
Hypothalamus and Limbic System, Lecture 2

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Emotion and reward

- Emotional experience, and the ability to reflect upon our emotions, forms an integral part of our lives, guiding our actions and enriching our sense of satisfaction. Rewards, both good and bad, play an integral role in modulating emotions and motivated behavior.
- As we shall see, emotions are mediated by the limbic system, which includes the hypothalamus. The limbic system is a complex set of interconnected brain areas that integrate information about sensory stimuli, memories, and cognitive plans to produce emotional learning and emotional experience.

Lecture 2: Emotion and Reward in the Limbic System

- Review of old theories of emotion.
- The hypothalamus and emotion: sham rage and stimulation of the hypothalamus.
- Overview of the purpose and anatomy of the limbic system.
- The amygdala and emotion.
 - Kluver-Bucy syndrome and amygdala lesions link the amygdala to emotional processing in monkeys.
 - Human neuroimaging and lesion studies have confirmed the role of the amygdala.
 - Fear conditioning and the study of aversive emotional systems in animals and humans.
 - The amygdala may also modulate emotional memory storage elsewhere in the brain.
- Reward systems in the brain.
 - Self-stimulation identifies reward circuits.
 - Physiology of reward circuits: reward encoding neurons provide a "learning signal".
 - Drugs of abuse act on reward circuits.

Darwin and emotion

- In 1872, Darwin wrote *The Expression of Emotions in Man and Animals*.
- This seminal work made apparent the absolute relevance of studying emotion in animal models.
- It also laid out the idea that autonomic responses are an intrinsic part of the emotional experience.
- The peripheral, skeletomotor, and autonomic aspects of emotion serve important functions in communication with others and in preparation for behavioral responses.



William James on emotion

- “What kind of emotion of fear would be left if the feeling neither of quickened heartbeats nor of shallow breathing, neither of trembling lips nor of weakened limbs, neither of goose-flesh nor of visceral stirrings, were present, it is quite impossible for me to think...I say that for us emotion dissociated from all bodily feeling is inconceivable.”

Theories of emotion

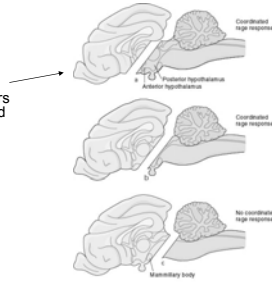
- Theories of emotion have evolved over the last 100+ years. In the late 19th Century, William James and Carl Lange developed a theory of emotion that held that:
 - Autonomic responses are reflex reactions that occur quickly, commencing, and sometimes finishing, before conscious perception of emotion occurs.
 - Emotional experience is the perception that arises from the autonomic changes. In other words, emotional experience follows and reflects autonomic reactivity.

Theories of Emotion (2)

- The James-Lange theory of emotion fails to account for the fact that emotional feelings can extend well beyond the time of autonomic arousal.
- In the 1920s, Walter Cannon and Philip Bard proposed an alternative theory. They argued that visceral sensation can not account for emotion, and that a central system for emotional experience that was separate from the brain system for visceral sensation was required.
- Cannon's and Bard's studies suggested that two subcortical areas, the hypothalamus and the thalamus, play a key role in mediating emotion. They advocated that these structures could regulate peripheral aspects of emotion (e.g. autonomic responses), as well as provide the cortex with appropriate information for cognitive processing of emotion.

Cannon-Bard theory of emotion and sham rage

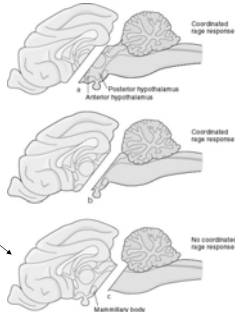
- Bard, a student of Cannon's, made serial transections, essentially disconnecting the cerebral cortex from outflow pathways in cats. When transection just included the forebrain (a), a range of behaviors constitutive of rage was observed when a cat was presented with innocuous stimuli.
- These behaviors included:
 - Arching of the back
 - Extension of claws
 - Hissing
 - Spitting
 - Pupil dilation
 - Increased blood pressure, heart rate and adrenal secretion



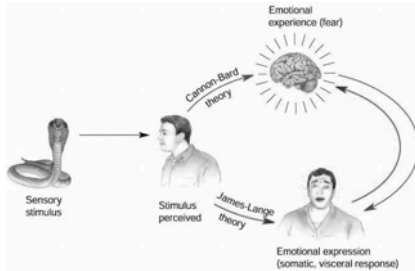
Ashby & Lange
Research in Animal Psychology
 Principles of Neuro Science

Cannon-Bard theory of emotion and sham rage (2)

- This rage was called "sham rage" because animals retained emotional responses, but the responses lacked aspects of emotional behavior that was normally observed during rage. Besides being elicited by innocuous stimuli, sham rage subsided rapidly upon stimulus removal and was undirected; animals even bit themselves.
- When Bard performed progressive transections (b and c), when the posterior hypothalamus was disconnected, no coordinated rage response was observed.



Two theories of emotion



Hypothalamus and emotion

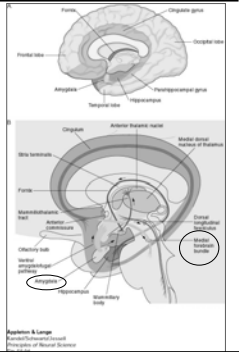
- The sham rage experiments established the hypothalamus as playing a prominent role in coordinating emotional behavior.
- Further studies by Stephen Ranson in the 1930s and by Walter Hess in the 1940s extended these findings. These investigators placed electrodes in the hypothalamus (Ranson in anaesthetized animals, and Hess in unanaesthetized animals) and applied stimulation. Hess found that stimulating different parts of the hypothalamus produced characteristic reactions that appeared to correspond to specific emotional states. For example, stimulation of the lateral hypothalamus caused autonomic and somatic responses consistent with anger: increased blood pressure, raising of the body hair, pupillary constriction, etc.
- These studies lead to the view that the hypothalamus can facilitate the coordination of peripheral emotional responses, a view that is supported by some lesion studies showing distinct emotional changes dependent upon the location of a hypothalamic lesion.

What triggers the hypothalamus (and other brain areas) to modulate emotional behavior?

- The control of emotional behavior requires that:
 - Emotionally significant stimuli be recognized so as to trigger specific emotional responses, presumably through the hypothalamus and other subcortical pathways.
 - Reward information (positive and negative) must in turn be transferred from the peripheral receptors that sense reward to cortical and sub-cortical structures that use this information to guide emotional learning about stimuli, to remember these stimuli, and to motivate behavior and emotional responses.
 - The limbic system is thought to carry out these functions and is comprised of a number of interconnected cortical and subcortical areas.

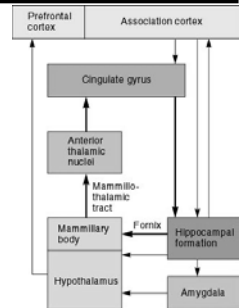
Limbic system anatomy

- In 1937, Papez proposed that the part of the cortex dedicated to processing emotion is the limbic lobe, as defined by Broca. The limbic lobe comprises a ring of "primitive" cortex around the brainstem, including the cingulate cortex, the parahippocampal gyrus, and the hippocampal formation.



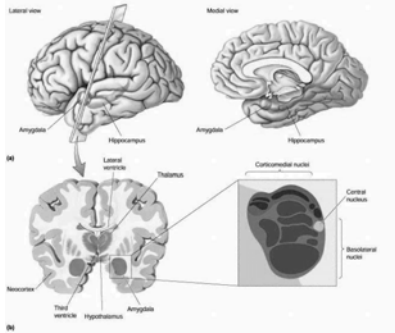
Limbic system anatomy (cont.)

- The neural circuit for emotion has since been extended by Paul MacLean and others. It now encompasses additional interconnected brain areas.
- The amygdala is now recognized as a key coordinator, linking cortical processing to the hypothalamus and other subcortical brain structures important for emotional behavior.



PNS Fig. 50.5

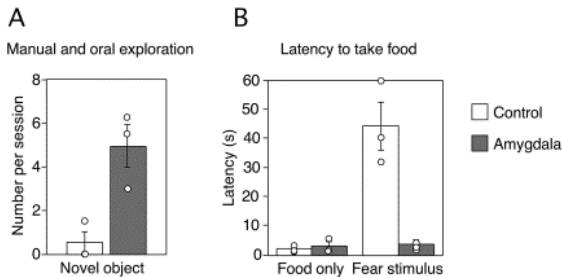
The amygdala is a key coordinator of emotional behavior



The amygdala and Kluver-Bucy syndrome

- The first good evidence linking the amygdala and related temporal lobe structures to emotion was obtained in 1939 by Heinrich Kluver and Paul Bucy. They removed the temporal lobes, including the amygdala and hippocampus, bilaterally in monkeys. They observed a dramatic change in emotional behavior:
 - Monkeys became tame, fearless, and had “blunted” emotions
 - Increased oral activity, including placing inedible objects in their mouth.
 - They exhibited increased sexual behavior, mounting inappropriate objects.
- Subsequent studies that made more precise lesions indicate that the amygdala was a key structure mediating the emotional effects.

Amygdala lesions and monkey emotional behavior

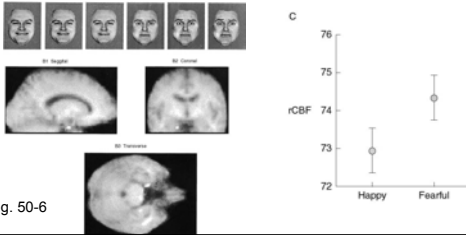


The amygdala in humans has been linked to emotional processing

- Microstimulation of the amygdala produces feelings of fear and apprehension.
- Isolated lesions of the amygdala, found in a rare disorder (Urbach-Wiethe disease) that leaves calcifications specifically in the amygdala bilaterally, impair patients from learning how to discern emotions in facial expressions. The disease does not affect the ability to discriminate fine differences in faces, nor the ability to recognize faces.

The amygdala in humans has been linked to emotional processing (2)

- Imaging studies have revealed that the amygdala is activated differentially by emotional facial expressions.
- Other functional imaging studies have shown the amygdala to respond to emotionally arousing stimuli.



PNS, Fig. 50-6

Fear conditioning is a tool for investigating neural substrates of emotion.

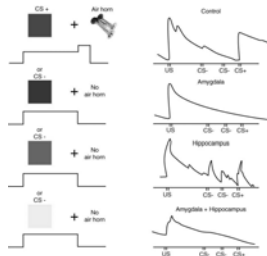
- Fear conditioning is a process in which a neutral stimulus (conditioned stimulus, CS) is paired with an aversive stimulus (unconditioned stimulus, US), so that the CS comes to predict an aversive outcome, eliciting fear behaviors even in the absence of the US.
- Fear conditioning can be found in a large range of animals, from rodents to rabbits to humans.
- As early as the 1920s, fear conditioning was demonstrated in infants. A white rat presented to an infant does not innately elicit fear, but pairing the rat with an aversive noise, produces crying and attempts to crawl away, even when the rat was presented without the noise.

Classic Experiments from Watson and Rayner demonstrating fear conditioning in an infant



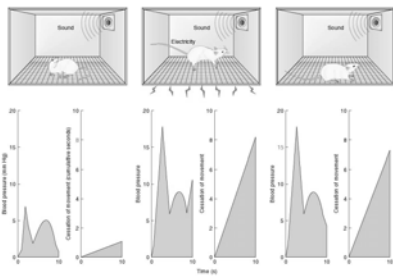
Fear conditioning in humans modulates skin conductance responses

- Skin conductance response (SCR) is a quantitative psychophysiological measure that has been correlated with emotional arousal. It is essentially, a measure of how sweaty your palms are, and it is more commonly known as the lie detector test.
- Patients with distinct lesions in the amygdala and/or the hippocampus have specific deficits in conditioning skin conductance responses.



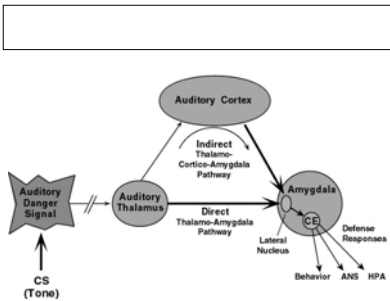
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Fear conditioning in rodents.

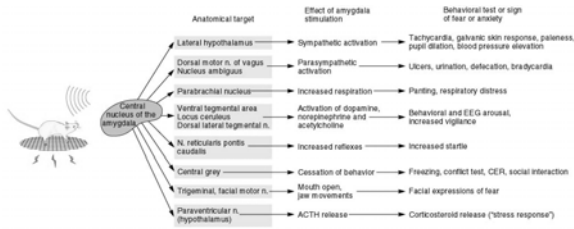


Aggleton & Lange
Kandel's *Principles of Neural Science*
Principles of Neural Science
Fig. 10.27

The amygdala has appropriate anatomical connections for mediating fear conditioning



Amygdala stimulation produces emotional behaviors through subcortical pathways



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 58.09

Numerous lines of evidence implicate the lateral nucleus of the amygdala in fear conditioning

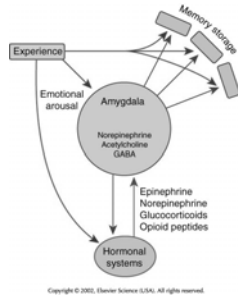
- Damage to the lateral nucleus prevents acquisition and expression of fear responses to auditory CSs.
- Neural responses to auditory CS and nociceptive US are found on the same single neurons in rat lateral nucleus.
- CS auditory responses are enhanced by conditioning in which the CS is paired with a US.

The amygdala may also modulate emotional memories stored elsewhere

- Memories of emotionally arousing events are more poignant than unemotional events. What mechanisms underlie this adaptive phenomenon?
- Emotionally arousing events activate the sympathetic nervous system and the HPA axis, resulting in the release of epinephrine and glucocorticoids.
- In addition to mediating aspects of the "flight-or-fight" response, these hormones have now been shown to improve emotional memory, and that the amygdala is critical for this process.
- Lesions of the amygdala block this memory-enhancing neuromodulatory function of many drugs and hormones.
- Infusion of drugs selectively into the basolateral complex may enhance memory storage, whereas infusions into the central nucleus do not. The basolateral nucleus is reciprocally connected with the hippocampus and the neocortex, both implicated in memory processes.

A schematic model for how hormonal systems can modulate memory storage via the amygdala

- Emotionally arousing events activate the sympathetic nervous system and the HPA axis, resulting in the release of epinephrine and glucocorticoids, which have been shown to enhance emotional memory.
- Lesions of the amygdala block this memory-enhancing neuromodulatory function of many drugs and hormones.
- Infusion of drugs selectively into the basolateral complex appears to enhance memory storage, whereas infusions into the central nucleus do not. The basolateral nucleus is reciprocally connected with the hippocampus and the neocortex, both implicated in memory processes.

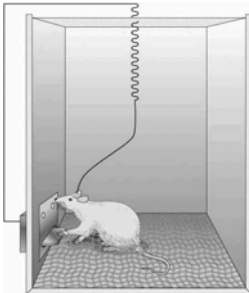


Emotional behavior and positive reward

- Emotional behavior occurs in response to positive rewards as well as negative rewards. Positive rewards can modulate the autonomic nervous system and behavior. Positive reinforcement, as all of you will learn during clinical training (?!), is a far more effective reinforcer than fear and negative rewards.
- How are positive reward signals encoded? How do they influence behavior?

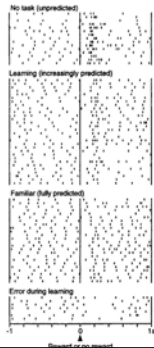
Electrical self-stimulation and reward

- In 1954, James Olds and Peter Milner found that brain stimulation to parts of the hypothalamus and related structures can act as a reinforcer. This stimulation worked independent of drive state (e.g. hunger), and has been replicated in many brain structures.
- A key finding in these studies is that brain stimulation activates neurons in the ventral tegmental area. These are midbrain dopamine neurons that form most of the mesolimbic and mesocortical projections involved in reward. Stimulating these neurons leads to dopamine release. Rats will often choose self-stimulation over food and sex.



Neurophysiological recordings from ventral tegmental neurons

- Wolfram Schultz and colleagues have characterized the physiological properties of midbrain dopamine neurons in behaving monkeys.
- They recorded from VTA neurons while monkeys performed tasks in which rewards could be learned to be expected. In these tasks, visual stimuli predicted rewards, but the animal did not know the association between stimulus and reward at the beginning of the experiment.



VTA neurons provide a learning signal

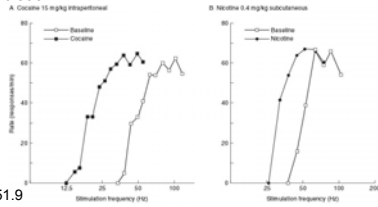
- The results from Schultz's experiments show that VTA neurons provide a learning signal that reflects reward expectation. From a computational viewpoint, the cells' firing rate is modulated when the reward received differs from the reward predicted.
- This learning signal can be used by other brain areas to guide behavior and to modulate emotional responses to reward predicting stimuli.

Drugs of abuse increase dopamine release in the brain

- Cocaine and amphetamines increase dopamine release in the brain, especially in the shell of the nucleus accumbens. The nucleus accumbens shell receives dopaminergic input from midbrain dopamine neurons, and it projects to the hypothalamus and limbic structures mediating emotional responses. Both drugs appear to work by blocking the dopamine transporter responsible for dopamine reuptake, thus leaving dopamine present in the synapse.
- Nicotine also enhances dopamine release, by acting on presynaptic cholinergic receptors.

Nicotine and cocaine modulate self-stimulation behavior

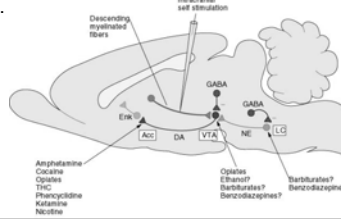
- In a self-stimulation experiment, rats were permitted to apply microstimulation to themselves at will. The rate at which they applied microstimulation depended upon the stimulation frequency.
- Strikingly, both cocaine and nicotine increase behavioral response rate for a given stimulation frequency compared to baseline. Thus, cocaine and nicotine appear to enhance the pleasure produced by self-stimulation.



PNS Fig. 51.9

Brain reward circuitry and self-stimulation

- The medial forebrain bundle, a group of descending myelinated fibers innervating the ventral tegmental area, is perhaps the most effective site for stimulation. This stimulation activates the VTA indirectly.
- Different drugs can intervene at different levels of this brain-reward circuitry.



PNS, Fig. 51.10

Summary of Emotion and Reward in the Limbic System

- We reviewed old theories of emotion, the basic purpose of the limbic system, and the basic anatomy of the limbic system.
- The hypothalamus plays an important role in generating emotional behaviors...but
- The amygdala has been implicated in playing a prominent role in integrating information and coordinating emotional behaviors in response to sensory stimuli, events, and memories. These findings were demonstrated in:
 - Fear conditioning studies in rodents
 - Monkey studies (Kluver-Bucy)
 - Human neuroimaging and lesion studies
 - Studies of memory modulation by hormones in lower animals.
- Reward processing occurs in distinct brain circuits.
 - Stimulation of these circuits can provide powerful reinforcement signals.
 - Dopaminergic neurons in the ventral tegmental area provide a learning signal that reflects a computation comparing the reward received to the reward expected.
 - Drugs of abuse act on reward circuits.
- Psychiatric disorders such as depression, anxiety disorders, and addiction, all involve limbic system neural circuitry.
