Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders

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Neuroimaging technology has provided unprecedented opportunities for elucidating the anatomical correlates of major depression. The knowledge gained from imaging research and from the postmortem studies that have been guided by imaging data is catalyzing a paradigm shift in which primary mood disorders are conceptualized as illnesses that involve abnormalities of brain structure, as well as of brain function. These data suggest specific hypotheses regarding the neural mechanisms underlying pathological emotional processing in mood disorders. They particularly support a role for dysfunction within the prefrontal cortical and striatal systems that normally modulate limbic and brainstem structures involved in mediating emotional behavior in the pathogenesis of depressive symptoms.

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Abbreviations

ACC	anterior cingulate cortex
BD	bipolar disorder
CBF	cerebral blood flow
CSF	cerebrospinal fluid
DA	dopamine
LCSPT	limbic–cortical–striatal–pallidal–thalamic
LTC	limbic–thalamo–cortical
mPFC	medial PFC
MDD	major depressive disorder
MDE	major depressive episodes
MRI	magnetic resonance imaging
NE	norepinephrine
OCD	obsessive-compulsive disorder
PAG	periaqueductal grey
PET	positron emission tomography
PFC	prefrontal cortex
VLPFC	ventrolateral PFC
VTA	ventral tegmental area

Introduction

Major depressive episodes (MDE) are several-week- to several-year-long periods in which conscious mental activity is dominated by persistent dysphoric emotions and thoughts, which coexist with disturbances of motivated and psychomotor behavior, sleep, appetite, energy, and libido [1]. Despite the application of the descriptive term 'depression', the dominant emotional symptoms of MDE can instead include anxiety, irritability, or anhedonia (inability to experience pleasure or reward) [1]. Such episodes may occur secondary to specific medical or neurological illnesses, other psychiatric disorders, or pharmacological agents. They may also arise in the absence of medical or psychiatric antecedents as primary, idiopathic disorders, termed 'major depressive disorder' (MDD) when only depressive episodes occur, or 'bipolar disorder' (BD; also known as 'manic-depressive illness') when manic episodes also occur. The most common mood disorder, MDD, rivals hypertension as the most frequently treated illness in primary health care, and is a leading cause of disability worldwide [2].

The etiology and pathophysiology of MDE remain poorly understood. Twin, adoption and family studies indicate that both genetic and environmental factors contribute to the risk for developing MDD and BD [1]. The environmental factors commonly proposed to be involved in the pathogenesis of MDE are psychosocial stressors, although causal links between stressors and MDE have been difficult to establish. Patients with recurrent MDE usually conclude that their pattern of depressive symptoms is not coupled to stressful life situations (with the exception of childbirth, as the post-partum period is the epoch of greatest risk in females). Nevertheless, stress plays a prominent role in the clinical phenomenology of MDD and BD, as ordinary work-demands and interpersonal interactions are perceived as being exceedingly stressful during MDE.

Primary mood disorders (in which the onset of MDD or BD temporally precedes that of other major medical or psychiatric disorders) have been associated with a variety of neuroendocrine, neurochemical, neurophysiological, and neuromorphometric abnormalities [1]. It is not known, however, whether these abnormalities cause a vulnerability to abnormal mood episodes, or whether they are compensatory changes to other pathogenic processes or sequelae of recurrent illness. The neurobiological systems affected by these abnormalities nevertheless suggest intriguing hypotheses for the development of the cognitive-emotional manifestations of mood disorders, which are discussed in this review.

Neuroimaging studies of mood disorders

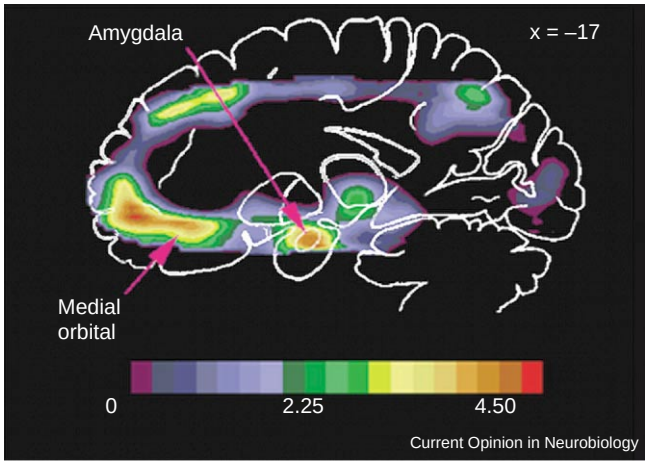
Neuroimaging technology has afforded the ability to investigate neurophysiological, neuroanatomical and neurochemical correlates of mood disorders *in vivo* [1,3]. The results of such studies are being complimented by converging data from post mortem studies, some of which have been specifically guided by neuroimaging data, to elucidate interactions between abnormalities of brain structure and function in primary mood disorders [3]. These experimental approaches are also being combined to investigate the therapeutic mechanisms of antidepressant and mood-stabilizing drugs, which are now known to modulate signal transduction pathways and neuroprotective/neurotrophic factor gene expression, as well as neurotransmitter function, in the brain regions where abnormalities are found in mood disorders [4•,5].

Progress has nevertheless been achieved amidst controversy about the specific locations and directions of abnormalities in depressed patient samples. Technical issues of image acquisition, data analysis and study design (e.g. differences in the subjects' medication status or behavioral condition during scanning) have contributed to some of the apparent inconsistencies across studies [3]. Nevertheless, the greatest obstacle to achieving consensus in the literature probably reflects fundamental problems in defining a phenotype which is homogenous with respect to imaging abnormalities [1].

Clinical neuroscientific investigations into the biology of mood disorders struggle with the limitation that psychiatric nosology remains at a syndromatic level, in which nonspecific behavioral signs and symptoms (e.g. insomnia, fatigue, low mood, impaired concentration), rather than pathophysiology, are used to define MDD. Consequently, specific links between syndrome and pathophysiology may not exist, and the MDD diagnostic criteria are expected to encompass an etiopathologically heterogenous group of disorders. Not surprisingly, the diagnosis of MDD *per se* has generally proven insufficient for identifying subject samples with reproducible neuroimaging abnormalities.

Additional clinical parameters that affect the sensitivity and specificity of imaging results in MDD include age at illness-onset, family history, melancholic features, and response to biological interventions. Thus, MDD patient samples who have either early-onset familial illness, melancholic subtype (MDE accompanied by anhedonia, insomnia in the early morning, anorexia or weight loss, psychomotor changes, and/or pathological guilt [1]), or responsivity to sleep deprivation or serotonin depletion show abnormal cerebral blood flow (CBF) and glucose metabolism in the amygdala, the ventral anterior cingulate cortex (ACC), the orbital, ventrolateral, and dorsomedial/dorsal anterolateral portions of the prefrontal cortex (PFC), the anterior insula, the ventral striatum, the posterior cingulate gyrus and the medial thalamus (for a review, see [3]; Figures 1–4). The abnormalities in many of these regions are, to some extent, mood-state-dependent, implicating areas where neurophysiological activity may increase or decrease to mediate or respond to the emotional and cognitive manifestations of the depressive syndrome. The pattern of metabolic changes during MDE suggests that brain structures that have been implicated by other types of evidence in mediating emotional and stress responses (e.g. the amygdala) are pathologically activated; brain areas thought to modulate or inhibit emotional expression are also activated (e.g. posterior orbital cortex); and, areas implicated in attention and sensory processing are deactivated (e.g. dorsal ACC) [6]. During antidepressant drug treatment, some of these state-dependent changes reverse in those patients who respond to treatment. Nevertheless, CBF and metabolism do not entirely normalize during symptom remission in many of these structures. The regions where neurophysiological abnormalities persist independently of mood-state have also been shown to contain abnormalities of grey matter volume and/or histology [3,7–9]

Figure 1

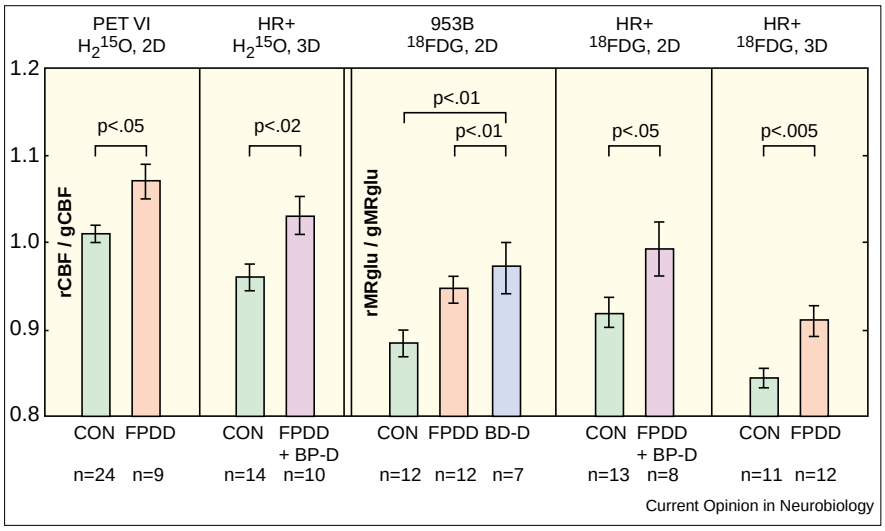


Areas of abnormally increased CBF in familial MDD shown in an image of t-values, produced by a voxel-by-voxel computation of the unpaired t-statistic to compare CBF between depressed and control samples [14]. The positive t-values in this sagittal section at 17 mm left of midline (x = –17) show areas of increased CBF in depressives relative to controls in the amygdala and medial orbital cortex. Abnormal activity in these regions in MDD was confirmed using higher resolution glucose metabolic measures in other studies [3,76]. Anterior is to the left. Modified from Price *et al.* [58].

The findings in such MDD samples contrast with those of elderly subjects who have a late age of MDD onset; instead, these elderly subjects have magnetic resonance imaging (MRI) and hemodynamic correlates of cerebrovascular disease [3,10] and of depressed subjects with neurodegenerative conditions [11]. The disparate findings between such late-onset cases versus early-onset, familial cases nevertheless appear to be unified by the neural circuits implicated by their respective anatomical correlates. The regional neuroimaging and neuropathological abnormalities in primary mood disorders coincide with the regions implicated by studies of depression arising in the context of neurodegenerative illness or cerebrovascular disease [11–13]. Such studies implicate limbic–thalamo–cortical (LTC) circuits, involving the amygdala, medial thalamus, and orbital and medial PFC, and limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuits, involving the components of the LTC circuit along with related parts of the striatum and pallidum (Figure 3) [14]. Because these conditions disturb the LCSPT and LTC circuitry in different ways, imbalances within these circuits, rather than overall increased or decreased synaptic activity in a particular structure, may increase the risk for developing MDE [14].

In contrast, surgical lesions that interrupt projections from the orbital cortex into the striatum can ameliorate depression if the limbic projections into the striatum or anterior cingulate are also severed, as would occur during neurosurgical interventions for intractable depression

Figure 2



Mean normalized physiological activity (± SEM) measured as either CBF or glucose metabolism is abnormally elevated in the left amygdala in mid-life depressed subjects relative to healthy controls. The five consecutive studies, obtained using different PET cameras (PET VI, HR+ and 953B are PET scanner model numbers, the latter two manufactured by Siemens/CTI) in different laboratories in independent subject samples, are summarized in Drevets *et al.* [9,14,102]. 2D and 3D refer to distinct image acquisition modes. In all five studies, the normalized blood flow or metabolism was significantly increased in depressive samples with either FPDD or BD relative to healthy controls. Because the first glucose metabolism study (center) showed that both FPDD and BD-D samples significantly differed from controls, but not from each other, subjects from these categories were combined for two of the subsequent studies (second and fourth panels). rCBF/gCBF, regional-to-global cerebral blood flow ratio; rMRglu/gMRglu, ratio of regional-to-global metabolic rates for glucose; CON, healthy controls; FPDD, familial pure depressive disease; BD-D, depressed phase of bipolar disorder.

(e.g. subcaudate tractotomy, prefrontal/limbic leukectomy, anterior cingulotomy [15–19]). Therefore, neural mechanisms of depression may more specifically involve dysfunction of the PFC or striatum that impairs the cortical modulation of limbic input (e.g. from the amygdala) to the cortex and brain stem [3]. On the basis of this general model, specific hypotheses regarding the pathogenesis of some cognitive-emotional features of MDE are suggested by the pattern of neuroimaging abnormalities within the PFC and amygdala in MDD.

Elevated physiological activity in the amygdala: implications for emotional behavior

Abnormal elevations of resting CBF and glucose metabolism in the amygdala have been consistently reported in depressives who have familial MDD or melancholic subtype, and have been inconsistently reported in BD (Figures 1,2; [3,14]). The magnitude of this abnormality as measured by positron emisson tomography (PET) has ranged from 5% to 7% (Figure 2), which, when corrected for spatial-resolution effects, would reflect an increase in the actual CBF and metabolism of about 50 to 70% [14,20]. This is in the physiological range, as CBF increases by about 50% in the rat amygdala during exposure to fear-conditioned stimuli as measured by tissue autoradiography [21]. Limitations in spatial resolution have precluded implication of specific amygdalar nuclei.

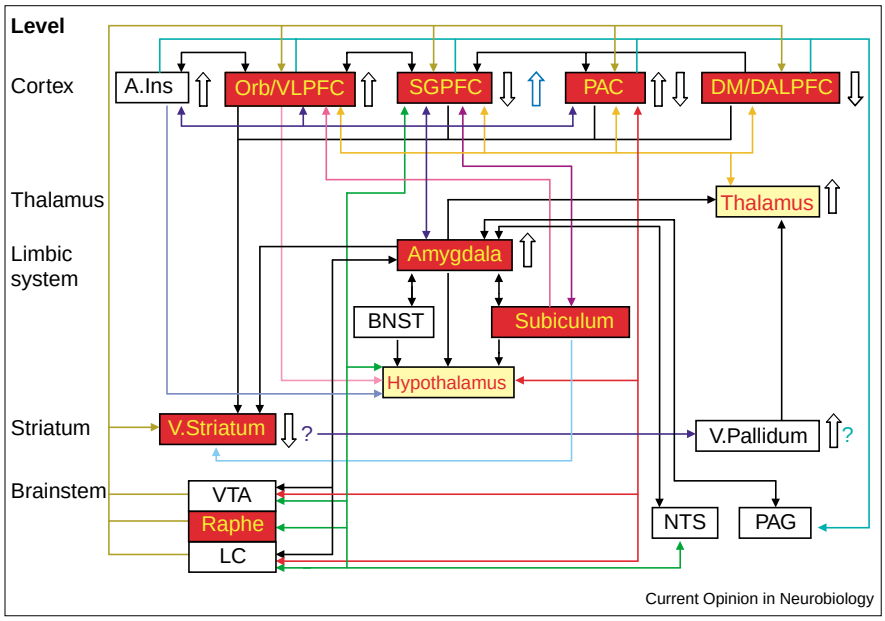
Amygdalar CBF and metabolism correlate positively with the severity of depression [14,22,23]. The positive correlation between neurophysiological activity in the amygdala and depression severity rated by Hamilton Depression Rating Scale scores may reflect the amygdala's role in organizing multiple aspects of emotional/stress responses (Figure 5) [24]. During antidepressant treatment that both induces and maintains symptom remission, amygdala metabolism decreases to normative levels, compatible with preclinical evidence that chronic antidepressant drug administration has inhibitory effects on amygdala function (for a review, see [25]).

Functional imaging studies acquired during behavioral or neuropsychological challenge suggest that the physiological responsivity of the amygdala may also differentiate depressives from healthy controls. For example, in the left amygdala, the normal increases in hemodynamic activity during exposure to pictures of fearful human faces is attenuated, whereas the corresponding response to sad faces is exaggerated in depressives relative to controls [26]. In addition, Nofzinger *et al.* [27] report that whereas amygdala metabolism is increased in depressives versus controls during wakefulness, the increase in metabolism that occurs during rapid eye movement (REM) sleep is also greater in depressives than in controls.

Implications for the pathogenesis of depressive thought content

Neuroimaging, electrophysiological and lesion analysis studies in humans and experimental animals have demonstrated that the amygdala is involved in the recall of emotional or arousing memories [28–30]. In humans, bursts of electroencephalographic (EEG) activity have been recorded in the amygdala during recollection of specific emotional events [31]. Moreover, electrical stimulation of

Figure 3



Anatomical circuits implicated by neuroimaging and neuropathological studies of familial mood disorders (primary references reviewed in [3]). The regional abnormalities summarized are hypothesized to contribute to the genesis of pathological emotional behavior. Regions shaded in red have neuromorphometric and/or histopathological abnormalities in primary MDD and/or BD (see text). Regions shaded in yellow have not been microscopically examined in mood-disordered patients, but are areas where structural abnormalities are suspected on the basis of the finding of third ventricle enlargement in children and adults with BD. Open arrows to the right of each region indicate the direction of abnormalities in CBF and metabolism reported in depressives relative to controls (cyan '?', PET data await replication). The blue open arrow indicates the direction of metabolic abnormalities after correcting the PET measures for partial volume effects of reduced grey matter volume (blue '?', decreased grey matter is suspected as the explanation for reductions in CBF and metabolism, but partial volume-corrected PET results have not been reported). Solid lines indicate *major* anatomical connections between structures (weak projections, such as that from the orbital cortex back to the subiculum [65], are not included), with closed arrowheads indicating the direction of projecting axons (reciprocal connections have arrowheads at both ends). Affected prefrontal cortical areas include the VLPFC and orbital PFC (Orb), the anterior cingulate gyrus ventral and anterior to the genu of the corpus callosum (subgenual PFC [SGPFC] and pregenual anterior cingulate [PAC], respectively), and the dorsomedial/dorsal anterolateral PFC (DM/DALPFC). A.Ins refers to the anterior (agranular) insula. The parts of the striatum under consideration are the ventromedial caudate and nucleus accumbens, which particularly project to the ventral pallidum. BNST, bed nucleus of the stria terminalis; LC, locus coeruleus; NTS, nucleus tractus solitarius; V, ventral. Modified from [3].

the human amygdala can evoke emotional experiences (especially fear or anxiety) [32] and recall of emotionally charged life-events from remote memory [33].

Taken together with the finding of elevated amygdala metabolism in MDD, these observations suggest the hypothesis that excessive amygdalar stimulation of cortical structures involved in declarative memory may account for the tendency of depressed subjects to 'ruminate' on memories of emotionally aversive or guilt-provoking life-events [34]. The intrusive nature of such thought patterns, and their responsiveness to antidepressant drugs, suggest that abnormal brain processes underlie these symptoms. In some cases, such ideation acquires a stereotypic or obsessional nature, and the same thought content may recur in each new MDE.

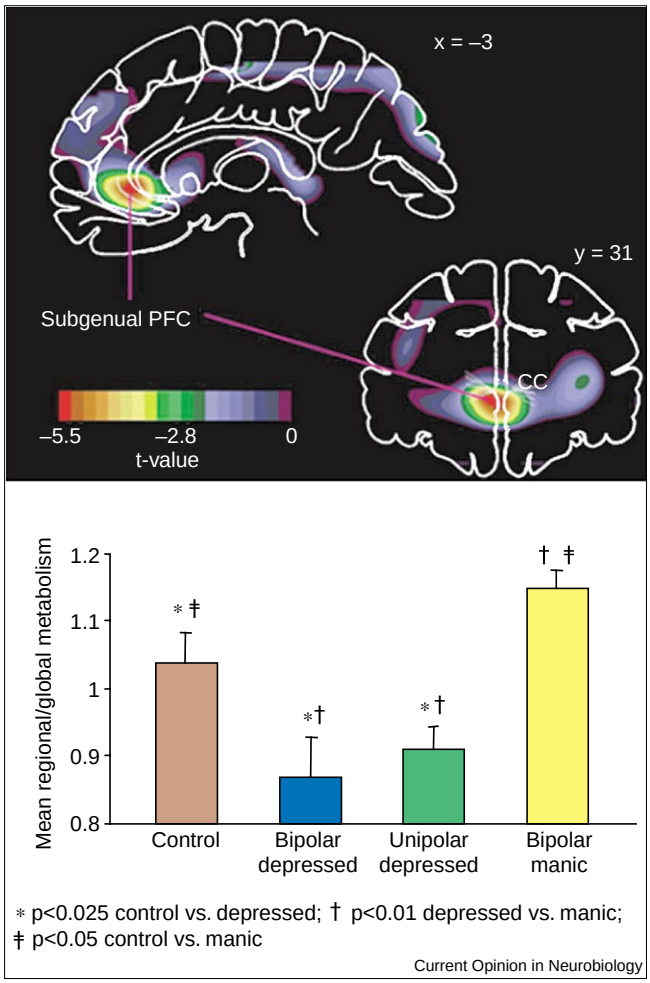
Amygdala dysfunction in mood disorders may also conceivably alter the initial evaluation and memory consolidation related to sensory or social stimuli with respect to their emotional significance. The amygdala is involved in the acquisition, consolidation and expression of emotional/arousing memories (e.g. aversive conditioning) [28–30,35,36] and plays a role in recognizing fear and sadness in facial expression [37–39] and fear and anger in spoken language [40]. Norepinephrine (NE) release in the amygdala plays a critical role in at least some types of emotional learning [41–43]. The activation of NE neurons is facilitated by the effect of stress hormone (glucocorticoid) secretion [43]. Depressed subjects have abnormally elevated secretion of both NE and cortisol [44,45,46••], which, in the presence of amygdala activation, may conceivably increase the likelihood that ordinary social or sensory stimuli are perceived or remembered as being aversive or emotionally arousing.

Role of the prefrontal cortex in modulating emotional behavior

Multiple areas of the medial and orbital PFC appear to play roles in modulating emotional behavior. These structures are thought to participate in modifying behavioral responses based upon competing or changing reinforcement contingencies [47–49]. Some of these areas also participate in modulating autonomic and endocrine responses to stress [50–52,53••,54••]. These areas share extensive, reciprocal projections with the amygdala, through which the amygdala modulates PFC neuronal activity and the PFC modulates amygdala-mediated responses to emotionally salient stimuli [52,53••–55••].

The medial PFC (mPFC) areas implicated in emotional behavior in humans and experimental animals include the infralimbic cortex, the ACC areas located ventrally ('subgenual') and anterior ('pregenual') to the genu of the corpus callosum, and the dorsomedial/dorsal anterolateral

Figure 4



Altered metabolism in the prefrontal cortex (PFC) ventral to the genu of the corpus callosum (i.e. subgenual PFC) in mood disorders. The top panel shows negative voxel t-values where glucose metabolism is *decreased* in depressives relative to controls in coronal (31 mm anterior to the anterior commissure, or y = 31) and sagittal (3 mm left of midline, or x = –3) planes of a statistical parametric image that compares depressives relative to controls [9]. The reduction in activity in this region appears to be accounted for by a corresponding reduction in cortex volume [8,9]. Anterior or left is to the left. Modified from Drevets *et al.* [9]. The bar histogram in the lower panel shows mean, normalized, glucose metabolic values in the subgenual PFC measured using MRI-based region-of-interest analysis. Metabolism is decreased in depressed subjects who are either BD ("Bipolar depressed") or MDD ("Unipolar depressed") relative to healthy controls. In contrast, subjects scanned in the manic phase of BD ("Bipolar manic") have higher metabolism than either depressed or control subjects in this region. *Difference between controls and bipolar depressives significant at $p<0.025$; †difference between depressed and manic significant at $p<0.01$; ‡difference between control and manic significant at $p<0.05$. CC, corpus callosum.

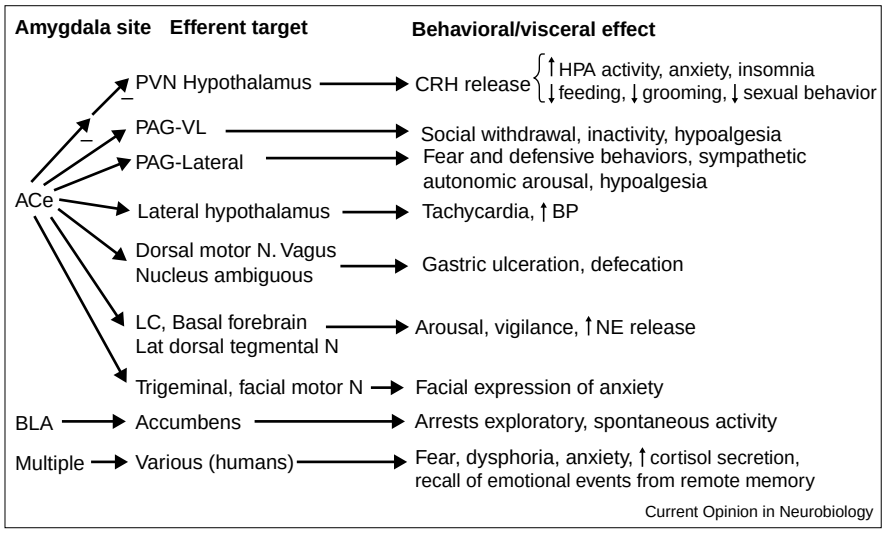
PFC extending from the rostral ACC onto the frontal pole [3,53••]. The projections between the amygdala and the mPFC have been implicated in attenuating fear responses and extinguishing behavioral responses to fear-conditioned stimuli that are no longer reinforced [52,54••]. Conversely, lesions of the ACC enhance freezing to fear-conditioned stimuli in rats, consistent with the hypothesis that this region is involved in the reduction of responses to fearful stimuli [52]. Moreover, neurons in the prelimbic cortex reduce their spontaneous firing activity in the presence of a conditioned, aversive tone to an extent that is inversely proportional to the magnitude of fear [55••]. This suppression of prelimbic cortex neuronal firing activity is inversely correlated with increases in amygdala neuronal activity [55••]. Finally, lesions of the infralimbic cortex interfere with the recall of extinction learning after long delays between the acquisition of extinction learning and reexposure to the initial conditioned stimulus [54••]. Extinction appears to require new learning through which the behavioral response to the conditioned stimulus is actively inhibited [56].

In the pregenual ACC, physiological activity is elevated during the depressed phase of some MDD subtypes [14,57] and during anxiety states elicited in healthy or anxiety-disordered subjects [3,6]. Electrical stimulation of this region elicits fear, panic or a sense of foreboding in humans, and vocalization in experimental animals (for a review, see [58]). Nevertheless, physiological activity also increases in the ACC during the generation of positive emotions in humans [59,60].

In the subgenual PFC, abnormalities in CBF and metabolism in familial MDD and BD are associated with a left-lateralized reduction in the cortex volume (Figure 4) [8,9,61•,62]. Physiological activity in this region is higher in the depressed than in the remitted phase of MDD, and increases in healthy humans during experimentally induced sadness [48,57,63] and in post-traumatic stress disorder (PTSD) subjects during internally generated imagery of past trauma [64].

The subgenual and pregenual ACC share reciprocal anatomical connections with areas implicated in emotional behavior such as the posterior orbital cortex, amygdala, hypothalamus, nucleus accumbens, periaqueductal grey (PAG), ventral tegmental area (VTA), raphe nucleus, locus coeruleus, and nucleus tractus solitarius (Figure 3; [65,66]). Humans with lesions that include the ventral ACC show abnormal autonomic responses to emotionally provocative stimuli, an inability to experience emotion related to concepts, and inability to use information regarding the probability of aversive social consequences versus reward in guiding social behavior [67]. In rats, bilateral or *right*-lateralized lesions of the mPFC strip, which includes infralimbic, prelimbic (approximately homologous to subgenual PFC [8]) and ACC cortices, *attenuate* corticosterone secretion, sympathetic autonomic responses, and gastric stress pathology during restraint stress or exposure to fear-conditioned stimuli [51,52,68]. In contrast, *left*-sided lesions of this cortical strip *increase* sympathetic arousal and corticosterone responses to restraint stress [68]. These data have led to the hypothesis that the right ventral mPFC facilitates expression of visceral responses during emotional processing, whereas the left modulates such

Figure 5



Putative roles of the amygdala in organizing multiple aspects of emotional/stress responses (adapted from Davis [24], LeDoux [29]), potentially accounting for the positive correlation between amygdala metabolism and depression severity in MDD [3]. The projections, depicted together with putative behavioral correlates of increased stimulation by the central nucleus of the amygdala (ACe), include the following. ACe facilitates stress-related corticotropin-releasing hormone (CRH) release via both intrinsic CRH-containing neurons and bisynaptic (double GABA-ergic, with minus signs indicating inhibitory connections) anatomical projections to the paraventricular nucleus (PVN) of the hypothalamus [103], potentially accounting for the increased limbic drive on CRH secretion in MDD (for a review, see [104]). The behavioral effects of CRH administration, based upon studies in rats, are reviewed in [45]. An excessive amygdalar drive on the PAG may conceivably contribute to depressive signs such as inactivity, panic attacks and reduced pain sensitivity: in experimental animals, stimulation of ventrolateral (VL) PAG produces social withdrawal, behavioral quiescence and hypoalgesia, whereas stimulation of lateral PAG produces defensive behaviors, sympathetic autonomic arousal, and hypoalgesia [58,74,105]. Excessive efferent amygdala transmission to the lateral hypothalamus and locus coeruleus (LC) could also potentially contribute to the elevated heart rate, behavioral arousal and insomnia seen in MDD [24,44]. Amygdalar stimulation of the dorsal motor nucleus (N) of the vagus nerve and the nucleus ambiguous is hypothesized to underlie the gastrointestinal symptoms (e.g. irritable bowel syndrome) sometimes seen during MDE. Stimulation of trigeminal and facial motor nuclei by the ACe, which have been implicated in the production of facial expressions of anxiety [24], may account for the facial muscle tension reported in depression [1]. Activation of the amygdalar projections to the nucleus accumbens arrests goal-directed behavior in experimental animals [78], suggesting a possible neural mechanism for the cessation of motivated or reward-directed behavior during MDE. In humans, electrical stimulation of the amygdala can produce anxiety, fear, dysphoria, increased cortisol secretion, and vivid recollection of emotionally provocative events from remote memory [32,33,106]. BLA, basolateral nucleus of the amygdala; BP, blood pressure; HPA, hypothalamic–pituitary–adrenal axis.

responses [68]. This hypothesis is noteworthy in light of the left-lateralized reduction of grey matter volume in the subgenual PFC in MDD and BD, and of PET data showing that *right* subgenual PFC metabolism correlates positively with depression severity in MDD [3]. Dysfunction of the left mPFC may thus conceivably contribute to the altered neuroendocrine and autonomic function evident in depression by disinhibiting responses driven by the right mPFC.

Finally, in the dorsomedial and dorsal anterolateral PFC, blood flow and metabolism are reduced in MDD [3,69,70]. In healthy humans, blood flow increases in these areas during performance of tasks that elicit emotional responses or require emotional evaluations [71,72]. During anticipation of an electrical shock, CBF increases in the dorsomedial PFC, yet the magnitude of CBF correlates inversely with changes in anxiety ratings and heart rate [73]. In rats, lesions of the rostral mPFC result in exaggerated heart-rate responses to fear-conditioned stimuli, and stimulation of these sites attenuates defensive behavior and cardiovascular responses evoked by amygdala stimulation [51]. In primates, these areas send extensive efferent projections to the PAG and the hypothalamus, through which they may modulate cardiovascular responses associated with emotional behavior (Figure 3) [53••,74]. In MDD, the dorsal anterolateral PFC has been shown to have abnormal reductions in the size of glia and neurons [7], raising the possibility that dysfunction of this region may interfere with the modulation of anxiety symptoms in mood disorders.

The orbital and ventrolateral prefrontal cortex

In the posterior and lateral orbital cortex, the anterior insula, and the ventrolateral PFC (VLPFC), metabolic activity is abnormally elevated in resting, unmedicated subjects with primary MDD [3]. Physiological activity also increases in these areas during experimentally induced anxiety states in healthy subjects and in subjects with obsessive-compulsive disorder (OCD), simple phobia or panic disorder [6,23,75]. Although CBF and metabolism increase in these areas in the depressed relative to the remitted phase, however, their magnitude correlates inversely with ratings of depressive ideation and severity [14,76]. Similarly, posterior orbital blood flow increases in OCD and in animal-phobic subjects during exposure to phobic stimuli and in healthy subjects during induced sadness, but the change in CBF correlates inversely with changes in obsessive thinking [75,76], phobic anxiety [23] and sadness [77].

These data appear to be consistent with electrophysiological and lesion analysis data showing that the orbital cortex participates in inhibiting behavioral and visceral responses associated with fearful, defensive, and reward-directed

behavior as reinforcement contingencies change. Nearly one-half of orbital cortex pyramidal cells alter their firing rates during the delay between stimulus and response, and this firing activity relates to the presence or absence of reinforcement [49]. These cells are thought to play roles in extinguishing unreinforced responses to aversive or appetitive stimuli [49,58,78]. The posterior and lateral orbital cortex and the amygdala send reciprocal projections to each other and to overlapping portions of the striatum, hypothalamus, and PAG, through which these structures modulate each other's neural transmission (Figure 3; [55••,65,74,78]). For example, the defensive behaviors and cardiovascular responses evoked by electrical stimulation of the amygdala are attenuated or ablated by concomitant stimulation of orbital sites that, when stimulated alone, produce no autonomic effects [79].

Humans with orbital cortex lesions perseverate in behaviors that are unreinforced and exhibit difficulty shifting cognitive strategies in response to changing task demands [49,80]. Likewise, monkeys with lesions of the lateral orbital cortex/VLPFC demonstrate 'perseverative interference', characterized by difficulty in learning to withhold prepotent responses to non-reinforced stimuli as reinforcement contingencies change [81]. Activation of the orbital cortex during depressive, obsessional or anxiety states may thus reflect endogenous attempts to interrupt unreinforced aversive thought and emotion [3]. Nevertheless, the abnormal reductions of grey matter, glia, and neuronal size reported in the orbital cortex and the VLPFC in MDD [7,82] raise the possibility that disturbed synaptic interactions between these regions and the amygdala, striatum, hypothalamus or PAG may impair the ability to inhibit nonreinforced or maladaptive emotional, cognitive, and behavioral responses. Such a deficit could conceivably lead to the perseverative cognitive and emotional responses to stressors seen during MDE.

Dysfunction of neural systems involved in processing motivation and reward

Another core feature of MDE is a pervasive absence of behavioral incentive. This is clinically manifested by apathy, anhedonia, amotivation, and loss of interest in hobbies, socialization, work, food, and sex. This condition renders positive life-events ineffective at altering the depressed state and causes potentially enjoyable or rewarding activities to be curtailed or engaged in only through extraordinary effort.

This symptom cluster appears to be phenomenologically related to the putative functions of the mesolimbic dopaminergic projections from the VTA into the ventral mPFC, amygdala, and ventral striatum [83,84]. These projections are thought to subserve a 'reward-related system' that mediates hedonia, motivation, behavioral reinforcement and psychomotor activity [85–88]. For example, dopamine (DA) release into the ventral striatum appears critical for the reinforcing properties of cocaine in rats [89,90], and is very tightly correlated with the euphoric response to dextroamphetamine in humans [91]. The temporal relationships between exposure to natural rewards, DA neuronal firing activity, and extracellular DA concentrations suggest that ventral striatal DA release is involved in forming associations between salient contextual stimuli and internal rewarding events [88,92]. The DA signal may also participate in regulating the timing of behavioral selection by facilitating switching between behaviors and attentional/cognitive sets as reinforcement contingencies change [93,94]. Mesolimbic DA release also modulates afferent synaptic transmission from non-dopaminergic projections into the ventral striatum, PFC, amygdala, hypothalamus, and other limbic structures that may play more critical roles in *maintaining* behavioral reinforcement [53••,78,83,88].

The anhedonia, amotivation and psychomotor slowing of depression, and the euphoria, hypermotivational state and psychomotor restlessness of mania, have led to the hypothesis that mesolimbic DA function is decreased and increased, respectively, in the depressed and manic phases of BD [83,84,95]. This hypothesis is corroborated by pharmacological evidence and cerebrospinal fluid (CSF) DA metabolite concentrations [95,96]. Anhedonia is also evident in depressive syndromes arising secondary to conditions such as Parkinson's disease or cocaine abstinence (in cocaine-dependent individuals) that are putatively associated with deficits of DA function [83,97].

In primary MDD and BD, some of the cortical and subcortical targets of the mesolimbic DA system have reduced grey matter volume and cellular abnormalities. The volume of the caudate and nucleus accumbens area is abnormally decreased in MRI and post mortem studies of MDD [98,99]. The amygdala and subgenual PFC have reductions in grey matter and glial cells, with no equivalent reduction in neurons (implying that a decrement in neuropil accounts for the volumetric reduction; for a review, see [3]). These histopathological changes may conceivably interfere with the neurotransmission related to reward processing.

In addition, projections from the ventral mPFC into the VTA [66,74] have been shown to modulate the electrophysiological responses of VTA DA neurons, suggesting another mechanism through which the abnormalities of structure and function in the subgenual PFC may alter reward-related processing. In rats, electrical or glutamatergic stimulation of mPFC areas that include prelimbic cortex elicits burst firing patterns from DA cells in the VTA and increases DA release in the nucleus accumbens [100,101]. These phasic, burst firing patterns of DA neurons are thought to encode information relating to stimuli that predict reward and to deviations between such predictions and the actual occurrence of reward [92]. The hypo- and hypermetabolism found in the subgenual PFC in the depressed and manic phases of BD, respectively, thus suggest the hypothesis that stimulation of VTA neurons by subgenual PFC neurons is correspondingly diminished and facilitated, respectively, in depression and mania [76]. Such functional

changes could conceivably be clinically manifested by the hedonic misperceptions and altered motivational states that characterize mood disorders.

Conclusions

The neuroimaging and neuropathological data recently acquired in studies of primary mood disorders have identified both structural and functional abnormalities in the orbital and medial PFC, the amygdala, and related parts of the striatum and thalamus. The areas where such studies demonstrate persistent metabolic abnormalities, reductions in cortex volume, and histopathological changes in primary mood disorders appear to modulate emotional behavior and stress responses, based upon evidence from brain mapping, lesion analysis, and electrophysiological studies of humans and experimental animals. These results thus support a neural model of depression in which dysfunction involving regions that modulate or inhibit emotional behavior may result in the emotional, motivational, cognitive, and behavioral manifestations of mood disorders.

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