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Neural circuits underlying the pathophysiology of mood disorders

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Although mood disorders constitute leading causes of disability, until recently little was known about their pathogenesis. The delineation of anatomical networks that support emotional behavior (mainly derived from animal studies) and the development of neuroimaging technologies that allow *in vivo* characterization of anatomy, physiology, and neurochemistry in human subjects with mood disorders have enabled significant advances towards elucidating the pathophysiology of major depressive disorder (MDD) and bipolar disorder (BD). In this review, we integrate insights from human and animal studies, which collectively suggest that MDD and BD involve dysfunction within an extended network including the medial prefrontal cortex and anatomically-related limbic, striatal, thalamic and basal forebrain structures.

Animal and human studies of mood disorders

Major depressive disorder (MDD) and bipolar disorder (BD) constitute the first and fifth leading causes of years lived with disability, respectively [1]. Yet, until recently, little was known about their pathogenesis, as these conditions are not associated with gross brain pathology or clear animal models for spontaneous recurrent mood episodes. The development of neuroimaging technologies that allow *in vivo* characterization of anatomy, physiology, and neurochemistry in human subjects with mood disorders has enabled significant advances toward elucidating their pathophysiology. Crucially, the interpretation of the abnormalities found using these technologies has depended upon by the concomitant delineation of anatomical networks that support emotional behavior.

Early studies identified the amygdala, hippocampus, and other parts of what was termed the 'limbic' system as central parts of the emotional brain. Beginning in the 1970s and 1980s and continuing through the last 15 years, neuroanatomical techniques based on axonal transport have been applied extensively to the limbic system and prefrontal cortex of monkeys. With these methods, a system has been described that links the medial prefrontal cortex (mPFC) and a few related cortical areas to the amygdala, the ventral striatum and pallidum, the medial thalamus, the hypothalamus, and the periaqueductal gray

and other parts of the brainstem. A large body of human data from functional and structural imaging, as well as analysis of lesions and histological material, indicates that this system is centrally involved in mood disorders.

In this review we discuss the neuroanatomy of the neural circuits implicated in mood disorders, synthesizing findings from studies of non-human primates and observations in humans, largely taken from clinical studies. The results of these studies, conducted using neuroimaging, lesion analysis, and *post mortem* methodologies, support models in which the pathophysiology of depression involves dysfunction in an extended network involving the mPFC and anatomically-related limbic, striatal, thalamic and basal forebrain structures. The abnormalities of structure and function evident within the extended 'visceromotor' network putatively impair this network's roles in cognitive processes such as reward learning and autobiographical memory, and may dysregulate visceral, behavioral and cognitive responses to emotional stimuli and stress [2], potentially accounting for the disturbances manifest within these domains in mood disorders.

Cognitive and emotional disturbances in MDD and BD

The clinical phenomenology of major depression implicates brain systems involved in the regulation of mood, anxiety, fear (e.g., panic attacks, phobias and post-traumatic stress syndromes commonly occur co-morbidly with depression), reward processing, attention, motivation, stress responses, social interaction, and neurovegetative function (i.e., sleep, appetite, energy, weight, libido) [1]. In BD, episodes of depression occur alternately with manic or hypomanic episodes, during which mood can become euphoric and labile, motivated and reward seeking behavior increases, and psychomotor activity and self-esteem become elevated. Thus, the same domains are implicated in depression and mania, although the characteristic disturbance appears opposite with respect to emotional valence.

Pathological changes in hedonic capacity and motivation figure prominently in the clinical phenomenology of depression, as well. For example, either depressed mood or anhedonia can manifest as the cardinal mood symptom required to establish the diagnosis of a major depressive episode (MDE) [1]. The term 'anhedonia' was initially described as the inability to experience pleasure [3]. Since pleasure is a complex construct, however, the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)

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[1] operationally defines anhedonia as diminished interest or pleasure in response to stimuli that were perceived as rewarding during the premorbid state. Between one-third and one-half of individuals diagnosed with MDD experience clinically significant anhedonia (see [3], for a review).

Empirical work has emphasized hedonic experience in depression, whereas studies of motivation are relatively absent. Some researchers found that individuals with depression rate positively-valenced stimuli as being less positive, less arousing, or less able to affect their mood versus controls, although a larger number of studies reported no group differences in these ratings (reviewed in [3]). A meta-analysis of studies that measured physiological or subjective affective responses found that depression was associated with blunted reactivity to both positively and negatively-valenced stimuli [4], suggesting that part of the decline in hedonic responses may be due to a generalized affective blunting. Nevertheless, in studies using the 'sweet taste test', individuals with depression do not differ from controls in reported hedonic impact, suggesting that depression is not associated with a deficit in the capacity to feel pleasure at the level of basic sensory experience [3].

Studies using reinforcement paradigms to explore anhedonia in MDD report that individuals with depressive symptoms fail to develop a response bias towards rewarded stimuli [5–7], providing evidence for insensitivity to reward-relevant information. It is unclear whether this deficit is driven by reduced hedonic capacity, diminished motivation, or both. One study that compared ratings of experienced emotion in depressed MDD, remitted MDD and healthy controls across four conditions (anticipating monetary rewards, anticipating an unpleasant sensory stimulus, no change, and avoiding an unpleasant sensory stimulus) demonstrated that a deficit in experienced emotion was specific to reward anticipation [8].

Cognitive and neuropsychological impairments are characteristic of major depression, and are reflected in the diagnostic criteria for an MDE as 'an impaired ability to think or concentrate' [1]. The literature is in disagreement, however, regarding the specific nature of cognitive symptoms in depressed patients. Some studies report wide ranging deficits that include impairments in early information processing, attention, memory, and executive functions, whereas other studies fail to identify such deficits [9,10]. Factors that likely contribute to the discrepancies across studies include heterogeneity within patient samples and medication status. For example, impairments of spatial recognition memory and delayed matching to sample tasks have been reported in medicated subjects with MDD and BD but such impairments generally have not been evident in unmedicated samples with MDD or BD (see [11,12], for a review).

Nevertheless, several specific cognitive impairments are demonstrable in unmedicated subjects, and in some cases, these deficits extend to subjects who have a history of MDD in remission or to otherwise healthy individuals at high familial risk for a mood disorder. For example, impairments in early information processing are manifest in unmedicated MDD samples, as exemplified by longer inspection times in depressed patients than in healthy controls, and deficits in verbal memory are apparent in

depressed BD subjects, and in the unaffected twins and non-twin siblings of BD subjects (reviewed in [12]). Similarly, autobiographical memory retrieval is impaired in unmedicated MDD subjects, irrespective of their current mood state, insofar as they generate memories that are over-general, particularly when asked to generate specific memories to emotionally positive cue words (e.g., [13]).

This latter finding is consistent with evidence that depressed subjects exhibit a mood-congruent processing bias, defined as a tendency to bias stimulus processing towards negative information as compared to positive or neutral information [14–16]. Within the context of attention or memory studies, depressed individuals bias stimulus processing towards sad information, as evidenced by enhanced recall for negatively versus positively valenced information on memory tests [16,17], greater interference from depression-related negative words versus happy or neutral words on emotional stroop tasks [18,19], faster responses to sad versus happy words on affective attention shifting tasks [15,20], preferential attentiveness to faces with sad versus neutral expressions on face dot-probe tasks [21,22], and more negative interpretation of ambiguous words or situations (reviewed in [12,23]). Depressed individuals also show oversensitivity to negative feedback in probabilistic reward tasks [10,11].

The neural substrates of mood disorders

Observations in experimental animals

There is considerable evidence that the amygdala and related medial prefrontal cortical areas are centrally involved in mood disorders, based on imaging and histopathological

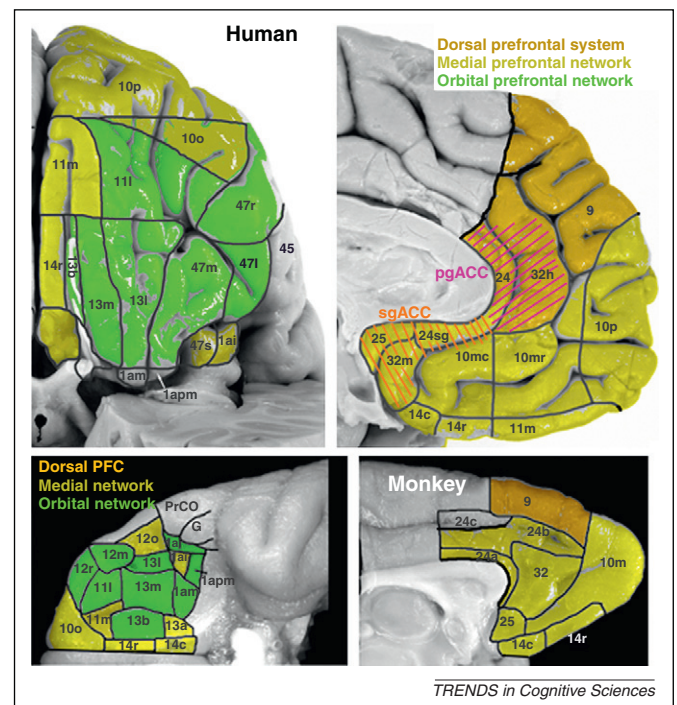


Figure 1. Maps of the orbital and medial surfaces of a human brain (above) and a macaque monkey brain (below), showing architectonic areas as defined in [2] (human) and [43] (monkey). The medial and orbital prefrontal networks are colored yellow and green, respectively. Note that these networks have been defined based on connectational data and that the medial network includes some areas on the orbital surface. In addition, the regions referred to as the subgenual and pregenual anterior cingulate cortex (sgACC and pgACC) are indicated on the human brain with orange and red stripes.

studies in humans, as well as deep brain stimulation in intractable patients [24]. Converging with this is a body of experimental anatomical evidence from animals, especially monkeys, that there is a connectional network that involves the amygdala and several areas in the mPFC, the adjacent medial edge of the orbital cortex, and a small region in posterolateral orbital cortex (these cortical areas are together known as the medial prefrontal network) [24,25] (Figure 1). These regions are also involved in a wider circuit that connects the amygdala and the medial network with other cortical areas in the anterior and medial temporal cortex and the posterior cingulate cortex (Figure 2), as well as with subcortical structures in the ventral striatum and pallidum, the medial thalamus, and the hypothalamus and brainstem (Figure 3). The data from animals indicates that this system is involved in forebrain modulation of visceral function in response to sensory or emotive stimuli, while the human evidence implicates it in emotion and mood disorders [24].

Distinct from the medial prefrontal related system, but adjacent and closely related to it, is a network of areas in the central orbital cortex (orbital prefrontal network; Figure 1). Unlike the medial network, the orbital network has connections with several sensory-related cortical areas, and appears to be critical for assessing objects and anticipating reward [25]. Depressed subjects show abnormalities in both networks during functional MRI studies involving reward and emotional processing tasks, although the medial network and related structures are more specifically related to mood disorders [26,27].

Observations in humans

In humans, the neuroimaging abnormalities found in mood disorders generally corroborated hypotheses regarding the neural circuitry of depression that were based initially on observations from the behavioral effects of lesions. For example, degenerative basal ganglia diseases and lesions of the striatum and orbitofrontal cortex increase the risk for developing major depressive episodes [24]. Because

these neurological disorders affect synaptic transmission through limbic-cortico-striato-pallido-thalamic circuits in diverse ways, it is likely that multiple types of dysfunction within these circuits can produce depressive symptoms.

Patients with early-onset mood disorders manifest neuromorphometric abnormalities that appear relatively selective for areas within the orbital and medial prefrontal cortex (OMPFC) and anatomically related structures within the temporal lobe, striatum, thalamus and posterior cingulate [24]. Cases with affective psychoses have also been differentiated from controls by gray matter loss within the OMPFC [28,29]. In contrast, elderly subjects with late-onset depression show a higher prevalence of neuroimaging correlates of cerebrovascular disease relative both to age-matched healthy controls and to elderly depressives with an early age at depression-onset [12]. MDD and BD cases that have either late-life illness onset or psychotic features show nonspecific signs of atrophy, such as lateral ventricle enlargement [12] (see Box 1 for a discussion of neuropathological correlations with neuroimaging abnormalities).

Limbic structures

Anatomy and connectivity

The connections of the amygdala are a good starting point for understanding emotion related circuitry. Experiments in rats, cats, and more recently monkeys have shown that the basal and lateral amygdala have reciprocal connections to the medial prefrontal network and, to a lesser extent, to the orbital network, as well as to related insular and temporal cortical areas, the mediadorsal thalamic nucleus and the ventromedial striatum [30] (Figure 2 and Figure 3). Outputs to hypothalamic and brainstem areas involved directly in visceral control arise from the central and medial nuclei, but also from the basal accessory and basal nuclei, especially in monkeys [30]. These projections terminate not just in the medial and lateral hypothalamus, but also in the periaqueductal gray, parabrachial nuclei, and autonomic nuclei in the caudal medulla. As such, they

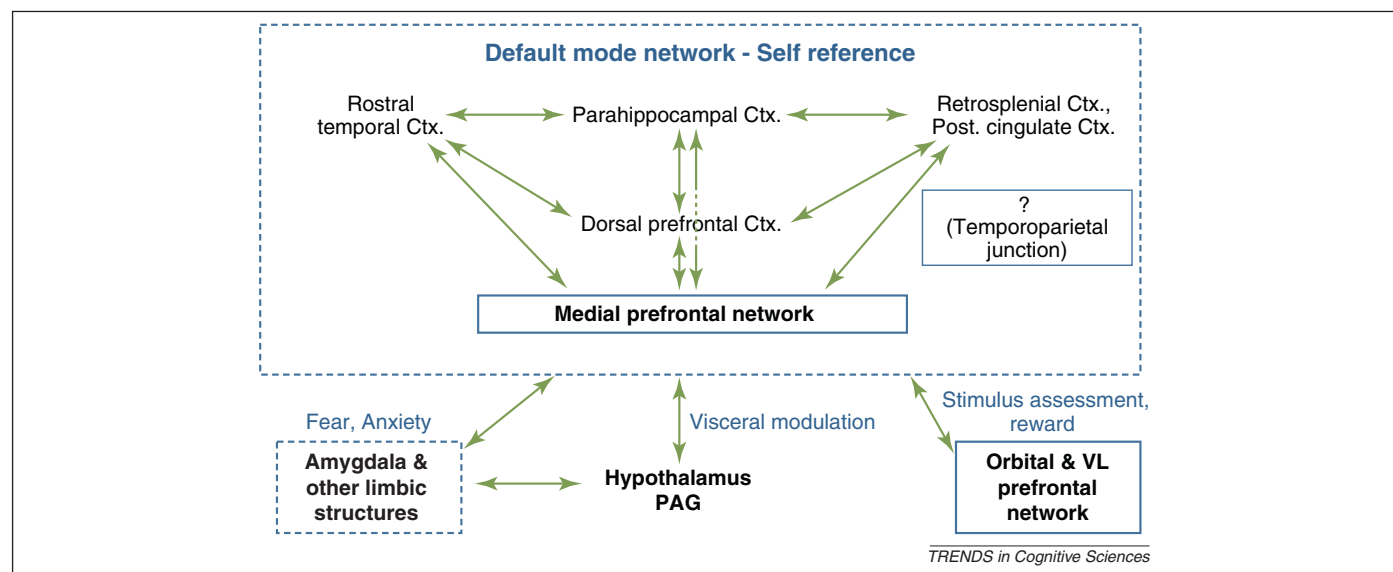


Figure 2. A diagrammatic illustration of connections between the medial prefrontal network and other cortical areas, as well as with the amygdala, hypothalamus and periaqueductal gray (PAG). Note that the medial network is part of the system that has been defined in humans as the 'default mode network' (DMN) and that connections have been defined in monkeys between all the components of the DMN, except the temporoparietal junction.

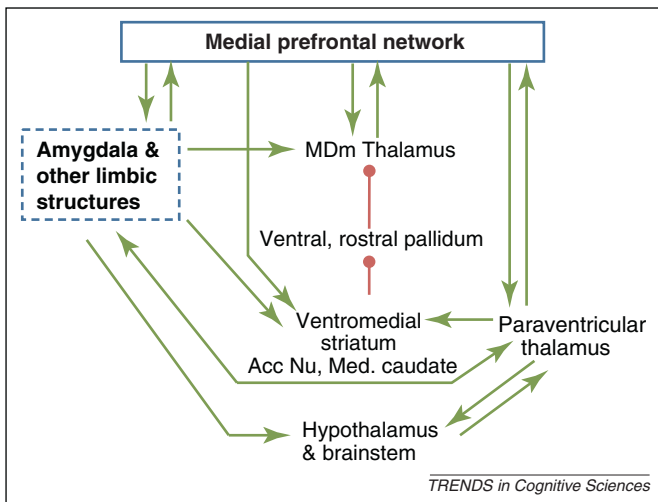


Figure 3. A diagrammatic illustration of the cortical-striatal-pallidal-thalamic loop circuit, involving the medial prefrontal network and the amygdala, together with the ventromedial striatum (nucleus accumbens and medial caudate nuclei), the ventral and rostral globus pallidus, and the medial part of the mediodorsal thalamic nucleus (MDm). The midline paraventricular thalamic nucleus also has prominent connections with the medial network, the ventromedial striatum, and the amygdala, as well as with the hypothalamus and brainstem. The substantial connections from the medial network to the hypothalamus and brainstem are not shown in this figure.

can modulate autonomic and endocrine mechanisms affecting a wide variety of visceral functions [31].

The strongest cortical connections of the large-celled basal amygdaloid nucleus are with the mPFC rostral and ventral to the genu of the corpus callosum, but there are also amygdaloid projections to the medial, caudal, and lateral orbital cortex (leaving the core of the orbital

Box 1. Neuropathological correlates of neuroimaging abnormalities

The structural imaging abnormalities found in mood disorders have been associated with histopathological abnormalities in *post mortem* studies. Such studies report reductions in gray matter volume, thickness or wet weight in the sgACC, posterior orbital cortex, and accumbens, and greater decrements in volume following fixation (implying a deficit in neuropil) in the hippocampus in MDD and/or BD subjects relative to controls [12,92]. The histopathological correlates of these abnormalities include reductions in glia with no equivalent loss of neurons, reductions in synapses or synaptic proteins, and elevations in neuronal density in MDD and/or BD samples in the sgACC, and of glial cell counts and density in the pgACC, dorsal anterolateral PFC (BA9), and amygdala (reviewed in [24]). The density of non-pyramidal neurons also appears decreased in the ACC and hippocampus in BD and in the dorsal anterolateral PFC (BA9) in MDD; reductions in synapses and synaptic proteins are evident in BD subjects in the hippocampal subiculum/ventral CA1 region, which receives abundant projections from the sgACC (see [12], for a review).

The glial cell type implicated most consistently is the oligodendrocyte. The concentrations of oligodendroglial gene products, including myelin basic protein, are decreased in frontal polar cortex (BA 10) and middle temporal gyrus in MDD subjects versus controls [12,93]. Compatible with these data the white matter volume of the corpus callosum genu and splenium are abnormally reduced in MDD and BD. Perineuronal oligodendrocytes also are implicated in mood disorders by electron microscopy [94,95] and reduced gene expression levels [12,96] in PFC tissue. Perineuronal oligodendrocytes are immunohistochemically reactive for glutamine synthetase, suggesting they function like astrocytes to take up synaptically released glutamate for conversion to glutamine and cycling back into neurons.

network in the central orbital cortex relatively free), the rostromedial insula, and the temporal pole and inferior temporal cortex, extending caudally to the primary visual cortex (V1) [2]. Other amygdaloid connections are with the entorhinal and perirhinal cortex and the hippocampus (subiculum), and the posterior cingulate cortex [32].

In the striatum, the amygdaloid projection terminates not only in the nucleus accumbens, but also in the adjacent medial caudate nucleus and ventral putamen. These striatal areas in turn project to the ventral and rostral pallidum, which itself sends GABAergic axons to the mediodorsal thalamic nucleus (MD; [2]). The pre- and sub-genual prefrontal cortex (PFC) also projects to the same ventromedial part of the striatum and is interconnected to the same region of MD [25]. The connections constitute essentially overlapping cortico-striato-pallido-thalamic and amygdalo-striato-pallido-thalamic loops [2]. As discussed below, these circuits form the core of the neural system implicated in mood disorders.

Observations in humans

In the amygdala, glucose metabolic abnormalities appear more selective for depressive subgroups. In the left amygdala, resting metabolism is abnormally elevated specifically in depressed subjects classified as BD-depressed, familial pure depressive disease (FPDD), or melancholic subtype [12]. These subgroups also share the manifestation of hypersecreting cortisol under stress [33]. In contrast, task-based hemodynamic responses of the amygdala show a pattern of abnormalities reflecting negative emotional processing biases in depression that appear more generalizable across depressed samples (see below).

Discrepant results exist across studies, conceivably reflecting clinical and etiological heterogeneity extant within the MDD and BD syndromes. For example, in the hippocampus, one study reported that reduced volume was limited to depressed women who suffered early-life trauma [34], whereas other studies reported that hippocampal volume correlated inversely with time spent depressed and unmedicated (e.g., [35]). In addition, the amygdala volume appears abnormally smaller in unmedicated BD subjects, but larger in BD subjects receiving mood stabilizing treatments that are associated with neurotrophic effects in experimental animals [36].

Depressed subjects show exaggerated hemodynamic responses of the amygdala to sad words, explicitly or implicitly presented sad faces, and backwardly-masked fearful faces, but blunted responses to masked happy faces (see [23,37], for a review). A similar pattern of abnormal amygdala responses to masked sad and happy faces is observed in unmedicated-remitted subjects with MDD [23,38], suggesting this abnormality is trait-like. Conversely, antidepressant drug administration shifts emotional processing biases toward the positive direction in both healthy and MDD samples [23,39]. This shift is in the normative direction, as healthy subjects show a positive attentional bias, as well as greater amygdala responses to masked happy versus sad faces [23,40].

Taken together, these data indicate that both the normative positive processing bias in healthy individuals and the pathological negative processing bias in MDD occur

automatically, below the level of conscious awareness, and are mediated, at least partly, by rapid, non-conscious processing networks involving the amygdala [23]. The differential response to masked-sad versus masked-happy faces in the amygdala is associated with concomitant alterations in the hemodynamic responses of the pregenual anterior cingulate cortex (ACC), hippocampus, anterior inferotemporal cortex, dorsolateral PFC, posterior cingulate and pulvinar. These regions may participate in setting a context or in altering reinforcement contingencies that conceivably may underlie these biases in MDD.

PFC

Anatomy and connectivity

In the 1990s, a series of axonal tracing experiments in macaque monkeys more completely defined the cortical and sub-cortical circuits related to the OMPFC and the amygdala. More specifically, two networks of interconnected regions that also have common connections with other cortical regions were recognized within the OMPFC. These networks have been referred to as [25] (Figure 1).

Recently, a similar analysis of the organization and connections of the lateral PFC (LPFC) has been performed. Based on architectonic and connectional analysis, three regions can be recognized in monkeys: a dorsal prefrontal region dorsal to the principal sulcus (DPFC), which is similar to the medial prefrontal network, a ventrolateral region ventral to the principal sulcus (VLPFC), which is related to the orbital prefrontal network, and a caudolateral region just rostral to the arcuate sulcus (CLPFC), which includes the frontal eye fields and is probably part of an attention system (Figure 1). As with the orbital and medial networks, areas in each region are preferentially connected to other areas in the same region and are connected to a specific set of areas in other parts of the cortex [41,42].

Orbital prefrontal network and VLPFC. Areas in the central and caudal part of the orbital cortex and the adjacent anterior agranular insular cortex comprise the orbital prefrontal network (Figure 1). This network is closely related to a similar system of cortical areas on the ventrolateral convexity of the PFC, which can be referred to as the ventrolateral PFC system (VLPFC) [2]. Both the orbital network and the VLPFC are characterized by connections with several sensory areas, including visual areas in the inferior temporal cortex (TEa) and the ventral bank of the superior temporal sulcus (STSv), somatic sensory areas in the dysgranular insula (Id), the frontal operculum (Opf) and parietal cortex (area 7b), and, for the orbital network, the primary olfactory and gustatory cortex [2]. Neurophysiological studies have also indicated that neurons in orbital network areas respond to multimodal sensory stimuli (for example, the sight, flavor, and texture of food stimuli). Remarkably, however, the neurons also alter their response in relation to the rewarding or aversive qualities of the stimuli. In addition to its role as a system for the integration of multimodal stimuli, therefore, the orbital network also functions as a system for the assessment of the affective value of these stimuli [2].

Medial prefrontal network and DPFC. For clarity, it is important to note that the cortical region termed the

‘medial PFC’ extensively overlaps with the region often referred to as the anterior cingulate cortex, especially its pre- and sub-genual parts (pgACC and sgACC; Figure 1). The principal difference is that the medial PFC also includes closely related areas rostral and ventral to the ACC, such as the medial part of area 10 and the cortex on the gyrus rectus. These areas are more closely connected to each other than they are to other parts of the cingulate cortex. In particular, the dorsal ACC, located superior to the rostral corpus callosum in humans, is part of a different cortical system, more closely related to the orbital network and the VLPFC [2]. The terms ‘medial PFC (mPFC)’ or ‘ventromedial PFC (vmPFC)’ will be used here for the region as a whole, but the terms sgACC or pgACC will be used in describing some human studies that have particularly focused on the areas immediately around the genu of the corpus callosum.

Whereas the orbital network is a sensory-related system, the medial network in the OMPFC is an output system that can modulate visceral function in relation to emotion or other factors. Importantly, the most prominent amygdaloid and other limbic connections are with areas of the medial network in the OMPFC [33]. The network comprises areas in the vmPFC, rostral and ventral to the genu, areas along the medial edge of the orbital cortex, and a small caudolateral orbital region at the rostral end of the insula [43] (Figure 1). The medial network receives few direct sensory inputs, but is characterized by outputs to visceral control areas in the hypothalamus (both medial and lateral) and periaqueductal gray (PAG). It is also connected to other cortical regions (the rostral part of the superior temporal gyrus (STGr) and dorsal bank of the superior temporal sulcus (STSd), the posterior cingulate cortex, and the entorhinal and parahippocampal cortex), forming a cortico-cortical circuit that is distinct from and complementary to the circuit related to the orbital network.

The medial network is closely related to the areas dorsal to it on the medial wall and those around the dorsomedial convexity, dorsal to the principal sulcus in monkeys, which constitute the dorsal prefrontal cortex (DPFC). This system includes areas 8b, 9, the dorsal part of area 46, as well as the polar part of area 10 (Figure 1). The DPFC is interconnected with itself and with the medial prefrontal network, and is also connected to the same set of other cortical areas as the medial network, including the posterior cingulate cortex, the rostral superior temporal gyrus, and the entorhinal and parahippocampal cortex. Furthermore, there are outputs from areas of the DPFC to the hypothalamus and PAG, so this system can also modulate visceral functions.

Notably, the medial network, the DPFC, and the other cortical areas that they are connected to (the posterior cingulate cortex, rostral temporal cortex, and medial temporal cortex) closely resemble the ‘default mode network’ (DMN), which has been defined by fMRI and functional connectivity MRI (fcMRI) in humans [44] (Figure 2). The DMN is characterized as interconnected areas that are active in a resting, introspective state but decrease activity during externally directed tasks (Figure 2). It has been linked to a variety of self-referential functions such as

understanding others' mental state, recollection and imagination [45].

Observations in humans

Emotional processing in the medial prefrontal network. The caudomedial PFC, especially the sgACC, participates generally in the experience and/or regulation of dysphoric emotion. In non-depressed subjects, hemodynamic activity increases in the sgACC during sadness induction, exposure to traumatic reminders, selection of sad or happy targets in an emotional go-no go study [14], and extinction of fear-conditioned stimuli (see [24], for a review). Moreover, enhanced sgACC activity during emotional face processing predicted inflammation-associated mood deterioration in healthy subjects under typhoid vaccine immune challenge [46]. Finally, remitted MDD subjects show decreased coupling between the hemodynamic responses of the sgACC, rostral superior temporal gyrus, hippocampus, and medial frontopolar cortex during guilt (self-blame) versus indignation (blaming others) [47].

The ventral pgACC and vmPFC situated anterior to the sgACC have been implicated in healthy subjects in reward processing, and conversely in depressed subjects, in anhedonia. In healthy humans, blood oxygen level-dependent (BOLD) activity in this region correlates positively with ratings of pleasure or subjective pleasantness in response to odors, tastes, water in fluid-deprived subjects, and warm or cool stimuli applied to the hand (see [48], for a review). The ventral pgACC shows activity increases in response to dopamine-inducing drugs and during preference judgments [48]. Conversely, in depressed subjects this region shows reduced BOLD activity during reward-learning and higher resting electroencephalographic (EEG) delta current density (putatively corresponding to decreased resting neural activity) in association with anhedonia ratings [48].

More dorsal regions of the pgACC show physiological responses to diverse types of emotionally valenced or autonomically arousing stimuli [49–51]. Higher activity in the pgACC holds positive prognostic significance in MDD, as depressives who improve during antidepressant treatment show abnormally elevated pgACC metabolism and magnetoencephalographic (MEG) and EEG activity prior to treatment relative to treatment-nonresponsive cases or healthy controls [52–54].

Moreover, in the supragenual ACC, depressed subjects show attenuated BOLD responses versus controls while recalling autobiographical memories [13], associated with lower subjective arousal ratings experienced during memory recall. Behaviorally, MDD subjects are impaired at generating specific autobiographical memories, particularly when cued by positive words. These deficits have been associated with reduced activity in the hippocampus and parahippocampus [13].

Notably, preclinical evidence indicates that distinct medial prefrontal network structures are involved in opponent processes with respect to emotional behavior [55]. Regions where metabolism correlates positively with depression severity include the sgACC and ventromedial frontal polar cortex: metabolism increases in these regions in remitted MDD individuals who experience depressive relapse under catecholamine or serotonin depletion

[56,57]. In contrast, the VLPFC and lateral orbital regions that include BA45a and BA47 s (Figure 1) and the lateral frontal polar cortex show inverse correlations with depression severity, which suggests that they play an adaptive or compensatory role in depression [12].

Within the OMPFC a relatively consistent abnormality reported in early onset MDD and BD has been a reduction in gray matter in left sgACC [12]. This volumetric reduction exists early in illness and in young adults at high familial risk for MDD [12,28], yet, longitudinal studies show progression of the abnormality in samples with psychotic mood disorders [29,58] and individuals with more chronic or highly recurrent illness show greater volume loss than those who manifest sustained remission [59]. The abnormal reduction in sgACC volume has been primarily identified in mood disordered subjects with evidence for familial aggregation of illness [28,58,60].

The co-occurrence of increased glucose metabolism and decreased gray matter within the same regions in mood disorders has been demonstrated most consistently by comparing neuroimaging data from depressed patients before versus after treatment and from remitted patients scanned before versus during depressive relapse [56,57]. In resting metabolic neuroimaging studies, in contrast, the reduction in gray matter volume in some structures appears sufficiently prominent to produce partial volume effects because of their relatively low spatial resolution of functional brain images, such that in some depressed samples resting metabolism appears reduced in the sgACC relative to healthy controls (see [12], for a review). In contrast, other studies report increased metabolic activity in the sgACC in primary or secondary depression, suggesting that these apparent discrepancies may be explained by differing magnitudes of gray matter loss across samples [12]. Consistent with this hypothesis, in MDD and BD individuals who show abnormal reductions of both gray matter volume and metabolism in the sgACC, correction of the metabolic data for partial volume (atrophy) effects reveals that metabolism is increased in the sgACC in the depressed phase, and decreases to normative levels with antidepressant treatment. This finding is consistent with evidence that sgACC metabolism decreases during symptom remission induced by a variety of antidepressant treatments, including electroconvulsive therapy and deep brain stimulation [12,61].

Similarly, during probabilistic reversal learning, depressed MDD subjects show exaggerated behavioral sensitivity to negative feedback versus controls, in association with blunted BOLD activity in the dorsomedial and ventrolateral PFC during reversal shifting and absence of the normative deactivation of the amygdala in response to negative feedback [11]. Disrupted top-down control by the PFC over the amygdala thus may result in the abnormal response to negative feedback consistently observed in MDD [15].

Cortical projections to hypothalamus and brainstem Anatomy and connectivity

Substantial outputs exist from the medial prefrontal network to the hypothalamus, PAG, and other visceral control centers [25]. The subgenual cortex provides the heaviest

projection, which terminates in both the medial and lateral hypothalamus, and in both dorsolateral and ventrolateral columns of the PAG. The origin of the projection extends beyond the medial prefrontal network to include the rostral superior temporal gyrus and area 9 in the DPFC, both of which are strongly related to the medial network. Electrical stimulation of the medial network areas in monkeys produces disturbances in functions such as heart rate and respiration [62].

Observations in humans

Functional MRI studies in humans show that activity in the mPFC correlates with visceral activation in response to emotional [63,64] or even non-emotional stimuli [65]. Humans with lesions of the vmPFC, centered on the medial prefrontal network, show complete or severe deficits in visceral responses to emotionally competent stimuli [66], as would be expected from the connectional data above. That is, they do not appear to be able to link cortical analysis of the stimulus or situation to the appropriate visceral response. In addition, they show striking deficits in experiencing emotion and in social functioning, including the ability to make appropriate choices and to control impulse behavior. This deficit has been linked to the absence of a 'somatic marker' provided by the visceral activation (or the neural signal that produces visceral activation) that normally assists non-conscious cognitive processes in controlling behavior [66].

From the viewpoint of mood disorders, over-activation of this visceromotor system (e.g., due to excessive activity in the mPFC or sgACC, evoking visceral disturbance) may contribute to the chronic sense of 'unease' that is a common component of depression. William James, who fell into a severe depressive episode when torn between his religious and scientific beliefs, gave one of the most striking self-descriptions of this aspect of depression. He wrote: "I awoke morning after morning with a horrible dread at the pit of my stomach, and with a sense of the insecurity of life that I never knew before. . . It gradually faded, but for months I was unable to go out into the dark alone. In general I dreaded to be left alone." [67].

Cortico-striatal-thalamic circuits related to OMPFC

Anatomy and connectivity

The PFC has specific connections with the striatum and thalamus and several circuits can be identified. The first are the reciprocal thalamo-cortical connections that relay subcortical input to the cortex through principal thalamic nuclei. The well-known cortico-striato-pallido-thalamic loops are closely related to these (Figure 3). The medial prefrontal network, in particular, is connected to both the medial segment of the mediodorsal thalamic nucleus (MDm) and the ventromedial part of the striatum [68,69] (Figure 3). Finally, there are circuits that involve the intralaminar and midline thalamic nuclei, which project to both the striatum and the cortex.

Medial segment of mediodorsal thalamic nucleus. The MDm receives substantial subcortical inputs from many limbic structures, including the amygdala, olfactory cortex, entorhinal cortex, perirhinal cortex, parahippocampal cortex, and subiculum [70]. Notably, all of these areas

also send direct (non-thalamic) projections to the OMPFC [24].

In addition to these inputs from limbic structures, which are excitatory and probably glutamatergic, MDm also receives GABAergic inputs from the ventral pallidum and rostral globus pallidus (see [24], for a review), which is part of the cortico-striato-pallido-thalamic loop involving the OMPFC (Figure 3). In MDm, the GABAergic terminals of afferent pallidal fibers synapse on the same dendrites as the excitatory terminals from the amygdala and other limbic structures [71]. It can be expected that these convergent but antagonistic inputs would interact to modulate the reciprocal thalamo-cortical interactions between the OMPFC and MDm. While the limbic inputs are dominant, ongoing patterns of thalamo-cortical and cortico-thalamic activity would be maintained, allowing for consistent behavior. When pallidal inputs become more prominent, ongoing patterns would be interrupted, allowing a switch from one behavior to another. The affected 'behaviors' would presumably include those that have been associated with the OMPFC: mood, value assessment of objects, and stimulus-reward association. In support of this hypothesis, lesions of the ventral striatum and pallidum, MD, or the OMPFC have been shown to cause perseverative deficits in stimulus-reward reversal tasks in rats and monkeys, such that the animals have difficulty switching away from previously rewarded, but now unrewarded stimuli [72–75]. A similar deficit in subjects with mood disorders might be the difficulty of 'letting go' of a negative mood or mind-set long after the resolution of any traumatic events that might have justified it.

Prefrontal projections to the striatum. The OMPFC projects principally to the rostral, ventromedial part of the striatum. The orbital network areas connect to a relatively central region that spans the internal capsule and includes parts of both the caudate nucleus and the putamen. Of more significance for mood disorders, however, the medial network areas project to the nucleus accumbens and the adjacent medial edge of the caudate nucleus bordering the lateral ventricle [69] (Figure 3). The amygdala input to the striatum is essentially coextensive with that of the medial network. These striatal regions, in turn, project to the ventral pallidum, which projects to the portion of MDm that is connected to the medial network areas [2].

Midline 'intralaminar' nuclei of the thalamus. In addition to the prefrontal connections with MD, there are also major connections with the midline-intralaminar nuclei of the thalamus, which include the paraventricular thalamic nucleus (PVT), as well as other nuclei that extend ventrally on the midline between the anterior and mediodorsal thalamic nuclei. These nuclei are reciprocally connected to the medial prefrontal network areas, with little connection to the orbital network, and they have a substantial projection to the same areas of the ventromedial striatum that receives input from the medial network areas [76,77] (Figure 3). They also have important connections with the amygdala, hypothalamus, and brainstem areas, including the PAG. As such, they are situated to relay information about visceral and emotional activity to both the medial prefrontal network and the cortico-striato-pallido-thalamic loop with which it interacts.

Considerable evidence links the PVT to the stress response [78,79]. In particular, lesions of the PVT block the habituation to chronic stress in rats [80], via a mechanism that involves corticosterone action in the PVT [81]. In humans, a similar habituation to the neuroendocrine stress response caused by chronic hypoglycemia [65] is associated with activity in the midline thalamus [82]. It is likely that the role of the PVT is general across many types of stressors.

Observations in humans

The neurophysiological activity of subcortical structures that share extensive connections with the medial prefrontal network show correlations with depressive symptoms. In the accumbens area, the elevation of metabolism under catecholamine depletion correlates positively with the corresponding increment in anhedonia ratings [56]. In addition, fMRI studies show that hemodynamic responses of the ventral striatum to rewarding stimuli are decreased in depressives versus controls and that higher levels of anhedonia are associated with blunted ventral striatal responses to rewarding stimuli in both healthy [48] and depressed subjects (see [3], for a review). Furthermore, during probabilistic reversal learning depressed subjects show impaired reward (but not punishment) reversal accuracy in association with attenuated ventral striatal BOLD response to unexpected reward [83].

Implications for neurocircuitry-based models of depression

Within the larger context of the limbic-cortical-striato-pallido-thalamic circuits implicated in the pathophysiology of depression, the functional implications of some limbic-cortical circuits involving the medial prefrontal network merit comment in light of the abundant basic science literature available to guide translational models. The anatomical projections from the medial prefrontal network to the amygdala, hypothalamus, PAG, locus coeruleus, raphe, and brainstem autonomic nuclei play major roles in organizing the visceral and behavioral responses to stressors and emotional stimuli (see [24], for a review). In rats, lesions of the mPFC enhance behavioral, sympathetic, and endocrine responses to stressors or fear-conditioned stimuli organized by the amygdala [84,85]. Nevertheless, these relationships are complex, as stimulation of the amygdala inhibits neuronal activity in the mPFC, and stimulation of infralimbic and prelimbic projections to the amygdala excites intra-amygdaloid GABAergic cells that respectively inhibit or excite neuronal activity in the central amygdaloid nucleus (ACe) [55].

For example, the amygdala is reported to mediate the stressed component of glucocorticoid hormone secretion, at least in part, by disinhibiting corticotropin-releasing factor (CRF) release from the hypothalamic paraventricular nucleus; the glucocorticoid response to stress is inhibited by stimulation of glucocorticoid receptors (GR) in the ventral ACC and lesions in this cortical region thus increase adrenocorticotrophic hormone (ACTH) and corticosterone (CORT) secretion during stress in rats [24]. It is conceivable that dysfunction within the medial prefrontal network would disinhibit the efferent transmission from the ACe

and BNST to the hypothalamus in depression accounting, for increased stressed cortisol secretion [24]. Notably, cortisol hypersecretion in mood disorders has been associated with increased metabolic activity in the amygdala and with reduced gray matter in rostral ACC [12,33,86].

Furthermore, dysfunction of the medial prefrontal network and the adjacent orbital network may impair reward learning, potentially contributing to the anhedonia and amotivation manifest in depression. The ACC receives extensive dopaminergic innervation from the ventral tegmental area (VTA) and sends projections to the VTA that regulate phasic dopamine (DA) release. In rats, stimulation of these mPFC areas elicits burst firing patterns in the VTA-DA neurons while inactivation of the mPFC converts burst firing patterns to pacemaker-like firing activity [24]. The burst firing patterns increase DA release in the accumbens, which is thought to encode information about reward prediction [3]. The mesolimbic DA projections from the VTA to the nucleus accumbens shell and the mPFC thus play major roles in learning associations between operant behaviors or sensory stimuli and reward. If the neuropathological changes in the ACC in mood disorders interfere with the cortical drive on VTA-DA neuronal burst firing activity, they may impair reward learning. Compatible with this hypothesis, depressives show attenuated DA release relative to controls in response to unpredicted monetary reward [87] and fail to develop a response bias towards rewarded stimuli during reinforcement paradigms [5–7].

Finally, the patterns of physiological activity within the DMN that involves the medial network are hypothesized to relate to self-absorption or obsessive ruminations [88,89]. In depressed subjects, increasing levels of DMN dominance over the putative ‘task-positive network’ (TPN; a group of structures that are consistently activated during volitional attention and thought) are associated with higher levels of maladaptive, depressive rumination and lower levels of adaptive, reflective rumination [90]. Crucially, hemodynamic activity increased in the anterior insular region corresponding to intrasulcal BA47 in depressed subjects at the onset of increases in TPN activity. Hamilton *et al.* [90] thus hypothesized that the DMN undergirds the representation of negative, self-referential information in depression and that the intrasulcal BA 47, when prompted by increased levels of DMN activity, initiates an adaptive engagement of the TPN. Notably, interpersonal psychotherapy, which can reduce depressive symptoms in MDD, enhances activity in the same anterior insular region (i.e., intrasulcal BA 47) [24]. Cognitive-therapeutic strategies for depression thus may depend upon enhancing the function of prefrontal systems that serve as convergence zones between multiple prefrontal networks, such as BA 47s [91] (Figure 1).

Concluding remarks

The experimental observations described here provide an indication of the circuitry and structures that are involved in mood disorders and related conditions. The description is not yet complete and there are many important details that have yet to be worked out, but important foci such as the subgenual prefrontal cortex and the amygdala can be

Box 2. Future directions

- The clinical designation of anhedonia has not heretofore discriminated between decrements in motivation and reductions in experienced pleasure, despite the significance of this distinction for translational research. A refined research definition of anhedonia that parses this symptom cluster into deficits in hedonic response to rewards versus diminished motivation to pursue rewards is, therefore, needed to delineate between deficits in the 'liking' versus the 'wanting' components recognized within the preclinical literature [3,97].
- Neurophysiological investigation of the properties of the medial prefrontal areas in animals, especially the areas immediately around the genu of the corpus callosum, are needed. Although there is good evidence that cortical areas in this region have an important role in modulating visceral reactions to emotive and other stimuli through their connections to the hypothalamus and brainstem, little is known about the mechanisms underlying this modulation. Several studies are currently investigating the areas of the orbitofrontal cortex that have begun to elucidate the role of these areas in reward and stimulus value assessment [98]. To date, however, there has been little or no equivalent investigation of the medial prefrontal areas.
- It is also crucial to investigate the properties of individual cortical areas within the medial and orbital prefrontal networks. Although these systems are each highly interconnected, they are not fully homogeneous and it may be expected that different architectonic areas within them have different properties. For example, a recent article indicates that area 10 at the frontal pole has a specific function in encoding [99]. Little is known, however, about the specific physiological functions of other medial prefrontal areas.
- Further human brain mapping studies that compare depressed and control samples using high-resolution fMRI are needed to determine the specific role of the components of the 'depression circuit' on which we have focused (sgACC/pgACC, amygdala, ventral striatum, and medial thalamus). This would require careful development of behavioral testing paradigms. For example, would the ventral striatum or medial prefrontal cortex show differential activity in relation to the specific function of suppression of negative thoughts? Similarly, would the subgenual area show differential activity that correlates with visceral responses to negative versus positive emotional stimuli?

identified and their relationships understood. The system is complex and, although there are many suggestions, it is not possible yet to identify the specific deficits that result in mood disorders (see also Box 2). The complexity of the system means that there are likely to be multiple factors that cause different aspects of these heterogeneous disorders. In spite of such confusion, the progress made in the past 15 to 20 years has been impressive. It is now possible to discuss mood disorders in terms of specific brain systems, and there is no question that there is a neurobiological basis for mood disorders.

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