Published in final edited form as:

Biol Psychiatry. 2011 June 15; 69(12): e43–e54. doi:10.1016/j.biopsych.2010.09.041.

Localization of dysfunction in major depressive disorder: Prefrontal cortex and amygdala

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Abstract

Despite considerable effort, the localization of dysfunction in major depressive disorder (MDD) remains poorly understood. We present a hypothesis about its localization that builds on recent findings from primate neuropsychology. The hypothesis has four key components: a deficit in the valuation of ‘self’ underlies the core disorder in MDD; the medial frontal cortex represents ‘self’; interactions between the amygdala and cortical representations update their valuation; and inefficiency in using positive feedback by orbital prefrontal cortex contributes to MDD.

Keywords

self-valuation; self-esteem; self-worth; self-reflection; mood; emotion; reward; devaluation; reversal; animal models; primate research; frontal lobe function

Introduction

Neurologists and neurosurgeons can treat Parkinson’s disease reasonably well because they know where the problem is and because they have a clear hypothesis about its pathogenesis. Because of this combination of knowledge and theory, they can often use carefully localized deep brain stimulation or stereotactically placed brain lesions to ameliorate their patients’ symptoms. In contrast, psychiatric illnesses such as major depressive disorder (MDD) have defied such specific localization. One problem is that no one really knows where the problem is. As a result, treatments of these diseases typically affect the whole brain, as in the case of pharmacologic or electroconvulsive therapies.

Localized treatments have been attempted in MDD, but because the specific neuroanatomical target remains elusive these anatomically based therapies lack a strong theoretical basis. Even when successful, no one knows quite why. Examples of

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Financial Disclosures

Dr. Drevets disclosed consulting fees from Pfizer Pharmaceuticals. All other authors report no biomedical financial interests or potential conflicts of interest.

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neurosurgical treatments for MDD include lesions in several structures: the frontal cortex beneath the genu of the corpus callosum, fiber tracts ventral to the caudate nucleus, the anterior part of the internal capsule, the prelimbic white matter, and the anterior cingulate cortex (1,2). Localized deep brain stimulation has targeted the subgenual medial frontal cortex and the internal capsule (3–5). These therapies have progressed with only an uncertain knowledge of the specific neural circuitry involved or the neurophysiological processes affected (6). This uncertainty may account for the variable efficacy of these interventions; for example, deep brain stimulation typically results in improvement in about one-half of cases and remission in about one-third (3,7).

To develop more effective therapeutic interventions, we need to know the primary site or sites of dysfunction, as well as the neural circuits underlying the pathophysiology of MDD. Fortunately, we do not need to start from scratch. Considerable neuroimaging and clinical evidence points to the medial and orbital frontal cortex, along with the amygdala, as functioning poorly in MDD (8,9). And, although we will not discuss them further here, anxiety disorders such as phobias, panic disorder, and post-traumatic stress disorder also appear to involve these structures (10) and often occur co-morbidly with MDD (11). Despite this knowledge, it remains difficult to discern which abnormalities cause the disorder and which reflect subsequent adaptation to the primary dysfunction. The lack of a clear distinction between cause and effect prevents more specifically targeted interventions.

In principle, research on the amygdala and frontal cortex in nonhuman animals could contribute to understanding MDD. Two problems, however, have made it difficult to marry clinical and neuroimaging research in humans with knowledge gained from research on nonhuman animals. First, animal research typically involves behaviors learned through Pavlovian or instrumental conditioning methods. Unfortunately, these laboratory behaviors are but blunt tools for exploring the interactions between conscious knowledge and emotion that characterize the daily life of humans, especially those with disorders of mood and anxiety. Despite this limitation, recent advances in primate neuropsychology can contribute to understanding MDD, and the largest part of this article considers some of these findings. Second, many researchers assume that brain areas called ‘prefrontal cortex’ or ‘orbitofrontal cortex’ in rodents are homologues of the large regions of cerebral cortex called by the same names in humans, monkeys, and other primates. The best comparative evidence indicates that they are not. The assumption that they are homologous, however, and that the rodent frontal cortex is essentially a replica-in-miniature of that in primates, has led to a certain amount of misunderstanding. Findings from rodents can be important for understanding MDD, especially when focused on brain structures that have homologues in rodents and humans. But the lineage leading to modern rodents diverged from humans tens of millions of years before monkeys and humans split, and the frontal cortex of rodents differs from that of primates in many important ways.

Comparative neuroanatomy indicates that only the caudal parts of the primate frontal lobe have homologues in rodent brains (12–17). Figure 1 illustrates the best-established macaque-human homologues with a color code. Within the frontal cortex of humans (left) and macaque monkeys (right), the areas shared with rodents (and probably with all mammals) are shown in purple (orbital frontal) and pink (medial frontal). These areas are characterized by their agranular cytoarchitecture, which means that they lack a clearly identifiable internal granular layer, called layer 4. However, the evidence for their homology goes well beyond that one feature to include specific aspects of corticostriatal connectivity; topology within the cerebral cortex; inputs from olfactory, gustatory, and visceral receptors; and relatively direct output to the autonomic nervous system. A discussion of this evidence and an illustration of rodent frontal cortex appears in Reference 15.

In this article, we have devised some new terms and abbreviations, especially for the agranular frontal areas. We recognize the disadvantages of new terms, but we have chosen to avoid using ‘prefrontal’ for the agranular areas in order to prevent misunderstandings. We call the medial group ‘MFa’, which stands for ‘agranular medial frontal cortex’. Likewise, we call the lateral areas ‘OFa’, for ‘agranular orbital frontal cortex’. In primates, MFa comprises areas 24, 25, and 32, also known as anterior cingulate, infralimbic, and prelimbic cortex, respectively. (The term ‘anterior cingulate cortex’ is sometimes used for any or all of these three areas, but we use this term only for area 24.) The primate OFa comprises the caudal parts of areas 13 and 14, along with the anterior part of the insula. We reserve the term ‘prefrontal cortex’ (PF) for areas that evolved in primates and have a homotypical cytoarchitecture (15). Collectively, these areas are known as the ‘granular prefrontal cortex’ or ‘granular frontal cortex’. We recognize a medial group of granular areas called the medial prefrontal cortex (PFm, light blue in Fig. 1) and an orbital group called the orbital prefrontal cortex (PFo, medium blue in Fig. 1). PFm includes part of area 10, also known as the frontal pole cortex, and medial parts of area 9. PFo includes the rostral, granular parts of areas 13 and 14, along with area 11. An easy way to remember these names is to consider them in pairs, in anatomical order, with medial at the top:

PFm lies rostral to MFa
PFo lies rostral to OFa

Price and Drevets (8) have reviewed the anatomical organization of these frontal areas in relation to mood disorders. They outline five ‘systems’ and ‘networks’: the orbital, medial, dorsal, ventral, and caudal PF cortex. Their orbital network includes PFo and OFa, and their medial network comprises PFm and MFa. This article attempts to build on their analysis by exploring the role of both the orbital and medial networks and amygdala–frontal interactions in MDD. We begin by reviewing the symptoms of MDD, then consider the localization of these dysfunctions, the effects of disrupting PFo–amygdala interactions, and some effects of PF lesions in monkeys.

Major depression

MDD patients show altered incentive and reward processing, leading to a lack of motivation, including abulia, as well as apathy and anhedonia (18,19). These patients manifest markedly lowered self-esteem and ruminate endlessly on the aversive aspects of events in their lives, their hopelessness about a better future, and their helplessness to do anything about it (20). They also show oversensitivity to negative feedback under certain circumstances (21); inflexibility in the face of changing reinforcement contingencies, as assessed in choice-reversal tasks (22–24); mood-dependent deficits in the integration of sensory and social information (25–28); impaired autobiographical memory (29); altered attentional set-shifting after the presentation of negative (sad) stimuli (30–32); and deficits in verbal memory (33).

Visceral, neuroendocrine, and autonomic disturbances also characterize MDD, and they often lead to altered weight, appetite, and sleep (34). Several studies have reported evidence for abnormally elevated sympathetic function in MDD, coupled with reduced parasympathetic tone on heart rate under resting conditions (35,36). These findings could account for the increased risk of sudden death and ventricular arrhythmia among MDD patients who develop cardiovascular disease (35). When cognitively challenged, depressed patients show less change than controls in heart-rate variability (HRV) in response to mildly stressful tasks (37,38).

We propose here a specific cause for some of these impairments. According to our hypothesis, the amygdala updates the valuation of representations in the medial and orbital

frontal cortex, among which is a representation of 'self'. A corollary of that hypothesis is that the representation of self is an emergent property arising from the interaction of the phylogenetically older areas of frontal cortex, MFa and OFa, with those that evolved in advanced primates, PFm and PFo, and underwent further modification during human evolution.

Neuroanatomical correlates

The evidence for localizing MDD dysfunction to the orbital and medial frontal cortex comes from many sources. Compared to healthy controls, patients with MDD show altered activation in the orbital and medial frontal cortex during exposure to emotionally charged stimuli and during performance of reward-processing tasks (39,40). Patients with cerebrovascular disease who develop depression have lesions in the orbital and medial frontal cortex, but other cerebrovascular patients—those without depression—do not (41). Patients with Parkinson's disease who manifest depression show altered metabolism or blood flow in the orbital and medial frontal cortex compared to non-depressed Parkinson's patients or healthy controls (42,43). Furthermore, reductions of cortical volume and thickness occur in several parts of the frontal cortex in depressed patients, with the most reliable and best characterized of these abnormalities occurring in PFo area 11 (44), the sulcal part of area 47 (45,46), and the subgenual frontal cortex (47–50). The latter region includes part of area 24, area 32, and area 25. In these key parts of the MFa, the reduction in cortical volume arises prior to the onset of symptoms in subjects at high familial risk for depression, appears early in the course of the illness, persists across depressive episodes, and occurs consistently in the most severe cases (48,49,51–53).

Few experiments have addressed the anatomical correlates of autonomic dysfunction in MDD, but one that did implicated PFm. Nugent et al. (38), noted above, studied depressed women challenged by a mildly stressful handgrip task. The experimenters measured heart-rate variability (HRV) by using a spectral analysis of the electrocardiogram, and they assessed the change in the sympathetic-to-parasympathetic regulation of HRV by computing the ratio of its low-to-high frequency power components. In both MDD patients and healthy controls, HRV regulation correlated with activation levels in the ventromedial part of area 10p (a part of PFm), but the sign of the correlation differed between the groups. Several studies in monkeys and other animals, such as the one illustrated in Figure 2, show that electrical stimulation elicits autonomic responses from MFa and OFa, but not from PFm or PFo (54–60). It seems likely, therefore, that interactions of PFm with MFa mediate the abnormal autonomic responses observed by Nugent et al. (Other autonomic responses are likely mediated through interactions of PFo with OFa.) Taken together, the findings cited so far implicate both granular and agranular parts of frontal cortex, as well as both its medial and orbital networks.

The amygdala has also been implicated in MDD. Electrical stimulation of the amygdala can produce fear, anxiety, dysphoria, sympathetic autonomic arousal, social withdrawal, and cortisol release (61,62). One of the most consistent findings in the mood disorders literature has been that patients with MDD show abnormal activation in the amygdala when presented with emotional stimuli. When depressed, their amygdala shows exaggerated activation during exposure to sad words (63) and sad faces (64,65), compared to control subjects. Conscious awareness of the stimulus is not necessary; similar results occur for fearful (66) and sad (64) faces masked to prevent awareness. Similar results also occur in remitted MDD patients (67), suggesting that this abnormality is a consistent trait rather than a transient state. In contrast to the exaggerated activation for sad and fearful faces, masked *happy* faces yield blunted activation in both depressed and remitted MDD patients (68). These patients thus seem to show a bias toward negative emotions, with excessive amygdala activation for

negative stimuli and blunted activation for positive ones. Neuropsychological studies of patients with mood disorders confirm their ‘negativity bias’ (26,32,69,70), a topic taken up again in the section ‘*Brain activation in MDD before and after treatment*’.

Other abnormalities in amygdala activation appear to be specific to subtypes of mood disorders. For example, the amygdala shows elevated resting metabolism in patients classified as bipolar disorder-depressed, as well as those with familial pure depressive disease, melancholic depression, and positive mood responses to a night of total sleep deprivation (71,72). In addition, activation of the left amygdala increases during relapses into depression induced by tryptophan depletion, but only in MDD patients who are homozygous for the long allele of the serotonin-transporter polymorphism (73).

Thus, several findings implicate the orbital frontal cortex, the medial frontal cortex, and the amygdala in MDD. And several correlates have been found with its affective and autonomic symptoms. But the underlying pathophysiological processes involved in MDD remain unknown, as does cause and effect. In the next two sections, we explore recent neuropsychological results from nonhuman primates in order to gain insight into this problem.

Prefrontal cortex and amygdala function in devaluation tasks

Recent findings from macaque monkeys have clarified the function of the amygdala and its interaction with PFO (74,75). Key findings have come from the *devaluation task*. This task assesses an animal’s ability to link objects with their current biological value. The task proceeds in two phases. In the first phase, monkeys learn about a large number of objects and their associated food rewards. Half of the objects are associated with Food 1 and half with Food 2, also called ‘outcomes’. In the second phase, monkeys are given a series of choice tests in which they must choose between two objects, one associated with Food 1 and the other associated with Food 2. Before some tests, the animals consume one kind of food to satiety, which has the effect of devaluing it. Intact, control monkeys tend to avoid choosing objects associated with the devalued food, a finding called the ‘devaluation effect’. Importantly, there is only one trial per pair of objects. As a result, the devaluation effect does not depend on learning about the objects and the now-devalued food. Instead, the updating of valuations occurs automatically; the monkeys predict the value of the food before they make a choice between the two objects.

As illustrated in Figure 3A (pink), monkeys with bilateral amygdala lesions typically fail to show the devaluation effect or show it only in a strongly attenuated form. These data indicate that the amygdala plays an essential role in guiding choices based on the current biological value of a food. Experiments in rats yield similar results (76–78).

PFO also plays a role in these valuations. Figure 3A shows findings from macaque monkeys on the devaluation task. Some monkeys received bilateral PFO ablations (blue) and others received a crossed surgical disconnection (green) of the amygdala and PFO (a unilateral amygdala lesion in one hemisphere along with unilateral PFO lesion in the other hemisphere, combined with section of the forebrain commissures). In all lesion groups, the devaluation effect was markedly attenuated. The monkeys chose objects according to their original preferences, with less influence of their selectively satiated state than in intact monkeys. The same groups of operated monkeys showed little or no change in food preferences and worked for food like control monkeys. So the impairment on the devaluation task cannot be explained by changes in food preference or motivation. Instead, results from this test show that the monkeys could not update valuations based on current biological needs and use those updated valuations to make adaptive choices. Lesions elsewhere in the prefrontal cortex are without effect on the devaluation task, including bilateral lesions of ventral PF

cortex (area 12/47) or the dorsolateral PF cortex (area 46) (79, 80). Likewise, damage to regions near the amygdala, such as the entorhinal cortex, perirhinal cortex, or hippocampus, have no effect (81, 82).

One additional result deserves mention. Reversible inactivation of the amygdala *during* the selective satiation procedure, but not afterward, attenuates the devaluation effect (83). This finding indicates that amygdala activity is critical during the selective satiation procedure, while the food value changes, but not after the updating process has run its course. Thus, the amygdala updates the value of the food as monkeys consume it, and this change in value is registered elsewhere in the brain, presumably including but not restricted to PFO.

The conclusion from this line of research is that, in the intact brain, amygdala–PFO interactions enable monkeys to link the representation of an object with the current biological value of a food. Importantly, monkeys do not need to experience receiving the food in its devalued state. This updating occurs automatically, and the monkeys predict the food's value before they make a choice. For practical reasons, this research has focused on the amygdala's role in signaling *decreases* in food value, but it probably signals *increases* in value, as well (84). In addition, although most work has involved positive outcomes, such as the receipt of a desirable food, the amygdala also updates the value of aversive outcomes (85).

The results from the devaluation task show that PFO, interacting with the amygdala, plays a critical role in updating the valuation of neural representations. Although PFO has long been thought to represent positive and negative valuations, it has only recently been appreciated that PFO neurons can represent value independent of stimulus identity (86–89). To perform the devaluation task, these valuations must be linked somehow to object representations. Inputs from the inferotemporal (IT) and perirhinal (PRh) cortex likely contribute to creating these linkages in conjunction with inputs from the amygdala. PFO also receives relatively direct inputs from olfactory, gustatory and visceral receptors via the OFa (which includes the agranular insular cortex). Thus, convergent inputs to PFO enable it to link the representation of objects (from IT and PRh) to values (from the amygdala) and to the sensory properties of foods (from OFa).

Prefrontal cortex and amygdala function in reversal tasks

Another result from monkey research yields a complementary finding; it points to the importance of positive feedback in the valuation of object representations in PFO. The task used in this research, called the *serial object-reversal learning task*, resembles the devaluation task in some ways, but differs in others. In the devaluation task, monkeys associate object representations with the current value of a food reward. In the serial object-reversal learning task, monkeys also associate object representations with a value. In this task, however, the value of the food reward does not change as it does in the devaluation task. Instead, the value of an object changes because the likelihood of obtaining a reward by choosing it varies, and this likelihood can be called an *object-reward mapping*. Lesions of PFO affect the learning of object-reward mappings, whether these mappings change in a probabilistic (90) or deterministic way. In the traditional object-reversal task, the mapping is deterministic: the object previously rewarded no longer produces reward when chosen, but choice of the previously unrewarded object always does. These mappings change from day to day.

The black curve in Figure 4A shows that intact control monkeys learn these reversals with progressively fewer errors as the object-reward mappings switch across seven serial reversals. The red curve in Figure 4A illustrates that selective bilateral amygdala lesions have no effect on learning these object-reward reversals (75, 91). Bilateral lesions of PFO

(Figure 4A, blue), however, significantly slow reversal learning (91, 92), a finding that has been replicated many times (93). Taken together with the results from the devaluation task, these results show that PFO contributes to updating valuations in two ways: (1) by registering the changes in outcome value as they occur, a function mediated via interaction with the amygdala, and (2) by registering changes in object-reward mappings.

A common interpretation of such reversal deficits invokes the concepts of 'perseveration' and 'response inhibition'. According to this view, the monkeys persist in choosing a previously rewarded object because of a deficiency in using the negative feedback to avoid choosing it. Sometimes negative feedback is simply the absence of reward, but aversive feedback also is processed within PFO (88) and could function in the same way. These conclusions have figured prominently in ideas about MDD and other anxiety and mood disorders, but recent monkey research has overturned those interpretations of reversal deficits. Instead of a failure to use negative feedback, and in contrast to accounts in terms of response inhibition or perseveration, new findings point to a greater importance of positive feedback guiding choices in this task (91).

This insight has come from a more detailed analysis of behavior than attempted previously. Previous studies only measured proportions of correct or incorrect choices averaged over blocks of trials. A more detailed, trial-by-trial analysis indicates that both PFO and amygdala lesions influence the use of positive feedback. As Figure 4B shows, however, they do so in opposite directions. Rudebeck and Murray (91) compared performance one trial after an error (called trial E+1), one trial after an error-correct sequence (EC+1), one trial after an error-correct-correct sequence [EC(2)+1], and so forth. This analysis shows that PFO lesions cause an inefficiency in using positive feedback (blue asterisks in Fig. 4B). Even when two, three, or four correct (and rewarded) responses intervene between an error and an upcoming choice, monkeys with PFO lesions make many more errors than do intact control monkeys. Similar findings have been reported in marmoset monkeys (94).

In contrast to the deficits seen after PFO lesions, selective bilateral amygdala lesions cause an *improvement* in using positive feedback to make future choices (red asterisk in Fig. 4B). After performing one correct (rewarded) trial following an error (the EC+1 trial type), monkeys with amygdala lesions out-perform intact monkeys in their future choices. (With more consecutive correct choices, this effect disappears, perhaps because the scores approach the maximum.) An intact amygdala, therefore, seems to diminish the monkey's efficiency in using positive feedback to perform the reversal task. We think that this occurs because the amygdala mediates a positive affective response to objects that have a prior history of reward. This positive affective response makes it harder for intact monkeys to avoid choosing the (now) incorrect object after a reversal. Figure 3B shows that amygdala lesions cause a sharp decrease in autonomic arousal responses to the anticipation of food availability. This probably reflects a blunted affective response, as well. In the context of object reversal learning, therefore, the absence of the amygdala and the positive affective response that it mediates may well translate to an improved ability to resist choosing the highly valued (but now incorrect) object.

Buckley et al. (95) applied the same trial-by-trial analysis to data from monkeys with PFO lesions that had been trained on an analog of the Wisconsin Card Sorting Task. In these tasks, traditionally attributed to frontal lobe function, subjects sort cards according to rules determined by one of several sensory dimensions, such as the color on the card, the number of items, or their shape. In the version of the task used in monkeys, the animals need to switch between color and shape rules. Whereas preoperatively their monkeys scored 77% correct on the EC+1 trial type, postoperatively the monkeys with PFO lesions scored only 50% correct. Like the monkeys studied by Rudebeck and Murray (91), the PFO lesion group

studied by Buckley et al. was inefficient in using positive feedback after rule changes, suggesting that PFO plays an important role in the valuation of rule representations as well as object representations.

These findings indicate that PFO lesions cause a deficit in using positive feedback, but not in the use of negative feedback (91, but cf. 94). Put the other way around, the intact PFO functions to enhance efficiency in using positive feedback to update valuations of objects and rules. The trial-by-trial analysis shows that the reversal deficit caused by PFO lesions should not be interpreted in terms of response inhibition, behavioral inhibition, or an inefficiency in “avoiding” objects based on negative feedback (either in the form of aversive feedback or the absence of expected reward). Perseveration occurs to a small extent, but it appears to be a minor aspect of the “PFO syndrome”. Rather, the deficit appears to result from an inefficient usage of positive feedback to update the particular values of object-outcome mappings and rule-outcome mappings. This updating needs to occur in order to make good choices in the serial object-reversal task (91) and when making object choices that optimize the probability of reward (90).

Several lines of evidence point to medial frontal areas as playing a key role in linking actions with outcomes, in parallel with the results just mentioned on linking object or rule representation with outcomes. Kennerley et al. (96) found that lesions of the anterior cingulate cortex, a key part of MFA, impair the use of positive feedback to stay with correct actions after action reversals. This finding agrees with an extensive literature pointing to medial frontal areas as being especially important in generating actions (97). Rudebeck et al. (90) likewise studied the effects of PFO and anterior cingulate cortex lesions on learning object-reward and action-reward associations in their study of probabilistic object-reward mappings. They found that PFO lesions produced a deficit in stimulus-based, but not action-based learning, whereas anterior cingulate cortex lesions had the opposite effect.

Along the same lines, Hadland et al. (98) studied the effect of lesions of the MFA on the ability of monkeys to link two different actions with two different food rewards. The monkeys learned that Food 1 instructed Action 1 on a joystick, which, if performed correctly, produced more of Food 1. Likewise, Food 2 instructed Action 2, which produced more of Food 2. The bilateral removal of the MFA (area 24, area 32, and the cingulate motor areas) caused impairments in choosing the action instructed by the food. This deficit did not result from an inability to tell Food 1 from Food 2 by sight: the same monkeys had normal abilities in object discrimination. Instead, these findings indicate that the MFA contributes to associating actions with outcomes.

Convergent findings come from a variant of the devaluation task. Using a devaluation task with actions rather than objects, Rhodes and Murray found that prefrontal cortex (area 32) of monkeys was essential for updating values associated with actions (unpublished observations). In addition, neurophysiological studies in awake, behaving monkeys have revealed that neurons in MFA signal the value of expected rewards (89).

To sum up the monkey research presented thus far, it appears that PFO plays a role in updating the value of object and rule representations, MFA plays a role in updating the value of action representations, and the amygdala updates the cortical representations of outcome valuations as they change. One implication of these findings for MDD might be that patients with dysfunction in medial frontal areas could have problems in properly valuing actions, whereas those with dysfunction in orbital frontal areas could have problems evaluating ‘things’. Furthermore, the findings in monkeys indicate that positive feedback has a more important role in updating the valuation of representations than does negative feedback. If frontal cortex dysfunction leads to an inefficiency in using positive feedback, as opposed to

normal efficiency in using negative feedback, this imbalance could have important implications for MDD. It could, for example, account for the ‘negativity bias’ that is consistently observed in both the behavior and neuroimaging of depressed individuals. But to strengthen the link to MDD, we need to introduce the concept of self-representation.

Role of prefrontal cortex in self-representation

The first step in linking representations of self to a value could be linking representations of one’s actions to a rewarding outcome (97). As discussed above, converging evidence from studies in monkeys suggests that the MFa is essential for linking actions with the value of predicted outcomes. In humans, there is evidence for the representation of both outcomes and actions in PFm and MFa. Lau et al. (99) attempted to identify action representations by studying the enhancement of activation that occurs when people attend to their actions. They found such an enhancement in the cingulate motor area when subjects attended to their movements. Neuroimaging studies in humans confirm that activations in anterior cingulate cortex are related to the learning of action-outcome associations, but not to learning stimulus-outcome associations (100).

Passingham et al. (97) have developed this idea to include the concept of self-representation. They suggested that attention to action develops into attention to intentions and reflections on self. They also propose that PFm and MFa represent one’s own thoughts and intentions. Several lines of neuroimaging evidence suggest that regions involved in representing actions are also involved in representing ‘self’. First, reflecting on one’s internal state (101,102) or on whether particular trait words apply to oneself (103) increases activation in the dorsal anterior cingulate cortex (area 24 of the MFa). Second, MFa shows activation when people consider personality characteristics about themselves or receive social feedback about themselves from others (104,105). Third, episodic memory retrieval causes activations in PFm and MFa that are specific for remembered events, as opposed to recently constructed (imagined) ones (106). Thus, retrieving events in which one’s self is embedded involves the PFm and MFa. Presumably, these areas are also engaged in the processing of events as they occur. Fourth, PFm and MFa show activations when humans reflect on the thoughts and intentions of others (107,108). These medial frontal regions, therefore, have been implicated in both theory of mind (inferring the mental states and intentions of others) and social cognition. According to Passingham et al. (97), inferring the intentions of others arises from the importance of these regions in representing one’s own intentions through self-reflection.

There is also evidence for a role of PFO and OFa in the evaluation of ‘self’. In one experiment (109), patients with bilateral damage to either PFO or OFa (or both) and healthy controls took part in a structured interview with a stranger. Patients with bilateral PFO or OFa damage, despite having an expressed understanding of the social conventions regarding conversations between strangers, behaved inappropriately as judged by objective observers. Furthermore, the patients consistently underestimated the extent of their inappropriate behavior based on their memory of what they had done. In a sense, they overvalued their social performance. After watching a videotape of their own interview, they changed their assessment. The patients then downgraded their behavior, based on how socially embarrassing their behavior had been, but they did not change their ratings of other (nonsocial) factors. These findings support the idea that PFO and OFa contribute to valuations of ‘self’, or at least of one’s own actions. The valence of the lesion effect merits emphasis: the lesion patients overrate their performance. Therefore, it seems that intact orbital frontal cortex functions to diminish the ratings of self and one’s own behavior.

The experiment just mentioned dealt with the fact that self-evaluations are reliably more positive than evaluations made by external observers. PFO also contributes to another widely

known human trait: Self-evaluations are also more positive than the evaluations of others (110). Healthy individuals were asked to rate themselves, in comparison to their average peers, on several personal traits. The valence of judgments, positive or negative, was reflected in activation levels observed in MFa, somewhere in or near area 25 [see also (105)]. Of special interest, activations in PFo correlated with how much each person's valuation of 'self' exceeded their valuations of others. The less positively people rated themselves relative to others, the greater the activation level in the medial PFo [and to a lesser extent also in the dorsal anterior cingulate cortex (area 24), a part of the MFa]. Again, the valence of these effects merits emphasis: increased activation of PFo seems to correlate with a 'negativity bias' for self-evaluation.

The idea that a healthy PFo contributes to a 'negativity bias' in self-evaluation has potential implications for MDD. In healthy individuals, PFo's influence—perhaps on representations of 'self' emerging from interactions between PFm and MFa—could contribute a 'dose of reality' to evaluations of one's own worth and value. This influence probably serves an adaptive social function, mitigating selfishness and other undesirable traits. As such, the 'dose of reality' is a good thing. Too much of that 'good thing', however, could cause representations of 'self' to decrease in value and remain low. Taken too far, the low self-esteem seen in MDD could result. We argued earlier that positive feedback plays a more important role in PFo function than does negative feedback. Putting this idea together with a 'dose of reality' function, we imagine that with some forms of PFo dysfunction positive feedback cannot efficiently mitigate factors that decrease self-valuations. In that case, the influence of PFo on self-representations in PFm and MFa could become increasingly negative. The 'dose of reality' could become an overdose. Positive events related to oneself would fail to promote an enhancement of self-worth when warranted, and might not even be computed by the brain. An impairment in autobiographical memory for positive events, a common feature of MDD (29), could reflect this kind of dysfunction.

We see two possibilities, one related to dysfunction in PFo, the other to normal PFo function. Perhaps depressed patients have an overactive PFo, a finding generally supported by the literature (40). On this view, a diminished effect of positive feedback could lead to an 'overdose of reality', as discussed above. But another possibility is that PFo functions normally to moderate a sense of self-worth as appropriate, and the deficiency results from a weakened positive influence on self valuation, perhaps in PFm and MFa. Either case would lead to a 'negativity bias'. The effect of treatments on this bias is taken up in the section '*Brain activation in MDD before and after treatment*'.

But there is another aspect of negativity bias that is worth considering here. Psychiatric illness rarely appears without a history, and MDD emerges during a patient's life. The current valuation of self must be affected by past valuations, and early valuations could have long-lasting effects. Furthermore, there is reason to think that self valuations are especially resistant to change because of a particular way in which they differ from other valuations. Whereas a food, for example, can be both wanted and liked—motivational and hedonic valuation, respectively—one's self cannot be *wanted* in the same sense. That is, self valuations are inherently hedonic and not motivational. Common experience shows that wants change quickly, but likes change slowly. One can become sated on chocolate in a matter of minutes and not want it then, but one's liking of chocolate does not change so fast. Thus the hedonic nature of self valuation could make it especially persistent, and this could explain why negativity biases are so difficult for MDD patients to overcome.

Hyper-emotionality in the absence of an expected event

We now take up Pavlovian conditioning and autonomic responses. Earlier, we pointed out that autonomic abnormalities occur commonly in MDD, and here we link these symptoms with PFO and amygdala function in monkeys. Depressed MDD patients show abnormally elevated activation in PFO during Pavlovian conditioning. These activations occur in PFO area 111, along the lateral orbital gyrus, during the anticipation of potential monetary losses and gains (40).

In work involving the Pavlovian conditioning of marmosets, Roberts and her colleagues have studied the role of PFO and the amygdala in autonomic responses. As already mentioned, marmosets with amygdala lesions show impaired anticipatory autonomic responses to expected food rewards. They have, for example, a smaller systolic blood-pressure response to the sight of a highly-valued food that will become available in 20 s (Fig. 3B) (111). This finding complements findings from neurophysiological studies in monkeys showing that amygdala neurons not only signal the value of conditioned and unconditioned stimuli (positive and negative) during Pavlovian learning (112,113), but also are active in relation to skin conductance responses (114).

In another, more typical form of Pavlovian conditioning, a tone (called the conditioned stimulus or CS) indicates the future availability of a food reward (the unconditioned stimulus or US). In that case, Reekie et al. (115) found an effect of PFO lesions on autonomic responses. On a probe test in which the CS stops and the predicted reward fails to appear, marmosets with PFO lesions maintain an abnormally high level of arousal (Fig. 4C).

These findings have important implications for MDD, although we acknowledge that our argument is somewhat indirect. First, we take a very liberal view of the findings summarized in this section. They involve a positive affective response when the CS predicts food availability. We will assume, however, that negative affective responses would be similarly affected by PFO and amygdala lesions. As a result, we predict that when MDD patients anticipate a negative event, a circumstance that is often described as 'dread', their PFO dysfunction will lead to an abnormally persistent negative affective response when the dreaded event fails to occur. This prediction is the 'aversive' analogue to what Figure 4C illustrates for a positive event. Our prediction gains some support from the results of Siegle et al. (63), who found that activation of the amygdala in response to self-referential negative or sad words persists for an abnormally long time in MDD patients.

To understand the possible consequences of an abnormally persistent affective response, we need to consider another line of animal research, one that indicates that the non-occurrence of predicted events leads to enhanced Pavlovian learning: the Pearce-Hall effect. In Pavlovian conditioning, as the CS becomes a more accurate predictor of the US, its associability declines. Pearce and Hall (116) found that when an extinction trial occurred after extended CS-US training, there was better learning of associations between the CS and a new US. An extinction trial is one in which the CS occurs, but the US does not. This is exactly what Reekie et al. (115) did in their experiment on marmosets. Within the Pearce-Hall model, this enhancement in the associability of a CS occurs because of the discrepancy between the predicted reinforcer (the US) and the received reinforcer. This difference is said to produce "surprise".

If the situation is similar in MDD, the same situation that causes abnormally prolonged affective responses also could cause enhanced learning about a CS. The results of Reekie et al. (115) provide the first part of this maladaptive package: PFO damage causes an autonomic and emotional arousal response that is abnormally prolonged when some dreaded event fails to materialize (Fig. 4C). The Pearce-Hall model provides the second part. It

suggests that the failure of the event to materialize leads to enhanced associability of a CS. Putting the two parts together, it is easy to suppose that the CS can become linked to the prolonged, negative affective response associated with the expected event.

The Pearce-Hall effect could partially account for the “catastrophic response to failure” exhibited in depressed subjects, who show an exaggerated affective response to spurious negative feedback on probabilistic reversal learning tasks (21). This effect is associated with an attenuation of the normal activation of ventral PF cortex (areas 12/47 and 45) and a failure of the normal deactivation of the amygdala as they perform this task (117). Reversal tasks could involve Pavlovian conditioning because, independent of their choices, subjects learn about the association of stimuli (CSs in this context) with outcomes. If a stimulus is not followed by a good outcome as predicted, as is certain to occur in probabilistic and reversal-learning tasks, this negative feedback resembles an extinction trial. In the presence of PFO pathology, the CS could then be associated with the abnormally persistent autonomic and affective response caused by the negative feedback in the context of prefrontal dysfunction.

There is another potential relevance to MDD. Typically in Pavlovian conditioning, a discrete cue (the CS) is the best predictor of the US. If no discrete cue predicts an outcome, however, the generalized context becomes the best predictor, albeit a poor one. When an aversive event becomes linked to a context, that context serves as a constant reminder of the US, putting the subject in “a sustained state of fearful apprehension” (118). This idea has been most clearly articulated in discussions of post-traumatic stress disorder, panic disorder, and generalized affective disorder (GAD) (118), although each of these conditions commonly occurs co-morbidly with MDD. Moreover, GAD and other anxiety disorders are frequent antecedents of MDD and increase the risk of developing “secondary” major depressive episodes (119). If a similar phenomenon occurs in MDD, the failure of a dreaded event to materialize would lead to increased associability of the context that predicts that event. The context could then become linked to the negative emotions associated with the anticipation of such events. Thus, a beneficial turn of events—the failure of a dreaded event to materialize—would have the perverse consequence of linking a generalized context with the negative affective response that the dreaded event would have produced.

Brain activation in MDD before and after treatment

Up to this point, we have proposed that the problem in MDD involves orbital and medial frontal areas and their interactions with the amygdala, including both the granular prefrontal areas unique to primates and the agranular frontal areas shared with other mammals. We also have proposed a pathophysiology involving the valuation of ‘self’, along with the valuation of object, action, and rule representations.

In this section, we revisit some of the issues raised earlier, with a focus on treatment and remission effects and future research. In the section ‘*Neuroanatomical correlates*’, we mentioned several findings implicating orbital and medial frontal cortex, along with the amygdala, in MDD. However, certain factors make these results difficult to interpret. Notably, the reduction in gray matter volume in some parts of MFA and PFO can be sufficiently prominent to produce partial volume effects in functional brain images, yielding complex relationships between activation measures and depression severity (120). For example, metabolic activation appears elevated in depressed samples of mild-to-moderate severity, but reduced in more severe, treatment-refractory cases (1,121) These variables make treatment and remission effects difficult to interpret.

Despite this limitation, many functional neuroimaging studies on MDD have made observations on treatment and remission effects, as reviewed elsewhere (122,123). In

general, they show that the depressed phase of MDD, relative to the remitted phase, correlates with increased activation in an extended anatomical network that includes portions of the medial (MFa and PFm) and orbital frontal cortex (PFo), together with the medial and anterior temporal lobe (including the amygdala). This pattern of results occurs in depressed patients studied before versus after treatment, and in remitted patients studied before versus during depressive relapses. Also relevant is evidence that distinct medial frontal structures mediate opponent processes in emotional behavior (124). Regions where neuroimaging activation correlates positively with depression severity include parts of MFa (areas 24 and 25) and PFm (the ventromedial frontal pole cortex, area 10p) (39,125,126). Activation decreases in these regions during both antidepressant treatment and deep brain stimulation of the subgenual MFa or the anterior capsule (4,126–128). Conversely, in recovered MDD patients who relapse when challenged with serotonin or catecholamine depletion, metabolism increases in these regions as the depressive symptoms return (125,129). These findings support the contention that both the primate-specific parts of the medial frontal cortex (PFm) and the phylogenetically older areas shared with other mammals (MFa) have correlates with MDD. These structures are not the only ones implicated in MDD, of course. Additional structures include the mid- and posterior cingulate cortex, ventromedial striatum (including the nucleus accumbens), and the medial thalamus, among others (8).

In the section '*Prefrontal cortex and amygdala function in reversal tasks*', we discussed the role of frontal cortex in learning stimulus-outcome relations. The neuroimaging literature provides support for the link between stimulus-outcome learning and the brain systems described here, as well as for dysfunction involving these systems in MDD. Before treatment, MDD patients show an impairment in the tendency to modulate behavior as a function of prior reinforcement. For example, Pizzagalli et al. (22) showed that while performing a probabilistic reward task, MDD patients showed significantly reduced reward responsiveness compared to healthy controls. In the absence of immediate reward, i.e., when they needed to predict an outcome, MDD patients were impaired at integrating reinforcement history over time and in expressing a response bias toward a more frequently rewarded cue. This selective impairment correlated with self-reported anhedonia. These patients had less activation in response to gains in the left nucleus accumbens and the caudate nucleus in both hemispheres (130), parts of the basal ganglia that are the targets of corticostriatal projections from OFa, MFa, PFo, and PFm (131). A decrease in nucleus accumbens activation is also seen in remitted MDD patients for pleasurable foods, a finding pertinent to anhedonic symptoms (132). Furthermore, depressed individuals fail to sustain nucleus accumbens activation over time compared with controls, which correlates with individual differences in self-reported positive affect (133). Recent research in rodents points to a role for the nucleus accumbens in incorporating cost functions into decision making, mainly in terms of effort costs (134). An underestimation of benefits or an overestimation of effort cost could contribute to both anhedonia and abulia in MDD. Corticostriatal projections from the agranular areas target the nucleus accumbens, and those from the granular prefrontal areas terminate in the caudate nucleus. Both could play a key role in the valuations that depend on object-outcome and action-outcome mappings. Future studies on the effect of treatments on estimations of cost and benefits could prove informative, especially in relation to corticostriatal activation.

In the section '*Hyper-emotionality in the absence of an expected event*', we discussed Pavlovian learning. In appetitive and aversive versions of Pavlovian conditioning, Martin-Soelch et al. (135) showed that MDD patients were impaired at learning the association between a CS and outcomes. During appetitive learning, the MDD patients showed less activation in the left PFo cortex and in the amygdala bilaterally compared to healthy controls. During aversive learning, the MDD patients showed less activation in PFo

bilaterally. Treatment effects on Pavlovian associations involving representations of self could prove particularly useful in understanding MDD.

Finally, in the section '*Role of prefrontal cortex in self-representation*', we discussed the 'negativity bias' seen in MDD. Using a backward masking paradigm, Victor et al. (28) presented both MDD patients and healthy controls with sad, happy, or neutral faces for 26 ms and then masked the first face with a neutral face. Because of the masking procedure, neither group gained a conscious awareness of the emotional valence of the first face. Healthy controls showed greater amygdala activation and faster behavioral responses to *happy* faces, compared to sad or neutral faces. This finding agrees with evidence that healthy humans show a processing bias toward positive stimuli. In contrast to this 'positivity' bias, both depressed and remitted MDD patients—when off medication—showed greater amygdala activation and faster behavioral responses to *sad* faces, compared to happy faces. This 'negativity bias' persists despite their lack of awareness about the valence of the masked face. Importantly, the negativity bias disappeared following antidepressant treatment with the selective serotonin reuptake inhibitor, sertraline. During successful treatment, MDD patients exhibited the normal bias toward happy faces, and this behavioral improvement correlated with neuroimaging results from PFO; before treatment, PFO showed no activation in response to happy faces, whereas during successful treatment a robust activation occurred in response to such stimuli.

Summary and conclusions

Historically, neurologists have identified brain regions where damage or disease has caused their patients' symptoms. In contrast, the localization of dysfunction in major psychiatric disorders has taken a back seat to pharmacologic and genetic studies. Nevertheless, neuroimaging and clinical studies have repeatedly implicated PFO, PFm, OFa, MFa, and the amygdala in MDD. In parallel, studies of nonhuman primates have pointed to the homologues of these brain structures as fundamental to affective responses and processing reward feedback.

Here, using insights gained mainly from the study of nonhuman primates, we suggest how dysfunction in amygdala–frontal interactions could produce certain key symptoms of MDD. This research shows that the amygdala updates the valuation of cortical representations. In monkeys, these valuations involve either objects, rules, or actions, but humans have in addition a representation of self. Problems with the valuation of self could produce low self-esteem. Understanding how the frontal lobe functions in the valuation of object-, rule-, and action representations in nonhuman primates will illuminate how homologous areas function in the valuation of self in humans. Beyond self-valuation, problems with the valuation of objects, behavioral rules, and actions could produce the anhedonia, apathy, and abulia that often characterizes MDD.

Two other lines of animal research indicate that when an emotional event fails to materialize, PFO lesions lead to an abnormally persistent autonomic and emotional response and CSs become more associable. Pavlovian learning mechanisms could then link CSs, stimuli that predict the emotional event, with the abnormally persistent autonomic and emotional responses and thus contribute to the 'negativity bias' common in MDD.

Additional monkey research suggests a more specific cause of MDD. This research, overturning ideas about frontal 'perseveration' and 'response inhibition', shows that PFO and PFm mediate the efficient use of positive feedback to update the valuation of cortical representations. Extended to a representation of 'self', dysfunction of this process could contribute to low self-esteem, a key feature of MDD. In humans, decreased activation in and

lesions of PFO correlate with excessively high self-esteem (109,110). These findings suggest that, when intact, PFO could provide self-representations in PFM and MFA with a ‘dose of reality’ to moderate exaggerated self-esteem. In cases of PFO dysfunction, inefficient use of positive feedback combined with this ‘dose of reality’ function could lead to representations of ‘self’ acquiring a negative valuation that becomes difficult to reverse.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute of Mental Health.

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Figure 1.

Cytoarchitectonic maps of the medial (top) and orbital (bottom) frontal cortex from humans (A) and macaque monkeys (B), based on the analysis of Price and his colleagues (16,17).

Abbreviations: cc, corpus callosum; ig, induseum griseum; Ia, agranular insular cortex (pl, posterolateral; pm, posteromedial; l, lateral; m, medial; i, inferior); G, gustatory cortex; PL, prelimbic cortex; IL, infralimbic cortex; AC, anterior cingulate cortex.

Figure 2.

Regions from which electrical stimulation elicits autonomic effects. The stippling shows the regions of a macaque monkey brain from which autonomic responses can be evoked. Left: A, granular and dysgranular insular cortex; B, anterior insular cortex; C, caudal orbitofrontal cortex; D, inferior temporal cortex, F, temporal pole. Right: A, subgenual anterior cingulate cortex; B, anterior cingulate cortex; C, infralimbic cortex; D, temporal pole. From Kaada et al. (59).

Figure 3.

Effect of bilateral ablations or crossed disconnections on the devaluation effect (A) and blood-pressure changes in anticipation of food (B). Abbreviations: PFo, monkeys with bilateral lesions of the orbital prefrontal cortex; Amyg, monkeys with bilateral excitotoxic lesions of the amygdala; PFo x Amyg, monkeys with surgical disconnection of PFo in one hemisphere from the amygdala in the other hemisphere; Control, unoperated monkeys; mmHg, millimeters of mercury.

Figure 4. Effect of bilateral ablations of PFO or amygdala on object-reversal learning (A and B) and conditioned blood pressure changes (C). Abbreviations: PFO, monkeys with bilateral lesions of orbital prefrontal cortex; Amyg, monkeys with bilateral excitotoxic lesions of the amygdala; Control, unoperated monkeys; mmHg, millimeters of mercury; E+1, the trial after an error; EC+1, the trial after a sequence of error-correct; EC(n)+1, the trial after an error trial followed by n correct trials; CS+, conditioned stimulus; R, reversal; Init, initial training on object discrimination.