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

Mary L. Phillips, M.D., Henry W. Chase, Ph.D., Yvette I. Sheline, M.D., Amit Etkin, M.D., Ph.D., Jorge R.C. Almeida, M.D., Ph.D., Thilo Deckersbach, Ph.D., Madhukar H. Trivedi, M.D.

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.

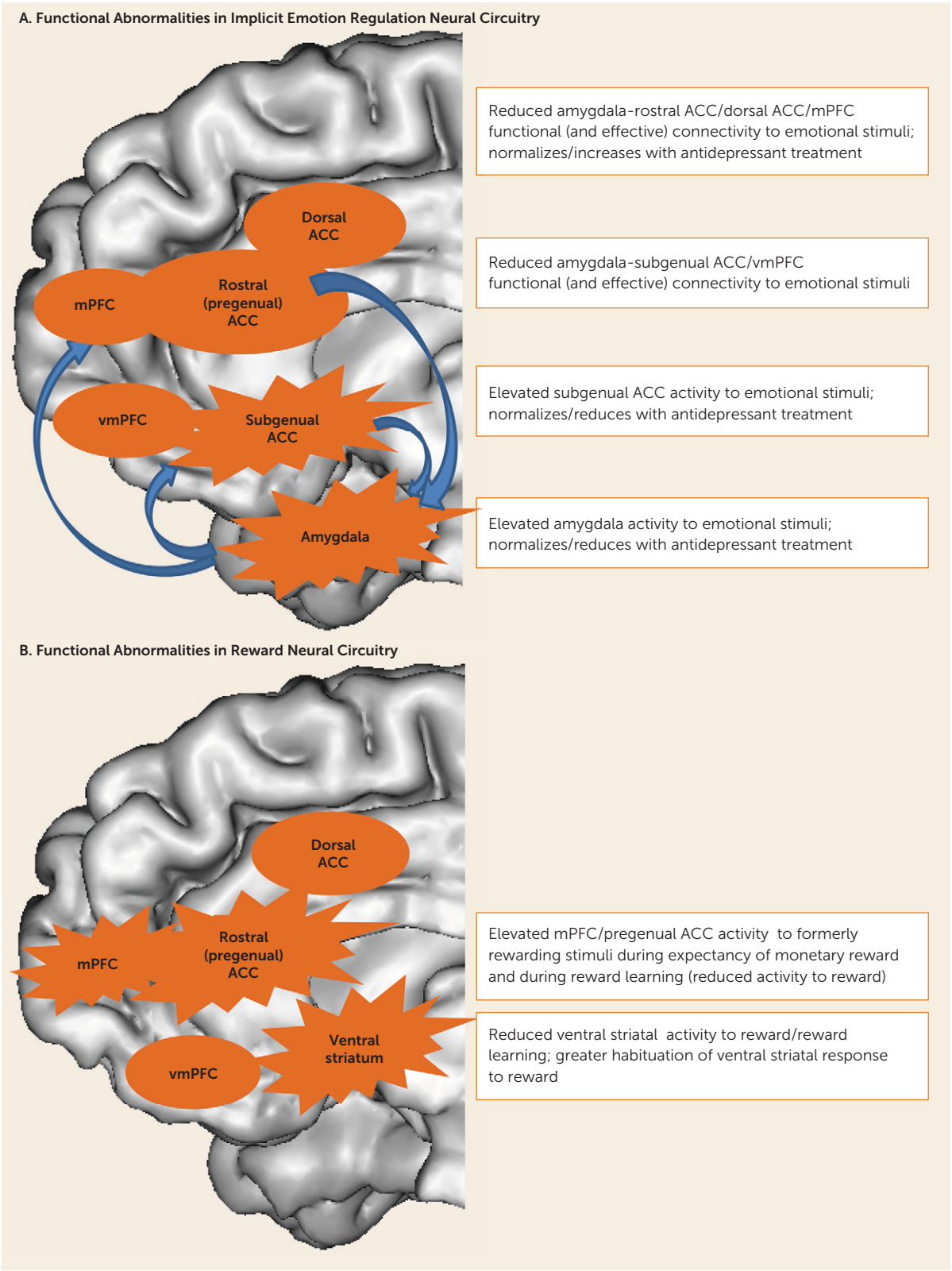
NEURAL CIRCUITS UNDERLYING IMPLICIT EMOTION REGULATION AND REWARD PROCESSING, AND THEIR MODULATION BY SPECIFIC NEUROTRANSMITTER SYSTEMS

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

FIGURE 1. Functional Abnormalities in Parallel Neural Circuits in Depression[a]



[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.

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 $H_2{}^{15}O$ 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 SRIs 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

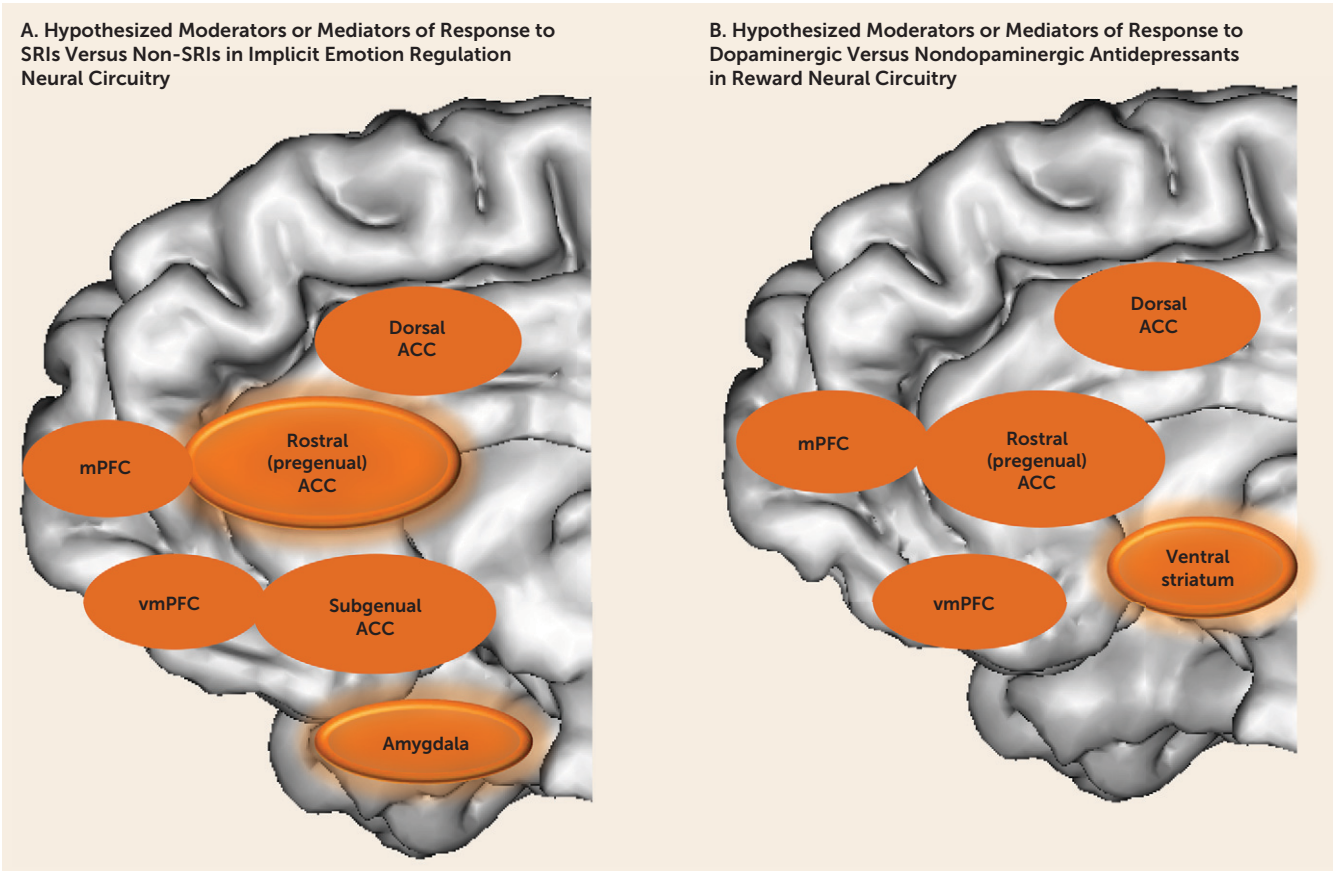
TABLE 1. Summary of Key Neuroimaging Findings in Major Depression[a]

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	

[a] SRI=serotonin reuptake inhibitor; CBT=cognitive-behavioral therapy. An asterisk indicates some inconsistent findings.

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

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



[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.

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.

AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh; the Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia; the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford; the Department of Psychiatry, Massachusetts General Hospital, Boston; and the Department of Psychiatry, UT Southwestern Medical Center, Dallas.

Address correspondence to Dr. Phillips (phillipsml@upmc.edu).

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REFERENCES

1. Collins PY, Patel V, Joestl SS, et al: Grand challenges in global mental health. Nature 2011; 475:27–30
2. Kupfer DJ, Frank E, Phillips ML: Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet 2012; 379:1045–1055
3. Phillips ML, Swartz HA: A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. Am J Psychiatry 2014; 171:829–843
4. Trivedi MH, Rush AJ, Wisniewski SR, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28–40
5. Phillips ML, Kupfer DJ: Bipolar disorder diagnosis: challenges and future directions. Lancet 2013; 381:1663–1671
6. Mayberg HS, Brannan SK, Tekell JL, et al: Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry 2000; 48:830–843
7. Kumar P, Waiter G, Ahearn T, et al: Abnormal temporal difference reward-learning signals in major depression. Brain 2008; 131:2084–2093
8. Pizzagalli DA: Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology 2011; 36:183–206

9. Chase HW, Nusslock R, Almeida JR, et al: Dissociable patterns of abnormal frontal cortical activation during anticipation of an uncertain reward or loss in bipolar versus major depression. Bipolar Disord 2013; 15:839–854
10. Pizzagalli DA, Holmes AJ, Dillon DG, et al: Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry 2009; 166:702–710
11. Keedwell PA, Andrew C, Williams SC, et al: The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry 2005; 58: 843–853
12. Insel T, Cuthbert B, Garvey M, et al: Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 2010; 167:748–751
13. Phillips ML, Ladouceur CD, Drevets WC: A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry 2008; 13:833–857
14. Jasinska AJ, Lowry CA, Burmeister M: Serotonin transporter gene, stress, and raphe-raphe interactions: a molecular mechanism of depression. Trends Neurosci 2012; 35:395–402
15. Klucken T, Wehrum S, Schweckendiek J, et al: The 5-HTTLPR polymorphism is associated with altered hemodynamic responses during appetitive conditioning. Hum Brain Mapp 2013; 34:2549–2560
16. Volman I, Verhagen L, den Ouden HE, et al: Reduced serotonin transporter availability decreases prefrontal control of the amygdala. J Neurosci 2013; 33:8974–8979
17. Hariri AR, Mattay VS, Tessitore A, et al: Serotonin transporter genetic variation and the response of the human amygdala. Science 2002; 297:400–403
18. Pezawas L, Meyer-Lindenberg A, Drabant EM, et al: 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 2005; 8:828–834
19. Dannlowski U, Konrad C, Kugel H, et al: Emotion specific modulation of automatic amygdala responses by 5-HTTLPR genotype. Neuroimage 2010; 53:893–898
20. Outhred T, Hawkshead BE, Wager TD, et al: Acute neural effects of selective serotonin reuptake inhibitors versus noradrenaline reuptake inhibitors on emotion processing: implications for differential treatment efficacy. Neurosci Biobehav Rev 2013; 37:1786–1800
21. Grady CL, Siebner HR, Hornboll B, et al: Acute pharmacologically induced shifts in serotonin availability abolish emotion-selective responses to negative face emotions in distinct brain networks. Eur Neuropsychopharmacol 2013; 23:368–378
22. McCabe C, Mishor Z, Cowen PJ, et al: Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. Biol Psychiatry 2010; 67:439–445
23. Windischberger C, Lanzenberger R, Holik A, et al: Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmaco-fMRI: a randomized cross-over study. Neuroimage 2010; 49:1161–1170
24. Murphy SE, Norbury R, O'Sullivan U, et al: Effect of a single dose of citalopram on amygdala response to emotional faces. Br J Psychiatry 2009; 194:535–540
25. Anderson IM, Del-Ben CM, Mckie S, et al: Citalopram modulation of neronal responses to aversive face emotions: a functional MRI study. Neuroreport 2007; 18:1351–1355
26. Harmer CJ, Mackay CE, Reid CB, et al: Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. Biol Psychiatry 2006; 59:816–820
27. van Marle HJ, Tendolkar I, Urner M, et al: Subchronic duloxetine administration alters the extended amygdala circuitry in healthy individuals. Neuroimage 2011; 55:825–831
28. Robinson OJ, Overstreet C, Allen PS, et al: The role of serotonin in the neurocircuitry of negative affective bias: serotonergic modulation of the dorsal medial prefrontal-amygdala "aversive amplification" circuit. Neuroimage 2013; 78:217–223
29. Passamonti L, Crockett MJ, Apergis-Schoute AM, et al: Effects of acute tryptophan depletion on prefrontal-amygdala connectivity while viewing facial signals of aggression. Biol Psychiatry 2012; 71: 36–43
30. de Almeida JR, Phillips ML, Cerqueira CT, et al: Neural activity changes to emotional stimuli in healthy individuals under chronic use of clomipramine. J Psychopharmacol 2010; 24:1165–1174
31. Bigos KL, Pollock BG, Aizenstein HJ, et al: Acute 5-HT reuptake blockade potentiates human amygdala reactivity. Neuropsychopharmacology 2008; 33:3221–3225
32. Di Simplicio M, Norbury R, Reinecke A, et al: Paradoxical effects of short-term antidepressant treatment in fMRI emotional processing models in volunteers with high neuroticism. Psychol Med 2014; 44: 241–252
33. Rhodes RA, Murthy NV, Dresner MA, et al: Human 5-HT transporter availability predicts amygdala reactivity in vivo. J Neurosci 2007; 27:9233–9237
34. Fisher PM, Meltzer CC, Price JC, et al: Medial prefrontal cortex 5-HT(2A) density is correlated with amygdala reactivity, response habituation, and functional coupling. Cereb Cortex 2009; 19:2499–2507
35. Stjepanović D, Lorenzetti V, Yücel M, et al: Human amygdala volume is predicted by common DNA variation in the stathmin and serotonin transporter genes. Transl Psychiatr 2013; 3:e283
36. Kobiella A, Reimold M, Ulshöfer DE, et al: How the serotonin transporter 5-HTTLPR polymorphism influences amygdala function: the roles of in vivo serotonin transporter expression and amygdala structure. Transl Psychiatr 2011; 1:e37
37. Inoue H, Yamasue H, Tochigi M, et al: Effect of tryptophan hydroxylase-2 gene variants on amygdalar and hippocampal volumes. Brain Res 2010; 1331:51–57
38. Surguladze SA, Radua J, El-Hage W, et al: Interaction of catechol O-methyltransferase and serotonin transporter genes modulates effective connectivity in a facial emotion-processing circuitry. Transl Psychiatr 2012; 2:e70
39. Domschke K, Baune BT, Havlik L, et al: Catechol-O-methyltransferase gene variation: impact on amygdala response to aversive stimuli. Neuroimage 2012; 60:2222–2229
40. Dayan P, Balleine BW: Reward, motivation, and reinforcement learning. Neuron 2002; 36:285–298
41. Schultz W: Multiple dopamine functions at different time courses. Annu Rev Neurosci 2007; 30:259–288
42. Takahashi YK, Roesch MR, Wilson RC, et al: Expectancy-related changes in firing of dopamine neurons depend on orbitofrontal cortex. Nat Neurosci 2011; 14:1590–1597
43. Gradin VB, Kumar P, Waiter G, et al: Expected value and prediction error abnormalities in depression and schizophrenia. Brain 2011; 134:1751–1764
44. Wise RA: Dopamine, learning, and motivation. Nat Rev Neurosci 2004; 5:483–494
45. Beckmann M, Johansen-Berg H, Rushworth MF: Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. J Neurosci 2009; 29:1175–1190
46. Ongür D, Price JL: The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys, and humans. Cereb Cortex 2000; 10:206–219
47. Ernst M, Nelson EE, McClure EB, et al: Choice selection and reward anticipation: an fMRI study. Neuropsychologia 2004; 42:1585–1597
48. Rogers RD, Ramnani N, Mackay C, et al: Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. Biol Psychiatry 2004; 55:594–602
49. Lawrence NS, Jollant F, O'Daly O, et al: Distinct roles of prefrontal cortical subregions in the Iowa Gambling Task. Cereb Cortex 2009; 19:1134–1143
50. Dillon DG, Holmes AJ, Jahn AL, et al: Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. Psychophysiology 2008; 45:36–49

51. Pedroni A, Koeneke S, Velickaite A, et al: Differential magnitude coding of gains and omitted rewards in the ventral striatum. Brain Res 2011; 1411:76–86
52. Haber SN, Knutson B: The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 2010; 35:4–26
53. Grabenhorst F, Rolls ET: Value, pleasure, and choice in the ventral prefrontal cortex. Trends Cogn Sci 2011; 15:56–67
54. Forbes EE, Brown SM, Kimak M, et al: Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. Mol Psychiatry 2009; 14:60–70
55. Schott BH, Minuzzi L, Krebs RM, et al: Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. J Neurosci 2008; 28:14311–14319
56. Buckholtz JW, Treadway MT, Cowan RL, et al: Dopaminergic network differences in human impulsivity. Science 2010; 329:532
57. Ceccarini J, Vrieze E, Koole M, et al: Optimized in vivo detection of dopamine release using 18F-fallypride PET. J Nucl Med 2012; 53: 1565–1572
58. Tremblay LK, Naranjo CA, Graham SJ, et al: Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. Arch Gen Psychiatry 2005; 62:1228–1236
59. Pessiglione M, Seymour B, Flandin G, et al: Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 2006; 442:1042–1045
60. Ossewaarde L, Verkes RJ, Hermans EJ, et al: Two-week administration of the combined serotonin-noradrenaline reuptake inhibitor duloxetine augments functioning of mesolimbic incentive processing circuits. Biol Psychiatry 2011; 70:568–574
61. Koob GF, Le Moal M: Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 2001; 24:97–129
62. Biswal B, Yetkin FZ, Haughton VM, et al: Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995; 34:537–541
63. Fox MD, Raichle ME: Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007; 8:700–711
64. Greicius MD, Flores BH, Menon V, et al: Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 2007; 62:429–437
65. Buckner RL, Krienen FM, Yeo BT: Opportunities and limitations of intrinsic functional connectivity MRI. Nat Neurosci 2013; 16:832–837
66. Murphy K, Birn RM, Bandettini PA: Resting-state fMRI confounds and cleanup. Neuroimage 2013; 80:349–359
67. Honey CJ, Sporns O, Cammoun L, et al: Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci USA 2009; 106:2035–2040
68. Shirer WR, Ryali S, Rykhlevskaia E, et al: Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex 2012; 22:158–165
69. Deco G, Jirsa VK, McIntosh AR: Emerging concepts for the dynamical organization of resting-state activity in the brain. Nat Rev Neurosci 2011; 12:43–56
70. Hutchison RM, Womelsdorf T, Allen EA, et al: Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 2013; 80:360–378
71. Greicius MD, Krasnow B, Reiss AL, et al: Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003; 100:253–258
72. Fox MD, Snyder AZ, Vincent JL, et al: The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 2005; 102:9673–9678
73. Andrews-Hanna JR, Reidler JS, et al: Functional-anatomic fractionation of the brain's default network. Neuron 2010; 65:550–562
74. Fox MD, Corbetta M, Snyder AZ, et al: Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc Natl Acad Sci USA 2006; 103:10046–10051
75. Vincent JL, Snyder AZ, Fox MD, et al: Coherent spontaneous activity identifies a hippocampal-parietal memory network. J Neurophysiol 2006; 96:3517–3531
76. Damoiseaux JS, Rombouts SA, Barkhof F, et al: Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci USA 2006; 103:13848–13853
77. Seeley WW, Menon V, Schatzberg AF, et al: Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007; 27:2349–2356
78. Etkin A, Prater KE, Schatzberg AF, et al: Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry 2009; 66:1361–1372
79. Aslan S, Lu H: On the sensitivity of ASL MRI in detecting regional differences in cerebral blood flow. Magn Reson Imaging 2010; 28: 928–935
80. Ye FQ, Berman KF, Ellmore T, et al: H(2)(15)O PET validation of steady-state arterial spin tagging cerebral blood flow measurements in humans. Magn Reson Med 2000; 44:450–456
81. Mori S, Zhang J: Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 2006; 51:527–539
82. Versace A, Andreazza AC, Young LT, et al: Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder. Mol Psychiatry 2014; 19:200–208
83. Delvecchio G, Fossati P, Boyer P, et al: Common and distinct neural correlates of emotional processing in bipolar disorder and major depressive disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. Eur Neuropsychopharmacol 2012; 22:100–113
84. Hamilton JP, Etkin A, Furman DJ, et al: Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. Am J Psychiatry 2012; 169:693–703
85. Almeida JR, Versace A, Mechelli A, et al: Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. Biol Psychiatry 2009; 66:451–459
86. Anand A, Li Y, Wang Y, et al: Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an fMRI study. J Neuropsychiatry Clin Neurosci 2007; 19: 274–282
87. Fu CH, Williams SC, Cleare AJ, et al: Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry 2004; 61:877–889
88. Sheline YI, Barch DM, Donnelly JM, et al: Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry 2001; 50:651–658
89. Victor TA, Furey ML, Fromm SJ, et al: Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. Arch Gen Psychiatry 2010; 67: 1128–1138
90. Davey CG, Allen NB, Harrison BJ, et al: Increased amygdala response to positive social feedback in young people with major depressive disorder. Biol Psychiatry 2011; 69:734–741
91. Moses-Kolko EL, Perlman SB, Wisner KL, et al: Abnormally reduced dorsomedial prefrontal cortical activity and effective connectivity with amygdala in response to negative emotional faces in postpartum depression. Am J Psychiatry 2010; 167:1373–1380
92. Suslow T, Konrad C, Kugel H, et al: Automatic mood-congruent amygdala responses to masked facial expressions in major depression. Biol Psychiatry 2010; 67:155–160

93. Victor TA, Furey ML, Fromm SJ, et al: The extended functional neuroanatomy of emotional processing biases for masked faces in major depressive disorder. PLoS ONE 2012; 7:e46439
94. Arnone D, McKie S, Elliott R, et al: Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. Am J Psychiatry 2012; 169:841–850
95. Mingtian Z, Shuqiao Y, Xiongzhao Z, et al: Elevated amygdala activity to negative faces in young adults with early onset major depressive disorder. Psychiatry Res 2012; 201:107–112
96. Tao R, Calley CS, Hart J, et al: Brain activity in adolescent major depressive disorder before and after fluoxetine treatment. Am J Psychiatry 2012; 169:381–388
97. Stuhrmann A, Dohm K, Kugel H, et al: Mood-congruent amygdala responses to subliminally presented facial expressions in major depression: associations with anhedonia. J Psychiatry Neurosci 2013; 38:249–258
98. Holsen LM, Lancaster K, Klibanski A, et al: HPA-axis hormone modulation of stress response circuitry activity in women with remitted major depression. Neuroscience 2013; 250:733–742
99. Hooley JM, Gruber SA, Parker HA, et al: Cortico-limbic response to personally challenging emotional stimuli after complete recovery from depression. Psychiatry Res 2009; 172:83–91
100. Holsen LM, Spaeth SB, Lee JH, et al: Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. J Affect Disord 2011; 131:379–387
101. Godlewska BR, Norbury R, Selvaraj S, et al: Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. Psychol Med 2012; 42:2609–2617
102. Robertson B, Wang L, Diaz MT, et al: Effect of bupropion extended release on negative emotion processing in major depressive disorder: a pilot functional magnetic resonance imaging study. J Clin Psychiatry 2007; 68:261–267
103. Keedwell PA, Andrew C, Williams SC, et al: A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. Biol Psychiatry 2005; 58:495–503
104. Knutson B, Bhanji JP, Cooney RE, et al: Neural responses to monetary incentives in major depression. Biol Psychiatry 2008; 63:686–692
105. Smoski MJ, Felder J, Bizzell J, et al: fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. J Affect Disord 2009; 118:69–78
106. Heller AS, Johnstone T, Shackman AJ, et al: Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. Proc Natl Acad Sci USA 2009; 106:22445–22450
107. Harvey PO, Pruessner J, Czechowska Y, et al: Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry 2007; 12: 767–775
108. Surguladze S, Brammer MJ, Keedwell P, et al: A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. Biol Psychiatry 2005; 57:201–209
109. Robinson OJ, Cools R, Carlisi CO, et al: Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. Am J Psychiatry 2012; 169:152–159
110. Moses-Kolko EL, Fraser D, Wisner KL, et al: Rapid habituation of ventral striatal response to reward receipt in postpartum depression. Biol Psychiatry 2011; 70:395–399
111. Vrieze E, Pizzagalli DA, Demyttenaere K, et al: Reduced reward learning predicts outcome in major depressive disorder. Biol Psychiatry 2013; 73:639–645
112. Dichter GS, Felder JN, Petty C, et al: The effects of psychotherapy on neural responses to rewards in major depression. Biol Psychiatry 2009; 66:886–897
113. Kempton MJ, Salvador Z, Munafò MR, et al: Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry 2011; 68: 675–690
114. Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, et al: Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp 2009; 30: 3719–3735
115. Campbell S, Marriott M, Nahmias C, et al: Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 2004; 161:598–607
116. Fischl B, Dale AM: Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA 2000; 97:11050–11055
117. Peterson BS, Warner V, Bansal R, et al: Cortical thinning in persons at increased familial risk for major depression. Proc Natl Acad Sci USA 2009; 106:6273–6278
118. Davey CG, Harrison BJ, Yucel M, et al: Regionally specific alterations in functional connectivity of the anterior cingulate cortex in major depressive disorder. Psychol Med 2012; 42:2071–2081
119. Ma C, Ding J, Li J, et al: Resting-state functional connectivity bias of middle temporal gyrus and caudate with altered gray matter volume in major depression. PLoS ONE 2012; 7:e45263
120. Anand A, Li Y, Wang Y, et al: Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol Psychiatry 2005; 57:1079–1088
121. Lui S, Wu Q, Qiu L, et al: Resting-state functional connectivity in treatment-resistant depression. Am J Psychiatry 2011; 168:642–648
122. Tang Y, Kong L, Wu F, et al: Decreased functional connectivity between the amygdala and the left ventral prefrontal cortex in treatment-naive patients with major depressive disorder: a resting-state functional magnetic resonance imaging study. Psychol Med 2013; 43:1921–1927
123. Cullen KR, Gee DG, Klimes-Dougan B, et al: A preliminary study of functional connectivity in comorbid adolescent depression. Neurosci Lett 2009; 460:227–231
124. Meng C, Brandl F, Tahmasian M, et al: Aberrant topology of striatum's connectivity is associated with the number of episodes in depression. Brain 2014; 137:598–609
125. Sheline YI, Price JL, Yan Z, et al: Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci USA 2010; 107:11020–11025
126. McCabe C, Mishor Z: Antidepressant medications reduce subcortical-cortical resting-state functional connectivity in healthy volunteers. Neuroimage 2011; 57:1317–1323
127. Duhameau B, Ferré JC, Jannin P, et al: Chronic and treatment-resistant depression: a study using arterial spin labeling perfusion MRI at 3 tesla. Psychiatry Res 2010; 182:111–116
128. Clark CP, Brown GG, Archibald SL, et al: Does amygdalar perfusion correlate with antidepressant response to partial sleep deprivation in major depression? Psychiatry Res 2006; 146:43–51
129. Chen Y, Wan HI, O'Reardon JP, et al: Quantification of cerebral blood flow as biomarker of drug effect: arterial spin labeling phMRI after a single dose of oral citalopram. Clin Pharmacol Ther 2011; 89: 251–258
130. Järnum H, Eskildsen SF, Steffensen EG, et al: Longitudinal MRI study of cortical thickness, perfusion, and metabolite levels in major depressive disorder. Acta Psychiatr Scand 2011; 124:435–446
131. Sexton CE, Mackay CE, Ebmeier KP: A systematic review of diffusion tensor imaging studies in affective disorders. Biol Psychiatry 2009; 66:814–823
132. Zhang A, Ajilore O, Zhan L, et al: White matter tract integrity of anterior limb of internal capsule in major depression and type 2 diabetes. Neuropsychopharmacology 2013; 38:1451–1459
133. Whalley HC, Sprooten E, Hackett S, et al: Polygenic risk and white matter integrity in individuals at high risk of mood disorder. Biol Psychiatry 2013; 74:280–286
134. de Kwaasteniet B, Ruhe E, Caan M, et al: Relation between structural and functional connectivity in major depressive disorder. Biol Psychiatry 2013; 74:40–47

135. Huang H, Fan X, Williamson DE, et al: White matter changes in healthy adolescents at familial risk for unipolar depression: a diffusion tensor imaging study. Neuropsychopharmacology 2011; 36: 684–691
136. Cullen KR, Klimes-Dougan B, Muetzel R, et al: Altered white matter microstructure in adolescents with major depression: a preliminary study. J Am Acad Child Adolesc Psychiatry 2010; 49:173.e1–183.e1
137. Zhu X, Wang X, Xiao J, et al: Altered white matter integrity in first-episode treatment-naive young adults with major depressive disorder: a tract-based spatial statistics study. Brain Res 2011; 1369:223–229
138. Huang H, Gundapuneedi T, Rao U: White matter disruptions in adolescents exposed to childhood maltreatment and vulnerability to psychopathology. Neuropsychopharmacology 2012; 37:2693–2701
139. Murphy ML, Carballedo A, Fagan AJ, et al: Neurotrophic tyrosine kinase polymorphism impacts white matter connections in patients with major depressive disorder. Biol Psychiatry 2012; 72:663–670
140. Keedwell PA, Chapman R, Christiansen K, et al: Cingulum white matter in young women at risk of depression: the effect of family history and anhedonia. Biol Psychiatry 2012; 72:296–302
141. Guo WB, Liu F, Chen JD, et al: Altered white matter integrity of forebrain in treatment-resistant depression: a diffusion tensor imaging study with tract-based spatial statistics. Prog Neuropsychopharmacol Biol Psychiatry 2012; 38:201–206
142. Carballedo A, Amico F, Ugwu I, et al: Reduced fractional anisotropy in the uncinate fasciculus in patients with major depression carrying the met-allele of the Val66Met brain-derived neurotrophic factor genotype. Am J Med Genet B Neuropsychiatr Genet 2012; 159B:537–548
143. Cole J, Chaddock CA, Farmer AE, et al: White matter abnormalities and illness severity in major depressive disorder. Br J Psychiatry 2012; 201:33–39
144. Zuo N, Fang J, Lv X, et al: White matter abnormalities in major depression: a tract-based spatial statistics and rumination study. PLoS ONE 2012; 7:e37561
145. Zhang A, Leow A, Ajilore O, et al: Quantitative tract-specific measures of uncinate and cingulum in major depression using diffusion tensor imaging. Neuropsychopharmacology 2012; 37: 959–967
146. Korgaonkar MS, Grieve SM, Koslow SH, et al: Loss of white matter integrity in major depressive disorder: evidence using tract-based spatial statistical analysis of diffusion tensor imaging. Hum Brain Mapp 2011; 32:2161–2171
147. Bezerra DM, Pereira FR, Cendes F, et al: DTI voxelwise analysis did not differentiate older depressed patients from older subjects without depression. J Psychiatr Res 2012; 46:1643–1649
148. Versace A, Almeida JR, Quevedo K, et al: Right orbitofrontal corticolimbic and left corticocortical white matter connectivity differentiate bipolar and unipolar depression. Biol Psychiatry 2010; 68: 560–567
149. Grotegerd D, Suslow T, Bauer J, et al: Discriminating unipolar and bipolar depression by means of fMRI and pattern classification: a pilot study. Eur Arch Psychiatry Clin Neurosci 2013; 263:119–131
150. Cardoso de Almeida JR, Phillips ML: Distinguishing between unipolar depression and bipolar depression: current and future clinical and neuroimaging perspectives. Biol Psychiatry 2013; 73: 111–118
151. Briceño EM, Weisenbach SL, Rapport LJ, et al: Shifted inferior frontal laterality in women with major depressive disorder is related to emotion-processing deficits. Psychol Med 2013; 43:1433–1445
152. Davidson RJ, Shackman AJ, Maxwell JS: Asymmetries in face and brain related to emotion. Trends Cogn Sci 2004; 8:389–391
153. Surguladze SA, Young AW, Senior C, et al: Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. Neuropsychology 2004; 18:212–218
154. Fournier JC, Keener MT, Mullin BC, et al: Heterogeneity of amygdala response in major depressive disorder: the impact of lifetime subthreshold mania. Psychol Med 2013; 43:293–302
155. Kahnt T, Heinzle J, Park SQ, et al: The neural code of reward anticipation in human orbitofrontal cortex. Proc Natl Acad Sci USA 2010; 107:6010–6015
156. Rolls ET, Grabenhorst F: The orbitofrontal cortex and beyond: from affect to decision-making. Prog Neurobiol 2008; 86:216–244
157. Dichter GS, Kozink RV, McClernon FJ, et al: Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes. J Affect Disord 2012; 136:1126–1134
158. Urosević S, Abramson LY, Harmon-Jones E, et al: Dysregulation of the behavioral approach system (BAS) in bipolar spectrum disorders: review of theory and evidence. Clin Psychol Rev 2008; 28: 1188–1205
159. Little JT, Ketter TA, Kimbrell TA, et al: Bupropion and venlafaxine responders differ in pretreatment regional cerebral metabolism in unipolar depression. Biol Psychiatry 2005; 57:220–228
160. Chen CH, Ridler K, Suckling J, et al: Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. Biol Psychiatry 2007; 62:407–414
161. Salvadore G, Cornwell BR, Colon-Rosario V, et al: Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. Biol Psychiatry 2009; 65:289–295
162. Roy M, Harvey PO, Berlim MT, et al: Medial prefrontal cortex activity during memory encoding of pictures and its relation to symptomatic improvement after citalopram treatment in patients with major depression. J Psychiatry Neurosci 2010; 35:152–162
163. Siegle GJ, Carter CS, Thase ME: Use of fMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatry 2006; 163:735–738
164. Fu CH, Williams SC, Cleare AJ, et al: Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol Psychiatry 2008; 64:505–512
165. Canli T, Cooney RE, Goldin P, et al: Amygdala reactivity to emotional faces predicts improvement in major depression. Neuroreport 2005; 16:1267–1270
166. Langenecker SA, Kennedy SE, Guidotti LM, et al: Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. Biol Psychiatry 2007; 62:1272–1280
167. Walsh ND, Williams SC, Brammer MJ, et al: A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. Biol Psychiatry 2007; 62: 1236–1243
168. Light SN, Heller AS, Johnstone T, et al: Reduced right ventrolateral prefrontal cortex activity while inhibiting positive affect is associated with improvement in hedonic capacity after 8 weeks of antidepressant treatment in major depressive disorder. Biol Psychiatry 2011; 70:962–968
169. Forbes EE, Olino TM, Ryan ND, et al: Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. Cogn Affect Behav Neurosci 2010; 10:107–118
170. Costafreda SG, Chu C, Ashburner J, et al: Prognostic and diagnostic potential of the structural neuroanatomy of depression. PLoS ONE 2009; 4:e6353
171. MacQueen GM: Magnetic resonance imaging and prediction of outcome in patients with major depressive disorder. J Psychiatry Neurosci 2009; 34:343–349
172. Taylor WD, Kuchibhatla M, Payne ME, et al: Frontal white matter anisotropy and antidepressant remission in late-life depression. PLoS ONE 2008; 3:e3267
173. Lui S, Parkes LM, Huang X, et al: Depressive disorders: focally altered cerebral perfusion measured with arterial spin-labeling MR imaging. Radiology 2009; 251:476–484
174. McGrath CL, Kelley ME, Holtzheimer PE, et al: Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry 2013; 70:821–829

175. Holtzheimer PE, Kelley ME, Gross RE, et al: Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry 2012; 69:150–158
176. Davidson RJ, Irwin W, Anderle MJ, et al: The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry 2003; 160:64–75
177. Mayberg HS, Silva JA, Brannan SK, et al: The functional neuroanatomy of the placebo effect. Am J Psychiatry 2002; 159:728–737
178. Williams LM, Rush AJ, Koslow SH, et al: International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol. Trials 2011; 12:4
179. Trivedi MH, McGrath PJ, Fava M, et al: Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC): rationale and design. J Psychiatr Res (in press)
180. Vosslamber S, van Baarsen LG, Verweij CL: Pharmacogenomics of IFN-beta in multiple sclerosis: towards a personalized medicine approach. Pharmacogenomics 2009; 10:97–108
181. Lee AY, Raya AK, Kymes SM, et al: Pharmacogenetics of complement factor H (Y402H) and treatment of exudative age-related macular degeneration with ranibizumab. Br J Ophthalmol 2009; 93:610–613
182. Lima JJ, Blake KV, Tantisira KG, et al: Pharmacogenetics of asthma. Curr Opin Pulm Med 2009; 15:57–62
183. Ouzounian M, Lee DS, Gramolini AO, et al: Predict, prevent, and personalize: genomic and proteomic approaches to cardiovascular medicine. Can J Cardiol 2007;23(suppl A):28A–33A
184. Dowsett M, Dunbier AK: Emerging biomarkers and new understanding of traditional markers in personalized therapy for breast cancer. Clin Cancer Res 2008; 14:8019–8026