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REVIEW

Diagnostic and therapeutic utility of neuroimaging in depression: an overview

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Abstract: A growing number of studies have used neuroimaging to further our understanding of how brain structure and function are altered in major depression. More recently, these techniques have begun to show promise for the diagnosis and treatment of depression, both as aids to conventional methods and as methods in their own right. In this review, we describe recent neuroimaging findings in the field that might aid diagnosis and improve treatment accuracy. Overall, major depression is associated with numerous structural and functional differences in neural systems involved in emotion processing and mood regulation. Furthermore, several studies have shown that the structure and function of these systems is changed by pharmacological and psychological treatments of the condition and that these changes in candidate brain regions might predict clinical response. More recently, "machine learning" methods have used neuroimaging data to categorize individual patients according to their diagnostic status and predict treatment response. Despite being mostly limited to group-level comparisons at present, with the introduction of new methods and more naturalistic studies, neuroimaging has the potential to become part of the clinical armamentarium and may improve diagnostic accuracy and inform treatment choice at the patient level.

Keywords: depression, mood disorder, neuroimaging, diagnosis, treatment

Introduction

Major depressive disorder (MDD) is a common condition with a significant effect on quality of life,[1] and considerable interest has been devoted to understanding the biological underpinnings of mood dysregulation as a way of improving syndromic detection and treatment outcomes. In affective disorders, the intrinsic complexity of brain neuroanatomy and its functional connectivity is further complicated by the considerable heterogeneity of these conditions and the effects of treatment on the brain, which makes advancement of knowledge particularly challenging. The introduction of magnetic resonance imaging (MRI) in both its structural and functional capacity has proved to be a crucial turning point, providing the necessary tools for investigating affective disorders. The number of structural and functional studies has exponentially increased since the introduction of MRI-based techniques, and these studies have provided a growing body of evidence supporting brain abnormalities in MDD. It has also become evident that, different from gross brain pathology, abnormalities in affective disorders are likely to be of a much smaller magnitude and markedly influenced by study design characteristics and a range of clinical and demographic factors. Nevertheless, sufficient knowledge about MDD has accumulated in the last few decades that it is now possible to postulate neurobiological circuits of mood dysregulation, which might guide the diagnosis of MDD and target candidate biomarker brain regions for clinical response. This is an increasingly important research area because of growing concern

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about progress in the development of novel treatments,[2] which has led to intensified efforts to understand how to maximize the efficacy of existing interventions.[3] In this selective review, we focus on recent structural and functional neuroimaging findings in MDD. We aim to provide a concise overview of recent advances in the development of models of the circuitry of mood dysregulation in depression, with an emphasis on MRI-based techniques developed as an aid to improve diagnosis and guide clinical response.

Methods

Relevant articles were identified from searches in PubMed, Embase, and Scopus. Search terms included the following: "depress*," "neuroimaging," "PET," "MRI," "magnetic resonance," "fMRI," "DTI," "diffusion tensor," and "neurofeedback," both in isolation and in combination. Articles' citation lists were also cross-referenced for inclusiveness. We identified studies that examined differences in brain structure and function between individuals with MDD and healthy controls. We also aimed to identify articles that investigated the relationship between these measures and response to treatment. Studies that tested the efficacy of MRI-based treatments were also identified. This work reports a selective narrative description of the identified studies.

Structural MRI

Many studies have used structural MRI to look for differences in brain volume and shape between patients with MDD and healthy controls (HCs) with both a region-of-interest approach and at the whole-brain level, using voxel-based morphometry (VBM). According to structural MRI and in contrast with bipolar disorder (BD), MDD is believed not to be characterized by global brain volumetric reduction.[4,5] A summary of the main findings from these studies are shown in Table 1. However, hundreds of case control studies to date have identified morphometric reductions in candidate regions in the medial systems of the prefrontal cortex (eg, orbitofrontal cortex, ventromedial prefrontal cortex, and anterior cingulate cortex),[6–10] as well as lateral prefrontal systems (eg, ventrolateral prefrontal cortex and dorsolateral prefrontal cortex).[7,8,11,12] Although recent meta-analyses have supported the view that frontal gray matter differences in these regions are important in MDD,[13,14] it should be noted that there is some inconsistency in results, with several null findings in these areas.[15–18]

Volumetric reductions have also been identified in subcortical systems implicated in affective regulation. These regions include the striatum (caudate and putamen),[16,18] the hippocampus,[19–22] and in some studies, the amygdala,[23,24] largely reflecting aberrant neurocircuitry shown in postmortem studies.[25,26] Volumetric reduction in the hippocampus remains, to date, the most replicated finding in MDD, as highlighted by several meta-analyses,[5,27,28] and is complemented by findings of altered shape,[29] whereas there are inconsistencies in reports of volumetric differences in the amygdala (the second most researched area).[5] Incongruences in the results can be explained in the light of significant heterogeneity in the patients included in these studies and the methods applied to measure differences.[5,27] Bora et al for instance, found evidence of amygdala morphometric reduction in MDD when comorbid anxiety was present.[13] Although prefrontal volumetric reduction has also been described in BD,[4] a recent meta-analysis calculated cumulative effect sizes of studies comparing bipolar and depressed patients versus healthy controls and found greater hippocampal reduction in MDD.[27] However, hippocampal volume reduction has been found in healthy individuals with a family history of depression,[30] indicating this may not be specific to current depression and may instead reflect underlying genetic risk.

In longitudinal studies investigating candidate brain regions as putative biomarkers for treatment response, the hippocampus has been shown to be reduced in depression and sensitive to volumetric increase after pharmacologic treatment and clinical improvement.[31] Thus, Arnone et al[32] in a VBM study, demonstrated bilateral volumetric gain in the hippocampus after a course of the antidepressant citalopram. This is in agreement with Frodl et al's[23] finding that greater hippocampal volume in depressed patients at baseline is associated with better clinical response at follow-up, suggesting that baseline hippocampal volumes might predict treatment response in MDD. Consistent with this finding, Vakili et al[33] demonstrated greater hippocampal volumes in responders in comparison with nonresponders, and in another study, lower hippocampal volumes at first presentation identified participants who became treatment nonresponders.[34]

Table 1 Summary of differences in brain function and volume between individuals with major depressive disorder and healthy controls

Brain area	Functional activity	Volume
Medial prefrontal cortex	↑	↓
Lateral prefrontal cortex	↓	↓
Striatum	↓	↓
Amygdala	↑	–
Hippocampus	↑	↓

Notes: Functional activity represents results from functional magnetic resonance imaging studies using tasks involving emotion processing. Up arrows indicate an increase, down arrows indicate a decrease, and a hyphen represents no change.

Similarly, Sämann et al[35] in a VBM study that investigated a large sample of 140 patients, identified a number of brain areas whose pretreatment volumes correlated with response to antidepressant treatment. These regions included the left hippocampal complex, the superior temporal gyrus, and the middle temporal gyrus.

However, these findings are not always consistent across studies. For example, another VBM study[36] found that the volumes of a number of areas were associated with treatment response to fluoxetine, but these were largely distinct from those identified by Sämann et al and notably did not include the hippocampus. Another recent study did not find any significant association between gray matter volume and treatment response,[37] although given the small size of this study, this null finding may be a result of inadequate statistical power. In addition, Lai and Hsu found no effect of 6 weeks' treatment with duloxetine on gray matter density in the hippocampus in a sample of depressed patients with comorbid panic disorder.[38]

Functional magnetic resonance imaging

In addition to structural findings, neuroimaging has provided invaluable insights into the functional pathophysiology of MDD through functional MRI (fMRI). A summary of the main findings in this area is provided in Table 1. As with structural findings, both medial and lateral prefrontal systems have been implicated. During negative affective processing tasks such as viewing sad or fearful faces, dorsolateral prefrontal areas reliably show reduced activation compared with controls,[39–41] whereas the anterior cingulate cortex (ACC) shows increased activation.[42–45] Functional alterations while processing negative stimuli have also been demonstrated in limbic regions, most notably in the amygdala, where exaggerated responses to negative stimuli are seen,[40,43,46–49] whereas processing of positive stimuli such as monetary gains is associated with reduced activity in areas associated with reward processing such as the striatum.[50–52]

There is some evidence this pattern of activation in response to emotional stimuli may be specific to MDD. Recent studies comparing BD patients with those with MDD have shown that BD is associated with elevated amygdala responses to positive stimuli, in comparison with increased responses to negative stimuli in MDD.[53,54] In addition, elevated amygdala responses to sad faces appear to be specific to a depressed state,[5] indicating this might differentiate between currently depressed individuals and those with a history of MDD.

These functional abnormalities have also been associated with treatment response. In particular, heightened reactivity to negative stimuli is normalized after treatment with antidepressant medication in the amygdala,[43,46,55] whereas reduced lateral prefrontal activity increases;[56,57] findings in keeping with theories positing that the effects of these drugs depend on the amelioration of excessive negative information processing.[58,59] It has also been shown that amygdala reactivity to positive emotions increases after treatment with antidepressant medication,[49] although this is not as consistently demonstrated.[46,60,61] Similarly, psychological therapies have been shown to normalize heighted amygdala responses to negative emotional stimuli,[62,63] and also to increase striatal responses to rewards,[64] suggesting psychological treatments might share similar mechanisms of action.

Fewer studies have looked at the prognostic value of functional measures, but some have shown that baseline ACC activity predicts response to pharmacological treatment. For example, Roy et al[65] used an emotional image-viewing task in a sample of MDD patients before 8 weeks' treatment with citalopram and found a positive correlation between ACC response to emotional pictures and response to treatment. This echoes findings from an earlier study that found that higher anterior cingulate activity while viewing negative pictures was associated with a larger treatment response after 8 weeks of treatment with venlafaxine,[66] as well as a more recent study that found that higher anterior cingulate and caudate activity while viewing sad faces was associated with greater improvement in symptoms with fluoxetine treatment.[36] Similar results have been found in other tasks; for example, tasks involving working memory[67] and response inhibition,[68] suggesting ACC activity may predict treatment response regardless of context.

However, some studies have failed to find associations between ACC activity and treatment response,[69–71] despite showing activity in other areas that correlated with treatment response. Furthermore, one recent study found that patients with higher baseline activity in the ACC while viewing emotional words was associated with poorer response to treatment,[72] contradicting findings from previous studies. Although there are some inconsistencies in findings, these are likely a result of confounding factors such as differences in sample characteristics and the type of intervention used. There are also numerous confounds that are problems in much of this research, reviewed in the "Discussion", but overall, ACC activity does appear to be a relatively reliable predictor of response to antidepressant treatment.

With regard to prediction of response to cognitive behavioral therapy, a number of studies of the anterior cingulate have found the opposite pattern from studies looking at

antidepressant response, with higher activity in response to sad faces at baseline associated with poorer treatment response.[62,73,74] Notably, using logistic regression, Fu et al[62] were able to individually classify patients as either responders or nonresponders on the basis of their baseline anterior cingulate activity while viewing sad faces with 87.5% accuracy, providing evidence that functional alterations in emotion processing systems can differentiate between patients and controls at an individual level. In addition, the contrast with findings in studies using antidepressants suggests that if this could be shown to be generalizable to real-world patient populations, it could be used to personalize patients' care such that they receive the most beneficial form of treatment from the outset, thus optimizing the overall treatment response.

Studies have also identified alterations in resting state activity in MDD, mostly showing increases in connectivity within the "default mode network,"[75,76] which has been suggested to reflect the excessive rumination seen in MDD.[77] Findings in other networks such as the "affective network" have been less consistent, with both increased[76] and decreased[78,79] connectivity reported. Taken together, these findings suggest dysfunction in networks involved in self-directed thought and emotion processing, which is consistent with the dysfunctional emotion processing shown in task-based MRI studies.

More recently, research has begun to build on these findings by using resting-state measures to differentiate between MDD patients and healthy controls at an individual level. One recent study[80] suggested that "regional homogeneity," a measure of correlations between nearby voxels, could be used to distinguish between groups with relatively high accuracy. However, circular analysis and failure to correct for multiple comparisons limits the conclusions that can be drawn from this study. Nevertheless, on the basis of the consistency of resting-state differences between MDD patients and healthy controls, this is a subject deserving of further research, perhaps using more reliable measures.

Antidepressant treatment has also been found to have effects on resting-state abnormalities in MDD. Li et al[81] found that after 12 weeks of antidepressant treatment, connectivity in the dorsal component of the default mode network was normalized, whereas increased connectivity in the anterior subnetwork persisted. In addition, studies have shown that treatment is associated with increased connectivity between cortical and subcortical areas involved in affect generation and regulation.[82]

Resting-state fMRI has also been used to predict treatment response in MDD. Lui et al[83] scanned patients who were subsequently prescribed a range of antidepressant medications and found that patients who responded to treatment showed decreased connectivity among the left amygdala, ACC, right insula, and precuneus relative to nonresponders. Many of these areas are part of the "affective network," in which abnormalities have been reported,[76,78,79] suggesting that dysfunction in this network at rest may be important in treatment response, as well having predictive power. To date, no studies have examined whether "default mode network" activity predicts treatment response, but given the number of studies reporting baseline dysfunction as well as changes with treatment, this may be a fruitful avenue for future research.

Positron emission tomography

Much like research using fMRI, studies of brain function before and after treatment by measuring blood flow and glucose metabolism using positron emission tomography have demonstrated that brain function changes after treatment. These studies have found similar results to fMRI studies, identifying hyperactivity in the medial prefrontal cortex in the presence of depressive symptoms. Antidepressant and psychotherapy intervention studies indicate that increased metabolism in prefrontal areas before treatment decreases after treatment and "normalizes" to levels of activity measured in healthy controls. In some other studies, however, metabolic rate after treatment decreased below normal levels.[84–87] Conversely, metabolic hyperactivity persists where there has been a lack of response to treatment.[84,87–89] Changes have also been measured in limbic and paralimbic areas, including posterior cingulate cortex, insula, hippocampus, and amygdala, with conflicting findings of decreased or increased metabolism or neural activity, depending on the study.[43,61,84–87,90]

Taken together, these findings add to the evidence for a functional deficit in mood regulation systems in MDD, which is related to treatment response. More recently, a study by McGrath et al[91] showed that insula hypometabolism was associated with remission to cognitive behavior therapy and poor response to escitalopram, whereas insula hypermetabolism was associated with remission to escitalopram and poor response to cognitive behavior therapy. Although this finding requires replication in future studies, it does suggest the insula might be a biomarker to predict a preferential response to different modes of treatment.

Furthermore, positron emission tomography has been used to measure serotonin 1A (5-HT1A) receptor binding, with the aim of understanding the nature of neurochemical changes in MDD and how these relate to treatment response. However, findings from these studies are contradictory, with

both increases and decreases in 5-HT1A receptor binding reported in MDD.[92,93] As noted by a recent review,[94] the inconsistency in findings is likely to be a result of methodological differences, and the field would benefit from gaining a better understanding of how different analysis methods can produce such contrasting results. The most important difference between studies is the choice of reference tissue, which is used to normalize radioligand binding in the region of interest. Results can vary greatly, depending on the choice of reference, and there is no agreement on which is the optimal method (see Shrestha et al[94] for a detailed review of this and further issues in these studies).

Similarly, there are inconsistencies in studies looking at changes in 5-HT1A receptor binding after antidepressant treatment[95,96] and in studies exploring the ability of pretreatment binding potential to predict response.[92,96] In sum, there is far too much variability in finding for this method to provide any useful information in relation to the diagnosis and treatment of MDD at present. However, further research focusing on the methodological differences responsible for these inconsistencies may help in this regard.

Diffusion tensor imaging

A more recent development in MRI is diffusion tensor imaging (DTI), which has allowed differences in white matter microstructure to be characterized in MDD. Many studies have reported reduced fractional anisotropy (FA), a measure of white matter integrity, in a number of pathways, including the superior longitudinal fasciculus[97,98] and genu of the corpus callosum.[99,100] However, findings are inconsistent, likely because of differences in sample characteristics and methods of analysis, and a number of studies have found no significant differences between patients and controls.[101–103] Given the evidence for frontolimbic dysfunction provided by functional and structural studies, it is surprising that only a few studies[104,105] have reported decreased FA in the uncinate fasciculus, a white matter pathway connecting these regions. Nevertheless, taken together, and despite the inconsistencies, these studies indicate that white matter microstructural abnormalities are present in MDD.

To date, only one study has examined the effect of psychological therapy on white matter integrity.[106] It found that after 4 weeks of guided imagery therapy, FA was increased in the supplementary motor area and decreased in the angular gyrus. Similarly, few studies have looked at the ability of DTI to predict response with pharmacological treatments in MDD. Alexopoulos et al[107] found that high pretreatment FA in an area close to the ACC was associated with remission when treated with antidepressants in a sample of 13 patients with late-life depression. However, a more recent study in older adults found the opposite pattern of results,[108] with higher values in patients who did not respond to treatment. Only two studies looking at pretreatment DTI measures of response to pharmacological treatment have been reported in younger adults.[109,110] In contrast to the finding in late-life depression, no difference in FA was found between treatment-responsive and treatment-nonresponsive patients in the anterior cingulate in either study. However Zhou et al[109] found decreased FA in the hippocampus of patients refractory to treatment, whereas Delorenzo et al[110] found that those who did not remit had lower FA in tracts connecting the raphe nuclei with the amygdala than those who remitted.

Further studies in adults have compared FA measurements in relation to treatment refractoriness after a course of antidepressant treatment in MDD. One recent study found reduced FA in the ventromedial prefrontal cortex of patients with chronic treatment-resistant depression compared with those with recurrent but remitted and first-episode depression and healthy controls.[111] Similarly, another study found reduced FA in the ventromedial prefrontal cortex of individuals with treatment-resistant depression versus healthy controls,[112] along with reduced values in the uncus and cerebellum. Findings from these studies are limited by differences in illness duration, treatment responsiveness, and other clinical differences; thus, generalization of findings might be difficult in relation to response prediction. Despite these limitations, the evidence supports the presence of differences in white matter integrity between patients who respond to antidepressant treatment and those who do not, although the exact nature of these differences needs further clarification. Further pretreatment DTI studies, particularly in younger samples, would be highly beneficial.

Machine learning and structural magnetic resonance imaging

Neuroimaging studies focused on individual-level analysis of data are necessary to be clinically useful for diagnosis and treatment prediction. Recent work has implemented "machine learning" techniques to explore the potential for neuroimaging to confirm clinical diagnosis based on neurobiological abnormalities (diagnostic biomarkers) and to assign individuals to diagnostic or therapeutic response categories at an individual level. Key to these techniques is a multivariate approach that allows identification of distributed patterns of activity in the brain and takes advantage of the large amount of data available in neuroimaging datasets.

Combining machine learning techniques with structural data has provided promising results in both diagnosis and prediction of treatment response. Recent studies using "support vector machine" (SVM) and "relevance vector machine" methods have been able to successfully discriminate between patients and controls with accuracies ranging from 67.3% to 90.3%.[113–115] In these studies, the areas with the highest contributions to classification are mostly medial and lateral frontal structures and limbic structures such as the hippocampus, replicating findings from other structural MRI studies showing structural differences between MDD patients and HCs. However, it should be noted that some of these patients had been taking antidepressant medications either before or at the time of scanning, which are known to affect gray and white matter volumes[116,117] and would need to be accounted for in the findings. In addition, sensitivity reached 93.3% in one study[115] but was around 70% in the other two studies, indicating a high risk of false-positives.

Studies have also used machine learning classification techniques to predict response to antidepressant treatment.[113,114,118] In these studies, participants were split into responders and nonresponders after treatment, and machine learning techniques were used to allocate patients to either category according to their pretreatment structural images. Gong et al[114] achieved a classification accuracy of 69.5% using gray matter images, whereas Costafreda et al[113] were able to classify patients with 88.9% accuracy. Using "transductive conformal predictors," a method that produces confidence measures for classification, Nouretdinov et al[118] were able to predict response to antidepressant treatment with 83.3% accuracy while also providing confidence measures for these predictions. Interestingly, unlike other treatment prediction studies, none of these found that differences in hippocampal gray matter contributed to classification. However, two studies found that the anterior cingulate contributed significantly,[113,118] echoing findings from fMRI studies of treatment response prediction.

These methods have also been applied to the prediction of response to psychological therapies, with mixed results. Costafreda et al[113] were unable to distinguish between those who did and those who did not respond to cognitive behavioral therapy, whereas another study[119] was able to successfully categorize patients according to their response to psychological treatment, albeit with a relatively low sensitivity of 71%.

Machine learning and fMRI

Machine learning classification methods have also been applied to data from task-based fMRI experiments, and results suggest this also has some potential as a diagnostic biomarker for MDD. Building on previous studies using univariate analysis, Fu et al[120] used SVM classifiers to attempt to distinguish between MDD and HC participants on the basis of blood oxygen level dependent activity while viewing sad faces. Although this method was successful in discriminating patients from controls, using whole-brain activation maps, this was achieved with a low rate of accuracy (68%) in comparison with "resting state" data[121] and structural data.[115]

Some research suggests a superior diagnostic accuracy might be obtained by combining multiple classifiers. Hahn et al[122] trained Gaussian process classifiers on activity during three separate tasks involving emotional and reward processing and integrated their predictions using a decision tree algorithm. This method resulted in a classification accuracy of 83% by combining all of the classifiers together. This indicates that optimal classification might be achieved through the integration of several neuroimaging measures, which could be a point of interest for future research. Moreover, even greater accuracy might be produced by methods combining both functional and structural data.

Importantly, these methods have also begun to be used to address the problem of symptomatic overlap between depression and other conditions. A major challenge in the diagnosis of depression is differentiating it from BD, a condition characterized by periods of depression but with the addition of manic or hypomanic episodes, and any neuroimaging-based diagnostic biomarker for MDD would need to discriminate between these two conditions. Recent studies have used machine learning classification methods to analyze data from facial emotion processing tasks in MDD and BD patients[54,123] and found that the two disorders can be accurately distinguished from one another with 80%–90% accuracy. Although there are some limitations in this research, such as the differences in medication between groups, that could contribute to the classification success, findings suggest that machine learning-based diagnostic classification could successfully distinguish individuals with MDD from those with other conditions.

There are also indications that machine learning analysis of task-based fMRI data may be useful in predicting response to treatment. Costafreda et al[119] applied SVM analysis to data from an emotional face processing task and found that participants could be classified as responders or nonresponders to cognitive behavioral therapy, based on baseline scans with a sensitivity of 71% and specificity of 86%, although the study used a relatively small sample of

16 participants. Studies applying these methods to predict response to medication have found less-promising results, with one study using the same face-processing task finding nonsignificant classification results.[120] Nonetheless, this is still a relatively unexplored area that may still provide some interesting insights, especially given the success seen in diagnostic classification studies.

Some studies have also used SVM classifiers with resting state functional connectivity data and have shown that medication-free patients and controls can be distinguished with around 95% accuracy.[121,124] The most highly discriminative regions were the amygdala and frontal regions, including the ACC, complementing findings from other structural and functional studies in MDD. Furthermore, using an unsupervised classifier, which attempts to categorize cases purely on their intrinsic characteristics, rather than fitting cases into categories defined by the experimenter, Zeng et al[125] showed that the resting state connectivity of the ACC allowed individuals to be grouped with 92.5% consistency with their diagnostic labels, providing further evidence there are distinct patterns of functionality at rest that characterize MDD. Indeed, it is possible that in the future, these techniques might form the basis for the division of MDD into neurobiologically distinct subtypes that could further improve diagnosis and treatment.

Machine learning and diffusion tensor imaging

Machine learning techniques have also begun to be used in conjunction with DTI to identify patterns of white matter deficits that can distinguish between patients and HCs. Korgaonkar et al[126] applied linear discriminant analysis to multiple DTI measures from medication-free MDD patients and controls and were able to classify individuals with an accuracy of 96%. Similarly, Fang et al[127] used machine learning in combination with whole-brain structural connectivity maps derived from DTI to classify individuals as either patients or controls, according to the strength of connectivity between different brain regions. This method achieved an accuracy of 91.7%, indicating that machine learning techniques combined with DTI data can correctly distinguish patients from controls with a high degree of accuracy and providing further evidence for white matter microstructural differences in MDD.

Neurofeedback and neuroimaging-based treatments

Recent developments in fMRI have enabled researchers to explore its potential for use as a treatment itself, rather than simply aiding treatment with psychological or pharmacological therapies. A number of recent studies have shown that when provided with real-time feedback of blood oxygen level – dependent signals while in the scanner, healthy participants are able to regulate the activity and connectivity of brain structures involved in emotion processing, many of which have been implicated in MDD.[128–131] Building on this, it has been proposed that neurofeedback may be able to correct functional abnormalities seen in these networks in MDD[132] by allowing patients to learn how to regulate activity, thereby correcting the impaired regulation present in the disorder. One recent small-scale pilot study of this therapy has shown promising results.[133] Patients were instructed to increase activity in areas involved in positive affect by recalling positive memories, and after four sessions, a significant reduction in depressive symptoms was seen in comparison with members of a control group, who performed a similar positive memory recall task without neurofeedback. However, it is important to note the significant limitations of this study, such as the out-of-scanner control task, which may have led to an overestimation of the effect of the treatment, and the inclusion of an entirely male sample, which limits generalizability.

Another recent study used a similar procedure but included an active control condition in which participants were given feedback from an area not thought to be involved in emotion processing, the intraparietal sulcus.[134] Regulation of the left amygdala while remembering positive memories resulted in an increase of self-reported happiness immediately after the session, but the longer-term effects of this procedure were not assessed.

Evidence for the efficacy of neurofeedback is very limited at present and larger-scale, blinded, randomized-controlled trials will be required to evaluate its potential for clinical use. Furthermore, it will be important to determine an optimal control intervention for these trials and the most effective aspect of brain function to target. Nevertheless, these early studies indicate it may be a promising candidate for a neuroimaging-based treatment for MDD.

Conclusion

Integrative pathways of mood regulation as diagnostic biomarkers

Neuroimaging research suggests that abnormalities in depression occur in a number of functionally interactive cortical and subcortical brain regions (please see Phillips et al[135,136] for a comprehensive review). Subcortical areas that include thalamus and ventral striatum are implicated in the processing

of novel emotional and nonemotional information, whereas limbic regions such as the amygdala and the hippocampus complex play an important role in mood monitoring.[137,138] These two regions functionally interact, and neuroimaging studies have demonstrated that amygdala activation correlates with emotional memory.[139,140] Moreover, the hippocampus has been shown to be susceptible to emotional experiences and to contribute to emotional recognition.[141,142] For example, enhanced neural responses to emotionally valenced stimuli have been found in the amygdala and hippocampus.[143,144]

Prefrontal regions, and particularly medial cortical areas, exercise active cognitive control and conscious appraisal of emotional state.[145] The prefrontal cortex is particularly important in top-down emotional control over limbic regions, especially when stimulus-outcome contingencies are important[146] and the medial part of the prefrontal cortex, which includes orbitofrontal cortex (OFC), dorsomedial prefrontal cortex, and the ACC, is pivotal in controlling emotional behaviors via extensive subcortical connections.[136,147] The lateral prefrontal cortical areas, which include the dorsolateral and ventrolateral prefrontal cortices, are known to coordinate higher cortical functions involved in top-down voluntary modulation of positive and negative emotions.[136,148,149] Feedback neuronal connections coordinate communication between the lateral prefrontal areas and the ventromedial prefrontal cortex[136,147] and between the dorsolateral prefrontal cortex and cortical associative areas, OFC, and subcortical structures involved in emotion regulation, such as the thalamus, hippocampus, and dorsal striatum.[136,150]

In depression, abnormalities in these functional networks have been demonstrated relatively consistently across studies, as shown by several recent meta-analyses,[151–153] and have been interpreted as reflecting dysfunctional regulation of subcortical activity by frontal areas during emotion processing, leading to suboptimal maintenance of affective states.[154] This view is further supported by fMRI studies showing impaired connectivity between frontal and limbic regions,[155–157] although DTI studies do not provide strong evidence of impaired structural connectivity between these areas.

These functional and structural changes in mood regulation systems have the potential for use as diagnostic biomarkers for MDD, as well as for future neurobiology-based classification and diagnostic systems. The growing amount of evidence reviewed here shows that machine learning methods can allow individual-level discrimination of MDD patients from healthy controls, according to structural and functional differences in regions involved in mood regulation, and may also be able to distinguish MDD from similar conditions such as BD. To date, there have been no attempts to diagnose MDD on the basis of combined data from multiple imaging modalities. This may be an area of interest for future research, as combining information from multiple sources may provide greater accuracy than data from any one source alone.

Neuroimaging and candidate biomarkers of response to treatment

A morphometric reduction in the hippocampus is to date the most replicated structural finding linked to prediction of treatment response and to greater volumetric loss in the hippocampus associated with poorer treatment response.[34,158] With regard to functional findings, hyperactivity in the ACC has been associated with response to treatment, normalizing after a course of treatment. Persistence of hyperactivity in this region has been shown to help identify poor treatment responders. Amygdala hyperactivity in response to negative emotions has been demonstrated to be characteristic of a depressed state and is sensitive to clinical improvement after a course of antidepressant treatment.[46] These findings suggest that structural and functional neuroimaging could contribute to the prediction of treatment response, and recent studies using machine learning methods indicate it is possible to predict treatment response at an individual level with a high degree of accuracy.

Another intriguing development is the possibility of determining differential treatment effectiveness for a given individual, based on neuroimaging measures. The results of McGrath et al[91] are revealing in this respect by suggesting the baseline metabolism in the insula may help determine whether a patient is likely to respond preferentially to pharmacological or psychological interventions. fMRI studies also suggest that ACC activity differentially predicts response to pharmacological and psychological treatment, although this needs further validation in future studies prospectively evaluating clinical benefits on larger naturalistic samples.

Limitations

The role of neuroimaging is likely to expand in the future to improve diagnostic specificity and help predict treatment response. At present, neuroimaging is unlikely to benefit patients at an individual level, to predict transition to a full syndrome in an "at-risk" mental state, or to help clarifying diagnostic uncertainty. With reference to cross-diagnostic validity, this is one of the greatest challenges faced by biological models of psychiatric disorders at present,[159–161] with a paucity of studies allowing cross-diagnostic comparisons. As a result, there are no neuroimaging-based biomarkers that can aid in the differential diagnosis of MDD, and this is a major challenge that will need to be overcome if they are to ever be clinically useful.

By far the main limitation is the relatively limited replicability of most findings, which questions the generalizability

of neurobiological models and limits their diagnostic use. Discrepancies can result from heterogeneity of depressive disorders, inclusion/exclusion of comorbidity, sample size, methodological differences, clinical differences in the patients included (eg, number of episodes, length of illness, degree of treatment resistance, presence and length of pharmacological treatment), and analysis techniques. In the case of fMRI, it is also possible that different interventions modulate brain circuitry differently, depending on which component they act on in the context of the hypothesis tested and in relation to task requirement. Some of these issues could be ameliorated by the use of larger samples, encompassing a range of MDD presentations, or by comparing subtypes of MDD and different treatments to understand the factors underlying the observed heterogeneity in results. Moreover, the field would greatly benefit from a degree of standardization of techniques across research groups and collaborative alliances, resulting in much larger numbers of participants available for analysis.

Of particular interest, participants in these studies tend to be highly selected individuals who differ from patients seen in the clinic with potentially milder severity of illness and absence of comorbidities, and therefore are not necessarily fully representative of the condition. In this context, and from a pragmatic perspective, naturalistic studies in larger samples might be better suited to identifying biomarkers that reflect conventional clinical populations.

Furthermore, there is little research using neuroimaging in people at high risk for depression. Some findings suggest that some of the structural and functional differences seen in MDD patients may also be present in healthy individuals at genetic risk of developing the condition.[30] This is an important issue, as it is likely that diagnostic biomarkers based on these differences could mistakenly diagnose these individuals as patients, despite being healthy. Conversely, individuals with MDD who do not have particular genetic variants associated with altered brain function and structure may be incorrectly diagnosed as healthy because of their reliance on trait, rather than state markers of MDD.

Although machine learning methods have been able to produce results at the level of individual patients, the accuracy of these methods is currently not high enough to permit their use in practice. In particular, most diagnostic studies do not achieve specificities close to 100%. Given the relatively low proportion of the population that has MDD, this would result in a large number of false-positives (see Lalkhen and McCluskey[162] for further discussion on this issue). This is less of a concern with regard to prognosis because of the relatively high number of patients who will respond to a given intervention. In addition, even a test with high but not perfect sensitivity and specificity would arguably be an improvement on the current system of prescription or choice of therapeutic modality based solely on clinicians' judgment.

Finally, an important issue in the development of any biomarker for the prediction of treatment response is whether it predicts response to treatment specifically or is predictive of prognosis, independent of the treatment being tested. In depression, factors such as spontaneous remission may account for a large proportion of improvement seen with treatment,[163] and it is impossible to tell whether predictive biomarkers are, in fact, predicting improvement because of treatment. This problem could potentially be avoided by including placebo treatment groups, although this is often not possible because of ethical considerations. Alternatively, this could be addressed, as shown by a recent study,[164] by integrating neuroimaging protocols into future clinical trials. Comparisons of predictive biomarkers for multiple treatments also might allow markers that are specific to individual treatments to be distinguished from those that are predictive of general improvement.

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