Toward a systems-oriented approach to the role of the extended amygdala in adaptive responding.

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Abstract

Waraczynski, M. Toward a systems-oriented approach to the role of the extended amygdala in adaptive responding. *NEUROSCI BIOBEHAV REV* XX(X) XXX-XXX, 2015. Research into the structure and function of the basal forebrain macrostructure called the extended amygdala (EA) has recently seen considerable growth. This paper reviews that work, with the objectives of identifying underlying themes and developing a common goal towards which investigators of EA function might work. The paper begins with a brief review of the structure and the ontological and phylogenetic origins of the EA. It continues with a review of research into the role of the EA in both aversive and appetitive states, noting that these two seemingly disparate avenues of research converge on the concept of reinforcement -- either negative or positive -- of adaptive responding. These reviews lead to a proposal as to where the EA may fit in the organization of the basal forebrain, and an invitation to investigators to place their findings in a unifying conceptual framework of the EA as a collection of neural ensembles that mediate adaptive responding.

Keywords: adaptive responding, anxiety, basal forebrain, bed nucleus of the stria terminalis, negative reinforcement, neural ensembles, positive reinforcement, reward

1.0 Introduction

The majority of behavioral research into the basal forebrain macrostructure known as the extended amygdala (EA) emphasizes its involvement in aversive states such as fear, anxiety, stress, and withdrawal from drug addiction. However, the EA seems equally involved in appetitive state. One goal of this review is to show how these two seemingly disparate states converge on the process of adaptive responding maintained through either positive or negative reinforcement. Behavioral studies of EA function focus particularly on the central nucleus of the amygdala and regions of the bed nucleus of the stria terminalis. Left relatively neglected is the swath of cells lying between these two areas, the sublenticular extended amygdala and the interstitial nucleus of the posterior aspect of the anterior commissure. Therefore, a secondary goal is to encourage investigators to integrate these areas into functional studies of the entire EA continuum. Finally, this review encourages investigators to unify their efforts around the creation of computational models of EA ensembles whose activity patterns coordinate particular response sets with particular internal and external environmental states.

We begin with a brief overview of EA anatomy with a focus on its ontogenetic and phylogenetic origins. This focus supports McDonald's (2003) conjecture that EA function might be characterized as a striatopallidal elaboration of basic amygdaloid function. This hypothesis is consistent with an ensuing review of the many behavioral phenomena linked to the EA. This review shows how the EA orchestrates diverse reactions and responses to the environment into an adaptive behavioral state during both aversive and appetitive situations, much as the amygdala enables specific reactions to specific stimuli and much as the striatopallidum orchestrates overt behaviors that are adaptive to and may even anticipate environmental circumstances.

2.0 What is the extended amygdala and where did it come from?

Our understanding of the evolution, development, and organization of the basal forebrain is in constant flux. Neuroanatomists and evolutionary neuroscientists continue to revise and reconstruct this understanding as new techniques improve our understanding of the embryological origin of particular cell groups, structures, and systems in the adult brain. Advances in comparative neuroanatomy also improve our understanding of the phylogenetic origin and evolution of these groups, structures, and systems. These advances aid our understanding of the EA. This section of this paper cannot definitively answer the questions posed in its heading but rather offers a précis of current understanding.

This paper will focus on functional data collected primarily from rodents and consequently will, unless otherwise specified, be concerned with the structures of the rodent (as representative of mammalian) extended amygdala. Therefore, here “extended amygdala” will refer to the column of cells that begins at the central and medial amygdaloid nuclei (CeA and MeA) and runs rostromedially through the sublenticular region immediately ventral to the globus pallidus (the SLEA) and the interstitial nucleus of the posterior limb of the anterior commissure (IPAC) to the cell groups that comprise the bed nucleus of the stria terminalis (BNST). This continuum is illustrated in parahorizontal view in Figure 1.

Some have posited that the shell of the nucleus accumbens is the rostral terminus of the EA, but Zahm (1998; 2000; Zahm et al., 01) convincingly argues that the accumbens shell resembles the striatopallidum (described in more detail below) more than the EA and is probably an area of transition between the two. The accumbens shell and the EA differ notably in the organization of their respective outputs. With the exception of some projections to the central grey and pedunculopontine area, output from the accumbens shell does not continue much more caudally than the hypothalamus (Zahm and Brog, 1992), while output from the EA continues well into myriad mid- and hindbrain structures (Dong et al., 2000, 2001a, 2001b; Dong and Swanson, 2004a and 2004b; Dong and Swanson 2006a and 2006b; Zahm, 2000). The shell’s transpallidal efferents to the thalamus and motor cortices more closely

resemble typical striatopallidal organization. Therefore, the accumbens shell will be considered here to be part of the ventral striatopallidum, not part of the EA.

The notion of an extended amygdala was first suggested by Johnston (1923), although he did not refer to it by that name. Based on careful cross-species observations, Johnston described the stria terminalis as “imbedded [sic] in a mass of gray [matter] which primarily connect[s] the anterior olfactory area with the region in which the amygdaloid complex develops” (p. 355). Heimer’s group later clarified the boundaries of the EA, gave it its name, and classified it as one of three major basal forebrain macrostructures, the others being the septopreoptic complex and the striatopallidum (Alheid, 2003; Alheid and Heimer, 1988; Alheid and Heimer, 1996; de Olmos and Heimer, 1999; Heimer et al., 1997; Zahm, 2006). The latter is usually divided into dorsal and ventral striatopallidum. The dorsal striatopallidum is largely what has traditionally been called the “basal ganglia” i.e., the caudate-putamen (striatum) and the globus pallidus. The ventral striatopallidum primarily comprises the nucleus accumbens, olfactory tubercle, and ventral pallidum.

All three macrostructures have in common (1) input from iso- and allocortical structures, principally the frontal cortex, the cortical and basolateral amygdala, and the hippocampus; (2) monoaminergic input from cell groups in the mid- and hindbrain; (3) output to mechanisms that control responding, defined broadly to include somatic, visceromotor, and autonomic reactions as well as overt movements; (4) re-entrant loops back to inputs. These macrostructures, especially the EA and striatopallidum, are heavily populated with GABAergic medium spiny projection neurons (MSNs) and, to a lesser degree, with aspiny glutamatergic projection neurons (Sun and Cassell, 1993; Cassell et al., 1999).

The EA is divided into central and medial subdivisions. The central EA is the cell column extending from the central nucleus of the amygdala through the IPAC and dorsolateral sublenticular extended amygdala (SLEAc) to the lateral and anterodorsal nuclei of the BNST. The medial EA is the column extending from the medial nucleus of the amygdala through the ventromedial sublenticular EA (SLEAm)

to the medial and ventroposterior nuclei of the BNST. The BNST is itself a highly diverse structure. A thorough review of the distinctions among its components is beyond the scope of this presentation; the interested reader is referred to deOlmos et al. (2004). Whereas the central EA has extensive efference, the medial EA appears to be primarily a route for relaying olfactory and vomeronasal input to the central EA, and for communicating with preoptic and hypothalamic areas involved in hormone regulation (Martinez-Garcia et al., 2007). A study of the efference and afference of the SLEA supports segregating the EA into central and medial divisions: The dorsolateral SLEA is interconnected with and shares efference and afference with the lateral BNST and the CeA while the ventromedial SLEA is similarly enmeshed with the medial BNST and MeA (Grove, 1988a and 1998b). Cells of the central EA are extensively interconnected via axon collaterals of the resident GABAergic medium spiny neurons; cells of the medial EA are not as interconnected (Grove, 1988a; Sun and Cassell, 1993; Veinante and Freund-Mercier, 1998).

A thorough review of the many efferents to and afferents from the EA is beyond the scope of this paper but reviews are available elsewhere (e.g., Alheid, 2003; Alheid and Heimer, 1986 and 1998; de Olmos and Heimer, 1999; Heimer et al., 1995 and 1997). Briefly, the EA receives input from a variety of sources, most notably the cortical and basolateral complexes of the amygdala, several limbic cortical areas such as cingulate, entorhinal, and insular cortex, the hypothalamus and preoptic area, and a variety of midbrain and hindbrain nuclei such as the dorsal raphe and central grey, the parabrachial region, and the nucleus of the solitary tract. The EA also receives input from many of the major monoaminergic cell groups of the brainstem; Kash (2012) provides a good review of sources of noradrenergic, serotonergic, and dopaminergic input to the EA, particularly the BNST. The EA differs from the striatopallidum in its receipt of significant dopaminergic input from the A8 (retrosubstantia nigra) cell group and a somewhat sparser contribution from the dorsal raphe/periaqueductal grey region, in addition to the more familiar A9 and A10 groups (Zahm, 2008; Hasue and Shammah-Lagnado, 2002).

The EA has extensive efference to hypothalamic and brainstem targets implicated in a variety of motivational and emotional functions (Grove, 1988b; Dong and Swanson, 2003; 2004a and 2004b; 2006a and 2006b; Dong et al., 2000, 2001a and 2001b). Virtually all of these targets reciprocate this input, making the EA system an interconnected network (Zahm, 2000 and 2006).

It is useful to consider the ontological origins of the EA in relation to the origins of the neighboring striatopallidum and amygdala. Embryonic telencephalon is divided into the pallium, which generally gives rise to cortical structures, and the subpallium, which generally gives rise to subcortical structures. EA structures derive primarily although not exclusively from the subpallium. Striatal cell groups (e.g., caudate-putamen; nucleus accumbens) derive from a part of the subpallium called the lateral ganglionic eminence and pallidal structures (e.g., globus pallidus; ventral pallidum), from the medial ganglionic eminence (Deacon et al., 1994; Garcia-Lopez et al., 2008). Structures of the amygdala derive from both the pallium (cortical and basolateral cell groups) and the subpallium (central and medial nuclei), a situation that has caused some to question whether “the amygdala” should be considered a structural and functional unit (Swanson and Petrovich, 1998).

The intrinsic organization of the *adult* EA shows striatopallidal characteristics. For example, the lateral aspect of the central EA contains striatal-like GABAergic medium spiny projection neurons while the medial aspect of the central EA contains pallidal-like aspiny glutamatergic projection neurons (Cassell et al., 1999). This striatopallidal nature is confirmed and elaborated upon by studies of the embryonic expression of regulatory genes commonly active in the basal forebrain (e.g., Pax6; Nkx2.1; Lhx6) and the distribution of phenotypic neuronal markers (e.g., somatostatin; calbindin). Based on fate mapping of cells expressing Pax6 and Islet 1, Bupesh et al. (2011a and 2011b) note that structures of the central EA derive from both the lateral and medial ganglionic eminences, while structures of the medial EA derive only from the medial ganglionic eminence. In addition, the *caudal* ganglionic eminence, which contributes many neurons to the striatum, also contributes cells to the extended amygdala, from the

centromedial amygdaloid nuclei contiguously through the BNST (Nery et al., 2002). As shown in Figure 1, there is a lateral (central EA) to medial (medial EA) continuum of projection neuron subtype, one that is mirrored in a roughly dorsoventral axis in the striatopallidum: The central EA contains GABAergic neurons that also express calbindin, enkephalin, and corticotropin releasing factor. The latter are also often positive for neurotensin or dynorphin. The medial EA is characterized by somatostatin/substance P-positive cells (Bupesh et al., 2011a; Garcia-Lopez et al., 2008). In the dorsal striatopallidum, cells of the caudate-putamen are positive for calbindin and enkephalin, while cells of the more ventral globus pallidus are positive for somatostatin (Reiner, 2010).

However, the EA also has amygdaloid characteristics not typical of the striatopallidum. The amygdala is mosaic in ontological origin (Medina et al., 2011 review the conservation of the amygdala's mosaic nature across tetrapod lineages). Based on the expression of an array of regulatory genes *other than* Pax6 and Islet1, Garcia-Lopez et al. (2008) show that the central amygdaloid nucleus derives from the same lateral ganglionic progenitor region as the striatum, but also contains cells that migrate tangentially from an anterior peduncular region, the same region from which the sublenticular EA derives. The medial amygdaloid nucleus derives from multiple embryonic zones, including some cells that migrate from the ventral pallidum, which typically gives rise to ventral cortical areas. The lateral BNST derives largely from the medial ganglionic eminence, while the anterior and posteromedial BNST derive from the anterior peduncular region. Some parts of the medial BNST appear to derive from a supraoptic-paraventricular domain of the alar hypothalamus (Garcia-Lopez et al., 2008; Bupesh et al., 2011b), consistent with the medial EA's association with hypothalamic control of hormone release. Some cells in the medial BNST may even arise outside of the telencephalon (Garcia-Lopez et al., 2008). In short, the EA -- like the amygdala but unlike the striatopallidum -- has a relatively complex pattern of ontological origin.

Phylogenetically, the amygdala, the EA, and the striatopallidum all appear to be quite ancient. Structures of the mammalian EA and amygdala have fairly clear homologues in reptiles and birds (Martinez-Garcia et al., 2007), which suggests that they are at least as old as the origin of amniotes more than 350 million years ago. Homologues in teleost fish (Maximino et al., 2013) and anamniote tetrapods (Martinez et al., 2007) are less certain but are apparent, which may push the origin of the EA back even further. As terrestrial vertebrates evolved, the amygdala and extended amygdala expanded in size and nuclear complexity (Moreno and Gonzalez, 2006; Martinez-Garcia et al., 2007; Johnston, 1923). Similarly, structures of the striatopallidum – particularly dorsal striatopallidum – are apparent in virtually all vertebrate lineages, and its evolution during the proliferation of terrestrial vertebrates also involved increased size and organizational complexity (Reiner, 2010).

During mammalian evolution, the EA elongated substantially in the rostrocaudal plane. The EA in reptiles and birds is relatively compact, with the caudal (central and medial amygdala) and rostral (BNST) poles close together. In mammals, the elongated corridor between those two poles is partially split by the intrusion of the internal capsule, a partial disconnect that is bridged by the sublenticular EA (Martinez-Garcia et al., 2007 and 2008). It is fair to conjecture that such territorial expansion may have added complexity to species' functional repertoires. Brain evolution often proceeds through changes in the developmental trajectory of a morphogenetic field that gives rise to a particular structure or cell line. If a structure enlarges and/or adds new characteristics, the new territory is available to selection pressures and may be pre-adapted to its own unique function(s). Given that the ancestral structure or cell line is still present to support the ancestral function, the functions of evolutionarily recent cells or structures tend to be different from – perhaps more complex than -- but related to those of the ancestral structure or cells (see Striedter, 2005, especially chapter 6 regarding the origin of novelty in the brain).

To give an example, there are clear homologues in medial EA structures across all vertebrate species. In the deeply ancestral lineages such as aquatic vertebrates, the medial EA seems to mediate reactions primarily to olfactory, vomeronasal, and possibly gustatory input, and is linked to hormonal regulation of reproductive functions (Martinez-Garcia et al, 2007 and 2008). These medial EA functions are conserved in terrestrial vertebrates, although some of their control may have shifted to a novel medial EA component in mammals (Medina et al., 2011). As amygdaloid and EA structures enlarged and differentiated during the evolution of terrestrial vertebrate lineages -- particularly mammals -- these new territories apparently came to serve new but analogous functions that incorporated auditory, visual, somatosensory, and even association cortical inputs. That is, these structural novelties help subserve the behavioral complexity of which these lineages are capable (Johnston, 1923; Martinez-Garcia et al., 2007).

The EA is situated between the amygdala and the striatopallidum and its combination of amygdaloid and striatopallidal characteristics has generated some contention among neuroanatomists. Swanson's group argues that the structures comprising the EA are -- along with the striatopallidum and the septopreoptic macrostructure -- all components of a unitary subcortical nuclear layer divided into striatal and pallidal parts. Specifically, they propose that the BNST plays the pallidum to the central and medial amygdala's striatum, while the ventral pallidum, SLEA, and the magnocellular preoptic region are pallidal to the ventral striatum (nucleus accumbens, IPAC a.k.a. fundus striatum, and olfactory tubercle) (Swanson and Petrovich, 1998; Swanson, 2003; Swanson 2012). Similarly, McDonald (2003) proposes that the EA is a striatopallidal structure that is involved in amygdaloid functions. Puelles et al. (2013) propose that the EA is a unique subpallial structure, the major component of a diagonal domain of the central subcortical forebrain that is contiguous rostrally with the diagonal band of Broca and caudally with the magnocellular nucleus. This review does not propose to resolve this debate. The ensuing review of EA function assumes the original conceptualization of the EA proposed by Heimer's group and

described at the beginning of this section: A continuum of cells originating in the central and medial amygdala and continuing rostrocaudally through the subnucleus and into the bed nucleus of the stria terminalis. An exploration of functions associated with the EA may inform our understanding of its place in the basal forebrain's organization.

3.0 What does the extended amygdala do?

While the amygdala proper has traditionally been associated with negative affective states such as fear and anxiety it is clearly important to positive affect as well (see Balleine and Killcross, 2006; Murray, 2007; Morrison and Salzman, 2010; Janak and Tye, 2015 for recent reviews). The excessive focus on negative affective states may be an artifact of the considerable success of fear conditioning as a model of the role of the amygdala in emotional learning (for reviews, see, e.g., Johansen et al., 2012; LeDoux, 2007; Phelps and LeDoux, 2005). That is, the fact that much of the published research on amygdala function comes from the study of fear and related negative affect may create the perception that the amygdala “does” negative states exclusively.

Similarly, much research into the function of the extended amygdala has focused on its role in aversive processes such as fear, anxiety, stress, and withdrawal from drug addiction. Yet the EA is also associated with positive motivation. This bivalent nature was recently illustrated by a group of elegant experiments reported by Jennings et al. (2013). These investigators selectively activated either glutamatergic or GABAergic projections from the BNST to largely non-dopaminergic (presumably GABAergic) ventral tegmental neurons. Activating glutamatergic projections led to conditioned place avoidance of the location in which these neurons were activated, inhibition of reward seeking behavior, and freezing in an open environment. Activating GABAergic projections had the opposite effects; mice would even nose poke to obtain stimulation of these neurons. In short, a heterogeneous population of

glutamatergic and GABAergic neurons in the BNST is associated with aversive and appetitive reactions and behaviors, respectively.

The notion that some brain systems are associated with both positive and negative experience is not new (see for example Ulrich-Lai and Herman, 2009; Bissonette et al., 2014; Mannella et al., 2013). Even the mesolimbic “reward system” has recently been associated with aversive state (Volman et al., 2013; Lammel et al., 2012). However, most reviews of brain systems underlying reward and aversion focus on interactions among frontal cortical areas, the ventral striatopallidum, and the amygdala, giving scant attention to the large swath of tissue lying among them, the extended amygdala. This section of this paper briefly and selectively reviews a large body of evidence supporting a pivotal role for the EA in a broad range of behavioral phenomena, both aversive and appetitive.

The apparent duality of EA function converges on the *unitary* process of the reinforcement of adaptive responses: negative reinforcement obtained through avoiding, escaping, and terminating aversive situations and positive reinforcement obtained through seeking out and interacting with appetitive situations. Both forms of reinforcement maintain adaptive responding: an organism’s ability to do that which enhances its survival, and to do so flexibly, with responses changing optimally and quickly as the environment changes.

3.1 The extended amygdala and aversive situations

3.1.1 Fear, anxiety, and stress reactions

Studies of the role of the EA in fear, anxiety, and stress have recently exploded in number, breadth, and depth. This literature is too extensive to review thoroughly here; the reader is referred to others’ work (e.g., Davis et al., 2010, Walker et al., 2009; Silberman and Winder, 2013). This section briefly reviews some particular findings and trends.

The acoustic startle reflex paradigm is a widely used animal model of fear and anxiety. This reflex occurs following loud sounds and can be potentiated by inducing fear (e.g., introducing a cue previously associated with footshock) or anxiety (e.g., presenting a species-specific aversive stimulus such as bright light for a nocturnal animal such as the rat). The degree to which the reflex is potentiated is taken as an index of how potently the presented stimulus generates fear or anxiety. Animal models of *situational* anxiety and stress reactions include measuring the amount of time the animal spends in the open arm of an elevated plus maze, the amount of time the animal spends immobile (“freezing”), and the amount of social interaction and exploration an animal engages in following a stressful experience. Stress is often induced via acute restraint or inescapable shock.

Based on the effects on acoustic startle potentiation of lesions and temporary inactivations, Davis and co-workers (e.g., Lee and Davis, 1997, Davis, 1998, Davis and Shi, 1999) propose a dissociation of function between the CeA and the BNST. Specifically, they state that medial CeA efference to the hypothalamus and brainstem effects the acute, stimulus-specific reactions that characterize “fear”. Fear is defined as the immediate withdraw from a particular stimulus that signals threat. In contrast, they propose that a pathway from the lateral CeA to the lateral BNST and thence to many brainstem areas mediates the sustained state change that is “anxiety”. Anxiety is associated with more diffuse, contextual stimuli rather than a specific stimulus. It is a more persistent state of avoidance of and withdrawal from the entire environment in which threat is perceived. (Walker et al., 2003; Walker et al., 2009; Davis et al., 2010). In short, medial CeA efference is associated with acute response to a particular stimulus, but the BNST is recruited during sustained state change in response to cues about the potentially threatening nature of the situation.

This is not to say that the BNST is irrelevant to stimulus-specific fear reactions. For example, muscimol inactivation of the rat BNST reduces innate fear of predator excretions, measured as the amount of freezing to and contact with those excretions (cat urine: Xu et al., 2012; a fox feces

component: Fendt et al., 2003). However, Sullivan et al. (2004) demonstrate that both BNST and CeA lesions attenuate freezing and HPA axis responses to contextual fear related stimuli while such reactions to a shock-associated tone cue were attenuated only by CeA lesions. They suggest that exposure to predator-related scents may induce rapid contextual conditioning. The anterior BNST receives dense input from the subiculum and ventral hippocampal formation (Swanson and Cowan, 1977; Cullinan et al., 1993), which input is associated with communicating contextual information. Because of this input, and because of the connections of the BNST with the ventral periaqueductal grey, which is involved in freezing, the BNST may coordinate with and appears to compensate for context fear conditioning usually effected by the amygdala when the latter is impaired. Such compensation appears to be downregulated when the amygdala is intact, perhaps to keep fear responding to appropriate levels and thus avoid pathological anxiety (Poulos et al., 2012).

EA control of anxiety and stress reactions is regionally specific. For example, following acute restraint, norepinephrine release into the BNST appears necessary to stress-induced reduction of open arm maze exploration while norepinephrine in the CeA appears necessary to stress-induced reduction of social interaction (Morilak et al., 2003). The control of stress and anxiety reactions is regionally specific even within the BNST. Figure 2 summarizes some of what is known about this neural circuitry. During stress and anxiety glutamatergic projections from the basolateral amygdala (BLA) to the anterodorsal BNST (adBNST) are inactive, but GABAergic projections from the oval BNST to the adBNST are active, silencing adBNST glutamatergic projections to the parabrachial nucleus (PBN), ventral tegmental area (VTA) and lateral hypothalamus (LH). In the absence of this glutamatergic input, respiration increases (PBN projection), locations associated with stress are avoided (VTA projection), and open field exploration is reduced (LH projection) (Kim et al., 2013). In addition, axons from the central amygdala (CeA) that release corticotropin releasing factor (CRF) activate neurons in the anteroventral BNST (avBNST). This activity facilitates HPA reactions via a glutamatergic/CRF-co-expressing projection

to the medial parvocellular paraventricular nucleus of the hypothalamus (PVN). At the same time, GABAergic projections from the CeA and the medial central amygdala (CeM) are also active, inhibiting cells in the posterior BNST (pBNST). The pBNST normally inhibits HPA reactions via a GABAergic projection to the PVN (Choi et al., 2007), which inhibition is now silenced

During anxiolysis the glutamatergic projections from the BLA are active, thereby activating the glutamatergic projections from the adBNST. Respiration decreases and place preference and open field exploration are promoted (Kim et al., 2013). The lack of CRF-ergic input from the CeA leaves avBNST glutamatergic/CRF-ergic inputs to the PVN inactive, and the HPA axis is not upregulated. The lack of GABAergic input from the CeA and CeM to the pBNST allows pBNST GABAergic neurons to inhibit the PVN, enabling HPA downregulation (Choi et al., 2007).

Giving a safety signal during inescapable shock decreases Fos activity in the ventrolateral BNST and decreasing that area's activity enables social exploration following stress (Christianson et al., 2011b). Jennings et al. (2013) propose that the avBNST's GABAergic efference to the VTA (not shown in Figure 2) allows for "anxiety buffering" during aversive events, which may promote reward-seeking when threat risk is perceived to be low. Intriguingly, the pBNST is one of several basal forebrain areas in which high calorie, palatable food ingestion alters gene expression in a way that ultimately dampens the HPA axis response to stress (Christianson et al., 2011a) which suggests a neural circuitry for "comfort eating", a form of anxiety buffering.

To summarize, various EA components are differently associated with reactions to stress and to fear- and anxiety-provoking situations. Neural activity in the EA is associated with protective reactions such as startle potentiation, freezing, and conservatism in exploration and to proactive or coping responses such as responding to safety signals, engaging in behaviors that dampen HPA activity, and buffering anxiety responses. Both protective and coping responses meet the definition of negative reinforcement: support of behaviors that alleviate, terminate, or avoid aversive states. Both are

ultimately adaptive responses to aversive environments: It is adaptive to fear and avoid danger, and it is also adaptive to be able to quell fear and avoidance in situations that signal a balance between threat and potential benefit.

3.1.2 Withdrawal from addictive drugs

The negative state induced by withdrawal from addictive drugs is very much related to fear, anxiety, and stress reactions. The importance of the EA in the negative affective state of withdrawal is thoroughly reviewed elsewhere (Koob, 2008a, 2009a, 2009b, and 2009c; Cui et al., 2013). This section briefly presents some findings of particular interest.

Negative affect induced by withdrawal is often assessed via conditioned place aversion. Consider opiate addiction and withdrawal, a common exemplar and one that induces substantial increase in Fos immunoreactivity (Veniente et al., 2003) and in CRE-mediated gene transcription (Shaw-Luchtman et al., 2002) throughout the central EA continuum. In this paradigm, animals are exposed to an opiate such as morphine, typically via subdural implantation of drug pellets. Exposed animals are then given an opiate antagonist such as naloxone to precipitate withdrawal. If the animals develop a conditioned place aversion to (i.e., spend less time in) the location in which withdrawal was induced then one might infer that withdrawal has induced negative affect.

Stress and anxiety are associated with the release of norepinephrine and CRF. Noradrenergic input to the BNST from the A1 cell group of the nucleus of the solitary tract is linked to withdrawal-induced aversive state (Aston-Jones et al., 1999). Blocking β receptors or stimulating α_2 adrenergic receptors in the BNST reduces withdrawal-associated place aversion (Delfs et al., 2000). Stimulating α_2 receptors suppresses withdrawal-induced expression of Narp, an immediate early gene associated with regulating AMPA receptor trafficking and therefore with mechanisms of synaptic plasticity that may be recruited

during place aversion learning (Reti and Baraban, 2003). Blocking CRF receptors in the BNST also reduces opiate withdrawal-associated place aversion (Stinus et al., 2005).

EA-based circuitry appears to underlie the affective and motivational aspects of withdrawal but not its somatic aspects such as shivering and changes in gastric motility. Conditioned place aversion is typically induced by relatively low doses of naloxone but somatic withdrawal signs require higher doses. Naloxone doses that induce conditioned place aversion also induce dose-dependent increases in cFos mRNA in basal forebrain areas including the BNST and CeA. On the other hand, cFos mRNA increases only at higher doses in mesencephalic and autonomic brain areas associated with somatic withdrawal symptoms, such as the locus coeruleus, nucleus of the solitary tract, periaqueductal grey, and ventral tegmental area (Frenois et al., 2002; Aston-Jones et al., 1999; Walker et al., 2000; Nakagawa et al., 2005).

Frenois et al. (2005) present evidence that withdrawal-induced place aversion is conditioned to the *entire environmental context* in which withdrawal takes place, not just to specific withdrawal-paired stimuli. cFos activity was measured in a variety of basal forebrain and brainstem areas associated with withdrawal-induced conditioned aversion. Two groups of morphine-dependent rats had identical withdrawal histories: Withdrawal was induced by a naloxone injection in one arm of a Y maze on one conditioning day. On another day, the same two groups experienced a saline injection in the other arm of the maze. Both groups showed clear avoidance of the naloxone-associated arm when allowed to freely explore the Y maze, demonstrating that withdrawal induced place avoidance. Several days later, one group was confined to the naloxone-paired arm in which they previously experienced withdrawal while the other group was confined to the saline-paired arm. *Both* groups showed similar levels of heightened cFos activity in several basal forebrain and brainstem areas – including the BNST and CeA -- relative to similarly confined control rats with no withdrawal history or control rats who experienced withdrawal in an environment outside the Y maze. That is, cFos levels increased in response to being placed *in the Y maze itself*, not in response to being placed in the particular maze arm in which

withdrawal was previously induced. These data must be interpreted cautiously: They do not show that EA-based circuitry is uniquely responsible for conditioning to the environmental context of the aversive experience, nor do they show that cFos increase correlated with negative state. However, they are at least consistent with a distinction between response to specific cues versus response to contextual cues and with the EA's implication in the latter.

3.1.3 Stress-induced reinstatement of drug seeking

The EA's roles in stress and anxiety and in addictive drug withdrawal combine in the phenomenon of stress-induced reinstatement of drug seeking. In this phenomenon, animals are trained to make a response to receive addictive drugs such as cocaine or heroin. The response on which drug delivery is contingent is then extinguished by allowing the animal to make the response but no longer delivering the drug. Once the drug seeking response is extinguished the animals are exposed to a stressor such as footshock or restraint, whereupon the drug seeking response is quickly reinstated. Presumably, drug seeking is aimed at terminating the negative affect and motivation induced by the stressor. (Drug seeking can also be reinstated by drug-associated cues, and structures of the EA have been implicated in cue-induced reinstatement as well [Mahler and Aston-Jones, 2012]).

Erb (2010) and Silberman and Winder (2013) comprehensively review evidence implicating CRF- and noradrenergic-dependent EA mechanisms in stress induced reinstatement, the same mechanisms linked to negative affect during withdrawal and during situations that provoke fear and anxiety. Figure 3 summarizes current ideas about the EA's role in this phenomenon. Chronic drug exposure is thought to increase glutamatergic excitatory drive in the BNST, especially the adBNST. Such drive is mediated at least in part by glutamatergic input from the basolateral amygdala (see Stamatakis et al., 2014 for review). This input activates BNST efferents to the ventral tegmental area, resulting in enhanced motivation to seek and consume the drug with which the animal has experience. (Note in Figure 3 that

some GABAergic efferents from the BNST to the ventral tegmentum co-release glutamate. This point is discussed in some detail in section 5.0.) Stress activates CRF release from intrinsic EA neurons and noradrenergic release from the A1 and A2 cell groups. Norepinephrine may act presynaptically to potentiate glutamate release from basolateral amygdala inputs and/or postsynaptically to sensitize adBNST cells to glutamatergic and CRF inputs (see McElligott and Winder, 2009; McElligott et al., 2010; McElligott et al., 2013). Recall that activating the adBNST has been associated with anxiolysis. Thus, reinstating drug seeking may be a means by which drug-experienced individuals cope with stress and anxiety.

An individual's experience with stress *irrespective of drug experience* may affect that individual's propensity for experiencing stress-induced reinstatement. Flavin and Winder (2013) speculate that prolonged norepinephrine release resulting from chronic stress may lead to long term changes that leave the BNST sensitized to subsequent stress exposure. Upon experiencing stress in the future -- instantiated as noradrenergic and CRF signaling in the BNST -- sensitized circuits underlying the negative symptoms of withdrawal are quickly re-engaged and stress-induced reinstatement results. Thus, individuals who have lived more stressful lives may be more prone to drug addiction relapse than others with similar drug use experience but less of a history with stress. Koob (2008b; Koob and LeMoal, 2001) relates this phenomenon to the concept of allostasis, a situation in which brain mechanisms come to adjust to a persistent change in both internal and external environmental demands by altering homeostatic set points and correctional mechanisms. Through positive feedback, brain systems become hyper-responsive to stimuli that previously elicited little or no response. In the case of drug addiction, stressors provoke drug seeking in drug-dependent individuals but do not provoke such motivation in non-exposed or non-dependent individuals.

Stress and anxiety also induce ethanol seeking in ethanol-dependent rats. Withdrawal from chronic ethanol exposure increases CRF activity in the EA (Olive et al., 2002; Cui et al., 2013). Neuropeptide Y

(NPY) in the EA may protect against stress-induced reinstatement of ethanol seeking. In fact, exposure to NPY during early withdrawal experiences may protect against transitioning to chronic ethanol *dependence* (Gilpin, 2012 Gilpin et al., 2011). Gilpin and Roberto (2012) propose that CRF stimulation of local GABA release within the EA is upregulated during chronic exposure to alcohol. This results in enhanced GABAergic inhibition of CeM output neurons and a net disinhibition of effectors that produce anxiety and stress reactions. NPY (and other neuropeptides) works against this. Others propose that NPY may work through action on Y1 receptors in the BNST, causing inhibition of local CRF-releasing neurons (Pleil et al., 2015). Whatever NPY's mechanism of effect, this work indicates that chronic ethanol ingestion may be driven at least in part by negative reinforcement via alleviation of anxiety.

3.1.4 Aggression

Threatening, stressful, and aversive situations often provoke aggression. Aggression is typically modeled in rodents with the resident-intruder paradigm. An intruder animal is introduced into a resident conspecific's home cage or territory. Aggression is measured as the latency to and duration of attacks and also as the number of displays such as lunges and tail rattles. Subordinate animals – those that lose the encounter – display a suite of reactions that include avoiding the aggressor, assuming submissive postures, or attempting to escape the cage or territory.

Resident-intruder studies reveal a role for the EA in aggression. In male CD-1 mice, immunoreactivity for α -type estrogen receptors in the ventral (but not dorsal) BNST is strongly and positively correlated with aggression toward intruders, as is such immunoreactivity in the lateral septum and anterior hypothalamus (Trainor et al., 2006). Intriguingly, the role of the BNST in aggression varies depending on the external and internal environment. In California mice, aggression toward intruders is correlated with changes in BNST neural activity and possibly gene transcription only during shorter photoperiod days (Trainor et al., 2010). In females of that species, aggression toward intruders is

maximal during diestrus but lower during proestrus and estrus (Davis and Marler, 2003). c-Fos expression in the BNST (as well as the lateral septum) tracks this plasticity of aggression over the estrus cycle but it does not do so in several other subcortical brain areas examined (Davis and Marler, 2004).

The EA is also implicated in conditioned defeat. In a variation of the resident-intruder paradigm, a test animal is placed in the home cage or territory of a larger, aggressive conspecific whereupon it is typically attacked and quickly defeated. The test animal is then placed back in its home cage or territory and a *non-aggressive* intruder is introduced. The test animal typically shows defensive posturing and other submissive behaviors and declines to explore or aggress against the intruder. In a study of conditioned defeat in Syrian hamsters, temporary inactivation of the BNST just prior to defeat *training* (i.e., introduction into the aggressor conspecific's home cage) did not affect the hamsters' acquisition of conditioned defeat. However, BNST inactivation just prior to defeat *testing* (i.e., introduction of a non-aggressive intruder into the test animal's home cage) reduced defensive and submissive reactions and increased exploration of the intruder (Markham et al., 2009). CRF antagonism produces similar results (Jasnow et al., 2004). That is, decreasing BNST activity tempers the animal's defensive reactions to a situation perceived as threatening but it does not affect the animal's ability to learn that a situation is threatening. In other words, the BNST is important to the animal's *response to* a threat, but not to its perception of a situation as threatening.

Hammack et al. (2012) propose that the BNST may be a common node shared by highly overlapping circuits that subserve conditioned defeat and the related phenomenon of learned helplessness. They note that CeA manipulations do not tend to affect learned helplessness but BNST manipulations do. Given the additional observation that CeA lesions impair normal fear conditioning but BNST lesions do not, these authors propose – much as do Davis et al. (2010) about fear and anxiety – that the CeA mediates *acute* reactions to immediate and unfamiliar aversive situations that ultimately *result in*

learned helplessness, while the BNST mediates the *chronic* behavior pattern in familiar situations that *characterizes* learned helplessness.

Several other aggression-related phenomena have been linked to the EA. For example, although not strictly a form of aggression, predation is also linked to neural activity in the EA, as well as the amygdala and hypothalamus. In contrast, normal feeding on ad lib available rat chow activates hypothalamic circuitry but not the amygdala or EA areas activated by predation (Comoli et al., 2005). Also, the neural circuitry underlying anabolic steroid-induced aggression overlaps substantially with the EA-based circuitry underlying anxiety, reviewed above (Oberlander and Henderson, 2012).

To summarize, the EA is implicated in mediating aggression, a reaction not just to being threatened but also to the perception of threat. Disrupting the EA is implicated in the loss of proactive aggressive responding, i.e., failure to defend oneself from being the victim of aggression (conditioned defeat) or to act to terminate it (learned helplessness).

3.1.5 Pain perception

Animal models of the aversive nature of pain often employ conditioned place aversion. A painful stimulus such as formalin injected into a footpad is delivered in a clearly identifiable environment. The degree of aversion to the pain-associated environment is measured as the amount of time spent in that environment during free exploration. Excitotoxic lesioning of the BNST reduces pain-induced place aversion, but not nociceptive behaviors such as writhing or the elevation, licking, and shaking of the injected paw (Deyama et al., 2007). This again suggests a role for the EA in adaptive response to environmental context as opposed to specific reactions to specific stimuli.

There is intriguing overlap between EA mechanisms implicated in pain responsivity and those implicated in anxiety, stress, and stress-induced reinstatement of drug seeking. CRF, norepinephrine, and NPY in the BNST all have roles in the negative affective component of pain. For example, formalin

injection induces CRF release in the dorsolateral BNST and blocking CRF₁ and CRF₂ receptors in that structure reduces pain-conditioned place aversion. NPY injection reduces conditioned place aversion and counteracts CRF's actions. CRF's influence is recovered if NPY₁ or NPY₅ receptors are blocked (Ide et al., 2013). β_2 adrenoreceptor blockade mimics CRF receptor blockade and may act through a protein kinase A-dependent system, implicating this mechanism in the synaptic plasticity of conditioned place aversion (Deyama et al., 2008 and 2009). Injecting the α_2 agonist clonidine into the BNST also reduces pain-induced place aversion, perhaps by suppressing noradrenergic-induced activation of endogenous neurons (Deyama et al., 2011). Calcitonin gene-related peptide (CGRP) released from the parabrachial area into the central EA modulates pain responsivity (Han et al., 2010) and CGRP innervation of the EA is also linked to anxiolysis (Gungor and Pare, 2014).

Bernard's group proposes three major pain systems (Gauriau and Bernard, 2002). One originates in the deep laminae of the spinal cord and projects to the caudal reticular areas and the parabrachium, and then ultimately to the prefrontal cortex. This system mediates the attentional and motivational aspects of pain, i.e., the fact that pain signals a problem that requires response. The second system projects from lamina 1 to the thalamus and is involved in the objective perception of the fact that a painful stimulus is present. The third system entails projections from lamina 1 of the dorsal horn of the spinal cord to the lateral parabrachial nucleus and thence to the EA – particularly the sublenticular EA (Bourgeois et al., 2001) -- via the lateral capsular central amygdala. (The identity of the lateral capsular central amygdala as "nociceptive amygdala" is extensively reviewed by Neugebauer et al., 2004.) This system also sends parabrachial input more directly to the hypothalamus, the periaqueductal grey, and the ventrolateral medulla (Gauriau and Bernard, 2002). Gauriau and Bernard (2002) propose that this system "... probably contribute(s) to specific components of aversive emotions, for example, the anxiety, the fear-evoked avoidance learning, the anti-nociception, and the autonomic adjustments that occur in the face of dangerous or painful situations" (p.255). Their reference to autonomic adjustments is similar

to Koob's relating stress-induced reinstatement of drug seeking to allostasis. That is, pain becomes another context in which the EA has a role in adaptation to an aversive environment.

3.1.6 Summary

The EA is strongly implicated in effecting response to a variety of aversive situations including fear, stress, and anxiety; attempts to alleviate the negative state resulting from withdrawal, particularly by seeking more drug; aggression in reaction to perceived threats; and forming negative associations with environments in which pain is experienced. Each of these converges on the concept of negative reinforcement: supporting behaviors and reactions that avoid, lessen, or terminate aversive situations that threaten survival.

Enhancing noradrenergic input to and/or CRF signaling within the EA generally engenders aversive state and reactions thereto, while reducing CRF- or NE-mediated signaling calms aversive state. There is ample and growing evidence that NPY may counter CRF's effects in a variety of functions (see Gilpin 2012). Although research has focused heavily on CRF and NE, multiple signaling pathways are undoubtedly important. For example, there is evidence that galanin signaling affects acute-restraint stress reactions in the EA in a regionally differentiated way (Morilak et al., 2003).

In contrast to the apparent role of CeA and CeM in orchestrating *specific* reactions to a *specific* threat or other aversive cues, the BNST seems to be involved in more general *state* changes, enabling the animal to avoid, withdraw or escape from, cope with, or even surrender to the environment, in response to diffuse, contextual cues. Such state changes may help inform action selection and action production mechanisms that generate the specific behaviors and reactions that are best adaptive to the specific current internal and external milieu. ("Best" includes both learned and innate response repertoires.) Furthermore, chronic experience with stressful, aversive environments may modify EA circuitry toward hyper-responsivity to aversive situations, generating defensive and protective responses even when they are not necessarily warranted.

3.2 The extended amygdala and appetitive situations

3.2.1 Reward learning

The EA has been linked to learning operant behaviors directed at achieving rewards, i.e., to positive reinforcement. The role of the EA in this process is still unclear and has been much less studied than the role of the ventral striatum, particularly the nucleus accumbens. The EA appears to be involved in ways more subtle than generating a “reward signal” when an appetitive stimulus is encountered: Excitatory glutamatergic neurotransmission increases in the ventrolateral BNST only when cocaine or food reward is earned by operant responding, not when these rewards are passively delivered (Dumont et al., 2007). That is, the EA seems to be sensitive to the interaction between an animal’s behavior and the effect that behavior has on the environment, not just to the presence or absence of an appetitive stimulus.

Large excitotoxic lesions centered on the SLEA disrupt sensitivity to the cost of obtaining a sucrose reward, measured as the point at which responding for the reward on a progressive ratio schedule breaks down (Brown et al., 1996). Cost sensitivity is a matter of tracking perceived reward value and perceived reward cost simultaneously and then determining when cost (how much work the animal does) exceeds value (what the environment provides in return). Cost sensitivity could therefore be affected by disturbing a mechanism that represents reward cost, a mechanism that represents reward value, and/or a mechanism that compares the two. It is not clear which mechanisms were disturbed by these excitotoxic lesions, but it does appear that the lesions affected the relationship between behavior and its effect.

Structures of the EA may also be implicated in reward prediction errors: cFos activity increases in the CeA and SLEAc when a conditioned stimulus (CS) no longer predicts a reward that it used to predict

(Bucci and MacLeod, 2007). This result should be interpreted with caution as the SLEAc is close to the cholinergic cell group in the nucleus basalis of Meynert, which is thought to have an important role in attention to any salient stimuli (see, e.g., Robbins et al., 1989; Voytko, 1996). Davis et al. (2010) partially address this issue. They used fMRI scanning to study the reaction of several human brain structures to faces that were paired with positive, negative, or neutral statements about the subject. Cells in the SLEAc and neighboring dorsal amygdala increased their activity when the subject was shown faces that had been paired with either positive or negative statements, but not to faces paired with neutral statements. Although this response habituated over the course of conditioning, neural activity in response to faces paired with emotionally-significant statements remained different from the response to faces paired with neutral statements. In contrast, cells in the ventral amygdala initially increased their activity to faces paired with all three types of statement, but those responses habituated equally over the course of exposure. The authors suggest that the medial ventral amygdala is associated with attention to any novel stimulus whereas the dorsal amygdala and SLEAc respond particularly to stimuli that predict emotionally-salient events.

3.2.2 Drug addiction

As reviewed above, integrating the EA into research on drug addiction has largely focused on the aversive aspects of drug withdrawal. However, the EA is also implicated in appetitive aspects of drug addiction. Just as addictive drug ingestion increases dopamine levels in the nucleus accumbens shell, it also increases dopamine release in the BNST (Carboni et al., 2000). Blocking opiate receptors in the BNST reduces heroin self-administration (Walker et al., 2000). Blocking D1 dopamine receptors renders cocaine less effective as a reward (Epping-Jordan et al., 1998) and reduces responding for ethanol reward (Eiler et al., 2003). Blocking GABA_A receptors in both the CeA and BNST reduces ethanol self-administration (Hyytia and Koob, 1995).

Chronic opiate exposure alters expression in the BNST of several genes whose transcription products are associated with synaptic plasticity, implicating the BNST in circuit adaptation during drug exposure (Befort et al., 2008). As discussed in the context of stress induced reinstatement of drug seeking, chronic experience with addictive drugs increases excitatory drive into the BNST, especially excitation mediated by glutamate. In turn, increasing BNST activity, especially in the adBNST, changes output to the VTA, increasing the motivation to seek and consume drugs. In an appetitive context, disconnecting the *ventral* BNST from the VTA reduces cocaine-induced conditioned place *preference* in rats with no prior drug experience (Sartor and Aston-Jones, 2012).

In human brain, the SLEA is part of a circuit connecting the dorsal anterior cingulate cortex to basal forebrain structures. As connectivity between these two areas decreases, the individual's risk for nicotine addiction increases. Individual variation in this circuitry is associated with polymorphism in the gene that codes for the $\alpha 5$ subunit of the nicotinic acetylcholine receptor, a subunit important to developing nicotine addiction (Hong et al., 2010).

Research into how the EA fits into the appetitive aspects of drug addiction is in its infancy. These promising findings suggest that there is more to the role of the EA than simply mediating the aversive state brought on by withdrawal and invite further investigation.

3.2.3 Salt appetite and taste

Appetite for a specific nutrient is an iconic example of appetitive state. Most mammals have appetites for sugars and salt. Although there is apparently little research on the role of the EA in appetite for sweet tastes, there is a considerable and growing literature on its role in salt appetite. Salt appetite can be induced by salt deprivation, adrenalectomy, injection of diuretics such as furosemide coupled with salt deprivation, injection of $\alpha 2$ antagonists such as yohimbine, or injection of

mineralcorticoids such as aldosterone or DOCA. The degree of induced salt appetite is then assessed by measuring consumption of a saline solution.

Sodium depletion increases cFos immunoreactivity in cell groups along the entire EA continuum. Bilateral CeA and BNST lesions abolish salt appetite induced by yohimbine and furosemide plus salt deprivation (Johnson et al., 1999). CeA influences on salt appetite appears to be regionally specific: Lateral CeA lesions reduce salt ingestion following both mineralcorticoid injection and sodium depletion (Galaverna et al., 1992; Zardetto-Smith et al., 1994) but medial CeA lesions reduce ingestion following only mineralcorticoid injection (Nitabach et al., 1989; Schulkin et al., 1989; Galaverna et al., 1992; Zhang et al., 1993).

Figure 4 summarizes the hypothesized role of the EA in salt appetite. In their comprehensive review of central regulation of salt appetite, Geerling and Loewy (2008) note that such regulation requires the integration of two signals: a tonic “salt need” signal arising from a variety of sources and a phasic “salt detected” signal arising largely from the gustatory system. They propose the basal forebrain as the site of integration, and describe evidence that includes the EA -- specifically, the ventrolateral BNST and the CeA -- in this function. GABAergic outputs from the ventrolateral BNST appear to inhibit oxytocin release from the paraventricular hypothalamus during sodium depletion. Oxytocin inhibits salt appetite, therefore inhibiting oxytocin release disinhibits salt appetite.

There is evidence linking EA structures to taste processing in general. BNST efferents inhibit neural activity in the nucleus of the solitary tract (Smith et al., 2005) and suppress tastant-induced activity in the parabrachial nucleus, suggesting that the EA might be involved in the suppression of taste sensitivity during stress (Li and Cho, 2006). Given the growing documentation of the EA’s role in mediating salt appetite under sodium depletion – i.e., appetitive motivation under conditions of need – and its apparent influence in taste circuitry in general, it may be fruitful to examine the EA’s role in mediating behavior relevant to other appetitive tastes.

3.2.4 Reproduction

Figure 5 illustrates how the medial EA may mediate reproductive function. Data linking the BNST to male reproductive capacity in rodents, particularly rats and hamsters, go back several decades (e.g., Emery et al., 1976; Valcourt and Sachs, 1979; Powers et al., 1987). Newman (1999) reviews evidence for functionally distinct subcircuits between the BNST and medial amygdala in hamsters. She hypothesizes that connections between the anterior medial amygdala and the posterointermediate BNST mediate general behavioral arousal in response to broadcast vomeronasal and olfactory signals that signal the potential presence of a receptive female. Connections between caudal medial amygdala and posteromedial BNST affect more specific cellular activity patterns that link discrete sensory inputs with specific behavioral responses. Similarly, male gerbils have an apparently GABAergic pathway from the ventral BNST to the retrorubral fields (not shown in Figure 5) that is relevant to sexual function. The degree to which this pathway is intact correlates with the degree of integrity of copulatory and ejaculatory function, and cFos activity in ventral BNST cells increases as the rats spend more time in copulation-related activities (Simmons et al., 2011).

Successful parenting is an important component of reproduction. Maternal retrieval of pups that have strayed from the nest provides a good model of parenting; it is a relatively easily observed and quantified index of parenting competence. Rat pup retrieval is correlated with cFos activity in the BNST, among other structures (Lonstein and De Vries, 2000). Physical interaction with the pups – not just seeing, smelling, or hearing them – is necessary for cFos induction (Numan and Numan, 1995). Ventral BNST areas that show cFos activation during maternal behavior project strongly to the medial hypothalamus, the ventral tegmental area, and the retrorubral fields, areas associated with enabling different components of maternal parenting (Numan and Numan, 1997).

Excitotoxic lesioning of the ventral BNST substantially disrupts pup retrieval while similar lesions of the dorsal BNST are less effective. The rats that faltered in pup retrieval were as able as non-lesioned

and dorsal BNST-lesioned rats to hoard food items the approximate weight and size of a pup, showing that retrieval failure was specific to maternal behavior and not a general motor deficit. Rats with ventral BNST lesions were also deficient in nursing and their offspring were of significantly lower weight than the offspring of unlesioned or dorsal-BNST lesioned rats (Numan and Numan, 1996).

Rutherford et al. (2011) propose an intriguing hypothesis that parenting -- normally seen as an appetitive behavior in that it promotes species survival -- becomes an aversive, stress-inducing situation if the parent is drug addicted. They review data showing that drug exposed human and rodent mothers are deficient in offspring care. In rodents, the degree of deficiency corresponds to the degree of prior drug experience. Cues that normally elicit maternal behavior become cues that elicit stress-induced reinstatement of drug seeking. That is, the negatively-reinforced motivation for drug seeking outcompetes the positively-reinforced motivation to care for offspring. If this hypothesis bears out, and if relevant mechanisms can be linked to the EA, this would provide a particularly noteworthy example of the dynamically bivalent nature of the EA.

3.2.5 Brain stimulation reward

Rats and other animals will avidly work for electrical stimulation of the medial forebrain bundle (MFB), a reward that competes and summates with more natural rewards such as sucrose and salt (Conover and Shizgal, 1994a and 1994b; Conover et al., 1994; Shizgal and Conover, 1996). The neural activity produced by rewarding MFB stimulation is thought to be the same activity produced when an animal encounters an appetitive stimulus that satisfies some current need. Even before the animal is trained to make a response to collect stimulation, MFB stimulation promotes arousal, approach and consummatory behaviors. MFB-stimulated rats avidly explore their surroundings, sniffing and tasting. Some rats will attempt to carry away and/or ingest elements of their environment while the stimulation is being delivered. Although the neural circuitry underlying this phenomenon is still unknown, the

present author has presented a hypothesis that the network of connections rooted in the central EA may be an important part of that substrate (Waraczynski, 2006). That hypothesis has gained some empirical support.

In one experiment, local neural activity in the EA was challenged with intracerebral injections of lidocaine (Waraczynski, 2003). Lidocaine's effects were assessed by measuring changes in the stimulation pulse frequency required to maintain half of the animal's maximum rate of the response on which stimulation was contingent, a parameter called the "required frequency". Injecting lidocaine into the lateral BNST ipsilateral to the stimulation electrode shifted required frequencies to higher values -- meaning that the stimulation lost reward efficacy -- but it did so only at a high dose. In contrast, lidocaine in the ipsilateral SLEAc increased required frequency at both low and high doses. Injecting lidocaine into the medial BNST, SLEAm, and any component of the EA contralateral to the stimulation site was ineffective. Inactivating the IPAC was effective, but there were too few animals in that group to draw firm conclusions. Lidocaine's effects were specific to the EA: Injections into targets throughout the septopreoptic macrostructure, from the septum through the diagonal band of Broca to the magnocellular preoptic nucleus, were ineffective except when they encroached on the SLEAc and neighboring anterior amygdaloid area (Waraczynski, 2007).

A related study showed that injecting the GABA_A agonist muscimol and the GABA_B agonist baclofen into the SLEAc *both ipsi- and contralateral* to the stimulation site significantly increased required frequency relative to the effects of saline injections. Injections into the lateral BNST were ineffective (Waraczynski, 2008). It is informative that GABA-receptor-mediated inhibition was effective when targeted at the SLEAc contralateral to the stimulation site whereas contralateral lidocaine injections were not effective. Lidocaine would primarily inhibit local conduction through neurites by blocking ion flow through sodium channels. GABA receptor stimulation would primarily hyperpolarize local somata. We have hypothesized elsewhere (Waraczynski et al., 2012) that the rewarding nature of MFB

stimulation might depend on activation of the SLEAc, and that the SLEAc ipsi- and contralateral to the stimulation electrode may play their roles in this phenomenon in different ways. Specifically, antidromic conduction of neural activity from the MFB stimulation site to the ipsilateral SLEAc may be important to its role, but such activity would not be as important in the contralateral SLEAc. If this is so, blocking conduction in axons and axon collaterals with lidocaine in the ipsilateral SLEAc should make MFB stimulation less rewarding but doing the same in the contralateral SLEAc should not be as effective. On the other hand, inhibiting SLEAc cells via GABA receptor stimulation should be effective when directed at both hemispheres. Our data are consistent with both expectations.

Although none of the work described above targeted the CeA or CeM, an earlier electrolytic lesion experiment partly speaks to their involvement in MFB self-stimulation. Lesions of either the central or basolateral amygdala ipsilateral to the stimulation site did not change required frequency. However, required frequency increased in the data from one rat that sustained a lesion affecting the very posterolateral aspect of the SLEA, near its border with the CeA (Waraczynski et al., 1990).

Many studies of brain reward systems focus on the nucleus accumbens, particularly its shell (NAcS). Our lab has shown that stimulating NAcS dopamine D2 receptors, alone or in combination with AMPA glutamate receptor blockade, does not appreciably alter required frequency. On the other hand, these manipulations have substantial effects when directed at the SLEAc. Dopamine D1 blockade (alone or in combination with AMPA blockade) is ineffective when directed at either site (Waraczynski et al, 2010, 2012, and 2015). We are currently trying to determine which cellular mechanisms associated with D2-stimulation might account for these results. For example, D2 stimulation acts through an IP₃-linked signaling cascade to block dendritic calcium influx through CaV_{1.3} channels, rendering affected neurons less excitable. Preliminary data show that CaV_{1.3} channel functionality may be important to MFB self-stimulation, but only in the SLEAc ipsilateral to the stimulation site (unpublished data). Because such influx is usually dependent on the backpropagation of action potentials into dendrites, this finding is

consistent with our hypothesis about the different roles of the ipsilateral versus contralateral SLEAc in MFB self-stimulation. The effects of $\text{CaV}_{1.3}$ blockade are strongest 24 hours after injection of the channel blocker diltiazem, which suggests that gene transcription linked to calcium influx through these channels might be involved.

Intriguingly, it is lateral MFB stimulation that is appetitive; *medial* MFB stimulation produces the same freezing and distress often used to assess fear conditioning. It is aversive. Rats with MFB stimulation electrodes placed between the lateral and medial MFB show mixed approach and avoidance. MFB fibers arising from the SLEA tend to run in the lateral to central part of the bundle, whereas fibers arising from the BNST tend to be found in the central and medial compartments of the bundle (Nieuwenhuys et al., 1982; Veening et al., 1982). These facts, combined with the fact that challenging the SLEA impairs MFB self-stimulation more than does challenging the BNST, suggest that the SLEA might be biased toward mediating appetitive state, while the BNST may be more mixed and perhaps biased toward mediating aversive state. Investigators interested in EA mechanisms of reward may be well served to expand their focus to include the SLEA. In fact, the SLEA is gaining some traction in animal studies of reward processes. For example, SLEA efferents to the VTA show the same increases in cFos activity during cue-induced reinstatement of cocaine seeking as do ventral BNST efferents (Mahler and Aston-Jones, 2012).

The study of brain stimulation reward may hold the best promise for developing quantitative computational models of EA function. Stimulus input can be quantitatively manipulated with precision and behavioral output can be quantitatively and precisely measured. Because motivation for MFB stimulation does not satiate, long test sessions are possible, allowing one to test models by collecting large quantities of data under stable motivational conditions. There is already a strong tradition of quantitatively modeling the neural systems underlying brain stimulation reward (Gallistel, Shizgal, and Yeomans, 1981; Waraczynski et al., 1987; Gallistel and Leon, 1991; Gallistel et al., 1991; Leon and

Gallistel, 1992; Mark and Gallistel, 1993; Gallistel, 1994; Simmons and Gallistel, 1994; Shizgal, 1997; Leon and Gallistel, 1998; Conover, Fulton, and Shizgal, 01; Sonnenschein et al., 2003). Shizgal's group has proposed and continues to meticulously test and expand a sophisticated "reward mountain" model of important processes underlying MFB self-stimulation (Arvanitogiannis and Shizgal, 08; Breton et al., 2009, 2013, and 2014; Solomon et al., 2015). Empirical studies using reward mountain-based measurement promise to dissociate drug and lesion effects on an animal's estimation of stimulation value from their effects on the price that the animal is willing to pay to obtain a reward of a certain value. Recent work already provides strong evidence that altering dopaminergic neurotransmission does not appear to affect an animal's estimation of stimulus value. Rather, it affects the animal's evaluation of the price it must pay for that stimulus (defined as the density of the variable interval schedule on which the stimulation is delivered), and/or amplifies the translation of stimulation-induced neural activity into reward value (Hernandez et al., 2010 and 2012; Trujillo-Pisanty et al., 2014). In contrast, electrolytic lesions in the region of the SLEA and preoptic area can alter the reward value of MFB stimulation (Trujillo-Pisanty et al., 2013). Should the EA prove to be an important component of brain stimulation reward circuitry, combining the reward mountain model with discoveries of EA reward-relevant physiology may produce a powerful theory of reward computation in the mammalian brain.

3.2.6 Summary

Much less is known about how the EA mediates appetitive states than is known about its role in aversive states. Based on the work reviewed above, the EA seems to be involved in responding to access rewards; creating an appetitive association between addictive drug delivery and the environment in which drugs are delivered; inducing a motivation to seek and consume stimuli that satisfy current physiological needs (or, in drug addiction, stimuli that are perceived to do so); mediating procreational

behaviors; and generating an approach and consummatory orientation. It may even be part of the system by which the mammalian brain computes the value of rewards obtained through the animal's own behavior. Each of these converge on the concept of positive reinforcement: the EA is implicated in finding, interacting with, and consuming stimuli that promote survival.

Recall that in aversive situations the more rostral areas of the EA (particularly the BNST) seem to mediate broad state changes in response to contextual cues while the caudal pole (CeA and MeA) seems to mediate specific reactions to specific stimuli. It is not yet clear whether a similar topography obtains in appetitive situations, but there are indications that more rostral EA areas mediate state changes in appetitive situations as well. For example, neural activity in the BNST is associated with general behavioral arousal in male rats exposed to female pheromones and with a general motivation to seek and consume salt in sodium depleted animals. When the SLEAc is functionally compromised, rats lose some of the arousal, exploratory, and approach orientation generated by MFB stimulation and they are less sensitive to the effort costs associated with earning a reward. These data encourage further investigation of the EA's role in appetitive state. In particular, it may be fruitful to make the SLEA a target for the optogenetic-based circuit dissection that has proven so productive in the study of BNST-based circuitry.

4.0 Where does the EA fit in basal forebrain organization?

It is almost certain that the amygdala, extended amygdala, and striatopallidum have unique yet parallel roles in adaptive responding. The basal forebrain is characterized by looping circuitry that activates a progressively larger set of circuits and systems during the execution of goal-directed behaviors. Manella et al. (2013) speculate on the phylogenetic origin of such concentric looping in their model of the evolutionary trajectory of a proposed goal valuation and selection mechanism. They propose that the evolutionarily oldest system is one that “energizes” simple, innate instrumental and

Pavlovian responses to particular stimuli, and ascribe this function to the ventral striatum. Next, an amygdala-based system evolved that enabled more complex Pavlovian learning, one that relies on the capacity to store and access information about stimuli and action outcomes encountered in the past. The most recent system, ascribed largely to mammalian and particularly primate brain, incorporates basal ganglia and frontal cortex circuitry. It facilitates the capacity to link multiple outcome representations with action representations, allowing the organism to anticipate future stimulus-response events and to choose among multiple behavioral options. As each system evolved it integrated itself into the already-existing systems, creating the looping circuitry observed in the mammalian brain.

Figure 6 illustrates a suggestion of such an organization that incorporates the extended amygdala. There is considerable evidence that the cortical and basolateral amygdala receive multimodal sensory input and give “state value” to environmental cues (see Murray, 2007 and Morrison and Salzman, 2010 for reviews). That is, activity in these nuclei signals the value of a stimulus *relative to the current need for or importance of* that stimulus. For example, cues of food presence elicit cortical and basolateral amygdala activity only to the degree that food is currently important to the animal. A food cue would not elicit much activity in a sated animal but it does in a hungry animal. (In contrast, threat cues should almost always provoke appropriate avoidance and escape reactions.)

The central and medial amygdala form both a structural and a functional transition zone between the cortical and basolateral amygdala and the EA. Via their own connections with hypothalamic and brainstem cell groups, they orchestrate acute, stimulus-specific reactions to specific emotionally and motivationally salient stimuli. Yet they are also part of the EA, in that they work with EA cell groups in the IPAC, SLEA, and BNST to evoke more lasting and general state changes. Murray (2007) proposes that the basolateral amygdala mediates specific affective reactions to specific sensory properties of a reinforcer (positive or negative) while the CeA mediates a more general affective reaction that helps promote actions and autonomic responses appropriate to a particular situation. The present model

expands on Murray's to impute response and action promotion to the entire EA. As described above and by others (e.g., McDonald, 2003) the EA is striatopallidal-like as well as amygdala-like. In this model, the major functional difference between EA and striatopallidum is that the former selects a constellation of approach or avoidance/escape patterns appropriate to a situation, while the latter selects and orchestrates specific skeletomotor action patterns. Pertinent to Zahm's (1998, 2000, 2001) characterization of the accumbens shell as transitional between EA and striatopallidum, the EA may well work in concert with the ventral striatopallidum to include overt action patterns in the constellation of situation-appropriate responses. In both the EA and striatopallidum, response and action selection are undoubtedly sculpted by learning experiences.

As a nexus between amygdala-centered Pavlovian reactions and striatopallidal-centered operant response selection, the EA may be an important structure for mediating Pavlovian to instrumental transfer (PIT), assuming the functions imputed by Corbit and Balleine (2005) to the CeA alone. In PIT, conditioned stimuli that elicit conditioned responses become discriminative stimuli that signal the occasion for particular operant responses. Classically conditioned appetitive cues enhance operant responses for positive reinforcement and retard responses maintained by negative reinforcement. Classically conditioned aversive cues do the opposite. As an animal gains experience with particular reliable conditioned stimuli, those specific stimuli can set the occasion for specific operant responses. Mannella et al. (2013) review evidence that an amygdala-to-nucleus accumbens circuit is important to PIT, yet this evidence is based in research that has not considered the swath of tissue lying between the amygdala and the accumbens, the EA. Their review clearly supports the amygdala's role in stimulus detection and valancing, and the ventral striatum's role in learning appropriate instrumental responses. However, with little data to support the conjecture, they attribute to the NAc the capacity to put the value of multiple potential outcomes of different quality into a common currency prior to outcome selection and action enabling. There is quantitative evidence that rewarding MFB stimulation shares

such a common currency with other appetitive stimuli such as saline (for sodium-depleted animals) and sucrose (see references in section 3.2.5). If, as data reviewed above suggest, the EA is relevant to MFB stimulation reward, perhaps it is the EA that translates stimuli into this common motivational currency.

5.0 How might research into EA function be unified?

It may be productive to see the EA continuum as a collection of neural ensembles, each of which controls a particular component of adaptive responding to particular aversive or appetitive situations. Neural ensemble modeling is increasingly successful in capturing how brain systems represent sensory input and percepts and how brain systems perform action selection and execution. These are often modeled as vectors of activity within and among neural populations. There are several advantages to building such mathematical models, including the fact that models help make predictions that are not obvious or that cannot even be generated from verbal models. Building such a model requires determining which inputs activate which ensembles with what resulting activity state, how global ensemble activity patterns shift as the exigencies of the animal's internal and external environment shift, and how those activity patterns create output that informs response production.

That the EA is capable of such modular and dynamic activity is already demonstrated. Examples reviewed above include the following: (1) Separate EA microcircuits are responsible for various components of anxiety reactions in open field and elevated maze environments; (2) the way in which β adrenergic receptor activation affects consequent BNST activity status during stress depends on the BNST's prior experience with noradrenergic input; (3) aggression in California mice is affected by EA circuitry whose activity status depends on photoperiod and estrus status; (4) EA circuits relevant to drug and ethanol abuse change their dynamics as the organism gains experience with a particular drug; (5) EA circuits relevant to salt appetite are responsive to changes in mineralcorticoid concentrations.

Computational modeling of neural ensemble dynamics has contributed substantially to our understanding of how the striatopallidum orchestrates action sequences. Borrowing from that tradition may be very useful in our analysis of the EA. Medium spiny neurons of the dorsal and ventral striatum have been described as “decision surfaces” specialized for learning pattern recognition and producing appropriate action sequences (Houk, 2005). Perhaps medium spiny neurons of the EA work similarly, selecting and producing situation-appropriate approach or avoidance response constellations. Figures 2 through 5 illustrate how EA ensemble activity state changes with environmental input, and how those state changes are correlated with functional change.

Experience with the environment sculpts the way in which striatal ensembles respond to recurring inputs, to help the organism adapt its response repertoire to commonly encountered (i.e., predictable) environments. Once thus sculpted, the ensembles then remain relatively permanent in the response patterns they coordinate, as long as the environment remains relatively constant and predictable. In contrast, ensembles that evaluate and respond to the environment’s appetitive or aversive nature relative to state – ensembles imputed here to the EA – might remain more labile. They should be dynamically responsive to internal and external environments that are in constant flux and that present unique and novel situations throughout the organism’s life time. For example, a food item of a particular caloric or salt content will vary in survival value depending on how recently the animal has eaten, its current nutrient level status, the acute importance of other needs such as attention to potential threats, and so on. EA ensembles can, however, be sculpted by environmental experience, as evidenced by the effects of drug and stress experience on EA activity state during drug withdrawal.

How does the EA mediate responses to both aversive and appetitive state? Recall that activating glutamatergic BNST outputs to the VTA engenders aversive state while activating GABAergic outputs engenders appetitive state (Jennings et al., 2013). The EA continuum has a large population of GABAergic medium spiny projection neurons and a somewhat smaller population of aspiny

glutamatergic projection neurons (Cassell et al., 1999). In addition, neurons that are usually classified as GABAergic – based on their expression of glutamate decarboxylase (GAD) and the vesicular GABA transporter (VGAT) -- have been found to release both GABA and glutamate (see, for example, Seal and Edwards, 2006 for a review). In the EA specifically, the majority (approximately 90%) of neurons that project from the BNST to the VTA are exclusively GABAergic but a minority (approximately 7%) appear to release glutamate along with GABA (Kudo et al., 2012; see also Geisler et al., 2007 and Jalabert et al., 2009). Glutamatergic phenotype is usually determined by immunohistochemically detecting one of several vesicular glutamate transporters (VGLUT). It may be important to note that Jennings et al. (2013) achieved their selective activation of BNST-to-VTA neurons by using Cre-recombinant VGAT (to target GABAergic neurons) and VGLUT-2 (to target glutamatergic neurons) transgenic mouse lines. GABAergic neurons that also release glutamate often carry the VGLUT-3 transporter rather than VGLUT-2 (Fremeau et al., 2002; Kudo et al., 2012). Therefore, optogenetically stimulating “GABAergic” neurons by targeting neurons expressing VGAT may stimulate GABAergic neurons that release only GABA *and* “dual phenotype” neurons that release both GABA and glutamate. That is, we should be very careful in assuming that optogenetically-stimulated “GABAergic” neurons are neurons that release GABA exclusively, a situation these researchers acknowledge (see Stuber et al., 2015).

In the natural state, dual phenotype neurons may release glutamate only under particular circumstances. For example, transmitter release in a circuit connecting the preoptic area to GnRH neurons in the hypothalamus is both photoperiod- and hormone-level dependent: the neurons transition from GABAergic to glutamatergic phenotype in the afternoon, but only in rats exposed to estrogen (Ottem et al., 2004). Or, both neurotransmitters may be released simultaneously, probably from separate release sites, to affect functions such as fine-tuning emerging inhibitory circuits (Noh et al., 2010) or modulating postsynaptic response to excitatory drive (Chance et al., 2002). In short, in the natural state, tipping the balance between aversive state and appetitive state is undoubtedly more

complicated than promoting the release of glutamate or GABA, respectively, but that distinction gives us something to start with.

Bissonette et al. (2014) recently reviewed the role of several brain areas and systems that are involved in both appetitive and aversive experience. They note that a system or group of cells that subserves both types of experience must show either a population-based distinction in neural activity across valences (some cells respond to appetitive stimuli and some to aversive) or an activity status-based distinction (a unitary group of cells with different response profiles for aversive versus appetitive stimuli). The extended amygdala appears to be a key player in an organism's ability to monitor its internal and external environment relative to its current survival needs and to flexibly alter its behavioral state to maximize survival chances. Following the stipulation of Bissonette et al., the particular response set that should be potentiated (food seeking, mate seeking, threat avoidance, etc.) may be encoded in unique activity patterns across the full range of the extended amygdala macrostructure or in activity in one set of cells for appetitive responding and another set for aversive responding. Given what we do know of EA circuitry, the population-based distinction seems more likely. Particular cell subpopulations – defined by the specific inputs that affect them and the specific outputs that they regulate – are likely devoted to particular response patterns. For example, the cells in the posterior BNST that are involved in stress and anxiety reactions are probably different from the posterior BNST cells involved in reproductive functions. On the other hand, the cells of the ventral BNST that regulate oxytocin release during salt appetite might also be operative in controlling oxytocin release during parenting behaviors. The distinction in that case might be between the specific inputs to the ventral BNST neurons whose axons project to hypothalamic cells regulating oxytocin release. In short, the particular response(s) evoked by the EA at any one time are likely a function of the unique pattern of neural activity across the entire structure.

We have a comparatively extensive knowledge of striatopallidal organization and physiology, a knowledge base that informs ensemble-based modeling. A similar knowledge base for the EA is needed. For example, does the EA have the equivalent of the D1-dominated direct path and D2-dominated indirect path organization characteristic of the striatum? Cassell et al. (1999) suggest that such a distinction does exist in EA. Are some EA neurons more prone to long term synaptic plasticity than others, as may be true in the striatum? How does the fact that the EA differs from the striatopallidum in interneuron population (Zahm et al., 2003) make the EA functionally different from the striatopallidum? Perhaps the striatopallidum uses interneuron-mediated interconnectivity to make sure that only one action pattern is potentiated while other, incompatible patterns remain inhibited. In contrast, the EA may be able to evoke multiple and even bivalent (“approach/avoidance”) reactions simultaneously to create a unique reaction constellation specifically tuned to the current situation.

It will take many years of work to begin to answer these questions and apply those answers to a comprehensive model of the role of the EA in adaptive responding. This review invites investigators who study particular EA subsystems (fear and anxiety; drug withdrawal; stress-induced reinstatement; reward function) to place their discoveries into a comprehensive framework such as the one proposed here, and to relate their discoveries of specific circuitry to the operation of the EA as a holistic entity.

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References

- Alheid, G.F., 2003. Extended amygdala and basal forebrain. *Ann NY Acad Sci* 985, 185-205.
- Alheid, G.F, Heimer, L., 1988. New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. *Neurosci* 27, 1-39.
- Alheid, G.F., Heimer, L., 1996. Theories of basal forebrain organization and the 'emotional motor system'. *Prog Brain Res* 107, 461-484.
- Arvanitogiannis A., Shizgal P., 2008. The reinforcement mountain: allocation of behavior as a function of the rate and intensity of rewarding brain stimulation. *Behav Neurosci* 122, 1126-1138.
- Aston-Jones, G., Delfs, J., Druhan, J., Zhu, Y., 1999. The bed nucleus of the stria terminalis: a target site for noradrenergic actions in opiate withdrawal. *Ann NY Acad Sci* 877, 486-498.
- Balleine, B.W., Killcross, S., 2006. Parallel incentive processing: an integrated view of amygdala function. *Trends Neurosci* 29, 272-279.
- Befort, K., Filliol, D., Ghat, A., Darq, E., Matifas, A., Muller, J., Lardenois, A., Thibault, C., Dembele, D., Le Merrer, J., Becker, J.A.J., Poch, O., Kieffer, B.L., 2008. Mu-opioid receptor activation induces transcriptional plasticity in the central extended amygdala. *Eur J Neurosci* 27, 2973-2984.

Bissonette, G.B., Gentry, R.N., Padmala, S., Pessoa, L., Roesch, M.R., 2014. Impact of appetitive and aversive outcomes on brain responses: linking the animal and human literatures. *Front Sys Neurosci* 8, 1-15.

Bourgeois, L., Gauriau, C., Bernard, J.-F., 2001. Projections from the nociceptive area of the central nucleus of the amygdala to the forebrain: a PHA-L study in the rat. *Eur J Neurosci* 14, 229-255.

Breton Y.A., Conover K., Shizgal P., 2014. The effect of probability discounting on reward seeking: a three-dimensional perspective. *Front Behav Neurosci* 8, 284.

Breton Y.A., Marcus J.C., Shizgal P., 2009. *Rattus Psychologicus*: construction of preferences by self-stimulating rats. *Behav Brain Res* 202, 77-91.

Breton Y.A., Mullett A., Conover K., Shizgal P., 2013. Validation and extension of the reward-mountain model. *Front Behav Neurosci* 7, 125

Brown, V.J., Latimer, M.P., Winn, P., 1996. Memory for the changing cost of a reward is mediated by the sublenticular extended amygdala. *Brain Res Bull* 39, 163-170.

Bucci, D.J., MacLeod, J.E., 2007. Changes in neural activity associated with a surprising change in the predictive validity of a conditioned stimulus. *Eur J Neurosci* 26, 2669-2676.

Bupesh, M., Abellan, A., Medina, L., 2011a. Genetic and experimental evidence supports the continuum of the central extended amygdala and a multiple embryonic origin of its principle neurons. *J Comp Neurol* 519, 3507-3531.

Bupesh, M., Legaz, I., Abellan, A., Medina, L., 2011b. Multiple telencephalic and extratelencephalic embryonic domains contribute neurons to the medial extended amygdala. *J Comp Neurol* 519, 1505-1525.

Carboni, E., Silvagni, A., Rolando, M.T.P., Di Chiara, G., 2000. Stimulation of *in vivo* dopamine transmission in the bed nucleus of the stria terminalis by reinforcing drugs. *J. Neurosci* 20, RC102 (1-5).

Cassell, M.D., Freedman, L.J., Shi, C., 1999. The intrinsic organization of the central extended amygdala. *Ann NY Acad Sci* 877, 217-241.

Chance, F.S., Abbott, L.F., Reyes, A.D., 2002. Gain modulation from background synaptic input. *Neuron* 35, 773-782.

Choi, D.C., Furay, A.R., Evanson, N.K., Ostrander, M.M., Ulrich-Lai, Y.M., Herman, J.P., 2007. Bed nucleus of the stria terminalis subregions differentially regulate hypothalamic-pituitary-adrenal axis activity: implications for the integration of limbic inputs. *J Neurosci* 27, 2025-2034.

Christianson, A.M., Herman, J.P., Ulrich-Lai, Y.M., 2011a. Regulatory interactions of stress and reward on rat forebrain opiodergic and GABAergic circuitry. *Stress* 14, 205-215.

Christianson, J.P., Jennings, J.H., Ragole, T., Flyer, J.G.N., Benison, A.M., Barth, D.S., Watkins, L.R., Maier, S.F., 2011b. Safety signals mitigate the consequences of uncontrollable stress via a circuit involving the sensory insular cortex and bed nucleus of the stria terminalis. *Biol Psychiatry* 70, 458-464.

Comoli, E., Ribiero-Barbosa, E.R., Negrao, N., Goto, M., Canteras, N.S., 2005. Functional mapping of the prosencephalic systems involved in organizing predatory behavior in rats. *Neurosci* 130 1055-1067.

Conover K.L., Fulton S., Shizgal P., 2001. Operant tempo varies with reinforcement rate: implications for measurement of reward efficacy. *Behav Processes* 56, 85-101

Conover, K., Shizgal, P., 1994a. Competition and summation between rewarding effects of sucrose and lateral hypothalamic stimulation in the rat. *Behav Neurosci* 108, 537-548.

Conover K.L., Shizgal P., 1994. Differential effects of postingestive feedback on the reward value of sucrose and lateral hypothalamic stimulation in rats. *Behav Neurosci* 108, 559-572.

Conover K.L., Woodside B., Shizgal P., 1994. Effects of sodium depletion on competition and summation between rewarding effects of salt and lateral hypothalamic stimulation in the rat. *Behav Neurosci* 108, 549-558.

Corbit, L.H., Balleine, B.W., 2005. Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of Pavlovian-instrumental transfer. *J Neurosci* 25, 962-970.

Cui, C., Noronha, A., Morikawa, H., Alvarez, V.A., Stuber, G.D., Szumlinski, K.K., Kash, T.L., Roberto, M., Wilcox, M.V., 2013. New insights on neurobiological mechanisms underlying alcohol addiction. *Neuropharm* 67, 223-232.

Cullinan, W.E., Herman, J.P., Watson, S.J., 1993. Ventral subicular interaction with the hypothalamic paraventricular nucleus: evidence for a relay in the bed nucleus of the stria terminalis. *J Comp Neurol* 332, 1-20.

Davis E.S., Marler C.A., 2003. The progesterone challenge: steroid hormone changes following a simulated territorial intrusion in female *Peromyscus californicus*. *Horm Behav* 44, 185–198.

Davis, E.S., Marler, C.A., 2004. c-FOS changes following an aggressive encounter in female California mice: a synthesis of behavior, hormone changes and neural activity. *Neurosci* 127, 611-624.

Davis, F.C., Johnstone, T., Mazzula, E.C., Oler, J.A., Whalen, P.J., 2010. Regional response differences across the human amygdaloid complex during social conditioning. *Cerebral Cortex* 20, 612-621.

Davis, M., 1998. Are different parts of the extended amygdala involved in fear versus anxiety? *Biol Psychiatry* 44, 1239-1247.

Davis, M., Shi, C., 1999. The extended amygdala: are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear versus anxiety? *Ann NY Acad Sci* 877, 309-338.

Davis, M., Walker, D.L., Miles, L., Grillon, C., 2010. Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. *Neuropsychopharm Rev* 35, 105-135.

Deacon, T.W., Pakzaban, P., Isacson, O., 1994. The lateral ganglionic eminence is the origin of cells committed to striatal phenotypes: neural transplantation and developmental evidence. *Brain Res* 668, 211-219.

Delfs, J.M., Zhu, Y., Druhan, J.P., Aston-Jones, G., 2000. Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. *Nature* 403, 430-434.

de Olmos, J., Beltramino, C.A., Alheid, G., 2004. Amygdala and extended amygdala of the rat: a cytoarchitectonical, fibroarchitectonical, and chemoarchitectonical survey, in: Paxinos, G. (Ed), *The Rat Nervous System*, 3rd edition, Elsevier Academic Press, San Diego, 509-603.

de Olmos, J., Heimer, L., 1999. The concepts of the ventral striatopallidal system and extended amygdala. *Ann NY Acad Sci* 877, 1-32.

Deyama, S., Nakagawa, T., Kaneko, S., Uehara, T., Minami, M., 2007. Involvement of the bed nucleus of the stria terminalis in the negative affective component of visceral and somatic pain in rats. *Behav Brain Res* 176, 367-371.

Deyama, S., Katayama, T., Ohno, A., Nakagawa, T., Kaneko, S., Yamaguchi, T., Yoshioka, M., Minami, M., 2008. Activation of the β -adrenoreceptor-protein kinase A signaling pathway within the ventral bed

nucleus of the stria terminalis mediates the negative affective component of pain in rats. *J Neurosci* 28, 7728-7736.

Deyama, S., Katayama, T., Kondoh, N., Nakagawa, T., Kaneko, S., Yamaguchi, T., Yoshioka, M., Minami, M., 2009. Role of enhanced noradrenergic transmission within the ventral bed nucleus of the stria terminalis in visceral pain-induced aversion in rats. *Behav Brain Res* 197, 279-283.

Deyama, S., Ide, S., Kondoh, N., Yamaguchi, T., Yoshioka, M., Minami, M., 2011. Inhibition of noradrenaline release by clonidine in the ventral bed nucleus of the stria terminalis attenuates pain-induced aversion in rats. *Neuropharm* 61, 156-160.

Dong H., Petrovich G.D., Swanson L.W., 2000. Organization of projections from the juxtacapsular nucleus of the BST: a PHAL study in the rat. *Brain Res* 859, 1–14.

Dong H., Petrovich G.D., Swanson L.W., 2001a. Topography of projections from amygdala to bed nuclei of the stria terminalis. *Brain Res Rev* 38, 192–246.

Dong, H., Petrovich, G.D., Watts, A.G., Swanson, L.W., 2001b. Basic organization of projections from the oval and fusiform nuclei of the bed nuclei of the stria terminalis in adult rat brain. *J Comp Neurol* 436, 430-455.

Dong, H., Swanson, L.W., 2003. Projections from the rhomboid nucleus of the bed nuclei of the stria terminalis: implications for cerebral hemisphere regulation of Ingestive behaviors. *J Comp Neurol* 463, 434-472.

Dong, H., Swanson, L.W., 2004a. Organization of axonal projections from the anterolateral area of the bed nuclei of the stria terminalis. *J Comp Neurol* 468, 277-298.

Dong, H., Swanson, L.W., 2004b. Projections from bed nuclei of the stria terminalis, posterior division: implications for cerebral hemisphere regulation of defensive and reproductive behaviors. *J Comp Neurol* 471, 396-433.

Dong, H., Swanson, L.W., 2006a. Projections from bed nuclei of the stria terminalis, dorsomedial nucleus: implications for cerebral hemisphere integration of neuroendocrine, autonomic, and drinking responses. *J Comp Neurol* 494, 75-107.

Dong, H., Swanson, L.W., 2006b. Projections from bed nuclei of the stria terminalis, anteromedial area: cerebral hemisphere integration of neuroendocrine, autonomic, and behavioral aspects of energy balance. *J Comp Neurol* 494, 142-178.

Dumont, E.C., Mark, G.P., Mader, S., Williams, J.T., 2005. Self-administration enhances excitatory synaptic transmission in the bed nucleus of the stria terminalis. *Nature Neurosci* 8, 413-414.

Eiler, W.J.A., Seyoum, R., Foster, K.L., Mailey, C., June, H.L., 2003. D₁ dopamine receptor regulates alcohol-motivated behaviors in the bed nucleus of the stria terminalis in alcohol-preferring (P) rats. *Synapse* 48, 45-56.

Emery, D.E., Sachs, B.D., 1976. Copulatory behavior in male rats with lesions in the bed nucleus of the stria terminalis. *Physiol Behav* 52, 803-806.

Epping-Jordan, M.P., Markou, A., Koob, G.F., 1998. The dopamine D-1 receptor antagonist SCH 23390 injected into the dorsolateral bed nucleus of the stria terminalis decreased cocaine reinforcement in the rat. *Brain Res* 784, 105-115.

Erb, S., 2010. Evaluation of the relationship between anxiety during withdrawal and stress-induced reinstatement of cocaine seeking. *Prog Neuro-Psychopharmacol and Biol Psychiat* 34, 798-807.

Fendt, M., Endres, T., Apfelbach, R., 2003. Temporary inactivation of the bed nucleus of the stria terminalis but not of the amygdala blocks freezing induced by trimethylthiazoline, a component of fox feces. *J Neurosci* 23, 23-28.

Flavin, S.A., Winder, D.G., 2013. Noradrenergic control of the bed nucleus of the stria terminalis in stress and reward. *Neuropharm* 70, 324-330.

Freneau, R.T., Burman, J., Qureshi, T., Tran, C.H., Proctor, J., Johnson, J., Zhang, H., Sulzer, D., Copenhagen, D.R., Storm-Mathisen, J., Reimer, R.J., Chaudry, F.A., Edwards, R.H., 2002. The identification of vesicular glutamate transporter 3 suggests novel modes of signaling by glutamate. *PNSA* 99, 14488-14493.

Frenois, F., Cador, M., Caille, S., Stinus, L., Le Moine C., 2002. Neural correlates of the motivational and somatic components of naloxone-precipitated morphine withdrawal. *Eur J Neurosci* 16, 1377-1389.

Frenois, F., Stinus, L., Di Blasi, F., Cador, M., Le Moine C., 2005. A specific limbic circuit underlies opiate withdrawal memories. *J Neurosci* 25, 1366-1374.

Galaverna, O., De Luca, L.A., Schulkin, J., Yao, S.Z., Epstein, A.N., 1992. Deficits in NaCl ingestion after damage to the central nucleus of the amygdala in the rat. *Brain Res Bull* 28, 89-98.

Gallistel, C.R., 1994. Foraging for brain stimulation: toward a neurobiology of computation. *Cognition* 50, 151-170.

Gallistel, C.R., Leon, M., 1991. Measuring the subjective magnitude of brain stimulation reward by titration with rate of reward. *Behav Neurosci* 105, 913-925.

Gallistel, C.R., Leon, M., Waraczynski, M., and Hanau, M.S., 1991. Effect of current on the maximum possible reward. *Behav Neurosci* 105, 901-912.

Gallistel, C.R., Shizgal, P., Yeomans, J.S., 1981. A portrait of the substrate for self-stimulation, *Psych. Rev.* 88, 228-273.

Garcia-Lopez, M., Abellan, A., Legaz, I., Rubenstein, J.L.R., Puellas, L., Medina, L., 2008. Histogenic compartments of the mouse centromedial and extended amygdala based on gene expression patterns during development. *J Comp. Neurol* 506, 46-74.

Gauriau, C., Bernard, J.-F., 2002. Pain pathways and parabrachial circuits in the rat. *Exp Physiol* 87, 251-258.

Geerling, J.C., Loewy, A.D., 2008. Central regulation of sodium appetite. *Exp Physiol* 93, 177-209.

Geisler, S., Derst, C., Veh, R.W., Zahm, D.S., 2007. Glutamatergic afferents of the ventral tegmental area in the rat. *J. Neurosci* 27, 5730-5743.

Gilpin, N.W., 2012. Neuropeptide Y (NPY) in the extended amygdala is recruited during the transition to alcohol dependence. *Neuropeptides* 46, 253-259.

Gilpin, N.W., Misra, K., Herman, M.A., Cruz, M.T., Koob, G.F., Roberto, M., 2011. Neuropeptide Y opposes alcohol effects on gamma-aminobutyric acid release in amygdala and blocks the transition to alcohol dependence. *Bio Psychiatry* 69, 1091-1099.

Gilpin, N.W., Roberto, M., 2012. Neuropeptide modulation of central amygdala neuroplasticity is a key mediator of alcohol dependence. *Neurosci Biobehav Rev* 36, 873-888.

Grove, E.A., 1988a. Neural associations of the substantia innominate in the rat: afferent connections. *J Comp Neurol* 277, 315-346.

Grove, E.A., 1988b. Efferent connections of the substantia innominata in the rat. *J Comp Neurol* 277, 347-364.

Gungor, N.Z., Pare, D., 2014. CGRP inhibits neurons of the bed nucleus of the stria terminalis: implications for the regulation of fear and anxiety. *J Neurosci* 34, 60-65.

Hammack, S.E., Cooper, M.A., Lezak, K.R., 2012. Overlapping neurobiology of learned helplessness and conditioned defeat: implications for PTSD and mood disorders. *Neuropharm* 62, 565-575.

Han, J.S., Adwanikar, H., Li, Z., Ji, G., Neugebauer, V., 2010. Facilitation of synaptic transmission and pain responses by CGRP in the amygdala of normal rats. *Molec Pain* 6, 1-14.

Hasue, R.H., Shammah-Lagnado, S.J., 2002. Origin of the dopaminergic innervation of the central extended amygdala and accumbens shell: a combined retrograde tracing and immunohistochemical study in the rat. *J Comp Neurol* 454, 15-33.

Heimer, L., Harlan, R.E., Alheid, G.F., Garcia, M.M., de Olmos, J., 1997. Substantia innominata: a notion which impedes clinical-anatomical correlations in neuropsychiatric disorders. *Neurosci* 76, 957-1006.

Heimer L., Zahm D.S., Alheid G.F., 1995. Basal ganglia, in: Paxinos G. (Ed), *The Rat Nervous System*, 2nd edition, Academic Press, New York, 579-628.

Hernandez, G., Breton, Y.-A., Conover, K., Shizgal, P., 2010. At what stage of neural processing does cocaine act to boost pursuit of rewards? *PLoS One* 5, e15081.

Hernandez G., Trujillo-Pisanty I., Cossette M-P., Conover K. & Shizgal P., 2012. Role of dopamine tone in the pursuit of brain stimulation reward. *J Neurosci* 32, 11032-41.

Hong, L.E., Hodgkinson, C.A., Yang, Y., Sampath, H., Ross, T.J., Buchholz, B., Salmeron, B.J., Srivastava, V., Thaker, G.K., Goldman, D., Stein, E.A., 2010. A genetically modulated, intrinsic cingulate circuit supports human nicotine addiction. *PNAS* 107, 13509-13514.

Houk, J.C., 2005. Agents of the mind. *Biol Cybern* 92, 427-437.

Hyttia, P., Koob, G.F., 1995. GABA_A receptor antagonism in the extended amygdala decreases ethanol self-administration in rats. *Eur J Pharmacol* 283, 151-159.

Jalabert, M., Aston-Jones, G., Herzog, E., Manzoni, O., Georges, F., 2009. Role of the bed nucleus of the stria terminalis in the control of ventral tegmental area dopamine neurons. *Prog Neuro-Psychopharmacol and Biol Psychiat* 33, 1336-1346.

Janak, P.H., Tye, K.M., 2015. From circuits to behaviour in the amygdala. *Nature* 517, 284-292.

Jasnow A.M., Davis M., Huhman K.L., 2004. Involvement of central amygdalar and bed nucleus of the stria terminalis corticotropin-releasing factor in behavioral responses to social defeat. *Behav Neurosci* 118, 1052–61.

Jennings, J.H., Sparta, D.R., Stamatakis, A.M., Ung, R.L., Pleil, K.E., Kash, T.L., Stuber, G.D., 2013. Distinct extended amygdala circuits for divergent motivational states. *Nature* 496, 224-228.

Johansen, J.P., Wolff, S.B., Luthi, A., LeDoux, J.E., 2012. Controlling the elements: an optogenetic approach to understanding the neural circuits of fear. *Biol Psychiatry* 71, 1053-1060.

Johnson, A.K., de Olmos, J., Pastuskovas, C.V., Zardetto-Smith, A.M., Vivas, L., 1999. The extended amygdala and salt appetite. *Annals NY Acad Sci* 877, 258-280.

Johnson, J.B., 1923. Further contributions to the study of the evolution of the forebrain. *J Comp Neurol* 35, 337-481.

Kash, T.L., 2012. The role of biogenic amine signaling in the bed nucleus of the stria terminalis in alcohol abuse. *Alcohol* 46, 303-308.

Kim, S.-Y., Adhikari, A., Lee, S.Y., Marshel, J.H., Kim, C.K., Mallory, C.S., Lo, M., Pak, S., Mattis, J., Lim, B.K., Malenka, R.C., Warden, M.R., Neve, R., Tye, K.M., Deisseroth, K., 2013. Diverging neural pathways assemble a behavioral state from separable features in anxiety. *Nature* 496, 219-223.

Koob, G.F., 2008a. A role for brain stress systems in addiction. *Neuron* 59, 11-34.

Koob, G.F., 2008b. Hedonic homeostatic dysregulation as a driver of drug-seeking behavior. *Drug Discovery Today: Disease Models* 5, 207-215.

Koob, G.F., 2009a. Dynamics of neuronal circuits in addiction: reward, antireward, and emotional memory. *Pharmacopsychiatry* 42, S32-S41.

Koob, G.F., 2009b. Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharm* 56, 18-31.

Koob, G.F., 2009c Brain stress systems in the amygdala and addiction. *Brain Res* 1293, 61-75.

Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharm* 24, 97-129.

Kudo, T., Uchigashima, M., Miyazaki, T., Konno, K., Yamasaki, M., Yanagawa, Y., Minami, M., Watanabe, M., 2012. Three types of neurochemical projection from the bed nucleus of the stria terminalis to the ventral tegmental area in adult mice. *J Neurosci* 32, 18035-18046.

Lammel, S., Lim, B.K., Ran, C., Huang, K.W., Betley, M.J., Tye, K.M., Deisseroth, K., Malenka, R.C., 2012. Input-specific control of reward and aversion in the ventral tegmental area. *Nature* 491, 212-217.

LeDoux, J., 2007. The amygdala. *Curr Biol* 17, R868-874.

Lee, Y., Davis, M., 1997. Role of the hippocampus, the bed nucleus of the stria terminalis, and the amygdala in the excitatory effect of corticotropin-releasing hormone on the acoustic startle reflex. *J Neurosci* 17, 6434-6446.

Leon, M., Gallistel C.R., 1992 The function relating the subjective magnitude of brain stimulation reward to stimulation strength varies with the site of stimulation. *Behav Brain Res* 52, 183-193.

Leon, M. and Gallistel, C.R., 1998. Self-stimulation rats combine subjective reward magnitude and subjective reward rate multiplicatively. *J Exp Psychol Anim Behav Process* 24, 265-277.

Li, C.-S., Cho, Y.K., 2006. Efferent projection from the bed nucleus of the stria terminalis suppresses activity of taste-responsive neurons in the hamster parabrachial nuclei. *Am J Physiol Regul Integr Comp Physiol* 291, R914-R926.

Lonstein, J.S., De Vries, G.J., 2000. Maternal behavior in lactating rats stimulates c-fos in glutamate decarboxylase-synthesizing neurons of the medial preoptic area, central bed nucleus of the stria terminalis, and ventrocaudal periaqueductal grey. *Neurosci* 100, 557-568.

Mahler, S.V., Aston-Jones, G.S., 2012. Fos activation of selective afferents to ventral tegmental area during cue-induced reinstatement of cocaine seeking in rats. *J Neurosci* 32, 13309-13325.

Mannella, F., Gurney, K., Baldassarre, G., 2013. The nucleus accumbens as a nexus between values and goals in goal-directed behavior: a review and new hypothesis. *Front Behav Neurosci* 7, 1-29.

Mark, T.A. and Gallistel, C.R., 1993. Subjective reward magnitude of medial forebrain stimulation as a function of train duration and pulse frequency. *Behav Neurosci* 107, 389-401.

Markham, C.M., Norvelle, A., Huhman, K.L., 2009. Role of the bed nucleus of the stria terminalis in the acquisition and expression of conditioned defeat in Syrian hamsters. *Behav Brain Res* 198, 69-73.

Martinez-Garcia, F., Novejarque, A., Lanuza, E., 2007. Evolution of the amygdala in vertebrates, in: Kass, J.H., Bullock, T.H. (eds), *Evolution of Nervous Systems: A Comprehensive Reference* (vol. 2), Elsevier Academic Press, San Diego, 255-334.

Maximino C., Lima, M., Oliveira, K., Batistia, A., Herculano, A., 2013. “Limbic associative” and “autonomic” amygdala in teleosts: a review of the evidence. *J Chem Neuro* 48-49, 1-13.

McDonald, A., 2003. Is there an amygdala and how far does it extend? An anatomical perspective. *Ann N Y Acad Sci* 985, 1-21.

McElligott, Z.A., Fox, M.E., Walsh, P.L., Urban, D.J., Ferrel, M.S., Roth, B.L., Wightman, R.M., 2013. Noradrenergic synaptic function in the bed nucleus of the stria terminalis varies in animal models of anxiety and addiction. *Neuropsychopharmacol* 38, 1665-1673.

McElligott, Z.A., Klug, J.R., Nobis, W. P., Patel, S., Grueter, B.A., Kash, T.L., Winder, D.G., 2010. Distinct forms of Gq-receptor-dependent plasticity of excitatory transmission in the BNST are differentially affected by stress. *PNAS* 107, 2271-2276.

McElligott, Z.A., Winder, D. G., 2009. Modulation of glutamatergic synaptic transmission in the bed nucleus of the stria terminalis. *Prog Neuropsychopharmacol Biol Psychiatry* 33, 1329-1335.

Medina, L., Bupesh, M., Abellan, A., 2011. Contribution of genoarchitecture to understanding forebrain evolution and development, with particular emphasis on the amygdala. *Brain Behav Evol* 3, 216-236.

Moreno, N., Gonzalez, A., 2006. The common organization of the amygdaloid complex in tetrapods: new concepts based on developmental, hodological and neurochemical data in anuran amphibians. *Prog Neurobio* 78, 61-90.

Morilak, D.A., Cecchi, M., Khoshbouei, H., 2003. Interactions of norepinephrine and galanin in the central amygdala and lateral bed nucleus of the stria terminalis modulate the behavioral response to acute stress. *Life Sci* 73, 715-726.

Morrison, S.E., Salzman, C.D., 2010. Re-valuing the amygdala. *Curr Opin Neurobiol* 20, 221-230.

Murray, E.A., 2007. The amygdala, reward and emotion. *Trends Cog Sci* 11, 489-497.

Nakagawa, T., Yamamoto, R., Fujio, M., Suzuki, Y., Minami, M., Satoh, M., Kaneko, S., 2005. Involvement of the bed nucleus of the stria terminalis activated by the central nucleus of the amygdala in the negative affective component of morphine withdrawal in rats. *Neurosci* 134, 9-19.

Nery, S., Fishell, G., Corbin, J.G., 2002. The caudal ganglionic eminence is a source of distinct cortical and subcortical cell populations. *Nature* 5, 1279-1287.

Neugebauer, V., Li, W., Bird, G.C., Han, J.S., 2004. The amygdala and persistent pain. *The Neuroscientist* 10, 221-234.

Newman, S.W., 1999. The medial extended amygdala in male reproductive behavior. *Ann NY Acad Sci* 877, 242-257.

Nieuwenhuys, R., Geeraedts, L.M.G., Veening, J.G., 1982. The medial forebrain bundle of the rat. I. General introduction. *J Comp Neurol* 206, 49-81.

Nitabach, M.N., Schulkin, J., Epstein, A.N., 1989. The medial amygdala is part of a mineralcorticoid-sensitive circuit controlling NaCl intake in the rat. *Behav Brain Res* 35, 127-134.

Noh, J., Seal, R.P., Garver, J.A., Edwards, R.H., Kandler, K., 2010. Glutamate co-release at GABA/glycinergic synapses is crucial for the refinement of an inhibitory map. *Nature Neurosci* 13, 232-238.

Numan, M., Numan, M.J., 1995. Importance of pup-related sensory inputs and maternal performance for the expression of Fos-like immunoreactivity in the preoptic area and central bed nucleus of the stria terminalis in postpartum rats. *Behav Neurosci* 109, 135-149.

Numan, M., Numan, M.J., 1996. A lesion and neuroanatomical tract-tracing analysis of the role of the bed nucleus of the stria terminalis in retrieval behavior and other aspects of maternal responsiveness in rats. *Dev Psychobiol* 29, 23-51.

Numan, M., Numan, M.J., 1997. Projection sites of the medial preoptic area and ventral bed nucleus of the stria terminalis neurons that express fos during maternal behavior in female rats. *J Neuroendocrin* 9, 369-384

Oberlander, J.G., Henderson, L.P., 2012. The *sturm und drang* of anabolic steroid use: angst, anxiety, and aggression. *Trends in Neurosci* 35, 382-392.

Olive, M.F., Koenig, H.N., Nannini, M.A., Hodge, C.W., 2002. Elevated extracellular CRF levels in the bed nucleus of the stria terminalis during ethanol withdrawal and reduction by subsequent ethanol intake. *Pharm Biochem Behav* 72, 213-220.

Ottem, E.N., Godwin, J.G., Krishnan, S., Petersen, S.L., 2004. Dual-phenotype GABA/glutamate neurons in adult preoptic area: sexual dimorphism and function. *J Neurosci* 24, 8097-8105.

Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* 48, 175-187.

Pleil, K.E., Rinker, J.A., Lowery-Gionta, E.G., Mazzone, C.M., McCall, N.M., Kendra, A.M., Olson, D.P., Lowell, B.B., Grant, K.A., Thiele, T.E., Kash, T.L., 2015. NPY signaling inhibits extended amygdala CRF neurons to suppress binge alcohol drinking. *Nature Neurosci* 18, 545-552.

Poulos, A.M., Ponnusamy, R., Dong, H., Fanselow, M.S., 2012. Compensation in the neural circuitry of fear conditioning awakens learning circuits in the bed nuclei of the stria terminalis. *PNAS* 107, 14881-14886.

Powers, J.B., Newman, S.W., Bergondy, M.L., 1987. MPOA and BNST lesions in male Syrian hamsters: differential effects on copulator and chemoinvestigatory behaviors. *Behav Brain Res* 23, 181-195.

Puelles, L., Harrison, M., Paxinos, G., Watson, C., 2013. A developmental ontology for the mammalian brain based on the prosomeric model. *Trends Neurosci* 36, 570-578.

Reiner, A., 2010. The conservative evolution of the vertebrate basal ganglia, in: Steiner, H., Tseng, K.Y. (Eds), *Handbook of Basal Ganglia Structure and Function*, Academic Press, San Diego, 29-62.

Reti, I.M., Baraban, J.M., 2003. Opiate withdrawal induced Narp in the extended amygdala. *Neuropsychopharm* 28, 1606-1613.

Robbins, T.W., Everitt, B.J., Marston, H.M., Wilkinson, J., Jones, G.H., Page, K.J., 1989. Comparative effects of ibotenic acid- and quisqualic acid-induced lesions of the substantia innominate on attentional function in the rat: further implications for the role of the cholinergic neurons of the nucleus basalis in cognitive processes. *Behav Brain Res* 35, 221-240.

Rutherford, H.J.V., Willimas, S.K., Moy, S., Mayes, L.C., Johns, J.M., 2011. Disruption of maternal parenting circuitry by addictive process: rewiring of reward and stress systems. *Front Psychiat* 2 (37), 1-17.

Sartor, G.C., Aston-Jones, G., 2012. Regulation of the ventral tegmental area by the bed nucleus of the stria terminalis is required for expression of cocaine preference. *Eur J Neurosci* 36, 3549-3558.

Schulkin, J., Marini, J., Epstein, A.N., 1989. A role for the medial region of the amygdala in mineralcorticoid-induced salt hunger. *Behav Brain Res* 103, 179-185.

Seal, R.P., Edwards, R.H., 2006. Functional implications of neurotransmitter co-release: glutamate and GABA share the load. *Curr Op Pharmacol* 6, 114-119.

Shaw-Luchtman, T.Z., Barrot, M., Wallace, T., Gilden, L., Zacharioui, V., Impey, S., Duman, R.S., Storm, D., Nestler, E.J., 2002. Regional and cellular mapping of cAMP response element-mediated transcription during naltrexone-precipitated morphine withdrawal. *J. Neurosci* 22, 3663-3672.

Shizgal, P., 1997. Neural basis of utility estimation. *Curr Op Neurobio* 2, 198-208.

Shizgal, P., Conover, K.. 1996. On the neural computation of utility. *Curr Dir Psychol Sci* 5, 37-43.

Silberman, Y., Winder, D.G., 2013. Emerging role for corticotropin releasing factor signaling in the bed nucleus of the stria terminalis at the intersection of stress and reward. *Front Psychiat* 4, 1-12.

Simmons, J.M. and Gallistel, C.R. 1994. Saturation of subjective reward magnitude as a function of current and pulse frequency. *Behav Neurosci* 108, 151-160.

Simmons, D.A., Hoffman, N.W., Yahr, P., 2011. A forebrain-retrobulbar pathway involved in male sex behavior is GABAergic and activated with mating in gerbils. *Neurosci* 175, 162-168.

Smith, D.V., Ye, M.K., Li, C.S., 2005. Medullary taste responses are modified by the bed nucleus of the stria terminalis. *Chem Senses* 30, 421-434.

Solomon, R.B., Trujillo-Pisanty, I., Conover, K., Shizgal, P., 2015. Psychophysical inference of frequency-following fidelity in the neural substrate for brain stimulation reward. *Behav Brain Res* 292, 327-341.

Stinus, L., Cador, M., Zorrilla, E.P., Koob, G.F., 2005. Buprenorphine and a CRF₁ antagonist block the acquisition of opiate withdrawal-induced conditioned place aversion in rats. *Neuropsychopharm* 30, 90-98.

Striedter, G.F. *Principles of Brain Evolution*, 2005. Sinauer Associates, Sunderland, Massachusetts.

Stuber, G.D., Stamatakis, A.M., Katak, P.A., 2015. Considerations when using Cre-driver rodent lines for studying ventral tegmental area circuitry. *Neuron* 85, 439-445.

Sonnenschein, B., Conover, K., Shizgal, P., 2003 Growth of brain stimulation reward as a function of duration and stimulation strength. *Behav Neurosci* 117, 978-994.

Striedter, G.F., 2005. *Principles of Brain Evolution*, Sinauer Associates, Sunderland, Massachusetts.

Sullivan, G.M., Apergic, J., Bush, D.E.A., Johnson, L.R., Hou, M., LeDoux, J.E., 2004. Lesions in the bed nucleus of the stria terminalis disrupt corticosterone and freezing responses elicited by a contextual but not by a specific cue-conditioned fear stimulus. *Neurosci* 128, 7-14.

Sun, N., Cassell, M.D., 1993. Intrinsic GABAergic neurons in the rat central extended amygdala. *J Comp Neurol* 330, 381-404.

Swanson, L.W., 2003. The amygdala and its place in the cerebral hemisphere. *Ann NY Acad Sci* 985, 174-184.

Swanson, L.W., 2012. *Brain Architecture: Understanding the Basic Plan*, 2nd edition. Oxford University Press, New York.

Swanson, L.W., Cowan, W.M., 1977. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. *J Comp Neurol* 172, 49-84.

Swanson, L.W., Petrovich, G.D., 1998. What is the amygdala? Trends Neurosci 21, 323-331.

Trainor, B.C., Greiwe, K.M., Nelson, R.J., 2006. Individual differences in estrogen receptor α in select brain nuclei are associated with individual differences in aggression. Hormones Behav 50, 338-345.

Trainor, B.C., Crean, K.K., Fry, W.H.D., Sweeney, C., 2010. Activation of extracellular signal-regulated kinases in social behavior circuits during resident-intruder aggression tests. Neurosci 165, 325-336.

Trujillo-Pisanty I., Conover K. & Shizgal P., 2014. A new view of the effect of dopamine receptor antagonism on operant performance for rewarding brain stimulation in the rat. Psychopharm 231,1351-64.

Trujillo-Pisanty, I., Martel, A., Conover, K., Arvanitogiannis, A., Shizgal, P., 2013. On the role of basal-forebrain MFB efferents in self-stimulation of the rat medial forebrain bundle. Program # 776.07, 2013. Abstracts Viewer/Itinerary Planner, Society for Neuroscience, Washington, D.C.

Ulrich-Lai, Y.M., Herman, J.P., 2009. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 10, 397-409.

Valcourt, R.J., Sachs, B.D., 1979. Penile reflexes and copulatory behavior in male rats following lesions of the bed nucleus of the stria terminalis. Brain Res Bull 4, 131-133.

Veening, J.G., Swanson, L.W., Cowan, W.M., Nieuwenhuys, R., Geeraedts, L.M.G., 1982. The medial forebrain bundle of the rat. II. An autoradiographic study of the topography of the major descending and ascending components. *J Comp Neurol* 206, 82-108.

Veinante, P., Freund-Mercier, M., 1998. Intrinsic and extrinsic connections of the rat central extended amygdala: an in vivo electrophysiological study of the central amygdaloid nucleus. *Brain Res* 794, 188-198.

Veinante, P., Stoeckel, M.-E., Lasbennes, F., Freund-Mercier, M.-J., 2003. c Fos and peptide immunoreactivities in the central extended amygdala of morphine-dependent rats after naloxone-precipitated withdrawal. *Eur J Neurosci* 18, 1295-1305.

Volman, S.F., Lammel, S., Margolis, E.B., Kim, Y., Richard, J.M., Roitman, M.F., Lobo, M.K., 2013. New insights into the specificity and plasticity of reward and aversion encoding in the mesolimbic system. *J Neurosci* 33, 17569-17576.

Voytko, M.L., 1996. Cognitive functions of the basal forebrain cholinergic system in monkeys: memory or attention? *Behav Brain Res* 75, 13-25.

Walker, D.L., Miles, L.A., Davis, M., 2009. Selective participation of the bed nucleus of the stria terminalis and CRF in sustained anxiety-like versus phasic fear-like responses. *Prog Neuro-Psychopharmacol and Biol Psychiat* 33, 1291-1308.

Walker, D.L., Toufexis, D.J., Davis, M., 2003. Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. *Eur J Pharm* 463, 199-216.

Walker, J.R., Ahmed, S.H., Gracy, K.N., Koob, G.F., 2000. Microinjections of an opiate receptor antagonist into the bed nucleus of the stria terminalis suppress heroin self-administration in dependent rats. *Brain Res* 854, 85-92.

Waraczynski, M., 2003. Lidocaine inactivation demonstrates a stronger role for central versus medial extended amygdala in medial forebrain bundle self-stimulation. *Brain Res* 962, 180-198.

Waraczynski, M., 2006. The central extended amygdala network as a proposed circuit underlying reward valuation. *Neurosci Biobeh Rev* 30, 472-496.

Waraczynski, M., 2007. Muscimol inactivation of the septo-preoptic complex affects medial forebrain bundle self-stimulation only when directed at the complex's ventrolateral components. *Behav Brain Res* 178, 98-107.

Waraczynski, M., 2008. GABA receptor agonism in the sublenticular central extended amygdala impairs medial forebrain bundle self-stimulation but GABA blockade does not enhance it. *Behav Brain Res* 187, 396-404.

Waraczynski, M., Cheong Ton, M.N.M, Shizgal, P., 1990. Failure of amygdaloid lesions to increase the threshold for self-stimulation of the lateral hypothalamus and ventral tegmental area. *Behav Brain Res* 40, 159-168.

Waraczynski, M., Kuehn, L., Schmid, E., Stoehr, M., Zwifelhofer, W., 2015. Comparison of the effects on brain stimulation reward of D1 blockade or D2 stimulation combined with AMPA blockade in the extended amygdala and nucleus accumbens. *Behav Brain Res* 278, 337-341.

Waraczynski, M., Salemme, J., Farral, B., 2010. Brain stimulation reward is affected by D2 dopamine receptor manipulations in the extended amygdala but not the nucleus accumbens. *Behav Brain Res* 208, 626-635.

Waraczynski, M., Stellar J.R., Gallistel, C.R., 1987. Reward saturation in medial forebrain bundle self-stimulation. *Physiol Behav* 41, 585-593.

Waraczynski, M., Zwifelhofer, W., Kuehn, L., 2012. Brain stimulation reward is altered by affecting dopamine-glutamate interactions in the central extended amygdala. *Neurosci* 214, 1-14.

Xu, H.-Y., Liu, Y.-J., Zhang, Y.-H., Zhang, J.X., Wu, Y.-J., 2012. Inactivation of the bed nucleus of the stria terminalis suppresses the innate fear responses of rats induced by the odor of cat urine. *Neurosci* 221, 21-27.

Zahm, D.S., 1998. Is the caudomedial shell of the nucleus accumbens part of the extended amygdala? A consideration of connections. *Crit Rev Neurobiol.* 12, 245-265.

Zahm, D.S., 2000. An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. *Neurosci Biobehav Rev* 24, 85-105.

Zahm, D.S., 2006. The evolving theory of basal forebrain functional-anatomical 'macrosystems'.
Neurosci and Biobehav Rev 30, 148-172.

Zahm, D.S., 2008. The dopaminergic projection system, basal forebrain macrosystems, and conditioned stimuli. CNS Spectr 13, 32-40.

Zahm, D.S., Brog, J.S., 1992. On the significance of subterritories in the "accumbens" part of the rat ventral striatum. Neurosci 50, 751-767.

Zahm D.S., Grosu S., Irving J.C., Williams E.A., 2003. Discrimination of striatopallidum and extended amygdala in the rat: a role for parvalbumin immunoreactive neurons? Brain Res 978, 141-154.

Zahm, D.S., Williams E.A., Latimer, M.P, Winn, P., 2001. Ventral mesopontine projections of the caudomedial shell of the nucleus accumbens and extended amygdala in the rat: Double dissociation by organization and development. J Comp Neurol 436, 111-125.

Zardetto-Smith, A.M., Beltz, T.G., Johnson, A.K., 1994. Role of the central nucleus of the amygdala and bed nucleus of the stria terminalis in experimentally-induced salt appetite. Brain Res 645, 123-134.

Zhang, D.M., Epstein, A.N., Schulkin, J., 1993. Medial region of the amygdala: involvement in adrenal-steroid-induced salt appetite. Brain Res 600, 20-26.

Figure Captions

Figure 1. A parahorizontal view of the extended amygdala continuum showing the distribution of projection cell subtypes. Abbreviations: CRF = corticotropin releasing factor; DYN = dynorphin; EA = extended amygdala; ENK = enkephalin; IPAC = interstitial nucleus of the posterior aspect of the anterior commissure; NT = neurotensin; SOM = somatostatin; SP = substance P.

Figure 2. Extended amygdala circuitry implicated in stress and anxiety reactions. (a) The relevant anatomical connections, color-coded for the type of neurotransmitter used by different cell types. (b) Neural activity pattern corresponding to the anxious state. Bold lines indicate active projections; dashed lines indicate inactive projections. The loss of glutamatergic output from the adBNST allows anxiety-related behaviors and reactions to occur; excitatory input from the avBNST to the PVN upregulates the HPA axis; the loss of inhibitory input from the pBNST further enables HPA upregulation. (c) Neural activity patterns associated with anxiolysis. Glutamatergic output from the adBNST enables exploratory behavior and buffers anxiety reactions; the loss of excitatory input and an increase in inhibitory input to the PVN downregulates the HPA axis.

Figure 3. EA circuitry involved in stress-induced reinstatement of drug seeking. (a) The relevant anatomical connection; see Figure 2 for color codes. The red and green neuron in the anterodorsal BNST represents a population of GABAergic projection neurons, some of which co-release glutamate. (b) Neural activity patterns during stress-induced drug seeking. Chronic experience with addictive drugs increases glutamatergic excitatory drive from cortical and basolateral amygdalar inputs to GABAergic cells of the anterodorsal BNST (BLA = basolateral amygdala; PFC = prefrontal cortex). In turn, GABAergic and glutamatergic input from the anterodorsal BNST to the ventral tegmental area (VTA) enhances motivation to seek and consume drugs with which the animal has experience. Anterodorsal BNST

activity is also promoted by input from intrinsic CRF-ergic BNST cells during stress. In addition, long term noradrenergic input from the A1 and A2 cell groups of the brainstem – a corollary of chronic stress – may act pre- and post-synaptically to make anterodorsal BNST neurons more responsive to glutamatergic and CRF-ergic input.

Figure 4. EA circuitry involved in salt appetite (a) The relevant anatomical connections Abbreviations:

NE = noradrenergic input activated by low sodium levels; NST = nucleus of the solitary tract; OVLT =

organum vasculosum of the lamina terminalis; PBN = parabrachial nucleus; PVN = paraventricular

nucleus of the hypothalamus; SFO = subfornical organ. (b) Neural activity patterns during sodium

depletion. High angiotensin levels and sodium depletion detected by brainstem regulators excite

activity in GABAergic cells of the ventrolateral BNST. GABA release into the PVN inhibits oxytocin

release, which in turn disinhibits salt appetite. (c) Neural activity patterns when sodium is replete. In

the absence of excitatory drive, GABAergic cells of the ventrolateral BNST no longer block oxytocin

release and salt appetite is inhibited.

Figure 5. EA circuitry implicated in reproductive functions. (a) Circuitry by which the medial amygdala

(MeA) and posterior BNST enable male copulatory function. Olfactory and vomeronasal cues provided

by reproductively receptive female conspecifics affect the anterodorsal medial amygdala and

posterointermediate BNST to enable general around and environmental exploration. Other sensory

input affects the caudal posteriodorsal medial amygdala and the posteromedial BNST to enable

copulatory actions such as mounting receptive females. (b) Circuitry that assists maternal parenting

behaviors such as retrieving and grooming pups. The sensory input provided by interacting with pups

affects the ventral BNST to enable maternal behaviors through action on a variety of cell groups, such as

the retrorubral fields (RRF), which are associated with pup retrieval and grooming; the ventral tegmental

area (VTA), associated with motivation to engage in maternal behavior; and the medial hypothalamus (MH), which regulates oxytocin levels. Oxytocin is associated with maternal bonding with pups.

Figure 6. A hypothesis of the EA's place in basal forebrain organization, relevant to mediating adaptive responding. See section 4.0 of the text for exposition.

Figure 1

Figure 2.

Stress and anxiety reactions

Figure 3.

Figure 4.

Figure 5.

Figure 6.