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REVIEW

Functional anatomy of ventromedial prefrontal cortex: implications for mood and anxiety disorders

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In recent years, an increasing number of neuroimaging studies have sought to identify the brain anomalies associated with mood and anxiety disorders. The results of such studies could have significant implications for the development of novel treatments for these disorders. A challenge currently facing the field is to assimilate the large and growing corpus of imaging data to inform a systems-level model of the neural circuitry underlying the disorders. One prominent theoretical perspective highlights the top–down inhibition of amygdala by ventromedial prefrontal cortex (vmPFC) as a crucial neural mechanism that may be defective in certain mood and anxiety disorders, such as major depression and post-traumatic stress disorder. In this article, we provide a critical review of animal and human data related to this model. In particular, we emphasize the considerable body of research that challenges the veracity (or at least completeness) of the predominant model. We propose a framework for constructing a more comprehensive model of vmPFC function, with the goal of fostering further progress in understanding the neuropathophysiological basis of mood and anxiety disorders.
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Introduction

The development of novel treatments for mood and anxiety disorders will likely depend on a more comprehensive understanding of the underlying neural circuitry. Neuroscientific research on the pathophysiology of mood and anxiety disorders has identified dysfunction in a number of cortical and subcortical brain areas. Among these findings, abnormal activity in the ventromedial prefrontal cortex (vmPFC) is probably the most widely reported.[1–4] The precise role of vmPFC in such disorders, however, is not well understood. vmPFC consists of several subregions that can be differentiated by cytoarchitecture and anatomical connectivity. Thus, a promising step toward elucidating the neural mechanisms underlying mood and anxiety disorders is to more fully characterize the functions of the various subregions of vmPFC.

A prominent neurobiological model of vmPFC's role in emotion maintains that it serves to suppress negative affect by inhibiting amygdalar output.[3,5–27] Although there exists a substantial corpus of data to support this account, in our view there is also a considerable amount of evidence that appears to advise against it. In this article, we review data from both types of studies, and we discuss the need for a more fine-grained model that can better account for vmPFC's seemingly disparate roles in affective states. We believe that a more comprehensive model of vmPFC function will promote translational research as well as augment the clinician's understanding of the psychobiological basis of mood and anxiety disorders.

We begin the article by providing an overview of vmPFC anatomy (section 'Anatomy'). Next, we examine a number of studies on fear extinction in rodents, which have been particularly influential both in the development of models that emphasize top–down inhibition of amygdala by vmPFC (section 'Fear extinction in rodents'), and in the use of such models as frameworks with which to interpret a wide range of human imaging data related to major depression, human fear extinction, phobic disorders and post-traumatic stress disorder (PTSD) (section 'Major depression, PTSD and anticipatory anxiety'). We then go on to argue that although a fair amount of data accord with this use of top–down inhibitory models in the interpretation of human imaging data, other studies challenge it by suggesting that vmPFC activity may underlie, rather than inhibit, the experience of negative affect. Finally, in section 'Alternative model', we outline a path toward developing a more comprehensive model of vmPFC function. In this

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section, we present data from a variety of studies that, when considered together, suggest that the diverse roles of vmPFC in affective states may result from broad functional differences between two anatomical vmPFC subregions. One subregion consists of the more posterior areas of vmPFC and appears to be positively associated with negative affect, whereas the other subregion consists of areas anterior and ventral to the genu of the corpus callosum and appears to be positively associated with positive affect.

The overall aim of the article is to foster further progress in understanding the neurobiological basis of mood and anxiety disorders.

Anatomy

Given that data regarding the relationship between emotion and vmPFC come from studies on a variety of animals—including rats, mice, monkeys and humans—we begin with a discussion of anatomy that compares and contrasts various subregions of vmPFC both within and between species.

The rat medial PFC can be divided into two subregions: the infralimbic cortex (IL) and prelimbic cortex (PrL). IL is located in a more ventral region of rat mPFC, whereas PrL is located in a more dorsal region. Although cross-species homologies can be difficult to determine, some investigators have suggested that rat IL is homologous to Brodmann's area 25 in monkeys[28] and humans,[16,29] and that rat PrL is homologous to Brodmann's area 32 in monkeys[28] and humans.[16] It is worth noting, however, that certain complications arise when comparing Brodmann's area 32 between monkeys and humans. In particular, Brodmann[30,31] indicates that his own delineation of area 32 in humans is *not* homologous to his delineation of area 32 in monkeys. In accordance with this, Ongür *et al.*[32] provide a more recent analysis of human area 32, which divides area 32 into two subregions (Figure 1). One human 32 subregion (32pl) is similar to monkey area 32, both in terms of location—both are situated ventrocaudal to the genu of the corpus callosum—and cytoarchitecture. The other human 32 subregion (32ac) lies dorsoanterior to the genu of the corpus callosum, in a position similar to that of monkey area 24c. Moreover, human 32ac and monkey 24c share important cytoarchitectural similarities, such as relative densities of pyramidal cells, leading Ongür *et al.*[32] to hypothesize that the two regions may be related.

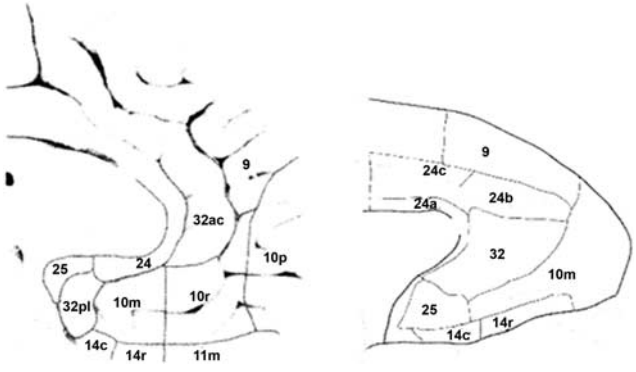

Figure 1 Subdivisions of medial prefrontal cortex (PFC) in human (left) and monkey (right). Reprinted from Ongür *et al.*[32]

Given these more recent subdivisions of area 32, the above claim—that rat IL is homologous to Brodmann's area 25, while rat PrL is homologous to Brodmann's area 32—could mean one of two things:

1. (i) Rat IL is homologous to human and monkey 25, while rat PrL is homologous to human 32pl and monkey 32.
2. (ii) Rat IL is homologous to human and monkey 25, while rat PrL is homologous to human 32ac and monkey 24c.

Anatomical connectivity data seem to support (i). Efferent projections from rat IL are similar to those of monkey 25, whereas the efferent projections from rat PrL are similar to those of monkey 32.[33–39]

However, data on fear conditioning and extinction raise certain complications for this picture. A number of studies on rats suggest that activity in PrL underlies the expression of conditioned fear,[27,40,41] whereas activity in IL underlies the extinction of conditioned fear.[10,27,41,42] Thus, assuming that (i) is true, one would expect for activity in human 32pl to positively correlate with expression of conditioned fear, and activity in human 25 to positively correlate with extinction of conditioned fear. But contrary to this expectation, human imaging data suggest that the regions that positively correlate with successful recall of fear extinction lie anterior to 25 (for example, 10m and 10r)[12,15,43] (see Figure 2, image 5E), whereas the regions that positively correlate with the expression of conditioned fear lie primarily in the dorsal anterior cingulate (which includes dorsal 32ac and dorsal 24).[15,44] Thus, these functional data stand in tension with (i). Moreover, they also stand in tension with (ii), in that they suggest that regions such as 10m and 10r (rather than 25) underlie successful recall of fear extinction.

One potential explanation of the apparent discrepancies between the anatomical and functional data concerns the fact that area 25 often suffers from signal dropout in functional magnetic resonance imaging studies. As primate vmPFC exhibits a significant pattern of posterior to anterior projections,[34] the extinction-related activity that is observed in more anterior regions of human vmPFC may, perhaps, be a downstream effect of extinction-related activity in area 25. However, until further evidence exists on whether activity in primate 25 does in fact positively correlate with successful recall of fear extinction, we believe it is premature to draw parallels between the neural mechanisms underlying fear extinction in rats and those underlying fear extinction in primates.

With these anatomical considerations in mind, we now move to the primary focus of the paper: how interactions between vmPFC and amygdala contribute to particular affective states.

Fear extinction in rodents

Perhaps the most influential data regarding the interactions between vmPFC and amygdala have been obtained from fear extinction studies in rats. Such studies have led a number of investigators to conclude that rat IL serves to suppress conditioned fear by inhibiting the central nucleus of the amygdala.[8,10–12,14,16–18,21–25,27] In support of this proposal, it has been found that both lesions of rat IL[42] and temporary inactivation of rat IL[22,41] impair recall of fear extinction. Furthermore, Milad and Quirk[10] found that IL neurons tended to fire during extinction recall, but not during fear conditioning or extinction learning. Taken together, these findings suggest that IL has a particularly important role in extinction recall.

Further data suggest that IL is not only important for the recall of fear extinction, but may also have a critical role in the formation of extinction memories. Milad and Quirk[10] found that stimulation of rat IL (during the presentation of a conditioned tone) impairs expression of conditioned fear, while Vidal-Gonzalez *et al.*[27] showed that stimulation of rat IL (during extinction training) enhances recall of fear extinction.

Although the precise mechanisms by which IL comes to extinguish conditioned fear are not fully understood, a common suggestion pertains to a group of inhibitory neurons within the amygdala—the intercalated (ITC) cells. IL appears to send moderate to heavy projections to ITC cells.[8,39] This is relevant for at least two reasons: first, lesions of rat ITC cells impair the expression of fear extinction,[45] and second, administration of neuropeptide S into mouse amygdala (which increases glutamatergic transmission to ITC cells) reduces anxiety and accelerates fear extinction.[46] Such findings have led a number of investigators to argue for a top–down model of emotion regulation in which (i) IL sends excitatory signals to ITC cells, (ii) ITC cells send inhibitory signals to the central nucleus of the amygdala (CeA) and (iii) the inhibition of CeA attenuates fear-related behavior.[14,16,20,25,27]

This model is a further extension of the more general claim (noted in the beginning of this section) that IL serves to suppress fear by inhibiting CeA output. With this in mind, consider how such models pertain to data on humans and other primates. As noted in section 'Anatomy', data from comparative anatomy suggest that rat IL is homologous to a particular subregion of primate vmPFC (area 25), while fear extinction studies suggest that both rat IL[10,22,27,41,42] and primate vmPFC[12,15,43] have a significant role in the successful recall of fear extinction.

Given the claim that rat IL serves to suppress fear by inhibiting CeA output, the functional similarities between rat IL and primate vmPFC may seem to invite parallel claims regarding the role of primate vmPFC. Indeed, some investigators have suggested that primate vmPFC, like rat IL, serves to suppress fear by inhibiting CeA output.[6,7,12,14,19] Consequently, there are two claims that deserve consideration:

1. (C1) Rat IL serves to suppress fear by inhibiting CeA output.
2. (C2) Primate vmPFC serves to suppress fear by inhibiting CeA output.

It is worth recalling, however, that although rat IL is homologous to primate 25 (a particular subregion of primate vmPFC), the human functional data suggest that successful recall of fear extinction positively correlates with regions that lie anterior to area 25 (for example, 10m and 10r).[12,15,43] Thus, until further evidence exists about the precise relationship between activity in primate 25 and successful recall of fear extinction, there remain significant restrictions on the extent to which one can draw inferences from what is known about the neural mechanisms by which rat IL comes to extinguish conditioned fear to claims about the neural mechanisms by which primate vmPFC comes to extinguish conditioned fear; especially since a number of anatomical studies make clear that areas such as 10m and 10r share little connectional similarity to either primate 25 or rat IL.[32–39,47]

Putting this issue aside for now, there is yet another issue that we would like to consider in more detail: the fact that hypotheses such as (C1) and (C2) are often used as frameworks with which to interpret neuroimaging findings on mood and anxiety disorders.[1,3,6,12,14,15,19,26] Although a fair amount of data seem to accord with this use of (C1) and (C2), we submit that data from additional studies provide reason to be wary of this use of (C1) and (C2).

Major depression, PTSD and anticipatory anxiety

Major depressive disorder

Consider, for instance, how (C1) and (C2) pertain to studies on major depressive disorder (MDD). A number of imaging studies suggest that patients with MDD exhibit abnormally high levels of activity within vmPFC (particularly in the subgenual cortex).[48–52] In addition, MDD patients who are responsive to antidepressant medication tend to exhibit decreased activity in the subgenual cortex after drug treatment,[51,53] and Mayberg *et al.*[52] found that MDD patients who are responsive to deep brain stimulation (DBS) likewise exhibit decreased activity in subgenual cortex after DBS treatment. These findings are especially relevant, as MDD is also associated with hyperactivity in the amygdala, and antidepressant treatment tends to decrease amygdalar activity in MDD patients.[54,55] It has further been found that activity within the subgenual cortex positively correlates with negative affect in healthy subjects,[56–58] and

that subgenual neurons tend to respond more to aversive stimuli than to positive or neutral stimuli.[59]

To accord with (C1) and (C2), such findings could be interpreted as evidence that heightened subgenual activity serves as a compensatory mechanism to downregulate the amygdala during times of negative affect (for a suggestion along these lines, see Drevets *et al.*[1]). This interpretation, however, faces some potential challenges. Mayberg *et al.*,[52] for example, suggest two possibilities regarding the mechanisms underlying the therapeutic effect of DBS on MDD: (a) DBS might activate inhibitory neurons and therefore decrease the net activity of the subgenual cortex, or (b) the high-frequency nature of DBS might cause deficits in metabolic activity or synaptic transmission (also see McIntyre *et al.*[60]). Hence, both possibilities—(a) and (b)—seem to suggest that subgenual hyperactivity is a cause (rather than a compensatory effect) of MDD. In direct support of this interpretation, Koenigs *et al.*[61] found that patients with damage to vmPFC are less likely to develop symptoms of depression. Similarly, recent studies by Scopinho *et al.*[62] and Slattery *et al.*[29] reveal that temporary inactivation of rat IL reduces symptoms of depression. Taken together, these findings seem to challenge the use of (C1) and (C2) in the interpretation of major depression. In particular, they appear to suggest that IL/vmPFC activity may actually underlie (rather than inhibit) symptoms of depression.

PTSD and anticipatory anxiety

Besides the use of (C1) and (C2) in the interpretation of MDD, some have also employed (C1) and (C2) in the interpretation of anxiety disorders, including PTSD, obsessive-compulsive disorder and phobic disorders.[6,7,12–14,19] In short, the proposal is that anxiety disorders may result from a failure of vmPFC to downregulate the amygdala. While this suggestion is consistent with much of the data on fear extinction (see sections 'Anatomy' and 'Fear extinction in rodents'), further data appear to challenge it.

First, we consider data on PTSD. Suppose, for instance, that it is correct that PTSD results from a failure of vmPFC to downregulate the amygdala.[7,12–14,19] Indeed, a number of human functional imaging studies associate PTSD with hypoactivity in vmPFC but hyperactivity in amygdala.[7,11,63,64] Given this proposal, one would expect lesions of vmPFC to *increase* one's risk of developing PTSD. Contrary to this expectation, however, work by Koenigs *et al.*[65] indicate that war veterans with damage to vmPFC are in fact *less* likely to develop PTSD. In accordance with this finding, at least two imaging studies have revealed heightened vmPFC activity in patients with PTSD.[66,67]

Next, we consider anticipatory anxiety. In a study by Simpson *et al.*,[68] in which anticipatory anxiety was induced in healthy subjects, vmPFC activity tended to decrease during anticipatory anxiety. At first glance, this result appears to contrast with the human lesion data from Koenigs *et al.*[65] But interestingly, Simpson *et al.*[68] also found that the degree to which vmPFC activity decreased (during anticipatory anxiety) *negatively correlated* with self-reported anxiety ratings. That is, subjects with the lowest levels of anxiety tended to exhibit the greatest decreases in vmPFC activity, whereas subjects with the highest levels of anxiety tended to exhibit the smallest decreases in vmPFC activity. In fact, the two subjects with the highest anxiety ratings even exhibited slight *increases* in vmPFC activity. Thus, the results of Simpson *et al.*[68] actually fit quite well with the human lesion data from Koenigs *et al.*,[65] and together these studies suggest that the pathological experience of negative affect characterizing anxiety disorders is not a straightforward result of defective top–down inhibition of amygdala by vmPFC.

vmPFC and stress-related responses

In light of the aforementioned findings, it is worthwhile to consider the relationship between vmPFC activity and stress-related symptoms, and in particular, how this relationship might pertain to mood and anxiety disorders.

Mood and anxiety disorders are often associated with dysregulation of both glucocorticoid and sympathetic responses. For example, war veterans with PTSD tend to exhibit abnormal increases in glucocorticoid levels, heart rate, blood pressure and skin conductance responses (SCRs) when presented with war-related stimuli;[69–72] and phobic subjects tend to exhibit these same responses when presented with phobic stimuli.[73–76] Similarly, patients with MDD tend to exhibit increased glucocorticoid levels, a higher resting heart rate, a higher heart rate in response to stress, and a higher mortality rate when diagnosed with coronary heart disease.[77–79] Such findings are particularly relevant in light of the important role of vmPFC in glucocorticoid release and sympathetic activity.

Consider the relationship between vmPFC activity and stress-related glucocorticoid release, which proceeds through a cascade of neural and hormonal signals. In short, stress-related stimuli activate particular brain regions—such as CeA and the medial nucleus of the amygdala—which in turn activate the paraventricular nucleus of the hypothalamus (PVN). Cells from PVN then release a peptide, corticotropin-releasing hormone, into the pituitary gland. The release of corticotropin-releasing hormone causes the pituitary gland to secrete adrenocorticotrophin hormone into the blood stream, which eventually results in the release of glucocorticoids from the adrenal cortex (see Feldman *et al.*[80] and Jankord and Herman[81]).

As previously noted, CeA and medial nucleus of the amygdala serve to activate PVN in stress-related contexts and are thereby involved in initiating the series of events, which eventually results in the release of glucocorticoids. Thus, assuming (C1) and (C2) are true, one would expect that IL/vmPFC

activity would inhibit PVN by downregulating amygdalar output. Data from Urry *et al.*[26] seem to support this possibility. In this study, the investigators presented healthy adults with negatively valenced images, and they found that activity in vmPFC negatively correlated with both amydalar activity and stress-related glucocorticoid secretion.

However, data from further studies run contrary to the claim that IL/vmPFC serves to inhibit PVN by downregulating amygdalar output. Radley *et al.*[82] examined stress-related Fos and corticotropin-releasing factor mRNA expression within rat PVN. They found that, in stress-related contexts, lesions of rat IL actually *decrease* (rather than increase) Fos and corticotropin-releasing factor mRNA expression within PVN. Similarly, Jahn *et al.*[83] found that glucose metabolism in monkey subgenual cortex correlates positively with plasma cortisol concentrations in a variety of stress-related contexts.[83] Consequently, the totality of data suggests that the relationship between IL/vmPFC activity and glucocorticoid release is rather complex. In particular, the data suggest that rat IL and primate vmPFC do not merely serve to inhibit stress-related PVN activity and glucocorticoid release, but rather, they may also serve to enhance it.

Next, consider the role of vmPFC activity in stress-related cardiovascular changes and SCRs. As with glucocorticoid release, increases in heart rate, blood pressure and SCRs are often associated with stress-related stimuli, and several studies suggest that CeA activity is a key contributor to these sympathetic increases.[84–88] Thus, in accordance with (C1) and (C2), one might expect vmPFC activity to be associated with an inhibition of these stress-related responses (that is, increases in heart rate, blood pressure and SCRs) via downregulation of CeA output. Data from Wager *et al.*[89] and Milad *et al.*[12] are relatively consistent with this suggestion. Wager *et al.*[89] presented healthy subjects with social stressors and found that activity within vmPFC correlated negatively with both self-reported anxiety ratings and the cardiac changes that were associated with these anxiety ratings. Similarly, Milad *et al.*[12] discovered that activity within human vmPFC tends to be associated with diminished SCRs during fear extinction training.

Although such data seem to support the use of (C1) and (C2) in the interpretation of mood and anxiety disorders, further studies again challenge this use of (C1) and (C2) by suggesting that vmPFC serves to enhance (rather than inhibit) stress-related cardiovascular increases and SCRs. Damasio *et al.*,[90] for instance, found that patients with vmPFC damage tend to exhibit diminished SCRs when presented with negatively valenced images, while Simpson *et al.*[68] found that activity in anterior vmPFC positively correlated with both self-reported anxiety ratings and elevation in heart rate. Moreover, a recent study by Tavares *et al.*[91] reveals that temporary inactivation of rat IL tends to attenuate stress-induced tachycardia. This finding is consistent with a number of electrophysiological studies, which have revealed that electrical stimulation of more ventral regions in mPFC—such as rabbit IL,[92] cat IL[93] and monkey subgenual cortex[94–96]—tends to elicit enhanced sympathetic activity: respiratory irregularities, pupillary dilation, hypertension and tachycardia.

Such findings on the relationship between vmPFC activity and sympathetic responses accord with a considerable amount of data on the anatomical projections from IL/vmPFC to different autonomic regions. Rat IL and monkey area 25—the only regions in rat/monkey mPFC that appear to send significant projections to the inhibitory ITC cells in the amygdala—also send direct projections to amygdalar regions that are thought to *enhance* amygdalar output: for example, the basolateral nucleus and medial nucleus (in rats and monkeys) and medial CeA (in rats).[35,36,39] More importantly, however, IL/25 projects directly to a number of autonomic regions, which have been found to enhance sympathetic activity, including the perifornical area, dorsomedial hypothalamus, dorsolateral periaqueductal gray, lateral parabrachial nucleus, cuneiform nucleus and lateral septum, among other regions.[4,33,35–37,39,47,82,97,98] Consider just a few of the findings that implicate such regions in the enhancement (rather than inhibition) of sympathetic activity: (i) disinhibition of perifornical area or dorsomedial hypothalamus (via γ-aminobutyric acid receptor antagonist) leads to increased sympathetic vasomotor activity and increased heart rate;[99] (ii) stimulation of dorsolateral periaqueductal gray (via *N*-methyl-D-aspartate receptor agonist) elicits anxiety-like behavior;[100] (iii) electrical or glutamate microstimulation of external lateral parabrachial nucleus elicits tachycardia and pressor responses;[101] (iv) electrical stimulation of cuneiform nucleus leads to elevation in arterial blood pressure;[102] and (v) immobilization stress is associated with both increased blood pressure and increased c-Fos expression in lateral septum, and moreover, inhibition of lateral septum (via γ-aminobutyric acid receptor agonist) inhibits this increase in blood pressure.[103] In light of such findings, it is therefore not surprising that IL/vmPFC activity is often associated with the *enhancement* (rather than inhibition) of stress-related sympathetic activity.

Alternative model

In summary, the anatomical and functional studies presented in this paper suggest that IL/vmPFC is functionally heterogeneous with respect to its role in amygdalar activity, stress-related responses and negative affect. In particular, some studies accord with (C1) and (C2) by suggesting that IL/vmPFC serves to decrease stress-related responses by inhibiting CeA output, while other studies suggest that IL/vmPFC serves to enhance stress-related responses either by enhancing CeA output or by directly stimulating certain autonomic regions, which lie outside of the amygdala.

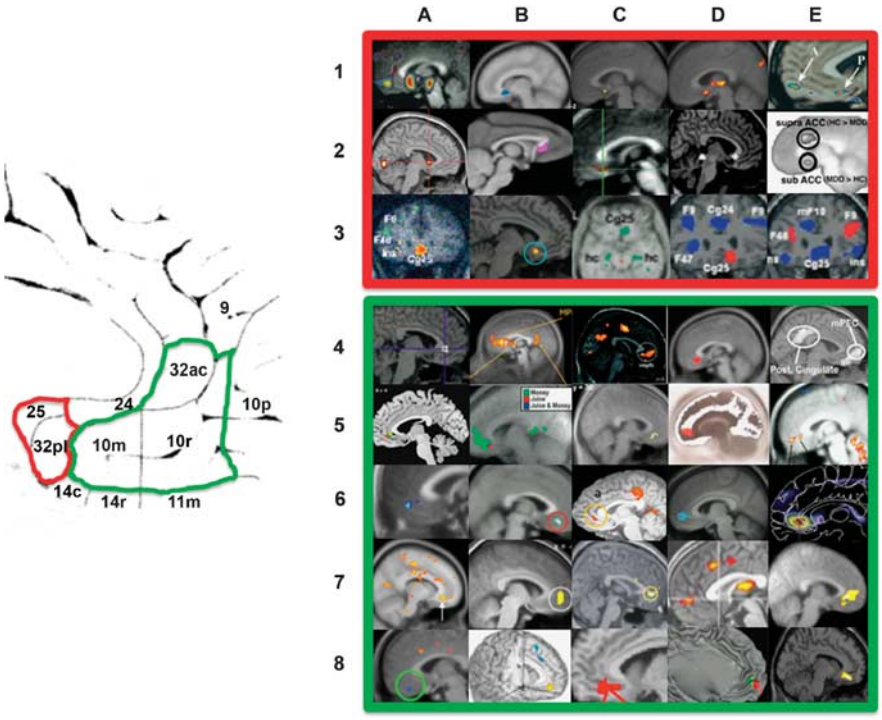

Figure 2 Left image: regions from Ongür *et al.*[32] that correspond to posterior ventromedial prefrontal cortex (vmPFC) (outlined in red) and perigenual vmPFC (outlined in green). Right image: rows 1–3 (outlined in red): neuroimaging studies suggesting that posterior vmPFC activity is positively associated with a wide range of emotion-related states that can be broadly characterized in terms of *negative affect*. Rows 4–8 (outlined in green): neuroimaging studies suggesting that perigenual vmPFC activity is positively associated with a wide range of emotion-related states that can be broadly characterized in terms of *positive affect*. For references, see Supplementary Table 1.

Consequently, these data should elicit significant caution in using (C1) and (C2) as frameworks with which to interpret neuroimaging data on mood and anxiety disorders. For, as things stand, it may well be the case that certain mood and anxiety disorders result not from a failure of vmPFC to downregulate the amygdala, but rather, from enhanced vmPFC activity, which results in heightened autonomic responses and negative affect. Hence, there is a clear need for more comprehensive models regarding the role of vmPFC in the expression and regulation of particular affective states.

One potential path toward developing such models would be to explore how various subregions of vmPFC differentially contribute to particular types of affective states. Preliminary justification for pursuing this approach comes from a variety of studies that, when taken together, suggest a functional differentiation between at least two anatomical subregions of vmPFC:

- Posterior vmPFC: situated roughly around areas 25 and 32pl (Figure 2, leftmost image, region outlined in red).
- Perigenual vmPFC: situated roughly around 10m, 10r and ventral 32ac (Figure 2, leftmost image, region outlined in green).

Studies in both psychiatric patients and healthy subjects seem to suggest a trend such that posterior vmPFC is positively associated with negative affect, while perigenual vmPFC is positively associated with positive affect.

As noted in section 'Major depressive disorder', patients with MDD tend to exhibit heightened activity in vmPFC, particularly in the subgenual cortex.[48–52] Accordingly, it has been found that patients with MDD exhibit decreased subgenual activity following successful treatment of MDD.[51–53] However, in apparent contrast to these findings, data from Drevets *et al.*[104] suggest that unipolar and bipolar depressives exhibit decreased subgenual activity, and Kennedy *et al.*[105] found that MDD patients who are responsive to cognitive-behavioral therapy tend to exhibit increased subgenual activity following cognitive-behavioral therapy treatment.

These apparent discrepancies in the existing data on depression may perhaps be resolved by a closer look at the different anatomical subregions of the subgenual cortex. Indeed, Mayberg *et al.*[52] note that the heightened subgenual activity associated with MDD tends to occur in a region that is caudal to the decreased subgenual activity associated with MDD. Moreover, in agreement with our above suggestion, the heightened subgenual activity associated with MDD occurs in posterior vmPFC (Figure 2, images 1C, 1D, 2A, 2E and 3D), whereas the decreased subgenual activity associated with MDD occurs in perigenual

vmPFC (Figure 2, image 6E). Similarly, the decreased subgenual activity following successful MDD treatment occurs in posterior vmPFC (Figure 2, images 1B, 3C and 3E), whereas the increased subgenual activity following successful MDD treatment occurs in perigenual vmPFC (Figure 2, image 4D).

Given these notable functional differences between posterior and perigenual vmPFC in MDD, we next consider how such differences might be further extended to other types of emotion-related data. Figure 2 shows activation sites in posterior and perigenual vmPFC for a variety of neuroimaging studies. The image on the far left serves as a reference point such that the region outlined in red (posterior vmPFC) corresponds to the images in rows 1 through 3, and the region outlined in green (perigenual vmPFC) corresponds to the images in rows 4 through 8. Although this collection of data is selective and by no means exhaustive, it nonetheless samples a significant number of findings related to our proposal.

The first set of images (rows 1–3, outlined in red) accords with our above suggestion that posterior vmPFC activity tends to be positively associated with a wide range of emotion-related states that can be broadly characterized as *negative affect*. In particular, these data indicate that posterior vmPFC activity is positively associated with negative mood (Figure 2, images 1E, 2C and 3A), distress of social exclusion (Figure 2, image 3B), anticipatory anxiety (Figure 2, images 1a and 2D), stress-related cortisol levels (Figure 2, image 2B) and major depression (Figure 2, images 1B, 1C, 1D, 2A, 2E, 3C, 3D and 3E).

The second set of images (rows 4–8, outlined in green) accords with our above suggestion that perigenual vmPFC activity tends to be positively associated with a wide range of emotion-related states that can be broadly characterized as *positive affect*. In short, these data suggest that perigenual vmPFC activity is positively associated with subjective value (Figure 2, images 4B, 4C, 5A, 5B, 5C, 7B, 7D and 7E), subjective social status (Figure 2, image 6D), subjective pleasantness of primary rewards (Figure 2, image 7C), decreased thermal pain (Figure 2, image 8A), fear extinction and suppression (Figure 2, images 5E, 6A and 6B), perception of attractive faces (Figure 2, image 4E), perception of neutral versus fearful/disgusted faces (Figure 2, image 6C), perception of fearful versus happy faces in controls relative to PTSD patients (Figure 2, image 7A), perception of traumatic/stressful versus neutral scripts in controls relative to PTSD patients (Figure 2, image 4A), placebo versus no placebo during pain induction (Figure 2, image 8C), positive social feedback (Figure 2, images 8B and 8D), enjoyable music listening in controls relative to depressives (Figure 2, image 8E) and successful treatment of MDD (Figure 2, images 4D and 5D).

Taken together, these two sets of findings raise the intriguing possibility that the functional heterogeneity of vmPFC, as it pertains to emotion, may result in part from distinct roles of posterior and perigenual vmPFC. That said, however, we acknowledge that this proposal is just one possible explanation among many. Any theoretical framework, which assumes that an 'increase' or 'decrease' in the activity of a particular brain area would have a straightforward effect on an individual's subjective emotional state may be a gross oversimplification of a complex and dynamic network. Rather, the effect of modifying activity in any particular brain area may depend critically on the exact conditions of the rest of the network. For example, it is conceivable that changes in vmPFC activity could exacerbate or alleviate negative emotion depending on the baseline activity of different vmPFC subregions, and/or the current state of the amygdala. This is particularly germane when considering experimental evidence derived from different manipulations of mood or brain states—major depression and neurological damage are chronic conditions, whereas paradigms involving electromagnetic stimulation or induction of negative emotion in healthy individuals are more acute and transient perturbations of the network. These approaches clearly differ with respect to the neural dynamics underlying mood state.

Keeping such issues in mind, we submit that the broad functional differences between posterior and perigenual vmPFC suggested by Figure 2 may nevertheless be of provisional service to the development of more fine-grained models of vmPFC function, and perhaps ultimately to a better understanding of the fundamental role of vmPFC in mood and anxiety disorders.

Conflict of interest

The authors declare no conflict of interest.

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