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New perspectives on central amygdala function

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The central nucleus of the amygdala (CEA) is a striatum-like structure orchestrating a diverse set of adaptive behaviors, including defensive and appetitive responses [1–3]. Studies using anatomical, electrophysiological, imaging and optogenetic approaches revealed that the CEA network consists of recurrent inhibitory circuits comprised of precisely connected functionally and genetically defined cell types that can select and control specific behavioral outputs [3,4,5•,6•,7–9,11,12]. While bivalent functionality of the CEA in adaptive behavior has been clearly demonstrated, we are just beginning to understand to which degree individual CEA circuit elements are functionally segregated or overlapping. Importantly, recent studies seem to suggest that optogenetic manipulations of the same, or overlapping cell populations can give rise to distinct, or sometimes even opposite, behavioral phenotypes [5•,6•,9–12]. In this review, we discuss recent progress in our understanding of how defined CEA circuits can control defensive and appetitive behaviors, and how seemingly contradictory results could point to an integrated concept of CEA function.

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The CEA and defensive responses

For nearly six decades, the CEA has been demonstrated to play a fundamental role in defensive responding (see [13]). Electrical stimulation and lesion studies were subsequently complemented by neurophysiological and pharmacological approaches culminating in the view that the CEA is a vital output station controlling and mediating a panoply of physiological and behavioral changes occurring in the face of threat (Figure 1) [1,2]. For example, it has been repeatedly demonstrated that acute manipulations of the CEA alter unconditioned defensive responses, such as freezing [5•,10,14,15•]. In addition, the CEA is not only involved in orchestrating innate behavioral output, but plays important roles during the acquisition, consolidation, and expression of conditioned behaviors [5•,10,14,16,17•].

Acquisition of conditioned defensive responses

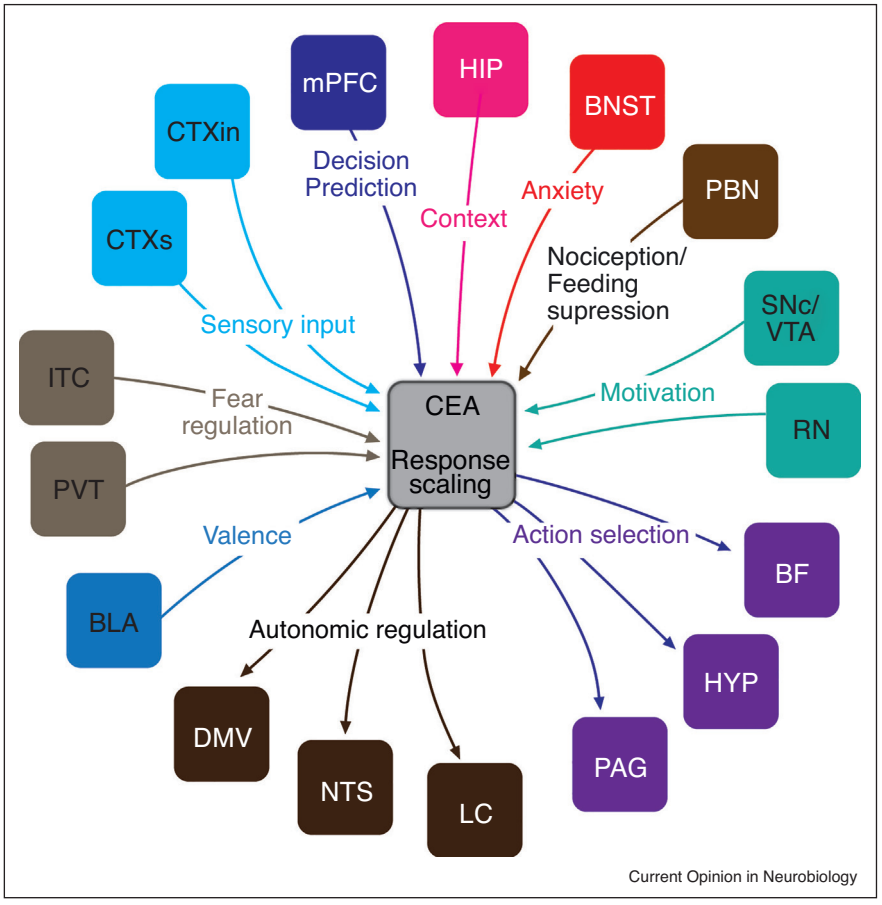
Consistent with a role for CEA circuits during learning, CEA neuronal responses to conditioned stimuli exhibit persistent changes upon learning [5•,14,17•,18]. These changes are likely to reflect, at least in part, plasticity at glutamatergic inputs originating from a number of upstream areas, including the basolateral amygdala, paraventricular thalamus, and ventral hippocampus (Figure 1) [10,17•,19,20•,21•].

The CEA receives nociceptive input from the parabrachial nucleus (Figure 1), and this input is necessary for acquiring the association between a neutral stimulus and the aversive outcome during conditioning [22•]. In addition to being a locus of associative learning, the CEA may also be involved in the computation of an aversive prediction error signal [23•,24]. The CEA sends information about the expected aversive outcome to the periaqueductal grey (PAG) which in turn receives afferent sensory input about the experienced aversive stimulus. Such a signal is believed to be fed back to various subnuclei including the lateral amygdala (LA) where it modulates aversive responses of LA neurons [23•]. Interestingly, this process might again involve the CEA, as optogenetic manipulations of CEA neurons expressing protein kinase C delta (PKCδ) control fear learning and synaptic plasticity in the LA [24].

Selection and expression of conditioned defensive responses

Defined regions of the CEA have distinct roles in classical fear conditioning, with the lateral subdivision (CEl) being important for acquisition [4,14]. There are two antagonistic populations of cells in the CEl that gate freezing via inhibitory interactions. CEl_{on} neurons are excited by a conditioned auditory stimulus, whereas CEl_{off} neurons are inhibited. In turn, inhibition of CEl_{off} neurons can disinhibit output neurons located in the medial

Figure 1



Long-range functional connectivity of the CEA. The CEA gathers information on sensory and higher-order processes from various cortical and subcortical regions. CEA circuits mediate scaling of a complex, coordinated response transmitted through outputs that are involved in autonomic regulation and behavioral action selection. mPFC, medial prefrontal cortex, HIP, hippocampus; BNST, bed nucleus of the striaterminalis; PBN, parabrachial nucleus; SNc/VTA, substantia nigra parscompacta/ventral tegmental area; RN, raphe nucleus; BF, basal forebrain; HYP-hypothalamus; PAG, periaqueductal grey; LC, locus coeruleus; NTS, nucleustractus solitaries; DMV, dorsal motor nucleus of the nervus vagus; BLA-basolateral amygdala; PVT, paraventricular nucleus; ITC, intercalated cells,CTXs, sensory cortex; CTXin, insular cortex.

subdivision of the CEA (CEm) thereby driving downstream targets involved in the generation of conditioned behaviors, such as the PAG.

CEA populations mediating defensive behavior can also be identified using molecular markers. Notably, CEl_{off} neurons express PKCδ and somatostatin-expressing cells (SOM) exhibit response properties resembling CEl_{on} neurons [5•,9,25]. It is important, however, to note that molecularly defined cell populations are likely to be larger and more diverse and contain additional functional subpopulations than those defined by recordings during cued auditory fear conditioning [7,14].

Optogenetic activation of SOM+ cells can generate freezing behavior in naïve animals [5•,10]. Given that SOM+ neurons not only locally inhibit PKCδ cells, but also send direct projections to the PAG [26], this suggests that conditioned freezing responses can be driven by alternative direct and indirect pathways, that would involve an additional dis-inhibitory module consisting of PKCδ cells and CEm projection neurons. It is possible that direct and indirect pathways integrate different inputs and confer the system with an additional level of flexibility.

One concept that has emerged from these recent studies is that CEA neuronal circuit activity is tightly regulated by local recurrent inhibitory interactions. For example, CEl_{off}/PKCδ+ and CEl_{on}/SOM+ neurons are connected such that when certain stimuli or contexts elicit excitation of one population, the other is inhibited. Such recurrent and reciprocal inhibitory interactions are consistent with 'winner-take-all' models which allow for rapid behavioral switching. Consistent with this notion, optogenetic