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Amygdalostriatal projections in the neurocircuitry for motivation: A neuroanatomical thread through the career of Ann Kelley

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Abstract

In MacLean's triune brain, the amygdala putatively subserves motivated behavior by modulating the "reptilian" basal ganglia. Accordingly, Ann Kelley, with Domesick and Nauta, influentially showed that amygdalostriatal projections are much more extensive than were appreciated. Caudal of the anterior commissure, the entire striatum receives afferents from deep basal nuclei of the amygdala. They highlighted that amygdalar projections to the rostral ventromedial striatum converged with projections from the ventral tegmental area and cingulate cortex, forming a "limbic striatum". Orthologous topographic projections subsequently were observed in fish, amphibians, and reptiles. Subsequent functional studies linked acquired value to action via this neuroanatomical substrate. From Dr. Kelley's work evolved insights into components of the distributed, interconnected network that subserves motivated behavior, including the nucleus accumbens shell and core and the striatal-like extended amygdala macrostructure. These heuristic frameworks provide a neuroanatomical basis for adaptively translating motivation into behavior. The ancient amygdala-to-striatum pathways remain a current functional thread not only for stimulus–response valuation, but also for the psychopathological plasticity that underlies addictionrelated memory, craving and relapse.

Keywords

Basolateral or medial or lateral or basomedial or central nucleus of the amygdala; Striatum; Extended amygdala; Bed nucleus of the stria terminalis; Nucleus accumbens; Caudate; Putamen; Afferent or efferent or projection or circuit; Incentive salience or motivation or reward; Pavlovian or classical or instrumental or operant conditioning; Addiction; Obesity

1. Introduction

The amygdala, not included in early conceptualizations of the neurocircuitry of emotion (Bard and Rioch, 1937; Bard, 1928; Cannon, 1931; Papez, 1937), is now a recognized substrate for emotional behavior. In the late-1930s, Klüver and Bucy (1937, 1939) described that bilateral temporal lobectomy in rhesus monkeys led to docility, decreased emotional reactivity, increased exploratory behavior, and object-inappropriate sexuality, hyperphagia,

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Conflict of interest statement

EPZ and GFK are co-inventors on a patent for the composition and use of non-peptide CRF_1 receptor antagonists (US20100249138), and EPZ is co-inventor on a patent for ghrelin-related anti-obesity treatments (US20100021487).

and hyperorality, findings that overlapped those of Brown and Schäfer five decades earlier (Brown and Schäfer, 1888). In the 1940s, more specific, bilateral amygdala lesions in cats by Spiegel et al. (1940) and then Bard and Mountcastle (1948) elicited rage behavior, further implicating a role for this structure in modulating emotional behavior. Accordingly, MacLean (1949, 1952), in his triune brain model, included the amygdala in his "paleomammalian limbic system," which he hypothesized subserved motivated and emotional behavior by modulating activity of the "reptilian" basal ganglia.

Subsequent studies confirmed that lesions that involve the amygdaloid complex "tamed" animals, increased "fearlessness," increased nonspecific overeating, and produced a deficit in motivated behavior colloquially referred to as "amygdala hangover" (Green et al., 1957; Rosvold et al., 1954; Schreiner and Kling, 1953; Walker et al., 1953; Weiskrantz, 1956; Woods, 1956). Conversely, electrical stimulation of the amygdala potentiated flight and defense reactions (de Molina and Hunsperger, 1959; Ursin and Kaada, 1960). As a result, Weiskrantz (1956) influentially hypothesized that amygdala lesions make it difficult for animals to identify the affective or reinforcing properties of stimuli, dissociating a stimulus' value from its sensory representation.

Ann Kelley, with Ned Kalin and colleagues at the University of Wisconsin, later offered support to this view by showing that bilateral amygdala destruction in rhesus monkeys blunted fear responses to discrete naturalistic stimuli (Kalin et al., 2001). Lesioned monkeys were less likely to withdraw to the back of their enclosure or delay retrieval of a food treat when exposed to a snake stimulus. Lesioned monkeys were also less likely to exhibit fear grimaces, submit, or perform coo or bark vocalizations when exposed to a threatening adult male conspecific. This study was unique from preceding lesion studies in nonhuman primates because it involved ibotenic acid destruction of cell bodies to spare fibers of passage and used magnetic resonance imaging to guide the site-specificity of the lesion. As such, together with a contemporary study (Meunier et al., 1999), it made a key contribution by linking similar findings from lesion studies in rodents with the emerging human neuroimaging literature (Kalin et al., 2001).

Nonetheless, following Weiskrantz' hypothesis that the amygdala influences emotional behavior by encoding a stimulus' sensory representation with value, the circuitry through which the amygdala might accomplish this remained unclear. Gloor (1955a,b) had surmised in 1955 that the amygdala modulates "complex somatic, autonomic and behavioral mechanisms integrated in subcortical structures". Many studies emphasized amygdalar projections that involved the hypothalamus or mediodorsal thalamus via the stria terminalis (de Molina and Hunsperger, 1959; Egger and Flynn, 1962, 1963, 1967; Fox, 1943; Hall, 1963; Kling and Hutt, 1958; Lammers and Lohman, 1957; Nauta, 1961).

2. Identification of amygdalostriatal projections

Other neuroanatomical evidence, however, supported MacLean's view that the limbic amygdala might directly modulate activity of the basal ganglia (MacLean, 1952). Indeed, Gurdjan wrote in 1928 that the caudate–putamen could not be differenti- ated from the amygdaloid complex in caudal rat brain sections. By tracing fiber degeneration after electrolytic lesions, Fukuchi (1952) described amygdala projections in ungulates, including a medial stria terminalis component that courses ventromedially into the ventral caudate in the vicinity of the nucleus accumbens (NAc) and a separate lateral component associated with the external capsule of the lentiform nucleus. Williams (1953) described fibers that course from the basolateral amygdala (BLA) of the bat via the anterior commissure and external capsule to the caudate nucleus. Lammers and Lohman (1957) made similar observations in the cat. Subsequently, in 1961, Dr. Walle Nauta, who would become Dr.

Ann Kelley's postdoctoral mentor, detailed that aspiration lesions of the amygdalo-piriform complex in monkeys resulted in the degeneration of fibers that project to the ventromedial putamen and NAc (Nauta, 1961).

Following the completion of her graduate studies with Dr. Susan Iversen at Cambridge University in 1979, Dr. Kelley joined the Nauta laboratory at the Massachusetts Institute of Technology. In the years since Dr. Nauta's survey, others substantiated the existence of direct amygdalostriatal pathways, including anatomical (Cowan et al., 1965; De Olmos and Ingram, 1972; Ishikawa et al., 1969; Knook, 1966; Krettek and Price, 1978) and electrophysiological (Gloor, 1955a; Ito et al., 1974; Powell et al., 1968; Sato, 1977) evidence of an amygdaloid projection to the NAc via the stria terminalis. These studies, including those enabled by the recently developed tract-tracing methods of anterograde transport of tritiated amino acids (Krettek and Price, 1978) and retrograde labeling (Groenewegen et al., 1980; Newman and Winans, 1980), supported the hypothesis that amygdala projections to the ventral striatum, including the ventral putamen, NAc, and olfactory tubercle, arise from the BLA and basomedial amygdala (BMA). Krettek and Price (1978) provided initial evidence in the rat and cat of a topographic organization; specifically, anterior-to-posterior BLA subregions projected preferentially to anterolateral-to-posteromedial aspects of the ventral striatum, respectively. Groenewegen and colleagues, using horseradish peroxidase (HRP) and bisbenzimid as retrograde labels in the cat, and Newman and Winans, using HRP in the hamster, confirmed a predominantly BLA origin of amygdaloid projections to the NAc. Both groups also proposed a rostral BLA-lateral NAc and caudal BLA-medial NAc topography. Groenewegen et al.(1980) additionally reported that the NAc received much greater input from the BLA than did the caudate, and Newman and Winans (1980) observed that the BLA projected more to the caudal than rostral NAc.

In 1982, Kelley et al., using anterograde autoradiographic and retrograde HRP techniques in rats, provided their influential account that amygdalostriatal projections were much more extensive than had been previously thought. First, they showed that caudal of the anterior commissure (i.e., along the globus pallidus), the entire striatum receives amygdala afferents, primarily from the BLA and, to a lesser degree, the BMA and lateral nucleus of the amygdala. It was only rostral of the anterior commissure that projections were absent in the dorsolateral striatum and became increasingly limited to the ventromedial striatum, as had been emphasized up to that time. Thus, the entire caudal striatum and not only the NAc and olfactory tubercle, were under "limbic" modulation. Second, they called attention to the fact that amygdalar projections to the rostral striatum, in preferentially targeting its ventromedial quadrant, closely overlapped projections from the ventral tegmental area (VTA) and rat cingulate cortex, forming a putative "limbic striatum". Third, they showed that the BLA projects not only to the ipsilateral striatum but also, to a lesser degree, the contralateral striatum. Fourth, they demonstrated two distinct amygdaloid efferents to the striatum, a sub-striatal one via the ventral amygdalofugal pathway (or longitudinal association bundle) and a second, more dorsal one via the stria terminalis. They concluded, "In view of the large volume and wide intrastriatal distribution of the [amygdaloid] connection it is tempting to speculate that the functional mode of a large part of the striatum may be decisively influenced by the animal's affects and motivational sets" (Kelley et al., 1982). Integrating the hypotheses of MacLean (1949, 1952) and Weiskrantz (1956), the modern view by which amygdalostriatal projections help put value into action was born.

3. Cortical-like, topographic projection of basal amygdala to dorsal and ventral striatum

Prior to Kelley's detailed analysis, limited anatomical (Fukuchi, 1952; Lammers and Lohman, 1957; Royce, 1978; Veening et al., 1980; Williams, 1953) and electrophysiological

(Dafny et al., 1975) evidence had linked the amygdala to the dorsal striatum. Since then, much has been learned. Russchen, Price, and colleagues, using anterograde techniques in the rat (phytohemagglutinin-L [PHA-L]) and cynomolgus monkey (tritiated amino acids), made observations consistent with those of Kelley of widespread projections from the basal nuclei of the amygdala to not only the ventral but also dorsal striatum (Russchen et al., 1985; Russchen and Price, 1984), absent its antero-dorsolateral quadrant. Saint-Cyr et al. (1990) obtained similar results in macaques with retrograde labeling, as did Ragsdale and Graybiel (1988) and Gorbachevskaia (1988) in the cat. Fass et al. (1984) even found evidence using fluorescent retrograde tracing that the rat BLA may, in fact, also project to the precommisural dorsolateral striatum, a connection that also was suggested in later wheat germ agglutinin (WGP)-HRP retrograde tracing by McDonald (1991). On the other hand, this projection was not seen using anterograde techniques (Kelley et al., 1982; Kita and Kitai, 1990; Ragsdale and Graybiel, 1988; Russchen et al., 1985; Russchen and Price, 1984) and remains disputed. Nonetheless, their study confirmed that not only the BLA but also the BMA and lateral nucleus send efferents to the striatum (McDonald, 1991; Russchen and Price, 1984). Fudge, Breitbart, and McClain, noting similarities in histochemistry, cytoarchitecture, and amygdala afferents between the NAc shell, lateral amygdalostriatal transition region, and aspects of the caudal ventral striatum in cynomolgus monkeys, further proposed that the entire rostral–caudal extent of the ventral striatum through these structures is a continuum of “limbic striatum” (Ernst and Fudge, 2009; Fudge et al., 2004) and not only the precommisural part, as was assumed before Ann Kelley sparked investigation of amygdaloid projections to the caudal striatum.

McDonald (1991) clarified the topographic organization of rat amygdalostriatal projections in partial agreement with earlier suggestions (Gorbachevskaya, 1990, 1991; Groenewegen et al., 1980; Kelley et al., 1982; Kita and Kitai, 1990; Krettek and Price, 1978; Russchen et al., 1985). First, a rostral–caudal topography indicates that the rostral two-thirds of the BLA projects to the dorsal stri- atum, but the most caudal BLA does not; instead, the caudal BLA selectively innervates the medial NAc (McDonald, 1991). Second, a medial–lateral topography indicates that more lateral coordinates within the BLA map to more lateral aspects of the dorsal striatum (e.g., ventrolateral caudatoputamen, fundus striati), whereas more medial coordinates map to more medial striatal subregions (e.g., dorsomedial caudatoputamen, NAc). Third, double-label fluorescent retrograde tracing showed that most (>65–75%) individual amygdala neurons that innervate the dorsal striatum (e.g., fundus striati, caudatoputamen) or ventral striatum (NAc) also send fibers to regions of the prefrontal cortex that project to the respective striatal region. Thus, consistent with the reviewed topographical organization, BLA neurons that project to more medial (or lateral) prefrontal cortical targets also send collaterals to more medial (or lateral) striatal targets. The results indicate coordinated amygdala modulation of corticostriatal circuits.

This triangular arrangement of amygalo-cortical-striatal projections was a key observation. Analogous to the triangular arrangement of cortico-cortico-striatal circuits, it supports the still prevailing view that the BLA is an “allocortical” structure that shares not only structural but also connective properties with traditional cortical neurons, quite unlike the adjacent, striatal-like CeA that shows fewer such efferents (Carlsen and Heimer, 1988; McDonald, 1991). Indeed, Kelley, Russchen, and colleagues had earlier inde- pendently noted the “patchy” nature of amygdalostriatal terminals in the rat and primate, akin to the patchy corticostriatal connections from the prelimibic medial prefrontal cortex (Kelley et al., 1982; Russchen et al., 1985). As with corticostriatal projections, glutamatergic pyramidal (class I) BLA neurons form excitatory, asymmetric synapses on dendritic spines of medium spiny neurons in the striatum (Christie et al., 1987; Dafny et al., 1975; Kita and Kitai, 1990; McDonald, 1992; Robinson and Beart, 1988). In contrast, γ-aminobutyric acid (GABA)-

ergic non-pyramidal (class II and III) BLA neurons do not appreciably connect to the striatum (Christie et al., 1987; McDonald, 1992).

4. Amygdalo-ventrostriatal projections: focus on the nucleus accumbens

While Kelley and colleagues' paper demonstrated that basal amygdala nuclei project to what had, until then, been considered "non-limbic" caudal striatum, it was also influential for further characterizing the already known connection from the amygdala to the rostral ventral striatum (Cowan et al., 1965; De Olmos and Ingram, 1972; Gloor, 1955a; Groenewegen et al., 1980; Ishikawa et al., 1969; Ito et al., 1974; Knook, 1966; Krettek and Price, 1978; Nauta, 1961; Newman and Winans, 1980; Powell et al., 1968; Yim and Mogenson, 1982). In what would become a defining theme of Dr. Kelley's research career, it squarely placed the NAc as an interface between the limbic system and the extrapyramidal motor systems to which it connected (Mogenson et al., 1980), including the globus pallidus, substantia nigra, and subthalamic nucleus.

Further details of amygdala-NAc connectivity closely followed. Using retrograde WGA-HRP labeling in cats, Phillipson and Griffiths (1985) showed that amygdaloid fibers most heavily innervate the anteromedial NAc where they converge with afferents from the VTA, thalamus, prefrontal and entorhinal cortices, and hippocampus. The BLA was shown to be the primary source of direct amygdala input to the NAc, with additional minor contributions from a restricted region of the CeA, BMA, and medial and cortical nuclei. Consistent with the sparser amygdaloid innervation of the posterior NAc (Phillipson and Griffiths, 1985), extracellular single-unit recordings in rats revealed that 30% of anterior NAc units responded to electrical stimulation of the ipsilateral BLA compared with only 16% of posterior NAc units (Callaway et al., 1991).

McDonald (1991) showed in rats that the caudal BLA preferentially inputs to the medial NAc, whereas the rostral BLA differentially innervates the lateral NAc. He also demonstrated that, within the rat striatum, only the medial NAc receives substantial input from dorsal and medial aspects of the caudomedial BLA. Interestingly, this same BLA subregion was found to send collaterals to the CeA and bed nucleus of the stria terminalis (BNST), indicating a coordinated, allocortical influence over an "extended amygdala" macrostructure (McDonald, 1991).

5. Extended amygdala: an indirect pathway from the amygdala to extrapyramidal motor system

In parallel to the direct BLA–striatal projections described by Kelley and colleagues, the neuroanatomical entity termed the extended amygdala (Heimer and Alheid, 1991) is a striatal-like substrate that indirectly conveys motivational information from the amygdala to extrapyramidal motor systems (Alheid, 2003). An extended amygdala basal forebrain macrostructure was originally suggested by Johnston (1923) and can be heuristically differentiated into central vs. medial divisions that differ in structure, connectivity, molecular content, and proposed functions (Alheid, 2003; Heimer and Alheid, 1991). The central division includes the CeA, the central sublenticular extended amygdala, the lateral BNST, and a transition area in the medial and caudal portions of the NAc. These structures are interconnected, with extrinsic connections to the lateral hypothalamus (Alheid, 2003; Koob, 2003). The medial division includes the medial BNST, MeA, and the medial sublenticular extended amygdala, differentiated from the central division by their interconnections and extrinsic relations to the medial hypothalamus (Alheid, 2003). The lateral BNST of the central extended amygdala contains several transmitters related to arousal and stress responses, including catecholaminergic terminals, CRF terminals, CRF

cell bodies, NPY terminals, and galanin cell bodies, and receives afferents from the prefrontal cortex, insular cortex, BLA, and amygdalopiriform area. The medial BNST of the medial extended amygdala, in contrast, contains high amounts of vasopressin, is sexually dimorphic, and is innervated by the infralimbic cortex, entorhinal cortex, and subiculum (Allen and Gorski, 1990; Dong et al., 2001; Gray and Magnuson, 1992; Hines et al., 1992; Kozicz, 2001; Kozicz and Arimura, 2000, 2001; Kozicz et al., 1997, 1998; McDonald et al., 1999; Phelix et al., 1992; Phelix and Paull, 1990). The central division may be more involved in receiving cortical and allocortical information and regulating the hypothalamic–pituitary–adrenal stress axis (Gray et al., 1993), whereas the medial division may differentially process olfactory information and subserve sympathetic and physiological responses (Lesur et al., 1989; Nijsen et al., 2001; Pompei et al., 1991).

The central extended amygdala is known to play a key role in not only fear conditioning (LeDoux, 2000) but also the emotional component of pain processing (Neugebauer et al., 2004). Work from Ann Kelley's laboratory further contributed to our understanding of the extended amygdala as a component of the neurocircuitry that subserves arousal and stress- and rewardrelated behavior. For example, Baldo, Kelley, and colleagues demonstrated substantial innervation of the BNST, sublenticular extended amygdala, and CeA by fibers that express the potentially aversive, arousal-related peptide hypocretin/orexin (Boutrel et al., 2010), overlapping with catecholaminergic (dopamine β-hydroxylase-immunopositive) fibers (Baldo et al., 2003). Their histochemical work supported the extended amygdala concept and provided further evidence of a sub-specialization between the medial vs. lateral CeA that is now increasingly accepted (Baldo et al., 2003).

Subsequently, Andrzejewski et al. (2004) provided evidence that the central extended amygdala also subserves positively reinforced, instrumental behavior. For example, intra-CeA administration of *N*-methyl-D-aspartate (NMDA) receptor antagonists reduced the acquisition and expression of operant responding for sucrose pellets in food-restricted rats and reduced the free intake of sucrose pellets in separate experiments. Food-approach behavior was less affected, however, which was interpreted as a role for the extended amygdala in the consummatory aspects of motivated behavior. They subsequently found that intra-CeA infusion of a dopamine D_1 receptor antagonist reduced the acquisition but not expression of responding for sucrose pellets at doses that did not influence free feeding (Andrzejewski et al., 2005). Consistent with a facilita- tory or permissive influence of the CeA on consummatory behavior, the Kelley laboratory demonstrated that inactivation of the CeA (via muscimol, a $GABA_A$ receptor agonist) blocked the hyperphagia that resulted from food deprivation or from intra-NAc administration of a μ-opioid or $GABA_A$ receptor agonist (Baldo et al., 2005; Will et al., 2004).

Major projections from the central extended amygdala, including those from its NAc aspect, target the medial ventral pallidum. They thereby overlap the efferents to the extrapyramidal motor system that arise from the direct BLA–NAc pathways described by Kelley and colleagues.

6. Compartmental organization of amygdalo-accumbens projections

During the time that the extended amygdala was first proposed to be a macrostructure, it was also becoming evident that the NAc was comprised of functionally distinct subdivisions, with its caudal three-fourths consisting of a pericommisural "core" enveloped on its medial, ventral, and lateral boundaries by a "shell". These compartments show differences in molecular content, cytoarchitecture, synaptic organization, connectivity, and functional properties (Zahm and Brog, 1992). For example, as later reviewed by Kelley (2004) and posthumously by her col- laborators (Meredith et al., 2008), the ventral subiculum of the

hippocampus projects primarily to the shell, whereas the dorsal subiculum innervates the core. Similarly, the prelimbic prefrontal cortex differentially targets the core, whereas the infralimbic and piriform cortices innervate the shell. On the efferent side, the more striatal-like core targets classic basal ganglia output structures, including the ventral pallidum, subthalamic nucleus, and substantia nigra, whereas the shell preferentially targets subcortical limbic structures, including the lateral hypothalamus, BNST, centromedial amygdala, VTA, and ventromedial ventral pallidum. Accordingly, the core and shell were proposed to subserve different aspects of motivated behavior, with the former involved more with learning and the execution of adaptive motor actions and the latter involved with visceral-endocrine responses to emotionally relevant stimuli (Kelley, 2004; Meredith et al., 2008).

To test whether amygdala subdivisions also differentially innervate the core vs. shell, Brog, Zahm, and colleagues used retrograde Fluoro-Gold (FG) labeling in rats to revisit the issue of amygdala- NAc topography. Consistent with McDonald's observations, the caudal BLA ("basal nucleus," using J.L. Price's nomenclature) and, to a lesser degree, BMA ("accessory basal nucleus") project to the medial shell, whereas the rostral BLA and BMA both project to the lateral shell (Brog et al., 1993). The core, in contrast to the shell, is less densely innervated by the entire rostral–caudal extent of the BLA, with a slight rostral BMA contribution (Brog et al., 1993). Using an anterograde approach, Wright, Bejer, and Groenewegen similarly found in rats that (i) the caudal parvicellular BLA projects to the dorsomedial shell, (ii) the caudal magnocellular BLA and BMA reach the ventral shell, and (iii) the rostral magnocellular BLA inputs the lateral shell. In terms of connections to the core/dorsal striatum, (i) the magnocellular and caudal parvicellular BLA innervate the "patches" of the core and ventral caudatoputamen (CPv), (ii) the rostral BMA targets the "matrix" of the core/CPv, and (iii) the caudal BMA avoids the core/CPv altogether (Wright et al., 1996).

Fudge et al. (2002) showed that the BLA and BMA are also the major amygdaloid inputs to the shell and extra-shell ventromedial striatum in cynomolgus monkeys, similar to the earlier findings of Kunishio et al. (1996). The parvicellular BLA targets the ventral shell and core, whereas the magnocellular subdivision inputs the ventral shell and ventromedial putamen. The intermediate subdivision broadly projects across the ventromedial striatum, avoiding the dorsomedial shell, which receives few BLA inputs in this species. In addition to inputs from deep basal nuclei, the NAc shell in macaques also has afferents from the CeA and periamygdaloid cortex; finally, only the dorsomedial NAc receives terminals from the medial amygdala. The results indicate a more diverse amygdaloid innervation of the primate shell than core (Fudge et al., 2002).

Studies in rats and hamsters likewise identified projections to the ventral striatum not only from the basal amygdalar nuclei but also, to a lesser degree, the anterior medial amygdala. In hamsters, Gomez and Newman (1992) used PHA-L anterograde tracing to identify a dense projection from the rostral MeA to NAc shell, fundus striati, and olfactory tubercle, findings replicated by Coolen and Wood (1998) who showed a sparser ventral striatal connection from the caudal posterdorsal medial amygdala. Canteras et al. (1995) likewise saw PHA-L-labeled projections from the rat anterodorsal medial amygdala to the caudal NAc shell, olfactory tubercle, and ventral fundus striati. Brog et al. (1993), using FG retrograde tracing, similarly found in rats that some neurons in the anterodorsal medial amygdala project to the NAc shell. Thus, not only the deep basal but also anterior medial nuclei of the amygdala differentially project to the ventral striatum, including the NAc shell. To date, the functional role of the striatum's MeA afferents remains unclear.

7. Ancient, conserved amygdalo-striatal circuitry

In addition to mammals (including rats, cats, hamsters, primates, and mice; Novejarque et al., 2011; Ubeda-Banon et al., 2007), orthologous amygdalo-striatal projections have now been described in opossum (McDonald and Culberson, 1986), fish (Lau et al., 2011; Northcutt, 2006), newts (Dube et al., 1990; Marin et al., 1997), frogs (Marin et al., 1997), and lizards (Gonzalez et al., 1990; Martinez-Garcia et al., 1993; Novejarque et al., 2004). For example, in frogs (*Xenopus laevis, Rana perezi*), the retrograde tracing of dextran amines showed that the lateral amygdala and lateral aspects of the medial amygdala project bilaterally to the ventrolateral telencephalon (homologous to the mammalian caudate–putamen; Marin et al., 1997). Also similar to mammals, dorsal and caudal aspects of the frog lateral amygdala differentially innervate the ventromedial wall of the telencephalon (homologous to the mammalian NAc (Marin et al., 1997)), along with afferents from the medial amygdala. Similarly, in amphibian newts (*Pleurodeles waltl*), the retrograde tracing of dextran amines from the lateral telencephalic wall (putative ortholog of the mammalian striatum) showed bilateral afferents from the lateral amygdala and ipsilateral afferents from the medial amygdala (Marin et al., 1997). Retrograde tracing from the newt ventral cellular prominence (putative ortholog of the mammalian NAc) identified projections from lateral aspects of the medial amygdala and a smaller contribution from the caudolateral amygdala (Marin et al., 1997). In lizards (*Podarcis hispanica*), the posterior dorsal ventricular ridge (orthologous to the mammalian amygdaloid complex) projects to the ventral striatum, including the NAc; the adjoining dorsolateral amygdala area also projects bilaterally to both the dorsal and ventral striatum (Novejarque et al., 2004). Finally, in zebrafish, coordinated activity in the medial zone of the dorsal telencephalic region (Dm) and dorsal nucleus of the ventral telencephalic area (Vm; teleost orthologs of the mammalian amygdala and striatum, respectively) predict avoidance behavior (Lau et al., 2011). Consistent with an amygdalo-striatal connection, the Dm sends efferents to the Vm in goldfish (Northcutt, 2006). Consistent with the findings of Weiskrantz and his successors in mammals (Weiskrantz, 1956), lesions of the Dm reduce the expression of conditioned avoidance behavior in goldfish (Portavella et al., 2004). The presence of similar amygdalo-striatal circuitry in not only mammals but also marsupials, amphibians, reptiles, and teleost fish contradicts MacLean's view that limbic modulation of the basal ganglia developed with paleomammalian species (MacLean, 1949, 1952). The data instead suggest an ancient role for amygdalo-striatal signaling in motivated behavior.

8. BLA–NAc transmission and plasticity

Across species (Gorbachevskaia, 1992, 1997; Johnson et al., 1994), dopaminergic afferents from the VTA converge postsynaptically on the same dendritic field of medium-spiny neurons in the NAc on which BLA neurons form excitatory synapses (Stuber et al., 2011). High-frequency electrical stimulation of the BLA in awake rats elicited glutamate and dopamine efflux in the NAc (Jackson and Moghaddam, 2001). Accordingly, opti- cal stimulation of *channelrhodopsin-2*-transduced BLA terminals elicited 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) receptor-dependent excitation of postsynaptic NAc medium-spiny neurons (Stuber et al., 2011). The glutamatergic BLA inputs to NAc dopamine terminals synaptically facilitate the release of dopamine, independent of the firing rate of ascending VTA afferents (Floresco et al., 1998; Jones et al., 2010a).

The NAc responses to BLA stimulation exhibit plasticity. Uno provided evidence of long-term potentiation (LTP) in response to high-frequency stimulation (Uno and Ozawa, 1991). Floresco and colleagues later found that tetanic stimulation of the BLA elicited dopamine D_1 and NMDA receptor-dependent short-term (25–30 min) potentiation of NAc firing

probability in response to further BLA stimulation (Floresco et al., 2001a). More recently, the cellular plasticity has been shown to be heterogeneous both within and across the caudal-to-rostral extents of the NAc. Following theta-burst BLA stimulation, some NAc neurons show a short-term depression (<10 min) of BLA-evoked firing probability, whereas others exhibit a longer potentiation. Most neurons in the rostral NAc show short-term depression (86%), whereas enhanced BLA-evoked responsiveness predominates in neurons of the caudal NAc (75%); the rostral–caudal gradient of plasticity response is D_2 receptor-dependent, such that sulpiride pretreatment prevents the regional heterogeneity (Gill and Grace, 2011).

9. Functional co-connectivity and convergence of BLA with other NAc afferents

Corresponding to the reviewed BLA–NAc topography, more caudal neurons in the BLA also co-target the medial NAc and prelimbic cortex, more rostral neurons co-target the lateral NAc and dorsal agranular insular cortex, and intermediate neurons co-target the lateral NAc and medial NAc (Shinonaga et al., 1994). Within a compartmental framework, the convergence of prelimbic cortex, hippocampal, and ventral subicular afferents with BLA afferents is seen within heterogeneous cell clusters of the shell. Some convergence occurs at the single-neuron level with afferents from these interconnected brain regions converging that converge on dendrites of individual NAc shell neurons (French and Totterdell, 2003). In contrast, complementary segregation of paraventricular thalamus from parvicellular BLA fibers is seen in the shell. Finally, afferents from the dorsal agranular insular cortex and mediodorsal thalamus avoid the lateral NAc shell altogether. In contrast to the reviewed shell afferents, projections from the prelimbic cortex, deep dorsal agranular insular cortex, and paraventricular thalamus all converge with BLA afferents in the “patches” but not “matrix” of the core (Groenewegen et al., 1999; Mulder et al., 1998; Wright and Groenewegen, 1995, 1996).

These zones of neuroanatomical interaction influence the synaptic transmission of converging pathways in an activitydependent fashion. Some of these interactions are facilitatory. For example, discrete amygdala pre-stimulation of a BLA-driven single unit in the shell can potentiate the response of that NAc neuron to stimulation of its converging subiculum afferent (Mulder et al., 1998). Theta train stimulation of the BLA can similarly increase converging ventral subiculum-evoked responses in some caudal but not rostral NAc neurons in a D_2 receptor-dependent manner (Gill and Grace, 2011). Likewise, single-pulse activation of converging BLA and mPFC afferents mutually facilitates spiking in their targeted NAc neuron, especially at subthreshold activation levels (McGinty and Grace, 2008, 2009b). Joint tetanic stimulation of converging fimbria and BLA projections likewise facilitates NAc responses evoked from either pathway (Floresco et al., 2001b). Finally, inactivation of converging ventral subiculum afferents can reduce the efficacy of BLA stimulation onto caudal NAc neurons (Gill and Grace, 2011).

In contrast, some converging interactions are competitive in a gating manner. For example, reducing the activation of the prefrontal cortex with an AMPA receptor antagonist or metabotropic glutamate 2/3 receptor (mGluR2/3) agonist disinhibited and hastened the onset of BLA-evoked NAc dopamine release (Jackson and Moghaddam, 2001). In contrast to the facilitatory effect of singlepulse subthreshold stimulation, high-frequency train stimulation of a BLA afferent that was sufficient to elicit NAc firing decreased the probability of mPFC-evoked firing of the same NAc neuron (McGinty and Grace, 2009a). Theta stimulation of BLA inputs can also decrease converging ventral subiculum-evoked responses in a significant minority of NAc neurons (Gill and Grace, 2011). Moreover, tetanic stimulation of the fimbria (hippocampal/subiculum afferent) in the absence of coincident BLA

stimulation yields LTP of hippocampal-evoked NAc responses via D_1 and NMDA receptor-dependent mechanisms, but long-term depression of the converging BLA–NAc pathway via D_1 and adenosine-R1-dependent mechanisms (Floresco et al., 2001b; Mulder et al., 1998). Finally, consistent with an inhibitory action of dopamine on BLA-evoked NAc responses, train pre-stimulation of converging VTA neurons reduced subsequent BLA-evoked NAc activation (Yim and Mogenson, 1982). Accordingly, increased NAc dopamine, via D_1 receptor activation, attenuates glutamatergic synaptic transmission of the BLA–NAc projection (Charara and Grace, 2003).

10. Functional significance of amygdala–ventrostriatal pathways

What aspects of emotional behavior do amygdalo-striatal projections help subserve in coordination with the converging, interactive cortico-striatal, thalamo-striatal, hippocampal–striatal, and ascending midbrain–striatal pathways? As reviewed earlier, Weiskrantz (1956) hypothesized that the amygdala helps associate a stimulus' affective value to its sensory representation. Consistent with a role for the amygdala in stimulus valuation, behavioral responses to negative reward prediction errors (e.g., as in frustrative non-reward or negative contrast), in which an "expected" reward is underprovided, are attenuated by amygdalectomy (Henke et al., 1972; Henke and Maxwell, 1973; Kemble and Beckman, 1970; McDonough and Manning, 1979). Amygdala lesions or inactivation also impairs the formation of conditioned avoidance responses (Nagel and Kemble, 1976) and Pavlovian fear conditioning (Davis, 1990; Miserendino et al., 1990) in rats. Jones, Spiegler, and Miskhin found that lesions that involve the amygdala impair the formation of stimulus-reward associations in monkeys, despite preserved stimulus recognition (Jones and Mishkin, 1972; Spiegler and Mishkin, 1981), a result elegantly corroborated by Gaffan and Harrison using secondary reinforcers (Gaffan and Harrison, 1987; Gaffan et al., 1988).

10.1. Amygdalo-striatal projections and the incentive value of stimulus-reward associations

In a series of reports published in 1989, Robbins et al. provided evidence that the amygdalo-ventrostriatal projections detailed by Kelley and colleagues convey Pavlovian stimulus-reward associations, representing acquired stimulus incentive value in a manner that influences behavior. First, bilateral excitotoxic lesions of the BLA reduced the maintenance of instrumental responding for a conditioned reinforcer (i.e., a conditioned stimulus associated with sexual reinforcement) under a second-order schedule of reinforcement but not for sexual reinforcement itself. The reduced responding was restored by intra-NAc administration of D-amphetamine, but this occurred differentially in the presence of the conditioned reinforcer (Everitt et al., 1989). Similarly, bilateral excitotoxic lesions of the basolateral amygdala complex reduced the acquisition of responding of water-deprived rats for a secondary reinforcer (i.e., a water-conditioned stimulus), without influencing noncontingent water intake, the discrimination of the water-conditioned stimulus, or the acquisition of a new operant response for water (i.e., the primary reinforcer). Intra-NAc D-amphetamine again selectively restored responding for the secondary reinforcer (Cador et al., 1989). Subsequently, Kelley and Delfs (1991) demonstrated that intracerebral D-amphetamine administration differentially and specifically facilitated responding for a conditioned reinforcer when administered into the NAc or surrounding ventromedial striatum compared with the ventrolateral or posterior striatum. Kelley and Throne (1992) also showed that NMDA receptor blockade specifically attenuated the invigorating action of intra-NAc D-amphetamine to promote responding for a conditioned reinforcer. Thus, the ascending mesolimbic dopamine system appears to "gain" the incentive value of Pavlovian stimulus-reward associations that are conveyed by glutamatergic amygdalo-ventrostriatal projections.

Consistent with this interpretation, Everitt et al. (1991) subsequently demonstrated that "disconnection" of the basolateral amygdala complex and ventral striatum, achieved through unilateral, asymmetrical (i.e., contralateral) excitotoxic lesions of each structure, compared with sham lesions or control ipsilateral lesions abolished the expression of classically conditioned preferences for places associated with 20% sucrose access in food-restricted rats. Pointing to a specific role for the amygdala–ventrostriatal pathway, bilateral lesions of the basolateral amygdala complex, ventral striatum, or ventromedial caudate–putamen but not dorsolateral striatum abolished the expression of established place preferences (Everitt et al., 1991). Setlow et al. (2002) demonstrated that contralaterally placed unilateral ("disconnection") lesions of the basolateral amygdala complex and NAc blocked the acquisition of Pavlovian second-order conditioned appetitive responses. Importantly, ipsilaterally lesioned controls (which still had an intact amygdalo-striatal projection in one hemisphere) showed normal second-order performance, which depends upon the acquired value of the first-order conditioned stimulus after being paired with food. The collective results support the hypothesis that amygdaloventrostriatal projections convey the acquired incentive value of classically conditioned, previously neutral, environmental stimuli.

10.2. Amygdalo-striatal projections and the association of actions with valued outcomes

The Kelley laboratory then provided evidence that amygdalostriatal projections also convey value in response-outcome relations. They showed that blockade of NMDA receptors in the NAc impairs the acquisition of both spatial- and operant responsereinforcement associations in food-restricted rats (Kelley et al., 1997; Maldonado-Irizarry and Kelley, 1995). Subsequently, Baldwin and Kelley demonstrated that blockade of NMDA receptors within the lateral/basolateral amygdala also blocked the acquisition (but not expression) of response-reinforcement associations (lever pressing for food). Unilateral blockade of amygdala and NAc NMDA receptors was likewise sufficient to impair the acquisition of operant responding for food, implicating an amygdalo-striatal interaction. The results were both neuroanatomically specific, because NMDA receptor blockade within the dorsal or ventral subiculum did not produce similar effects, and behaviorally specific, because general changes in motor behavior or consummatory behavior were not seen (Baldwin et al., 2000).

The basolateral amygdala is not essential for the acquisition of instrumental conditioning per se, however, because the rats in the studies of Kelley and colleagues were impaired, not absent, in their acquisition. Indeed, Balleine and collaborators showed that food-restricted rats with complete bilateral excitotoxic lesions of the lateral/basolateral amygdala or asymmetric contralateral "disconnection" lesions of the BLA and NAc compartments exhibited normal acquisition of instrumental responding for food under different conditions (Balleine et al., 2003; Shiflett and Balleine, 2010). Rather, BLA lesions appear to impair the encoding of action outcomes. For example, lesioned rats did not show differences between responding for otherwise valued (not pre-fed) vs. devalued (pre-fed) reinforcers in choice extinction and choice reward tests. Responding in lesioned rats also did not decrease appropriately when a reinforcer was provided noncontingently during a session, which otherwise should degrade both its value and the action–outcome contingency. Finally, unlike in sham controls, responding in lesioned rats in a discriminative outcome procedure, in which the reinforcer obtained during a session identified which of two possible operant responses would yield a reinforcer during that session, was insensitive to the discriminative outcome. Basolateral amygdala-lesioned rats did not appear to utilize the discriminative (value) information present in the action's outcome; instead, they persistently emitted their preferred operant response even when it did not yield reinforcer delivery (Balleine et al., 2003).

A specific role for BLA–ventrostriatal interactions in representing the predictive association between actions and their valued outcomes is implicated by the finding that asymmetric

"disconnection" excitotoxic lesions of the BLA and NAc core but not ipsilateral lesions also rendered rats insensitive to sensory-specific reinforcer devaluation by pre-feeding (Shiflett and Balleine, 2010). Also consistent with this hypothesis, pharmacological "disconnection" of the BLA from the NAc by unilateral inhibition of the BLA (via muscimol) and contralateral NAc (via α-flupenthixol) reduced the expression of high-ratio-requirement (i.e., fixed-ratio 16) operant responding for food but not free food intake in food-restricted rats. The same effects were seen following bilateral administration of either pharmacological treatment but not following ipsilateral administration, implicating BLA–NAc interactions (Simmons and Neill, 2009).

The insensitivity to outcome value that results from contralateral BLA–NAc core lesions is specific to the core compartment because combining BLA lesions with contralateral NAc shell lesions does not yield the same effect (Shiflett and Balleine, 2010). A double dissociation, asymmetric lesion disconnection of the BLA from the NAc shell but not core reduces the outcome-specific, cued invigoration of instrumental responding characteristic of Pavlovian-instrumental transfer. Thus, when presented with a cue stimulus that had previously been classically conditioned with reinforcer delivery, rats with contralateral BLA–NAc shell lesions failed to increase their operant responding for the same reinforcer (i.e., outcome-specific "transfer" of the Pavlovian excitation). Deficits in outcome-specific Pavlovian transfer to instrumental responding likewise are seen in rats with bilateral lesions of the BLA (Corbit and Balleine, 2005) or NAc shell (Corbit et al., 2001) or following bilateral inactivation of the NAc shell (Corbit and Balleine, 2011). Such effects are not seen on baseline response rates or in rats with ipsilateral BLA–NAc shell lesions or contralateral BLA–NAc core lesions (Shiflett and Balleine, 2010). Recent high-resolution functional neuroimaging data implicated activation of a ventral portion of the human BLA in outcome-specific Pavlovian-instrumental transfer (Prevost et al., 2012). Thus, whereas BLA–NAc core interactions convey the relations of actions to valued outcomes, BLA–NAc shell interactions may represent the incentive relations of Pavlovian cues to valued outcomes. Both processes serve to guide behavior.

10.3. Amygdalo-striatal projections and the discriminative stimulus control of reward seeking

Ambroggi et al. (2008) provided evidence that amygdalo- ventrostriatal projections also convey the discriminative, reward-predictive value of previously neutral stimuli. Foodrestricted rats were first allowed to learn that one auditory discriminative stimulus signaled the availability of 10% sucrose solution via lever pressing, whereas a different auditory stimulus signaled non-availability. Unilateral inhibition ("disconnection") of the BLA complex (via baclofen and muscimol) and contralateral NAc core (via the D_1 receptor antagonist SCH23390) selectively reduced the ratio but not latency of sucrose-directed responding in the presence of the discriminative stimulus and did so to a greater degree than did ipsilateral inactivation. They further showed that the discriminative stimulus evoked sustained excitation of BLA neurons (several seconds), whereas the non-discriminative stimulus elicited an identical initial (~100 ms) excitation, which then rapidly returned to baseline. Within the NAc core, in contrast, discriminative stimuli uniquely or differentially excited the majority of neurons compared with non-discriminative stimuli during both the early (~100–200 ms) and sustained (seconds) phases of excitation. The mean onset of NAc excitation lagged behind BLA excitation by ~40 ms, consistent with downstream information processing. Consistent with coupling as well, those neurons within the BLA and NAc that most rapidly (~100 ms) showed differential excitation in response to discriminative vs. non-discriminative stimuli showed similarly fast response latencies to one another (Ambroggi et al., 2008). Basolateral amygdala inactivation reduced both the discriminative stimulus- and non-discriminative stimulus-induced excitation of ipsilateral

NAc core neurons, consistent with the proposed BLA–NAc flow of information. Accordingly and replicating reviewed electrophysiological findings (Ito et al., 1974; Powell et al., 1968; Sato, 1977; Yim and Mogenson, 1982), electrical stimulation of the BLA rapidly excited 16% of ipsilateral NAc neurons. More compelling, BLA-evoked NAc neurons in the ipsilateral hemisphere were disproportionately the same ones that were excited by the discriminative stimulus, and most of these had monosynaptic-like BLA-evoked latencies (4–20 ms; Ambroggi et al., 2008). The results support the hypothesis that the direct BLA–NAc core projection conveys the acquired incentive value of previously neutral, discriminative stimuli that signal the availability of valued outcomes.

Accordingly, Jones et al. (2010a,b) found that discriminative stimuli predictive of operant access to sucrose pellets in foodrestricted rats elicit greater dopamine release in the NAc core than do non-discriminative stimuli. Unilateral inactivation of the BLA (via muscimol and baclofen) was sufficient to reduce discriminative stimulus-evoked approach behavior and increase instrumental response latencies. Unilateral BLA activation selectively reduced discriminative stimulus-elicited neuronal excitation (Jones et al., 2010b) and dopamine levels (Jones et al., 2010a) in the ipsilateral NAc core, without influencing the effects of the non-discriminative stimulus on these endpoints. Moreover, excitation in the NAc shell and contralateral NAc core were unaffected by BLA inactivation (Jones et al., 2010b). The results suggest that discriminative stimuli may facilitate reward-directed behavior in part via BLA-evoked excitation and dopamine efflux in the core compartment of the NAc.

In a fascinating set of complementary findings, Popescu et al. (2009) demonstrated in cats that coordinated gamma oscillations emerge between local field potentials in pyramidal neurons of the BLA complex and medium spiny neurons of the ventral putamen during the acquisition of a discriminative stimulus. Under baseline (pre-learning) conditions, they observed that coherence of gamma oscillations was much greater between striatal and BLA field potentials than between cortico-amygdalar, thalamo-amygdalar, cortico-striatal, or thalamo-striatal relations. Consistent with the existence of a BLA $\rightarrow$ ventrostriatal projection underlying the gamma coherence: (1) the gamma coherence between the BLA and ventral putamen uniquely exhibited a reliable phase lag, (2) spontaneous BLA and striatal unit activity showed coupling during periods of high-amplitude gamma oscillations, and (3) BLA inactivation (via muscimol) differentially reduced the power of striatal gamma activity under baseline conditions. Food-restricted cats were then allowed to learn that one auditory tone immediately preceded the availability of a palatable liquid (i.e., pureed sweet potatoes and turkey baby food), whereas another tone did not. Initially, both stimuli elicited comparable transient increases in coherent BLA-striatal gamma activity. With learning, however, the discriminative stimulus elicited greater BLA-striatal gamma coupling than did the non-predictive stimulus. The emerging coherent gamma differential between the two stimuli correlated directly with the emergence and frequency of discriminative stimulusevoked anticipatory licking at the sipper. With reversal learning, the new discriminative stimulus also came to elicit larger increases in coordinated BLA-striatal gamma activity in direct relation to changes in anticipatory licking. All of these changes were unique to the BLA–ventral putamen relation and were not seen between the other pairs of recording sites. The results suggest that not only BLA projections to the NAc core but also connections to the functionally related ventral putamen transmit the reward-predictive value of previously neutral discriminative stimuli and provide insights into the possible mechanism of influence.

Consistent with the overarching view that excitation of the BLA-to-NAc projection conveys incentive instrumental value, selective optogenetic, *channelrhodopsin-2*-dependent activation of the pathway is reinforcing to mice in a D_1 receptor-dependent manner (Stuber et al., 2011). Conversely, selective optogenetic, *halorhodopsin*-dependent silencing of the

pathway during repeated pairings of a neutral auditory stimulus and contiguous access to sucrose solution blocks the development of cued anticipatory or consummatory licking at the reward sipper otherwise seen in controls (Stuber et al., 2011).

10.4. Hypothesized role of amygdalo-striatal projections in disincentive motivation

Killcross et al. (1997b,c) proposed that projections from the BLA to the ventral striatum also may mediate the acquisition of negative incentive value, such as by shock-paired stimuli in a conditioned punishment procedure, and thereby also subserve instrumental choice behavior vis-a-vis noxious events. Accordingly, systemic administration of the indirect dopamine agonist D-amphetamine or dopamine antagonist α-flupenthixol potentiated or diminished, respectively, the influence of not only a conditioned reinforcer but also a conditioned punisher on instrumental responding, without influencing operant responding with neutral stimuli (Killcross et al., 1997a). Consistent with the hypothesis that the amygdalo-striatal projection helps convey negative incentive value to stress-paired stimuli or actions, Setlow et al. (2000) showed that the glucocorticoid-facilitated retention of passive avoidance of footshock was eliminated by asymmetric, contralateral ("disconnection") lesions but not ipsilateral, excitotoxic lesions of the BLA and NAc. Also consistent with this view, lesion or inactivation of the BLA can block NAc dopaminergic responses to previously conditioned aversive stimuli. For example, intra- BLA administration of the GABA agonist tetrodotoxin blocked the depression of NAc core dopamine efflux that otherwise resulted from exposure to a LiCl-conditioned (aversive) olfactory stimulus. In parallel with its action on core dopamine efflux, BLA inactivation also eliminated the expression of place aversion to the aversive stimulus (Louilot and Besson, 2000).

11. Psychopathological role of amygdalo-striatal circuits in motivated behavior

11.1. "Light side" of the central extended amygdala

In addition to playing a role in the reinforcing effects of food as shown by the Kelley laboratory (Andrzejewski et al., 2004, 2005), the central extended amygdala plays a key role in the acute, primary reinforcing effects of drugs of abuse. For example, local administration of dopamine D_1 receptor antagonists directly into the medial NAc, CeA (Caine et al., 1995), and lateral BNST (Epping-Jordan et al., 1998) reduced intravenous cocaine self-administration. Similarly, the reinforcing effects of ethanol were blocked by intra-CeA administration of GABAergic and opioidergic antagonists (Heyser et al., 1999; Hyytia and Koob, 1995), and excitotoxic lesions of the CeA reduced ethanol self-administration (Moller et al., 1997).

The correspondence of activation of the CeA to increased drug, ethanol, or palatable food consummatory behavior is consistent with Kelley and colleagues' finding that silencing the CeA prevents increases in food consummatory behavior (Baldo et al., 2005; Will et al., 2004).

11.2. "Dark side" of the central extended amygdala

In addition to mediating the positive reinforcing effects of some substances of abuse, the central extended amygdala has been implicated in neuroadaptive processes that come to motivate behavior during withdrawal or extended drug taking via negative reinforcement mechanisms (Cottone et al., 2009; Koob, 2003, 2009, 2010; Koob and Le Moal, 2005; Parylak et al., 2011). Some of these changes involve within-neurochemical system, opponentprocess "anti-reward" neuroadaptations. For example, whereas the acute reinforcing and rewarding effects of cocaine involve increased extracellular dopamine in the medial NAc (Pontieri et al., 1995), continuous self-administration of cocaine for 12 h

ultimately decreases levels in the same region (Parsons et al., 1995). Decreased activity of NAc dopamine and serotonergic systems is also seen during drug withdrawal in animal models (Diana et al., 1992; Parsons et al., 1995; Rossetti et al., 1992a,b,c; Weiss et al., 1992).

Other changes involve the between-neurochemical system recruitment of brain stress circuitry within the extended amygdala, perhaps reflecting a functional opponent-process to excessive, drug-induced reward system activation. For example, as our group has reviewed previously (Koob, 2003, 2009, 2010; Koob and Le Moal, 2005; Koob and Zorrilla, 2010; Logrip et al., 2011; Parylak et al., 2011; Zorrilla and Koob, 2010), acute withdrawal from drugs of abuse, ethanol, and palatable high-sucrose diets is associated with activation of CeA corticotropin-releasing factor (CRF) systems. Furthermore, systemic or site-specific administration of CRF antagonists into components of the extended amygdala can differentially reduce the anxiety-like behavior, motivational deficits for other reinforcers, and increased self-administration of addictive substance that are seen during withdrawal in animal models of addiction. A similar role for aversive dynorphin-κopioid receptor activation within the central extended amygdala has been proposed (Shippenberg et al., 2007; Wee and Koob, 2010).

The central extended amygdala also appears to play a major role in the stress-induced reinstatement of drug-, ethanol-, and palatable-food seeking (Kalivas and McFarland, 2003; Koob, 2010; Koob and Zorrilla, 2010; Logrip et al., 2011; McFarland et al., 2004; Nair et al., 2009; Parylak et al., 2011; Shaham et al., 2000, 2003; Shalev et al.,2002, 2010; Zorrilla and Koob, 2010). For example, inactivation of the CeA or BNST can prevent stress-induced reinstatement, as does microinfusion of CRF antagonists or noradrenergic antagonists into the CeA or lateral BNST. Altogether, the results suggest a major role for anti-reward and stress-like neuroadaptations within the central extended amygdala in promoting drug-seeking or self-administration behavior (Koob, 2009, 2010; Koob and Le Moal, 2005; Koob and Zorrilla, 2010; Logrip et al., 2011; Parylak et al., 2011).

11.3. BLA–ventral striatum: emotional memory and acquired (dis)incentive value

In the context of addiction, projections from the deep basal nuclei of the amygdala (BLA, BMA) to the extended amygdala, corticostriatal circuits, and ventral striatum can be conceptualized as conveying the drug- or withdrawal-conditioned incentive value through which previously neutral stimuli gain control over behavior (Kelley et al., 2005). Thus, the projections subserve instrumental phenomena such as drug cue-induced reinstatement of drug-seeking and drug-cue directed operant behavior (Milton et al., 2008a); Pavlovian phenomena such as conditioned approach (e.g., place preferences) or conditioned withdrawal (e.g., place aversion) behavior (Milton et al., 2008b); and Pavlovian cue-induced, outcome-specific facilitation of drug-seeking behavior.

Accordingly, excitotoxic lesions of the BLA block cocaineseeking behavior under a second-order schedule (Whitelaw et al., 1996), effects recapitulated by pharmacological “disconnection”, in which a dopamine antagonist is administered into the BLA, and an AMPA-kainate receptor antagonist is administered into the contralateral NAc (Di Ciano and Everitt, 2004). Basolateral amygdala inactivation also reduces cocaine cue-induced locomotor activity (Chefer et al., 2011). Moreover, excitotoxic lesions of the BLA (Meil and See, 1997), BLA inactivation (Grimm and See, 2000; Kantak et al., 2002), D_1 antagonism in the BLA (See et al., 2001), and *zif268* knockdown in the BLA (Hellemans et al., 2006) all prevent cue-induced reinstatement of extinguished drug seeking (but not self-administration of the primary drug reinforcer). Similarly, intra-BLA administration of the mGluR5 antagonist MTEP reduced cue-induced reinstatement of ethanol-seeking behavior (Sinclair et al., 2012), and intra-BLA blockade of opioid receptors reduced context-induced

reinstatement of ethanol seeking (Marinelli et al., 2010). Consistent with these findings, cue-induced reinstatement of drug and ethanol seeking are associated with increased neuronal activation and glutamatergic synaptic transmission in the BLA (Gass et al., 2011; Jupp et al., 2011; Madsen et al., 2012).

The BLA is also involved in multiple stages of Pavlovian stimulus-drug reward and stimulus-withdrawal aversion association learning and memory. For example, rats with BLA lesions do not develop conditioned opioid withdrawal (Schulteis et al., 2000). The activation state of dopamine D_1 and D_2 receptors in the BLA bidirectionally modulates the ability of morphine to promote conditioned place preferences in opiate-naive and withdrawn, opiate-dependent subjects, respectively (Lintas et al., 2011, 2012). Inhibition of protein kinase Mζ within the BLA prevents the maintenance of opioid-conditioned place preferences and opioid withdrawal-conditioned place aversions (He et al., 2011). Knockdown of protein synthesis or several plasticityrelated molecules within the BLA (e.g., *zif268*, neuronal protein kinase cyclin-dependent kinase 5) can impair the consolidation or reconsolidation of drug-conditioned place preferences, drug withdrawal-conditioned place aversions, and the memory for drug contexts that otherwise would reinstate drug-seeking behavior (Fuchs et al., 2009; Li et al., 2010; Theberge et al., 2010; Wu et al., 2012). Accordingly, drug- and palatable food-conditioned stimuli (Ciccocioppo et al., 2001; Kelley et al., 2005; Kufahl et al., 2009; Lucas et al., 2008, 2012; Schiltz et al., 2005, 2007; Weiss et al., 2000) as well as withdrawal-conditioned stimuli (Frenois et al., 2005; Hellemans et al., 2006; Li et al., 2009; Lucas et al., 2012) elicit neuroactivational responses in the BLA in both animals and humans (Bonson et al., 2002; Childress et al., 1999; Grant et al., 1996; Kilts et al., 2001). The degree to which direct amygdalo-striatal projections mediate these functions compared with complementary projections from the BLA to cortico-striatal and extended amygdala circuitry remains to be determined.

11.4. BLA–dorsal striatum: once conditioned value, now conditioned habit?

Although a key contribution of Kelley, Domesick, and Nauta's neuroanatomical study in 1982 was to reinforce the existence of direct projections from the deep basal nuclei of the amygdala to the caudate–putamen in the dorsal striatum, the functional significance of these connections still remains largely unknown 30 years later. Both primate and rodent studies have implicated the posterior dorsomedial striatum, networked with the medial parafasicular nucleus and prefrontal cortical areas, in the cognitive control of goal-directed action selection. In contrast, the dorsolateral striatum, networked with ventrolateral and ventral anterior nuclei and sensorimotor cortices, subserves the learning and perfor- mance of non-goal-directed, outcome-independent habits (Shiflett and Balleine, 2011). The competition between these regions has been implicated in action selection (i.e., controlled, goal-directed behavior vs. uncontrolled habitual behavior). The role of prominent cortical and thalamic afferents to each of these regions, forming cortico-striatal–pallidal–thalamic loops that influence the competition of stimulus–response valuation and, thereby, action selection, have received substantial attention. Those described by Kelley and colleagues from the allocortical BLA have not.

Interestingly, however, several recent functional neuroimaging findings suggest that obese humans show heightened food cueevoked functional activation and connectivity of the dorsal striatum and amygdala. Such effects may undesirably facilitate food stimulus (palatable food smell)-behavioral response (eat) relations. First, obese subjects showed greater regional brain glucose uptake with positron emission tomography in the dorsal caudate and amygdala compared with controls (Nummenmaa et al., 2012). Second, obese subjects showed heightened amygdala functional magnetic resonance imaging (fMRI) responses to food stimuli than did controls (Stoeckel et al., 2008). Third, obese subjects showed differentially increased hemodynamic fMRI responses in the caudate/dorsal striatum

in response to pictures of palatable vs. bland food compared with controls (Nummenmaa et al., 2012; Rothemund et al., 2007; Stoeckel et al., 2008). Fourth, the palatable food imagery-related functional connectivity of the amygdala with the dorsal caudate was greater in obese subjects than in controls (Nummenmaa et al., 2012). The collective results suggest the hypothesis that abnormal food cue-evoked excitation of an amygdalo-caudate pathway may contribute to habitual (i.e., automatic, uncontrolled, and not goaldirected) excessive food intake. Further investigation of projections from the BLA to different compartments of the dorsal striatum appears warranted.

12. Conclusion

Thus, the original hypothesis of MacLean that the amygdala was a key part of the "paleomammalian limbic system" that adaptively modulates activity of the "reptilian" basal ganglia was transitioned to modern neurobiology by the pioneering work of Ann Kelley and her associates. From her work with Nauta and later with her own team, a clearer picture evolved on the motivational significance of BLA projections to the ventral striatum and the extended amygdala macrostructure. Direct amygdalo-ventrostriatal projections, in conjunction with well-studied cortico-striatal–pallidal–thalamic and hippocampal–striatal circuits, form part of a distributed motivational network (Ernst and Fudge, 2009; Gruber and McDonald, 2012; Kelley, 2004; Koob and Le Moal, 2006; Meredith et al., 2008; Sesack and Grace, 2010; Thompson and Swanson, 2010) that, by associating actions and predictive cues with the value of successive events (Morrison and Salzman, 2010), guide the acquisition and expression of adaptive motor behavior. In parallel, the central extended amygdala represents an indirect amygdalo-striatal entity that influences stimulus–response valuation both by acutely mediating primary reinforcement and by neuroadaptive stress and anti-reward processes that contribute to negative reinforcement mechanisms. Dr. Kelley's work has provided a heuristic framework for elucidating not only the neurocircuitry of motivation and emotion but also, and perhaps more importantly, the plasticity in the neurocircuitry that underlies the psychopathology of motivation.

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Highlights

► Ann Kelley studied functionally distinct direct vs. indirect amygdalostriatal pathways. ► The entire caudal striatum receives afferents from deep basal amygdalar nuclei. ► The rostral ventromedial striatum differentially receives amygdalar input. ► The ancient amygdala-to-striatum pathways participate in stimulus–response valuation. ► Plasticity in the pathways underlies addiction-related memory, craving and relapse.