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REVIEW

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Mood dysregulation and stabilization: perspectives from emotional cognitive neuroscience

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Abstract

Mood is conceptualized as a long-lasting emotional state, which can have profound implications for mental and physical health. The development of neuroimaging methods has enabled significant advances towards elucidating the mechanisms underlying regulation of mood and emotion; however, our understanding of mood and emotion dysregulation in stress-related psychiatric disorders is still largely lacking. From the cognitive-affective neuroscience perspective, achieving deeper, more mechanistic understanding of mood disorders necessitates detailed understanding of specific components of neural systems involved in mood dysregulation and stabilization. In this review, we provide an overview of neural systems implicated in the development of a long-term negative mood state, as well as those related to emotion and emotion regulation, and discuss their proposed involvement in mood and anxiety disorders.

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Introduction

Accumulating evidence suggests that mood states in general, and dysregulated mood states in particular, can have a profound impact on mental and physical health. Major depressive disorder (MDD) for example, commonly conceptualized as a disorder of mood dysregulation is a leading cause of worldwide disability (McKenna *et al.* 2005). Yet, our current understanding of the mechanisms underlying mood dysregulation and stabilization is still very limited.

In the past decade, research in emotional cognitive neuroscience has begun to outline the neurocircuitry involved in higher level processes that regulate emotion (Critchley, 2005; Ochsner & Gross, 2005), and recent studies suggest that MDD patients have difficulties in recruiting brain regions involved in cognitive control and regulation of emotions (Erk *et al.* 2010; Johnstone *et al.* 2007). However, the link between failure to properly regulate emotional responses and mood disorder psychopathology has not been firmly established, and failed emotional regulation has also been associated with various forms of anxiety disorders (Amstadter, 2008), suggesting that failure to appropriately regulate activity in the emotion-processing networks under stressful circumstances can be seen in stress-related psychiatric disorders in general. Shared symptoms and high comorbidity repeatedly found between mood disorders and anxiety disorders (de Graaf *et al.* 2002; Kessler *et al.* 2005) further support the notion of potentially shared mechanisms of psychopathology. However, from the cognitive-emotional neuroscience perspective a deeper, more mechanistic understanding of MDD and of other related psychopathologies, e.g. anxiety disorders, requires delineation of the specific roles of various components of complex neural systems involved in mood and emotion regulation.

In this paper we review existing findings regarding neural mechanisms implicated in mood dysregulation

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and stabilization, with emphasis on these linked to the development of the most common manifestation of mood dysregulation – depression. We first consider the constructs of emotion and mood, and review recent human neuroimaging studies that examined the neurocircuitry of emotion and emotion regulation, and that of mood and mood instability. Next, we discuss the neuroimaging literature that examined recent approaches aiming to enhance emotion modulation and to improve mood symptoms. Throughout, we also attempt to highlight evidence that points towards the differences and the commonality in the neurocircuitry implicated in MDD and other stress-related psychiatric disorders.

Emotion and mood

Although the terms emotion and mood are frequently used interchangeably, and both denote an affective/motivational state, it is necessary here to clarify the distinction between the constructs of mood and emotion in considering the mechanisms of mood dysregulation and stabilization. In this review, we adopt a convention that has been used extensively in the literature to distinguish between these two terms, according to which, 'emotion' is understood as having a character of reactivity, usually brief, intense and circumscribed, related to a specific environmental event (Ekman, 1999). On the other hand, mood is conceived as a more stable and constant characteristic, with a tendency to be more comprehensive and not as linked to specific circumstances (Ellis & Moore, 1999). The usefulness of this distinction can be immediately evident when considering the potential differences in the neurocircuitry involved or in the psychopathology linked to these constructs. As a transient, cue-linked affective state, emotion-regulation deficits are likely to contribute to emotional arousal and exaggerated affect e.g. acute fear often present in the anxiety disorders, while mood dysregulation is more likely to lead to chronic, sustained negative moods, pervasive sadness or anhedonia, that are a hallmarks of mood disorders like MDD. This in turn, suggests that if indeed different neural mechanisms are involved in emotional modulation and mood dysregulation, understanding these differences will lead to better understanding of both common and distinct neurocircuitry involved in the psychopathology of MDD and anxiety disorders.

It is important, however, to keep in mind that while the proposed distinction is useful to highlight the differences between the two constructs, moods and emotions are generally viewed as closely interconnected. For example, moods are thought to facilitate emotional reactivity to mood-congruent stimuli. In line with this concept, a recent study demonstrated that induction of depressed mood disrupts the neurocircuitry of emotion regulation and enhances pain unpleasantness (Berna *et al.* 2010). This result is consistent with our own findings, demonstrating that sadness enhances the experience of pain via neural activation in the anterior cingulate cortex (ACC) and amygdala (Yoshino *et al.* 2010). Interestingly, the same relationship might not hold in the presence of overt psychopathology; a recent meta-analysis indicated that depressed individuals in general report a reduced emotional response to negative stimuli (Bylsma *et al.* 2008). Although depressive mood should potentiate negative emotional reactivity by the logic of mood facilitation, this seems to be not necessarily the case in MDD patients who have excessive negative mood. This meta-analysis as well as a recent study (Ellis *et al.* 2009) support the emotion context insensitivity hypothesis (Rottenberg *et al.* 2005) which predicts that individuals experiencing sad mood will show diminished reactivity to emotionally evocative stimuli and will not differentiate emotional responses across contexts. Finally, in addition to mood affecting emotional responses, transient emotional response could also affect long-term mood development. It is intuitively plausible that mood states reflect to some degree a cumulative function of experience of shorter term, emotional episodes. It is interesting to note here that, as we discuss later, it is possible that specific cognitive styles or biases are particularly relevant for both experiencing frequent negative emotion and less positive emotion, and also for the development of a longer term negative mood state seen in MDD.

Neurocircuitry of emotion and emotion regulation

The neurocircuitry of emotion has been extensively studied using functional neuroimaging approaches (Phan *et al.* 2002, 2004*b*). Among the brain regions linked to emotions, the amygdala is the region that most reliably activates to stimuli that predict threat, implicating its involvement in fear and anxiety states (Etkin, 2010). For example, positron emission tomography and functional magnetic resonance imaging (fMRI) studies have reported amygdala activation in response to emotionally negative pictures/photographs (Britton *et al.* 2006; Hariri *et al.* 2002; Irwin *et al.* 1996; Lane *et al.* 1997; Paradiso *et al.* 1999; Phan *et al.* 2003; Reiman *et al.* 1997; Taylor *et al.* 1998), odours (Zald & Pardo, 1997), and tastes (Zald *et al.* 1998). In concert with this proposed role, abnormalities in amygdala response have been reported in many

stress-related psychiatric disorders. For example, exaggerated amygdala activation is the consistent finding in anxiety disorders, e.g. post-traumatic stress disorder (PTSD), social phobia, and specific phobia (Shin & Liberzon, 2010). In addition, fMRI studies have also reported excessive amygdala activation to negatively valenced stimuli in acutely depressed patients (Davidson *et al.* 2003; Fu *et al.* 2004; Sheline *et al.* 2001; Surguladze *et al.* 2005), which normalizes following antidepressant treatment (Fu *et al.* 2004; Sheline *et al.* 2001).

Emotional responses, however, do not occur independently of attentional resources, cognitive context, strategic goals and other complex brain functions that can influence and modify these responses. The capacity to modulate emotional responses by attention or cognitive goals has been termed 'emotion regulation' encompassing different types of regulatory processes that can control the physiological, behavioural, and experimental components of affective responses (Gross & Thompson, 2007). Deficits in regulatory capacity of emotions, rather than abnormal activation of primary regions involved in the generation of emotional responses could also contribute to abnormal emotional responses, expressed in exaggerated amygdala activation. The regions of the prefrontal cortex (PFC) have most consistently been implicated in cognitive control processes, including emotion regulation. For example, numerous fMRI studies have observed increases in activities in the ventrolateral, dorsolateral, and dorsomedial prefrontal cortices (vlPFC, dlPFC, and dmPFC) when participants were instructed to deploy cognitive strategies such as reappraisal that reduce negative emotional experience (Ochsner & Gross, 2005). However, the precise location and laterality of these PFC regions vary among studies, perhaps because of subtle differences in stimuli, emotions, or strategy used (Ochsner & Gross, 2008). In spite of these differences, the dlPFC is generally implicated in the effortful manipulation or interpretation of the stimulus (Delgado *et al.* 2008; Ochsner *et al.* 2002). Reduced dlPFC activation during active emotion regulation has been reported in MDD (Erk *et al.* 2010) and social anxiety disorder (SAD) patients (Goldin *et al.* 2009). A recent study also suggests that such reduced dlPFC activation during active regulation is associated with a lack of sustained emotion regulation effect seen in MDD (Erk *et al.* 2010).

The vmPFC and hippocampus are also implicated in regulation of amygdala activity. The example is reported in the process of extinction learning (Quirk & Mueller, 2008). As in other types of learning, extinction occurs in three phases: acquisition, consolidation, and retrieval. Following the animal literature, recent human imaging studies distinguish between extinction acquisition and extinction retrieval by examining subjects both during extinction training as well as 24 h later (Delgado *et al.* 2006; Rauch *et al.* 2006). During extinction retrieval, several studies have reported significant activation of the vmPFC (Kalisch *et al.* 2006; Milad *et al.* 2007; Phelps *et al.* 2004). Furthermore, Milad *et al.* observed that the amount of extinction retrieval was highly correlated with vmPFC activity and vmPFC thickness (Milad *et al.* 2005). The hippocampus is also activated during extinction retrieval in studies that manipulate context (Kalisch *et al.* 2006; Milad *et al.* 2007), suggesting that a prefrontal-hippocampal network is involved in contextual modulation of extinction. Consistent with the idea that PTSD is related to the failure to consolidate and retrieve memory for extinction, PTSD patients exhibit deficits in extinction retention (Orr *et al.* 2000), along with reduced vmPFC and hippocampal volume and activity, and increased amygdala activity (Bremner, 2006; Gilbertson *et al.* 2002; Liberzon & Martis, 2006; Shin *et al.* 2006).

To fully understand the neurocircuitry implicated in emotions and emotion regulation, data from anatomical connectivity studies have to be considered. Structural connectivity studies suggest that the dlPFC does not project directly to the amygdala (Barbas, 2000; McDonald *et al.* 1996), and its influence on the amygdala is thought to be mediated by vmPFC (Hartley & Phelps, 2010). Recently, the idea that the lateral PFC regions engaged by cognitive emotion regulation strategies may influence the amygdala, diminishing fear through similar vmPFC connections that are thought to inhibit the amygdala during extinction have been proposed and demonstrated by identifying an overlapping region of the vmPFC across these techniques for diminishing fear (Delgado *et al.* 2008). These results are consistent with the suggestion that vmPFC may play a general regulatory role in diminishing fear across a range of paradigms (Kim *et al.* 2003; Urry *et al.* 2006). Interestingly, the data from a recent study (Johnstone *et al.* 2007) suggest the inappropriate engagement of lateral PFC-vmPFC-amygdala inhibitory circuitry during efforts to reappraise negative emotional stimuli might also be one of the factors involved in MDD pathophysiology.

Neurocircuitry of mood and mood instability

Although MDD is a complex set of symptoms, a profound change in mood is its most characteristic feature. MDD thus provides a rich context for exploring the neurocircuitry of mood and mood instability.

The area most reproducibly implicated in MDD is the subgenual ACC (sgACC). This region was initially shown to display an MDD-associated reduction in blood flow and glucose metabolism, with a corresponding reduction in grey-matter volume of the left sgACC (Drevets *et al.* 1997). Since this initial report, reduced sgACC volume has been repeatedly replicated (Drevets *et al.* 2008). On the other hand, imaging studies that assessed sgACC activity controlling for partial volume effects, indicated increased resting glucose metabolism or blood oxygen level-dependent (BOLD) activity in the sgACC and inflalimbic cortex of depressed patients (Inagaki *et al.* 2007; Kumano *et al.* 2007; Mah *et al.* 2007). In line with these data, sgACC metabolism and cerebral blood flow are higher in the depressed, ummedicated phase *vs.* the remitted phase in MDD subjects (Drevets *et al.* 2002; Hasler *et al.* 2008; Mayberg *et al.* 1999; Neumeister *et al.* 2004). These data are consistent with observations that experimentally induced sadness increases regional blood flow in the sgACC (George *et al.* 1995; Mayberg *et al.* 1999). Furthermore, various MDD treatments, including antidepressant treatment (Holthoff *et al.* 2004; Mayberg *et al.* 2000), electroconvulsive therapy (Nobler *et al.* 2001), and deep-brain stimulation of the sgACC (Mayberg *et al.* 2005), lead to decreased activity of the sgACC following treatment. Although ample literature implicates sgACC as a critical structure in MDD pathology as mentioned above, it is important to emphasize that other parts of the ACC, e.g. dorsal ACC (dACC), commonly implicated in conflict monitoring (Botvinick, 2007; Yeung *et al.* 2004), might also be involved in MDD pathophysiology (Davidson *et al.* 2002). For example, decreased dACC activation has been repeatedly reported with neuroimaging techniques (Bench *et al.* 1992; George *et al.* 1997; Holmes & Pizzagalli, 2008), and evidence suggests that MDD patients might display conflict monitoring dysregulation in paradigms generating competition among response options (Ottowitz *et al.* 2002). These deficits might be related to MDD symptomatology such as indecisiveness. Interestingly, antidepressant effects of deep-brain stimulation on sgACC have been reported to be associated with not only decreased blood flow in sgACC, but also increased blood flow in the downstream areas including dACC (Mayberg *et al.* 2005).

In addition to pervasive sadness, MDD seems also to involve diminished activation of positive emotion. Anhedonia, or loss of pleasure or interest in previously rewarding stimuli, is seen as one of the core features of MDD (APA, 2000). Thus, MDD could involve failure to activate a positive emotional response in the appropriate context, or difficulty in sustaining a response involving positive emotion, in addition or as an alternative to abnormal regulation of negative mood states. As for the neural substrates, the nucleus accumbens (NAc), and fronto-striatal network have been implicated in reward processing (Knutson & Cooper, 2005; Knutson & Wimmer, 2007; Wise, 2002) and positive emotion regulation (Kim & Hamann, 2007). A recent study (Heller *et al.* 2009) suggested that patients with MDD suffer from an inability to sustain reward-related activity that is reflected in the fronto-striatal network across time, and that this deficit is associated with reduced positive affect. Interestingly, the neurotransmitter which is most strongly linked to reward processing is dopamine. Previous research indicated that midbrain dopaminergic neurons show a pattern of signalling the magnitude, delay and probability of rewards (Roesch *et al.* 2007; Schultz, 2007) and code negative motivation and aversive events (Matsumoto & Hikosaka, 2009), while MDD has been associated with abnormalities in dopaminergic function in some studies (Kapur & Mann, 1992; Nestler & Carlezon, 2006). However, for many years research into the pathophysiology of MDD focused mainly on the serotonergic system because of the efficacy of most commonly prescribed antidepressants – selective serotonin reuptake inhibitors (SSRIs). Future research will have to further clarify dopamine's role in the pathophysiology of MDD. Recent reports of serotonin involvement in reward processing (Kranz *et al.* 2010) further support the possible involvement of reward system abnormalities in the psychopathology of MDD. Although complex interactions between neuromodulators like serotonin and dopamine in reward systems exist, a computational theory proposed that serotonin controls the time scale of reward prediction, and that the increased rate of discounting future reward value may explain certain aspects of depressive behaviour: when future rewards have values near zero, the optimal strategy is not to act (Doya, 2002). We studied brain activations linked to the choice of delayed reward, and found increased activity in the dorsal raphe nucleus, which is the serotonergic nucleus and provides a substantial proportion of serotonin's innervation to the forebrain (Tanaka *et al.* 2004). Considering that serotonin appears to play a major role in MDD, future experiments using delayed reward paradigms could be designed to further examine potential pathophysiology in patients with MDD.

Finally, as stated earlier, in the case of humans neither emotional nor mood states exist outside the cognitive context, and thus cognition can serve as a potent modulator of mood, and cognitive styles and biases can contribute to both the development and the

alleviation of long-term negative mood states seen in MDD. Per definition, negative view of the self, of the world, and of the future, as well as recurrent and uncontrollable negative thoughts that often revolve around the self, are debilitating symptoms of depression (APA, 2000). At the same time, one of the most effective interventions for depression, cognitive behavioural therapy (CBT), focuses on modifying biased interpretations and dysfunctional automatic thoughts and proposes that changes in cognition will lead to improvement of negative mood (Beck, 1976). Understanding the neurocircuitry involved in the modulatory effects of cognition on mood, e.g. negative view of the future and self, is important in understanding the neurocircuitry of mood and mood instability.

In this context, negative view of the future may be conceptualized as the enhanced anticipation of negative events. Functional neuroimaging studies, including ours, have been used to study the neurocircuitry of this phenomenon. Most of such studies have employed emotional expectancy cues that can be characterized as instantiating high levels of certainty with regard to the emotional valence of forthcoming pictures. Using this methodology, the expectation of a negative event induced activation in multiple prefrontal regions including the dlPFC (Nitschke *et al.* 2006), vlPFC (Herwig *et al.* 2007*a*, 2007*b*; Simmons *et al.* 2004; Ueda *et al.* 2003), mPFC (Ueda *et al.* 2003), OFC (Nitschke *et al.* 2006), ACC (Bermpohl *et al.* 2006; Herwig *et al.* 2007*a*, 2007*b*; Nitschke *et al.* 2006; Ueda *et al.* 2003), amygdala (Nitschke *et al.* 2006; Ueda *et al.* 2003) and insula (Nitschke *et al.* 2006; Simmons *et al.* 2004, 2006). Recently, using fMRI, we studied anticipation of negative condition, and demonstrated that ACC modulates preparatory activation for the coming negative event (Onoda *et al.* 2008). Although such hypervigilance to impending threat can be adaptive by virtue of allowing an individual to prepare for and prevent aversive outcomes, it may also lead to experiencing frequent negative emotions and developing a longer term negative mood state. Although there are few studies examining neural activation associated with anticipation of emotional stimuli in MDD at the present, such studies appear to be important in understanding the potential role of cognitions in mood dysregulation.

Negative view of the self is one of the key cognition biases seen in MDD. Researchers have reliably demonstrated a depression-related bias in the self-referential processing of the negative emotional stimuli (Banos *et al.* 2001; Bradley & Mathews, 1983; Derry & Kuiper, 1981; Dobson & Shaw, 1987). In addition, other work suggested that a negative self-focus can increase negative emotionality in both healthy controls (Pyszczynski & Greenberg, 1987) and depressed patients (Ingram, 1990). Recent neuroimaging studies of healthy participants have implicated medial PFC (mPFC) in self-referential processing (Fossati *et al.* 2003, 2004; Kelley *et al.* 2002; Northoff & Bermpohl, 2004; Northoff *et al.* 2006). In addition, imaging studies of self-referential encoding tasks indicate that the mPFC, the ACC and the amygdala are activated during the processing of emotional information (Fossati *et al.* 2003, 2004; Gusnard *et al.* 2001; Phan *et al.* 2004*a*). Our study of healthy participants (Yoshimura *et al.* 2009) also found activation in both the mPFC and rostral ACC (rACC) during the self-referential processing of negative emotional words. However, little is known about the brain function that underlies negative views of the self in depressive patients. Recently, we examined brain activation associated with the self-referential processing of negative emotional stimuli in MDD (Yoshimura *et al.* 2010). Compared to normal controls, depressed patients showed hyperactivity in the mPFC and rACC during the self-referential processing of negative words (Fig. 1). Furthermore, the activity in these regions during self-referential processing was correlated with depressive symptom severity, and rACC activity mediated the correlation between mPFC activity and depressive symptoms. Increased functional connectivity between the rACC, mPFC, and amygdala, was found in MDD, relative to control participants, suggesting that the relationship between the mPFC, rACC, and amygdala might reflect the interaction between self-referential and negative emotional information processing in the development of depressive symptoms.

Approaches to enhance emotional modulation

Although the ability to respond emotionally to salient cues is critical for adaptive human function, our ability to modify or control the nature of our emotional responses as circumstances change is equally important. Recent attention has been given to the role of such emotion regulation in the development and maintenance of stress-related psychiatric disorders. Indeed, there is an emerging consensus linking emotional dysregulation with depression (Ochsner & Gross, 2007), and with anxiety disorders (Amstadter, 2008). As a result, emotion regulation training is commonly included, explicitly or implicitly in CBT (Berking *et al.* 2008) which is effective for anxiety disorders (Hofmann & Smits, 2008) and MDD (Simons *et al.* 1986). Although at this point little is known about the specific

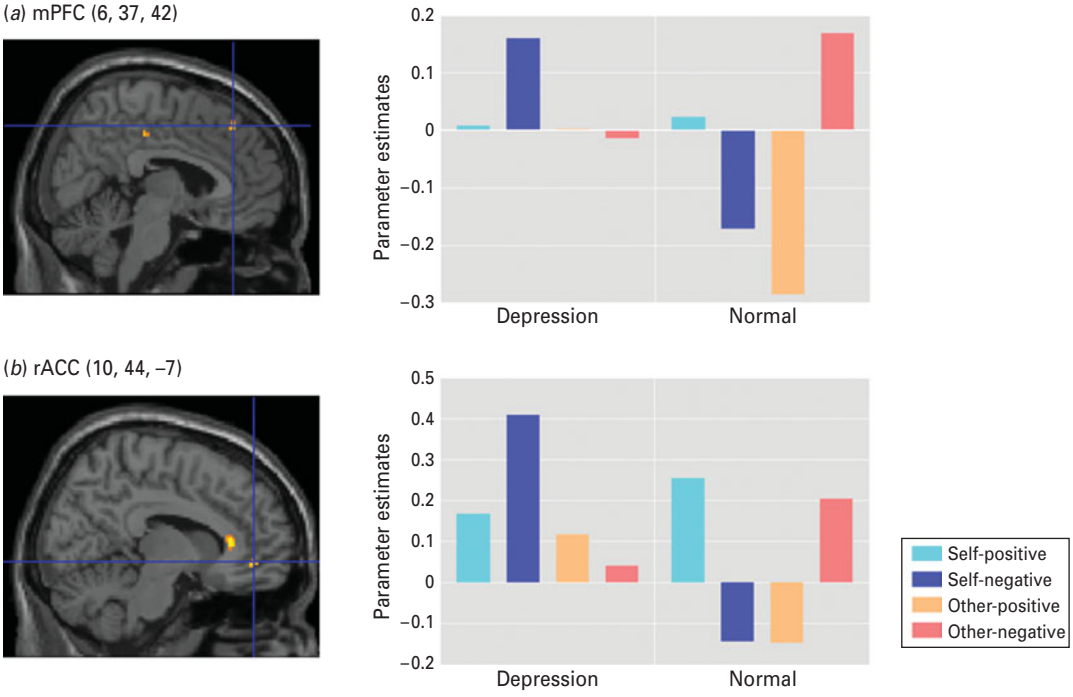

Fig. 1. Brain activation of MDD and normal controls performing a self-referential task using positive and negative emotional words as stimuli (Yoshimura *et al.* 2010). Axial sections display (*a*) the medial prefrontal cortex (mPFC) and (*b*) rostral anterior cingulate cortex (rACC), showing significant effect (second-order interaction from three-way ANOVA). Clusters of activity are overlaid on T1-weighted anatomical images. Graphs to the right of each image display signal change (parameter estimates) across each group and condition, relative to the control condition (uncorrected $p<0.001$, $\geqslant 10$ voxels). The light blue bar corresponds to the self-positive condition, the dark blue bar to the self-negative condition, the orange bar to the other-positive condition, and the red bar to the other-negative condition.

emotion-regulation strategies or abilities that can be enhanced to effectively treat all stress-related psychiatric disorders, anxiety disorders in particular might involve dysfunction in the extinction of fear learning (Rauch *et al.* 2006), and are effectively treated by extinction-based exposure therapies (Foa, 2006; Garakani *et al.* 2006; Rothbaum & Schwartz, 2002). Recent research suggests that facilitation of extinction learning through pharmacological means may enhance the efficacy of such extinction-based therapies (Anderson & Insel, 2006; Quirk & Mueller, 2008; Ressler *et al.* 2004; Walker *et al.* 2002). However, neural mechanisms involved in this type of facilitation are not well outlined and thus functional neuroimaging studies examining these processes are urgently needed.

Among the cognitive strategies to modulate emotion, reappraisal has proved effective for down-regulating intense negative emotions (Ochsner & Gross, 2004), and is proposed to mirror the cognitive processes used during CBT. One of the goals of CBT is to enable the patient to form more realistic evidence-based appraisals of situation, thereby regulating the associated emotional responses (Allen *et al.* 2008). Such a process probably assumes abnormally high activation in the amygdala as a 'generator' of specific symptoms and relies on strengthening of the lateral PFC-vmPFC-amygdala inhibitory circuitry as described earlier. Consistent with this suggestion, a recent study reported that fMRI activation in response to fearful faces in the amygdala and sgACC a, a subregion of the vmPFC, predicts success of CBT in PTSD patients (Bryant *et al.* 2008). The efficacy of such treatment may rely on the functional integrity of this neural circuitry and the success with which individuals are able to engage these regulatory mechanisms.

Approaches to improve mood symptoms

MDD is usually treated with either medication or an evidence-based psychotherapy. Among the medications, antidepressants which potentiate serotonin neurotransmission are the first-line treatement for MDD. Recently there has been growing interest in the neurotorophic actions of antidepressants, (Manji *et al.*

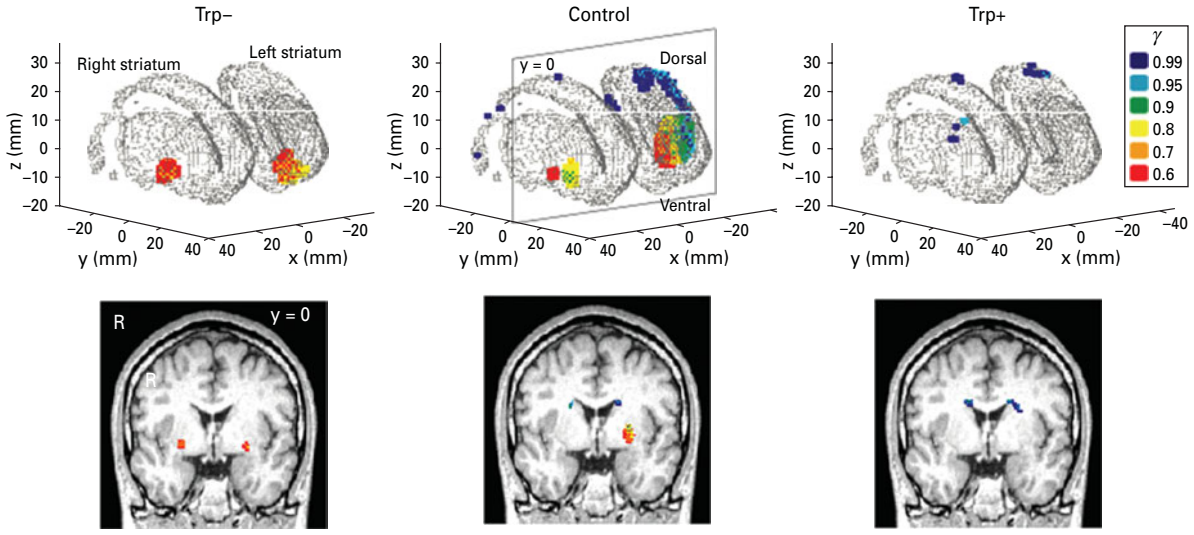

Fig. 2. Regression analysis of BOLD signal by expected future reward with different discount rates (Tanaka *et al.* 2007). Voxels within the striatum (3D mesh surface) showing a significant correlation ($p < 0.001$ in one-sample t test, uncorrected for the multiple comparison, $n = 12$ subjects) with $V(t)$ at different settings of γ are shown with colour codes (red: $\gamma = 0.6$; orange: 0.7; yellow: 0.8; green: 0.9; cyan: 0.95; blue: 0.99). Red- to yellow-coded voxels, correlated with reward prediction at shorter scales, are predominantly located in the ventral part of the striatum (ventral putamen and nucleus accumbens), while the green- to blue-coded voxels, correlated with reward prediction at longer time scales, are located in the dorsal part of the striatum (dorsal putamen and caudate body). $V(t)$ is the reward value at time t. γ is the discount factor, and a small γ (high discounting rate) leads to an inability to select a delayed reward over a smaller immediate reward.

2001), and it has been observed that SSRIs have a direct influence on adult neurogenesis (Jacobs *et al.* 2000), particularly in the dentate gyrus within the hippocampus (Malberg *et al.* 2000; Sheline *et al.* 2003). Such actions may be able to reverse structural and cellular deficits associated with depression and may facilitate learning and memory processes in which serotonin has also been shown to have a central role (Meneses, 2003). It is important to emphasize that dopamine, implicated in reward processing as mentioned above and in memory processing (Takahashi *et al.* 2008), might also be involved in the antidepressant action. Historically, amphetamines were one of the first agents used to combat symptoms of depression (Warneke, 1990). Indeed, several pharmacological agents that stimulate dopamine have antidepressant-like effects (Papakostas, 2006), and sertraline [arguably a more effective SSRI agent (Cipriani *et al.* 2009)] increases the extracellular levels of not only of serotonin but also of dopamine in the NAc and striatum of rats (Kitaichi *et al.* 2010). Serotonin and dopamine interact interdependently, and learning and memory depends at least in part on short- or long-lasting changes of synapses affected by the modulatory influence of serotonin and dopamine occurring at the synaptic level. Interestingly, it has recently been suggested that positive re-biasing of automatic processing produced by acute antidepressant treatment might, in an interpersonal environment, lead to changes in the strategic processing and behaviour associated with conscious emotional processing which becomes translated into improved mood (Harmer, 2008). In our own studies conducted under three different tryptophan conditions (depletion, Trp −; loading, Trp +; and control), which induced changes in total plasma tryptophan levels correlated with the cerebrospinal serotonin levels (Carpenter *et al.* 1998; Williams *et al.* 1999), we suggested that serotonin may adjust the rate of delayed reward discounting (Tanaka *et al.* 2007; Schweighofer *et al.* 2008). In these studies, we observed significant differences in activation of the striatum for reward prediction at different time scales that was modulated by serotonin level (Tanaka *et al.* 2007) (Fig. 2). Thus, SSRIs may allow a different perspective for our ongoing evaluation of the future, at least in part through the improved ability to predict future reward. Such modulatory effect by serotonin and dopamine on learning and memory could play a role in improving mood, with the time delay factor that is also characteristic of the antidepressant effects of SSRI biases (Harmer, 2008). In other words, the therapeutic actions of antidepressants, at least partially, can be attributed

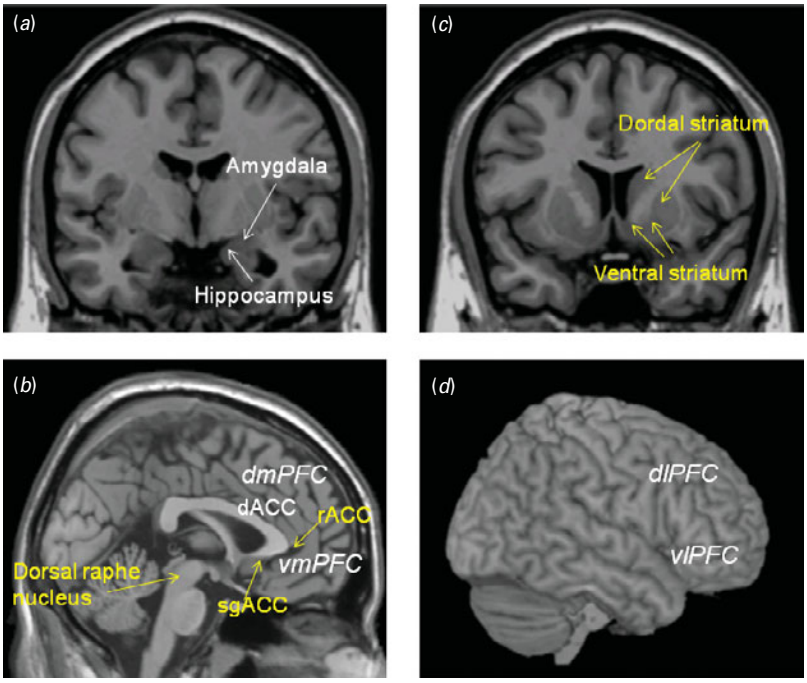

Fig. 3. Magnetic resonance imagines showing the key brain areas in emotion and mood regulation. (*a*) The hippocampus and amygdala; (*b*) the ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), subgenual anterior cingulate cortex (sgACC), rostral anterior cingulate cortex (rACC), dorsal anterior cingulate cortex (dACC), and the dorsal raphe nucleus; (*c*) dorsal striatum and ventral striatum, (*d*) dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC). Areas in yellow lettering are those we consider more relevant to long-term mood regulation and MDD pathophysiology than emotion regulation and anxiety disorder pathophysiology in this review.

to their effects on learning rather than direct effects on mood itself, and this mechanism can help to explain in part why the effects of antidepressants are seen some time after initiation of treatment. Interestingly, a recent study reported that behavioural activation therapy for MDD, results in improved functioning of reward neurocircuitry, including the dorsal striatum during reward anticipation (Dichter *et al.* 2009).

In addition to antidepressant medication, other treatments are also effective in improving mood symptoms of MDD. These include, CBT and other forms of psychotherapy, such as interpersonal therapy (de Mello *et al.* 2005), electroconvulsive therapy (UKECT Review Group, 2003), electrical stimulation of the vagus nerve (Nahas *et al.* 2005), and chronic stimulation of the sgACC (Mayberg *et al.* 2005).

Among these treatments, CBT, along with antidepressant medication has been the focus of the most intensive research efforts, both with regard to the outcome it produces, and the mechanisms that might explain its effect. A recent review suggested that CBT effectively exercises the PFC, possibly yielding increased inhibitory function of this region, while antidepressant medications might target amygdala function more directly (DeRubeis *et al.* 2008). CBT may bring about the conscious, volitional changes in the way that patients process emotion-relevant information, whereas antidepressants bring about the more automatic unconscious modulatory effects on learning, memory, and cognitive biases. This difference might play a role in the return of depressive symptoms after medication is stopped. It may explain, at least in part, the difference between CBT and antidepressant therapy in terms of their effects in the early and later phase of the illness such as the enduring effect of CBT (DeRubeis *et al.* 2008). At a psychological level, the aim of CBT for depression can be seen as teaching patients to see things in a broader perspective and to incorporate more contexts into their analysis of emotional information. As proposed recently (Bar, 2009), restructuring the ability for broad perspective (and thus more associative processing) may be important in general to elicit improvements of mood symptoms. However, there is initial evidence that general emotional support may also beneficially alter an individual's appraisal of a potentially stressful event. Recently, we demonstrated that emotional support enhances PFC activity, which in turn may lead to a weakened affective

response in the ACC (Onoda *et al.* 2009). It is possible that 'emotional support' is perceived as positive social interaction, and social interaction has a well-established role in regulation of neuroendocrine stress response (Foley & Kirschbaum, 2010), that in turn has been implicated in MDD pathophysiology (Gold *et al.* 2002; Holsboer, 2000).

Summary

In the current review, we briefly outlined neural regions implicated in the development of a long-term negative mood state, as well as those linked to emotions and emotional regulation, and discussed their potential relevance to the pathophysiology of mood and anxiety disorders. Summary observations we consider important for better understanding of the neural mechanisms of mood dysregulation and stabilization are as follows (for key brain regions see Fig. 3): (1) Exaggerated amygdala activation seems to be the consistent finding common for both mood and anxiety disorders. (2) A large and growing body of research implicates the ventromedial and dorsolateral sectors of the PFC as key neural substrates underlying emotion regulation. (3) Pharmacological agents that facilitate extinction learning or that facilitate improved ability to predict future reward could serve as adjuncts to CBT for anxiety disorders and MDD, respectively; however, functional neuroimaging studies examining effects of these strategies on brain activation patterns are urgently needed. (4) Involvement of the sgACC implicated in regulation of negative emotional state is especially prominent in neuroimaging studies of MDD. (5) In addition to suggested emotion regulation deficiency, diminished activation of positive emotion and negative cognitive biases appear to be the potential contributors to the development of a long-term negative mood state seen in MDD, implicating ventral striatum and ACC circuitry in these processes. (6) Approaches to restructure the ability for broad perspective, to alter self-referential thinking or even to change perception of social support may elicit improvements of mood symptoms by altering the activity of lateral and medial regions of PFC. We hope that the present review can help us to better understand the mechanisms of mood dysregulation and stabilization from the perspective of emotional-cognitive neuroscience.

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Statement of Interest

None.

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