Amygdala

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Amygdala

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Definition

The amygdala is a historically grouped complex of 13 nuclei in the brain, together receiving inputs from and projecting to nearly every part of the central nervous system, supporting a wide variety of functions including associative learning, emotional learning, and responsivity, as well as ingestive, sexual, and social behavior.

Introduction

The amygdala is a historically grouped complex of 13 nuclei in the brain, each differing in structure, connectivity, and function and together receiving inputs from and projecting to nearly every part of the central nervous system (Swanson and Petrovich 1998). Amygdala circuits support a wide variety of functions including associative learning, emotional learning, and responsivity, as well as ingestive, sexual, and social behavior (Aggleton 2000). Traditionally the amygdala has been divided into the basolateral (BLA), medial (MeA), central (CeA), and cortical (CoA) nuclei, and this will be the vastly oversimplified scheme used for the purposes of this entry (Fig. 1) (McDonald 1998). Amygdalar nuclei might potentially be grouped as structural extensions of the neocortex, claustrum, and striatum but can also be functionally separated into four systems: main olfactory, accessory olfactory, autonomic, and frontotemporal cortical systems. While some argue that the historical category of "amygdala" ought to be eliminated, there are also advocates of the term "extended amygdala," which states that central and medial amygdala form continuous structures with the lateral and medial divisions of the bed nucleus of the stria terminalis, and thus those regions should be included as members in the amygdaloid complex (Swanson and Petrovich 1998). Cats, rats, and monkeys each have cortical connectivity with the amygdala that relay visual, auditory, and somatosensory information. More direct connectivity from olfactory, gustatory, and visceral areas is also preserved across these species bypassing much of higher-level cortical processing (McDonald 1998).

Historically, the amygdala has been mischaracterized as the "fear center of the brain"; however, the fear response is only a subset of negative affective states resulting in withdrawal, escape, and avoidance responses that involve amygdalar function (LeDoux 2003; Paré and Quirk 2017). The amygdala is not limited to negative emotional states, as amygdalar nuclei also play an important role in positive emotional states resulting in attraction or approach response, and is

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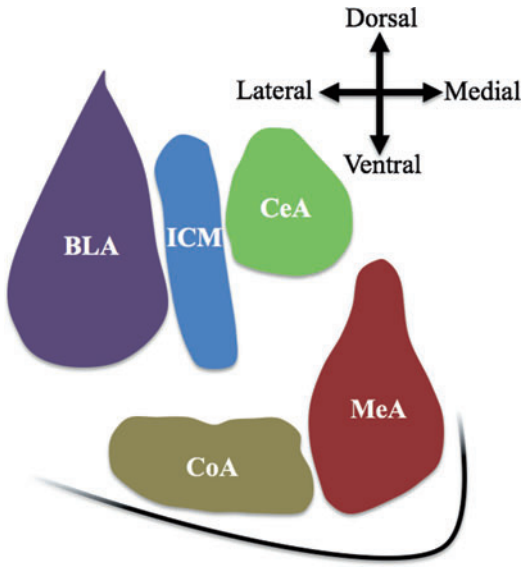

Amygdala, Fig. 1 A simplified representation of the basolateral (BLA), medial (MeA), central (CeA), and cortical (CoA) nuclei of the amygdala

thus better characterized as playing an important functional role in emotional learning more generally (Gallagher and Chiba 1996). In addition to emotional and associative learning, the amygdala plays a key role in the acquisition and consolidation of emotional memories by interacting with hormonal and neuromodulatory systems (McGaugh 2004).

Historical Developments

In 1819, Burdach first described the collection of gray matter in the anterior portion of the medial temporal lobe, which appeared to form the shape of an almond, that he coined the "amygdala" (from the Greek for "almond," Latin for "two tonsils"). In 1867, Meynert provided an anatomical description of the structure. By 1923, Johnston provided a rich anatomical description of the "amygdaloid complex" which he dissociated into a set of phylogenetically older set of nuclei (the central, medial, and cortical nuclei) and a newer set of nuclei (the basal and lateral nuclei) associated with olfaction (Swanson and Petrovich 1998).

In 1888, Brown and Schafer were the first to describe a taming effect on monkeys after the removal of their temporal lobes. However, the amygdala was thought to be primarily associated with olfaction until Kluver and Bucy studied the effect of temporal lobe lesions in monkeys in 1939, where they observed a wide variety of changes in tameness, hyper- and hypoemotionality, and hypersexuality that became known as Kluver-Bucy syndrome (Gallagher and Chiba 1996). In the late 1940s, MacClean developed a theory of the "visceral brain," which included the amygdaloid complex as a more primitive and emotional "limbic system" (LeDoux 2003). In 1952, evidence was found that temporal lobe seizures were initiated with a primary neurological discharge originating from the amygdaloid region. Building on Hess's discovery that stimulation of the hypothalamus could elicit a range of autonomic and stereotyped behavioral responses, along with similar studies of the brainstem, a series of simulation experiments in cats, dogs, and primates strengthened the amygdala's hypothesized role in generating these responses (Gloor 1955). By creating more targeted lesions of the amygdaloid complex, Weizkrantz demonstrated its role in emotional learning by giving neutral cues biological significance and by showing that amygdalar damage alone could account for the symptoms observed in Kluver-Bucy syndrome (Gallagher and Chiba 1996).

From the 1960s onward, the neuroscientific study of the amygdala progressively developed "tunnel vision," driven by NIH funding treatment of anxiety disorders. Given the region's robust responsivity to fearful stimuli, the neuroscientific community published a vast number of papers associating the amygdala specifically with fear (Paré and Quirk 2017). The first study highlighting the role of the amygdaloid complex in classical fear conditioning was published in 1963. In 1972, it was demonstrated that amygdalar lesions led rats to exhibit reduced freezing responses to exposure to a natural predator (cat) and to a conditioned stimulus (CS) after being paired with a shock, suggesting a key role in defensive responsiveness (Aggleton in Aggleton 1992). Subsequent key contributions detailing the functional

role of the amygdala in fear conditioning cemented fear research as the most dominant paradigm in amygdala research (LeDoux in Aggleton 1992; Davis in Aggleton 1992).

Functional Properties of Amygdalar Nuclei (BLA, CeA, MeA, CoA)

The basolateral amygdala (BLA), often thought of as the sensory interface of the amygdala, receives primarily excitatory thalamic and cortical sensory projections and consists of the lateral (LA), basal, and accessory basal nuclei (LeDoux 2003; Paré and Quirk 2017). Lesions to the basolateral amygdala lead to impaired conditioning where a stimulus acquires biological value and results in impaired second-order Pavlovian conditioning. Lesions to the BLA also eliminate the unconditioned stimulus (US) devaluation effect. US devaluation occurs after training a CS-US pairing, and subsequently pairing that US with a different aversive CS, resulting in a diminished CR (Gallagher in Aggleton 1992). Connectivity between the BLA and prefrontal regions allows for top-down control (Paré and Quirk 2017). The BLA is also recruited for the consolidation of emotional memory, by mediating the memory-modulating effects of stress hormones (corticosterones and glucocorticoids such as cortisol) and affecting multiple neuromodulatory systems (norepinephrine, cholinergic) (McGaugh 2004).

The central amygdala (CeA) is often thought of as the amygdalar nucleus responsible for generating behavioral and autonomic responsivity in relation to the sensory stimuli relayed from the BLA and is the main output nucleus of the amygdala with projections to brainstem, hypothalamic, thalamic, and cortical regions (Pitkanen in Aggleton 1992). The central nucleus has the capability of triggering a wide variety of autonomic responses such as tachycardia, bradycardia, hypoalgesia, endocrine arousal, respiratory changes, and the release of insulin. Lesions to the CeA result in deficits in appetitive conditioning. CeA damage also impairs conditioned bradycardia and abolishes the fear enhancement of the startle response (Gallagher in Aggleton 1992).

The medial amygdala (MeA), functionally associated with the accessory olfactory system which emphasizes inputs from the vomeronasal organ, plays a role in pheromone and odor processing, social recognition, predator identification, and sexual behavior. The MeA receives inputs from the accessory olfactory bulb and has projections to hypothalamic regions associated with defensive and reproductive behavior (Pitkanen in Aggleton 1992; Swanson and Petrovich 1998).

The cortical amygdala (CoA) is part of the main olfactory system and receives spatially distinct inputs from the glomeruli of olfactory bulb, which are responsible for representing specific types of odorants. The innate aversion and attraction to certain odors depend on the connections between the olfactory bulb and cortical amygdala, and these responses often reflect the evolutionary history of that species. For instance, if a rat is presented with odors prevalent in predator feces or urine, such as 2,5-dihydro-2,4,5-trimethylthiazoline (TMT), the cortical amygdala will trigger innate behavioral responses such as freezing or escape behaviors despite never having actually encountered the predator within its lifetime (Rosen et al. 2015).

Two Examples of Emotional Processing: Auditory and Context Fear Conditioning

In classical fear conditioning, a neutral cue or sensory stimulus (CS) is paired with a noxious US until the CS elicits a fear response. Fear is generally expressed as freezing and startle responses coupled with autonomic changes in heart rate and respiration (Davis in Aggleton 1992). In the canonical fear circuit, during auditory fear conditioning, a tone CS enters the LA via the medial geniculate nucleus of the thalamus and cortical auditory projections (LeDoux 2003; Davis in Aggleton 1992). As the CS becomes associated with the US, a dorsal group of LA cells induce plasticity (Chapman and Chattarji in Aggleton 1992). These neurons project to the CeA

which generates the autonomic and defensive behaviors via the hypothalamus (sympathetic nervous system), periaqueductal gray (freezing), and neuromodulatory systems associated with arousal (LeDoux 2003).

It is now generally accepted that the canonical fear circuit is more complex than previously envisioned. It has been shown that amygdala-projecting auditory thalamic and cortical neurons also demonstrate CS responsiveness, suggesting that the LA is not the only site of plasticity in the canonical fear circuit (Paré and Quirk 2017). LA projections to CeA are hypothesized to be mediated by feedforward inhibition from the GABAergic cells in the intercalated cell mass. Lesion studies suggest that the intercalated cells are necessary for fear extinction; they are primarily GABAergic and are hypothesized to manage the inhibitory tone of the amygdala. The intercalated cell mass also receives inputs from medial frontal cortex which play an important role in maintaining the extinction of fear (Paré et al. 2004).

When fear conditioning takes place in a particular place or context, then the fear response can generalize to that context. Contextual information is relayed from hippocampal regions to the BLA (LeDoux 2003). The medial prefrontal cortex is also posited to play a role in the representation of emotion-sensitive contextual information for context fear. Stimulation of the hippocampal neurons which project to the BLA elicits an evoked field potential in BLA, and damage to this circuitry impairs freezing to the conditioned context (LeDoux 2003). Interestingly, if an animal is allowed to avoid the place where conditioning occurred or learns how to escape from the conditioned stimulus, then BLA lesioned rats indicate the retention of fear memory (McGaugh 2004).

Future Directions

Future directions in the field include understanding how particular cell groups in specific subnuclei of the amygdala work with the hippocampus and the prefrontal cortex to regulate the hypothalamic-pituitary-adrenocortical axis, which have consequences for a wide variety of hormonal and neuromodulatory systems related to system-wide arousal responses (McGaugh 2004). Fear researchers are seeking to generalize their findings to more ecologically and ethologically valid experimental paradigms than traditional Pavlovian conditioning paradigms. The frontier of amygdala research involves using advanced techniques (such as optogenetic activation, precise neural recordings, and viral tracing methods) to contextualize the function of each amygdalar nuclei and their cell types within the complex networks of neural systems in which they are embedded.

Cross-References

- ▶ Classical Conditioning
- ▶ Conditioned Response (CR)
- ▶ Conditioned Stimulus (CS)
- ▶ Hippocampus
- ▶ Hypothalamus
- ▶ Neuron
- ▶ Neurotransmitters

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