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Neuronal diversity of the amygdala and the bed nucleus of the stria terminalis

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THE AMYGDALA COMPLEX

Discovery and seminal studies on the amygdala

The amygdala is an almond-shaped structure located deep within the temporal lobe, first identified by Karl Friedrich Burdach at the beginning of the 20th century (Burdach, 1819). More than a 100 years later, a wave of interest on the amygdala complex was initiated in 1937 after the publication of a study of Heinrich Klüver investigating the brain substrate underlying the effect of the psychedelic alkaloid mescaline (Klüver & Bucy, 1937). Together with his neurosurgeon colleague, Paul Bucy, they performed bilateral removal of the temporal lobes of rhesus monkeys and described the behavioral alterations induced by the bilateral ablation (Bucy & Klüver, 1955; Klüver & Bucy, 1937); these induced a wide range of behavioral perturbations including hyperorality, hypersexuality, visual agnosia, and docility. Strikingly, the monkeys exhibited a lack of fear in the presence of stimuli innately threatening to healthy monkeys, for example, an object with a similar shape as a snake. Other lesion studies in monkeys confirmed the involvement of the amygdala not only in fear but also in a diverse range of other emotions, including emotions of positive valence (Weiskrantz, 1956). Similar symptoms induced by neuropathological alterations in humans are since then named the Klüver-Bucy syndrome (Terzian & Ore, 1955). Contemporary to these studies in monkeys, a human rare recessive genetic disorder was described, the Urbach-Wiethe disease, where a specific bilateral calcification of the amygdala is observed (Urbach & Wiethe, 1929). Only 400 cases have been reported since 1929, but the behavioral study of these patients combined with brain imaging has confirmed the involvement of the amygdala in fear (Adolphs, Tranel, Damasio, & Damasio, 1994, 1995; Feinstein, Adolphs, Damasio, & Tranel, 2011). Although all the seminal studies in monkeys reported behavioral alterations for both positive and negative emotional valence, the following half-century of research has mostly been dedicated to the more sensational impact of the amygdala in fear responses (Blanchard & Blanchard, 1972; LeDoux, 2003; LeDoux, Iwata, Cicchetti, & Reis, 1988; Paré, Quirk, & Ledoux, 2004; Rogan, Stäubli, & LeDoux, 1997). For example, in some studies, stimuli of both positive and negative valence were presented to a patient suffering from Urbach-Wiethe, but only the response to the fearful stimuli was analyzed (Adolphs et al., 1995). With the exception of a couple of studies analyzing the response of

the amygdala to both positive and negative valence in monkeys (Fuster & Uyeda, 1971), the field had to wait until the early 2000s, to see a shift of paradigm based on original studies of behavioral and physiological data in humans (Baxter & Murray, 2002; Pichon, Miendlarzewska, Eryilmaz, & Vuilleumier, 2015) and animal models (Beyeler et al., 2016; Lee, Amir, Haufler, & Pare, 2017; Namburi et al., 2015; Paton, Belova, Morrison, & Salzman, 2006; Shabel & Janak, 2009; Tye, Stuber, de Ridder, Bonci, & Janak, 2008). Those studies established the amygdala as a causal player in emotional valence, rather than a brain region controlling exclusively fear. However, the five last decades of research focused on the role of the amygdala in fear conditioning have allowed to demonstrate the causal role of specific amygdala nuclei, and underlying synaptic mechanisms of fear learning, expression, and extinction (Herry et al., 2008; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990; Namburi et al., 2015; Quirk & Mueller, 2008; Quirk, Repa, & LeDoux, 1995; Rogan et al., 1997).

Recent functional imaging studies in human have confirmed that the amygdala is involved in both positive and negative emotional valence in healthy individuals (Pichon et al., 2015; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Viinikainen, Kätsyri, & Sams, 2012; Vrtička, Sander, & Vuilleumier, 2012), however, studies in human epileptic patients showed that direct electrical stimulation of the amygdala induces fear responses, supporting the causal role of the amygdala in fear (Inman et al., 2018). Finally, it has consistently been shown that the activity of the amygdala is altered in patients with different types of anxiety disorders or post-traumatic stress disorders (PTSD) (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Etkin & Wager, 2007; Killgore & Yurgelun-Todd, 2005; Pejic, Hermann, Vaitl, & Stark, 2013; Yassa, Hazlett, Stark, & Hoehn-Saric, 2012), highlighting the importance of understanding the inner workings of those brain regions in order to identify potential targets for the development of innovative and efficient therapies.

Constellation of amygdala nuclei

The amygdala complex includes up to 13 nuclei depending on the classifications (Sah, Faber, Lopez De Armentia, & Power, 2003), but is always segregated in five major sections (Fig. 1) (1) the basolateral amygdala (BLA) divided into a dorsal section (lateral amygdala, LA), and basal section (basal amygdala, BA), (2) the basomedial amygdala (BMA), (3) the central amygdala (CeA) further split into medial, lateral, and central sections (CeM, CeL, and CeC), (4) the medial amygdala (MeA), and finally (5) the cortical amygdala (CoA). These nuclei can be distinguished based on their cytoarchitectonic properties and connectivity. Retrograde and anterograde tracing studies have shown that these nuclei have dense intranuclear and internuclear connections, as well as divergent afferent and efferent connections with cortical and subcortical regions. Developmentally, the CeA and MeA originate from the same cellular lineage, presenting a striatal-like organization, compared to the BLA which arises from a different lineage and presents a cortical-like organization (Sah et al., 2003; Swanson & Petrovich, 1998) (Fig. 1). Thus, the CeA is composed almost exclusively of inhibitory neurons, and the MeA is mainly composed of GABAergic neurons but also contains glutamatergic cells (~33%) (Li et al., 2017). In contrast, the BLA and BMA are mainly composed of excitatory projection neurons (Erö, Gewaltig, Keller, & Markram, 2018; Fritsch et al., 2009; McDonald & Augustine, 1993; Nitecka & Ben-Ari,

1987). As for many other cortical-subcortical circuits (Alexander & Crutcher, 1990), the main connections in the amygdala run from the cortical-like to the striatal-like regions, the latter providing the major output of the amygdala complex.

The extended amygdala

The developmentally different origins of the striatal and cortical amygdala have brought authors to question the classical definition of the amygdala nuclei and proposed alternative classifications. In the 1980s, Alheid and colleagues argued that the CeM should be extended rostrally and medially, therefore including the bed nucleus of the stria terminalis (BNST) (Alheid & Heimer, 1988). In this framework, the central extended amygdala cortico-subcortical loop, including the BNST, is one of the three cortico-subcortical loops composing the basal forebrain, in parallel with the hippocampal septal-diagonal-band loop, and the cortico-striato-pallidal loop (Alheid, 2003). More recently, it has even been argued that the amygdala complex is an arbitrarily defined unit of cell groups (Swanson & Petrovich, 1998). These authors suggest an alternative classification where amygdala nuclei are divided into four functional systems: frontotemporal, autonomic, main olfactory, and accessory olfactory systems.

Human fMRI studies have shown activation of the BNST in the conditions of uncertainty, during anticipatory anxiety in arachnophobics, and during hypervigilant threat monitoring, suggesting the contribution of the BNST to the modulation of anxiety rather than fear responses (Straube, Mentzel, & Miltner, 2007; Yassa et al., 2012). This is in agreement with early models by Michael Davis and colleagues (Davis, 1998; Davis, Walker, Miles, & Grillon, 2010). Accordingly, the BNST was overactive in patients suffering from generalized anxiety disorders (GAD) and PTSD. However, growing evidence from rodents (Gungor & Paré, 2016; Martinon et al., 2019) and human fMRI studies clearly show that the BNST is also active in response to fear-evoking stimuli, whereas the CeA is also involved in the modulation of anxiety (Andreatta et al., 2015; Mobbs et al., 2010; Shackman & Fox, 2016). This is not surprising considering that the CeA and BNST have heavy reciprocal connections and both project to many overlapping brainstem autonomic centers, for review see Shackman and Fox (2016).

Cellular diversity in the amygdala and BNST

Anatomical studies in humans, monkeys, cats, and rodents have revealed strong similarities across mammalian species, although there are also differences in the organization of the different amygdaloid nuclei (Fig. 1A–C) (Janak & Tye, 2015; Pitkänen, 2000a). As in humans, functional imaging of the distinction among the different nuclei of the amygdala is challenging, and while parsing the functional contribution of selective cell types is not possible yet, animal models have been essential to disentangle the role of specific cell types within the different nuclei of the amygdala complex. Together with fast amino acid neurotransmitters, neurons of amygdala nuclei also produce numerous neuropeptides and express several neuromodulator receptors (Fig. 1D), generating a wide range of multiplexed neural populations, which ensure different functional roles. This chapter will mainly focus on advances in our knowledge on neural diversity based on recent genetic, molecular, and anatomical identification of neuron types in rodents, especially in rats and mice.

THE BASOLATERAL AMYGDALA (BLA)

The BLA is the most studied nucleus of the amygdaloid complex and is the main input region of the amygdala complex. As in any other regions of the brain, neurons of the BLA can be defined by multiple features including their molecular markers such as neurotransmitters or gene expression; anatomical properties such as size, synaptic inputs, or projection targets; electrophysiological properties; or activation relative to environmental cues or motor actions.

Anatomical, neurochemical, and electrophysiological properties of the BLA

The BLA is divided into a dorsal section, the lateral amygdala (LA) and a basal section, the basal amygdala (BA) sections (Fig. 1). In mouse, the BLA is composed of 60% of neurons (Erö et al., 2018), while it represents 40% of the cells in rats (Tuunanen & Pitkänen, 2000), and is down to 20%–35% in humans (Faber-Zuschratter et al., 2009; García-Amado & Prensa, 2012). Stereological analysis of thionin stained coronal sections of the BLA in adult rats has shown that the LA is composed of ~60,000 neurons while the basal part (BA) is composed of ~47,000 neurons (~110,000 in the entire BLA) (Tuunanen & Pitkänen, 2000). The Blue brain atlas, based on Nissl staining in mice, recently found similar numbers for the LA (62,000 neurons) (Erö et al., 2018), and 131,000 neurons in BA, which is about twice the number previously described, and is likely the result of differences in atlas delineations across studies. Stereological counting of human BLA found 5.48 million LA neurons and 5.02 million BLA neurons, bringing the estimated total number of human BLA neurons to 11 million (García-Amado & Prensa, 2012; Rubinow et al., 2016).

Based on Golgi staining in rats, BLA neurons were divided in two main classes (1) pyramidal, or class I neurons, described as excitatory neurons which release glutamate and representing up to 95% of the neurons, and (2) class II neurons, which are smaller, ovoid cells representing 5% of Golgi-impregnated neurons (McDonald, 1982). Pyramidal neurons have three to seven dendrites emerging from their soma, usually with one prominent dendrite which has been compared to the apical dendrite of cortical neurons (Sah et al., 2003). Unlike pyramidal neurons in the cortex or hippocampus, BLA pyramidal neurons are not organized in parallel but appear randomly distributed (McDonald, 1982; Sah et al., 2003). Importantly, axons of pyramidal neurons, project out of the BLA, with several collaterals that arborize within the BLA (McDonald, 1982). Class II neurons have two to six primary dendrites, are characterized by spine-sparse dendrites, and dense local axonal arborizations. They can be classified as multipolar, bitufted, bipolar, and chandelier cells depending on the dendritic branching pattern. These cells are clearly local interneurons releasing gamma amino-butyric acid (GABA). In monkeys, the proportion of GABA immunoreactive cells was found to reach 25% (McDonald & Augustine, 1993) but a similar organization of GABA immune-positive cells was described in rats and monkeys (McDonald & Augustine, 1993; Nitecka & Ben-Ari, 1987). In rats, immunohistochemical analysis of the distribution of the glutamate decarboxylase-67 (GAD-67) has shown that GABA interneurons represent ~15% of BLA neurons (Fritsch et al., 2009). More recently brain-wide systematic, computerized analysis of neural densities in mice, has even found a smaller proportion of BLA inhibitory neurons (9%), bringing the proportion of excitatory pyramidal neurons up to 91% (Erö et al., 2018).

With the exception of few long-range inhibitory interneurons, projecting to the entorhinal cortex (McDonald & Zaric, 2015a) or the basal forebrain (McDonald, Mascagni, & Zaric, 2012), inhibitory interneurons synapse locally, whereas excitatory neurons are projection neurons. Ex vivo electrophysiological intracellular recordings of pyramidal neurons within the BLA have shown that they fire broad action potentials (half-width 1.2 ms) with varying degrees of action potential frequency adaptation, and that action potential trains are followed by a lasting after-hyperpolarization (AHP, 1–5 s). Conversely, inhibitory interneurons fire short-duration action potentials (half-width of 0.7ms) show little spike frequency adaptation (Faber & Sah, 2002; Rainnie, Asprodini, & Shinnick-Gallagher, 1993; Sah et al., 2003).

The BA has further been divided into three subfields, based on the size of the pyramidal cell soma in cats and rodents: the magnocellular, intermediate, and parvicellular subdivisions (Hall, 1972; Price, Russchen, & Amaral, 1987; Savander, Go, LeDoux, & Pitkänen, 1995). The magnocellular section corresponds to the anterior BA, where pyramidal neurons have larger cell bodies (Price et al., 1987) whereas projection neurons in the parvicellular subdivision have smaller cell bodies (Price et al., 1987). Finally, the intermediate BA was first described in rats as the transition zone between the magnocellular and parvocellular BA, where the decreasing anteroposterior gradient of large pyramidal cells and the increasing gradient of the small pyramidal cell intersect (Fig. 2A) (Savander et al., 1995). Recent 3D imaging of brain rendered transparent with the CLARITY technique and containing a subset of BLA pyramidal neurons expressing eYFP, allowed to visualize this anteroposterior gradient of size (Beyeler et al., 2018). Intrinsic connectivity between the magnocellular, intermediate, and parvocellular sections was analyzed and identified reciprocal connections across the three subfields, including an extensive projection from the posterior parvocellular section to the intermediate and magnocellular regions (Sah et al., 2003; Savander et al., 1995). The main intra-amygdaloid targets of the BA are the CeM and the anterior CoA (Savander et al., 1995).

Seminal lesion and pharmacological studies have demonstrated that the BLA, and especially the LA is necessary for learning cue and context fear associations (Cousens & Otto, 1998; Goosens & Maren, 2001; Phillips & LeDoux, 1992), and direct optogenetic stimulation of the LA can elicit a defensive response in a naïve mouse (Johansen et al., 2010). However, the BLA has also been shown to control reward behaviors (Kim, Pignatelli, Xu, Itohara, & Tonegawa, 2016; Namburi et al., 2015; Tye et al., 2008), and single-cell recordings in the BLA of animal models including rodents and monkeys have shown that neurons of this region are responding to stimuli of positive and stimuli of negative valence (Beyeler et al., 2016; Fuster & Uyeda, 1971; Paton et al., 2006; Shabel & Janak, 2009). Recordings of BLA neurons in monkeys, rats, and mice have shown that around 50% of the units respond to predictive cues of positive or negative valence (Beyeler et al., 2016; Kyriazi, Headley, & Pare, 2018; Paton et al., 2006), with an overrepresentation of neurons responding to positive valence in monkeys (Paton et al., 2006) and mice (Beyeler et al., 2016), and an even distribution of neuron responding to both valences in rats (Kyriazi et al., 2018). Additionally, pioneering work has shown that some BLA neurons track the value of a sensory stimulus during reversal of conditioned and unconditioned stimuli (CS and US) association (Paton et al., 2006; Schoenbaum, Chiba, & Gallagher, 1999) emphasizing the critical role of the BLA in valence coding. Finally, a recent study has also identified that even if relatively few cells

encode valence in the BLA, valence can be decoded from the neural activity at the population level (Kyriazi et al., 2018). In order to understand how a single brain region can encode such opposite behaviors, it is necessary to integrate additional features beyond the location in the brain, including synaptic input, projection targets, and molecular markers (Beyeler, 2016; Janak & Tye, 2015).

Excitatory projection neurons

The BLA has two main output fiber bundles which originate in the amygdala: the stria terminalis and the amygdalofugal pathway (Leonard & Scott, 1971; Mori et al., 2017). The stria terminalis connects the amygdala to the septal area of the basal forebrain and hypothalamus, while the amygdalofugal pathway is believed to contain both afferent and efferent connections to the basal forebrain, hypothalamus, and thalamus. Through these two pathways and direct axonal projections, the BLA targets a wide range of cortical and subcortical downstream regions. For a comprehensive list of downstream targets of the BLA, please refer to Pitkänen (2000b). Over the past decade, optogenetic experiments have allowed to identify selective roles of BLA projections and/or projector populations. In this section, we will review recent findings on the functional role of the most studied BLA projection.

Functional role of BLA projections (Table 1)—Multiple BLA projections to cortical and subcortical regions have been revealed to regulate defensive behaviors. For example, optogenetic activation of BLA projections to the CeA (BLA-CeA) drives real-time place aversion (Namburi et al., 2015). Similarly, opto-activation of the BLA projections to the ventral hippocampus (BLA-vHPC) (Felix-Ortiz et al., 2013; Felix-Ortiz & Tye, 2014), the mPFC (BLA-mPFC) (Felix-Ortiz et al., 2016), and the anterodorsal BNST (BLA-adBNST) were shown to increase anxiety-related behaviors. Other studies probing the BLA-mPFC projections have shown that it is causally involved in fear conditioning (Burgos-Robles et al., 2017; Herry et al., 2008; Klavir, Prigge, Sarel, Paz, & Yizhar, 2017; Yizhar & Klavir, 2018), as well as the projection to the entorhinal cortex (BLA-eCx) (Majak & Pitkänen, 2003; Sparta et al., 2014). Interestingly, a chronic restraint stress in mice dysregulates the activity of the BLA-mPFC pathway by enhancing glutamate release in the mPFC (Lowery-Gionta et al., 2018). Conversely, optogenetic activation of BLA projections to the nucleus accumbens (BLA-NAc) has repeatedly been shown to support positive reinforcement (Britt et al., 2012; Namburi et al., 2015; Stuber et al., 2011), and pharmacological disconnection of the BLA and NAc identified that the BLA-NAc pathway is critical for cocaine seeking (Di Ciano & Everitt, 2004). Interestingly, ex vivo optogenetic circuit mapping has demonstrated preferential feedback connectivity within functionally related circuits. Specifically, it has been shown that mPFC inputs in BLA are much stronger onto BLA-mPFC and BLA-vHPC neurons compared to PFC inputs onto BLA-NAc projecting neurons (McGarry & Carter, 2017).

The accumulation of results reporting the regulation of valence-related behavior by BLA projections supports the hypothesis that anatomically divergent populations of the BLA differentially encode valence. Moreover, recordings combined with optogenetic photoidentification of specific neural subpopulations have shown that BLA-NAc units are

preferentially excited by a positive cue and BLA-CeA units are preferentially excited by a negative one (Beyeler et al., 2016). Consistently, recordings of synaptic inputs on BLA-NAc and BLA-CeM neurons show that inputs on BLA-NAc projections are potentiated after reward learning and depressed after fear conditioning, whereas inputs on BLA-CeM neurons are depressed after reward learning and potentiated after learning the association of a cue and a reward (Namburi et al., 2015). Importantly, in vivo recordings have also revealed heterogeneity of single-neuron activity within projection-defined populations (Beyeler et al., 2016; Burgos-Robles et al., 2017; Senn et al., 2014), which supports a model where valence-coding of a projector population can be inferred from the projection target of its neurons, but the projection target of a single neuron is not sufficient to deduce its valence coding properties.

Topography of projection neurons—Retrograde tracing in rats showed that the majority of BLA-prelimbic (PL) projectors are mostly located in the caudal BLA, while BLA neurons projecting to the dorsal agranular insular cortex (BLA-aIC) are mainly found in the rostral BLA (Shinonaga, Takada, & Mizuno, 1994). The distribution of BLA-mPFC projection neurons are sparsely located in the LA and more densely populate the BA, and topographically organized, depending on the termination of their axons in the mPFC. Indeed, neurons projecting to more anterior mPFC such as the ACC, are located in the anterior BA, while neurons projecting to more caudal mPFC such as the PL, are densest in the posterior BA (Reppucci & Petrovich, 2016). In mice, the BLA-NAc projectors targeting the medial or lateral part of the nucleus accumbens were described to be diffusely distributed in the BLA (Shinonaga et al., 1994), while BLA-NAc targeting the NAc medial core and shell was described to be located in the more ventral and medial BLA (Beyeler et al., 2018; Kim et al., 2016). A systematic study of the medial-to-lateral coordinates in the rat striatum identified a medial-to-lateral topography of BLA-striatum neurons in the BLA (McDonald, 1991). Moreover, an anterior-to-posterior BLA projects preferentially to anterolateral-to-posteromedial aspects of the NAc (Krettek & Price, 1978; Zorrilla & Koob, 2013). Notably, in mice, BLA-CeM projectors are densest in LA compared to BLA-NAc and BLA-vHPC cells and are mainly lateral in the BA, which is the opposing topographic pattern of BLA-NAc neurons, which have an opposing role in valence (Beyeler et al., 2018). The BLA and CeA both projects to ventral and dorsal sections of the lateral hypothalamus (LH), respectively, and BLA-LH projectors are sparse in the LA and have a high density in the BA along the entire anteroposterior axis (Reppucci & Petrovich, 2016). Interestingly, the authors found almost no overlap between BLA-mPFC and BLA-LH neurons, suggesting these two projection arise from different populations (Reppucci & Petrovich, 2016). Although topographic organization has been described for most of BLA projector populations, these are mainly gradients and overall, projector populations are intermingled in the BLA.

Collateralization of projection neurons—Collateralization is a defining feature of projection neurons, and synapses of one projection-defined population onto different downstream regions might support diverse behavioral effects. Multiple studies have described collateralization patterns of BLA projectors. Almost 50% of BLA-PL neurons send axon collaterals to the medial NAc, whereas about 30%–40% BLA-aIC or BLA-PL neurons issue axon collaterals to the lateral NAc (Shinonaga et al., 1994). The axons

bifurcating to both the aIC and lateral NAc arose preferentially from the rostral BLA, and those bifurcating to PL and lateral NAc, arose preferentially from the intermediate BLA, while axons bifurcating to both PL and medial NAc emerged mainly from the caudal BLA (Shinonaga et al., 1994). Anterograde tracing based on the viral expression of the fluorescent protein eYFP, and of the fused protein synaptophysin-mcherry showed that BLA-vHPC, BLA-CeA, and BLA-NAc populations collateralize to downstream targets of one another, with up to 50% of the main downstream region relative fluorescence (Beyeler et al., 2016). BLA-NAc projectors collateralize to the mPFC, with the strongest fluorescence in PL compared to IL, and mildly to the CeA and vHPC. The BLA-CeA projectors collateralize mainly to the NAc, mildly to the mPFC and almost not in the vHPC. Finally, BLA-vHPC projectors send collaterals mainly in the mPFC and anterior NAc, and weakly in caudal NAc and CeA (Beyeler et al., 2016). Taking into account the collateralizations to multiple brain regions increases the heterogeneity of defining features of each BLA neuron. Noteworthy, genetic markers potentially correspond to defining those features that could map onto the collateralization pattern as well as the valence coding properties of projection neurons.

Genetic markers of projections neurons—As in other cortical regions, glutamatergic neurons in the BLA express the calcium/calmodulin-dependent protein kinase II (CaMKII) (McDonald, Muller, & Mascagni, 2002). Interestingly, every pyramidal cell contains CaMKII, while cell bodies of small non-pyramidal neurons do not, making CaMKII an exclusive marker of glutamatergic pyramidal neurons in the BLA (McDonald et al., 2002). At the ultrastructural level, CaMKII is localized in the pyramidal cell bodies, thick proximal dendrites, thin distal dendrites, in most dendritic spines, in the axon initial segments, as well as in axon terminals forming asymmetrical synapses (McDonald et al., 2002).

A subset of glutamatergic neurons of the BLA expresses the thymus cell antigen 1 (Thy1) (Jasnow et al., 2013). Optogenetic and chemogenetic activations of Thy1-expressing neurons inhibit fear consolidation and accelerate memory extinction, respectively (Table 1) (Jasnow et al., 2013; McCullough et al., 2016), while optogenetics inhibition of Thy1 neurons decreases fear extinction. Interestingly, two electrophysiologically distinct populations of BLA neurons were identified depending on their response to the extinction of an association of a cue and an electric shock (Herry et al., 2008). The first population increased its firing frequency in response to the predictive cue during and after fear conditioning and reduced its firing frequency to the cue during extinction training. The second population only increased its firing rate in response to the cue during extinction training and was named ‘fear-off’ neurons (Herry et al., 2008). Further molecular analysis of Thy1 neurons using RNA sequencing identified genes strongly upregulated in the Thy1 population, including the genes coding for the neurotensin receptor 2 (Ntsr2) and Rspo2 (Rspondin-2) (McCullough et al., 2016). Importantly, pharmacological manipulation of neurotensin receptor 2 (NT2) suggests that neurons expressing Ntsr2 within the BLA are putative “Fear-OFF” neurons (McCullough et al., 2016).

To date, no genetic markers have been identified within selective projector populations of the BLA. However, RNA-sequencing has demonstrated enrichment of mRNA when comparing different projector populations. Specifically, BLA-CeM projectors were shown to have more than 4 times the amount of mRNA of the neurotensin receptor 1 (NT1) in comparison to the

BLA-NAc projectors (Namburi et al., 2015). However, these markers are not exclusive and do not allow to genetically target a specific projector population. A recent study that performed activity-dependent profiling combined with extensive gene screening (Allen Brain Atlas, 2016; Kim et al., 2016) has shown that the anterior magnocellular and posterior parvocellular projection neurons can be defined by the expression of different gene markers. Indeed, neurons expressing the gene *Rspo2,* which codes for R-spondin-2, are located in the anterior BLA and correspond to the magnocellular neurons, while neurons expressing the *Ppp1r1b* gene, which codes for the protein phosphatase 1 regulatory inhibitor subunit 1B (DARPP-32), are located in the posterior BLA and correspond to parvocellular neurons (Kim et al., 2016). Interestingly, optogenetic stimulation of $Rspo2^+$ cells elicits a defensive response in naïve mice whereas stimulation of $Ppp1r1b^+$ cells promotes an appetitive response (Table 1) (Kim et al., 2016). Both populations send projections to the NAc and CeA, and $Rspo2^+$ cells monosynaptically contact $PKC\delta^+$ cells of the CeC, whereas $Ppp1r1b^+$ cells innervate the other cellular subtypes of the CeM and CeL (Kim et al., 2017). The anteroposterior topography of the *Rspo2* and *Ppp1r1b* gene markers does not overlap with the distribution of BLA-NAc and BLA-CeA populations which are intermingled with mediolateral and dorsoventral gradients (Beyeler et al., 2018).

A recent study using cholecystokinin (CCK) reporter mouse line (CCK-ires-Cre-Ai14) has identified that BLA projection neurons can also be divided into CCK(+) and CCK(−) (Shen et al., 2019) neurons. Optogenetic activation of the projection of these two BLA populations into the NAc-core drives different behaviors of negative and positive valence, respectively (Table 1). Interestingly, the CCK(+) projection neurons overlap with the $Rspo2^+$ expressing neurons along the entire anteroposterior axis of the BLA and target almost exclusively medium spiny neurons expressing the dopamine 2 receptor (D2-MSN) in the NAc (Shen et al., 2019).

Inhibitory interneurons

As discussed in the first section, GABAergic neurons represent around 10% of the neurons within the mouse BLA (Erö et al., 2018). Interestingly, in the early stages of a rodent model of epileptogenesis, GABAergic interneurons display a more extensive loss compared to the loss of principal cells, concomitantly with a reduced frequency, but not amplitude, of miniature IPSCs (Fritsch et al., 2009). However, the predictive factors of the degeneration of GABAergic interneurons remain unknown. A thorough characterization of the molecular identity of neural populations in the BLA has the potential to determine markers of neural susceptibility to pathological conditions, representing a remarkable translational potential for psychiatric disorders and epilepsy. As in cortical areas, inhibitory interneurons in the BLA encompass a large diversity of molecular markers including calcium-binding albumin proteins (i.e., parvalbumin [PV], calbindin [CB], or calretinin [CR]), neuropeptides (i.e., somatostatin [SOM], cholecystokinin [CCK], vasoactive intestinal peptide [VIP], or neuropeptide Y [NPY]), enzymes such as nitric oxide synthase (NOS), as well as membrane receptors such as the serotonin 2A receptor ($5\text{-}HT_{2A}$) or the endocannabinoid receptor 1 (eCB1) (Fig. 2) (Kemppainen & Pitkänen, 2000; McDonald & Betette, 2001; McDonald & Mascagni, 2002; McDonald, Muller, & Mascagni, 2011; Rhomberg et al., 2018; Spampanato, Polepalli, & Sah, 2011; Wang, Liu, Wang, Gao, & Zhan, 2017). Notably, some

populations are mutually exclusive, while others are partially or fully overlapping. Importantly CB and CR cell types are non-overlapping, with the CB neurons representing ~60% of all BLA interneurons, and CR neurons accounting for ~20% of the remaining GABAergic cells (Fig. 2B) (Kemppainen & Pitkänen, 2000; Krabbe, Grundemann, & Luthi, 2018; McDonald & Mascagni, 2001a). Part of CR interneurons express VIP and/or CCK (Spampanato et al., 2011). On the other hand, CB interneurons are divided into nonoverlapping types expressing either PV, SOM, or CCK individually (Mascagni & McDonald, 2003; McDonald & Mascagni, 2002).

Parvalbumin (PV)—Neurons expressing the calcium-binding protein PV are interconnected through chemical and electrical synapses and provide strong perisomatic inhibition to local principal neurons (Fig. 2C). The PV population can further be segregated into basket cells, contacting the soma and proximal dendrites, and axo-axonic cells, contacting selectively the axon initial segment (Kemppainen & Pitkänen, 2000; Veres, Nagy, & Hajos, 2017). In monkeys, one-quarter of PV cells also express the calcium-binding protein (CB), but no PV cells express CR, CCK, or SOM (Mascagni, Muly, Rainnie, & McDonald, 2009). However, PV cells express a high levels of a1-containing $GABA_a$ receptors, α7-containing nicotinic acetylcholine receptors, and dopamine-D2 receptors (Rowniak, Kolenkiewicz, & Kozlowska, 2017). Functionally, PV and SOM local interneurons have been shown to differentially drive behavioral responses to aversive cues (Wolff et al., 2014). Specifically, optogenetic activation of PV cells during an auditory cue, while mice are acquiring the association of this cue with a footshock, significantly increases freezing to the cue during retrieval (Table 1). On the contrary, similar activation during the footshock induces a decrease of freezing during cue retrieval, suggesting PV cells gate learning depending on the timing of their activation (during conditioned [CS] or unconditioned stimuli [US]) (Wolff et al., 2014). In the same study, optogenetic photoidentification has shown that PV neurons are excited during the predictive cue, and indirectly disinhibit the dendrites of principal neurons via SOM inhibitory interneurons (Table 1, Fig. 2C). Finally, PV interneurons are inhibited during the footshock (Wolff et al., 2014). Altogether, the PV-SOM disinhibitory mechanisms could enhance the auditory inputs on principal dendrites, hence promoting tone-shock associative learning (Wolff et al., 2014). Interestingly, PV neurons were shown to be regulated by the environment during postnatal development. First, early life stress in rats (postnatal days 8–12) increases threat response in peri-weaning rats (23 days old), concomitantly to a reduction of synapses formed by PV cells, on pyramidal and PV somata (Santiago, Lim, Opendak, Sullivan, & Aoki, 2018). Second, rearing young rats (25 days old) in an enriched environment decreases anxiety-like behaviors in adults (60 days old) and is associated with an increase in the number of PV neurons (Urakawa et al., 2013). Finally, quantification of the expression of the immediate-early gene cFos has shown that anxiolytic drugs activate PV neurons (Hale et al., 2010; Lukkes, Burke, Zelin, Hale, & Lowry, 2012).

Somatostatin (SOM)—Conversely, to PV cells, SOM interneurons mainly target the distal dendrites of pyramidal cells (Muller, Mascagni, & McDonald, 2007; Wolff et al., 2014), and only 15% of SOM terminals form synapses with PV, VIP, or SOM interneurons (Muller et al., 2007). Hence, SOM neurons are ideally positioned to control synaptic input

and plasticity on pyramidal dendrites. Interestingly, the few long-range GABAergic interneurons, which target the entorhinal cortex, express SOM, CB, and NPY (Fig. 2B) (McDonald et al., 2012; McDonald & Zaric, 2015a). Neurons expressing the cholinergic muscarinic receptor M2 also express GAD, as well as SOM and NPY, but not PV, CR, or CCK (McDonald et al., 2011). In opposition with PV cell, optogenetic activation of SOM interneurons during an auditory cue, while mice are acquiring the association between this cue and a footshock, decreases freezing to the cue, during retrieval (Table 1) (Wolff et al., 2014). Consistently, photoidentification showed that during acquisition, SOM neurons are inhibited to the shock-predictive cue (Wolff et al., 2014). However, as PV cells, SOM neurons are also inhibited during the footshock (Wolff et al., 2014), suggesting inputs other than PV are decreasing the firing of SOM during an aversive stimulation. Immunohistochemistry for the immediate early gene cFos in rats has shown that SOM neurons are specifically activated after exposure to the elevated-plus-maze, but not after presentation of a predator odor (ferret) (Butler et al., 2012).

Cholecystokinin (CCK)—In the BLA, interneurons expressing CCK are segregated in two subpopulations, one characterized by large soma (CCK_L), while the second one has smaller cell bodies (CCK_S, Fig. 2) (Katona et al., 2001; Krabbe et al., 2018; McDonald & Mascagni, 2001b). The CCK_L cells coexpress CB and are the only GABAergic population expressing the endocannabinoid receptor 1 (CB1). On the contrary, CCK_S neurons express CR and/or VIP (Katona et al., 2001; McDonald & Mascagni, 2001b). As PV basket cells, CCK cells synapse onto the soma and proximal dendrites of the pyramidal cells (Mascagni & McDonald, 2003; Veres et al., 2017). Importantly, electron microscopic investigation has revealed that CB1 receptors are located presynaptically on CCK_L axon terminals which establish symmetrical GABAergic synapses with their postsynaptic targets (Katona et al., 2001). Noteworthy, CB1 regulation of inhibitory synaptic transmission onto BLA pyramidal neurons strongly depends on the projection target of the principal neuron. Indeed, ex vivo electrophysiological recordings in mice have shown that, although both BLA-mPFC projecting neurons, BLA-IL and BLA-PL, receive uniform inhibition from CB1/CCK interneurons, retrograde endocannabinoid signaling induces twice more depolarization-induced suppression of inhibition (DSI) at synapses between CB1/CCK and BLA-IL neurons than at synapses between CB1/CCK and BLA-PL neurons (Vogel, Krabbe, Grundemann, Wamsteeker Cusulin, & Luthi, 2016).

Mascagni and McDonald (2003) described for the first time that some pyramidal projection neurons have low levels of CCK immunoreactivity in the rat BLA. Consistently, a recent study using the CCK-ires-Cre-Ai14 genetic mouse line has shown that CCK expressing neurons are immunoreactive for the glutamatergic marker CaMKIIα in the BLA (Shen et al., 2019). Surprisingly, they found that more than 90% of the CCK neurons labeled in this mouse line are co-expressing CaMKIIa and less than 3% of the CCK neurons co-express the GABAergic marker GAD67 (Shen et al., 2019).

Neuropeptide Y (NPY)—NPY is a 36 amino acid neuropeptide and is considered the most abundant neuropeptide in the rodent and human brain and is highly present in the BLA (Allen et al., 1983; Tasan et al., 2016). Direct amygdala and BLA micro-infusions of NPY in

rats have been shown to be anxiolytic (Heilig et al., 1993; Sajdyk, Vandergriff, & Gehlert, 1999). In the BLA, NPY mainly originates from local interneurons, and moderately from afferent and efferent projections (Leitermann, Rostkowski, & Urban, 2016; McDonald & Zaric, 2015b; Tasan et al., 2016). Within GABAergic neurons, ~15% was suggested to contain NPY, while more than 80% of NPY neurons also express GABA (McDonald, 1989; McDonald & Pearson, 1989). NPY is generally expressed in SOM neurons, and almost all NPY cells co-express SOM (McDonald, 1989). Importantly, more than 80% of these SOM/NPY neurons in the BLA form symmetrical (inhibitory) synapses at distal dendrites and dendritic spines of CaMKIIa-pyramidal neurons (Muller et al., 2007). NPY has three types of G-protein coupled receptors in the amygdala: Y1, which is mainly postsynaptic, Y2, which is predominantly pre-synaptic, and is involved in inhibitions of NPY, GABA, or glutamate release, and finally Y5 (Sosulina, Schwesig, Seifert, & Pape, 2008; Stanic et al., 2006; Tasan et al., 2016; Wolak et al., 2003). Interestingly, Y1 stimulation has been shown to be anxiolytic (Wahlestedt, Pich, Koob, Yee, & Heilig, 1993), while Y2 activation is anxiogenic (Nakajima et al., 1998).

Electrophysiological markers—Ex vivo electrophysiological recordings of BLA inhibitory interneuron identified four types of neurons depending on their response to transient depolarizing current injection: burst-firing, regular-firing, fast-firing, and stutter-firing interneurons. Interestingly, the histochemical analysis showed that over 60% of burst-firing and stutter-firing interneurons express PV (Rainnie, Mania, Mascagni, & McDonald, 2006), highlighting the combinatorial physiological and neurochemical diversity of BLA interneurons (Sosulina, Graebenitz, & Pape, 2010). Voltage-dependent potassium channels (Kv) are critical factors determining the electrophysiological properties of a neuron (Covarrubias et al., 2008; Rudy et al., 1999). The Kv3.1 and Kv3.2 subunits are highly expressed in PV interneurons, compared to CCK interneurons which express almost none of these units (Rudy & McBain, 2001). Kv4 is composed of α-subunits (1, 2, or 3), sometimes associated with a β-subunits such as KChip (1, 2, 3, or 4) which regulates the function of Kv4 channels. Dualimmunofluorescence studies revealed that Kv4.3 colocalizes with KChip1 in PV, CCK-8, and SOM interneurons of the BLA (Dabrowska & Rainnie, 2010). This suggests KChip1 as a molecular marker of CB-like but not CR-like subpopulation of BLA interneurons. In vivo recordings in rats combined with immunohistochemistry have identified that the firing of specific subtypes of BLA interneurons is associated with local field potential oscillations. Specifically, the firing of CB interneurons, which target dendrites of pyramidal cells, is precisely theta-modulated, while other interneuron types including PV cells are heterogeneously modulated (Bienvenu, Busti, Magill, Ferraguti, & Capogna, 2012).

Intercalated masses—Intercalated (ITC) cells are the smallest in the amygdala and are inhibitory interneurons (Fig. 1). They were shown to relay negative valence to the BLA, including fear and pain information (Asede, Bosch, Luthi, Ferraguti, & Ehrlich, 2015; Bienvenu et al., 2015; Kuerbitz et al., 2018; Strobel, Marek, Gooch, Sullivan, & Sah, 2015). These cells form discontinuous clusters in three locations: between the LA and CeL, between the ventral BA and MeA, and between the BA and adjacent cortex (Fig. 1) (Millhouse, 1986). Anatomically, one or two parent dendrites arise from either extremity of the oval ITC cell bodies and divide three or four times (Hall, 1972). The resulting branches

carry a modest number of spines, and the dendritic arborizations are frequently parallel to the region adjacent nuclei, with some dendrites intermingled with the dendrites of the surrounding nuclei (Hall, 1972). ITC cells receive strong projections from the infralimbic prefrontal cortex (IL) in both primates and rodents, which have been postulated to allow cortical control of emotional learning such as fear extinction (Quirk & Mueller, 2008). Intracellular recordings found that all ITC recorded cells were orthodromically responsive to infralimbic stimuli, and their responses usually consisted of high-frequency trains of four to six spikes, a response pattern never seen in neighboring amygdala nuclei (Amir, Amano, & Pare, 2011). Notably, ITC cells highly express the transcription factor FoxP2 (Forkhead box protein P2) (Kaoru et al., 2010) and NPY (Wood et al., 2016).

THE CORTICAL (CoA), MEDIAL (MeA), AND BASOMEDIAL AMYGDALA (BMA)

The cortical amygdala (CoA)

In humans, the CoA corresponds to the most medial region of the amygdala complex, while it is the most ventral in mice (Fig. 1). As all cortices, the CoA has been divided into layers (I, II, and III—IV) and is mainly composed of glutamatergic projection neurons. In cats, the inferior part of the stria terminalis courses between the small celled part of the basal and the medial part of the CoA (Hall, 1972). The layer I contains dendritic arborizations extending from layer II and layer III—IV (Hall, 1972). Layer II is composed of a variety of cell types, with pyramidal cells being the most numerous and having their apical dendrites frequently oriented obliquely instead of vertically toward the pia surface (Hall, 1972). The dendritic arborizations of pyramidal cells carry spines except on the primary dendrites with a sparse distribution on the proximal part of the secondary branches (Hall, 1972). Developmentally, the CoA has a ventropallial origin, leading mainly to glutamatergic projection neurons (Martinez-García, Novejarque, Gutierrez-Castellanos, & Lanuza, 2012). The CoA has been described to contain neurons that are characteristically immunoreactive for CR (Martinez-García et al., 2012). This cortical region receives inputs from the olfactory bulb, which are topographically identifiable from individual glomeruli of the olfactory bulb (Sosulski, Bloom, Cutforth, Axel, & Datta, 2011). Noteworthy, this is not the case for the piriform cortex, even if it also receives direct inputs from the olfactory bulbs (Sosulski et al., 2011). Although distinct in the CoA, input patches are overlapping, providing an opportunity for olfactory integration of information from multiple glomeruli. The differential pattern of olfactory inputs to the CoA and piriform cortex suggests an anatomical substrate for the generation of learned and innate behaviors (Sosulski et al., 2011). When analyzed independently of projection target or gene markers, neurons of the cortical amygdala (CoA, Fig. 1) represent odor objects of both positive and negative valence using distributive population codes (Iurilli & Datta, 2017). Consistently, optogenetic inhibition of CoA reduces innate responses to the odors of both positive and negative valence (Root, Denny, Hen, & Axel, 2014). Interestingly, neurons activated by odors of positive or neutral valence are mainly recruited in the posterior section of the CoA, compared to neurons activated by an odor of negative valence which is equally distributed in the anteroposterior axis (Root et al., 2014).

The medial amygdala (MeA)

Anatomically, the MeA lies caudally to the ventral striatum and is mainly composed of GABAergic projection neurons (Fig. 1)(Alheid & Heimer, 1988). Golgi staining in the cat amygdala has shown that cells in the MeA are relatively small with 2–4 thin primary dendrites arising from the cell body, which then divide 1–3 times, producing a sparse arborization (Hall, 1972). Neurons in the MeA, receive input from the accessory olfactory bulbs, and project directly, and indirectly through the BNST, to nuclei of the medial hypothalamus (Dong, Petrovich, Watts, & Swanson, 2001; Dong & Swanson, 2004; Krettek & Price, 1978; Swanson & Petrovich, 1998). The MeA has been functionally subdivided in the anterior MeA (MeA-a), which is connected with circuits controlling defensive and reproductive behaviors, the posterodorsal MeA (MeA-pd) connects mainly with structures involved in reproductive behaviors (Canteras, Simerly, & Swanson, 1995; Pardo-Bellver, Cadiz-Moretti, Novejarque, Martinez-García, & Lanuza, 2012), and finally, the posteroventral MeA (MeA-pv) projecting to circuits involved in defensive behaviors (Canteras, 2002). This anatomical division overlaps with the expression of three LIM homeobox (Lhx) genes, which encode transcription factors. Specifically, the MeA-a mainly expresses Lhx5, whereas the MeA-pd highly expresses Lhx6, and the MeA-pv expresses Lhx9 (Choi et al., 2005). The MeA-a contains a high density of glutamatergic (Poulin, Castonguay-Lebel, Laforest, & Drolet, 2008) and nitric oxide neurons (McDonald, Payne, & Mascagni, 1993). Developmentally, Lhx5 neurons of the MeA-a originate from the hypothalamic supra-opto-paraventricular domain (Abellan, Vernier, Retaux, & Medina, 2010), while Lhx6 neurons of the MeA-pd are GABAergic cells originating from the caudo-ventral medial ganglionic eminence, and Lhx9 cells of the MeA-pv originate from the ventral pallium, and are consequently glutamatergic projection neurons (Choi et al., 2005). Neurons of the MeA have also repeatedly been shown to regulate social behaviors (Li et al., 2017; Yao, Bergan, Lanjuin, & Dulac, 2017) and GABAergic neurons of MeA-pd promote social behaviors of both negative (e.g., aggression) and positive valence (e.g., mating and social grooming) (Hong, Kim, & Anderson, 2014). Neurons in the MeA can also be genetically identified by the unique marker laminin beta-3 (Zirlinger, Kreiman, & Anderson, 2001) and express numerous receptors including oxytocin receptors (Yao et al., 2017), estrogen receptors, and corticotropin-releasing factor receptor 2 (CRFR2) (Frankiensztajn, Gur-Pollack, & Wagner, 2018). MeA cells expressing CRFR2 receptor mRNA are active during a social experience of negative valence (social defeat stress) (Fekete et al., 2009). In addition, a subpopulation of MeA neurons expressing kisspeptin protein modulates anxiety and sexual partner preference in male mice (Adekunbi et al., 2018), whereas neurons expressing the estrogen receptor-alpha control body weight (Xu et al., 2015). The activity of GABAergic SOM neurons, measured by cFos immunostaining, is increased in rats by exposure of the animals to a predator odor (ferret odor) or to an anxiogenic environment (elevated-plus-maze) (Butler et al., 2012). Interestingly, neurons expressing NPY were shown to be activated only by the predator odor but not by exposure to the elevated-plus-maze (Butler et al., 2012).

Noteworthy, stimulation of midbrain dopamine neurons induces the activation of the MeA (Chung, Miller, Sun, Xu, & Zweifel, 2017) and MeA neurons express dopamine D1 receptor (D1R), which are mainly localized in the MeA-pv in mice (Miller, Marcotulli, Shen, &

Zweifel, 2019). Recently, it was shown that distinct subpopulations of MeApv-D1R neurons differentially innervate the ventromedial hypothalamus (vmHPT) and BNST and that these projections have opposing effects on investigation or avoidance of threatening stimuli (Miller et al., 2019). Specifically, optogenetic activation of MeApv(D1R)-BNST neurons decreases avoidance of predator stimuli, whereas activation of $MeApv_{(D1R)}$-vmHPT increases avoidance of those same stimuli (Miller et al., 2019).

The basomedial amygdala (BMA)

The BMA is located ventral to the BA (Fig. 1). In both the cat and the rat, the BMA is composed of small- to medium-sized cells that are readily distinguished from those of the BLA on the basis of their smaller size (Krettek & Price, 1978). The BMA is present in the posterior two-thirds of the amygdaloid complex and throughout the greater part of its extent, it is adjacent to the BA, dorsally, and the CoA, ventrally (Krettek & Price, 1978). According to Pitkänen (2000b), the BMA is also divided into an anterior magnocellular part and a posterior parvicellular subdivision. Despite its prominent size and knowledge of its delineation and cytoarchitecture, few functional studies have targeted the BMA. One study in rats performed chemical inhibition of the BMA using the $GABA_A$ agonist muscimol, which induced an increase in mean arterial pressure and heart rate, whereas the inhibition of neighboring regions did not induce such cardiovascular changes (Mesquita et al., 2016). In contrast, chemical activation through bilateral microinjection of a $GABA_A$ antagonist blocked the cardiovascular responses usually observed when an unknown rat is introduced into the cage of a recorded rat. Consistently, direct optogenetic activation of the BMA increases anxiety-like behaviors in mice, as does the optogenetic activation of the vmPFC inputs to this nucleus (Adhikari et al., 2015). Finally, neurons of the BMA project to the ventromedial nucleus of the hypothalamus (VMH) through direct glutamatergic projections and indirect projections relayed in the anterior BNST (aBNST) (Martinez, Carvalho-Netto, Ribeiro-Barbosa, Baldo, & Canteras, 2011; McDonald, Shammah-Lagnado, Shi, & Davis, 1999). Direct BMA-VMH projections do not contain GABAergic fibers (Yamamoto, Ahmed, Ito, Gungor, & Pare, 2018). Within the VMH, BMA and aBNST, axons are segregated, with the BMA axons terminating in the VMH glutamatergic core, while the aBNST axons terminate in the GABAergic shell. Glutamatergic BMA-VMH inputs excite most core neurons, without eliciting a response in shell neurons (Yamamoto et al., 2018). In contrast, aBNST sent mostly GABAergic projections that inhibited both shell and core neurons (Yamamoto et al., 2018). The dual regulation of VMH by BMA and aBNST might provide flexibility to these downstream regions regulating defensive and social behaviors.

THE CENTRAL AMYGDALA (CeA)

The central nucleus of the amygdala (CeA) has three structurally distinct nuclei: the lateral (CeL), capsular (CeC), and medial (CeM) nuclei of the amygdala (Cassell, Gray, & Kiss, 1986; McDonald, 1982; Petrovich, Scicli, Thompson, & Swanson, 2000) (Fig. 1). Following Pavlovian fear conditioning, neuronal activity of the CeL is required for the fear acquisition, whereas activity in the CeM is required for the expression of conditioned fear responses (Ciocchi et al., 2010). The CeM is the main amygdala output structure to brainstem centers that mediate autonomic and behavioral aspects of fear, including freezing behavior (Hopkins

& Holstege, 1978; LeDoux et al., 1988; Rizvi, Ennis, Behbehani, & Shipley, 1991; Schwaber, Kapp, Higgins, & Rapp, 1982). Activation of CeM is sufficient to induce freezing responses, whereas inactivation of CeL alone produces unconditioned freezing, indicating that CeM is under tonic inhibitory control from CeL interneurons (Ciocchi et al., 2010; Gozzi et al., 2010; Pape, 2010). CeL also contains populations of projections neurons, some of which control cortical activity via basal cholinergic neurons and can shift fear responses from freezing behavior toward an active escape (Gozzi et al., 2010).

The CeA is a GABAergic structure (McDonald & Augustine, 1993; Pare & Smith, 1993), which together with the bed nucleus of the stria terminalis (BNST) forms the extended amygdala complex (Walker & Davis, 2008). GABAergic neurons in the CeA coexpress a variety of neuropeptides including, but not limited to CRF, SOM, dynorphin (DYN), enkephalin (ENK), neurotensin (NT), VIP, and CB (Cassell et al., 1986; Roberts, Woodhams, Polak, & Crow, 1982; Shimada et al., 1989; Wray & Hoffman, 1983) (Fig. 1). These peptidergic neurons also coexpress a variety of distinct markers, including cell-type specific receptors, kinases, and phosphatases (Fig. 3). Neurons expressing markers like protein kinase C δ (PKCδ) or tachykinin 2 (Tac2) have been implicated in the modulation of CeA activity, modulation of CeM output, and behavioral outcomes (Andero et al., 2016; Haubensak et al., 2010). Heterogeneity of the inhibitory peptidergic neurons in the CeL allows multilevel gating of fear responses by tonic CeM inhibition (Ciocchi et al., 2010) or disinhibition of cortical neurons (Gozzi et al., 2010). As a result, cell-type-specific plasticity of inhibitory neurons within the CeL and CeM circuitry determines the final behavioral output balanced between discrimination vs generalization of conditioned fear responses (Ciocchi et al., 2010; Tye et al., 2011).

The peptidergic neurons are not entirely mutually exclusive. In the rat CeA, neurons expressing CRF reside in CeL (Pomrenze et al., 2015) and approximately half of them are immunoreactive for DYN (Marchant, Densmore, & Osborne, 2007) and SOM (Pomrenze et al., 2015). To the contrary, neurons expressing ENK do not overlap with DYN (Marchant et al., 2007) or CRF (Day, Curran, Watson, & Akil, 1999; Marchant et al., 2007; Veinante, Stoeckel, & Freund-Mercier, 1997) but do overlap with NT (Day et al., 1999; Roberts et al., 1982) and PKCδ expressing neurons in the CeL (Haubensak et al., 2010). Accordingly, PKCδ and CRF neurons belong to nonoverlapping neuronal populations (Pomrenze et al., 2015), but nearly all CRF neurons in the CeL coexpress striatal-enriched protein tyrosine phosphatase (STEP) (Dabrowska et al., 2013). In contrast to the BLA or LA, few calcium-binding proteins are found in the CeA neurons. Although studies have shown CB-positive immunoreactivity, no PV neurons have been found in the CeA (Pitkänen & Amaral, 1993).

Fast amino acid neurotransmitters

CeA is a striatal-like structure, which contains GABAergic interneurons and GABAergic projection neurons (McDonald & Augustine, 1993; Pare & Smith, 1993; Penzo, Robert, & Li, 2014). GABAergic output neurons from CeM are under complex synaptic control from CeL interneurons (Ciocchi et al., 2010; Pape, 2010). These CeL neurons also provide inhibitory inputs to other CeL and CeC neurons (Pitkänen, Savander, & LeDoux, 1997). In contrast to well-established CeM outputs, extrinsic projections from the CeL are more

restricted (Petrovich & Swanson, 1997). In addition to dense inputs to the adjacent CeM, CeL sends projections via the stria terminalis to the BNST, to the hindbrain parabrachial nucleus (Petrovich et al., 2000), and to basal cholinergic neurons (Gozzi et al., 2010). As the bundle of fibers composing stria terminalis contains variety of peptides, including VIP, CCK, substance P (SP), NT, ENK, and SOM, they represent the major efferent peptidergic system, which might modulate synaptic transmission in a peptide-specific manner in addition to modulation by GABA (Roberts et al., 1982). Some of these peptides might be excitatory in nature. For example, optogenetic stimulation of CRF neurons in rat CeL produces cFos expression in non-CRF neurons in the CeL (Pomrenze et al., 2015), an effect dependent on CRF receptor type 1 (CRFR1). CRF has been also shown to increase the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) in the rat (Ji, Fu, Adwanikar, & Neugebauer, 2013) and mouse CeL (Silberman & Winder, 2013a) through its action on CRFR1 and CRFR2.

Electrophysiological properties of CeA neurons

Originally, rat CeA neurons were categorized into two electrophysiological types depending on the shape of spike afterhyperpolarizations (AHPs): (Schiess, Asprodini, Rainnie, & Shinnick-Gallagher, 1993; Schiess, Callahan, & Zheng, 1999) type “A” non-adapting neurons that fire repetitively and type “B” neurons that show complete spike-frequency adaptation during sustained depolarization (Lopez de Armentia & Sah, 2004; Schiess et al., 1999). Later studies further characterized at least four main physiological types of neurons in the CeA, distinguished based on their responses to intracellular current injections. From all four types, low threshold bursting (LTB) neurons constitute the majority of CeM neurons (Dumont, Martina, Samson, Drolet, & Paree, 2002). They generate spike doublets or bursts in response to hyperpolarizing current pulses, whereas depolarizing currents elicit trains of action potentials with variable degrees of spike frequency accommodation. LTB neurons typically also display inward rectification, reflecting activation of hyperpolarization-activated cationic current (I_H) (Dumont et al., 2002), mediated by hyperpolarization-activated cyclic nucleotide-gated (HCN 1–4) channels (Benarroch, 2013). The opening of HCN channels elicits membrane depolarization toward the threshold for action potential generation and reduces membrane resistance and thus the magnitude of excitatory and inhibitory postsynaptic potentials (Benarroch, 2013).

Regular spiking neurons (RS) constitute the majority of neurons in rat CeL. Like LTB neurons, RS cells also display variable degrees of time-dependent inward rectification (I_H current). However, in contrast to LTB cells, these neurons do not show spike bursts in response to hyperpolarizing current pulses (Dumont et al., 2002).

Although late firing (LF) neurons are very rare in rat CeL and CeM (Dumont et al., 2002), nearly all neurons in rat CeC are classified as LF type (Chieng, Christie, & Osborne, 2006). These neurons are characterized by a noticeable delay between the beginning of depolarizing current injection and firing onset (Dumont et al., 2002). The fourth, fast-spiking (FS) neuron type is also rare in rat CeA and is characterized by high firing rates with no spike frequency adaptation (Dumont et al., 2002).

Regulation of the activity of CeA outputs

The activity of CeA neurons has been investigated in great detail with respect to modulation by oxytocin (OT) and vasopressin (VP) (Huber, Veinante, & Stoop, 2005). These neuropeptides are extrinsic in nature to the CeA but have proven to be critical modulators of CeA output (Huber et al., 2005). There are two groups of OT-responsive neurons in the CeA. One group of interneurons is located in the CeL and is excited by OTR activation. These OT-responsive neurons are putative Type II neurons (Gozzi et al., 2010) and partially overlap with neurons expressing mRNA for PKCδ (Haubensak et al., 2010). Once excited by OT, they enhance GABAergic transmission in the CeM projection neurons. Therefore, CeM output neurons are inhibited by OTR activation but directly excited by vasopressin V1A receptors (V1AR) (Huber et al., 2005). OT-responsive CeL neurons have been shown to play an important role in mediating escape behavior to an imminent threat. Fear conditioning to imminent yet escapable threat potentiates excitatory inputs from the BLA onto OT sensitive CeL neurons, and this positively correlates with reduced freezing behavior and active escape (Terburg et al., 2018) (Fig. 3).

From CeM, separate neuronal populations project to the ventrolateral periaqueductal gray (v1PAG), where they modulate freezing behavior, and to the dorsal vagal complex (DVC), where they modulate cardiovascular responses (Viviani et al., 2011). These two populations of CeM projection neurons also differ in their electrophysiological properties, CeM-PAG projecting neurons are more depolarized at rest and have lower membrane resistance but higher membrane capacitance in comparison to CeM-DVC projecting neurons. The average spiking frequencies of CeM-PAG projecting neurons are also significantly higher than CeM-DVC neurons. Notably, OT selectively inhibits CeM neurons projecting to PAG such as activation of OTR increased GABA transmission in CeM-PAG but not in CeM-DVC projecting neurons (Viviani et al., 2011).

An overlap between peptidergic phenotypes and the electrophysiological subtypes of CeA neurons is largely unknown. Below we make an attempt to attribute electrophysiological properties to defined subpopulations of CeA neurons when feasible. However, caution needs to be applied regarding species differences, as a majority of the electrophysiological studies originate from rat CeA, whereas the majority of studies on the role of neuropeptidergic subpopulations in behavior emerge from transgenic mice models.

Peptidergic neuron types

Corticotropin-releasing factor (CRF)—Within rat and mouse CeA, CRF neurons are mostly localized in the CeL (Fadok et al., 2017; Fellmann, Bugnon, & Gouget, 1982; Swanson, Sawchenko, Rivier, & Vale, 1983). They share many common characteristics with CRF neurons in dorsolateral BNST ($BNST_{DL}$), including cellular morphology of medium spiny neurons (Cassell & Gray, 1989; Phelix & Paull, 1990; Pomrenze et al., 2015; Sun & Cassell, 1993), selective expression of neuron-specific phosphatase STEP (Dabrowska, Hazra, Guo, Li, et al., 2013), production of GABA (Cassell, Freedman, & Shi, 1999; Dabrowska, Hazra, Guo, Li, et al., 2013; Day et al., 1999), and efferent projections to similar brain structures, including reciprocal projections to the BNST (Dabrowska, Martinon, Moaddab, & Rainnie, 2016; Petrovich & Swanson, 1997; Pomrenze et al., 2015).

In recent years, the development of animal models expressing Cre-recombinase (Cre) under the control of specific peptidergic promoters allowed precise interrogation of the role of peptidergic neurons in modulating behavior. Using an optogenetic strategy in fear-conditioned Cre-CRF mice, activation of CRF neurons in the CeL promotes an active defensive behavior (flight) in contrast to neighboring SOM neurons, which were shown to mediate passive fear responses (freezing) (Fadok et al., 2017). Accordingly, selective silencing of CRF, but not SOM or PKCδ-expressing neurons in the CeL, completely abolishes conditioned flight behavior. Notably, the resultant behavioral output was dependent on the strength of mutual inhibitory connections between CRF and SOM neurons in the CeL. Whereas CRF neurons provide GABAergic inhibitory input to both SOM and PKCδ neurons in the CeL, CRF neurons receive input mainly from SOM rather than PKCδ neurons (Fig. 3) (Fadok et al., 2017). Notably, CRF and SOM cells also receive distinct afferent inputs from the BLA and ventral hippocampus (vHPC), respectively (Fadok et al., 2017). Here, CRF and SOM neurons were identified as mutually exclusive neuronal populations mediating distinct behavioral outcomes (Fadok et al., 2017). However, this is in contrast with a more recent study showing high levels of co-localization between CRF and SOM neurons in mouse CeL, but not CeM (McCullough, Morrison, Hartmann, Carlezon, & Ressler, 2018). Substantial overlap was also found between CRF and SOM neurons in rat CeL (Pomrenze et al., 2015). Although functional separation of these neuronal populations might not be as apparent, CRF neurons are clearly distinct from neuronal populations expressing PKCδ in both mice (Fadok et al., 2017; McCullough et al., 2018) and rat CeL (Pomrenze et al., 2015) (Table 1, Fig. 3).

CRF neurons and CRFR signaling in the CeL are important for proper fear discrimination which is measured as the ability to preferentially respond to a discrete cue previously paired with the unconditioned stimulus (US) vs un-paired cue. Following fear conditioning, CRF neurons undergo plasticity, which allows them to selectively respond to threat-predictive cues. CRF neurons then enhance the excitability of another population of neurons in the CeA, via a CRFR1-dependent mechanism, and this process is critical for the proper discrimination of threat-predictive cues (Sanford et al., 2017). As CeL also sends substantial CRF projection to the BNST (Petrovich & Swanson, 1997), activation of the BNST-projecting CRF neurons might affect sustained fear- and anxiety-related behaviors (Lee & Davis, 1997). Indeed, selective optogenetic silencing of CRF release from the CeA to the BNST during contextual fear acquisition disrupts sustained fear responses, measured as freezing behavior (Asok et al., 2018) (Table 1). In mouse CeA, CRF neurons have also been implicated in the modulation of anxiety (Paretkar & Dimitrov, 2018). For example, chemogenetic activation of CRF neurons was sufficient to increase anxiety-like behavior measured in the elevated plus-maze (EPM, Table 1). Specific activation of locus coeruleus (LC)-projecting CeA CRF neurons had a similar anxiogenic effect (Table 1) (Paretkar & Dimitrov, 2018).

In the intrinsic neuronal network of the CeA, CRF neurons serve as inhibitory interneurons and provide inhibitory control of other CeL neurons, including SOM and PKCδ neurons (Fadok et al., 2017) and, to a lesser extent, other CRF neurons (Partridge et al., 2016). Chronic, unpredictable stress was shown to alter synaptic transmission and connectivity between CRF neurons in mouse CeL (Partridge et al., 2016). Also, in rat CeL, optogenetic

stimulation of CRF neurons evokes $GABA_A$ receptor-dependent synaptic transmission in approximately half of non-CRF neurons in the CeL (Pomrenze et al., 2015). However, after optogenetic stimulation of CRF neurons, increased cFos expression was observed in non-CRF neurons of rat CeL, an effect that could be prevented by blocking CRFR1. These results suggest that CRF neurons provide both inhibitory (via GABA) and excitatory (via CRFR1) information in the CeL (Pomrenze et al., 2015).

Notably, although hypothalamic CRF is associated with hypothalamic-pituitary-adrenal (HPA) axis activation following acute stressors, these stressors or immunological challenges do not readily activate CRF neurons in the CeA. Although systemic injection of interleukin-1 beta (IL-1h) causes a robust activation of ENK neurons in rat CeL, and moderate activation of NT neurons, very few neurons in the CeL (1%) coexpress cFos and CRF mRNA (Day et al., 1999). In contrast, innate fear response induced by predator odor, 2,5-dihydro-2,4,5-trimethylthiazoline (TMT) exposure significantly elevated CRF, but not ENK mRNA in the CeL (Asok, Ayers, Awoyemi, Schulkin, & Rosen, 2013).

Somatostatin (SOM)—SOM neurons constitute one of a major neuronal population in mouse CeL. They display heterogeneous electrophysiological properties and belong to RS or LF neuron types. SOM neurons have been crucially implicated in the positive modulation of conditioned fear (Fear-ON neurons, Fig. 3) (Li et al., 2013). Selective silencing of SOM neurons in SOM-IRES-Cre mice during fear conditioning markedly impairs fear memory, measured as a reduction of freezing behavior. Activation of SOM neurons, on the other hand, is sufficient to induce freezing in naïve freely moving mice (Li et al., 2013). SOM neurons are largely nonoverlapping with PKCδ neurons, which have been identified as Fear-OFF neurons (Haubensak et al., 2010). LA input-specific and experience-dependent strengthening of glutamatergic synapses onto SOM CeL neurons were shown to enable the expression of conditioned fear, as suppression of the potentiation impairs fear memory.

SOM neurons provide potent inhibition to other neurons in the CeL. SOM neurons likely overlap with the tonically inhibitory, Type I, serotonin receptor 1A ($5\text{-}HT_{1A}$)-expressing interneurons described by Fadok et al. (2017) and Gozzi et al. (2010). These Type I neurons are distinguished from the Type II, OT-responsive neurons by the presence of a prominent depolarizing after-potential (Tsetsenis, Ma, Lo Iacono, Beck, & Gross, 2007). Firing of Type II neurons can be enhanced by $5\text{-}HT_{1A}$-mediated inhibition of Type I neurons, consistent with a direct inhibitory connection between Type I and Type II cells in the CeL (Gozzi et al., 2010) (Fig. 3). Accordingly, $5\text{-}HT_{1A}$-receptor-mediated inhibition of Type I (putative SOM) CeA neurons is sufficient to suppress conditioned freezing responses (Tsetsenis et al., 2007) (Table 1, Fig. 3).

Enkephalin (ENK)—Separate neuronal populations in the CeA express CRF and ENK peptides (Veinante et al., 1997). Similarly to other neurons in the CeA, ENK neurons are GABAergic (Day et al., 1999; Petrovich & Swanson, 1997; Steiner & Gerfen, 1998). ENK belongs to the family of endogenous opioid peptides and primarily acts via the delta and mu-opioid receptors (MOPR) (Mansour, Hoversten, Taylor, Watson, & Akil, 1995). Opioid transmission is crucial for pain perception and analgesia, which plays an important role during a threat or predator confrontation (Helmstetter & Fanselow, 1987; Olson, Olson,

Vaccarino, & Kastin, 1998). Accordingly, conditioned fear responses (Petrovich et al., 2000), as well as innate fear responses (Wilson & Junor, 2008) upregulate opioid levels. Chemogenetic activation of ENK neurons produces robust analgesia in mice with sciatic nerve constriction as well as the reduction in anxiety-like behavior (Paretkar & Dimitrov, 2019) (Table 1). The CeA is part of the circuitry mediating hypoalgesia induced by conditioned stimuli or systemic morphine administration (Chieng et al., 2006). In situ hybridization studies demonstrated that mRNA levels of ENK (but not CRF) increase in CeA neurons (CeL and CeC but not CeM) after rats are placed in an environment that was previously associated with fear conditioning (Petrovich et al., 2000), providing an increased opioid tone in a threatening environment (Chieng et al., 2006; Petrovich et al., 2000). However, CeA can also mediate hyperalgesia during alcohol withdrawal (Avegno et al., 2018). From CeL and CeC, ENK neurons, similarly to CRF neurons, send projections to the CeM (Veening, Swanson, & Sawchenko, 1984) and the BNST (Arluison et al., 1994; Roberts et al., 1982), which also expresses high levels of opioid receptors (Mansour et al., 1995). In some CeA subregions, ENK innervation is coincident with high levels of tyrosine hydroxylase (TH) fibers (Chieng et al., 2006).

Activation of MOPRs inhibits all electrophysiological types of CeL neurons via a direct, G protein-coupled inwardly-rectifying potassium channel (GIRK)-dependent, the postsynaptic mechanism (Chieng et al., 2006). Although the peptidergic profile of these neurons is unknown, MOPR activation has a greater inhibitory impact on bipolar/fusiform neurons, rather than triangular or multipolar neurons in the CeA. Opioids have been shown to directly inhibit CeA output neurons projecting to the lateral parabrachial nucleus, the BNST, and thalamic reticular nucleus (Chieng et al., 2006). In contrast to CeL, CeM neurons express kappa opioid receptors (KOPR) rather than MOPR, hence might be more sensitive to dynorphin release (Chieng et al., 2006).

Dynorphin—DYN also belongs to a class of opioid peptides, but fear conditioning does not affect KOPR mRNA in the CeA or dynorphin levels. However, blocking KOPR in the CeA reduces conditioned fear measured in the fear-potentiated (FPS) startle paradigm, but it does not affect anxiety measured in the EPM (Knoll et al., 2011). CRF was shown to facilitate the release of DYN in the CeA, whereas subsequent activation of KOPR modulates the presynaptic effects of CRF (Kang-Park, Kieffer, Roberts, Siggins, & Moore, 2015). KOPRs have also been shown to modulate GABAergic synaptic responses and ethanol effects in the CeA (Kang-Park, Kieffer, Roberts, Siggins, & Moore, 2013; Van't Veer & Carlezon, 2013).

Other molecular markers

Protein kinase C delta (PKCS)—Neurons expressing PKCδ are localized in the CeL and CeC (Haubensak et al., 2010). They are GABAergic and distinct from those expressing CRF or DYN; almost half of the PKCδ neurons express ENK and more than half express OTR, which has been implicated in inhibitory gating of CeM (Huber et al., 2005; Viviani et al., 2011). In fact, similarly to OTR-expressing neurons, PKCδ neurons project to and inhibit CeM output neurons to the brainstem that control freezing and make a connection with other PKCδ-negative neurons in the CeL. The great majority of PKCδ neurons were identified as LF type, and a small fraction as RS neurons (Haubensak et al., 2010) (Fig. 3).

PKCδ neurons appear to play a crucial role in the modulation of intrinsic CeA circuitry involved in fear conditioning. After discriminatory fear conditioning, whereas a group of CeL neurons acquires an excitatory response (Fear-ON neurons), another group of CeL neurons displays a strong inhibitory response to the CS (Fear-OFF neurons). Notably, both ON and OFF CeL neurons inhibit CeM output. Following cued fear conditioning, levels of discrimination between paired vs un-paired cue could be predicted from tonic activity of CeA neurons such as a decrease in tonic activity of CeM output neurons is associated with generalization, whereas decreases in tonic activity of CeL OFF and ON neurons predicted better discrimination, consistent with tonic inhibition of CeM output neurons by both CeL ON and CeL OFF neurons (Haubensak et al., 2010). CeL Fear-OFF neurons largely overlap with neurons expressing PKCδ (Haubensak et al., 2010). Accordingly, optogenetic stimulation of PKCδ neurons increases anxiety-like behavior and fear generalization, and overall degree of fear generalization correlates with spontaneous activity of PKCδ neurons (Botta et al., 2015) (Fig. 3, Table 1).

In addition to CeM output neurons (Haubensak et al., 2010), a subpopulation of CeL neurons projects to cholinergic neurons in the basal forebrain (substantia innominata and nucleus basalis of Meynert), which control cortical arousal (Gozzi et al., 2010). These two parallel CeA outputs have been shown to control behavioral output balanced between passive freezing (via CeM output to the brainstem) and active exploration (via CeL-mediated disinhibition of cortical neurons). Under regular conditions (freezing ON), CeL projection neurons are tonically inhibited by Type I neurons [putative SOM neurons (Gozzi et al., 2010), which correspond to type B neurons described in rats (Lopez de Armentia & Sah, 2004; Sah & Lopez De Armentia, 2003; Schiess et al., 1999)]. Therefore, brainstem projecting CeM neurons are disinhibited and induce freezing. However, when Type I neurons are silenced (freezing OFF), Type II, OTR-expressing CeL projection neurons (Huber et al., 2005), putative PKCδ neurons (Haubensak et al., 2010), become active. This leads to (1) inhibition of brainstem-projecting CeM output (freezing OFF), and (2) disinhibition of cholinergic neurons, which increase cortical arousal and promote active escape (Gozzi et al., 2010; Tsetsenis et al., 2007) (Fig. 3).

PKCδ neurons are also sensitive to opioids such that 95% of morphine-induced cFos activation in the CeL is found in PKCδ neurons (Xiu et al., 2014). Lastly, PKCδ neurons are also activated by diverse anorexigenic signals in vivo and are required for the inhibition of feeding by these signals. Activation of PKCδ neurons in the CeL suppresses food intake (Cai et al., 2014).

Tachykinin 2 (Tac2)—In the CeA, neurons expressing the peptide tachykinin (Tac2) were shown to play a significant role in fear memory consolidation (Andero et al., 2016). The Tac2 pathway includes the peptide neurokinin B (NkB), encoded by the Tac2 gene, and its specific receptor neurokinin 3 (Nk3R) (Severini, Improta, Falconieri-Erspamer, Salvadori, & Erspamer, 2002). Tac2 and its receptor are highly expressed within the CeM (Andero, Dias, & Ressler, 2014; Duarte, Schutz, & Zimmer, 2006). As determined in Tac2-GFP mice, Tac2 neurons do not overlap with neurons expressing PKCδ, but they do overlap considerably with neurons expressing STEP in the CeM, and the great majority of neurons expressing Nk3R also express STEP. Notably, STEP extensively co-localizes with CRF neurons in rat

CeA (Dabrowska, Hazra, Guo, Li, et al., 2013). Optogenetic stimulation of Tac2 neurons in transgenic mice during fear acquisition does not alter the locomotor activity or freezing levels but it enhances fear memory consolidation (Andero et al., 2016).

THE BED NUCLEUS OF THE STRIA TERMINALIS (BNST)

The BNST is a forebrain structure and part of the extended amygdala complex, which coordinates autonomic, neuroendocrine, and behavioral responses to stressors (Cullinan, Herman, & Watson, 1993; Herman & Cullinan, 1997; Walker & Davis, 2008). Rodent BNST is a heterogeneous structure, which contains at least 16 distinct subnuclei, making the BNST one of the most complex structures of the mammalian brain (Larriva-Sahd, 2006). The BNST translates stress into long-term changes in defensive behaviors, including anxiety-like behavior (Dabrowska, Hazra, Guo, Dewitt, & Rainnie, 2013; Daniel & Rainnie, 2016; Davis et al., 2010; Sparta, Jennings, Ung, & Stuber, 2013). BNST lesions in rats disrupt expression of contextual fear (Sullivan et al., 2004), as well as conditioned fear responses to long-lasting cues (Davis et al., 2010; Waddell, Morris, & Bouton, 2006), but not too short, discrete cues (Gewirtz, McNish, & Davis, 1998; Hitchcock & Davis, 1991; LeDoux et al., 1988). However, growing evidence suggests that, together with the CeA, the BNST also modulates conditioned fear responses to discrete cue, and more specifically, level of fear generalization vs fear discrimination (Goode & Maren, 2017; Gungor & Pare, 2016). For example, BNST lesion has been shown to significantly improve rats' ability to discriminate between cue previously paired with foot-shock vs unpaired cue (Duvarci, Bauer, & Pare, 2009). Recent studies suggest the involvement of the BNST in learning to discriminate between distinct stimuli representing safety vs threat (De Bundel et al., 2016), phasic vs sustained fear (Lange et al., 2017), and signaled vs un-signaled threats (Goode & Maren, 2017; Moaddab & Dabrowska, 2017; Martinon et al., 2019) (for review see Goode & Maren, 2017; Gungor & Pare, 2016; Janecek & Dabrowska, 2019; Shackman & Fox, 2016). Furthermore, the BNST is involved in the modulation of addictive behaviors, as it was shown to be necessary for the stress-induced reinstatement of drug seeking (Erb, Salmaso, Rodaros, and Stewart, 2001; Erb, Shaham, and Stewart, 2001). Moreover, together with the CeA, the BNST has been suggested to mediate anxiety and dysphoria associated with addiction withdrawal (Funk, O'Dell, Crawford, & Koob, 2006; Harris & Winder, 2018).

BNST subnuclei express a variety of neuronal populations, which can be categorized based on their electrophysiological properties into at least three types (Types I–III) (Hammack, Mania, & Rainnie, 2007). These types are accompanied by distinct patterns of mRNA expression of ion channel subunits (Hazra et al., 2011), neuropeptidergic profile (Ju & Han, 1989; Moga, Saper, & Gray, 1989; Shimada et al., 1989), as well as a myriad of cell-type-specific receptors or enzymes, many of which respond to stress or anxiety-provoking stimuli (Dabrowska, Hazra, Guo, Li, et al., 2013; De Bundel et al., 2016; Pelrine et al., 2016). Notably, activation of distinct BNST subnuclei (Kim et al., 2013), or even distinct cell populations (e.g., CRF vs NPY), often leads to contrasting physiological and behavioral effects (Daniel & Rainnie, 2016).

Fast amino acid neurotransmitters

The BNST is a largely GABAergic structure in the rat (Dabrowska, Hazra, Guo, Dewitt, & Rainnie, 2013; Stefanova, Bozhilova-Pastirova, & Ovtscharoff, 1997; Sun & Cassell, 1993) and mouse brain (Jennings et al., 2013; Nguyen, Dela Cruz, Sun, Holmes, & Xu, 2016). The dorsolateral BNST ($BNST_{DL}$), which contains oval nucleus ($BNST_{OV}$) (Dabrowska, Hazra, Guo, Dewitt, & Rainnie, 2013; Day et al., 1999; Ju & Han, 1989; Poulin, Arbour, Laforest, & Drolet, 2009), and juxtacapsular nucleus ($BNST_{JXT}$) (Larriva-Sahd, 2004, 2006), is populated exclusively with GABAergic neurons (Fig. 4). Rat $BNST_{JXT}$ contains two morphological types of GABAergic projections neurons and two types of interneurons (Larriva-Sahd, 2004), whereas the $BNST_{OV}$ includes at least 11 neuron types (Fig. 4). $BNST_{OV}$ contains both projection neurons as well as local interneurons, both GABAergic (Larriva-Sahd, 2006), hence most of the axonal outputs from the $BNST_{DL}$ are inhibitory (Cullinan et al., 1993; Esclapez, Tillakaratne, Tobin, & Houser, 1993). Glutamatergic neurons account for a minority of BNST neurons (Jennings et al., 2013; Nguyen et al., 2016). In rat BNST, putative glutamatergic neurons expressing vesicular glutamate transporter 2 (VGLUT2) have been primarily found in the ventral part of anterior BNST ($BNST_{VEN}$), including the fusiform nucleus ($BNST_{FUS}$) and in several divisions of posterior BNST ($BNST_{POST}$), including the principal nucleus (Poulin et al., 2009). Presence of glutamatergic neurons in mouse $BNST_{VEN}$ has been confirmed in VGLUT2-IRES-Cre mouse (Georges & Aston-Jones, 2002; Gungor, Yamamoto, & Pare, 2018; Jennings et al., 2013) and based on the expression of the excitatory amino acid carrier 1 (EAAC) (Nguyen et al., 2016). In contrast, VGLUT3-labeled neurons were found in the anterior lateral group of the BNST (Jalabert, Aston-Jones, Herzog, Manzoni, & Georges, 2009) (Fig. 4).

Electrophysiological properties of the BNST neurons

Neurons of the anterolateral cell group of the BNST ($BNST_{ALG}$) can be categorized into three major neuron types (Type I—III) based on electrophysiological phenotype alone (Daniel, Guo, & Rainnie, 2017; Hammack et al., 2007) and/ or based on a single-cell mRNA expression of ion channel subunits (Hazra et al., 2011). In an unbiased cluster analysis, the composition of ion channels subunits on a single neuron level could predict intrinsic membrane properties and $BNST_{ALG}$ neuron Type and vice versa (Hazra et al., 2011). These electrophysiological phenotypes were originally defined in rat $BNST_{ALG}$ by Rainnie and colleagues (Hammack et al., 2007) and described as three unique patterns of voltage deflections in response to transient depolarizing and hyperpolarizing current injections. Type I neurons are characterized by a depolarizing sag in response to hyperpolarizing current injection, indicative of hyperpolarization-activated cation current (I_h). Type I neurons show a steady firing rate and do not exhibit burst-firing activity (Hazra et al., 2011). Type I neurons were later defined as regular spiking by Pare and colleagues (Rodriguez-Sierra, Turesson, & Pare, 2013). In contrast, Type II neurons exhibit rebound firing after the hyperpolarizing current steps, burst firing activity, and/or a prevalent low-threshold depolarizing wave indicative of a prominent IT current (T-type), mediated by Ca^{2+} channel encoded by the Cav3 genes (CaV3.1–3.3) (Astori et al., 2011), in addition to prominent I_h current (Hazra et al., 2011). Type II neurons were later defined as low-threshold bursting (Rodriguez-Sierra et al., 2013). Notably, Type II neurons are the most abundant and heterogeneous population of rat BNST neurons and can be further subdivided into three distinct subgroups based on their

genetic makeup of ion channel subunits and cellular markers (Hazra et al., 2011). Finally, Type III cells are classified based on the presence of a pronounced fast inward rectification in response to hyperpolarizing current injection indicative of an inwardly rectifying potassium current I_{KIR}, encoded by Kir2.1-Kir2.4 genes (Hazra et al., 2011). Type III neurons were defined as fast-inward rectifiers and found primarily in the anterolateral portion of the BNST (Rodriguez-Sierra et al., 2013). In contrast to Type II, Type III neurons do not exhibit I_T current or prominent I_h current (Daniel et al., 2017). Accordingly with previous in situ hybridization studies (Cullinan et al., 1993), mRNA transcripts for GAD67 were detected in all types of $BNST_{ALG}$ neurons (Hazra et al., 2011).

Although neurons that meet the description of Type I–III in rats were also found in both mouse and primate $BNST_{ALG}$ (Daniel et al., 2017), they occur in these species at different proportions. Type II cells are the most common cell type in the rat (Hazra et al., 2011) but they are much less prevalent in mouse and rhesus macaque. Interestingly, in contrast to the rat, Type III cells are the most common cell type in both mouse and primate $BNST_{ALG}$ (Daniel et al., 2017). Notably, whereas all three electrophysiological phenotypes were observed in primate $BNST_{ALG}$, only 75% of the cells could be classified in those types. For example, a new group of macaque neurons displayed a unique stutter-firing pattern (Daniel et al., 2017). Notably, specific neuropeptidergic profiles of Type I—III $BNST_{ALG}$ neurons have rarely been defined.

Peptidergic neuron types

GABAergic neurons, populated in rat and mouse $BNST_{ALG}$, contain high expression levels of neuropeptides, including but not limited to CRF, ENK, NT, DYN, NPY, VIP, OT, CB, vasopressin (AVP), galanin, and other (Dabrowska et al., 2011; Dabrowska, Hazra, Guo, Dewitt, & Rainnie, 2013; Day et al., 1999; Larriva-Sahd, 2006; Miller, Vician, Clifton, & Dorsa, 1989; Skofitsch & Jacobowitz, 1985) (Fig. 4).

Corticotropin-releasing factor (CRF)—BNST is one of the major sources of extra-hypothalamic CRF synthesis in mouse and rat brain (Cummings, Elde, Ells, & Lindall, 1983; Gray & Magnuson, 1987; Veinante et al., 1997). In rat $BNST_{ALG}$, CRF neurons are GABA-ergic and clustered in the $BNST_{OV}$ (Dabrowska, Hazra, Guo, Li, et al., 2013; Ju & Han, 1989; Swanson et al., 1983), whereas CRF neurons in the $BNST_{VEN}$, including the $BNST_{FUS}$, might be glutamatergic (Dabrowska, Hazra, Guo, Dewitt, & Rainnie, 2013; Pomrenze et al., 2015) (Fig. 4). The great majority of Type III $BNST_{ALG}$ neurons express CRF mRNA on a single-cell level, although subpopulations of Type I and Type II neurons also express CRF mRNA (Dabrowska, Hazra, Guo, Li, et al., 2013). Notably, the CRF-producing neurons from the $BNST_{OV}$ and $BNST_{FUS}$ contribute to the BNST output to hypothalamic, midbrain, and brainstem nuclei in mouse and rat brain (Dabrowska et al., 2016; Gray & Magnuson, 1987; Pomrenze et al., 2015; Vranjkovic, Gasser, Gerndt, Baker, & Mantsch, 2014). Moreover, in addition to local CRF-producing neurons, $BNST_{ALG}$ and $BNST_{VEN}$ both receive substantial CRF/GABA inputs from the CeL (Erb, Shaham, & Stewart, 2001; Pomrenze et al., 2015; Sakanaka, Shibasaki, & Lederis, 1986), which seem to mostly target non-CRF neurons in the BNST (Jaferi & Pickel, 2009). Accordingly, the application of CRF was shown to excite primarily non-CRF neurons in the BNST (Ide et al.,

2013; Kash & Winder, 2006). However, a recent study using Cre-CRF transgenic rat showed that CRF released from the CeL activates local CRF neurons in the $BNST_{DL}$ to promote anxiety-like behavior (Pomrenze et al., 2019). The primary source of CRF release in the BNST is still under dispute as in addition to CRF afferents from the CeL (Erb, Salmaso, et al., 2001; Pomrenze et al., 2015), CRF might also be released from local CRF neurons (Veinante et al., 1997) (Table 1).

The distribution of CRF neurons differs between rat and mouse BNST (Wang et al., 2011). In rat BNST, CRF neurons are clustered in the $BNST_{OV}$ and $BNST_{FUS}$ (Dabrowska, Hazra, Guo, Li, et al., 2013; Swanson et al., 1983), which has been confirmed in Cre-CRF rat (Pomrenze et al., 2015). In contrast, mouse CRF neurons appear more loosely scattered throughout both dorsal and ventral BNST in CRF-tomato (Silberman, Matthews, & Winder, 2013), $CRFp3.0Cre^{GFP}$ (Dabrowska et al., 2016; Martin et al., 2010) and in CRF-IRES-Cre (Ai9) transgenic mice (Nguyen et al., 2016). Of note, considerable differences have also been described between transgenic CRF reporter mouse lines (Chen, Molet, Gunn, Ressler, & Baram, 2015).

These species differences in CRF neuron distribution and cellular organization suggest potential differences in function. Whereas approximately 20% of CRF neurons in CRF-Cre Ai9 mouse BNST show cFos expression in response to unpredictable foot-shocks exposure (Lin et al., 2018), in rat, CRF neurons do not coexpress cFos after acute stressors or immunological challenges (Day et al., 1999; Kozicz, 2002; Wang et al., 2011). On the other hand, CRF neurons in rat $BNST_{OV}$ seem sensitive to repeated or chronic stress exposure (Dabrowska, Hazra, Guo, Li, et al., 2013). For instance, repeated restraint stress (RRS) facilitates long-term potentiation (LTP) selectively in Type III, putative CRF neurons of the $BNST_{ALG}$, but it does not affect LTP in other types of BNST neurons. Notably, this effect of stress is associated with reduced expression of STEP protein in the $BNST_{ALG}$ (Dabrowska, Hazra, Guo, Li, et al., 2013). STEP is a key inhibitor of synaptic plasticity (Braithwaite, Paul, Nairn, & Lombroso, 2006) and is expressed exclusively in Type III neurons (mRNA) and virtually all CRF neurons of the $BNST_{DL}$ (protein) (Dabrowska, Hazra, Guo, Li, et al., 2013).

Although CRF neurons in the BNST are thought to mediate behavioral and autonomic responses to stressors, including fear and anxiety-like behaviors (Dabrowska, Hazra, Guo, Li, et al., 2013; Kim et al., 2006), their exact role in these processes still remains elusive. Subpopulations of CRF neurons in the $BNST_{OV}$ express 5-HT2C receptors (Marcinkiewcz et al., 2016), which have been shown to mediate serotonin-induced enhancement of cued fear (Pelrine et al., 2016; Ravinder et al., 2013). Chemogenetic inhibition of the CRF neurons in the $BNST_{OV}$ prevents this effect (Marcinkiewcz et al., 2016). The role of CRFR signaling in the $BNST_{DL}$ in the regulation of fear and anxiety is much better understood. For example, infusion of exogenous CRF into the $BNST_{DL}$, but not CeA, has been shown to increase vigilance measured as increased startle amplitude, a phenomenon known as CRF-potentiated startle (Lee & Davis, 1997; Walker et al., 2009). Similarly, a bright light-potentiated startle is mediated by CRFR1 in the BNST (Walker et al., 2009). Similarly, intra-BNST administration of CRF was shown to produce a CRFR1-dependent anxiety-like behavior in the EPM as well as conditioned place aversion (Sahuque et al., 2006). Recently,

inhibiting CRF release from the CeA to the BNST has been shown to disrupt anxiety-like responses in mice (Asok et al., 2018) and rats (Pomrenze et al., 2019), an effect mediated by CRFR1 in the BNST. However, overexpression of CRF in the $BNST_{DL}$ does not change startle amplitude or anxiety-like behaviors in rats (Sink et al., 2013) or mice (Regev et al., 2011) and affects sustained fear differently, depending on whether it is induced before or after fear conditioning (Sink et al., 2013) (Table 1).

In contrast to the role of CRFR1 in the $BNST_{DL}$ in promoting anxiety, optogenetic stimulation of GABA-ergic, CRFR2-expressing neurons in mouse $BNST_{POST}$ was shown anxiolytic in the EPM (Henckens et al., 2017). Optogenetic stimulation of CRFR2-expressing neurons immediately following stress exposure attenuated stress-induced anxiety and corticosterone levels, whereas their inhibition impaired stress recovery. From all members of the CRF-peptide family, Urocortin 3 (Ucn3) showed the highest concentration in the $BNST_{POST}$, emphasizing Ucn3 as a putative ligand for the CRFR2-expressing neurons (Henckens et al., 2017) (Table 1). In contrast to the postsynaptic CRFR2 found in the $BNST_{POST}$ (Henckens et al., 2017), presynaptic CRFR2 have been found in the $BNST_{DL}$ (Dabrowska et al., 2011), where they modulate OT release (Martinon & Dabrowska, 2018).

CRF neurons in the BNST have also been implicated in the regulation of binge alcohol drinking and drug-seeking behavior. Indeed, chemogenetic inhibition of VTA-projecting CRF neurons from the $BNST_{DL}$ significantly reduces alcohol intake in CRF-IRES-Cre mice (Pleil et al., 2015; Rinker et al., 2017). Conversely, VTA-projecting, CRF neurons from the $BNST_{VEN}$ mediate stress-induced reinstatement of cocaine seeking (Silberman & Winder, 2013b; Vranjkovic et al., 2014). Accordingly, CRF signaling in the BNST is essential for alcohol relapse (Funk et al., 2006) and stress-induced reinstatement of cocaine-seeking behavior (Erb, Salmaso, et al., 2001; Erb & Stewart, 1999) (Table 1).

Both CRF and Ucn1 (via CRFR1) have been shown to modulate inhibitory transmission in the BNST by increasing amplitude of $GABA_AR$-dependent inhibitory postsynaptic currents (IPSC). Whereas CRF enhances postsynaptic responses to GABA in mouse $BNST_{VEN}$ (Kash & Winder, 2006), NPY has been shown to decrease GABA release via NPY Y2 receptor (Y2R) activation, (Kash & Winder, 2006) suggesting opposing effects of CRF and NPY on the regulation of GABA transmission in the $BNST_{VEN}$.

Neuropeptide Y (NPY)—NPY-expressing neurons, as well as NPY-positive terminals, were found in the BNST of rats, mice (Allen et al., 1983; Chronwall et al., 1985; Pleil et al., 2015; Shen, 1987) and primates (Adrian et al., 1983; Gaspar, Berger, Lesur, Borsotti, & Febvret, 1987; Walter, Mai, Lanta, & Gorcs, 1991). These NPY neurons produce GABA (Pompolo, Ischenko, Pereira, Iqbal, & Clarke, 2005) and were shown to coexpress SOM in rodents (McDonald, 1989). NPY neurons fall into all three categories of Type I—III neurons in mouse BNST with the highest prevalence of Type I neurons, in both $BNST_{AL}$ and $BNST_{VEN}$. These NPY neurons show a state of higher synaptic excitability comparing to NPY-negative neurons in mouse BNST (Walter et al., 2018). In addition, the BNST expresses NPY receptors Y1R and Y2R in the anterodorsal BNST (Parker & Herzog, 1999), but not in the $BNST_{OV}$ (Nobis, Kash, Silberman, & Winder, 2011). NPY neurons from the BNST have been shown to project to the hypothalamus, including the medial preoptic area

(Pompolo et al., 2005), indicating that NPY neurons also contribute to the BNST output. BNST also receives NPY innervation from the arcuate nucleus of the hypothalamus, and activation of the projection increases feeding behavior (Betley, Cao, Ritola, & Sternson, 2013; Kash et al., 2015).

NPY signaling in the BNST has also been associated with stress coping. Greater behavioral flexibility in response to chronic variable stressors has been associated with increased NPY expression in the BNST (Hawley et al., 2010). An inversed correlation was detected between numbers of NPY-positive neurons in the BNST and anxiety-like behavior measured in the Light Dark box (Sharko, Kaigler, Fadel, & Wilson, 2016). Chronic restraint stress was shown to increase NPY and Y2R expression in the BNST in a stress-susceptible but not a stress-resilient mouse strain. In addition, stress increased basal GABA-ergic transmission but decreased NPY ability to inhibit evoked GABA-ergic transmission in the $BNST_{DL}$ (Nobis et al., 2011).

NPY has shown functional antagonism with CRF in the BNST. For example, CRF is excitatory, whereas NPY is inhibitory toward rat Type II BNST neurons (Ide et al., 2013). Similarly, opposing effects were also observed in regard to the regulation of GABA transmission in mouse BNST and the regulation of alcohol craving (Kash & Winder, 2006). Y1R agonist significantly reduces binge alcohol drinking (Pleil et al., 2012) by suppressing the activation of CRF neurons. Infusion of Y1R antagonist has an opposite effect, suggesting that a deficit in endogenous NPY signaling plays a role in the development of binge-like drinking. In contrast to binge drinking, NPY neurons in rat BNST are not involved in the effects of acute ethanol exposure (Sharko et al., 2016).

Enkephalin (ENK)—Nearly half of rat $BNST_{OV}$ neurons express detectable amounts of ENK mRNA (Kozicz, 2002). Accordingly, ENK immunoreactivity was found in the $BNST_{OV}$, BNST rhomboid nucleus, and to a lesser extent, the $BNST_{FUS}$ (Gray & Magnuson, 1987; Veening et al., 1984; Veinante et al., 1997). In mouse anterior BNST, almost all preproENK mRNA-expressing neurons also coexpress GAD67 mRNA. Notably, ENK neurons do not co-localize with populations expressing CRF or NT (Day et al., 1999; Veinante et al., 1997).

ENK neurons are primary stress-sensitive neurons of the $BNST_{OV}$. They are activated in response to a novel environment, amphetamine/cocaine administration (Day et al., 2001), or hyperosmotic stress in rats (Kozicz, 2002). Interestingly, lesion studies showed that DA inputs are necessary for the stress-induced activation of ENK neurons in the $BNST_{OV}$ (Kozicz, 2002). Following IL-~ injection, the great majority of cells activated in the $BNST_{OV}$ were ENK-positive, whereas some NT-ir neurons and very few CRF neurons were activated as well. Notably, all the activated neurons were GABA-ergic. Neurons expressing ENK mRNA have been found in a population of electrophysiologically defined Type II $BNST_{ALG}$ neurons (Daniel & Rainnie, 2016). Some of these Type II neurons also express PKCδ mRNA (Daniel & Rainnie, 2016). Dopamine D2 receptors on PKCδ neurons in the $BNST_{DL}$ have been shown necessary for discriminative learning between stimuli representing threat vs safety (De Bundel et al., 2016) (Table 1).

In addition to the local ENK neurons, BNST also receives ENK inputs from the CeA (Rao, Yamano, Shiosaka, Shinohara, & Tohyama, 1987). Similarly to the CeA, ENK has also been shown to modulate GABA transmission in the BNST. For example, MOPR activation with ENK analog DAMGO or morphine was shown to reduce GABA transmission in rat ventrolateral BNST (Dumont & Williams, 2004). ENK/GABA neurons from mouse anterior BNST synapse onto GABA-ergic neurons in the VTA, where they disinhibit DA neurons via mu opioid-receptor dependent mechanism (Dumont & Williams, 2004). In contrast to ENK/GABA neurons, a small amount of pre-proENK neurons expressing VGLUT2 mRNA was found in mouse $BNST_{POST}$ (Kudo et al., 2014).

Dynorphin (DYN)—DYN-positive neurons were found in mouse $BNST_{DL}$ of PreproDYN-IRES-Cre mice (Crowley et al., 2016). These GABA/DYN neurons release DYN, which acts on presynaptic KOPRs, and inhibits glutamatergic input from the BLA to the BNST. This projection is directly associated with anxiety-like behavior such as genetic deletion of KOPRs from the BLA inputs leads to an anxiolytic effect measured in the EPM. DYN is a potent modulator of both excitatory and inhibitory synaptic transmission in the brain (Crowley et al., 2016). KOPRs have been shown to inhibit GABA-ergic transmission via mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling in mouse BNST (Li et al., 2012). In rat BNST, acute stress was shown to stimulate the release of DYN (Bruchas, Land, & Chavkin, 2010; Morley, Elson, Levine, & Shafer, 1982), whereas early life stress exposure causes long-lasting changes in KOPRs function (Karkhanis, Rose, Weiner, & Jones, 2016). KOPR transmission has also been associated with stress-induced drug and alcohol seeking and withdrawal effects (Erikson, Wei, & Walker, 2018; Le, Funk, Coen, Tamadon, & Shaham, 2018). Infusion of KOPR agonists into the BNST was sufficient to induce drug-seeking behavior (Le et al., 2018).

Neurotensin (NT)—Similarly to ENK and CRF, the heaviest NT immunoreactivity was found on cell bodies and fibers of $BNST_{DL}$ neurons of mouse and rat. In anterior BNST, NT was found primarily in fibers and a substantial number of $BNST_{OV}$ neurons showed immunoreactivity for both CRF and NT (Ju & Han, 1989). A small percentage of these CRF- and NT-ir neurons project to the nucleus of the solitary tract and the dorsal motor nucleus of the vagus nerve, areas related to the regulation of cardiovascular function. Systemic injection of interleukin-1 β, in addition to activating ENK neurons, was shown to activate a population of NT neurons in the $BNST_{DL}$ (Day et al., 1999). Similarly to other neuropeptides in the BNST, NT also modulates synaptic transmission in the BNST by robustly potentiating GABAAR-mediated synaptic currents via presynaptic neurotensin receptors (NTR) (Kash & Winder, 2006; Krawczyk et al., 2013). Under normal physiological conditions, NT increases inhibitory transmission, acting synergistically with the CRF in the BNST (Krawczyk et al., 2013). However, chronic unpredictable stress leads to an enhanced contribution of NT over CRF. Notably, blockade of NTR in the $BNST_{OV}$ prevents stress-induced anxiety-like behavior measured in the EPM (Normandeau et al., 2018). NT also serves as a retrograde synaptic messenger. For instance, D1-mediated LTP in the $BNST_{OV}$ was positively correlated with motivation to self-administer cocaine, which also required local NT release in rats (Krawczyk et al., 2013).

Oxytocin (OT)—Stress-sensitive neurons producing OT have been found in ventromedial division of mouse BNST. These neurons are activated in response to a social defeat in female, but not male, monogamous California mice (Steinman et al., 2016). In addition, OT receptors (OTR) are distributed in the anteromedial BNST of California mice and mediate vigilance responses in unfamiliar social contexts in females (Duque-Wilckens et al., 2018). Although OT neurons have been found in ventromedial BNST of California mice, these neurons have not been found in the rat brain. In rats and other species, BNST receives dense OT innervation from the PVN (Dabrowska et al., 2011; Knobloch et al., 2012). The BNST has also one of the highest levels of OTRs expression, the function of which has been related to the regulation of social behaviors (Consiglio, Borsoi, Pereira, & Lucion, 2005; Dumais, Bredewold, Mayer, & Veenema, 2013; Insel & Shapiro, 1992; Kalamatianos et al., 2010). For example, OT content in $BNST_{POST}$ correlates with social discrimination in rats (Dumais, Alonso, Immormino, Bredewold, & Veenema, 2016). However, similarly to their role in the CeL (Viviani et al., 2011), OTRs in the $BNST_{DL}$ are also involved in the regulation of fear and anxiety. Specifically, OTRs in the $BNST_{DL}$ facilitate the acquisition of cued fear in male rats as measured in the FPS (Martinon et al., 2019; Moaddab & Dabrowska, 2017).

PACAP—In male rodents, chronic variable stress has been shown to increase pituitary adenylate cyclase-activating polypeptide (PACAP)-expressing cells and transcripts and its cognate PAC1 receptor transcript in the $BNST_{OV}$ (King et al., 2017). PACAP in the BNST was shown to produce anorexia, weight loss, and reduce water intake in male and female rats (Kocho-Schellenberg et al., 2014). Intra-BNST administration of PACAP or the PAC1 receptor-specific agonist facilitates a relapse of cocaine-seeking behavior. On the contrary, a PAC1 receptor antagonist attenuated stress-induced reinstatement of cocaine-seeking, implicating PACAP signaling as a critical component underlying stress-induced reinstatement of drug-seeking behavior (Miles, May, & Hammack, 2019). The BNST also receives extrinsic PACAP innervation (Koves, Arimura, Gorcs, & Somogyvari-Vigh, 1991; Kozicz, Vigh, & Arimura, 1998a; Missig et al., 2014).

Vasoactive intestinal polypeptide (VIP)—VIP immunoreactivity (ir) has been found in anterior BNST on both cell bodies as well as fibers, including the inputs from the amygdala (Erikson et al., 2018; Kozicz et al., 1998a) and dorsal raphe (Petit, Luppi, Peyron, Rampon, & Jouvet, 1995). Interestingly, VIP-ir axon terminals were shown to make synaptic connections with CRF and ENK dendrites and cell bodies in the $BNST_{DL}$ (Kozicz, Vigh, & Arimura, 1998b).

Cholecystokinin (CCK)—CCK-ir is similar to that of VIP, especially in anterior BNST (Giardino et al., 2018). CCK-expressing neurons in mouse BNST are found in the anteromedial BNST ($BNST_{AM}$) and co-localize with GABA; these neurons provide sparse input to the lateral hypothalamus (LH), where they innervate neurons expressing hypocretin (orexin). Notably, these CCK neurons were shown to modulate emotional valence in a manner opposite to CRF actions. Whereas activation of CRF BNST-LH projections produces an aversive state, activation of the CCK BNST-LH projection has been shown to produce

positive valence (Giardino et al., 2018). In addition to local CCK neurons, BNST also receives an extrinsic CCK innervation (Seroogy & Fallon, 1989).

Substance P (SP)—The distribution of SP-ir is present in medial parts of the $BNST_{POST}$. The distribution of SP in the BNST overlaps that of VIP to a large extent, but SP fibers are generally found in more medial aspects. Substance P (SP) and its cognate neurokinin-1 receptor (NK1R) in the BNST were shown to be involved in alcohol-related addictive behaviors (Schank et al., 2015).

Calcium-binding proteins and other neurotransmitters

Similarly to CeA, BNST neurons rarely express calcium-binding proteins. Although CR-expressing neurons account for a small proportion of BNST cells (primarily found in the $BNST_{OV}$), no PV expressing cells are found in the BNST (Nguyen et al., 2016). However, the other calcium-binding protein including CB has been found in the principal nucleus of mouse BNST (Morishita, Maejima, & Tsukahara, 2017), in a sexually dimorphic manner, with a higher number of CB neurons in males than females (Morishita et al., 2017). Only a few cholinergic neurons (stained for choline acetyltransferase, ChAT) (Bota, Sporns, & Swanson, 2012) have been found in several BNST nuclei in both the anterior and posterior divisions (Armstrong, Saper, Levey, Wainer, & Terry, 1983; Bota et al., 2012). In contrast, the relatively strong presence of ChAT fibers has been shown in the $BNST_{ALG}$, where muscarinic M2 receptors were shown to modulate glutamatergic transmission (Guo et al., 2012).

CONCLUDING REMARKS

Altogether, the amygdala complex and the BNST contain a wide range of neuronal populations, which are each defined by a molecular marker, a synaptic input, or a projection target, common to all individual neurons composing one population. At each of those three levels of analysis, individual neurons can have divergent patterns beyond the one gene, one input or one output experimentally targeted, adding collateral features to each population, and therefore granting neurons to belong to multiple neuronal populations. In search of features defining functional populations, multiple studies have identified populations defined by either one molecular marker or one anatomical property. Only a few studies have combined multiple features of one type (i.e., two or three genetic markers) (De Bundel et al., 2016; Giardino et al., 2018), or across types (i.e., genetic markers and projection target) (Carter et al., 2013; Han et al., 2015; Kim et al., 2017; Miller et al., 2019). How anatomical and genetic features multiplexed to determine the functional role of neuronal populations remains to be discovered in the amygdala and BNST neurons and integration of both anatomical and molecular properties represent an ineluctable path to decipher the circuits controlling emotional behaviors in healthy and pathological conditions.

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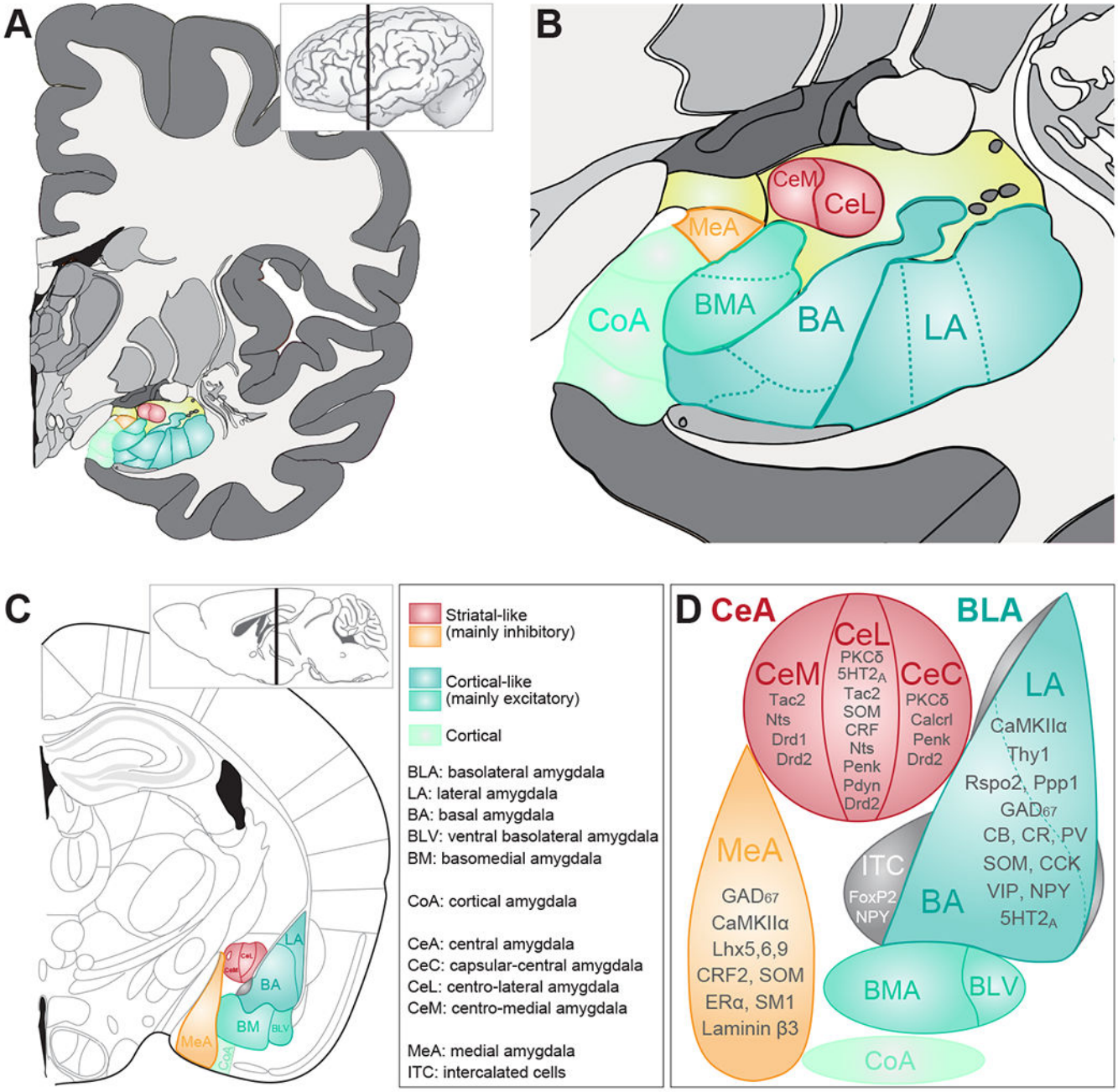

FIG. 1.

The amygdala complex and genetically identified populations. (A) Atlas of a human brain coronal section illustrating the different nuclei of the amygdala. (B) Detailed nuclei of the human amygdala. (C) Atlas of coronal sections of the adult mouse brain highlighting the different nuclei of the amygdala. (D) Schematic representation of the different amygdala nuclei and identified genetic markers. *Adapted from the Allen human brain atlas (modified Brodmann) and the Paxinos mouse brain atlas (4th edition).*

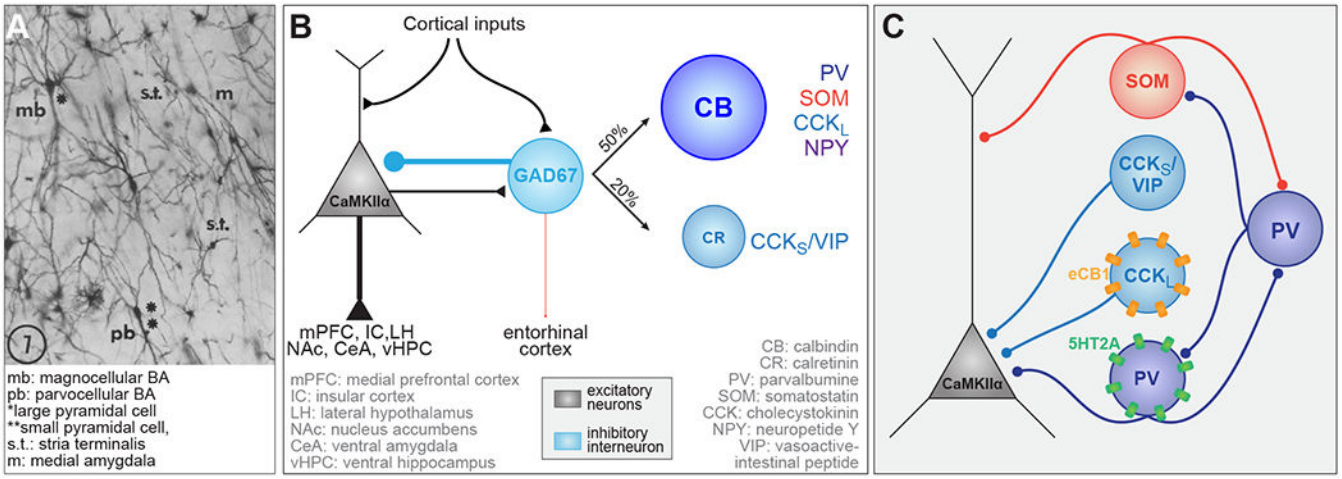

FIG. 2.

Size, connectivity, and gene markers of BLA neurons. (A) Image of a frontal section of a cat brain including magnocellular and parvocellular pyramidal cells of the BA. (B) Diagram of the connectivity of pyramidal and inhibitory neurons in the BLA, and distribution of markers in the inhibitory interneurons. (C) Microcircuit diagram of the postsynaptic target of five types of inhibitory interneurons of the BLA. *Adapted from* Hall, E. (1972). *The amygdala of the cat: A Golgi study*. Zeitschrift für Zellforschung und Mikroskopische Anatomie, 134, *439–458*.

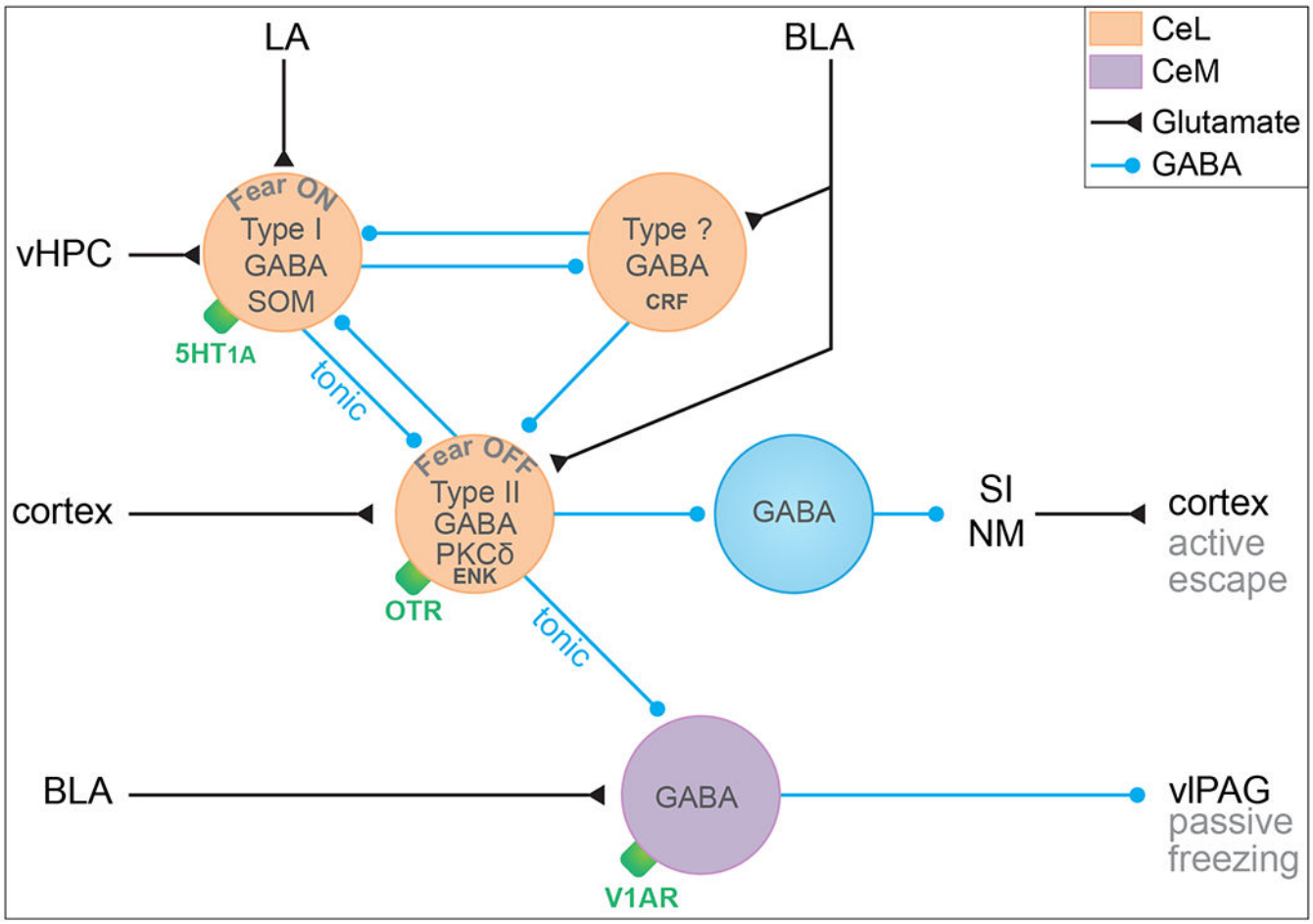

FIG. 3.

Top-down control of CeA output and fear responses by a diverse population of CeA interneurons. Type I neurons of the CeL (Fear ON neurons, serotonin 5-HT_{1A} receptors expressing, putative SOM neurons) provide tonic inhibition to other CeL interneurons, including Type II neurons. Type II neurons express OTR and partially overlap with PKCδ neurons (Fear OFF neurons). Almost half of the PKCδ neurons express ENK. Type II neurons tonically inhibit CeM output neurons (V1AR-expressing), which project to vlPAG and induce freezing responses. These Type II neurons also project to basal forebrain (SI and NM), where they dis-inhibit cholinergic neurons, which then promotes cortical arousal and active escape to an imminent threat. Activation of CRF neurons in the CeL has also been shown to promote an active defensive behavior (flight) in contrast to neighboring SOM neurons, which were shown to mediate passive fear responses (freezing). CeA receives neuron-specific glutamatergic inputs from the BLA, PFC, and LA.CRF and SOM neurons receive distinct afferent inputs from the BLA and vHPC, respectively. *CeL*, lateral nucleus of the central amygdala; *CeM*, medial nucleus of the central amygdala; *BLA*, basolateral amygdala; *LA*, lateral amygdala; *vHPC*, ventral hippocampus; *vlPAG*, ventrolateral periaqueductal gray; *SI*, substantia innominata; *NM*, nucleus basalis of Meynert; *OTR*, oxytocin receptor; *CRF*, corticotropin-releasing factor; *V1AR*, vasopressin 1A receptor; *ENK*, enkephalin; *SOM*, somatostatin; *PKCδ*, protein kinase C delta.

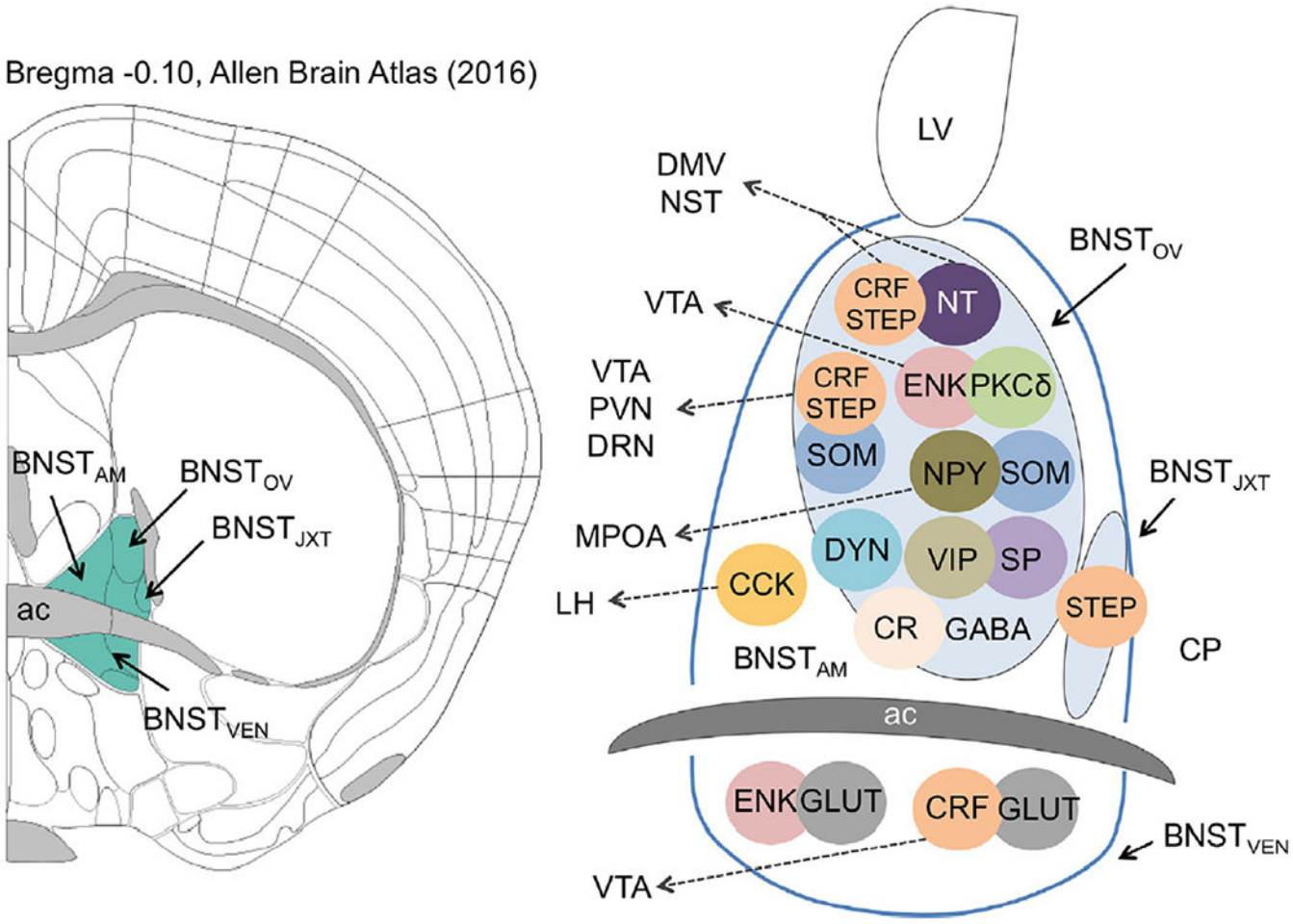

FIG. 4.

Neuronal diversity of the dorsolateral BNST (BNST$_{DL}$). BNST$_{DL}$ contains a variety of peptidergic neurons in the oval (BNST$_{OV}$), juxtacapsular (BNST$_{JXT}$) and ventral nucleus of the BNST (BNST$_{VEN}$). BNST$_{OV}$ and BNST$_{JXT}$ contain exclusively GABA-ergic neurons, whereas BNST$_{VEN}$ might also contain glutamatergic neurons. A substantial number of BNST$_{OV}$ neurons produce both CRF and NT, whereas all CRF neurons in the BNST$_{OV}$ co-express STEP. STEP is also present on BNST$_{JXT}$ neurons. In contrast, ENK neurons do not overlap with populations expressing CRF or NT, but express PKCδ mRNA. NPY neurons were shown to co-express SOM in rodents. *Dotted arrows*—BNST$_{DL}$ neurons send neuron-type specific outputs. *BNST$_{AM}$*, anteromedial nucleus of the BNST; *LV*, lateral ventricle; *CP*, caudate putamen; *NTS*, nucleus of the solitary tract; *DMV*, dorsal motor nucleus of the vagus nerve; *VTA*, ventral tegmental area; *PVN*, paraventricular nucleus of the hypothalamus; *DRN*, dorsal raphe nucleus; *MPOA*, medial preoptic area; *LH*, lateral hypothalamus; *CRF*, corticotropin-releasing factor; *STEP*, striatal enriched protein tyrosine phosphatase; *NT*, neurotensin; *ENK*, enkephalin; *SOM*, somatostatin; *NPY*, neuropeptide Y; *DYN*, dynorphin; *PKCδ*, protein kinase C delta; *VIP*, vasoactive intestinal polypeptide; *SP*, substance P; *CR*, calretinin; *GLUT*, glutamate.

TABLE 1

Manipulations and recordings of gene-defined, input-defined and projection-defined populations.

Feature		Experiment	Behavior or recorded neural response	Valence	Bidirectional[a]	Reference
Basolateral amygdala (BLA)						
Gene	Rspo2 (anterior)	ChR2	Freezing	−	Yes	Kim et al. (2016)
	Ppp1 (posterior)	ChR2	Self-stimulation	+	Yes	Kim et al. (2016)
	Thy-1	ChR2	Enhanced extinction	+	Yes	Jasnow (2013), McCullough et al. (2016)
		DREADDS-Gq	Increase extinction retention	+	×	McCullough et al. (2016)
	PV	ChR2	Increase CS-shock freezing	−	Yes	Wolff et al. (2014)
		Single-unit	Excited to the CS-shock	−	×	Wolff et al. (2014)
	SOM	ChR2	Decrease CS-shock freezing	+	Yes	Wolff et al. (2014)
		Single-unit	Inhibited to the CS-shock	+	×	Wolff et al. (2014)
Input	insula-BLA	ChR2	Approach (RTPP)	+	×	Wang et al. (2018)
	ACC-BLA	NpHR	–	−	No	Allsop et al. (2018)
Output	BLA-NAc	ChR2	Optogenetic self-stimulation	+	×	Namburi et al. (2015), Britt et al. (2012), Stuber et al. (2011)
		Single-unit	Preferentially excited to CS-sucrose	+	×	Beyeler (2016)
	$BLA_{CCK(+)}$-NAc	ChR2	RTPA, decrease sucrose consumption	−	×	Shen et al. (2019)
	$BLA_{CCK(-)}$-NAc	ChR2	RTPP, optogenetic self-stimulation	+	×	Shen et al. (2019)
	BLA_{Rspo2}-NAc	ChR2	Freezing and stimulation avoidance (RTPA)	−	×	Kim, Zhang, Muralidhar, LeBlanc, and Tonegawa (2017)
	BLA-CeL	ChR2	Anxiolytic	+	Yes	Tye et al. (2011)
	BLA-CeM	ChR2	Place aversion	−	×	Namburi et al. (2015)
	BLA-CeA	Single-unit	Preferentially excited to CS-quinine	−	×	Beyeler (2016)
	BLA-vHPC	ChR2	Anxiogenic	−	Yes	Felix-Ortiz et al. (2013)
		Single-unit	Unbiased	±	×	Beyeler (2016)
	BLA-mPFC	ChR2	Anxiogenic		Yes	Felix-Ortiz, Burgos-Robles, Bhagat, Leppla, and Tye (2016), Lowery-Gionta et al. (2018)
		ChR2	Increase CS-shock freezing	−	Yes	Burgos-Robles et al. (2017)
		Single-unit	Preferentially excited to CS-shock	−	×	Burgos-Robles et al. (2017)

Feature			Experiment	Behavior or recorded neural response	Valence	Bidirectional[a]	Reference
	BLA-PL		Single-unit	Active during CS-shock (early extinction)	−	×	Senn et al. (2014)
	BLA-IL		Single unit	Active during CS-shock after extinction	+	×	Senn et al. (2014)
	BLA-adBNST		ChR2	Anxiogenic	−	×	Kim et al. (2013)
Central amygdala (CeA)							
Gene	PKCd	CeL	Single-unit	Inhibited by CS-shock (CeL_{OFF})	+?	×	Haubensak et al. (2010)
		CeL	ChR2	No valence-related behavior	±	Yes	Kim et al. (2017)
		CeC	ChR2	Freezing	−	Yes	Kim et al. (2017)
		CeL	ChR2	Anxiogenic	−	Yes	Botta et al. (2015)
		CeL	ChR2	Anxiolytic	+	×	Cai, Haubensak, Anthony, and Anderson (2014)
		CeL	ChR2	Food intake suppression	−?	Yes	Cai et al. (2014)
		CeL-SI	ChR2	Avoidance (CPA)	−	×	Cui et al. (2017)
	SOM	CeL	ChR2	Decrease CS avoidance	+	Yes	Yu, da Silva, Albeanu, and Li (2016)
		CeL	ChR2	Self-stimulation	+	Yes	Kim et al. (2017)
		CeM	ChR2	Self-stimulation	+	Yes	Kim et al. (2017)
		CeL	ChR2	Freezing	−	Yes	Li et al. (2013)
		CeL	ChR2	Decrease CS-flight	+	No	Fadok et al. (2017)
		CeL	ChR2	CS-freezing	−	No	Fadok et al. (2017)
		CeL	Single-unit	Excited during CS-shock and freezing	−	×	Fadok et al. (2017)
	CRF	CeL	ChR2	CS flight	−	Yes	Fadok et al. (2017)
		CeL	ChR2	Decrease CS-freezing	−	No	Fadok et al. (2017)
		CeL	Single-unit	Excited during CS-flight	−	×	Fadok et al. (2017)
	5HT2A	CeA	ChR2	Increase food intake	+	Yes	Douglass et al. (2017)
		CeA	ChR2	Decrease freezing to aversive US	−	Yes	Isosaka et al. (2015)
	CRF	CeL	DREADD-Gq	Anxiogenic	−	×	Pomrenze et al. (2019), Paretkar and Dimitrov (2018)
	PKCδ-D2	CeL	Pharmacology	Increased fear discrimination	−	×	De Bundel et al. (2016)
	ENK	CeL	DREADDs-Gq	Anxiolytic, analgesia	+	×	Paretkar and Dimitrov (2018)
Input	insula-CeA		ChR2	Avoidance (RTPA)	−	×	Wang et al. (2018)
	PBNCGRP-CeC/L		ChR2	Appetite suppression	−	No	Carter, Soden, Zweifel, and Palmiter (2013)
	PBN_{CGRP}-CeC/L		ChR2	Defensive behaviors	−	No	Han, Soleiman, Soden, Zweifel, and Palmiter (2015)

Feature			Experiment	Behavior or recorded neural response	Valence	Bidirectional[a]	Reference
	PVT-CeL$_{SOM}$		ChR2	Inhibition decrease FC	−	No	Penzo et al. (2015)
	BLA$_{RSpo2}$-CeC$_{PKC\delta}$		ChR2	Defensive response	−	Yes	Kim et al. (2017)
Output	CeA-vIPAG		ChR2	Hunting (prey approach)	+	No	Han et al. (2017)
	CeL-SI	PKCd	ChR2	Avoidance (CPA)	−	×	Cui et al. (2017)
Bed nucleus of the stria terminalis (BNST)							
Gene	CRF	BNSTov	DREADDs-Gi	5-HT induced enhancement of cued fear	−	×	Marcinkiewcz et al. (2016)
	OTR	BNSTdl	Pharmacology	Increased cued fear	−	×	Moaddab and Dabrowska (2017), Martinon et al. (2019)
	PKCδ-D2	BNSTov	Pharmacology	Increased fear discrimination	−	×	De Bundel et al. (2016)
	CRFR2	BNST$_{post}$	ChR2	Anxiolytic	+	×	Henckens et al. (2017)
	5-HT2C	BNSTdl	Pharmacology	Increased cued fear	−	×	Ravinder, Burghardt, Brodsky, Bauer, and Chattarji (2013), Pelrine, Pasik, Bayat, Goldschmiedt, and Bauer (2016)
Input	CeA-BNST	CRF	ArchT	Anxiolytic	+	×	Asok et al. (2018)
	CeA-BNST	CRF	DREADDs-Gq	Anxiogenic	−	×	Pomrenze et al. (2019)
Output	BNST-VTA	CFR	DREADDs-Gi	Anxiolytic	−	×	Marcinkiewcz et al. (2016)
	BNST-VTA	CRF	DREADDs-Gi	Reduced alcohol intake	−	×	Pleil et al. (2015), Rinker et al. (2017)
	BNST-LH	CRF	ChR2	Increased negative valence	−	×	Giardino et al. (2018)
	BNDT-LH	CCK8	ChR2	Increased positive valence	+	×	Giardino et al. (2018)

×, not tested; *RTPP/A,* real-time place preference/avoidance; *CPA,* conditioned place avoidance; *PL and IL,* prelimbic and infralimbic prefrontal cortex; *PBN,* parabrachial nucleus; *PVT,* paraventricular nucleus of the thalamus; *(?),* debated.

[a]Study reporting bidirectional manipulation of the tested behavior/s.