Prefrontal involvement in the regulation of emotion: convergence of rat and human studies

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Emotion regulation is a process by which we control when and where emotions are expressed. Paradigms used to study the regulation of emotion in humans examine controlled responses to emotional stimuli and/or the inhibition of emotional influences on subsequent behavior. These processes of regulation of emotion trigger activation of the ventromedial prefrontal cortex and inhibition of the amygdala. A similar pattern of activation is seen in rodents during recall of fear extinction, an example of emotional regulation. The overlap in circuitry is consistent with a common mechanism, and points toward future experiments designed to bridge human and rodent models of emotion regulation.

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Introduction: definition of emotion regulation

Regulation of emotion is a diverse set of control processes aimed at manipulating when, where, how and which emotion we experience and express [1]. These control processes can occur at both automatic and conscious levels of processing. Emotion can be regulated to accomplish various goals. For example, from an intrapersonal perspective, we regulate our emotions in at least two ways: to maximize opportunities for positive emotions and to minimize opportunities for negative emotions. First, we more deliberately attend to information, events and people that make us feel good and avoid or ignore those that evoke negative emotions. We control which emotions we experience through the selection or creation of particular situations. Second, once an emotional experience has arisen, we can manipulate the magnitude of our response to suppress negative emotions quickly and amplify or perpetuate positive emotions.

From an interpersonal perspective, people need to regulate the magnitude of their emotional expression in reference to display rules. There are societal norms for how much one should express certain emotions (e.g. extreme pride is mostly acceptable only in politics and sports). Many clinical disorders of emotion or mood are characterized by otherwise 'normal' emotions that have lasted too long or are too extreme given the external environment. Additionally, one might need to produce a facial expression of emotion in the absence of a phenomenological emotional experience when the situation demands it (e.g. smiling in response to the poor humor of your boss).

In summary, regulation of emotion involves a diverse set of cognitive processes that occur both automatically and with effort. Such processes enable individuals to enjoy mostly positive emotions while avoiding negative emotions [2], to increase or decrease emotional intensity, and to manufacture emotional facial expression in reference to social norms. What have we learned about the neural systems supporting these psychological processes? Although studies of humans and rats have often focused on very different kinds of paradigms for studying regulation of emotion, the neural areas associated with regulation of emotion have been remarkably convergent across these levels of analysis. We summarize recent examples of prefrontal involvement of emotion regulation using rat and human models, and suggest future experiments capable of bridging these two lines of research.

Paradigms in humans: suppression, reappraisal and integration with cognition

Within the past two years, most of the human research in regulation of emotion has consisted of suppression or reappraisal paradigms. In suppression paradigms, participants are instructed to inhibit any reaction to emotional stimuli (e.g. sad films [3]; unpleasant pictures [4••]). In reappraisal paradigms, participants are instructed to reinterpret the picture in a new way to reduce or increase their emotional reaction (unpleasant pictures [5–7]). These paradigms focus on the regulation of the primary emotional experience. An advantage of these paradigms is that participants can be explicitly instructed to exert regulatory processes. A disadvantage of these paradigms is that the main evidence of emotion regulation is the subject's self-report, which is subjective. A second approach is to examine the regulation of emotional influences on subsequent behavior, rather than regulation of the experience itself. An advantage of these paradigms is that

changes in subsequent behavior provide measures of regulation of emotion that are less subjective than participant reports. Some studies have examined the suppression or application of emotional influences on subsequent decisions [8••,9]. Another study used an emotional 'go nogo' task, in which participants were required to regulate the behavioral tendencies to approach or avoid stimuli associated with emotion [10].

Regulation circuits in humans

What common neural substrates have emerged from human studies using these paradigms to examine regulation of emotion? Research in the past two years has reinforced the role of the prefrontal cortex in the regulation of emotion. In particular, a host of brain imaging studies have found activation in the orbitofrontal and/or inferior frontal cortex in association with suppressing or reappraising negative emotional stimuli (e.g. Brodmann's area [BA] 11 [3,4••,7]; BA 47 [3,5,6]) and with suppressing the influence of negative emotional stimuli on subsequent behavior (BA 47 [8••]). For example, activation in this frontal region is associated with attempts to downregulate emotional responses to negative pictures by reframing the negative scenes as less negative (either by viewing the picture with a sense of detachment or by imagining the improvement of the depicted scenario) [5]. Activation in this region is also associated with preventing a negative mood from influencing one's choice in a roulette game [8••]. Negative moods increase the salience of any potential threat and people are more likely to risk less when in a negative mood state. Activation in the left lateral orbitofrontal cortex is associated with suppressing this prepotent tendency. However, the one study conducted in patients with orbitofrontal lesions (primarily BA 11) did not find deficits in the ability to suppress emotional responses to negative and positive emotional stimuli [11].

Additionally, prefrontal cortex is theorized to have an inverse relationship with amygdala activity during regulation of emotion. Some studies have found increased prefrontal cortex activity in association with decreases in left amygdala activity when participants are required to reappraise negative emotional stimuli [5,6], but others have not [7]. Conversely, increased amygdala activity is found when participants are instructed to increase their negative emotional responses [7]. Amygdala activity is also correlated with slower reaction times when approach behavior is required in the context of fearful or neutral facial expressions [10].

Increases in dorsal anterior cingulate activity have also been found in studies using suppression and reappraisal paradigms (BA 10/32 [3,5–7]). Similar to the other prefrontal areas, dorsal anterior cingulate activity tends to increase in relation to amygdala activity while participants strive to inhibit their emotional reactions.

The involvement of multiple frontal areas and their inverse relationship with amygdala activity raises the question of whether these areas support distinct processes comprising regulation of emotion. Many researchers hypothesize that the orbitofrontal or inferior frontal cortex region executes inhibitory control over the amygdala [3,7,12]. Specifically, the orbitofrontal or inferior frontal cortex mediates the top-down control of a prepotent tendency stored in the amygdala. The inverse relationship between BA 10 and the amygdala, coupled with a lack of direct connectivity, has led to the hypothesis that the orbitofrontal cortex mediates this relationship [4••,7]. BA 10 might maintain the goal of downregulating emotion and transferring this information to the orbitofrontal region, which then carries out the suppression of amygdala activity. Activity in BA 25/32 is theorized to underlie autonomic and endocrine changes associated with emotional suppression (e.g. increased skin conductance response [SCR] associated with suppression of negative emotion).

Paradigms and circuits in rats: extinction of conditioned fear

Although it is a challenge to study regulation of emotion in rats, recent progress has been made on extinction of conditioned fear. In extinction, a tone previously paired with footshock is repeatedly presented without the shock, so that conditioned fear responses diminish. Because extinction does not erase the fear association, it can be thought of as regulating fear expression [13]. Similar to other forms of learning, extinction occurs in two phases: an initial learning phase and a subsequent recall phase. Early lesion studies implicated the ventromedial prefrontal cortex (vmPFC) in long-term retention and/or recall of extinction [14,15]. The vmPFC includes the prelimbic cortex (BA 32) and the infralimbic cortex (BA 25). Recent studies suggest that vmPFC is an important site of extinction-related plasticity. Interfering with protein synthesis [16] or protein kinases [17] in the vmPFC has no effect on short-term extinction, but impairs consolidation of extinction. Lesion studies have been followed up with pharmacological inactivation studies showing that rats have difficulty recalling extinction that was learned with the medial prefrontal cortex (mPFC) off-line [18•]. Similar effects were recently reported with hippocampal inactivation [19•], suggesting that hippocampal inputs to the vmPFC are responsible for gating the expression of extinction. Indeed, extinction training potentiated hippocampal inputs to vmPFC [20]. The expression of extinction depends heavily on contextual factors, and this might be mediated by a hippocampal–prefrontal circuit that gates amygdala-dependent fear expression (see [21]).

Consistent with human studies showing prefrontal inhibition of the amygdala, recent rat studies have extended this idea to implicate specific circuits. The amygdala

contains islands of GABAergic interneurons, known as intercalated (ITC) cells, that inhibit the central nucleus output neurons. Stimulation of the mPFC increases immediate-early gene expression in ITC cells [22], decreases the excitability of central output neurons [23] and reduces conditioned freezing [24]. Thus, the mPFC could gate fear expression through a powerful 'off-switch' within the amygdala, in the form of intercalated neurons [25]. From a clinical point of view, one would want to selectively activate the ITC cells, which could be difficult. However, recent findings suggest that this might be accomplished through manipulation of dopamine D1 receptors [26], μ-opioid receptors [26], or oxytocin receptors [27]. mPFC could also inhibit fear through projections to subcortical areas involved in fear expression [28•]. For example, vmPFC projections to the dorsal raphé have been suggested to mediate the beneficial effects of 'controllability' in aversive instrumental conditioning [29••].

Extinction circuits in humans

Recently, functional and structural imaging techniques have been used to map extinction in humans. In agreement with rodent studies, extinction training activated the vmPFC in addition to the lateral amygdala [30]. Spurred by across-day extinction studies in rats, researchers are starting to test for recall of extinction in human subjects [31,32]. Paralleling the results of rat studies, in humans recall of extinction (fear inhibition) learned the previous day is correlated with vmPFC blood oxygenation level-dependent (BOLD) responses [32] and vmPFC cortical thickness [33••]. Thus, the ventral prefrontal regions correlated with reduced fear expression during extinction (BA 10, 25, 32) are a subset of the regions involved in reappraisal and suppression and the regulation of emotional influence on cognition [3–5,7].

The prefrontal cortex is not purely inhibitory

Recent findings in rats suggest that the mPFC can also stimulate fear expression, under certain circumstances. Pharmacological inactivation of the mPFC in rats that have previously been fear conditioned reduces the expression of conditioned fear [18•,34,35], and interfering with molecular events necessary for plasticity in mPFC prevents acquisition of olfactory conditioning [36••] and trace fear conditioning [37]. The apparent discrepancy between these findings and the role of the mPFC suggests differences among subregions of mPFC. Recent evidence in rats suggests that the more ventrally located infralimbic cortex (IL; BA 25) has an inhibitory role, whereas the more dorsally located prelimbic cortex (PL; BA 32) is excitatory. The IL targets the ITC cells and central-lateral amygdala [38] (both inhibitory), whereas the PL targets the basal subdivision of the amygdala [38,39], which is necessary for fear expression [40]. Firing in PL neurons is followed 20 ms later by firing in the basal amygdala [41•], suggesting a direct excitatory projection. Neurons in PL and IL respond oppositely to conditioned fear stimuli [42•], and inactivation of IL (but not PL) impairs response inhibition in appetitive conditioning [43]. A similar dorsal versus ventral distinction in PFC is emerging in human imaging studies. As opposed to subgenual cingulate, supragenual cingulate was positively correlated with fear acquisition [32] and a negative interpretation of face stimuli [44]. Thus, the mPFC might be capable of bidirectional control of fear through divergent projections to the amygdala.

Conclusions and future directions

From the preceding discussion, there are several apparent areas of convergence between rat and human studies on regulation of emotion. Re-evaluation of negative stimuli, either through cognitive re-appraisal or suppression (humans) or through extinction (humans and rats), activates vmPFC and inhibits the amygdala. This suggests the existence of a medial inhibitory system capable of controlling amygdala responsiveness and expression of negative emotion. The circuitry of cognitive and Pavlovian processes might overlap in the regulation of emotion. There is also an excitatory circuit within the PFC that augments fear expression, which is located dorsal to fear-inhibiting regions of mPFC and could be capable of exciting the amygdala. Despite the convergence, however, there are several gaps that should be addressed by future experiments.

First, additional methods in more diverse subject populations are needed to determine the general applicability of this circuitry. For example, most of the human research consists of fMRI studies of healthy female adults (but see: elderly adults [7]; children [3]). Women have been most often studied because of gender differences found in early studies of emotion, and because women react most consistently to commonly used emotional stimuli. Research conducted in males and different age groups will be important. Other techniques such as event-related potentials (ERPs), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and lesion approaches will help to translate rat findings obtained from evoked potential, microstimulation, unit recording and lesion studies.

Second, we need to understand psychological commonalities within the circuitry for regulation of emotion. To accomplish this, future studies might employ multiple regulation processes within the same experimental group. For example, a single study could examine both suppression and reappraisal, or both the regulation of emotional experience and the regulation of emotional influence on subsequent behavior. To bridge the human and rat literature, human studies could compare extinction, reappraisal and suppression to test the hypothesis that they share a common circuitry.

Third, future research should branch out from studies requiring the regulation of negative emotional stimuli.

Studies that distinguish different negative emotions (anger versus fear), in addition to positive emotions, are needed. Positive emotion, in particular, presents measurement problems in both humans and rats and, therefore, has not received much attention. mPFC has been attributed a role in regulating sexual behavior in rats [45] and humans [46]. See [47] for a role of mPFC in extinction of appetitive conditioning.

Fourth, we need to characterize the differences between PFC subregions in rats and humans and identify homologous structures and their interactions. For example, inter-regional cross-correlations of neuronal spike trains in rats can be compared to seed or path analysis in fMRI data. The ultimate goal of such work would be to identify behavioral and/or pharmacological techniques to augment the positive-biasing of emotional behavior by the PFC in people suffering from disorders of regulation of emotion.

Update

Since writing this paper, a new fMRI study by Kalisch *et al.* [48•] has appeared showing that recall of extinction learned the previous day activates the vmPFC and hippocampus in a context-dependent manner, suggesting that regulation of fear after extinction in humans involves a hippocampal-prefrontal circuit.

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