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Invited review

Amygdala and bed nucleus of the stria terminalis circuitry: Implications for addiction-related behaviors

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ABSTRACT

Complex motivated behavioral processes, such as those that can go awry following substance abuse and other neuropsychiatric disorders, are mediated by a distributive network of neurons that reside throughout the brain. Neural circuits within the amygdala regions, such as the basolateral amygdala (BLA), and downstream targets such as the bed nucleus of the stria terminalis (BNST), are critical neuroanatomical structures for orchestrating emotional behavioral responses that may influence motivated actions such as the reinstatement of drug seeking behavior. Here, we review the functional neurocircuitry of the BLA and the BNST, and discuss how these circuits may guide maladaptive behavioral processes such as those seen in addiction. Thus, further study of the functional connectivity within these brain regions and others may provide insight for the development of new treatment strategies for substance use disorders.

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1. Introduction

The amygdala, located within the medial temporal lobe, is divided into at least 13 distinct subnuclei; the most clearly defined being the basolateral amygdala (BLA), the lateral amygdala (LA), and the central amygdala (CeA) (Amaral and Price, 1984; Amunts et al., 2005). The CeA connects the amygdala proper with the extended amygdala, located between the amygdala and the nucleus accumbens (NAc). The extended amygdala is comprised of the bed nucleus of the stria terminalis (BNST) as well as other interconnected nuclei such as the dorsal substantia innominata (Cassell et al., 1999) (Table 1).

Primary functions of the amygdala include emotional learning and regulation (Phelps and LeDoux, 2005), memory formation (Packard and Cahill, 2001), and reward processing (Baxter and Murray, 2002). The BNST is made up of a vast array of cell types including GABAergic and glutamatergic efferent populations, as well as GABAergic and cholinergic interneurons (Ju and Swanson, 1989; Ju et al., 1989). Overlapping with these populations are cells expressing an assortment of neuropeptides including NPY, CRF, enkephalin, dynorphin, and substance P (Kozicz et al., 1997). The BNST is involved in sustained fear behaviors (Walker and Davis, 2008; Walker et al., 2009), anxiety-like behaviors (Walker and Davis, 1997, 2008; Cecchi et al., 2002), and stress induced reinstatement of drug seeking (Erb et al., 2000, 2001a, 2001b; Wang et al., 2001).

Human neuroimaging studies have provided strong evidence for the role of the amygdala and extended amygdala structures in drug and alcohol addiction. A meta-analysis of data collected from fMRI and PET studies revealed that the amygdala and nucleus accumbens (NAc), an area that receives dense innervation from the amygdala, show the most robust neural activation in response to drug-associated cues (Chase et al., 2011). Additionally, two functional fMRI studies found correlations between NAc activity and drug cravings (Kufahl et al., 2005; Risinger et al., 2005). Changes in the

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Table 1
Overview of BLA and BNST connectivity.

Circuit	Approach used	Projection type	Reference
VTA → BLA	Tracing	Dopaminergic	(Albanese and Minciacchi, 1983)
Thal → BLA	Tracing	Unknown	(van Vulpen et al., 1989)
Hipp → BLA	Tracing	Glutamatergic	(Ottersen, 1982)
mPFC → BLA	Tracing	Glutamatergic	(Ottersen, 1982)
BLA → NAc	Tracing, Optogenetics, behavior	Glutamatergic	(Kelley et al., 1982; Stuber et al., 2011)
BLA → Hipp	Tracing	Glutamatergic	(Pitkanen et al., 2000)
BLA → BNST	Optogenetics, behavior	Glutamatergic	(Kim et al., 2013)
BLA → mPFC	Electron microscopy	Glutamatergic	(Bacon et al., 1996)
Cortex → BNST	Tracing, electron microscopy, electrophysiology	Glutamatergic	(McDonald, 1998)
CeA → BNST	Tracing, optogenetics	GABAergic	(Dong et al., 2001; Li et al., 2012)
Hipp → BNST	Tracing	Glutamtergic	(Cullinan et al., 1993)
PFC → BNST	Tracing	Glutamatergic	(McDonald, 1998)
VTA/PAG → BNST	Pharmacology	Dopaminergic	(Meloni et al., 2006)
NTS,VLM,VNAB → BNST	Anatomical, neurochemical, behavior	Noradrenergic	(Forray and Gysling, 2004)
DRN → BNST	Electron microscopy	Serotonergic	(Phelix et al., 1992)
BNST → VTA	Tracing, optogenetics, behavior	Glutamatergic and GABAergic	(Georges and Aston-Jones, 2001, 2002; Jalabert et al., 2009; Jennings et al., 2013; Kim et al., 2013; Kudo et al., 2012)
BNST → LH	Tracing	Unknown	(Dong and Swanson, 2004)
BNST → PVN	Tracing	GABAergic, CRFergic	(Roland and Sawchenko, 1993; Champagne et al., 1998; Dong et al., 2001; Dong and Swanson, 2006)

amygdala have also been associated with alcohol use disorders. An MRI study found that the amygdala is smaller in children of parents with alcohol use disorders (Hill et al., 2001). Furthermore, gray matter is decreased in the medial prefrontal cortex (mPFC), a region that receives strong innervation from the amygdala, in patients with alcohol use disorders (Pfefferbaum et al., 1998).

In this review we outline amygdala and BNST afferent and efferent connectivity, as well as animal studies that have implicated these circuits in the development and maintenance of drug addiction.

2. Role of BLA in addiction

The amygdala is thought to be necessary for attributing emotional value to cues that predict salient events. The BLA, in particular, has an integral role in processing affective states (Phelps and LeDoux, 2005). Importantly, the BLA has been implicated as a critical modulator of reinstatement of drug seeking in rodents (Fuchs et al., 2005). Lesions of the BLA disrupt cue-induced reinstatement of cocaine self-administration (Meil and See, 1997), conditioned reinforcement for a natural reward (Burns et al., 1993), and disrupts the acquisition of cocaine seeking during a second order schedule of reinforcement (Whitelaw et al., 1996). However, BLA lesions alone do not disrupt self-administration for cocaine (Meil and See, 1997) or natural reinforcers (Corbit and Balleine, 2005), suggesting the BLA plays a critical role in secondary reinforcement of natural rewards and drugs of abuse.

3. BLA afferents

The BLA receives strong innervation from the thalamus, hippocampus, and medial prefrontal cortex (Fig. 1A) (Ottersen, 1982; Albanese and Minciacchi, 1983; van Vulpen et al., 1989). The BLA also receives dopaminergic innervation from the ventral tegmental area (VTA, Fig. 1A) (Albanese and Minciacchi, 1983), and this circuit may underlie behavioral changes in drug addiction. Dopamine receptor antagonist in the BLA blocks cued reinstatement of drug seeking behavior (See et al., 2001). Likewise, studies have shown increases in extracellular dopamine in the BLA during the presentation of a cue that predicts a cocaine reinforcer (Weiss et al., 2000). Dopamine receptor activation *in vivo* increases the firing rate of fast-spiking interneurons, suggesting that dopamine release in the BLA decreases the firing rate of BLA projection neurons (Rosenkranz and Grace, 1999). Thus, dopamine's role in cued reinstatement in the BLA is may be through suppressing BLA output.

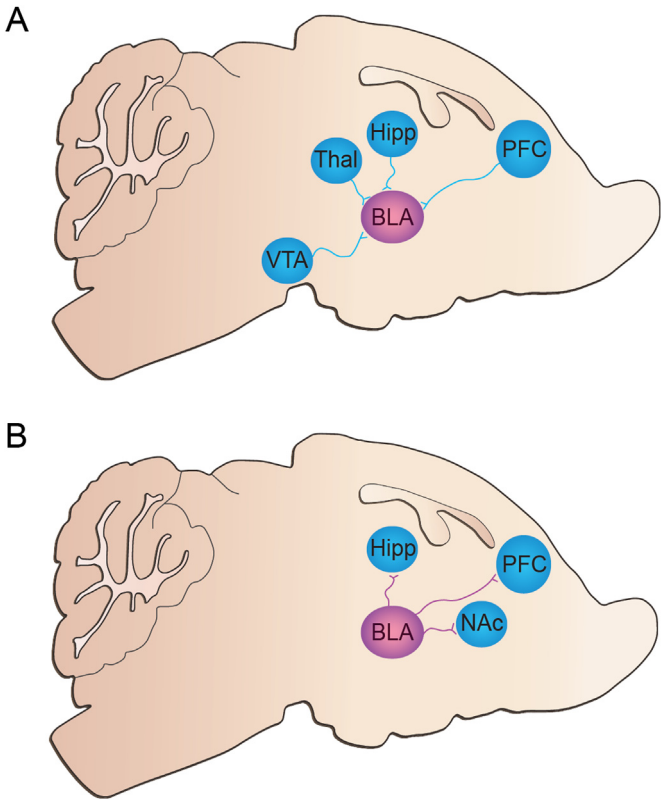

Fig. 1. Schematic detailing BLA afferent and efferent connectivity (**A**) The BLA receives inputs from the ventral tegmental area (VTA), thalamus (Thal), hippocampus (Hipp), and prefrontal cortex (PFC). (**B**) The BLA sends projections to the Hipp, PFC, and nucleus accumbens (NAc).