AMYGDALA MICROCIRCUITS MEDIATING FEAR EXPRESSION AND EXTINCTION

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Abstract

This review summarizes the latest developments in our understanding of amygdala networks that support classical fear conditioning, the experimental paradigm most commonly used to study learned fear in the laboratory. These recent advances have considerable translational significance as congruent findings from studies of fear learning in animals and humans indicate that anxiety disorders result from abnormalities in the mechanisms that normally regulate conditioned fear. Due to the introduction of new techniques and the continued use of traditional approaches, it is becoming clear that conditioned fear involves much more complex networks than initially believed, including coordinated interactions between multiple excitatory and inhibitory circuits within the amygdala.

Keywords
amygdala; fear conditioning; emotions; learning; memory

For didactic reasons, we begin with the original model of fear conditioning proposed in the early 90’s [1,2]. Indeed, while subsequent work has required that this model be amended, its basic outline has not changed, allowing readers to put recent advances into perspective. Based on lesion, inactivation, and unit recording studies reviewed elsewhere [3•], it was initially proposed that convergence of synaptic inputs about the conditioned (CS) and unconditioned (US) stimuli leads to the potentiation of synapses conveying CS information to the lateral amygdala (LA). As a result, LA neurons would later respond more strongly to the CS and these cells, via their projection to the central (Ce) nucleus and from there to brainstem and hypothalamic fear effectors, would trigger conditioned fear responses. Thus, in the original model, LA was conceptualized as the main input station of the amygdala for CS information, and Ce as the main output station for conditioned fear responses. These two basic tenets have withstood experimental scrutiny.¹

Transmission of CS information from LA to fear output Ce neurons

While the original model invoked direct projections from LA to Ce, and from there, to fear effector neurons (Fig. 1A), it was pointed out [9] that there are no direct links between LA,
the main point of entry for thalamic and cortical information about CSs [10,11], and the
medial sector of Ce (CeM), contributing most amygdala projections to brainstem fear
effectors (Fig. 1B) [12,13]. These results suggested that downstream of LA, was one or more
population(s) of cells relaying CS information to CeM. The anatomical literature [9,14,15]
suggested two potential candidates (Fig. 1B): GABAergic neurons in the lateral sector of Ce
(CeL) and glutamatergic cells of the basal amygdala nuclei (BA: basolateral–BL,
basomedial – BM). On the surface, given the different transmitters they use, CeL and BA
neurons are expected to exert opposite influences on CeM cells when activated by LA
inputs: an inhibition via CeL and an excitation via BA.

Supporting the notion that BA, not CeL, neurons are the critical relay downstream of LA,
CeM neurons acquire excitatory responses to the CS as a result of fear conditioning [16••,
17••]. Moreover, optogenetic excitation of CeM cells elicits freezing [16••]. However, while
post-training BA lesions completely abolish conditioned fear responses [18], pre-training
BA lesions have no effect [18–20]. This suggests that in an intact brain, the BA nuclei are at
least required to relay CS-evoked LA responses to CeM, but that if fear conditioning occurs
in their absence, LA can affect CeM via another route.

Corroborating this interpretation, two recent studies examined the contribution of BL [21••]
or BL and BM neurons [22••] to conditioned fear. Both reported that as a result of fear
conditioning, >30% of BL and BM neurons acquired excitatory responses to the CS.
Moreover, combined BL-BM inactivation just before testing fear recall largely reduced
conditioned fear responses [22••]. Interestingly, while most BL cells stopped firing at CS
offset, BM responses typically outlasted the CS by ≥40s, paralleling the persistence of
conditioned fear after the CS. This observation suggests that BA neurons are not passive
relays of rapidly adapting LA inputs about the CS [23] but that through interactions with
each other or other structures, they actively extend the signals they receive from LA.

Multiple interacting layers of inhibition control CeM fear output neurons

As mentioned above, the contrasting effects of pre- vs. post-training BA lesions suggest that
besides BA, there is an additional relay between LA and CeM. The possibility that CeL
neurons performed this function was initially dismissed because they were expected to
generate a feed-forward inhibition of CeM. However, recent findings suggest that this
reasoning might be incorrect. Below, we summarize the organization of inhibitory inputs to
CeM and then consider their contribution to conditioned fear.

A first extrinsic source of GABAergic inputs to CeM are CeL neurons [15,24]. Until
recently, little was known about the intrinsic connectivity of Ce neurons except that they
form inhibitory synapses with each other [25,26]. However, major advances were made in
the last two years (Fig. 1C). For instance, it was revealed that different populations of CeL
neurons target CeM cells projecting to the periaqueductal gray (PAG, controlling behavioral
freezing) or dorsal vagal complex (DVC, generating the cardiovascular correlates of fear),
with those controlling PAG-projecting (but not DVC-projecting) cells expressing oxytocin
receptors (OR) [27•]. Another study [28••] took advantage of the differential expression of

1Here, note that we purposefully sidestep the question of where the CS-US association is stored. Indeed, while there is substantial
support for the notion that cortical and/or thalamic synapses onto LA neurons are potentiated as a result of fear conditioning [3•], there
is also incontrovertible evidence that thalamic and cortical neurons acquire an increased CS responsiveness, likely contributing to
enhance CS-evoked LA responses [4•,5•]. However, the uncertainty surrounding this question is not critical for the purpose of this
review because most recent advances deal with processing steps downstream of LA. A second aspect not considered here is the
relative contribution of different amygdala nuclei to active vs. passive fear responses. While it is clear that the basal nuclei, in part via
their striatal projections, are critical for active fear responses [6], recent evidence also implicates Ce in switching between passive and
active modes of fear responding [7•]. A third area not considered here is the regulation of the amygdala by the medial prefrontal
cortex. However, the reader is referred to an excellent review on this topic [8].

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protein kinase C-delta (PKCδ) in CeL neurons to analyze the intrinsic Ce network. PKCδ+ cells account for ≈50% of CeL cells and overlap with the OR-expressing cells just mentioned. By taking advantage of elegant molecular genetic approaches, it was shown that PKCδ+ and PKCδ− CeL cells form inhibitory synapses with each other and project to CeM (Fig. 1C)[28••]. Consistent with the idea that inhibitory inputs originating in CeL control PAG-projecting CeM neurons, silencing PKCδ+ cells increased levels of conditioned freezing [28••]. Overall, these results indicate that CeM neurons are subjected to tonic inhibitory inputs arising in CeL. This raises the possibility that disinhibition might contribute to the CS responsiveness of CeM neurons [16••,29•]. We return to this idea below.

A second source of GABAergic inputs to CeM are intercalated (ITC) neurons [30]. ITC cells appear as small densely packed clusters distributed in the external capsule and the so-called intermediate capsule, the fiber bundle separating the basolateral (BLA) complex from Ce (Fig. 1D). ITC cells in the external capsule project to BLA [31,32] and will not be considered further here. In contrast, ITC clusters at BLA-Ce border project to Ce. Several ITC cell clusters are present in this region: (1) dorsally, there is one or more cluster(s) close the dorsolateral edge of CeL (ITCd); (2) more ventrally, there is one or more thinner and elongated ITC clusters lateral or ventrolateral to CeM (ITCv); (3) ventral to CeM, at rostral amygdala levels, there is a large main ITC cluster (ITCm).

The first studies on ITC connectivity were performed in guinea pigs and emphasized the existence of a topographical correspondence between the position of ITC cells, where they project in Ce and where they derive most of their BLA inputs [33,34]. They also revealed the existence of directionally polarized connections between ITC cell clusters [33]. Recent studies in rats [35•] and mice [36,37•,38] indicate that these principles are well preserved across species. As illustrated for the rat amygdala in figure 1D, ITCd neurons receive glutamatergic inputs from LA and send a GABAergic projection to CeL, whereas ITCv and ITCm receive excitatory inputs from BA and project to CeM. Furthermore, ITCd cells inhibit ITCv neurons, a projection that is not reciprocated.

Do inhibitory inputs arising in CeL and/or ITC neurons regulate the CS responsiveness of CeM cells? Mounting evidence indicates so. First, pre-training inactivation of Ce globally, CeL only [16••,39•] or selective silencing of a subset of PKCδ+ neurons [28••] interfere with conditioned fear. Second, recording of mice CeL neurons 24-h after fear conditioning disclosed two populations of cells [16••] with inhibitory (CeL-Off) or excitatory (CeL-On) responses to the CS. It was further shown that CeL-Off and -On cells correspond to PKCδ+ and PKCδ− neurons [28••]. The presence of reciprocal inhibitory connections between CeL-Off and CeL-On cells led to the proposal that when the CS is presented, the excitation of CeL-On cells causes the inhibition of CeL-Off neurons resulting in the disinhibition of CeM fear output neurons [16••,28••]. At odds with this model however, the incidence of CeL-On and CeL-Off neurons was found to be similar and both project to CeM ([16••,28••]).

Another study in rats [17••] revealed that during habituation and at the end of training, the same proportion (≈10%) of CeL cells showed positive or negative responses to the CS. Thus, the same profile of CS responsiveness was seen in CeL during high and low fear states. During the recall test 24-h later, the incidence of CeL-Off neurons tripled with no modifications in that of CeL-On cells. If CeL-On neurons mediate the inhibition of CeL-Off cells, how could the incidence of CeL-Off neurons augment from training to recall when that of CeL-On cells is unchanged? One possibility is that CeL-On to CeL-Off synapses are potentiated as a result of fear conditioning. Another is that different inhibitory inputs, extrinsic to CeL, are involved. For instance, because LA projects to ITCd but not ITCv neurons, CS presentations might cause the glutamatergic activation of ITCd cells, leading to
the inhibition of CeL-Off and ITCv neurons, with the final result of disinhibiting CeM neurons (Fig. 2A). Support for this possibility comes from a recent biophysical modeling investigation [40•] and from the finding that following fear recall, Zif268+ expression increases in ITCd neurons but not in ventrally located ITC cells [37•].

Fear extinction depends on multiple parallel mechanisms

The CS responsiveness of CeM neurons closely parallels fear expression levels [16•••,17•••] and is reduced by extinction training [17•••]2. From the previous section, it follows that this effect could depend on increased inhibitory pressures from CeL and/or ITCv neurons. Here, we review recent developments on this theme but first consider alterations in BLA and cortical activity that might bring about these changes.

Whereas the CS responsiveness of LAv [42] and many auditory cortical neurons (Armony et al., 1998) resists extinction, that of LAd cells quickly diminishes [23]. Extinction training also alters the CS responsiveness of BA neurons, but its impact varies depending on the type of responses initially acquired during fear conditioning [21•••,22•••]. Indeed, as a result of fear conditioning, some BA neurons develop excitatory (“fear cells”) and others inhibitory (“extinction cells”) responses to the CS. Whereas extinction cells develop excitatory CS responses following extinction training, some fear cells maintain their original responsiveness, some become unresponsive, others develop inhibitory responses to the CS [21•••,22•••].

The origin of these extinction-related shifts in CS responsiveness is currently unclear. However, inactivation studies indicate that they are critical to extinction learning [21•••,22•••, 44]. There is evidence that the rapid extinction of LAd responses to the CS results from a depotentiation of thalamic synapses [45]. This would imply that the extinction-resistant CS responses observed in some LAv and BA neurons are dependent on cortical inputs. At the same time, the reciprocal changes in CS responsiveness induced in fear and extinction cells by extinction training might reflect a differential regulation of their excitability by extrinsic inputs [21••] and/or inhibitory local-circuit BA neurons (Fig. 2B). In fact, evidence for the latter mechanism was recently obtained [46•]. Another area of uncertainty concerns the consequences of extinction-related changes in the CS responsiveness of BLA neurons. In part, this is due to the fact that little is known regarding the connectivity of fear and extinction cells. Indeed, it is possible that extinction and fear neurons form contrasting connections within or outside the amygdala. For instance, one could conceive of a scenario where extinction cells preferentially contact ITCv neurons, whereas fear cells preferentially contact CeM neurons (Fig. 2B).

While extinction training largely reverses the changes in CeL responsiveness induced by fear conditioning [17••], it is unclear whether this reversal is simply a reflection of the rapid extinction of CS-evoked responses in LAd neurons [23] and/or the result of plasticity in the intra-CeL network. In contrast, there is much support for the notion that an increased recruitment of ITCv cells by BA inputs contributes to reduce the CS responsiveness of CeM cells in extinction. Indeed, selective ITC lesions [47] or pharmacological inhibition of BA inputs to ITC cells [48] interfere with extinction. Moreover, extinction training causes a potentiation of BA inputs to ITCv cells, an effect that requires infralimbic (IL) activity and causes increased feedforward inhibition in CeM [49••]. The IL-dependence of ITC involvement in extinction is also supported by the fact that IL inputs trigger high-frequency

2Although the original fear memory likely undergoes a synaptic reorganization in extinction [reviewed in 3•], it is certainly not erased. Rather, it is thought that extinction mainly depends on the development of an active inhibitory memory that differs from the original CS-US association in many ways, including its susceptibility to the passage of time and marked context dependence [41].
spike bursts in ITC cells [35•]. Consistent with these observations, extinction is associated
with increased levels of Zif268 [37•] and fos [50] expression in ventrally (but not dorsally)
located ITC cells. Collectively, these observations support a model of extinction where the
reduced recruitment of ITCd cells by extinguished LAd inputs leads to a disinhibition of
CeL-Off and ITCv cells during the CS. This effect, coupled to convergence of IL and BA
inputs in ITCv neurons, would result in the potentiation of BA synapses to ITCv cells,
allowing the CS to elicit more feed-forward inhibition in CeM neurons via ITCv and CeL-
Off neurons (Fig. 2B).

In conclusion, while the last few years have witnessed major advances in our understanding
of the amygdala networks supporting the acquisition and extinction of conditioned fear,
many areas of uncertainty persist. One of the most pressing challenges for future
investigations will be to identify the inputs and targets of the various subtypes of BA, CeL,
and ITC neurons. Once this information becomes available, a clearer picture will no doubt
derm.

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the experiments described here. This work was supported by R01 grant MH-083710 from NIMH.

References and recommended reading


• 3. Pape HC, Pare D. Plastic synaptic networks of the amygdala for the acquisition, expression,
and extinction of conditioned fear. Physiol Rev. 2010; 90:419–463. This paper provides a thorough
overview of the extensive literature on the mechanisms underlying the acquisition, expression,
and extinction of classically conditioned fear responses. [PubMed: 20393190]

• 4. Weinberger NM. The medial geniculate, not the amygdala, as the root of auditory fear
conditioning. Hear Res. 2011; 274:61–74. This thought-provoking review challenges the notion
that the lateral amygdala is the key site for auditory fear learning and memory storage. The
author provides evidence that the criteria used to support this claim are also met by the auditory
thalamus. [PubMed: 20466051]

microcircuit for associative fear learning in auditory cortex. Nature. 2011; 480:331–335. This paper shows that the cerebral cortex is a key site of synaptic plasticity for auditory fear
conditioning. The evidence presented suggests that footshocks activate basal forebrain
cholinergic neurons leading to ACh release in cortex. This produces a nicotinic activation of
layer I interneurons in cortex, the inhibition of parvalubinin positive cells and disinhibition of
their target pyramidal cells. The latter effect would coincide with CS inputs, facilitating
associative plasticity in the auditory cortex. [PubMed: 22158104]

6. Killcross S, Robbins TW, Everitt BJ. Different types of fear-conditioned behaviour mediated by

Gross CT, Bifone A. A neural switch for active and passive fear. Neuron. 2010; 67:656–66. This study shows that two subpopulations of CeL neurons mediate the switch between passive and
active fear responses. Selective inhibition of one subpopulation of neurons (type-I cells) results in
decreased conditioned freezing response together with increased cortical arousal. Of interest,
type-II CeL neurons express oxytocin receptors and are inhibited by type-I cells. [PubMed:
20797541]

8. Sotres-Bayon F, Quirk GJ. Prefrontal control of fear: more than just extinction. Curr Opin


17. Duvarci S, Popa D, Pare D. Central amygdala activity during fear conditioning. J Neurosci. 2011; 31:289–294. This study describes the activity of CeM and CeL neurons during fear conditioning. The authors report that unit activity in CeM correlates tightly with fear expression. In contrast, CeL cells are heterogeneous in this respect with some exhibiting increased (CeL+) and others decreased (CeL−) CS-responsiveness after fear conditioning. Interestingly, from training to the recall test 24 h later, the proportion of CeL− cells triples with no change in the incidence of CeL+ cells, suggesting that an inhibitory input extrinsic to CeL mediates the disinhibition of CeM neurons. [PubMed: 21209214]


21. Herry C, Ciocchi S, Senn V, Demmou L, Muller C, Luthi A. Switching on and off fear by distinct neuronal circuits. Nature. 2008; 454:600–606. This groundbreaking study disclosed the existence of two subpopulations of BL neurons that exhibit a high CS responsiveness in high fear (fear neurons) or low fear (extinction neurons) states. Moreover, it showed that local BL inactivation prevents behavioral switching between low and high fear states. [PubMed: 18615015]

22. Amano T, Duvarci S, Popa D, Pare D. The fear circuit revisited: contributions of the basal amygdala nuclei to conditioned fear. J Neurosci. 2011; 31:15481–15489. This study reports that CS responsiveness of most BL and BM neurons correlates tightly with fear expression. Selective inactivation of either nuclei alone had no effect on conditioned fear expression even though it impaired extinction recall. Yet, combined BL and BM inactivation results in impaired fear expression suggesting that there is a functional redundancy between these two nuclei in mediating conditioned fear expression. [PubMed: 22031894]


27. Viviani D, Charlet A, van den Burg E, Robinet C, Hurni N, Abatis M, Magara F, Stoop R. Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. Science. 2011; 333:104–7. This study shows that separate subsets of CeM neurons project to the periaqueductal gray (PAG) to mediate behavioral freezing and the dorsal vagal complex (DVC) to mediate cardiovascular responses. PAG-projecting, but not DVC-projecting, CeM neurons are selectively inhibited by oxytocin through inhibitory projections that stem from CeL. As a result, oxytocin decreases conditioned freezing responses without affecting cardiovascular responses. [PubMed: 21719680]


35. Amir A, Amano T, Pare D. Physiological identification and infralimbic responsiveness of rat intercalated amygdala neurons. J Neurophysiol. 2011; 105:3054–3066. To identify ITC cells on the basis of their firing pattern, this study used juxtacellular recordings and neurobiotin labeling of ITC cells. Unlike neurons in neighboring amygdala nuclei, most ITC cells generated high-frequency trains of 4–6 spikes in response to stimulation of the infralimbic cortex. This unique pattern of infralimbic responsiveness can now be used to identify ITC cells during fear conditioning. This study also revealed that the connectivity of ITC cells is conserved across species. [PubMed: 21471396]


index of activity, this study provides evidence for the contrasting involvement of different medial ITC cell clusters in fear expression and extinction. The dorsal ITC cluster is activated during fear expression whereas the ventral cluster is activated during fear extinction. [PubMed: 21451049]


39. Wilensky AE, Schafe GE, Kristensen MP, LeDoux JE. Rethinking the fear circuit: the central nucleus of the amygdala is required for the acquisition, consolidation, and expression of Pavlovian fear conditioning. J Neurosci. 2006; 26:12387–12396. This is the first study to demonstrate that, rather than being only a passive output station of the amygdala for fear expression, the central amygdala is also required for the acquisition of conditioned fear responses. Moreover, this study provides evidence that consolidation of fear memories depends on protein synthesis dependent plasticity in the central amygdala. [PubMed: 21436395]

40. Li G, Amano T, Pare D, Nair SS. Impact of infralimbic inputs on intercalated amygdala neurons: a biophysical modeling study. Learn Mem. 2011; 18:226–240. This biophysical modeling study shows that infralimbic inputs can cause a significant increase in the firing rate of ITC cells despite inhibitory inter-ITC connections, further supporting the notion that IL can control extinction of conditioned fear through the activation of the ITC cells. [PubMed: 21436395]


44. Sierra-Mercado D, Padilla-Coreano N, Quirk GJ. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology. 2011; 36:529–38. [PubMed: 20962768]


46. Popescu AT, Pare D. Synaptic interactions underlying synchronized inhibition in the basolateral amygdala: evidence for existence of two types of projection cells. J Neurophysiol. 2011; 105:687–696. Consistent with the idea that two distinct types of projection cells exist in the basolateral amygdala, this study shows that a small subset (~15%) of projection cells exhibit a unique relationship to inhibitory interneurons. The activation of this subset of projection cells results in the recruitment of interneurons and the consequent inhibition of the rest of the projection cells in BA. [PubMed: 21084688]


49. Amano T, Unal CT, Pare D. Synaptic correlates of fear extinction in the amygdala. Nat Neurosci. 2010; 13:489–494. Using an ex vivo approach, this study shows that fear extinction is associated with increased levels of synaptic inhibition in CeM fear output neurons. This increased inhibition resulted from a potentiation of basal amygdala inputs to ITC cells that project to CeM and required prefrontal activity during extinction training. [PubMed: 20208529]

Highlights

Transmission of information about conditioned stimuli from the lateral amygdala to fear output neurons in the central medial amygdala is indirect.

Glutamatergic basal amygdala neurons connect the input and output stations of the amygdala for conditioned fear.

Multiple interacting layers of inhibition control fear output neurons in the central medial nucleus of the amygdala.

Fear extinction depends on multiple parallel mechanisms.
Fig. 1.
Intra-amygdaloid networks involved in fear conditioning. (A) Original model, as proposed in the early 90’s. The model invoked direct projections from LA to Ce brainstem-projecting neurons. However, Ce neurons projecting to brainstem fear effectors are concentrated in its medial sector. LA lacks projections to CeM and instead targets CeL. (B) Other amygdala nuclei could potentially bridge the gap between LA and CeM: CeL and the basal nuclei (BA). CeL and BA neurons contributing projections to CeM use different transmitters: GABA and glutamate, respectively. (C) Recent advances in our understanding of the intrinsic Ce network. CeL contains at least two types of CeM-projecting cells, expressing PKCδ or not. The two subtypes project to CeM and inhibit each other. A proportion of PKCδ+-neurons express ORs and contact CeM neurons projecting to the PAG, controlling behavioral freezing. ORs are not expressed by CeL neurons projecting to DVC-projecting CeM neurons. The projection site(s) of the CeM cells contacted by PKCδ−-neurons is (are) currently unknown. Also unclear is whether LA inputs to CeL form differential connections with PKCδ+- and PKCδ−-neurons. As a result of fear conditioning, PKCδ−-neurons develop...
excitatory responses to the CS, hence the label “On” whereas PKCδ+ cells show inhibitory responses to the CS, hence the designation “Off”. Reduced activity in CeL-Off cells is thought to produce a disinhibition of CeM fear output neurons. (D) Location and connectivity of ITC cells regulating the excitability of CeM neurons. ITCd neurons receive glutamatergic inputs from LA and send a GABAergic projection to CeL. ITCv receive excitatory inputs from BA and project to CeM. Furthermore, ITCd cells inhibit ITCv neurons, a projection that is not reciprocated. The connectivity of ITCm neurons (not shown) is similar to that of ITCv cells.
Fig. 2.
Hypothetical model of intra-amygdala interactions involved in fear expression and extinction. Solid and dashed lines indicate connections that are more or less active, respectively. The model includes established facts and hypothetical connections that together account for much of the available data. In particular, we hypothesize that fear and extinction cells form different connections within BA as well as with ITCv and CeM neurons. Within BA, fear (F) and extinction (E) cells would be subjected to inhibitory inputs from different subsets of GABAergic interneurons, the latter being under the control of different excitatory inputs (see scheme). Furthermore, we expect fear cells to project to CeM whereas extinction (and possibly extinction-resistant cells) to project to ITCv neurons. Although not indicated on the schemes, it is also possible that extinction cells influence ITCv neurons via the infralimbic cortex. Hippocampal inputs are not included here but they likely form differential connections with extinction and fear cells as well as with associated interneuron pools, allowing for the context-dependent gating of extinction. (A) The available evidence suggests that the increased CS responsiveness of CeM output neurons after fear conditioning depends on two parallel mechanisms: disinhibition from CeL and ITCv inputs as well as excitation by glutamatergic BA neurons. CeM disinhibition: CS presentations excite LAd neurons, leading to the recruitment of ITCd neurons and a subset of CeL cells, likely PKCδ− (CeL-On) cells. ITCd cells would then inhibit ITCv cells, disinhibiting CeM cells. In parallel, ITCd cells would also inhibit subsets of CeL neurons, possibly PKCδ+ (CeL-Off) neurons. The activation of PKCδ− (CeL-On) cells by LAd inputs would cause a further inhibition of PKCδ+-neurons and disinhibition of CeM cells. CeM excitation: The activation of LA neurons by the CS causes subsets of BA neurons (“Fear neurons”, F) to fire. Presumably, these cells project to CeM. The firing of other BA neurons (“Extinction cells”, E) would be inhibited by the recruitment of local-circuit interneurons, possibly receiving inputs from LAd and/or BA fear neurons. (B) In extinction, the reduced CS responsiveness of CeM neurons would depend on increased feedforward inhibition by ITCv neurons and disfacilitation from glutamatergic BA inputs. CeM disfacilitation: The extinction of LAd responses to the CS results in a diminished recruitment of BA fear neurons and a reduced activation of the interneurons that inhibit extinction cells in high fear states. The disinhibition of extinction cells causes increased excitation of a different set of interneurons, controlling fear cells. CeM inhibition: the reduced CS responsiveness of LAd...
neurons would cause a disfacilitation of ITCd neurons, consequent disinhibition of ITCv neurons. This effect would coincide with an increased excitation of ITCv cells by inputs from BA extinction cells, thus resulting in an increased feedforward inhibition of CeM cells. The disfacilitation of ITCd neurons would also cause a disinhibition of subsets of CeL cells, possibly corresponding to PKCδ⁺ neurons. This effect would be reinforced by the reduced activation of PKCδ⁻ cells secondary to reduced LAd inputs.