Amygdala Structure, Function, and Clinically Relevant Pathways

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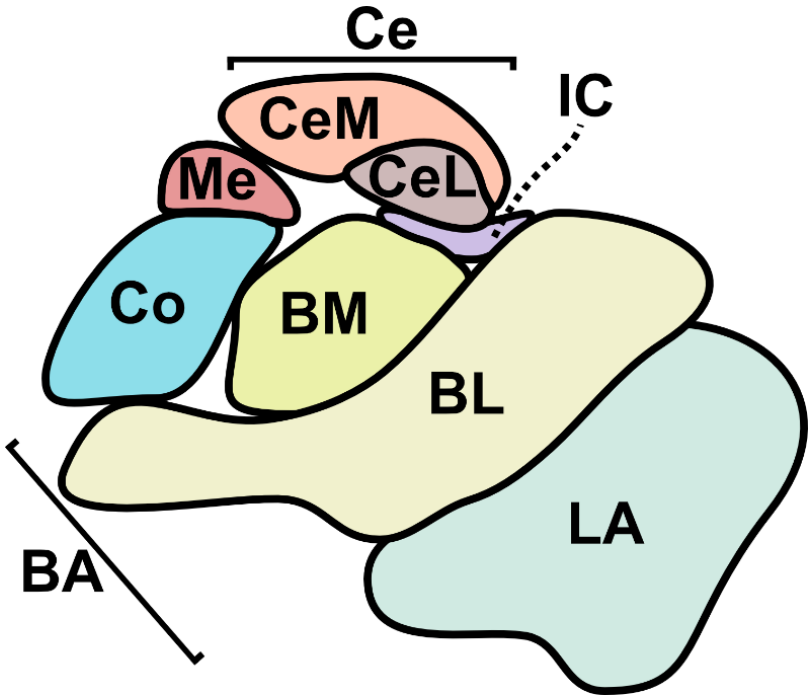
Anatomy

The amygdala consists of nuclei which can be grouped into (i) the basolateral nuclear group (BLA), (ii) the superficial cortex-like laminated region (sCLR) which contains the cortical nuclei (Co), and (iii) the centromedial nuclear group.[1] The BLA consists of the lateral nucleus (LA) and basal nucleus (BA). In turn, the BA consists of the basolateral nucleus and the basomedial nucleus. The centromedial nuclear group consists of the central nucleus (Ce), medial nucleus (Me), and intercalate cell mass (IC). In turn, Ce consists of a lateral (CeL) subdivision and a medial (CeM) subdivision. The centromedial nuclear group (Ce, Me, and IC) along with the bed nucleus of the stria terminalis (BNST) and sublenticular substantia innominata together comprise the centromedial extended amygdala.

The cellular composition of the BLA nuclei and the sCLR's Co nuclei resembles that of the cerebral cortex in that the majority of the neurons are pyramidal-like glutamatergic cells while the rest are local GABAergic inhibitory interneurons.[1] The inhibitory interneurons include parvalbumin-containing neurons which mainly synapse on the soma and proximal dendrites of the pyramidal cells and somatostatin-containing neurons which mainly synapse on the distal dendrites of the pyramidal neurons. By contrast, the composition of the Ce and Me nuclei resembles the striatum in that many of the neurons are similar to GABAergic medium spiny neurons.



Overview of Amygdala Connectivity

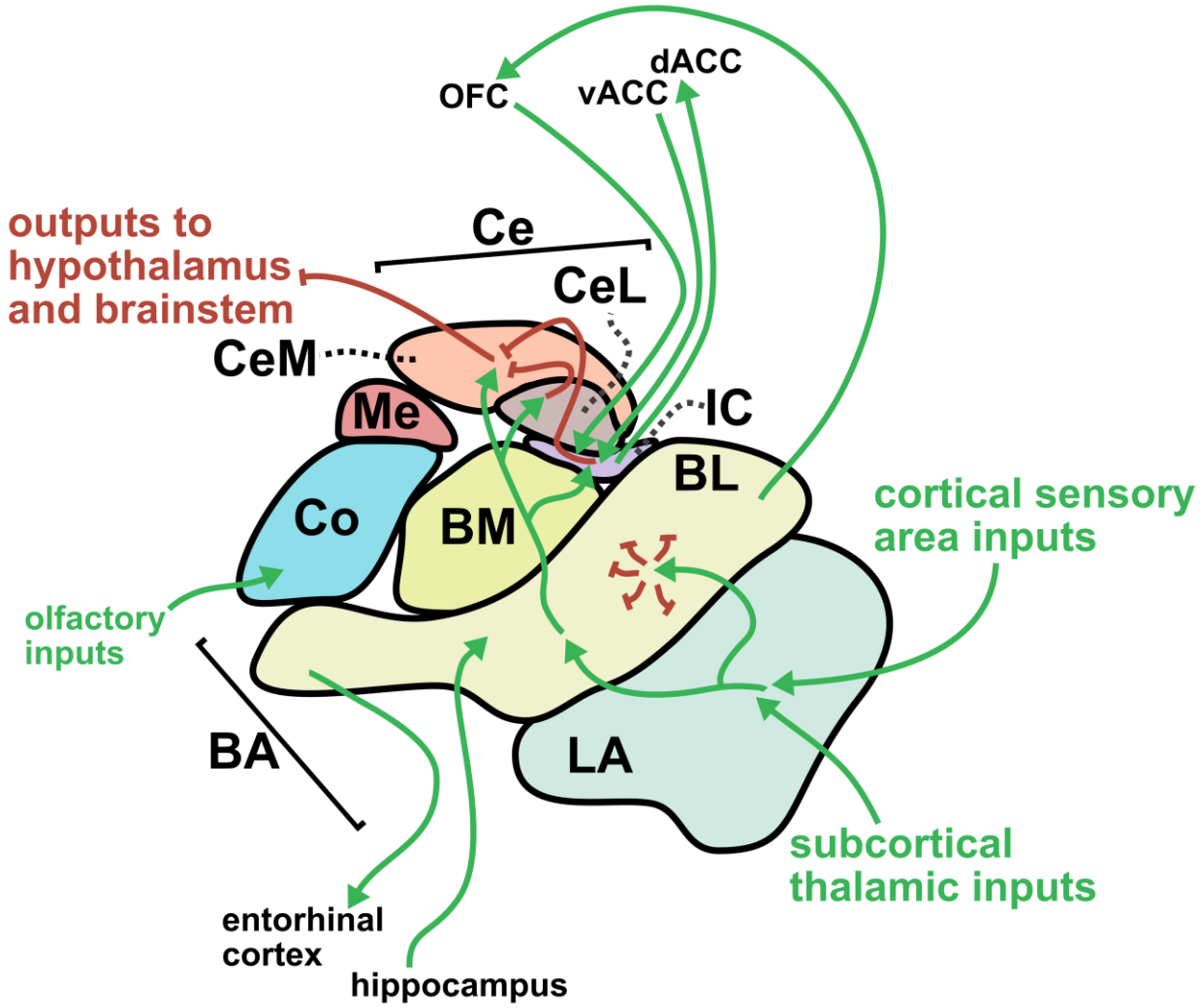
Signals flow into the amygdala primarily via synapses in the BLA. Inputs from cortical sensory areas and from the thalamus (relaying subcortical signals) synapse on neurons in the LA.[1] These inputs in the LA facilitate coincidence detection and associative learning tying together the sensory cortical representations of the world with subcortical information coming in via the thalamus. The LA pyramidal-like neurons send excitatory signals to the BA's projection neurons and to the BA's interneurons. (It should be noted that the subnuclei of the BA are also interconnected with the prefrontal cortex, hippocampus, and striatum). Next, the BA projects glutamatergic inputs to the CeM's GABAergic projection neurons. These BA glutamatergic projections additionally synapse on the inhibitory interneurons of the IC and the CeL, both of which regulate the CeM neurons. (An additional layer of complexity comes from further inhibitory interneuron circuits within the LA, BA, IC, CeL, and CeM). Finally, the CeM's GABAergic projection neurons send output signals to the hypothalamus and brainstem.

Sensory inputs to the amygdala's LA come from several sources.[1] Sensory association areas of the temporal cortex carry visual and auditory information. These areas are part of the ventral stream of sensory processing, which encodes analyses of complex features to facilitate face recognition and auditory recognition. The insular cortex, which encodes somatosensory and visceral sensations, also sends inputs to the LA. Subcortical sensory inputs to the LA come via the thalamus. In addition to LA inputs, the CeM receives visceral and nociceptive inputs directly from the pons. The sCLR receives olfactory input from the olfactory bulb as well as from higher olfactory areas.

Interestingly, the amygdala sends outputs back to cortical sensory association areas as well as primary sensory areas.[1] These modulate the valence of specific sensory stimuli, which can be thought of as a way to assign emotional value to particular stimuli.

The amygdala has strong bidirectional interactions with the orbitofrontal cortex (OFC).[1] In particular, the OFC receives strong inputs from the BA and targets the IC's GABAergic neurons. The amygdala also interacts with the dorsal anterior cingulate cortex (dACC) and ventral anterior cingulate cortex (vAAC). The BA sends outputs to the dACC while the vACC projects back to the BA. The BA projects to the entorhinal cortex and receives inputs from the hippocampus as well, which may help tie emotional significance of particular events undergoing processing to associated memories. Finally, the amygdala receives subcortical inputs from arousal systems, including basal forebrain cholinergic inputs, ventral tegmental area (VTA) dopaminergic inputs, noradrenergic locus coeruleus inputs, and rostral raphe serotonergic inputs. The amygdala also projects back to all of these neuromodulatory regions and can influence the arousal systems.

CeM outputs to the hypothalamus and brainstem facilitate visceral behavioral responses to fear. These projections trigger various endocrine and autonomic peripheral nervous system responses such as secretion of adrenocorticotropic hormone (ACTH) into the blood and increased activation of the sympathetic nervous system.



Fear Learning

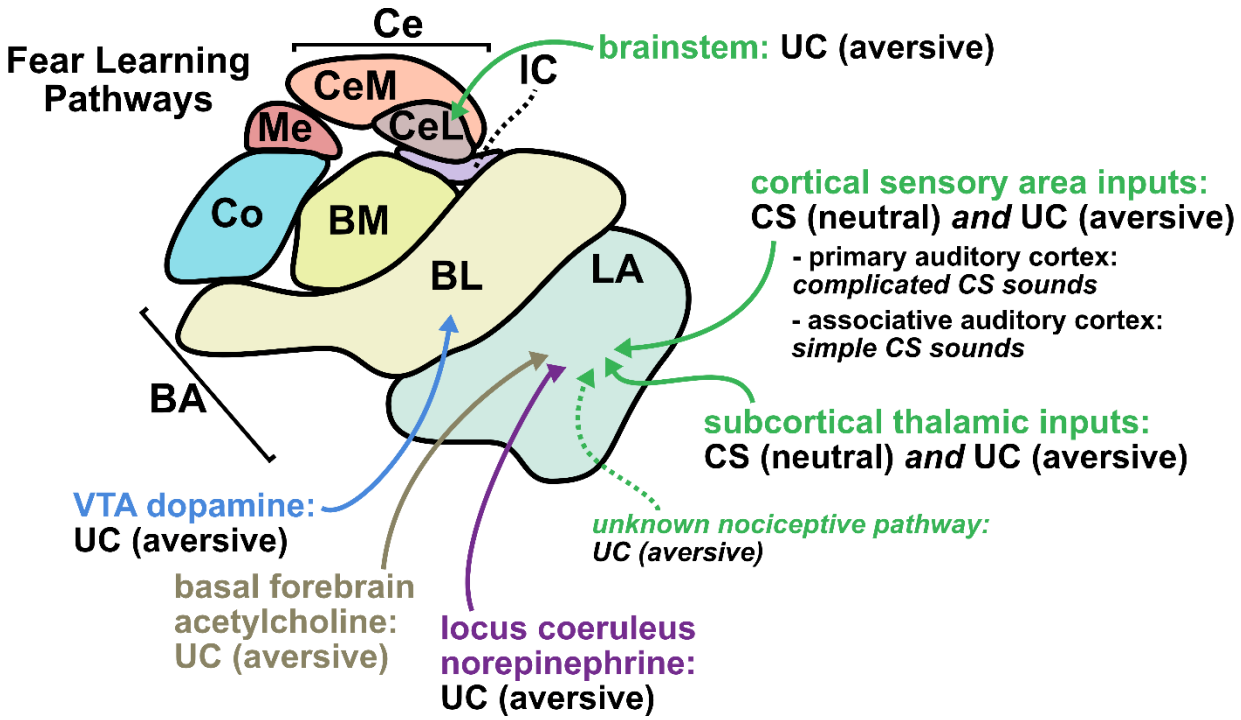
As mentioned earlier, the convergence of cortical inputs and subcortical inputs onto LA neurons facilitates associative learning between neutral stimuli and unpleasant stimuli. The neutral stimulus is often referred to as the "conditioned stimulus" (CS) while the unpleasant stimulus is referred to as the "unconditioned stimulus" (UC). In classical animal studies, the CS might take the form of a neutral sound (e.g. a tone) while the UC is often an electrical shock to the feet. It is variable as to which input pathways carry information about the CS and which input pathways carry information about the UC.[2]

In auditory fear learning, both the subcortical thalamic pathway afferents and the auditory cortex afferents have been shown to carry sensory CS information into the LA.[2] When an animal must discriminate between two distinct CS sounds to learn which sound is associated with a foot shock UC, the auditory cortical pathway is thought to be necessary because plasticity in the auditory cortex facilitates the discriminative learning. Interestingly, the primary auditory cortex has been shown to carry information about

complex multifrequency sounds into the LA while the more ventral associative areas of the auditory cortex bring information about simpler tone sounds.

Both the cortical and subcortical pathways have also been shown to carry parts of the UC. In particular, the parabrachial nucleus of the brainstem has been shown to encode nociceptive UC information. To transfer this information, the parabrachial nucleus projects to the CeM and CeL nuclei of the amygdala.[2–4] However, the parabrachial nucleus does not project to the LA.[2] It remains unknown if there is a separate (probably glutamatergic) input to the LA which carries aversive information for associative fear learning.

It should also be noted that evidence implicates neuromodulatory systems as carrying part of the UC signal during fear learning. Locus coeruleus noradrenergic projections have been shown to contribute about half of the strength of the fear learning signal.[5] That is, when silenced during fear learning in rats, a 50% decrease in learned fear occurred. Additionally, a subpopulation of dopaminergic neurons from the VTA which projects to the BA has been shown to contribute about 30% of the strength of the fear learning signal.[6] That is, when silenced during fear learning in mice, a 30% decrease in learned fear occurred. Acetylcholine inputs from the basal forebrain into the BLA have also been demonstrated to be necessary for efficient fear learning.[7] These neuromodulators may also be released, though to a lesser degree, during fear memory recall. Finally, serotoninergic neurons (especially from the raphe nuclei) have been implicated to sometimes act on the 5-HT$_{1A}$ receptors of GABAergic interneurons of the LA to inhibit fear learning in LA pyramidal cells.[1] That said, serotonin can have other effects in the BLA and its influence is not fully understood.[8]

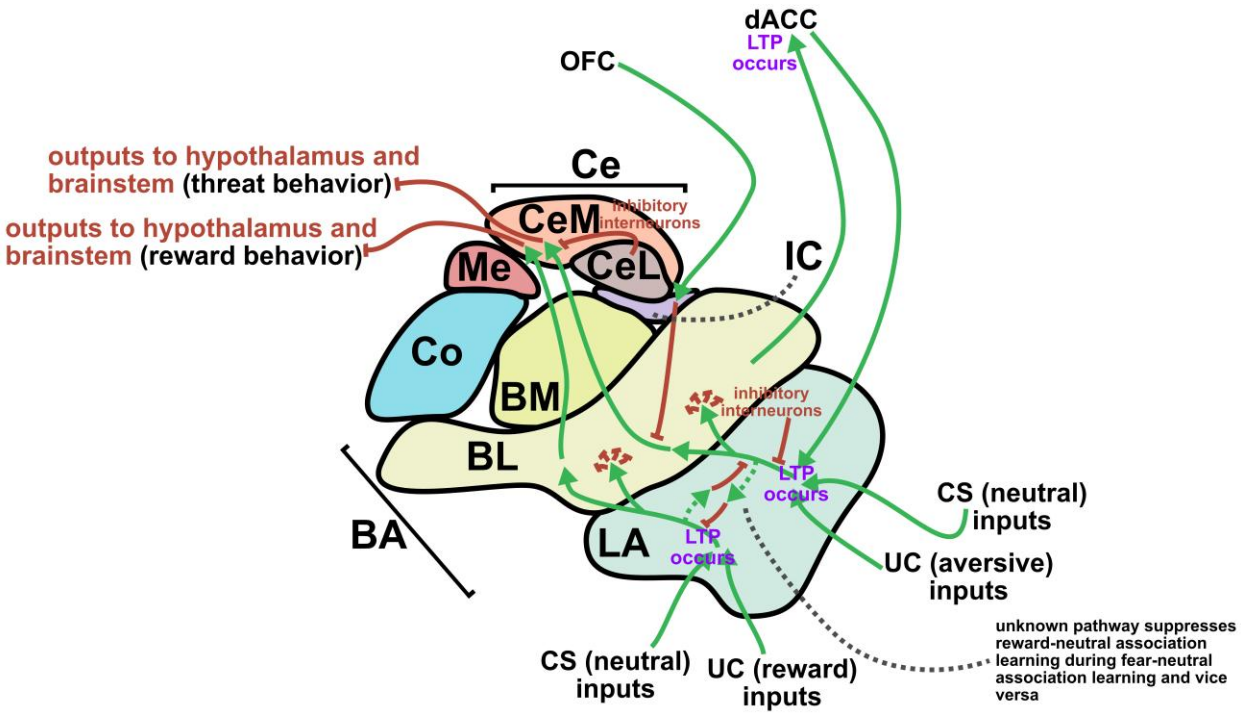


The amygdala represents a central part of circuits relating to fear and anxiety as well as of circuits of general emotional valence. Elevated amygdala activity with decreased top-down regulation from the vmPFC has been shown in people with higher anxiety.[1,9] It is important to note that the vmPFC overlaps with the ACC and OFC, which were discussed earlier. The vmPFC can facilitate the process of fear extinction: the decline of a learned fear via repeated exposure of a neutral CS without the associated aversive UC. As such, decreased functional connectivity between the amygdala and vmPFC is common in people with anxiety disorders.

The vmPFC facilitates fear extinction by sending excitatory input from the OFC to GABAergic neurons in the IC, which then inhibit the BA's inputs to the CeM. The BA itself also sends excitatory projections up to the vmPFC which can induce the vmPFC's fear extinction circuits. A distinct group of excitatory neurons in the BA target the dACC, which then sends excitatory projections back to the amygdala's BLA to facilitate fear learning (in contrast to the vmPFC projections).[10,11] Indeed, LTP occurring via this circuit within the dACC contributes to the formation and maintenance of fear memory. In this way, the dACC is a direct part of the learning network which creates fear memories.

Inhibitory interneurons within the amygdala act as important regulators of anxiety responses.[12] In the BLA, inhibitory interneurons can suppress the magnitude of anxiety by releasing GABA onto the pyramidal projection neurons. Inhibitory interneurons in the CeL can also constrain the activity of amygdala output projection neurons of the CeM, which leads to decreased fear behavior. But it should be noted that the BLA can receive sensory input associated with either threatening or rewarding stimuli. Because of this, its projection neurons trigger different behavioral responses (threat or reward behaviors) depending on the nature of the stimulus.

There exist non-overlapping populations of putative projection neurons in the BLA which are thought to fire in response to threat and reward stimuli separately.[12,13] These populations are thought to develop via the Hebbian associative learning described previously, which leads to formation of fear pathways for some stimuli, but can also promote association of rewarding stimuli with neutral stimuli and thus form learned emotional pathways of positive valence.[13] Additionally, inhibitory interneurons of the BLA suppress threat-related projection neurons when reward-related projection neurons are active and vice versa. With anxiety disorders, these interneuron circuits are frequently dysregulated in that negative valence is assigned to neutral or reward stimuli, leading to activation of only the threat-related projection pathway.



Extended Networks of the Amygdala and Anxiety

As has been discussed to some degree so far, the amygdala does not function in isolation. It makes numerous reciprocal connections with other brain areas to facilitate its operation. Some of the most important of these include cortical regions like the vmPFC, OFC, and ACC, which were discussed earlier. But extended subcortical structures like the BNST and hippocampus (which have so far only been mentioned briefly) also play major roles.

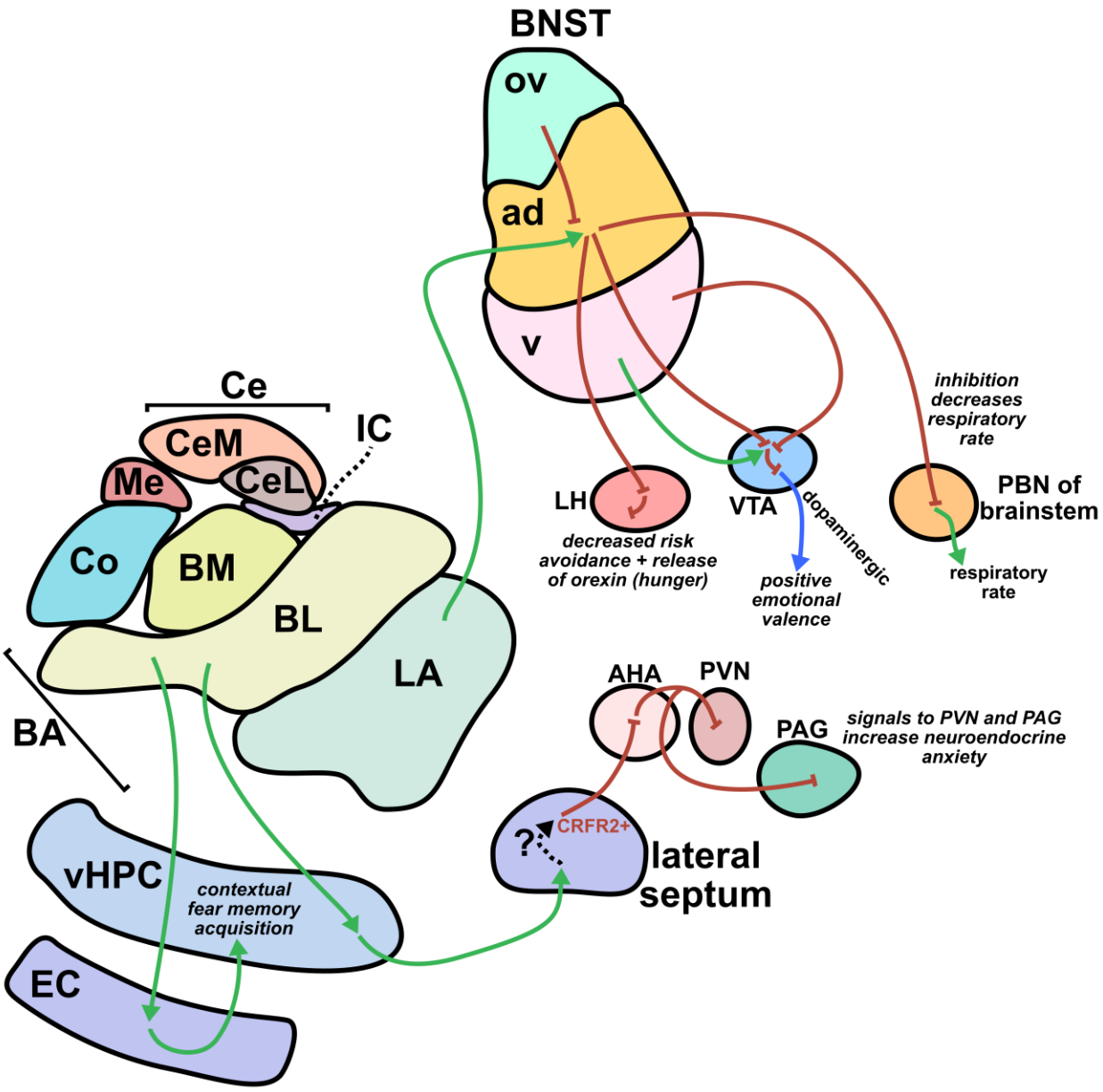
The BNST is a collection of nuclei nearby to the amygdala which is recruited during sustained fear and anxiety responses.[13] It is thought that the BNST specifically activates during prolonged stressful periods of greater than 10 minutes in duration.[14] The BLA sends glutamatergic projections into the BNST's anterodorsal (ad) nucleus. Interestingly, these excitatory inputs to the BNST ad nucleus promote anxiolytic outcomes. Additionally, local inhibition of the ad nucleus from the BNST's oval (ov) nucleus promotes anxiogenic outcomes. The BNST's ad nucleus facilitates anxiolytic states by sending its own (predominantly) GABAergic projections to the VTA to increase positive emotional valence, to the lateral hypothalamus (LH) to decrease risk avoidance, and to the parabrachial nucleus of the brainstem to decrease respiration rate.[15]

BNST ad projections to the VTA are mostly GABAergic neurons synapsing onto VTA inhibitory interneurons.[16] It should be noted that there are also ventral BNST (vBNST) GABAergic and glutamatergic projections which synapse onto different populations of VTA inhibitory interneurons, triggering anxiogenic phenotypes and anxiolytic phenotypes respectively.[17] A major population of BNST ad projections to the lateral hypothalamus are GABAergic neurons preferentially synapsing onto GABAergic target neurons. Among these is a subpopulation of GABAergic projection neurons targeting GABAergic lateral

hypothalamus neurons which also produce orexin (a neuropeptide which stimulates food intake behaviors and promotes wakefulness).[16] BNST ad GABAergic projections to the parabrachial nucleus probably inhibit glutamatergic neurons which themselves would otherwise signal for increased respiratory rate.[18]

The amygdala also interacts with the hippocampus. As mentioned earlier, the BLA sends excitatory inputs to the hippocampal formation by first synapsing at the entorhinal cortex (EC), which then sends its own excitatory inputs to the hippocampus.[13] These inputs are necessary for acquisition of contextual fear memories, likely mediated by the BLA amygdala's fear learning mechanism in combination with hippocampal memory representations.

In addition, the BLA sends glutamatergic synapses directly onto pyramidal cells in the ventral hippocampus (vHPC) CA1 region, increasing anxiety-like behavior when these BLA projections are active. In part, the vHPC mediates its effects on anxiety through glutamatergic projections to the lateral septum, which sends its own projections onwards to the hypothalamus. The vHPC glutamatergic projections stimulate activation of corticotropin releasing factor receptor 2 (CRFR2) expressing GABAergic projection neurons in the lateral septum through a mechanism which is not fully understood.[13,19] These GABAergic projection neurons inhibit the anterior hypothalamic area (AHA), which itself inhibits the paraventricular nucleus (PVN) of the hypothalamus as well as the periaqueductal gray (PAG). In this way, the lateral septum disinhibits the paraventricular nucleus and the periaqueductal gray, which leads to neuroendocrine and behavioral outcomes associated with persistent anxiety.



Conclusion

While this writeup serves as an initial primer on the amygdala, there remain a plethora of relevant neural circuits to explore beyond what has been described here. Nonetheless, I hope that the information provided will offer a useful starting point for learning about the amygdala's structure, function, and effects on mammalian emotions. As further reading, I specifically recommend references #1, #9, #12, and #13.

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