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Identifying Predictors, Moderators, and Mediators of Antidepressant Response in Major Depressive Disorder: Neuroimaging Approaches

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Abstract

Objective—Despite significant advances in neuroscience and treatment development, no widely accepted biomarkers are available to inform diagnostics or identify preferred treatments for individuals with major depressive disorder.

Method—In this critical review, the authors examine the extent to which multimodal neuroimaging techniques can identify biomarkers reflecting key pathophysiologic processes in depression and whether such biomarkers may act as predictors, moderators, and mediators of treatment response that might facilitate development of personalized treatments based on a better understanding of these processes.

Results—The authors first highlight the most consistent findings from neuroimaging studies using different techniques in depression, including structural and functional abnormalities in two parallel neural circuits: serotonergically modulated implicit emotion regulation circuitry, centered on the amygdala and different regions in the medial prefrontal cortex; and dopaminergically modulated reward neural circuitry, centered on the ventral striatum and medial prefrontal cortex. They then describe key findings from the relatively small number of studies indicating that specific measures of regional function and, to a lesser extent, structure in these neural circuits predict treatment response in depression.

Conclusions—Limitations of existing studies include small sample sizes, use of only one neuroimaging modality, and a focus on identifying predictors rather than moderators and mediators of differential treatment response. By addressing these limitations and, most importantly, capitalizing on the benefits of multimodal neuroimaging, future studies can yield moderators and mediators of treatment response in depression to facilitate significant improvements in shorter- and longer-term clinical and functional outcomes.

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Major depressive disorder has a lifetime prevalence of 16.2%, causes greater total morbidity, loss of productivity, and suicide than any other noncommunicable disorder, and contributes significantly to decreased quality of life (1, 2). Despite significant advances in neuroscience, treatment development has lagged, primarily because of a lack of applicable clinical neuroimaging or other biomarkers: no widely accepted biomarkers are available to assist diagnostics or treatment choice for individual patients. The timely selection of the optimal treatment for patients with depression is critical to improving remission rates. Owing to the biological heterogeneity and variable symptom presentation of depression, it is unlikely that a single clinical or biological marker can guide treatment selection. Rather, multiple biological measures may be needed to refine our understanding of the underlying pathology and provide more reliable markers to guide treatment. Unfortunately, predictor research has been limited by the use of a single clinical or biological marker and as a result has explained a small degree of variance.

As has been highlighted previously (3), neuroimaging technologies have the potential to identify objective neurobiological markers reflecting underlying pathophysiologic processes in a given psychiatric illness, which can ultimately facilitate the development of personalized treatments based on a better understanding of these underlying processes. Moreover, with the advancement of different types of neuroimaging technologies and data analytic techniques, there are now enormous opportunities to adopt multimodal neuroimaging approaches to examine the functional and structural integrity of parallel distributed neural circuits implicated in a given illness. In turn, this approach can both help identify multiple biomarkers reflecting underlying pathophysiologic processes in illnesses such as depression, and help in determining the extent to which such biomarkers can serve as predictors of treatment response in the illness. Typically, however, studies in depressed individuals have focused on examination of one neural circuit of interest and have not employed multimodal neuroimaging techniques to refine our understanding and thereby provide more reliable biomarkers of functional and structural abnormalities in parallel neural circuits of interest. Furthermore, a relatively small number of studies have used neuroimaging to help identify biomarker predictors of antidepressant response in depression, and, as noted, they have focused primarily on one neural circuit. Moreover, no study to date has focused on identifying neuroimaging moderators, pretreatment variables that predict differential treatment response, or neuroimaging temporal mediators, variables whose change early during treatment is associated with future treatment outcome, in depression. Identification of the former can improve treatment selection for depressed individuals. Identification of the latter can help stop ineffective treatment early, in addition to facilitating our understanding of early, even if not longer-term, causal neural mechanisms of treatment response in these individuals (4). Elucidating neuroimaging moderators and mediators can thus provide not only valuable insights into neural mechanisms of illness but also valuable clinical information to help guide the choice of treatment for these individuals early on.

In this review, we first examine the extent to which multimodal neuroimaging techniques can be used to identify biomarkers reflecting key underlying pathophysiologic processes in depression. We describe two parallel neural circuits, namely, implicit emotion regulation and reward neural circuits, that are relevant to understanding pathophysiologic processes underlying core symptom dimensions in depression. We examine the extent to which these

neural circuits are modulated by different neurotransmitter systems, and the nature of functional, gray and white matter structural, and resting-state functional connectivity, as well as blood flow abnormalities, in these neural circuits in depressed individuals. We then examine the extent to which biomarkers reflecting functional and structural abnormalities in these circuits may have utility as predictors and, more importantly, as moderators and mediators of treatment response to specific antidepressant treatments. We end by discussing future directions for neuroimaging studies of treatment response prediction in depression.

NEURAL CIRCUITS IMPLICATED IN THE PATHOPHYSIOLOGY OF DEPRESSION

Core depressive symptom dimensions, including persistent low mood, anxiety, and anhedonia, reflect predominant features of dysfunctional emotion regulation and reward processing. While abnormalities in multiple distributed neural circuits underlying different levels of effortful and implicit emotion regulation and reward processing are probably implicated in the pathophysiology of depression and other affective disorders (3, 5), the most consistent findings involve two patterns of distinct functional abnormalities: those in 1) serotonergically modulated implicit emotion regulation neural circuitry centered on the amygdala and different medial prefrontal cortical regions, and 2) dopaminergically modulated reward neural circuitry centered on the ventral striatum and medial prefrontal cortex (6–9) (Figure 1). Abnormalities in these parallel neural circuits may be associated with different symptom dimensions and therefore guide appropriate treatment selection. For example, abnormalities in implicit emotion regulation circuitry may be associated with persistent low mood and anxiety, while abnormalities in reward neural circuitry may result in apathy and anhedonia (10, 11). Examining relationships between abnormalities in these neural circuits and different symptom dimensions in depressed individuals also parallels the dimensional approach of Research Domain Criteria advocated by the National Institute of Mental Health (12) and can ultimately identify critical brain-behavior relationships that may transcend conventional diagnostic categories of psychiatric illness. For example, abnormalities in implicit emotion regulation circuitry may be associated with behaviors linked to constructs in the negative valence systems domain, such as acute and sustained threat, fear, and anxiety. On the other hand, abnormalities in reward circuitry may be associated with behaviors linked to constructs in the positive valence systems domain, such as reward expectancy and anhedonia. In the following sections, we describe in more detail the nature of these distributed neural circuits, their modulation by specific neurotransmitter systems, and the abnormalities in these circuits that are reported in depressed individuals.

NEURAL CIRCUITS UNDERLYING IMPLICIT EMOTION REGULATION AND REWARD PROCESSING, AND THEIR MODULATION BY SPECIFIC NEUROTRANSMITTER SYSTEMS

Implicit Emotion Regulation Circuitry

A large body of animal and human neuroimaging studies highlights the role of the amygdala and different medial prefrontal cortical regions in implicit emotion regulation, including the

subgenual anterior cingulate cortex, the ventromedial prefrontal cortex, the rostral/pregenual anterior cingulate cortex, the dorsal anterior cingulate cortex, and the mediodorsal prefrontal cortex, in addition to the hippocampus. Distinct roles of these regions have been reported in different implicit emotion regulation subprocesses, including automatic behavioral control, automatic attentional control, and automatic cognitive change (13). Specifically, the subgenual anterior cingulate and ventromedial prefrontal cortices are implicated in automatic behavioral control (e.g., fear extinction), which may be associated with the roles of these regions in encoding emotional salience; the rostral/pregenual anterior cingulate cortex is a key region involved in automatic attentional control; and the dorsal anterior cingulate and mediodorsal prefrontal cortices and the hippocampus, in addition to the ventromedial prefrontal cortex, may be more involved in automatic cognitive change processes (e.g., error monitoring and behavioral rule learning paradigms occurring without subjective awareness) (13).

Growing evidence suggests that serotonin modulates activity in implicit emotion regulation neural circuitry, particularly the amygdala and medial prefrontal cortical regions (14). For example, multiple neuroimaging studies have found differences in activity and functional connectivity in this circuitry across genetic variants in the promoter region of the gene for the serotonin transporter (5-HTTLPR) (15–19). This circuitry has been modulated by serotonergic challenge with serotonin reuptake inhibitors (SRIs) (20–26), even with the combined serotonin and norepinephrine reuptake inhibitor (SNRI) duloxetine (27); by serotonergic depletion with acute tryptophan depletion (21, 28, 29); and by the tricyclic antidepressant clomipramine, affecting serotonin and norepinephrine reuptake (30). Overall, these findings indicate that increasing serotonin level is associated with reduced activity in this circuitry, particularly in the amygdala, to threat-related stimuli (although see references 31, 32), while decreasing serotonin level is associated with increased functioning within this circuitry (33, 34). Furthermore, there is evidence indicating an impact of genetic variation in 5-HTTLPR and other genes affecting serotonergic functioning on amygdala and hippocampal volumes (35–37). A smaller number of studies indicate that other neurotransmitters, for example, catecholamines such as norepinephrine, may also modulate functioning in this circuitry (20, 38, 39).

Reward Circuitry

A large body of neuroimaging in animals and, increasingly, in human subjects highlights the role of ventral striatal and predominantly medial prefrontal cortical circuitry in reward processing, as well as the modulating role of dopamine in this circuitry (40). Rodent studies have elucidated a well-delineated reward circuitry, centered on the ventral striatum/nucleus accumbens, that receives excitatory afferents from the ventral tegmental area dopamine system, which in turn modulates ventral striatal activity during encoding of reward prediction and the mediation of motivational state influences on reward learning (41). The orbitofrontal cortex may exert a regulatory role in reward signaling (42).

Human neuroimaging studies further highlight the role of the ventral striatum (7, 43, 44) and the medial prefrontal cortex, including the ventromedial prefrontal cortex, and different anterior cingulate cortical regions (3, 13, 45, 46), in reward processing. The medial

prefrontal cortex is proposed to support modulation of visceral activity to affective stimuli (46), while the pregenual and dorsal anterior cingulate cortices support reward regulation. Studies have reported that the pregenual/dorsal anterior cingulate cortices are activated during choice selection for possible high versus low future gains (47, 48), risky decision making (49), and reward and loss expectancy (50) and show robust functional coupling with the ventral striatum to reward omission following expectation of large rewards (51). Other prefrontal cortical regions, especially the ventromedial prefrontal cortex, support encoding of reward value (52, 53).

Further support for the key modulating role of dopamine on reward circuitry comes from human neuroimaging studies reporting modulation of reward circuitry by genes affecting dopamine transmission (54), associations between greater ventral striatal activity and greater phasic ventral striatal dopamine release in healthy adults (55) (which may be related to impulsivity [56]), and dopamine release in the anterior cingulate and medial prefrontal cortices during a reward task (57). Pharmacological functional MRI (fMRI) studies indicate that increasing levels of dopamine and other monoamines with administration of oral dextroamphetamine modulates ventral striatal activity in healthy and depressed individuals (58), and that levodopa modulates ventral striatal activity and reward-related decision making in healthy adults (59). One study (60) reported that the SNRI duloxetine led to increased ventral striatal activity to reward anticipation in healthy volunteers, although the study did not examine the relationship between ventral striatal activity and dopamine release.

Other neurotransmitters and hormonal systems also modulate activity in reward circuitry (40). For example, glucocorticoids modulate dopaminergic ventral striatal activity during reward learning, and also modulate transmission of different neuropeptides in the ventral striatum (61). GABA and glutamate may also affect reward learning-related ventral striatal activity (40).

Other Neuroimaging Modalities Examining Implicit Emotion Regulation and Reward Circuits

Resting-state functional connectivity—Examination of resting-state functional connectivity fMRI is based on the discovery that low-frequency (<0.1 Hz) blood-oxygen-level-dependent fluctuations in distant but apparently functionally related gray matter regions show strong correlations at rest (62, 63). There is growing interest in resting-state functional connectivity studies for several reasons. First, the use of “stimulus-free” resting-state fMRI unburdens experimental design, subject compliance, and training demands, making it attractive for studies of clinical populations (64), although spontaneous differences in subject behavior, arousal, and head motion may be confounders (65, 66). Second, in studies modeling both high-resolution structural and functional connectivity in the same individuals, resting-state functional connectivity strength, persistence, and spatial statistics have been correlated with large-scale anatomical structure, suggesting that a significant component of the signal correlations reflects constraints of anatomical connectivity (67). Other components are dynamic and task-modulated (68) and spontaneously change at short intervals (69, 70).

Multiple studies have demonstrated the ability of resting-state fMRI to identify regions and networks of regions that appear to be functionally related, initially among motor regions (62). Subsequent work has demonstrated functional connectivity by resting-state fMRI among distributed association regions that comprise multiple distributed networks, such as the default network (71–73) and many other networks important to attention, memory, cognitive control, and affective processing (74–77). Regarding neural circuits of particular interest to this review, one study (78) elucidated the resting-state functional connectivity of the major amygdala subregions (basolateral and centromedial), showing that the basolateral amygdala was connected with sensory and higher-order cortical regions, while the centromedial amygdala was connected with subcortical regions.

Arterial spin labeling—Arterial spin labeling is a noninvasive perfusion MRI technique, used to quantify cerebral blood flow. Arterial spin labeling is based on the subtraction of two consecutively acquired images: one with and another without magnetically labeled water in arterial blood (79). Comparisons between arterial spin labeling and H₂¹⁵O positron emission tomography (PET) studies in healthy individuals demonstrate significant positive correlations between measures of resting cerebral blood flow derived from the two neuroimaging techniques (80). Thus, arterial spin labeling is a promising MRI technique to quantify cerebral blood flow that, unlike PET, does not expose individuals to ionizing radiation.

Diffusion imaging—Diffusion imaging is an MRI-based method that can measure the macroscopic axonal organization in the living brain (81). One of the most commonly reported outcome measures in diffusion imaging analysis is fractional anisotropy, a measure of the degree and directionality of diffusion of water molecules and, by inference, greater fractional anisotropy suggesting the presence of more coherently bundled myelinated fibers in a given tract. Lower fractional anisotropy can be due to changes in the density of the axons, axonal diameter, myelination, coherence of the fiber tract, or localized water content. Key white matter tracts connecting prefrontal cortical and subcortical regions in implicit emotion regulation and reward processing neural circuits include the corpus callosum, the anterior cingulum, the uncinate fasciculus, and the superior longitudinal fasciculus (82).

FUNCTIONAL AND GRAY MATTER STRUCTURAL ABNORMALITIES IN IMPLICIT EMOTION REGULATION AND REWARD CIRCUITS IN DEPRESSION

Some of the most consistent findings regarding functional abnormalities in implicit emotion regulation circuitry in depressed individuals are abnormally elevated activity in the amygdala and/or anterior cingulate cortex; reduced functional connectivity between the amygdala and medial prefrontal cortical regions in response to negative emotional stimuli; and, to a lesser extent, reduced activity in response to positive emotional stimuli (83–96). Interestingly, there is some evidence that abnormally reduced amygdala activity to positive emotional stimuli may be associated with anhedonia in depressed individuals (97). There are inconsistent findings of either maintenance of abnormally elevated or abnormally reduced activity in this circuit, especially in the amygdala, during remission from depression (98–

100). Longitudinal neuroimaging studies, however, have reported a normalization of abnormally elevated activity in this circuit in response to pharmacotherapy, especially treatment with SRIs (24, 86–88, 94, 96, 101, 102).

An increasing number of studies have reported functional abnormalities in reward circuitry in depressed adults. Depressed adults have been reported to show abnormally elevated rostral anterior cingulate cortical activity to previously rewarding stimuli (103). Other studies of depression have reported either elevated (104) or reduced (105) activity in the pregenual and dorsal anterior cingulate cortices during expectancy of monetary reward, and a failure to deactivate the pregenual anterior cingulate cortex during reward learning (7). Furthermore, elevated ventral/pregenual anterior cingulate cortical activity, together with reduced capacity to maintain ventral striatal activity to rewarding/positive emotional stimuli, has been reported to be associated with greater anhedonia in depressed adults (106, 107). Some studies have indicated significantly reduced ventral striatal activity to rewarding stimuli and during reward learning in depressed compared with healthy adults (7, 10, 43, 108, 109), and increased habituation of ventral striatal activity to reward (110). Others have not found these associations (104). Additional evidence suggests associations between greater anhedonia and diminished reward learning in depressed individuals (111) and a normalization of functional abnormalities in reward circuitry with successful response to psychotherapy (112) (Figure 1).

While it is beyond the scope of this review to describe findings in detail, an extensive literature has documented abnormally reduced gray matter volume in regions overlapping with implicit emotion regulation and reward circuits in depressed individuals, in particular in the ventromedial prefrontal and anterior cingulate cortices and in subcortical regions (113–115). Studies examining cortical thickness, an index of neuronal integrity and arborization (116), have reported 28% lower right cortical thickness in individuals at high risk for depression (117).

Parallel Findings From Resting-State Functional Connectivity, Arterial Spin Labeling, and Diffusion Imaging Studies

There is a rapidly growing literature focusing on resting-state connectivity in a variety of neural regions and networks in depressed individuals. While there have been many inconsistent findings, key findings in neural circuits supporting implicit emotion regulation and reward processing indicate either abnormally increased or abnormally decreased resting-state connectivity between different anterior cingulate cortical subregions and other prefrontal cortical regions (118, 119); abnormally reduced resting-state connectivity between subcortical regions, including between the amygdala and the striatum, and between the anterior cingulate and ventromedial prefrontal cortices (86, 118–122); decreased resting-state connectivity between the subgenual anterior cingulate cortex and cortical areas (123); and abnormal patterns of resting-state connectivity between striatal and ventral prefrontal cortical regions and the whole brain (124). Resting-state connectivity has also been reported to be abnormally increased across three large-scale networks, including the affective (subgenual) network, in depressed individuals (125). Subcortical-anterior cingulate cortical resting-state connectivity has been shown to increase after SRI treatment (86), although

SRI and antidepressant medications targeting catecholamine systems have been shown to decrease resting-state connectivity in healthy volunteers (126).

A small number of studies have employed arterial spin labeling to examine regional cerebral blood flow in implicit emotion regulation neural circuitry in depression. A study comparing six patients with chronic treatment-resistant depression and six healthy subjects (127) showed significantly greater resting cerebral blood flow in predominantly left-sided medial prefrontal cortical and subcortical regions in the depressed group. Another study (128) reported that depressed individuals who responded to partial sleep deprivation had greater baseline amygdala blood flow relative to individuals who did not respond, and that cerebral blood flow in this region was reduced after treatment. In parallel, a study in healthy individuals (129) showed that a single oral dose of the SRI citalopram was associated with reductions in cerebral blood flow in implicit emotion regulation circuitry regions, including the amygdala and the ventromedial prefrontal cortex. Another study (130) found decreased perfusion in the prefrontal and anterior cingulate cortices in depressed adult nonremitters after a 6-month follow-up compared with healthy adults, but did not find any perfusion differences between depressed and healthy adults at baseline.

A meta-analysis of diffusion imaging data in mood disorders reported that 21 of 27 studies found significantly lower fractional anisotropy in the left and right frontal and temporal lobes or in white matter tracts connecting prefrontal cortical, subcortical, and other cortical regions in individuals with mood disorders relative to healthy volunteers (131). More recent studies confirm this general pattern in individuals with, and those at risk for, depression (132–146), although there are some exceptions (147).

ELUCIDATING ABNORMALITIES IN IMPLICIT EMOTION REGULATION AND REWARD CIRCUITS IN DEPRESSION: A COMPARISON WITH BIPOLAR DISORDER

Specific themes emerge from the studies described above. These include, in implicit emotion regulation circuitry, abnormally elevated amygdala activity and reduced amygdala-medial prefrontal cortical functional connectivity to negative emotional stimuli in particular, paralleled by reductions in gray matter volumes in subcortical and prefrontal cortical regions. Resting-state functional connectivity studies indicate abnormally reduced, but also abnormally increased, resting-state functional connectivity between these regions, while arterial spin labeling studies report patterns of predominantly abnormally increased resting blood flow in the amygdala and in medial prefrontal cortical regions. Diffusion imaging findings indicate abnormally reduced fractional anisotropy in white matter tracts connecting these regions. These findings suggest compromised functioning in this circuitry, including insufficient regulation of subcortical structures such as the amygdala by medial prefrontal cortical regions, especially to negative emotional stimuli. The smaller number of findings in reward circuitry indicate abnormally elevated activity in anterior cingulate cortical subregions, especially the pregenual anterior cingulate cortex, during reward anticipation and receipt, and abnormal, predominantly reduced, ventral striatal activity during different stages of reward learning, although there are inconsistent findings.

Further understanding of these findings can be facilitated by comparing the functional and structural abnormalities in these circuits in depressed individuals with those observed in individuals with other mood disorders, in particular bipolar disorder. For example, findings suggest distinguishable functioning and structure in implicit emotion regulation circuitry in depressed individuals with major depressive disorder compared with depressed individuals with bipolar disorder; studies have also reported differential patterns of functional and white matter structural abnormalities in this circuitry in the two disorders (85, 148, 149; see reference 150 for a review). These studies indicate greater amygdala activity in response to negative than to positive emotional stimuli, predominantly left-sided reductions in fractional anisotropy, and abnormally increased left-sided ventromedial prefrontal cortical-amygdala inverse functional connectivity to positive emotional stimuli in depressed individuals with major depressive disorder. In contrast, in depressed individuals with bipolar disorder, findings indicate bilateral reductions in both ventromedial prefrontal cortical-amygdala functional connectivity and fractional anisotropy in underlying white matter tracts.

These studies suggest that the depression of major depressive disorder, unlike bipolar depression, may be characterized more by left-sided than by bilateral abnormalities in implicit emotion regulation circuitry and underlying white matter tracts. This may be associated with reduced left prefrontal cortical activity during emotion processing in individuals with major depressive disorder (151). Given the putative role of the left prefrontal cortex in processing approach-related emotions (152), this bias away from left prefrontal cortical activity during emotion processing may result in the well-documented attentional bias away from positive and toward negative emotional stimuli (153) and associated findings of abnormally increased amygdala (and anterior cingulate cortical) activity to negative emotional stimuli, described above. Links among these phenomena require further study, however. Bipolar disorder, by contrast, may be associated with bilateral dysregulation of the amygdala by different prefrontal cortical regions and may result in the emotional lability and abnormally elevated amygdala activity to both negative and positive emotional stimuli reported in individuals with bipolar disorder (3). In support of this, one recent study showed a positive correlation between the magnitude of amygdala activity to positive emotional stimuli and levels of subthreshold manic symptoms in depressed individuals with major depressive disorder (154).

Increasing evidence also suggests differential patterns of abnormalities in reward circuitry in individuals with major depressive disorder compared with those with bipolar spectrum disorders. For example, a recent review highlighted, in individuals with bipolar disorder across different mood states and different bipolar subtypes, abnormally elevated activity in the left ventrolateral prefrontal cortex, a region implicated in tracking reward value and arousal during anticipation of potentially rewarding stimuli (155, 156), during anticipation of uncertain reward or uncertain losses (3). This pattern of abnormal neural activity is not reported in individuals with current or remitted major depressive disorder (9, 157). Given the role of the left prefrontal cortex in processing approach-related emotions (152) and reports of heightened reward sensitivity in individuals with bipolar disorder (158), elevated left ventrolateral prefrontal cortical activity may represent a neural marker of heightened reward sensitivity that distinguishes bipolar disorder from major depressive disorder.

Meta-analyses have also indicated reductions in hippocampal and striatal volumes in individuals with major depressive disorder relative to those with bipolar disorder (113), which may be associated with greater amygdala activity to negative emotional stimuli, as described above, or may result from different patterns of psychotropic use in the two disorders (3); further study is needed. Findings from resting-state studies directly comparing individuals with the different disorders are few and are difficult to interpret (3). Overall, findings thus suggest that bipolar disorder may be distinguished from major depressive disorder by patterns of function and white matter structure in the two neural circuits of interest in this review.

Despite the advances that neuroimaging techniques have provided in increasing our understanding of pathophysiologic processes in depression—specifically in implicit emotion regulation and reward circuits—the extent to which neuroimaging measures reflecting these processes moderate (and mediate) differential treatment response in individuals with depression remains understudied. An increasing number of small studies, however, have sought to identify neuroimaging predictors of treatment response in depression, as described in the following sections.

NEUROIMAGING STUDIES OF PREDICTORS OF ANTIDEPRESSANT RESPONSE

Functional Neuroimaging Studies

Functional neuroimaging studies that have identified predictors of treatment response in depression have focused largely on the examination of implicit emotion regulation neural circuitry and have included an SRI medication as the treatment of study. These studies focused in particular on the role of the anterior cingulate cortex and medial prefrontal cortex (8). The most striking finding from these studies was an association between hypermetabolism, as measured with PET, or greater activity, measured with fMRI, in the pregenual anterior cingulate cortex and better response to a single SRI. No such association was found for response to the dopaminergic medication bupropion (159). fMRI studies that examined responses to emotional (predominantly negative emotional) stimuli with fMRI found a similar association between greater baseline activity in regions throughout the dorsal-ventral extent of the anterior cingulate/medial prefrontal cortex and better treatment response (predominantly but not exclusively to SRI medications) in depression (160–162). Other studies reported that greater pretreatment anterior cingulate/medial prefrontal cortical activity predicted a negative treatment outcome to psychotherapy (163, 164).

fMRI studies of treatment response prediction in depression also indicate an important role for the amygdala. One study of cognitive-behavioral therapy (CBT) reported that greater pretreatment amygdala activity predicted better outcome (163), while a study of the rapid antidepressant ketamine reported the opposite effect (161). Another study reported that greater amygdala activity to emotional facial expressions predicted greater reduction in depressive symptoms 8 months after different types of treatment (165). Other studies using nonemotional stimuli provide further evidence pointing toward the roles of the anterior cingulate/medial prefrontal cortex and the amygdala as predictors of treatment response in

depression. One study (166) showed that, among other subcortical regions, left amygdala activity during successful performance on an inhibitory control task and pregenual anterior cingulate cortex activity during unsuccessful inhibition (commission errors) predicted improvement in depression symptoms after a 10-week treatment with escitalopram. Another study, however, showed that a lower response at baseline in the dorsal anterior cingulate cortex was associated with an improved clinical outcome with an 8-week treatment with fluoxetine (167). Another study reported that lower pretreatment activity in the ventrolateral prefrontal cortex, a region implicated in more effortful, “voluntary” emotion regulation (13), during attempts to down-regulate positive emotion was associated with better response to either fluoxetine or the SNRI venlafaxine in depressed adults (168).

Collectively, these studies suggest that measures of metabolism/activity in the anterior cingulate and medial prefrontal cortices (and, to a lesser extent, the amygdala) may differ in patients who benefit from psychotherapy compared with SRIs or dopaminergic antidepressants and that measuring metabolism/activity in these areas may provide guidance for future treatment choices.

Few studies have examined the extent to which function in reward circuitry predicts antidepressant response. One small study in youths reported that higher pretreatment ventral striatal and lower medial prefrontal cortical activity to reward may be associated with greater reduction in anxiety after CBT or combined treatment with CBT and an SRI (169), but the study did not examine predictors of response to dopaminergic antidepressants. More neuroimaging studies are thus required to identify measures of reward circuitry function that may predict response to dopaminergic antidepressants.

Other Neuroimaging Modalities

While the extent to which gray matter abnormalities may predict or moderate treatment outcome in depression is unclear (160, 170, 171) and the extent to which these and other structural measures may mediate treatment response remains unexamined, a small number of studies suggest that other neuroimaging modalities measuring resting-state connectivity and blood flow, cortical thickness, and white matter connectivity may help identify predictors of treatment response. For example, a study of late-life depression reported that response to the SRI sertraline was associated with lower frontal fractional anisotropy values (172). An arterial spin labeling study reported increased perfusion in the right ventral anterior cingulate cortex and in striatal, hippocampal, and cortical regions in depressed patients who responded to at least two antidepressants (an SRI, venlafaxine, or a tricyclic antidepressant) compared with nonresponders (173), findings that parallel earlier PET studies of treatment response prediction in depression (see above). One PET study reported that resting metabolism in the right anterior insula, another region implicated in emotion regulation and self processing, moderated response to CBT compared with an SRI (174).

Limitations of Existing Neuroimaging Studies of Predictors of Antidepressant Response

Neuroimaging studies can yield measures reflecting pathophysiologic processes of depression, of which some may help predict treatment response (Table 1). Many studies, however, used small samples and focused on identifying predictors of successful treatment

response, either to a single SRI or to antidepressant medication in general, rather than identifying moderators and mediators of differential treatment response. Most studies employed a single neuroimaging modality and examined predominantly one neural circuit of interest, namely, amygdala-anterior cingulate/medial prefrontal cortical circuitry supporting implicit emotion regulation. Findings from some of these studies resulted in development of a novel deep brain stimulation treatment for the 30% of individuals whose depression is treatment resistant (175). Overall, however, the necessarily narrow focus of these smaller-scale neuroimaging studies has, unfortunately, resulted in limited translation of otherwise very interesting findings into widespread clinical practice.

FUTURE DIRECTIONS FOR NEUROIMAGING STUDIES OF TREATMENT RESPONSE PREDICTION IN DEPRESSION

Clinical studies have traditionally made a choice between using large samples to test well-defined hypotheses and using smaller samples to allow in-depth assessment for hypothesis generating. The majority of neuroimaging studies, however, have focused on small samples with few assessments. Neuroimaging studies with large sample sizes are thus required for sufficient power to test key hypotheses and to subdivide data into training and testing data sets for first identifying and subsequently establishing moderators and mediators of treatment response. Furthermore, identifying, as early as possible after commencing treatment, measures that moderate and mediate treatment response remains a crucially important, but as yet unmet, need in clinical practice. Few studies have included neuroimaging assessments in early phases of treatment, and, of those that have (6, 176), none have examined how such early changes in neuroimaging measures moderated or mediated subsequent treatment response. The inclusion of baseline and early-stage (e.g., 1 week after treatment onset) neuroimaging assessments and of more than one treatment in clinical trial platforms will help identify moderators and early mediators of differential treatment response, as opposed to focusing on predictors of successful response to a single treatment or to treatment in general. Additionally, while previous neuroimaging findings suggested a neural signature of placebo response (177), no studies have examined the extent to which neuroimaging measures act as moderators or mediators of differential response to placebo compared with drug. Future studies should do so.

Studies would also benefit from examining more than one neural circuit, using multiple neuroimaging modalities, to examine the extent to which relationships among measures of the functional and structural integrity of parallel yet distributed neural circuits may moderate and mediate differential treatment response in depressed individuals. Here, the choice of medications in treatment platforms could include antidepressants, at various dosages, that would be expected to differentially affect function in serotonergically modulated implicit emotion regulation and dopaminergically modulated reward processing neural circuits (Figure 2). These measures could be integrated with electrophysiological, neurocognitive, and clinical measures, using, for example, factor analysis, to identify key brain-behavior relationships that may moderate and mediate differential treatment response in depression (178, 179). Finally, as in studies of cardiovascular disease, asthma, breast cancer, lung cancer, multiple sclerosis, macular degeneration, and other medical illnesses (180–184),

future studies should identify personalized biosignatures developed from several clinical and biological markers reflecting underlying pathophysiologic processes. The combination of these approaches is more likely to be successful and to result in significant improvements in shorter- and longer-term clinical and functional outcome for the large number of individuals who suffer from depressive illnesses.

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FIGURE 1. Functional Abnormalities in Parallel Neural Circuits in Depression^a

A. Functional Abnormalities in Implicit Emotion Regulation Neural Circuitry

B. Functional Abnormalities in Reward Neural Circuitry

^a ACC=anterior cingulate cortex; mPFC=medial prefrontal cortex; vmPFC=ventromedial prefrontal cortex. In panel A, the star-shaped nodes represent regions in which more consistent patterns of abnormally elevated activity are reported in depression. The blue arrows represent functional (and effective) connectivity among the key neural regions in this circuitry. In panel B, the star-shaped nodes represent regions in which more consistent patterns of abnormally elevated or decreased activity are reported in depression.

FIGURE 2. Hypothesized Moderators or Mediators of Antidepressant Response in Depression^a

A. Hypothesized Moderators or Mediators of Response to SRIs Versus Non-SRIs in Implicit Emotion Regulation Neural Circuitry

B. Hypothesized Moderators or Mediators of Response to Dopaminergic Versus Nondopaminergic Antidepressants in Reward Neural Circuitry

^a SRI=serotonin reuptake inhibitor; ACC=anterior cingulate cortex; mPFC=medial prefrontal cortex; vmPFC=ventromedial prefrontal cortex. Findings from neuroimaging studies examining predictors of antidepressant treatment response in depression (8, 159–168) allow us to hypothesize that greater pretreatment activity and resting blood flow in the medial prefrontal cortex and pregenual anterior cingulate cortex implicit emotion regulation circuitry (panel A) may moderate response to SRIs versus nonserotonergic antidepressants. Changes in these measures after commencing such treatments may mediate response to SRIs. Few studies have examined how measures of structure and function in reward circuitry (panel B) predict treatment response in depression. Given previous findings that greater activity and resting blood flow in predominantly serotonergically modulated implicit emotion regulation circuitry regions (especially the medial prefrontal cortex and anterior cingulate cortex) predict better response to SRIs, it is plausible to hypothesize that greater activity and resting blood flow in predominantly dopaminergically modulated reward circuitry regions (especially the ventral striatum) may moderate response to dopaminergic versus nondopaminergic antidepressants in depression. Changes in these measures after commencing such treatments may mediate response to dopaminergic antidepressants.

TABLE 1

Summary of Key Neuroimaging Findings in Major Depression^a

Finding	Implicit Emotion Regulation Circuitry	Reward Circuitry
Neuroimaging abnormalities		
Functional abnormalities	Elevated amygdala activity to emotional (especially negative) stimuli Elevated anterior cingulate cortical activity (all regions) to negative and, to a lesser extent, positive emotional stimuli Reduced amygdala-medial prefrontal cortical functional connectivity to emotional stimuli Normalization of abnormal activity by SRI medications	Elevated anterior cingulate (rostral, pregenual, dorsal subregions) cortical activity to previously rewarding stimuli and during reward expectancy *Elevated ventral/pregenual anterior cingulate cortical activity and reduced capacity to maintain ventral striatal activity to rewarding stimuli associated with greater anhedonia *Reduced ventral striatal activity to rewarding stimuli and during reward learning; increased habituation of ventral striatal activity to reward Normalization of functional abnormalities in reward circuitry with successful response to psychotherapy
Gray and white matter structural abnormalities	Reduced gray matter volume in ventromedial prefrontal and anterior cingulate cortices and in different subcortical regions Reduced right cortical thickness	
Resting-state functional connectivity abnormalities	Multiple findings: elevated and reduced resting-state connectivity in different anterior cingulate cortical and other prefrontal cortical regions; reduced resting-state connectivity in subcortical regions; elevated subcortical-anterior cingulate cortical resting-state connectivity after SRI medication	Abnormal patterns of resting-state connectivity between striatal and ventral prefrontal cortical regions and the whole brain
Arterial spin labeling abnormalities	*Elevated subcortical (including amygdala) and medial prefrontal cortical resting cerebral blood flow SRI medication may reduce resting cerebral blood flow in amygdala and ventromedial prefrontal cortex	
Diffusion imaging abnormalities	*Reduced fractional anisotropy in white matter tracts connecting prefrontal cortical and subcortical regions	
Neuroimaging predictors of antidepressant treatment response		
Functional neuroimaging findings	Pretreatment hypermetabolism or greater activity to emotional (especially negative) stimuli in the anterior cingulate cortex (mainly the pregenual subregion) predicts better response to SRI medication Pretreatment greater activity in the anterior cingulate/medial prefrontal cortex predicts negative treatment outcome to psychotherapy Pretreatment greater amygdala activity to emotional stimuli predicts better response to different antidepressant medications and CBT (but not to ketamine)	
Other neuroimaging modalities	Lower fractional anisotropy predicts response to SRI medication (in late-life major depression); elevated arterial spin labeling measures of cerebral blood flow in the ventral anterior cingulate cortex (and other regions) may be associated with better response to SRI medication	

^aSRI=serotonin reuptake inhibitor; CBT=cognitive-behavioral therapy. An asterisk indicates some inconsistent findings.