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# Prefrontal control of fear: more than just extinction

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Although fear research has largely focused on the amygdala, recent findings highlight cortical control of the amygdala in the service of fear regulation. In rodent models, it is becoming well established that the infralimbic (IL) prefrontal cortex plays a key role in extinction learning, and recent findings are uncovering molecular mechanisms involved in extinction-related plasticity. Furthermore, mounting evidence implicates the prelimbic (PL) prefrontal cortex in the production of fear responses. Both IL and PL integrate inputs from the amygdala, as well as other structures to gate the expression of fear via projections to inhibitory or excitatory circuits within the amygdala. We suggest that dual control of the amygdala by separate prefrontal modules increases the flexibility of an organism's response to danger cues.

## Addresses

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## Back to cortical control of fear

Over a century ago, the prevalent notion was that evolutionary recent cortical areas exert control over evolutionary older subcortical areas [1,2]. Later, the prefrontal cortex (PFC) emerged as a critical regulator of aversive conditioning [3,4]. More recently, focus shifted to the amygdala as a hub of emotions [5,6], when it was reported that interfering with activity in the PFC or other cortical areas did not prevent fear learning. A wealth of data supports the role of the amygdala in fear learning. Nonetheless, interest in the role of PFC in emotion re-emerged with the discovery that the medial PFC (mPFC) was necessary for extinction of conditioned fear [7,8]. In the last few years, it has become clear that mPFC contains different subregions, playing unique roles in fear learning and extinction. In particular, it was shown that the infralimbic (IL) region of the mPFC is a critical site of plasticity for the inhibition of fear responses after extinction, and new findings are uncovering the mechanisms

involved. In contrast, mounting evidence implicates the prelimbic (PL) region of the mPFC in the production of fear responses. Both IL and PL are thought to exert their influences via the amygdala, suggesting that the amygdala must work with mPFC to orchestrate fear responses. Here, we review these recent findings, and consider the possible significance of this dual cortical control of amygdala-based fear responses.

## IL-mediated inhibition of fear after extinction

Although previous recording and lesion studies have implicated IL in extinction [9], recent findings have identified specific molecular cascades in IL involved in extinction learning. It is well established that *N*-methyl-D-aspartate receptors (NMDAR) within the amygdala are necessary for extinction [10,11], but more recent reports implicate IL NMDAR in extinction, especially in the period immediately following extinction [12–14]. The role of IL in extinction consolidation is further supported by recent findings using post-extinction infusions into IL of the inactivating agent muscimol [15], a cannabinoid antagonist [16], or dopamine (D1) antagonist [17]. Several of these pathways are thought to interact with brain-derived neurotrophic factor (BDNF) to form long-term memory. Accordingly, histone acetylation of the BDNF gene promoter in IL was found to be correlated with extinction [18], and mice exhibiting a deficient BDNF gene showed impaired extinction and reduced IL volume [19,20]. Furthermore, mice with deficient 5-HT transporter activity showed poor extinction and shrunken IL dendrites [21], and similar behavioral findings were obtained for cAMP-responsive element-binding protein-mediated gene expression in IL [22]. Together, these molecular, pharmacological, and genetic studies suggest new targets in IL for facilitating extinction consolidation.

What might constitute a physiological signature of extinction learning in IL? The degree of extinction success is correlated with high-frequency bursting in IL neurons immediately after extinction training [12]. Bursting in IL could increase local calcium currents as well as increase the depolarization and calcium entry in downstream targets of IL, which would favor the development of extinction-related plasticity at both sites. Extinction-related bursting could be due to potentiation of synaptic inputs, and/or increases in intrinsic excitability. In support of the latter possibility, it was recently shown that conditioning and extinction decreased and increased, respectively, the intrinsic excitability of IL neurons [23<sup>\*</sup>]. Interestingly, following extinction, IL neurons tended to burst in response to intracellularly injected

current. This suggests that IL neurons are more responsive to their inputs following extinction. In support of this, studies using the activity marker c-Fos show that IL activity was increased in rodents that successfully retrieved extinction [24<sup>\*</sup>], but not in strains that are extinction-deficient [25<sup>\*</sup>,26]. In adolescent rats, where extinction does not require NMDAr, IL was not necessary for extinction, nor was IL activated by extinction [27<sup>\*</sup>]. Thus, NMDAr-mediated potentiation of fear inhibitory circuits appears to be a hallmark of adult extinction.

### PL-mediated excitation of fear expression

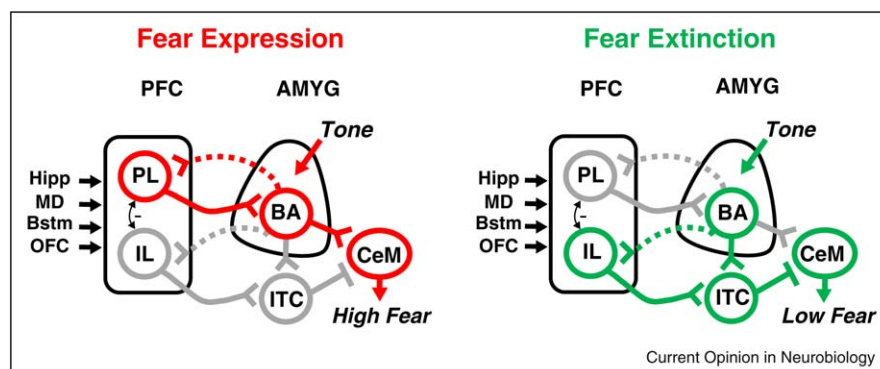
Although earlier studies suggested a role of PL in excitation of fear [28,29], new studies using a variety of techniques have confirmed and extended that role [51]. Inactivation restricted to PL reduced expression of conditioned fear to contextual and auditory stimuli, but had no effect on the expression of innate fears, or the development of plasticity related to conditioning or extinction [15,30]. In other words, PL activity is necessary for fear expression, but not for fear plasticity (in the amygdala or other structures). Consistent with such a role, PL neurons are activated by conditioned stimuli [24<sup>\*</sup>,31<sup>\*\*</sup>]. However, unlike neurons in lateral amygdala whose conditioned responses last only a few hundred milliseconds [32], PL neurons show sustained increases in activity that mirror the time course of freezing responses, lasting tens of seconds [31<sup>\*\*</sup>]. PL is the first site to show conditioned responses that model fear responses, and suggests that similar sites may be found in targets of PL such as the basal nucleus of the amygdala (BA). Furthermore, PL activity is increased in rats that fail to retrieve extinction memory [24<sup>\*</sup>,31<sup>\*\*</sup>], and decreased by pharmacological

agents that reduce fear expression, such as propranolol [33] and cannabidiol [34]. Thus, to a large extent, PL output predicts the magnitude of a fear response.

### Outputs and inputs of IL and PL

The opposite effects of IL and PL on fear expression are thought to be mediated by outputs to different targets within the amygdala [29,35]. IL projects to the intercalated cell masses (ITC) and lateral division of the central nucleus (CeL) both of which consist of GABAergic neurons that inhibit amygdala output neurons of the medial division of the central nucleus (CeM). In contrast, PL targets the BA. This suggests that ITC cells should be critical for extinction, whereas BA should be critical for fear expression. Due to the small size of ITC islands, it has been difficult to target them experimentally. Capitalizing on a unique distribution of receptor subtypes, however, it was recently observed that lesions or activation of ITCs impaired or facilitated extinction, respectively [36<sup>\*</sup>,37<sup>\*</sup>]. In contrast to ITCs, the situation with BA is more complex. Focal inactivation of BA prevented not only renewal of fear after extinction, but also expression of extinction, depending on the time point of inactivation [38<sup>\*\*</sup>]. This suggests that BA is recruited only when it is necessary to switch from a fear state to a low fear state, or vice versa. In support of this switching function, there exist separate classes of BA neurons encoding fear or extinction [38<sup>\*\*</sup>]. Such findings point toward the existence of a BA network, which interacts with an ITC-CeL network to modulate CeM output neurons. Also, non-amygdala outputs of PL and IL, such as the nucleus accumbens for appetitive behavior [39] and raphe nucleus for 'controlability' [40] are emerging as important for emotional regulation.

Figure 1



Prefrontal control of fear expression and extinction. During fear expression (left) and extinction (right) of auditory fear conditioning, tone responses from the amygdala (amyg) get integrated by the prelimbic (PL) or infralimbic (IL) prefrontal cortex with converging information from diverse sources such as hippocampus (Hipp), brainstem monoamines (Bstm), mediadorsal thalamus (MD), and orbital prefrontal cortex (OFC) to determine whether or not to produce a fear response. Fear excitation involves PL projections back to basal amygdala (BA), whereas fear inhibition involves IL projections to amygdala-intercalated cells (ITC). In turn, BA excites neurons in the medial division of the central nucleus of the amygdala (CeM) to produce fear responses, while ITCs inhibit these amygdala output neurons thereby inhibiting fear responses. Thus, the same conditioned stimulus (e.g. a tone) signals either high fear (red) or low fear (green) states in the appropriate circumstances.

IL and PL receive inputs from a number of sources that could facilitate fear regulation. An important fear-related input is the amygdala itself. Within the BA, both fear and extinction neurons project to mPFC [38<sup>••</sup>], although it is unclear whether they project differentially to IL and PL. This suggests that the amygdala may recruit IL and PL [41–43], which in turn regulate amygdala output. Another key input is the ventral hippocampus (Hipp), which unlike the dorsal hippocampus, projects monosynaptically to PL, IL, and BA [44]. Extinction training is correlated with increases in the size of ventral Hipp–mPFC evoked potentials [45], suggesting potentiation of hippocampal inputs to IL. Weakening this pathway with low-frequency stimulation or stress impairs extinction [45,46]. It has been suggested that the hippocampus drives bursting in IL neurons, which may strengthen tone inputs from BA, leading to inhibition of fear expression to the tone [9]. PL and IL also receive a massive input from the mediodorsal nucleus of the thalamus (MD), which is potentiated for several days following (but not right after) extinction training [45]. In light of these connectivity findings, we are beginning to understand how PL and IL can integrate contextual information with emotional salience and other inputs, to regulate fear expression and extinction (see Figure 1).

### Why does the amygdala ‘need’ the prefrontal cortex for fear?

Given that auditory fear conditioning can occur in the absence of cortical areas, one might be tempted to think that the amygdala, together with its subcortical connections, is sufficient for normal fear learning and expression. However, as reviewed above, PL and IL are required for fear expression and extinction, under normal circumstances. This suggests that the mPFC has access to information that the amygdala does not, which enables emotional regulation, such as the emotional history of a stimulus (amygdala), context and time (hippocampus), internal state (brainstem monoamines), and cognitive-mnemonic information (orbital and lateral PFC). These convergent signals are integrated by mPFC neurons and, if a threshold is exceeded, they drive fear. Indeed, the sustained conditioned responses of PL neurons may represent the outcome of such integration. The brief conditioned response of lateral amygdala neurons projecting to PL may provide a bias signal to mPFC that favors (but does not ultimately determine) the production of a fear response. In the same way, integration of diverse types of information in IL may be needed to determine whether or not to express extinction to a given stimulus, in a given context, at a given time, etc. In addition, PL excitatory and IL inhibitory networks could interact via reciprocal inhibitory connections [47]. Consequently, prefrontal control of the amygdala increases the flexibility of an organism’s response to danger cues.

In addition to diverse inputs, mPFC also has divergent outputs capable of coordinating different and sometimes competing brain systems [48,49<sup>•</sup>]. During extinction, for example, at the same time that the mPFC is terminating a fear response (via amygdala ITC neurons), it may also be triggering an appetitive approach response (via nucleus accumbens), and learning controllability (via the raphe nucleus). During renewal of fear, the excitatory drive emanating from mPFC would converge with amygdala projections to the periaqueductal grey, to produce defensive responses, while at the same time suppressing approach behaviors, via the midbrain dopaminergic system [50]. Studies within the next few years are likely to focus on how PFC interacts with the amygdala and other areas during competition between aversive and appetitive behaviors.

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### References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
  - of outstanding interest
1. Darwin C: *The Expression of the Emotions in Man and Animals*. Chicago: University of Chicago Press; 1965: 1872.
  2. Jackson JH: **Croonian Lectures on evolution and dissolution of the nervous system**. *Lancet* 1884, **i**:555-558.
  3. Gibbs CM, Powell DA: **Neuronal correlates of classically conditioned bradycardia in the rabbit: studies of the medial prefrontal cortex**. *Brain Res* 1988, **442**:86-96.
  4. Disterhoft JF, Olds J: **Differential development of conditioned unit changes in thalamus and cortex of rat**. *J Neurophysiol* 1972, **35**:665-679.
  5. LeDoux JE: **Emotion and the amygdala**. In *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*. Edited by Aggleton JP. Wiley-Liss, Inc.; 1992:339-351.
  6. Davis M: **The role of the amygdala in conditioned fear**. In *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*. Edited by Aggleton JP. Wiley-Liss, Inc.; 1992:255-306.
  7. Quirk GJ, Garcia R, Gonzalez-Lima F: **Prefrontal mechanisms in extinction of conditioned fear**. *Biol Psychiatry* 2006, **60**:337-343.
  8. Sotres-Bayon F, Cain CK, LeDoux JE: **Brain mechanisms of fear extinction: historical perspectives on the contribution of prefrontal cortex**. *Biol Psychiatry* 2006, **60**:329-336.
  9. Quirk GJ, Mueller D: **Neural mechanisms of extinction learning and retrieval**. *Neuropsychopharmacology* 2008, **33**:56-72.
  10. Falls WA, Miserendino MJ, Davis M: **Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala**. *J Neurosci* 1992, **12**:854-863.
  11. Sotres-Bayon F, Bush DE, LeDoux JE: **Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala**. *Neuropsychopharmacology* 2007, **32**:1929-1940.
  12. Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ: **Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex**. *Neuron* 2007, **53**:871-880.

13. Sotres-Bayon F, Diaz-Mataix L, Bush DE, LeDoux JE: **Dissociable roles for the ventromedial prefrontal cortex and amygdala in fear extinction: NR2B contribution.** *Cereb Cortex* 2009, **19**:474-482.
14. Laurent V, Westbrook RF: **Distinct contributions of the basolateral amygdala and the medial prefrontal cortex to learning and relearning extinction of context conditioned fear.** *Learn Mem* 2008, **15**:657-666.
15. Laurent V, Westbrook RF: **Inactivation of the infralimbic but not the prelimbic cortex impairs consolidation and retrieval of fear extinction.** *Learn Mem* 2009, **16**:520-529.
16. Lin HC, Mao SC, Su CL, Gean PW: **The role of prefrontal cortex CB1 receptors in the modulation of fear memory.** *Cereb Cortex* 2009, **19**:165-175.
17. Hikind N, Maroun M: **Microinfusion of the D1 receptor antagonist, SCH23390 into the IL but not the BLA impairs consolidation of extinction of auditory fear conditioning.** *Neurobiol Learn Mem* 2008, **90**:217-222.
18. Bredy TW, Wu H, Crego C, Zellhoefer J, Sun YE, Barad M: **Histone modifications around individual BDNF gene promoters in prefrontal cortex are associated with extinction of conditioned fear.** *Learn Mem* 2007, **14**:268-276.
19. Yu H, Wang Y, Pattwell S, Jing D, Liu T, Zhang Y, Bath KG, Lee FS, Chen ZY: **Variant BDNF Val66Met polymorphism affects extinction of conditioned aversive memory.** *J Neurosci* 2009, **29**:4056-4064.
20. Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, Jing D, Tottenham N, Amso D, Somerville LH, Voss HU, Glover G, Ballon DJ, Liston C, Teslovich T, Van Kempen T, Lee FS, Casey BJ: **A genetic variant BDNF polymorphism alters extinction learning in both mouse and human.** *Science* 2010, **327**:863-866.
21. Wellman CL, Izquierdo A, Garrett JE, Martin KP, Carroll J, Millstein R, Lesch KP, Murphy DL, Holmes A: **Impaired stress-coping and fear extinction and abnormal corticolimbic morphology in serotonin transporter knock-out mice.** *J Neurosci* 2007, **27**:684-691.
22. Mamiya N, Fukushima H, Suzuki A, Matsuyama Z, Homma S, Frankland PW, Kida S: **Brain region-specific gene expression activation required for reconsolidation and extinction of contextual fear memory.** *J Neurosci* 2009, **29**:402-413.
23. Santini E, Quirk GJ, Porter JT: **Fear conditioning and extinction differentially modify the intrinsic excitability of infralimbic neurons.** *J Neurosci* 2008, **28**:4028-4036.
- By combining slice recordings with fear extinction, the authors provide cellular evidence that the infralimbic cortex regulates fear expression through bidirectional changes in intrinsic excitability, induced by conditioning and extinction.
24. Knapska E, Maren S: **Reciprocal patterns of c-Fos expression in the medial prefrontal cortex and amygdala after extinction and renewal of conditioned fear.** *Learn Mem (Cold Spring Harbor, NY)* 2009, **16**:486-493.
- By using c-fos as an activity marker, this is the first study to map prefrontal and amygdala areas during fear conditioning, extinction, and renewal. In support of dual control of fear by prefrontal cortex, they found that prelimbic cortex is activated during all high fear states, and the infralimbic cortex is activated during all low fear states.
25. Hefner K, Whittle N, Juhasz J, Norcross M, Karlsson RM, Saksida LM, Bussey TJ, Singewald N, Holmes A: **Impaired fear extinction learning and cortico-amygdala circuit abnormalities in a common genetic mouse strain.** *J Neurosci* 2008, **28**:8074-8085.
- The authors of this study exploited interstrain differences in mice to identify neural correlates underlying extinction failure and success. Consistent with the role of the infralimbic cortex in successful extinction retrieval, the mouse strain that failed to extinguish had lower infralimbic activity relative to controls.
26. Muigg P, Hetzenauer A, Hauer G, Hauschild M, Gaburro S, Frank E, Landgraf R, Singewald N: **Impaired extinction of learned fear in rats selectively bred for high anxiety — evidence of altered neuronal processing in prefrontal-amygdala pathways.** *Eur J Neurosci* 2008, **28**:2299-2309.
27. Kim JH, Hamlin AS, Richardson R: **Fear extinction across development: the involvement of the medial prefrontal cortex as assessed by temporary inactivation and immunohistochemistry.** *J Neurosci* 2009, **29**:10802-10808.
- This study shows that fear extinction engages different neural circuits across development. Extinction in young rats requires the amygdala but not the prefrontal cortex, while extinction in adult rats requires both the amygdala and prefrontal cortex.
28. Blum S, Hebert AE, Dash PK: **A role for the prefrontal cortex in recall of recent and remote memories.** *Neuroreport* 2006, **17**:341-344.
29. Vidal-Gonzalez I, Vidal-Gonzalez B, Rauch SL, Quirk GJ: **Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear.** *Learn Mem* 2006, **13**:728-733.
30. Corcoran KA, Quirk GJ: **Activity in prelimbic cortex is necessary for the expression of learned, but not innate, fears.** *J Neurosci* 2007, **27**:840-844.
31. Burgos-Robles A, Vidal-Gonzalez I, Quirk GJ: **Sustained conditioned responses in prelimbic prefrontal neurons are correlated with fear expression and extinction failure.** *J Neurosci* 2009, **29**:8474-8482.
- Consistent with the idea that the prelimbic cortex is necessary for the expression of conditioned fear, this study shows that the neural activity of prelimbic neurons mirror freezing responses. The authors suggest that prelimbic neurons convert phasic inputs from the basolateral amygdala into sustained outputs.
32. Maren S, Quirk GJ: **Neuronal signalling of fear memory.** *Nat Rev Neurosci* 2004, **5**:844-852.
33. Rodriguez-Romaguera J, Sotres-Bayon F, Mueller D, Quirk GJ: **Systemic propranolol acts centrally to reduce conditioned fear in rats without impairing extinction.** *Biol Psychiatry* 2009, **65**:887-892.
34. Lemos JI, Resstel LB, Guimaraes FS: **Involvement of the prelimbic prefrontal cortex on cannabidiol-induced attenuation of contextual conditioned fear in rats.** *Behav Brain Res* (1):2009:105-111.
35. Paré D, Quirk GJ, LeDoux JE: **New vistas on amygdala networks in conditioned fear.** *J Neurophysiol* 2004, **92**:1-9.
36. Likhtik E, Popa D, Apergis-Schoute J, Fidacaro GA, Paré D: **Amygdala intercalated neurons are required for expression of fear extinction.** *Nature* 2008, **454**:642-645.
- Before this study, the role of intercalated cells in fear extinction was based on anatomical and physiological studies and had not been tested directly. In this study the authors resolved this issue by demonstrating that a novel toxin that selectively damages intercalated neurons impairs the expression of extinction.
37. Jungling K, Seidenbecher T, Sosulina L, Lesting J, Sangha S, Clark SD, Okamura N, Duangdao DM, Xu YL, Reinscheid RK *et al.*: **Neuropeptide S-mediated control of fear expression and extinction: role of intercalated GABAergic neurons in the amygdala.** *Neuron* 2008, **59**:298-310.
- Consistent with the role of amygdala-intercalated cell masses, the authors of this study found that the newly discovered neuropeptide S facilitates fear extinction by enhancing excitatory neurotransmission at lateral amygdala-intercalated synapses.
38. Herry C, Ciocchi S, Senn V, Demmou L, Müller C, Luthi A: **Switching on and off fear by distinct neuronal circuits.** *Nature* 2008, **454**:600-606.
- The authors of this groundbreaking study identified populations of basal amygdala neurons that are selectively active during high fear (fear neurons) or low fear (extinction neurons) states. Further, focal inactivation of this region prevents behavioral changes between low and high fear states, suggesting a switching function in this amygdala region.
39. McGinty VB, Grace AA: **Selective activation of medial prefrontal-to-accumbens projection neurons by amygdala stimulation and Pavlovian conditioned stimuli.** *Cereb Cortex* 2008, **18**:1961-1972.
40. Baratta MV, Zarza CM, Gomez DM, Campeau S, Watkins LR, Maier SF: **Selective activation of dorsal raphe nucleus-projecting neurons in the ventral medial prefrontal cortex by controllable stress.** *Eur J Neurosci* 2009, **30**:1111-1116.

41. Floresco SB, Tse MT: **Dopaminergic regulation of inhibitory and excitatory transmission in the basolateral amygdala-prefrontal cortical pathway.** *J Neurosci* 2007, **27**:2045-2057.
42. Laviolette SR, Lipski WJ, Grace AA: **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* 2005, **25**:6066-6075.
43. Tan H, Lauzon NM, Bishop SF, Bechard MA, Laviolette SR: **Integrated cannabinoid CB1 receptor transmission within the amygdala-prefrontal cortical pathway modulates neuronal plasticity and emotional memory encoding.** *Cereb Cortex* 2009. [Epub ahead of print].
44. Hoover WB, Vertes RP: **Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat.** *Brain Struct Funct* 2007, **212**:149-179.
45. Hugues S, Garcia R: **Reorganization of learning-associated prefrontal synaptic plasticity between the recall of recent and remote fear extinction memory.** *Learn Mem* 2007, **14**:520-524.
46. Garcia R, Spennato G, Nilsson-Todd L, Moreau JL, Deschaux O: **Hippocampal low-frequency stimulation and chronic mild stress similarly disrupt fear extinction memory in rats.** *Neurobiol Learn Mem* 2008, **89**:560-566.
47. van Aerde KI, Heistek TS, Mansvelter HD: **Prelimbic and infralimbic prefrontal cortex interact during fast network oscillations.** *PLoS One* 2008, **3**:e2725.
48. Miller EK, Cohen JD: **An integrative theory of prefrontal cortex function.** *Ann Rev Neurosci* 2001, **24**:167-202.
49. Rich EL, Shapiro M: **Rat prefrontal cortical neurons selectively code strategy switches.** *J Neurosci* 2009, **29**:7208-7219. Using unit recording and a modified t-maze task, the authors characterize the way in which infralimbic and prelimbic neurons differentially switch between hippocampal-dependent and caudate-dependent strategies.
50. Jhou TC, Fields HL, Baxter MG, Saper CB, Holland PC: **The rostromedial tegmental nucleus (RMTg), a GABAergic afferent to midbrain dopamine neurons, encodes aversive stimuli and inhibits motor responses.** *Neuron* 2009, **61**:786-800.
51. Choi DC, Maguschak KA, Ye K, Jang SW, Myers KM, Ressler KJ: **Prelimbic cortical BDNF is required for memory of learned fear but not extinction or innate fear.** *Proc Natl Acad Sci USA* 2010, **107**:2675-2680.