

Emotional processing in anterior cingulate and medial prefrontal cortex

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Negative emotional stimuli activate a broad network of brain regions, including the medial prefrontal (mPFC) and anterior cingulate (ACC) cortices. An early influential view dichotomized these regions into dorsal–caudal cognitive and ventral–rostral affective subdivisions. In this review, we examine a wealth of recent research on negative emotions in animals and humans, using the example of fear or anxiety, and conclude that, contrary to the traditional dichotomy, both subdivisions make key contributions to emotional processing. Specifically, dorsal–caudal regions of the ACC and mPFC are involved in appraisal and expression of negative emotion, whereas ventral–rostral portions of the ACC and mPFC have a regulatory role with respect to limbic regions involved in generating emotional responses. Moreover, this new framework is broadly consistent with emerging data on other negative and positive emotions.

Controversies about anterior cingulate and medial prefrontal functions

Although the medial walls of the frontal lobes, comprising the anterior cingulate cortex (ACC) and the medial prefrontal cortex (mPFC), have long been thought to play a critical role in emotional processing [1], it remains uncertain what exactly their functional contributions might be. Some investigators have described evaluative (appraisal) functions of the ACC and mPFC, such as representation of the value of stimuli or actions [2–4] and the monitoring of somatic states [5]. Others hold that the ACC is primarily a generator of physiological or behavioral responses [6,7]. Still others have described a regulatory role for these regions, such as in the top-down modulation of limbic and endocrine systems for the purpose of emotion regulation [3,8–11]. An additional source of uncertainty lies in the way in which any one of these proposed functions might map onto distinct subregions of the ACC or mPFC (Box 1).

Undoubtedly the most influential functional parcellation of this type has been the proposal that there exists a principal dichotomy between caudal–dorsal midline regions that serve a variety of cognitive functions and rostral–ventral midline regions that are involved in some form of emotional processing [12]. However, even this

broadly and long-held view of basic functional specialization in these regions has been shaken by considerable evidence over the past decade indicating that many types of emotional processes reliably recruit caudal–dorsal ACC and mPFC regions [13,14].

Here, we review recent human neuroimaging, animal electrophysiology, and human and animal lesion studies that have produced a wealth of data on the role of the ACC and mPFC in the processing of anxiety and fear. We chose to focus primarily on the negative emotions of anxiety and fear because they are by far the most experimentally tractable and most heavily studied, and they afford the closest link between animal and human data. We subsequently briefly examine whether a conceptual framework derived from fear and anxiety can be generalized to other emotions.

Given the complexity [15] and multidimensional nature [16] of emotional responses, we address the specific functions or processes that constitute an emotional reaction, regardless of whether they are classically seen as emotional (e.g. a withdrawal response or a feeling) or cognitive

Glossary

Appraisal: evaluation of the meaning of an internal or external stimulus to the organism. Only stimuli that are appraised as motivationally significant will induce an emotional reaction, and the magnitude, duration and quality of the emotional reaction are a direct result of the appraisal process. Moreover, appraisal can be automatic and focus on basic affective stimulus dimensions such as novelty, valence or value, or expectation discrepancy, or may be slower and sometimes even require controlled conscious processing, which permits a more sophisticated context-dependent analysis.

Fear conditioning: learning paradigm in which a previously neutral stimulus, termed the conditioned stimulus (CS), is temporally paired with a non-learned aversive stimulus, termed the unconditioned stimulus (US). After pairing, the CS predicts the US and hence elicits a conditioned response (CR). For example, pairing of a tone with a foot shock results in elicitation of fear behavior during subsequent responses to a non-paired tone.

Extinction: learning process created by repeatedly presenting a CS without pairing with an US (i.e. teaching the animal that the CS no longer predicts the US) after fear conditioning has been established. This results in formation of an extinction memory, which inhibits expression of, but does not erase, the original fear memory.

Reappraisal: specific method for explicit emotion regulation whereby a conscious deliberate effort is engaged to alter the meaning (appraisal) of an emotional stimulus. For example, a picture of a woman crying can be reappraised from a negative meaning to a positive one by favoring an interpretation that she is crying tears of joy.

Regulation: general process by which conflicting appraisals and response tendencies are arbitrated between to allow selection of a course of action. Typically, regulation is thought to have an element of inhibition and/or enhancement for managing competing appraisals and response tendencies.

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Box 1. Anatomy of the ACC and mPFC

Within the ACC, a subdivision can be made between a more ventral portion, comprising areas 24a, 24b, 24c, 25, 32 and 33 [pregenual (pgACC) and subgenual ACC (sgACC) in Figure 1] and a more dorsal portion, comprising areas 24a', 24b', 24c', 24d, 32' and 33 [dorsal ACC (dACC) in Figure 1]. This distinction is consistent with that of Vogt and colleagues between an anterior and a midcingulate cortex [63]. In the dACC, a further distinction exists between anterior and posterior portions of the dACC (adACC and pdACC), similar to partitioning of the midcingulate into anterior and posterior portions by Vogt *et al.* [64] and consistent with partitioning between rostral and caudal cingulate zones [65].

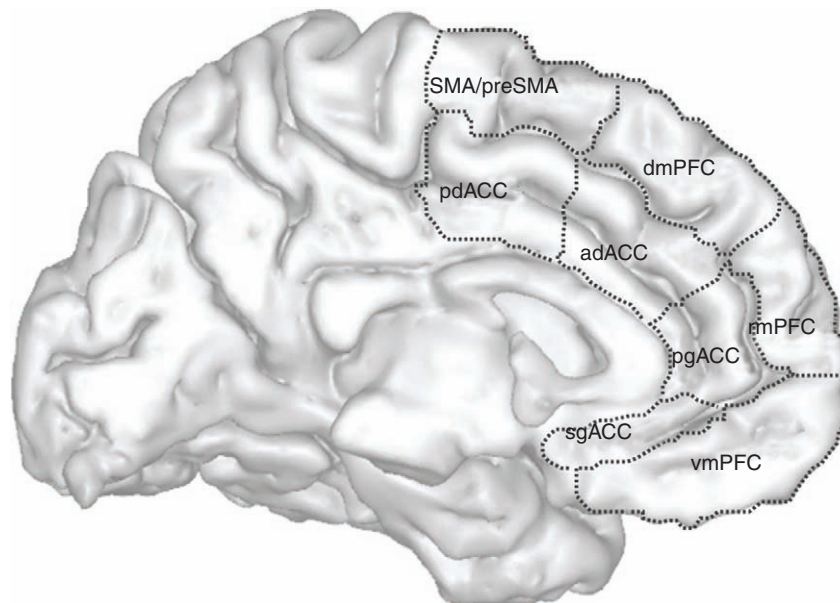
These subdivisions are also reflected in patterns of connectivity. Connectivity with core emotion-processing regions such as the amygdala, PAG and hypothalamus is strong throughout the sgACC, pgACC and adACC, but very limited in the pdACC [46,66–70]. In general, cingulo-amygdalar connectivity is focused on the basolateral complex of the amygdala.

ACC subregions can also be distinguished based on connectivity with premotor and lateral prefrontal cortices, which are heaviest in the pdACC and adACC [67,71]. In summary, the pattern of anatomical connectivity supports an important role for the sgACC, pgACC and

adACC in interacting with the limbic system, including its effector regions, and for the adACC and pdACC in communicating with other dorsal and lateral frontal areas that are important for top-down forms of regulation [72].

Like the ACC (Figure 1), the mPFC can be divided into several functionally distinct subregions, although borders between these subregions are generally less clear, and differential anatomical connectivity is less well described. Amygdalar, hypothalamic and PAG connectivity with mPFC subregions is considerably lighter than the connectivity of adjacent ACC subregions, with the strongest connections observed for the ventromedial (vmPFC) and dorsomedial PFC (dmPFC) [46,68–70].

Much like the nearby ACC subregions, the supplementary motor area (SMA) is heavily interconnected with primary motor cortex and is the origin for direct corticospinal projections [65,73]. The pre-SMA, by contrast, is connected with lateral prefrontal cortices, but not with primary motor cortex [65,73]. Premotor and lateral prefrontal connections are also present, albeit to a lesser degree, in the dmPFC [71]. Thus, the patterns of connectivity are similar between abutting ACC and mPFC subregions, with the difference being primarily in the density of limbic connectivity, which is substantially greater in the ACC.



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Figure 1. Parcellation of ACC and mPFC subregions. Abbreviations: sg, subgenual; pg, pregenual; vm, ventromedial; rm, rostromedial; dm, dorsomedial; ad, anterior dorsal; pd, posterior dorsal.

(e.g. attentional focusing on a relevant stimulus). We also distinguish between processes involved in emotional stimulus appraisal and consequential response expression [17] and those involved in emotion regulation. Regulation occurs when stimuli induce conflicting appraisals and hence incompatible response tendencies or when goal-directed activity requires suppression of interference from a single, emotionally salient, task-irrelevant stimulus source. We found that an appraisal or expression versus regulation contrast provides a robust framework for understanding ACC and mPFC function in negative emotion.

Fear conditioning and extinction in humans

The paradigms used in the acquisition and extinction of learned fear are particularly valuable for isolating the

neural substrates of fear processing because the anticipatory fear or anxiety triggered by the previously neutral conditioned stimulus (CS) can be dissociated from the reaction to the aversive unconditioned stimulus (US) *per se*. This is not possible in studies that, for example, use aversive images to evoke emotional responses. Furthermore, comparison between fear conditioning and fear extinction facilitates an initial coarse distinction between regions associated with either the appraisal of fear-relevant stimuli and generation of fear responses (fear conditioning), or the inhibitory regulation of these processes (extinction).

Several recent quantitative meta-analyses of human neuroimaging studies examined activations associated with fear CS presentation compared to a control CS never paired with the US [13,14,18]. In Figure 1a we present

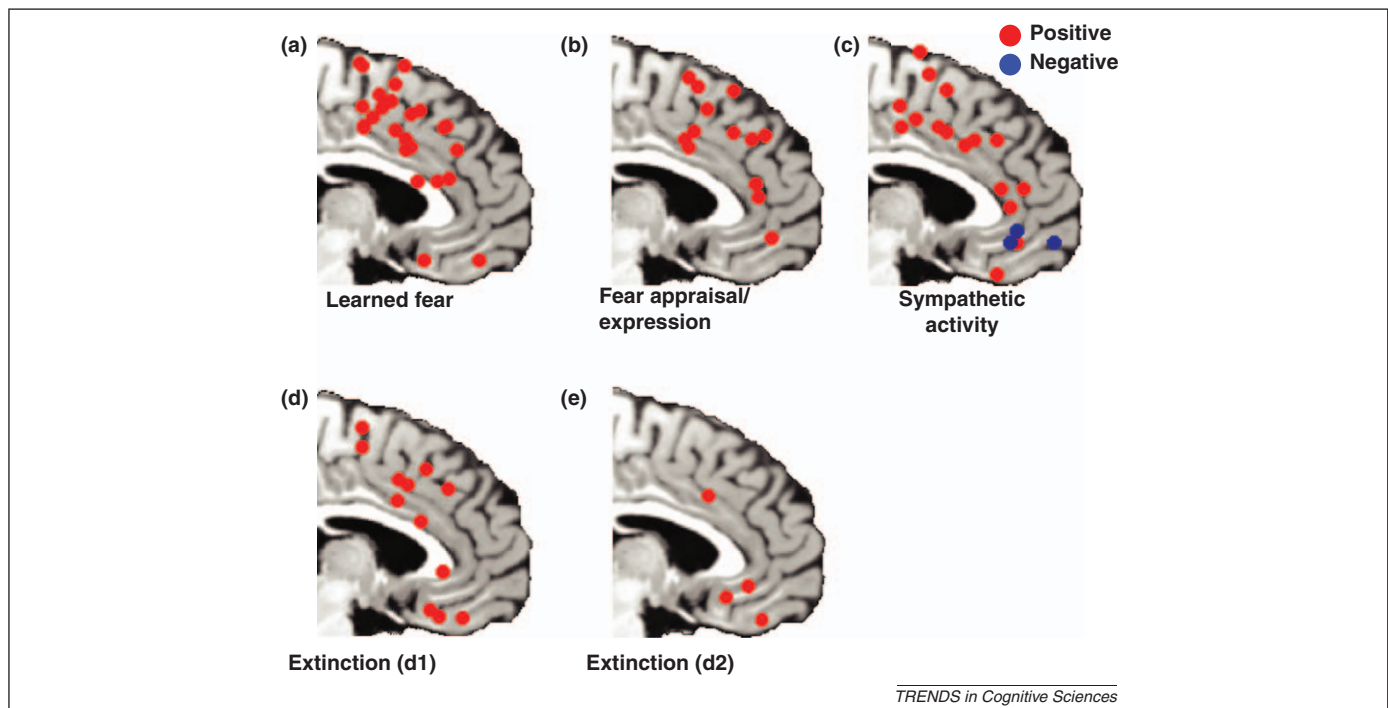


Figure 1. Activation foci associated with fear and its regulation. Predominantly dorsal ACC and mPFC activations are observed during classical (Pavlovian) fear conditioning (a), as well as during instructed fear paradigms, which circumvent fear learning (b). Likewise, sympathetic nervous system activity correlates positively primarily with dorsal ACC and mPFC regions and negatively primarily with ventral ACC and mPFC regions, which supports a role for the dorsal ACC and mPFC in fear expression (c). During within-session extinction, activation is observed in both the dorsal and ventral ACC and mPFC (d), whereas during subsequent delayed recall and expression of the extinction memory, when the imaging data are less confounded by residual expression of fear responses, activation is primarily in the ventral ACC and mPFC (e). Information on the studies selected for this and all following peak voxel plots can be found in the [online supplemental material](#).

plots of the location of each activation peak reported in the ACC or mPFC in the relevant fear conditioning studies, collapsing across left and right hemispheres. It is readily apparent that activations in fear conditioning studies are not evenly distributed throughout the ACC and mPFC, but rather are clustered heavily within the dorsal ACC (dACC), dorsomedial PFC (dmPFC), supplementary motor area (SMA) and pre-SMA. These activations, however, might reflect a variety of different processes that occur simultaneously or in rapid temporal succession, for example CS appraisal and expression of conditioned responses (CRs). These processes are intermixed with, and supported by, learning processes, namely, acquisition, consolidation and storage of a fear memory (CS-US association), and retrieval of the fear memory on subsequent CS presentations.

The acquisition component of fear conditioning can, to some extent, be circumvented by instructing subjects about CS-US contingencies at the beginning of an experiment. Such instructed fear experiments nevertheless also consistently activate the dorsal ACC and mPFC (Figure 1b) [14,19]. Similarly, recalling and generating fear in the absence of reinforcement several days after conditioning activate dorsal midline areas, and are not confounded by fear learning [20]. Rostral parts of the dorsal ACC/mPFC are specifically involved in the (conscious) appraisal, but not direct expression, of fear responses, as shown by reduction of rostral dACC and dmPFC activity to threat by high working memory load in the context of unchanged physiological reactivity [2,14], and correlations of rostral dACC and dmPFC activity with explicit threat evaluations but not physiological threat reactions [21].

Response expression, conversely, seems to involve more caudal dorsal areas in SMA, pre-SMA and pdACC, and caudal parts of dmPFC and adACC, although some of the evidence for this contention is indirect and based on studies of the arousal component inherent to most fear and anxiety responses. For example, Figure 1c shows clusters that correlate with sympathetic nervous system activity, irrespective of whether the context was fear-related or not. Positive correlations are found throughout the mPFC, but are again primarily clustered in mid-to-caudal dorsal mPFC areas. Lesion [22] and electrical stimulation studies [23] confirmed this anatomical distribution.

Considering these data in conjunction with observations that dACC activity correlates with fear-conditioned skin conductance responses [24] and with increases in heart rate induced by a socially threatening situation [25], as well as findings that direct electrical stimulation of the dACC can elicit subjective states of fear [26], strongly suggests that the dorsal ACC and mPFC are involved in generating fear responses. Neuroimaging studies of autonomic nervous system activity also indirectly suggest that the same areas do not exclusively function in response expression, but might also support appraisal processes. For example, the dorsal ACC and mPFC are associated with interoceptive awareness of heart beats [27], and, importantly, recruitment of the dorsal ACC and mPFC during interoceptive perception is positively correlated with subjects' trait anxiety levels [27]. Thus, the dorsal ACC and mPFC seem to function generally in the appraisal and expression of fear or anxiety. These studies leave uncertain the role that the dorsal ACC and mPFC might play in the acquisition of conditioned fear,

Box 2. Studies of fear conditioning and extinction in rodents

A rich literature has examined the role of the rodent medial frontal cortex in the acquisition and extinction of conditioned fear, as well as the expression of conditioned and unconditioned fear [74]. These studies facilitate a greater degree of causal inference than imaging studies. Much like the human dorsal ACC and mPFC, the rodent mPFC is strongly activated during fear conditioning [75,76]. Lesion or acute inactivation studies have revealed a role for the ventrally located infralimbic (IL) and dorsally located prelimbic (PL) subregions in conditioned fear expression when recall tests are performed within a few days after initial conditioning [77–81]. Interestingly, the mPFC does not seem to be required during fear acquisition itself, as evidenced by intact initial fear learning after disruption of IL or PL prior to conditioning [82–85]. As with expression of fear memories, activity in the rodent mPFC is also required for expression of unconditioned fear [86,87].

In terms of extinction, the recall and expression of an extinction memory more than 24 h after learning requires activity in IL [80,82,84,88] and to some degree PL [85,89]. By contrast, within-session extinction of CRs during repeated non-reinforced presentations of the CS does not require activity in IL or PL [80,82,84,88]. Thus, the role of the mPFC during extinction closely follows its role during fear conditioning: it is required for recall or expression, but not for initial acquisition.

Electrical microstimulation of the rodent mPFC generally does not directly elicit fear behavior or produce overt anxiolysis, but rather

exerts a modulatory function, gating behavioral output elicited by external fear-eliciting stimuli or by direct subcortical stimulation [90–93]. Curiously, given the role of the mPFC in fear expression, it has been found that these effects are generally, but not exclusively, fear-inhibitory and occur with stimulation in all mPFC subregions [90–93]. Of note, however, one recent study found a fear-enhancing effect of PL stimulation, but a fear-inhibiting effect of IL stimulation [92]. Together, these findings suggest that a model of mPFC function in fear or extinction must account for interactions of the mPFC with other elements of the fear circuit, because the mPFC itself functions primarily by modifying activity in other brain areas.

With respect to one important interacting partner, the amygdala, it has been reported that stimulation in the IL or PL inhibits the activity of output neurons in the central amygdalar nucleus (CEA) [94], as well as the basolateral amygdalar complex (BLA) [95]. IL and PL stimulation can also directly activate BLA neurons [96]. Thus, the mPFC can promote fear expression through BLA activation and can inhibit amygdala output through CEA inhibition. CEA inhibition, however, is achieved through the action of excitatory glutamatergic mPFC projections onto inhibitory interneurons in the amygdala, probably through the intercalated cell masses [97,98]. Innervation of the intercalated cell masses originates predominantly from IL rather than PL [99,100], which supports a preferential role for IL in inhibitory regulation of the amygdala.

although converging evidence from studies in rodents (Box 2) suggests only a minor role in acquisition.

To elucidate how fear is regulated, we next discuss activations associated with extinction of learned fear. In extinction, the CS is repeatedly presented in the absence of reinforcement, leading to the formation of a CS–no US association (or extinction memory) that competes with the original fear memory for control over behavior [28–30]. Hence, extinction induces conflicting appraisals of, and response tendencies to, the CS because it now signals both threat and safety, a situation that requires regulation, as outlined above. We further distinguish between within-session extinction (Figure 1d, day 1) and extinction recall, as tested by CS presentation on a subsequent day (Figure 1e, day 2). Within-session extinction is associated with activation in both the dorsal ACC and mPFC (dACC, dmPFC, SMA and pre-SMA) and the ventral ACC and mPFC (pgACC and vmPFC; Figure 1d). Given the close association of dorsal ACC and mPFC with fear conditioning responses, it should be noted that the activations observed within these regions during fear extinction might in fact reflect remnants of fear conditioning, because in early extinction trials the CS continues to elicit a residual CR. Activation within the ventral ACC and mPFC is thus a candidate neural correlate of the fear inhibition that occurs during extinction (for convergent rodent data, see Box 2). Accordingly, acute reversal of a fear conditioning contingency, during which a neutral, non-reinforced, CS is paired with an aversive stimulus, whereas the previously reinforced CS is not and now inhibits fear, is associated with activation in the pgACC [31]. Likewise, exposure to distant threat is associated with ventral ACC and mPFC activation, presumably acting in a regulatory capacity to facilitate planning of adaptive responses, whereas more imminent threat is associated with dorsal ACC and mPFC activation, which is consistent with greater expression of fear responses [32]. Along with ventral ACC and mPFC activation dur-

ing extinction, decreases in amygdalar responses have also been reported [33,34], consistent with the idea that amygdalar inhibition is an important component of extinction.

In support of this conclusion, recall of extinction more than 24 h after conditioning, a process that is less confounded by residual CRs, yields primarily ventral ACC and mPFC activations (pgACC, sgACC, vmPFC; Figure 1e). It should be stressed, however, that extinction, like conditioning, involves multiple component processes, including acquisition, consolidation, storage and retrieval of the extinction memory, and the related appraisal of the CS as safe, of which CR inhibition is only the endpoint. The limited number of human neuroimaging studies of extinction do not allow a reliable parcellation of these processes, although a rich literature on rodents suggests that, like for fear conditioning, the role of the mPFC is primarily in expression rather than acquisition of inhibitory fear memories (Box 2). Moreover, our conclusions are also supported by findings of negative correlations primarily between ventral areas (pgACC and vmPFC) and sympathetic activity (Figure 1c), and with activation in an area consistent with the periaqueductal gray matter (PAG), which mediates heart rate increases under social threat [25,35].

In summary, neuroimaging studies of the learning and extinction of fear in humans reveal evidence of an important differentiation between dorsal ACC and mPFC subregions, which are implicated in threat appraisal and the expression of fear, and ventral ACC and mPFC subregions, which are involved in the inhibition of conditioned fear through extinction.

Emotional conflict regulation

Convergent evidence of the functional differentiation between dorsal and ventral ACC and mPFC comes from work on emotional conflict. Two recent studies used a task that required subjects to categorize face stimuli according to their emotional expression (fearful vs happy) while

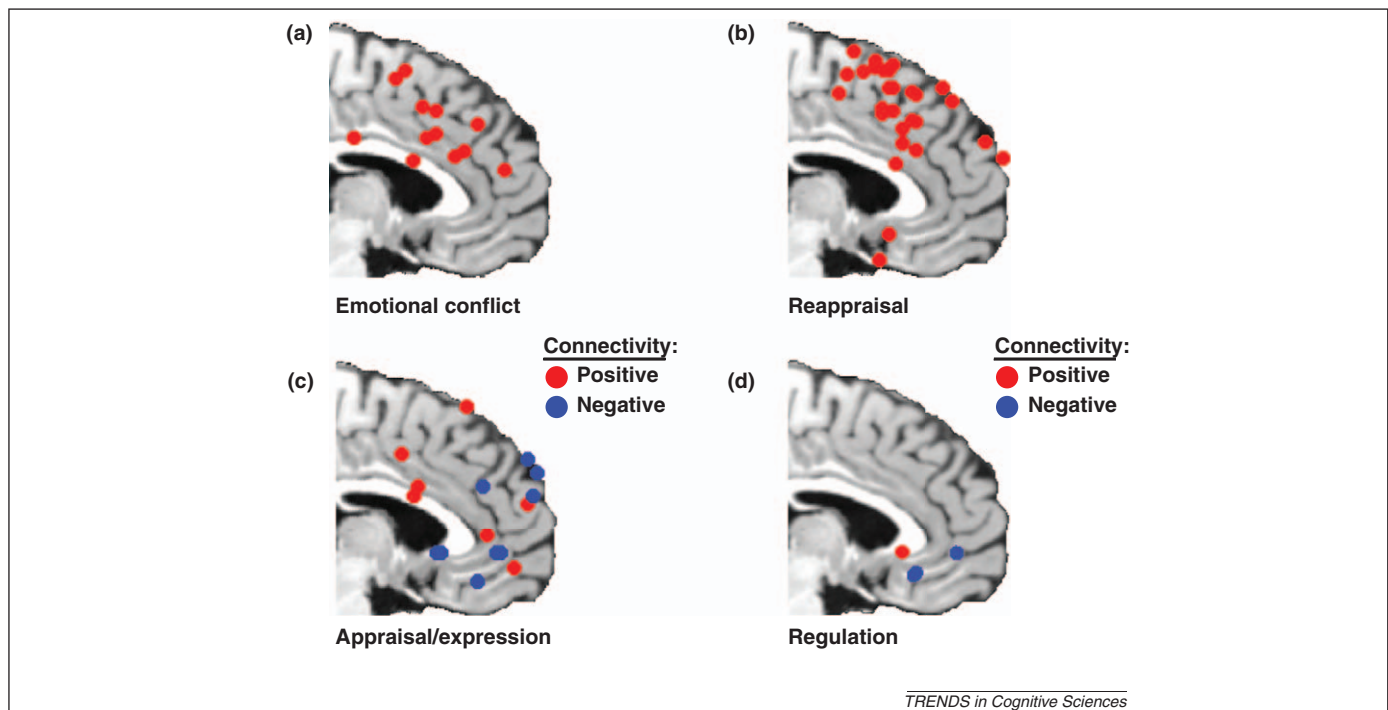


Figure 2. (a) Emotional conflict across a variety of experimental paradigms is associated with activation in the dorsal ACC and mPFC. (b) Decreasing negative emotion through reappraisal is associated with preferential activation of the dorsal ACC and mPFC. Targets of amygdalar connectivity during tasks involving appraisal or expression (c) or regulation (d) of negative emotion. Positive connectivity is observed primarily during appraisal or expression tasks, and most heavily in the dorsal ACC and mPFC. By contrast, negative connectivity is observed primarily in the ventral ACC and mPFC across both appraisal or expression and regulation tasks. These connectivity findings are therefore consistent with the dorsoventral functional-anatomical parcellation of the ACC and mPFC derived from activation analyses.

attempting to ignore emotionally congruent or incongruent word labels (Happy, Fear) superimposed over the faces. Emotional conflict, created by a word label incongruent with the facial expression, substantially slowed reaction times [8,36]. Moreover, when incongruent trials were preceded by an incongruent trial, reaction times were faster than if incongruent trials were preceded by a congruent trial [8,36], an effect that has previously been observed in traditional, non-emotional conflict tasks, such as the Stroop and flanker protocols [37]. According to the conflict-monitoring model [38], this data pattern stems from a conflict-driven regulatory mechanism, whereby conflict from an incongruent trial triggers an upregulation of top-down control, reflected in reduced conflict in the subsequent trial. This model can distinguish brain regions involved in conflict evaluation and those involved in conflict regulation [38,39]. In studies of emotional conflict, regions that activated more to post-congruent incongruent trials than post-incongruent incongruent trials, interpreted as being involved in conflict evaluation, included the amygdala, dACC, dmPFC and dorsolateral PFC [8,36]. The role of dorsal ACC and mPFC areas in detecting emotional conflict is further echoed by other studies of various forms of emotional conflict or interference, the findings of which we plot in Figure 2a.

By contrast, regions more active in post-incongruent incongruent trials are interpreted as being involved in conflict regulation, and prominently include the pgACC [8,36]. Regulation-related activation in the pgACC was accompanied by a simultaneous and correlated reduction in conflict-related amygdalar activity and does not seem to involve biasing of early sensory processing streams [39],

but rather the regulation of affective processing itself [36]. These data echo the dorsal-ventral dissociation discussed above with respect to fear expression and extinction in the ACC and mPFC.

The circuitry we find to be specific for regulation of emotional conflict (ventral ACC and mPFC and amygdala) is very similar to that involved in extinction. Although these two processes are unlikely to be isomorphic, and each can be understood without reference to the other, we consider the striking similarity between extinction and emotional conflict regulation to be potentially important. Much like the relationship between improved emotional conflict regulation and decreased conflict evaluation-related activation in the dorsal ACC and mPFC, more successful extinction is associated with decreased CS-driven activation in the dorsal ACC and mPFC of humans and rodents [40,41]. Thus, the most parsimonious explanation for these data is that emotional conflict evaluation-related functions involve overlapping neural mechanisms with appraisal and expression of fear, and that regulation of emotional conflict also involves circuitry that overlaps with fear extinction. These conceptual and functional-anatomical similarities between evaluation and regulation of emotional conflict and fear also support the generalizability of our account of ACC and mPFC functional subdivisions beyond simply fear-related processing, but more generally to negative emotional processing. Of note, although the intensity of the negative emotions elicited during fear conditioning and evoked by emotional conflict differ significantly, they nonetheless engage a similar neural circuitry, probably because both fear and emotional conflict reflect biologically salient events.

Top-down control of emotion

During emotional conflict regulation, emotional processing is spontaneously modulated in the absence of an explicit instruction to regulate emotion. Emotional processing can also be modulated through deliberate and conscious application of top-down executive control over processing of an emotional stimulus. The best-studied strategy for the latter type of regulation is reappraisal, a cognitive technique whereby appraisal of a stimulus is modified to change its ability to elicit an emotional reaction [42]. Reappraisal involves both the initial emotional appraisal process and the reappraisal process proper, whereby an additional positive appraisal is created that competes with the initial negative emotional appraisal. Thus, we would expect reappraisal to involve the dorsal ACC and mPFC regions that we observed to be important for emotional conflict detection (Figure 2a). Consistent with this prediction, a meta-analysis found that reappraisal was reliably associated with activation in the dorsal ACC and mPFC (Figure 2b) [43].

This reappraisal meta-analysis, interestingly, did not implicate a consistent role for the ventral ACC and mPFC [43], which suggests that reappraisal does not primarily work by suppressing the processing of an undesired emotional stimulus. Nevertheless, activity in the ventral ACC and mPFC in some instances is negatively correlated with activity in the amygdala in paradigms in which reappraisal resulted in downregulation of amygdalar activity in response to negative pictures [44,45]. Thus, the ventral ACC and mPFC might be mediators between activation in dorsal medial and lateral prefrontal areas, involved in reappraisal [43], and the amygdala, with which lateral prefrontal structures in particular have little or no direct connectivity [46]. Consistent with this idea, the ventral ACC and mPFC are also engaged when subjects perform affect labeling of emotional faces [47] or when they self-distract from a fear-conditioned stimulus [48], two other emotion regulation strategies that result in downregulation of amygdalar activity.

These data suggest that controlled top-down regulation, like emotional conflict regulation, uses ventral ACC and mPFC areas to inhibit negative emotional processing in the amygdala, thus dampening task interference. The ventral ACC and mPFC might thus perform a generic negative emotion inhibitory function that can be recruited by other regions (e.g. dorsal ACC and mPFC and lateral PFC) when there is a need to suppress limbic reactivity [10]. This would be a prime example of parsimonious use of a basic emotional circuitry, conserved between rodents and humans (Box 2), for the purpose of higher-level cognitive functions possible only in humans.

Amygdala-ACC and -mPFC functional connectivity

Our analysis of the neuroimaging data has emphasized task-based activation studies. Complementary evidence can be found in analyses of functional connectivity, because ACC and mPFC subregions can be distinguished through their differential anatomical connectivity (Box 1). In some ways, psychological context-specific temporal covariation (i.e. task-dependent connectivity) between regions might provide an even stronger test of the nature of inter-regional

relationships than consistency with regions that simply coactivate in a task. Figure 2c,d shows the ACC and mPFC connectivity peaks for all such connectivity studies, irrespective of the specific paradigm or instructions used (primarily general negative stimuli), as long as the task facilitated discrimination between appraisal or expression (Figure 2c) and regulation (Figure 2d). The spatial distribution of peaks during appraisal/expression tasks shows a relative preponderance of positive connectivity peaks in the dorsal ACC and mPFC and of negative connectivity peaks in the ventral ACC and mPFC. In addition, during regulation tasks, connectivity was restricted to the ventral ACC and mPFC and was primarily negative (Figure 2d). These data thus lend further support to our proposal of a dorso-ventral separation in terms of negative emotion generation (appraisal and expression) and inhibition (regulation).

Integration with other perspectives on ACC and mPFC function and other emotions

Although less developed than the literature on fear and anxiety, studies on other emotions are broadly consistent with our formulation of ACC and mPFC function. On the negative emotion appraisal and expression side, direct experience of pain, or empathy for others experiencing pain, activates the dorsal ACC and mPFC [49], and lesions of the dACC also serve as treatment for chronic pain [50]. Similarly, increased sensitivity to a range of negative emotions is associated with greater engagement of the dorsal ACC and mPFC, including disgust [51] and rejection [52], and transcranial-magnetic-stimulation-induced disruption of the dmPFC interferes with anger processing [53]. Uncertainty or ambiguity, which can induce anxiety and relates to emotional conflict, leads to activation in the dACC and dmPFC [54]. On the regulation side, endogenously driven analgesia by means of the placebo effect has been closely tied to the pgACC, which is thought to engage in top-down modulation of regions that generate opioid-mediated anti-nociceptive responses, such as the amygdala and PAG [55,56]. It remains unclear how sadness is evaluated and regulated, and what role the sgACC plays in these processes, because it is a common activation site in response to sad stimuli [57].

Positive emotion, which can serve to regulate and diminish negative emotion, has been associated in a meta-analysis with activation in the sgACC, vmPFC and pgACC [58]. Extinction of appetitive learning activates the vmPFC [59], much as extinction of learned fear does. The evaluation of positive stimuli and reward is more complicated. For instance, Rushworth and co-workers proposed that the processes carried out by the adACC are mirrored by similar contributions to reinforcement-guided decision-making from the orbitofrontal cortex, with the distinction that the adACC is concerned with computing reinforcement value of actions whereas the orbitofrontal cortex is concerned with gauging the reinforcement values of stimuli [60].

Taken together, these data broadly support our dorsal-ventral distinction along appraisal-expression versus regulation lines, with respect specifically to negative emotion. Conversely, it is not obvious how to accommodate our

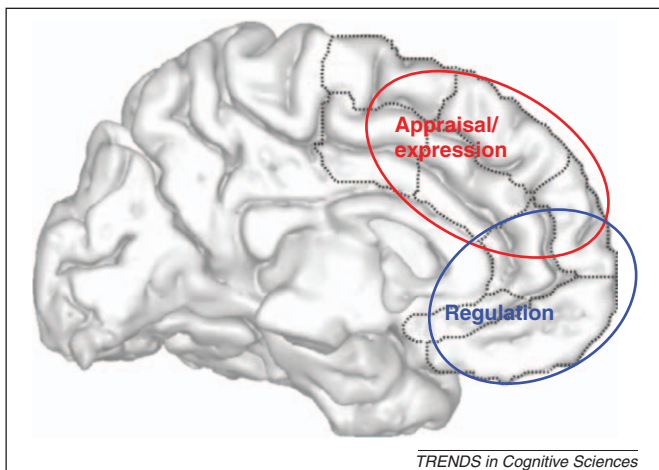


Figure 3. Graphical depiction of the ACC and mPFC functional model aligned across an appraisal or expression versus the regulation dimension for negative emotion. The imperfect separation of these functions across the dorsal and ventral ACC and mPFC noted in the reviewed studies is represented schematically as an intermixing of red (appraisal or expression) and blue (regulation) circles.

Box 3. Future directions

- Further work is needed, in particular in exploring the neurophysiological basis for appraisal and expression versus regulation-related signaling in the ACC and mPFC of experimental animals. Specifically, how does this coding take place at the single-cell level and how do these effects result in the dorsal-ventral division in ACC and mPFC functions observed in human imaging studies?
- We have left out discussion of other regions, such as the insula and brainstem, that are probably important partners of the ACC and mPFC, although far less is known about these interactions. Additional work is required to bring to these interactions the depth of understanding currently available for interactions with the amygdala. Moreover, a better systems-level understanding of how ACC and mPFC activity is shaped by its input regions, such as the amygdala, hippocampus and thalamus, is necessary.
- Although we hint at levels of similarity between our model of ACC and mPFC in negative emotion and other models of the roles of this region in other functions, additional work is required to directly contrast and harmonize other conceptualizations of ACC and mPFC functions to create a more comprehensive framework capable of making predictions about a wide range of task contexts.
- With a few notable exceptions [40,61], the sophisticated cognitive neuroscience models described above have not been extended to populations with anxiety-related disorders. A great deal of work will be needed to translate our increasingly nuanced descriptions of ACC and mPFC functions into a better understanding of psychopathology.

analysis with the suggestion that the vmPFC specifically assesses stimulus values [10], but not action values, with the opposite being the case for the dACC [60]. Thus, this should be seen as an early attempt to integrate these and other models of ACC and mPFC function and can serve to stimulate further research in this area.

It is also worth examining why the conceptualization proposed in this review differs significantly from the earlier view of a cognitive-affective division [12]. Although the meta-analysis reported in the earlier paper did not indicate which specific studies were included, it seems that much of the support for this scheme comes from studies of patients

with affective disorders, in whom ventral ACC and mPFC dysfunction can be more readily observed in the context of deficits in regulation [40,61]. Moreover, the dorsal-ventral dissociation between dACC activation in a counting Stroop and pgACC in an emotional counting Stroop [12] has not held up to subsequent evidence (Figure 2a) or direct contrasts between emotional and non-emotional conflict processing [36], nor does the emotional counting Stroop involve a true Stroop conflict effect in the way that the counting Stroop does [62].

Concluding remarks

This review has highlighted several important themes. First, the empirical data do not support the long-held popular view that dorsal ACC and mPFC regions are involved in cognitive but not emotional functions, whereas ventral regions do the reverse [12]. Rather, the key functional distinction between these regions relates to evaluative function on the one hand, and regulatory function on the other hand for the dorsal and ventral ACC and mPFC, respectively (Figure 3). This new framework can also be broadly generalized to other negative and positive emotions, and points to multiple exciting lines of future research (Box 3).

Disclosure statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tics.2010.11.004](https://doi.org/10.1016/j.tics.2010.11.004).

References

- 1 Papez, J.W. (1937) A proposed mechanism of emotion. *Arch. Neurol. Psychiatry* 38, 725–743
- 2 Kalisch, R. *et al.* (2006) Levels of appraisal: a medial prefrontal role in high-level appraisal of emotional material. *Neuroimage* 30, 1458–1466
- 3 Ochsner, K.N. and Gross, J.J. (2005) The cognitive control of emotion. *Trends Cogn. Sci.* 9, 242–249
- 4 Rushworth, M.F. *et al.* (2007) Functional organization of the medial frontal cortex. *Curr. Opin. Neurobiol.* 17, 220–227
- 5 Bechara, A. *et al.* (2000) Emotion, decision making and the orbitofrontal cortex. *Cereb. Cortex* 10, 295–307
- 6 Craig, A.D. (2009) How do you feel – now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70
- 7 Critchley, H.D. (2005) Neural mechanisms of autonomic, affective, and cognitive integration. *J. Comp. Neurol.* 493, 154–166
- 8 Etkin, A. *et al.* (2006) Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* 51, 871–882
- 9 Quirk, G.J. and Beer, J.S. (2006) Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. *Curr. Opin. Neurobiol.* 16, 723–727
- 10 Schiller, D. and Delgado, M.R. (2010) Overlapping neural systems mediating extinction, reversal and regulation of fear. *Trends Cogn. Sci.* 14, 268–276

- 11 Vogt, B.A. *et al.* (1992) Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb. Cortex* 2, 435–443
- 12 Bush, G. *et al.* (2000) Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn. Sci.* 4, 215–222
- 13 Etkin, A. and Wager, T.D. (2007) Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am. J. Psychiatry* 164, 1476–1488
- 14 Mechias, M.L. *et al.* (2010) A meta-analysis of instructed fear studies: implications for conscious appraisal of threat. *Neuroimage* 49, 1760–1768
- 15 Levenson, R.W. (2003) Blood, sweat, and fears: the autonomic architecture of emotion. *Ann. N. Y. Acad. Sci.* 1000, 348–366
- 16 Pessoa, L. (2008) On the relationship between emotion and cognition. *Nat. Rev. Neurosci.* 9, 148–158
- 17 Roseman, I.J. and Smith, C.A. (2001) Appraisal theory: overview, assumptions, varieties, controversies. In *Appraisal Processes in Emotion: Theory, Methods, Research* (Scherer, K.R. *et al.*, eds), pp. 3–19, Oxford University Press
- 18 LaBar, K.S. and Cabeza, R. (2006) Cognitive neuroscience of emotional memory. *Nat. Rev. Neurosci.* 7, 54–64
- 19 Klucken, T. *et al.* (2009) Neural, electrodermal and behavioral response patterns in contingency aware and unaware subjects during a picture–picture conditioning paradigm. *Neuroscience* 158, 721–731
- 20 Kalisch, R. *et al.* (2009) The NMDA agonist D-cycloserine facilitates fear memory consolidation in humans. *Cereb. Cortex* 19, 187–196
- 21 Raczka, K.A. *et al.* (2010) A neuropeptide S receptor variant associated with overinterpretation of fear reactions: a potential neurogenetic basis for catastrophizing. *Mol. Psychiatry* 15, 1067–1074
- 22 Critchley, H.D. *et al.* (2003) Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 126, 2139–2152
- 23 Gentil, A.F. *et al.* (2009) Physiological responses to brain stimulation during limbic surgery: further evidence of anterior cingulate modulation of autonomic arousal. *Biol. Psychiatry* 66, 695–701
- 24 Milad, M.R. *et al.* (2007) A role for the human dorsal anterior cingulate cortex in fear expression. *Biol. Psychiatry* 62, 1191–1194
- 25 Wager, T.D. *et al.* (2009) Brain mediators of cardiovascular responses to social threat: part I: Reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage* 47, 821–835
- 26 Meyer, G. *et al.* (1973) Stereotactic cingulotomy with results of acute stimulation and serial psychological testing. In *Surgical Approaches in Psychiatry* (Laitinen, L.V. and Livingston, K.E., eds), pp. 39–58, University Park Press
- 27 Critchley, H.D. *et al.* (2004) Neural systems supporting interoceptive awareness. *Nat. Neurosci.* 7, 189–195
- 28 Bouton, M.E. (2004) Context and behavioral processes in extinction. *Learn. Mem.* 11, 485–494
- 29 Delamater, A.R. (2004) Experimental extinction in Pavlovian conditioning: behavioural and neuroscience perspectives. *Q. J. Exp. Psychol. B* 57, 97–132
- 30 Myers, K.M. and Davis, M. (2002) Behavioral and neural analysis of extinction. *Neuron* 36, 567–584
- 31 Schiller, D. *et al.* (2008) From fear to safety and back: reversal of fear in the human brain. *J. Neurosci.* 28, 11517–11525
- 32 Mobbs, D. *et al.* (2009) From threat to fear: the neural organization of defensive fear systems in humans. *J. Neurosci.* 29, 12236–12243
- 33 Milad, M.R. *et al.* (2008) Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. *J. Psychiatr. Res.* 42, 515–520
- 34 Phelps, E.A. *et al.* (2004) Extinction learning in humans: role of the amygdala and vmPFC. *Neuron* 43, 897–905
- 35 Wager, T.D. *et al.* (2009) Brain mediators of cardiovascular responses to social threat, part II: Prefrontal-subcortical pathways and relationship with anxiety. *Neuroimage* 47, 836–851
- 36 Egner, T. *et al.* (2008) Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. *Cereb. Cortex* 18, 1475–1484
- 37 Egner, T. (2007) Congruency sequence effects and cognitive control. *Cogn. Affect. Behav. Neurosci.* 7, 380–390
- 38 Botvinick, M.M. *et al.* (2001) Conflict monitoring and cognitive control. *Psychol. Rev.* 108, 624–652
- 39 Egner, T. and Hirsch, J. (2005) Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nat. Neurosci.* 8, 1784–1790
- 40 Milad, M.R. *et al.* (2009) Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol. Psychiatry* 66, 1075–1082
- 41 Burgos-Robles, A. *et al.* (2007) Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. *Neuron* 53, 871–880
- 42 Gross, J.J. (2002) Emotion regulation: affective, cognitive, and social consequences. *Psychophysiology* 39, 281–291
- 43 Kalisch, R. (2009) The functional neuroanatomy of reappraisal: time matters. *Neurosci. Biobehav. Rev.* 33, 1215–1226
- 44 Johnstone, T. *et al.* (2007) Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J. Neurosci.* 27, 8877–8884
- 45 Urry, H.L. *et al.* (2006) Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *J. Neurosci.* 26, 4415–4425
- 46 Amaral, D.G. *et al.* (1992) Anatomical organization of the primate amygdaloid complex. In *The Amygdala: Neurobiological Aspects of Emotion, Memory and Mental Dysfunction* (Aggleton, J.P., ed.), pp. 1–66, Wiley-Liss
- 47 Lieberman, M.D. *et al.* (2007) Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. *Psychol. Sci.* 18, 421–428
- 48 Delgado, M.R. *et al.* (2008) Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron* 59, 829–838
- 49 Lamm, C. *et al.* (2010) Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage* DOI: 10.1016/j.neuroimage.2010.10.014
- 50 Wilkinson, H.A. *et al.* (1999) Bilateral anterior cingulotomy for chronic noncancer pain. *Neurosurgery* 45, 1129–1134
- 51 Mataix-Cols, D. *et al.* (2008) Individual differences in disgust sensitivity modulate neural responses to aversive/disgusting stimuli. *Eur. J. Neurosci.* 27, 3050–3058
- 52 Eisenberger, N.I. *et al.* (2003) Does rejection hurt? An fMRI study of social exclusion. *Science* 302, 290–292
- 53 Harmer, C.J. *et al.* (2001) Transcranial magnetic stimulation of medial-frontal cortex impairs the processing of angry facial expressions. *Nat. Neurosci.* 4, 17–18
- 54 Nomura, M. *et al.* (2003) Frontal lobe networks for effective processing of ambiguously expressed emotions in humans. *Neurosci. Lett.* 348, 113–116
- 55 Eippert, F. *et al.* (2009) Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron* 63, 533–543
- 56 Petrovic, P. *et al.* (2002) Placebo and opioid analgesia – imaging a shared neuronal network. *Science* 295, 1737–1740
- 57 Phan, K.L. *et al.* (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16, 331–348
- 58 Wager, T.D., *et al.* (2008) The neuroimaging of emotion. In *Handbook of Emotions* (3rd edn) (Lewis, M., ed.), pp. 249–271, The Guilford Press
- 59 Finger, E.C. *et al.* (2008) Dissociable roles of medial orbitofrontal cortex in human operant extinction learning. *Neuroimage* 43, 748–755
- 60 Rushworth, M.F. *et al.* (2007) Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. *Trends Cogn. Sci.* 11, 168–176
- 61 Etkin, A. *et al.* (2010) Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *Am. J. Psychiatry* 167, 545–554
- 62 Algom, D. *et al.* (2004) A rational look at the emotional Stroop phenomenon: a generic slowdown, not a Stroop effect. *J. Exp. Psychol. Gen.* 133, 323–338
- 63 Vogt, B.A. (2004) Cingulate gyrus. In *The Human Nervous System* (2nd edn) (Paxinos, G., and Mai, J.K., eds.), pp. 915–949, Elsevier
- 64 Vogt, B.A. *et al.* (2003) Structural and functional dichotomy of human midcingulate cortex. *Eur. J. Neurosci.* 18, 3134–3144

- 65 Picard, N. and Strick, P.L. (2001) Imaging the premotor areas. *Curr. Opin. Neurobiol.* 11, 663–672
- 66 Ghashghaei, H.T. *et al.* (2007) Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *Neuroimage* 34, 905–923
- 67 Beckmann, M. *et al.* (2009) Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J. Neurosci.* 29, 1175–1190
- 68 Chiba, T. *et al.* (2001) Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, *Macaca fuscata*. *Brain Res.* 888, 83–101
- 69 Rempel-Clower, N.L. and Barbas, H. (1998) Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. *J. Comp. Neurol.* 398, 393–419
- 70 An, X. *et al.* (1998) Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys. *J. Comp. Neurol.* 401, 455–479
- 71 Bates, J.F. and Goldman-Rakic, P.S. (1993) Prefrontal connections of medial motor areas in the rhesus monkey. *J. Comp. Neurol.* 336, 211–228
- 72 Mansouri, F.A. *et al.* (2009) Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. *Nat. Rev. Neurosci.* 10, 141–152
- 73 Nachev, P. *et al.* (2008) Functional role of the supplementary and pre-supplementary motor areas. *Nat. Rev. Neurosci.* 9, 856–869
- 74 Sotres-Bayon, F. and Quirk, G.J. (2010) Prefrontal control of fear: more than just extinction. *Curr. Opin. Neurobiol.* 20, 231–235
- 75 Burgos-Robles, A. *et al.* (2009) Sustained conditioned responses in prelimbic prefrontal neurons are correlated with fear expression and extinction failure. *J. Neurosci.* 29, 8474–8482
- 76 Herry, C. *et al.* (1999) Plasticity in the mediodorsal thalamo-prefrontal cortical transmission in behaving mice. *J. Neurophysiol.* 82, 2827–2832
- 77 Resstel, L.B. *et al.* (2008) The expression of contextual fear conditioning involves activation of an NMDA receptor–nitric oxide pathway in the medial prefrontal cortex. *Cereb. Cortex* 18, 2027–2035
- 78 Blum, S. *et al.* (2006) A role for the prefrontal cortex in recall of recent and remote memories. *Neuroreport* 17, 341–344
- 79 Corcoran, K.A. and Quirk, G.J. (2007) Activity in prelimbic cortex is necessary for the expression of learned, but not innate, fears. *J. Neurosci.* 27, 840–844
- 80 Laurent, V. and Westbrook, R.F. (2009) Inactivation of the infralimbic but not the prelimbic cortex impairs consolidation and retrieval of fear extinction. *Learn Mem.* 16, 520–529
- 81 Laviolette, S.R. *et al.* (2005) A subpopulation of neurons in the medial prefrontal cortex encodes emotional learning with burst and frequency codes through a dopamine D4 receptor-dependent basolateral amygdala input. *J. Neurosci.* 25, 6066–6075
- 82 Quirk, G.J. *et al.* (2000) The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *J. Neurosci.* 20, 6225–6231
- 83 Runyan, J.D. *et al.* (2004) A role for prefrontal cortex in memory storage for trace fear conditioning. *J. Neurosci.* 24, 1288–1295
- 84 Sierra-Mercado, D., Jr *et al.* (2006) Inactivation of the ventromedial prefrontal cortex reduces expression of conditioned fear and impairs subsequent recall of extinction. *Eur. J. Neurosci.* 24, 1751–1758
- 85 Morgan, M.A. and LeDoux, J.E. (1995) Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav. Neurosci.* 109, 681–688
- 86 Maaswinkel, H. *et al.* (1996) Effects of an electrolytic lesion of the prelimbic area on anxiety-related and cognitive tasks in the rat. *Behav. Brain Res.* 79, 51–59
- 87 Shah, A.A. and Treit, D. (2003) Excitotoxic lesions of the medial prefrontal cortex attenuate fear responses in the elevated-plus maze, social interaction and shock probe burying tests. *Brain Res.* 969, 183–194
- 88 Lebron, K. *et al.* (2004) Delayed recall of fear extinction in rats with lesions of ventral medial prefrontal cortex. *Learn. Mem.* 11, 544–548
- 89 Hugues, S. *et al.* (2004) Postextinction infusion of a mitogen-activated protein kinase inhibitor into the medial prefrontal cortex impairs memory of the extinction of conditioned fear. *Learn Mem.* 11, 540–543
- 90 al Maskati, H.A. and Zbrozyna, A.W. (1989) Stimulation in prefrontal cortex area inhibits cardiovascular and motor components of the defence reaction in rats. *J. Auton. Nerv. Syst.* 28, 117
- 91 Milad, M.R. and Quirk, G.J. (2002) Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature* 420, 70–74
- 92 Vidal-Gonzalez, I. *et al.* (2006) Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. *Learn Mem.* 13, 728–733
- 93 Zbrozyna, A.W. and Westwood, D.M. (1991) Stimulation in prefrontal cortex inhibits conditioned increase in blood pressure and avoidance bar pressing in rats. *Physiol. Behav.* 49, 705–708
- 94 Quirk, G.J. *et al.* (2003) Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *J. Neurosci.* 23, 8800–8807
- 95 Rosenkranz, J.A. *et al.* (2003) The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. *J. Neurosci.* 23, 11054–11064
- 96 Likhtik, E. *et al.* (2005) Prefrontal control of the amygdala. *J. Neurosci.* 25, 7429–7437
- 97 Amano, T. *et al.* (2010) Synaptic correlates of fear extinction in the amygdala. *Nat. Neurosci.* 13, 489–494
- 98 Ehrlich, I. *et al.* (2009) Amygdala inhibitory circuits and the control of fear memory. *Neuron* 62, 757–771
- 99 McDonald, A.J. *et al.* (1996) Projections of the medial and lateral prefrontal cortices to the amygdala: a *Phaseolus vulgaris* leucoagglutinin study in the rat. *Neuroscience* 71, 55–75
- 100 Vertes, R.P. (2004) Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse* 51, 32–58