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Review

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. 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". Caudal of the anterior commissure, the entire striatum receives afferents from deep basal nuclei of the amygdala. 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 addiction-related memory, craving and relapse.

Contents

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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, 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 differentiated 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. These and other findings formed part of a larger body