Furthermore, the left subiculum showed the highest accuracy in differentiating between nonresponding patients and early responding patients. A sensitivity of 76.9% and specificity of 80% was observed. These inconsistent results may be due to the different clinical features of MDD patients, the subdivision strategy of the hippocampus, and the analysis approaches which merit further investigation.

By applying a multivariate pattern analysis, one MRI study [63] found that prior to the initiation of antidepressant medication fluoxetine, increased gray matter density in the rostral anterior cingulate and posterior cingulate cortices increased the probability of a full clinical response. In contrast, greater gray matter density in the orbitofrontal cortex increased the risk of persistent residual symptoms after pharmacological treatment.

Functional findings and potential clinical utility in MDD

Functional measurement of brain include nuclear imaging and MRI. The cerebral blood flow can be measured using positron emission tomography (PET), single photon emission computed tomography (SPECT), and MR perfusion [64–66]. The cerebral metabolic characteristics can be evaluated with 18-fluordeoxyglucose (FDG) PET [67]. Furthermore, PET and SPECT can provide data on the location and density of neurotransmitter receptors or transporters, such as serotonin and γ-aminobutyric acid (GABA) radioligands in depression [65,68]. Functional MRI (fMRI) is an important method which can measure the brain activity at rest or during a certain challenge or task [69]. Furthermore, fMRI could also provide the information of neural activity correlations, i.e., functional connectivity among multiple brain regions or networks [70,71].

Functional biomarker for MDD classification

Craddock *et al*. [72] first conducted a multivariate pattern analysis to distinguish MDD patients from healthy controls based on resting-state functional connectivity (RSFC) data in 2009. The authors used feature selection and SVM approach and reported classification accuracy of 83.33% (hold-out validation). In recent years, using the similar methods, many studies also investigated the resting-state fMRI data of brain to discriminate MDD from healthy controls and achieved accuracy from 45% to 99% [73–85]. It is noteworthy that there were huge differences of acquisition parameters, analytical methods, sample size, and clinical characteristics of participants among these studies. Thus, the low classification accuracy should not be considered as an objection against the current work, while the high classification accuracy should be interpreted with caution, especially in studies with small sample size.

In a SVM data-driven neural pattern classification analysis based on RSFC, Cáceda *et al*. [86] reported that the binary classifier discriminated between depressed suicide attempters and depressed suicidal ideators (mean accuracy = 0.788). This was determined by the different functional connectivity pattern between the default mode and the limbic, salience, and central executive networks. These findings indicated that measurements of intrinsic brain functional connections may have clinical applications if used as objective biomarkers of suicide risk. However, the results should be interpreted with caution, due to a limited sample size, and should be further validated in future prospective studies.

Functional biomarker for MDD subtyping

Using resting state fMRI data from a large multicenter sample of 1188 subjects, Drysdale *et al*. [7] conducted a canonical correlation analysis (CCA) to explore a two-dimensional mapping between functional connectivity changes and MDD symptoms. The authors conducted a hierarchical clustering analysis on two components that were derived from CCA. They found four neurophysiological subtypes ("biotypes"), that differed in the altered functional connectivity in the limbic and frontostriatal networks. Moreover, these biotypes had the potential to predict the treatment response of the transcranial magnetic stimulation (TMS). These potential diagnostic classifiers were validated as having high sensitivity and specificity (82%–93%) in a multicenter validation and out-of-sample replication analyses.

Recently, one study [87] tried to replicate the procedures used in Drysdale *et al*.'s study [7] using a different and more heterogeneous sample of 187 individuals with MDD and anxiety disorder. Similar to the original study, the authors conducted a canonical correlation analysis and

hierarchical clustering analyses. They performed additional tests which were not conducted in the original study, by selecting RSFC features based on their correlation with clinical characteristics before performing CCA. However, the results showed that the high canonical correlations that were observed in this validation study were not statistically significant, nor were replicated outside of the training set. Although the authors found an optimal three cluster solution, further investigation found that this cluster classification would also emerge in a data set which came from a single Gaussian distribution, and with no underlying clusters. It is worth noting that the latter study was not an exact replication of the original study. The differences were in some of the pre-processing steps, the measurements of depressive symptoms and in the clinical features of the participants. Thus, it is difficult to determine whether this failure to replicate the original results was due to discrepancies between the studies, or due to false positive findings in the original study. Future studies are required to discriminate between the accurate biologically and clinically meaningful MDD subgroups and the random fluctuation of the neuroimaging data.

Functional biomarker for prognosis prediction

Pan *et al*. [88] examined the RSFC in the reward network at baseline to predict the onset of depression in a total of 637 adolescents. The results showed that the increased left ventral striatum node FC in the reward network predicted an increased risk for future depression. Meanwhile, this striatal node FC strength did not predict the onset of other common adolescent psychiatric disorders, including anxiety disorder, attention deficit hyperactivity disorder and substance use. Shapero *et al*. [89] investigated whether baseline brain imaging data (including an emotional face match task fMRI and resting-state fMRI) predicted the onset of depression in non-symptomatic children. The results showed that RSFC alterations in the default mode network (DMN) and cognitive control network that differentiated high-risk and low-risk group predicted the onset of depression during adolescence. Increased functional activation to both happy and fearful faces was correlated with greater decreases in self-reported depression symptoms at follow-up. However, the results should be interpreted with caution as the sample size was relatively small (28 high-risk and 16 low-risk participants). Recently one study demonstrated that the classification between never-depressed children with familial risk for MDD who converted to MDD and those who did not convert to MDD based on baseline RSFC showed better performance (92% accuracy, 90% sensitivity, and 93% specificity) than classification based on baseline clinical rating scales [90].

Langenecker *et al*. [91] found that the group with future recurrence of MDD showed decreased baseline activation in bilateral middle frontal gyrus during commission errors compared to those without future recurrence of MDD and healthy controls. MDD patients with recurrence also exhibited greater resting-state connectivity of the subgenual anterior cingulate to the right middle frontal gyrus and brain regions in the cognitive control network. In another task fMRI study, the depression relapses was predicted by brain activation in the medial prefrontal cortical (mPFC) and contraindicated by visual cortical activation when viewing sad and neutral film clips in the remitted MDD group [92]. The results indicated that the mPFC reactivity predicted rumination, while visual cortical reactivity predicted distress tolerance.

Functional biomarker for treatment response prediction

Using RSFC analyses, Lui *et al*. [93] discovered that the refractory depression was associated with altered functional connectivity, mainly in the thalamo-cortical circuits. The non-refractory depression was associated with more distributed decreased connectivity in the limbic-striatal-pallidal-thalamic circuit. These results suggested that nonrefractory and refractory depression had distinct functional deficits in distributed brain networks.

Repetitive transcranial magnetic stimulation (rTMS) is a promising somatic treatment that depends on changing local and distant neural circuits within the brain [94]. It has been widely applied to improve cognitive and emotional dysfunctions, the restoration of neural activity and network connectivity in neuropsychiatric disorders [95–98]. In a resting-state fMRI study, 47 unipolar or bipolar patients with a medication-resistant depressive episode received 20 sessions of rTMS to the dorsomedial prefrontal cortex after MRI scan [99]. The non-responders had higher baseline anhedonia symptomatology when compared to responders. Meanwhile, the non-responders showed a decreased baseline functional connectivity in the reward neurocircuitry when compared to responders. The results suggested that the anhedonia symptom and the changes in reward-circuit functional connectivity may have the potential to differentiate non-responders from responders to dorsomedial prefrontal rTMS in major depression before the initiation of treatments. In another resting-state fMRI study, Liston *et al*. [100] examined the functional connectivity within and between the DMN and the central executive network (CEN) before and after a 5-week course of TMS. The results showed that TMS normalized depression-related subgenual hyperconnectivity in the DMN but not in the CEN. TMS also tended to induce anticorrelations between the dorsolateral prefrontal cortex and the medial prefrontal DMN nodes. Additionally, the baseline resting-state subgenual cingulate hyperconnectivity predicted the subsequent improvement of depressive symptom in patients.

There is a consensus that the combination of different treatments generally improves therapeutic effects in depression [101]. However, approximatively one third of all patients still fail to recover following several kinds of treatments [102,103]. To identify potential predictors of MDD patients who are unlikely to respond to the first-line treatments, McGrath *et al*. [104] included 82 MDD patients that were not receiving treatments in a two-phase treatment study. After fluorodeoxyglucose PET scanning, these patients were randomly distributed to receive 12 weeks of treatment with either escitalopram, or a cognitive behavioral therapy (CBT). The patients without remission after 12 weeks of first phase treatment were treated with an additional escitalopram and CBT for 12 weeks. The results showed significantly higher metabolism in the subcallosal cingulate of non-responders when compared to responders. Similarly, another study also reported the correlation between the increased subcallosal cingulate metabolism and poorer treatment outcomes following CBT or venlafaxine therapy [105]. These findings were supported by the studies that reported remissions from depressive symptoms in MDD patients after anterior cingulotomy [106] and those patients that received deep brain stimulation to the subcallosal cingulate [107]. With these potential predictors of failure to standard antidepressant treatments, clinicians could anticipate alternative treatments for those patients, by partially avoiding the trial-and-error process in current clinical practice.

Functional biomarker for guiding treatment selection

Though previous neuroimaging studies have indicated that brain activity patterns before treatment have the potential to predict the treatment outcome, but these studies have generally focused on a specific treatment [108,109]. To develop clinical meaningful biomarkers, we should find those biomarkers which are able to predict the patients' response to a specific treatment and predict non-response to an alternative treatment. To achieve this goal, many studies have examined the MDD patients' response to 2 or more different treatments, including medication, CBT, TMS, and electroconvulsive therapy (ECT).

The anterior cingulate cortex (ACC) was consistently suggested to be associated with outcomes to various types of treatments of depression [110–113]. One randomized controlled trial investigated the cerebral metabolic changes in MDD responders to CBT and venlafaxine during fluorine-18-fluorodeoxyglucose PET scan [112]. The results showed that the CBT and venlafaxine responders could be differentiated by altered metabolism in the anterior and posterior parts of the subgenual cingulate cortex and the caudate. Similarly, another study using resting state fMRI identified that functional connectivity patterns in the subcallosal cingulate cortex and three other brain regions, including the left anterior ventrolateral/insula prefrontal cortex, dorsal midbrain, and left ventromedial prefrontal cortex distinguished between responders and non-responders to antidepressant medications (escitalopram or duloxetine) and to CBT [113]. Specifically, positive summed functional connectivity for these three regions was associated with CBT associated remission and medication-related treatment failure, while negative summed functional connectivity scores were correlated with remission to medication and CBT treatment failure. Regarding TMS treatment, Salomons *et al*. [99] reported that a successful treatment was associated with decreased subgenual ACC-caudate connectivity and increased dmPFC-thalamus connectivity in treatment-refractory MDD following a 4-week course of dmPFC-repetitive TMS.

Using fluorodeoxyglucose-PET, one RCT study found that the remitters and non-responders to treatments with the antidepressant escitalopram and CBT could be differentiated by the resting metabolism of the right anterior insula [114]. Specifically, relative to whole-brain mean metabolism, the insula hypo-metabolism was related to the remission to CBT but poor response to escitalopram, while the insula hypermetabolism was related to remission to escitalopram but poor response to CBT.

These findings showed promising evidence that psychoradiological biomarkers may provide clinically meaningful information in monitoring and predicting treatment responses and selection of treatments. Guided by these imaging biomarkers, clinicians may choose the most effective treatment or the combination of different treatments for MDD patients before the initiation of treatment. The interventions such as TMS and ECT could be started early for treatment-refractory MDD patients to optimize the timing, the intensity, and the form of therapeutic interventions. In the future, these biomarkers need to be further validated through prospective examinations and as a component of multivariate treatment prediction models.

Challenges and future directions

Although psychoradiology has shed some light in classification, subtyping and prediction of illness onset, relapse, and treatment response in MDD patients [115], there are still many practical challenges in this emerging field which need to be solved before implementation in clinical practice.

First, among various neuroimaging findings in the depressed brain, only a few were replicable. One possible reason may be the discrepancies of acquisition parameters and the analytical methods that were used in previous studies. For example, MRI-based brain measurements can be affected by various factors, such as the number of head

coil channels [116], inconsistent subject positioning [117], inconsistent image contrast [118], difference in MR scanner vendors and the field strength. In addition, physiologic factors including heart beating, cardiopulmonary function, age and sex are all biological confounds that can influence the quality of MR images [119]. As the number of multicenter studies using multiple MRI scanners is growing, it is important to establish standardized data acquisition and image quality control solutions.

Recently, the MR group in the Chinese Society of Radiology published the first expert consensus report on the clinical psychoradiological MR examination of schizophrenia patients in China [120]. This consensus report proposed that MR examination for patients with schizophrenia or with suspected diagnosis of this disease should include high spatial resolution (1 mm at least) structural imaging and quantitative analyses of gray matter volume and cortical thickness to explore the cerebral structural changes. This report also proposed requirements for the safety of patients and additional environmental considerations before and during MR examinations. Based on the current expert consensus report for schizophrenia, it is imperative to establish a specific guideline for clinical psychoradiological MR examination and imaging analyses in MDD.

Another possible reason for the inconsistency in neuroimaging findings may be due to the heterogeneity in the inclusion criteria of patients, demographic features or study protocols among studies. To solve these issues, one possible solution is to conduct larger-scale multicenter and multimodal studies in which heterogeneity of participants could be leveraged to identify more biologically homogeneous subgroups of patients. Multimodal imaging, which combine structural MRI, DTI, fMRI, and even PET data could provide cerebral structural, functional, and metabolic information at the same time [121,122]. Investigating the imaging data acquired from different imaging modalities and methodologies in a relatively large and homogeneous sample of MDD patients would help to elucidate the underlying neuropathological mechanism of depression.

Second, the psychoradiological biomarkers reviewed are not with sufficient clinical utility in diagnosis at the individual level. Under the conventional psychiatric pattern of diagnoses, MDD, bipolar depression, anxiety disorder, and other psychiatric disorders may share similar neurocognitive alterations and overlapped emotional dysfunctions [123]. A previous study has shown that these psychiatric disorders also share similar anatomic and functional changes in some brain networks [124]. Considering the clinical and imaging heterogeneity that overlap across diagnoses, future studies need to establish neurobiologically distinct subgroups and new clinically meaningful nosological categories that are based on objective biomarkers. Collecting large samples from multiple sites with dense phenotyping (including but not restricted to MRI) to identify biologically distinct patient groups may be the next step. Additionally, the examination should not only focus on the confound-free MDD patients, but should also consider more complex MDD samples with at least one comorbidity that coincides with the real clinical situation.

Third, the clinical value of the current biomarkers that predict treatment outcome and guiding treatment selection studies were limited by heterogenous study design [125], including type, dosage, and duration of treatment, timing for clinical and imaging measurements, clinical features of patients, criteria for secondary psychiatric diagnoses or adjunctive treatments, and statistical methods for data interpretation. For example, without the placebo group, some studies were not able to accurately distinguish the effects on symptom change between treatment-dependent and treatment-independent patients. Although some studies included patients with a wash-out period of medication, it is difficult to conclude that the observed treatment outcomes were not related to the residual effects of previous treatments. Furthermore, there may be other biological mediators and processes which could regulate the treatment response. However, there are some encouraging findings with high potential for the translation in clinical practice even if still in a proof-of-concept stage. Consistent with our discussion about the role of ACC and hippocampus in treatment selection and treatment response prediction, one recent systematic review reported that higher pre-treatment gray matter volume of the ACC and hippocampus is associated with response to antidepressant treatment [126]. A selection of these biomarkers could enhance the accuracies of the predictions at the individual level using machine learning approaches. These potential treatment biomarkers need to be replicated and validated in large, independent samples with more homogeneous study design and the correlations between biomarkers and mechanism of response procedure need to be further investigated.

Fourth, to advance a data-driven perspective, but still realize clinically meaningful goals, we may need to consider which measures could serve as the most relevant anchors for analysis [127]. Using features derived from structural MRI data, such as gray matter volume, white matter volume, cortical thickness, FA and surface area, classification accuracies between MDD and healthy controls ranged from 54.6% [128] to 90.3% [129] in the current literature. While using features derived from functional MRI data, including both resting-state fMRI and task fMRI, classification accuracies varied from 45.0% [84] to 99.0% [85]. It seems that the classification performance of functional imaging was slightly better than that of structural imaging when it is judged only from these figures. It is worth noting that these studies differ greatly in the sample size, demographic and clinical

features. Thus, it is not easy to draw definite conclusions about the classification value of structural and functional imaging on MDD.

In regard to the retest reliability of neuroimaging measures, the reliability of structural imaging is high, that of resting-state fMRI is low to moderate, and that of task-based neuroimaging can be highly variable [127]. As the assessment of cerebral structure of psychiatric disorders is already part of the clinical routine in some inpatient services, the application of structural MRI data for individual-level classification, subtyping, and prediction may be more easily implementable in the clinical context.

Conclusions

In summary, using psychoradiological methods, the structural and functional cerebral alterations have been identified in MDD. These findings showed promise as neuroimaging biomarkers for classification, subtyping, and prediction. While evidence of cerebral structural and functional changes associated with MDD classification and subtyping was heterogeneous and/or sparse, the ACC and hippocampus have been consistently suggested to be important biomarkers in treatment selection and treatment response prediction. With the emerging multicenter studies and the development of advanced statistical integration techniques, considerable interdisciplinary collaboration that involves radiologists, psychiatrists, psychologists, and computer scientists should foster an optimized psychoradiological examinations flow for MDD patients and set up prospective clinical study to identify and validate the accuracy and reliability of previous findings.

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Compliance with ethics guidelines

Ziqi Chen, Xiaoqi Huang, Qiyong Gong, and Bharat B. Biswal declare that they have no financial conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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