The Impact of Emotional Arousal on Amygdala Activity, Memory Consolidation, and Long-Term Potentiation in the Hippocampus

Isaac Zhang[1]

[1]Bellevue International School

ABSTRACT

The amygdala is important for the perception and expression of emotion. Research on the amygdala has shown that its activation through emotional arousal leads to enhanced memory of certain events. Emotional experience is known to induce the release of hormones epinephrine and cortisol, which are essential for responding to stressful events. These hormones initiate pathways between the amygdala, locus coeruleus and vagus nerve as well as aid in the activation of the hippocampus, a brain region involved in forming solid memories that can endure the tests of time. Through these hormones, the amygdala can instigate long-term potentiation (LTP) and spike-timing dependent plasticity (STPD) through hormone binding and modulation of gamma and theta frequency neuronal oscillations in the brain. Oftentimes, memories which are remembered best are emotionally saturated, but the biochemistry responsible for this effect is not yet fully understood. This review will analyze and summarize the research of many decades on this perplexing topic to hopefully help untangle a small component of the complex and intricate design of the human creation.

Introduction

Through the formation of neurons and synaptic connections in the brain, information can be stored. However, because our brains cannot handle the constant input from the environment, a lot of this information is discarded. How does the brain decide what is kept and what is forgotten? The human body and brain respond to emotion in quite a special way; our bodies have many mechanisms which help respond to emotional experiences. Interestingly, emotional arousal has a direct relationship with memory. Through the study of the limbic system, evidence points towards the amygdala as the modulator of memory consolidation and prioritization. Different mechanisms involving nerves, cell groups, hormones, and receptors form an emotion-induced network which serves to activate the amygdala. Once the amygdala has received signals and information from this network, it projects to the hippocampus, an important memory brain region. In this way, memories associated with emotion can be prioritized over others, one of many aspects of brain function which help determine the relevance of the things we perceive.

This review will introduce the amygdala as the center of emotion-induced memory formation through studies that prove the connection between the effects of emotion on memory performance and the amygdala. Next, the mechanisms which serve to activate the amygdala, such as nerve fiber and hormone connections, as well as induce memory consolidation in neighboring brain regions will be discussed. Lastly, new information involving the disconnect between emotions and memory will be introduced, and potential new studies which could utilize this disconnect to answer potential questions that haven't yet been thoroughly addressed will be proposed.

The Amygdala mediates emotion-induced memory-enhancement

The amygdala is a part of the limbic system which reacts to the perception of emotions in oneself and others, especially emotions related to fear [1-5]. Due to its role in emotion processing, scientists believed that the amygdala was responsible for an emotion-induced memory-enhancing effect. To prove this, initial trials stimulated lab rats through footshock and ultrasound as ways to scare the mice and thus emotionally activate their amygdala [6-9]. Once trained, their memory was tested with spatial maze puzzles [10] and inhibitory avoidance tasks [11-12]. In both cases, mice were shown to have enhanced memory of their surroundings which allowed them to improve on spatial mazes and learn to avoid environments associated with aversive events.

C-fos is a proto-oncogene which is expressed in neurons following depolarization. Because depolarization occurs in active cells, whenever a certain structure has heightened activity, c-fos will be expressed in that area. Thus, c-fos densities in the brain can be analyzed to determine which brain regions responded to the fearful stimulus. After analysis, scientists were able to prove that aversive stimuli can induce amygdalar activity in the brain [13-14]. This proves that footshock, other fearful stimuli, and the resulting memory enhancement through the amygdala are connected, but does this effect also occur in humans? Because humans and rats are biologically similar, if a redundancy is found in humans this will provide more evidence that the amygdala is the key.

In human studies, test subjects were emotionally aroused with visuals to activate the amygdala. Similar to c-fos in rats, Positron Emission Tomography (PET) scanning can be used in humans to measure cerebral glucose metabolism in the brain and thus determine which regions are activated by stimuli. It was found through PET that the emotional stimuli increased amygdala activity, and this increased activity positively correlated with the strength of memory retention after watching an emotional visual [15]. Subsequent research produced similar results, with emotional arousal enhancing memory consolidation for cognitive skills, wordlists, and college lectures, regardless of type (pleasant or aversive) [16-19].

In extreme cases, such as with Urbach-Wiethe disease, the amygdala undergoes calcification and damage, causing patients to be unable to judge emotions in facial expression [20]. Furthermore, patients were unable to remember positive and negative pictures and showed memory impairments in selective tests [21-22]. Post-traumatic stress disorder (PTSD) is an opposite extreme. Intense stress due to trauma is shown to cause abnormally high amygdala activity [23-24]. Victims of PTSD express enhanced memory for traumatizing events, damaged mental health, and emotions such as distress, anxiety, and sadness. Both examples show the connection between the amygdala, emotions, and memory: emotions cause increased amygdala activity and memory enhancement, while lack of proper amygdala function leads to difficulty perceiving and remembering emotional events and information.

Epinephrine and Glucocorticoids require noradrenergic activation to stimulate the amygdala and thus mediate an emotion-induced memory enhancing effect

Through multiple studies, scientists have just begun to understand the complex memory processes which the amygdala mediates. An initial question which needs to be addressed is how emotional arousal leads to activation of the amygdala. To answer this question, three important stress-related hormones must be introduced.

Responding to stress involves peripheral epinephrine and cortisol (corticosterone in rats). Peripheral epinephrine (adrenaline) is a steroid hormone part of the sympathetic nervous system, known for its “fight or flight” response [25-26]. Alpha and beta-adrenergic receptors (also known as adrenoceptors) which bind epinephrine are located in smooth muscle cells and adipose tissue throughout the body [27], as well as along certain nerves and neurons connected to the brain. Cortisol is a type of glucocorticoid hormone which is controlled by the hypothalamic-pituitary-adrenal (HPA) axis [28-29]. When cortisol is released, it binds to glucocorticoid (GR) receptors, which are located in the hippocampus and amygdala [30-32]. Because these two are stress-related hormones, they are useful for analyzing the effects of emotional arousal on brain function.

Emotionally saturated experiences, such as during aversive or highly rewarding experiences, cause both cortisol and epinephrine to be released from adrenal glands [29]. Increased concentrations of epinephrine and cortisol have both been proven to activate the amygdala and enhance memory in rats and humans [29, 33-42]. By binding to their complementary receptors on the amygdala and other memory-forming brain regions, epinephrine and glucocorticoids can influence memory consolidation [42-46]. In order to do so, they must pass through the blood-brain barrier, a semipermeable wall which blocks entrance to the brain [47].

Epinephrine released peripherally activates the amygdala through an indirect pathway

Even in an extremely stressful scenario, peripheral epinephrine is unable to pass through the blood-brain barrier [48-49]. Because of this, epinephrine must activate the amygdala with a signal. Norepinephrine, a hormone which functions as a neurotransmitter in the brain, is our signal molecule. It is produced by neural projections originating from the locus coeruleus (LC) and transferred to the amygdala [25, 50]. Similar to adrenaline, norepinephrine is capable of binding to adrenergic receptors; because these receptors can be found on the amygdala, norepinephrine binding causes amygdala activation [10, 12, 44, 47, 51-52].

Indeed, post-training infusions of norepinephrine and adrenoceptor agonists have been shown to improve memory for spatial mazes, inhibitory avoidance, and fear conditioning [10, 53-54]. Drugs that block norepinephrine and adrenoceptors in the amygdala completely nullify the ability for epinephrine to enhance memory [55-56], and when concentrations of epinephrine are depleted, memory deficits are reversed with direct infusion of norepinephrine. Moreover, LC stimulation increases amygdala firing which has been proven to depend on norepinephrine release [50]. This provides substantial evidence that norepinephrine is important for epinephrine to contact memory-forming structures, but epinephrine must first activate the LC to produce norepinephrine and activate the amygdala. Because epinephrine cannot pass through the blood-brain barrier, another mechanism must be used to activate the LC first. This is where the vagus nerve comes into play.

The vagus nerve induces release of norepinephrine into the amygdala

Known as the tenth cranial nerve, the vagus nerve is part of the parasympathetic nervous system, responsible for lowering heart and breathing rate after a stressful event. Following epinephrine administration, increased neural impulses have been detected along the vagus nerve [57] and when β-adrenergic receptors on the vagus nerve were blocked, excitatory activity in the vagus nerve was not observed. This shows that epinephrine binding increases vagus nerve activity. However, with adrenoceptors located throughout the body, how can it be determined if the vagus nerve is one of the essential pathways to the brain? Through three separate tests, Chen and Williams [58] proved that this is true.

In the first test, rats were implanted with vagal nerve electrodes and placed in a long box. 10 sugar pellets (a food reward) were placed at the end of the box as well as three hurdles throughout the course to ensure that rats would have to put in effort to reach the reward. During training, four different rat groups were given either sham or vagus nerve stimulation (VNS) and either a reduction in sugar pellets from 10 to 1 (reward shift) or no change. In this case, the emotion which scientists were trying to induce in the rats was frustration and loss of motivation due to reduction in reward, which could be measured by the latency of the rats to consume the pellet. After training, decreased amounts of pellets caused increased latency to jump over the hurdles and consume the reward, even without VNS. While memory retention for this reward shift extended for as long as 7 days after VNS training, this did not occur in sham stimulated rats.

In the second test, electrophysiology and microdialysis was used to record neural impulses of vagal fibers and concentrations of norepinephrine in the amygdala. During the test, rats were split into three experimental and four control groups. In experimental groups, epinephrine injections were followed by sotalol after 60 minutes. In control groups, saline was administered 60 minutes after injections of sotalol. Post-epinephrine injections caused consistent increases in vagal firing and norepinephrine concentration which remained statistically significant above baseline.

Once sotalol was injected, experimental groups decreased in vagal nerve firing, with a higher concentration of sotalol reducing activity by 50% relative to baseline at the end of recording, while norepinephrine levels remained relatively constant. In control groups, significant decreases in vagal nerve firing and norepinephrine were observed, but values never rose above baseline.

In the final test, immunohistochemistry was used to label c-fos (similar to aversive stimuli testing in section 1) and DBH, an enzyme used for norepinephrine synthesis. Electrodes which stimulated the vagus nerve in rats caused increased Fos activity in the amygdala and NTS, a channel which connects the vagus nerve to the LC. Elevated DBH and Fos levels were also recorded in the LC, indicating that vagus nerve stimulation increases norepinephrine activity and release. These findings both support the claims that epinephrine increases vagal nerve firing [57] and that the vagus nerve can activate the amygdala with norepinephrine through a synaptic connection with the LC. Their results are also corroborated by studies done by many others [59-64]. Thus, the epinephrine pathway consists of epinephrine to the vagus nerve, the activation of the LC, and production of norepinephrine which is carried to the amygdala.

Glucocorticoids require norepinephrine to induce direct activation of the amygdala

Unlike epinephrine, cortisol is capable of passing through the blood-brain barrier [28], allowing cortisol easy access to GR receptors on many brain regions, such as the amygdala. Despite this, glucocorticoids must rely on the noradrenergic system in order to affect memory storage [65-66]. To demonstrate this, Roozendaal et al. [67] experimented with cyclic AMP (cAMP), protein kinase (PKA), adrenoceptors, and GRs to find a connection between glucocorticoids, norepinephrine, and the amygdala. They inhibited and activated certain pathways to observe the effect on inhibitory avoidance task performance in rats. In the study, rats received either β-adrenoceptor antagonist atenolol, α-adrenoceptor antagonist prazosin, or cAMP-dependent PKA inhibitor Rp-cAMPS into the amygdala followed by GR agonist RU 28362 posttraining. RU 28362-induced retention enhancement was blocked by Rp-cAMPS and atenolol, but not prazosin. This shows that GR activation of the amygdala requires cAMP production and norepinephrine binding to β-adrenoceptors. Next, rats were given GR antagonist RU 38486 followed by α-adrenoceptor activation or a dose of clenbuterol, a β-adrenoceptor agonist. RU 38486 blocked retention enhancement induced by α-adrenoceptors and impaired the effect of posttraining clenbuterol. Additionally, clenbuterol-induced enhancement of retention was attenuated by prazosin infusions, indicating that β-adrenoceptors which help the GRs activate the amygdala are reliant on α-adrenoceptor activation by norepinephrine.

Taken together, the α / β-adrenoceptor-cAMP/PKA pathway is quite complex: norepinephrine must first bind to alpha and β-adrenoceptors, with α-adrenoceptors modulating β-adrenoceptor activation. Once β-adrenoceptors are activated, cAMP is produced, initiating PKA phosphorylation. Finally, PKA signaling leads to amygdala activation and memory enhancement. This proves that the β-adrenoceptor-cAMP/PKA pathway must be active but that glucocorticoid binding to GRs is also necessary [52, 68]. In a second test, Roozendaal et al. [66] used yohimbine, a drug which increases norepinephrine levels in the brain, and got similar results. When yohimbine was administered with corticosterone, retention of objects was enhanced in rats [66], but memory-enhancing effects were not apparent when yohimbine was administered without corticosterone. Yohimbine also increases levels of phosphorylated CREB (pCREB), a protein which is activated by norepinephrine binding on the amygdala [69]. Although corticosterone or yohimbine administered alone did not affect pCREB reactivity, corticosterone and yohimbine administered together significantly increased pCREB activity in the amygdala [69-70]. This shows that even though yohimbine increases norepinephrine levels, norepinephrine cannot increase pCREB reactivity or activate the amygdala without corticosterone. Thus, the glucocorticoid pathway involves binding to and activation of the amygdala in tandem with norepinephrine release and binding to β- and α-adrenoceptors. Overall, evidence indicates that norepinephrine, epinephrine, and corticosterone work together to activate the amygdala and cause memory enhancement to occur. Epinephrine induces the release of norepinephrine through the vagus nerve and LC, which assists glucocorticoids in amygdala activation by binding to alpha and β-adrenoceptors on the amygdala surface. In this way, three hormones respond to emotional arousal and initiate complex memory storage and LTP pathways.

The amygdala projects to the hippocampus to enhance memory consolidation/retention

The amygdala does not store or enhance memories by itself; instead, it modulates memory consolidation processes through the hippocampus, another brain region from the limbic system. The hippocampus is essential for the consolidation of short-term memories into the long-term and the formation of declarative and spatial memories in the brain [71-74]. Changes in neuroplasticity, known as long-term potentiation (LTP), help form new synapses between hippocampal neurons so information of past events can be stored [75-76] and spatial and contextual information which is recollected from our past perceptions can be processed. This is shown by the improvements in inhibitory avoidance and spatial maze tasks in rodents, retention of visuals, word lists, skills, etc. in humans, as well as famous tests such as Pavlov's dogs [77-78]. In these cases, emotion caused neuroplastic changes through a possibly amygdala-initiated pathway.

Physiology and anatomy have confirmed that the amygdala is connected to the hippocampus through a channel called the perforant pathway (PP) [79-80]. The PP extends to all fields of the hippocampus, such as the CA regions and dentate gyrus (DG), which forms episodic memories. Because the amygdala modulates memory consolidation, it is likely that the hippocampus is involved in this process due to its predominant role in memory. However, whether or not emotional-induced amygdala activation can increase LTP in the hippocampus must be determined.

To prove that amygdala activation causes LTP in the hippocampus, Akirav and Levin [81] primed the amygdala to see its effects on LTP and population spike (PS) and excitatory postsynaptic potentials (EPSP), two signals of efficient synaptic transmission and LTP [81], in the DG. In addition, field potentials following high-frequency stimulation (HFS) on the PP were recorded to determine temporal effects. Amygdala priming significantly increased EPSP and LTP in the DG of rats, and HFS to the PP produced similar results.

In another study by Akirav and Levin [82], rats were held underwater with a metal net to induce fear and stress. Afterwards, they received tetanic stimulation (priming) to the amygdala and HFS to the PP. Priming to the amygdala significantly increased LTP and HFS significantly increased EPSP, but amygdala priming increased EPSP and LTP much more than HFS [82]. When amygdala neurons were blocked, LTP was attenuated in the hippocampus [83]. The results of these studies provide additional evidence that the amygdala induces changes in neuroplasticity and LTP in the hippocampus [84-89].

The amygdala modulates memory by initiating memory processes in the hippocampus

Understanding the mechanisms behind the interaction between the amygdala and hippocampus will help to elucidate the memory-consolidation process. There are two ways that the amygdala has been shown to induce LTP in the hippocampus to prioritize memory consolidation of certain perceptions -- priming of the hippocampus for the reception of hormones such as norepinephrine and glucocorticoids, and coordination of oscillatory theta and gamma waves.

The amygdala potentiates neuroplastic changes in the hippocampus by priming it for emotion-induced release of norepinephrine and glucocorticoids

To influence memory formation, hormones norepinephrine and corticosterone have been shown to bind to and activate the hippocampus. Norepinephrine has been found to increase the magnitude and duration of long-term synaptic potentiation in the CA3 region of the hippocampus during HFS stimulation of rat hippocampal slices, and beta-adrenergic agonists such as isoproterenol produced similar results, while antagonists such as propranolol or timolol blocked hippocampal LTP [90]. Even propranolol applied to the hippocampus shortly after induction of LTP from the amygdala completely abolished memory effects of LTP [91].

The hippocampus contains a substantial number of GRs. Glucocorticoids which are released in response to emotional arousal and bind to the hippocampal GRs have been shown to cause increased hippocampal LTP and primed burst potentiation (PBP) [92-96], a long-term increase in PS and EPSP which occurs from shifts in electrical potential of the hippocampal CA1 region. Increases in PBP thus acts as an indicator of signal transmission and activity in the hippocampus, which is induced by glucocorticoid binding.

Norepinephrine and corticosterone can be depleted with DSP-4 and metyrapone (Met), respectively. By removing norepinephrine and/or corticosterone, scientists could observe changes in hippocampal LTP which indicate the necessity of stress hormones. Without amygdala priming, DSP-4, Met, and 5-HT were not significantly different from control LTP groups. This makes sense because the amygdala mediates norepinephrine and glucocorticoid release.

However, once the amygdala was primed, DSP-4 and Met caused decreased EPSP in the hippocampus, while control groups had much higher EPSP levels. This shows that when norepinephrine and glucocorticoids are depleted, the hippocampus has decreased signaling and activity, attenuating memory consolidation [97-99]. Control tests did not alter hormone levels and had higher EPSP, which makes sense because the amygdala increases LTP in the hippocampus.

When norepinephrine or glucocorticoids were depleted, signaling and activity in the hippocampus decreased. EPSP/LTP were significantly lower in depleted groups compared to control groups that had natural hormone levels. Thus, the hippocampus relies on norepinephrine[100] and glucocorticoids to potentiate LTP once receiving memory signals from the amygdala.

Synchronous hippocampal theta-gamma oscillations comodulate memory consolidation

Neurons naturally oscillate at unique frequencies when interacting and forming connections with other neurons [101]; oscillation helps to support synaptic plasticity by coordinating presynaptic neurotransmitter release with postsynaptic depolarization (known as spike timing) [101-102]. When neurons oscillate within a certain time window (10-20ms), synchronized activity can induce LTP. This form of LTP which is dependent on the precise timing of spike activity in neurons is called spike-timing dependent plasticity (STPD) [103].

Two important oscillatory waves expressed in the hippocampus are the theta (6-12Hz) and gamma (30-90Hz) waves, with gamma frequencies split into low gamma (~30-55Hz) and mid-frequency gamma (~55-90Hz) [104-105]. Theta waves have been shown to modulate gamma waves, with the cycle of low gamma oscillation always at a 5:1 ratio and mid gamma always at a 9:1 ratio to the rhythm of the theta cycle. Additionally, gamma power (increases depending on sensory drive) in low and mid gamma frequencies is phase modulated by theta waves, which means theta waves encode important information by causing changes in phases of the gamma cycle [105]. Phase-phase (P-P) coupling is the synchronization of phase values between oscillations. Comparisons of phase oscillations have revealed correlations between theta and gamma waves[106], which has been suggested to control spike patterns to induce STDP.

In an experiment by Trimper et al. [107], spiking and local field potentials (LFP) were measured simultaneously in three major regions of the hippocampus: the DG, CA3, and the CA1 while rats performed a novel object recognition memory task. Scientists were hoping to untangle the dynamics of gamma / theta wave interaction and find correlations with cognition and behavior.

During exploration of the novel object, there was increased slow gamma coherence between the DQ and CA3, and between the CA3 and CA1, which was highest during the falling slope and trough of the theta cycle and smallest during rising slope and peak [108-109]. The magnitude of theta-phase modulations was also calculated, and theta waves were found to phase modulate slow gamma power in all three brain regions. Previous studies have shown that regions such as the CA3 and CA1 synchronize in low gamma frequencies [104, 110], so the data from the object recognition test likely reflects genuine theta-gamma synchrony. Regardless of behavioral state, all three brain regions were phase-aligned to the theta and slow gamma waves [107]. Due to spike-timing being phase aligned to theta and gamma oscillations, changes in STPD could potentially occur.

To prove that hippocampal oscillations could affect associative memory for the novel object encounters, rats performed an object-location recognition memory task where each rat ran laps on a track while exploring novel objects. Rats are known to prefer novelty, so decreased exploration time can be interpreted as retention of the objects. Exploration time decreased significantly when rats discovered the same objects again on the second lap, indicating memory formation for that object. While the rats were running laps, slow gamma power and synchrony was found to be highest during novel object exploration and lowest during repeated object exploration, which lead to enhancement or attenuation of memory, respectively. This effect was present in both the DQ-CA3 connection and the CA3-CA1 connection, indicating the formation of STDP through the oscillations of low gamma waves.

In a spatial maze task by Shirvalker et al. [111], theta-gamma comodulation / power correlation (TGC) and synchronization were found to be significantly higher in rats that demonstrated good memory on all trials, while reduced TGC increased the probability of memory failure. Other tests observed similar effects when forming memories in humans [112-113], monkeys [114], and rats [104, 109, 115-117]. In sum, theta-gamma comodulation acts as a neural code [118]: slow wave gamma oscillations help to synchronize spike timing in different regions of the hippocampus, and these slow wave gamma oscillations are mediated by theta waves, which phase modulate gamma power and frequency. This suggests that theta waves help the hippocampus interact with other brain regions to integrate non-memory related information

During an object memory test, brief electrical stimulation was found to elicit low gamma synchrony between the CA3 and CA1. Rats that were electrically shocked and elicited low gamma synchrony had enhanced memory consolidation for specific object encounters [104, 119]. Additionally, CA3 neuron action potentials and spiking were found to be coordinated with downstream CA1 LFPs following BLA-induced gamma synchrony in the hippocampus, indicating that the low gamma oscillations were responsible for changes in LTP and memory consolidation. This supports the previous hypothesis that CA3-CA1 synchronous oscillations enhance memory consolidation through changes in STDP, but also brings up evidence for an amygdala-mediated change in gamma waves.

When mice underwent auditory Pavlovian fear-conditioning, increased theta coupling was recorded specifically between the CA1 and amygdala, which led to increased fear memory consolidation in rats [120-122]. In a Pavlovian reward test, rats were found to have greater coherent theta oscillations between the amygdala theta phase and hippocampal CA1 gamma phase which led to higher expectations of future reward, indicating memory consolidation of the reward and stimulus [123]. This suggests that the amygdala can induce low gamma synchrony through theta-wave cross-structure coupling with the CA1 [120]. In a more recent study [124], optogenetic stimulation amygdala neurons were found to elicit theta-modulated gamma oscillations in the CA1, but only when amygdala stimulation included theta and gamma frequencies. This supports the claim that the amygdala can induce theta-gamma wave synchrony to benefit memory.

Conclusion

Through thorough research, we now have a much greater knowledge and understanding of the mechanisms, networks, and pathways which connect emotion, the amygdala, and memory. Different characters play a part in this memory journey, all eventually allowing the amygdala to form a connection with the hippocampus and send in signals and encoded neural messages to activate memory consolidation processes for an emotionally arousing experience. Yet despite our newest insights in this field of science, the mystery of the human body has not been fully solved. There are many missing pieces of the information we currently have that have yet to be discovered.

Acknowledgements

I would like to thank Horizon Inspires and the Horizon Academic program for their guidance in writing this paper, especially Dr. Patrick Liu for his instruction and insight.

References

Davis, M. & Whalen P. J. The amygdala: vigilance and emotion. *Molecular Psychiatry* **6**, 13-34 (2001). https://doi.org/10.1038/sj.mp.4000812

Anderson, A. K. Feeling emotional: the amygdala links emotional perception and experience. *Social Cognitive and Affective Neuroscience* **2**, 71-72 (2007). https://doi.org/10.1093/scan/nsm022

Ressler, K. J. Amygdala Activity, Fear, and Anxiety: Modulation by Stress. *Biological Psychiatry* **67**, 1117-1119 (2010). https://doi.org/10.1016/j.biopsych.2010.04.027

Bonnet, L., Comte, A., Tatu, L., Millot, J., Moulin, T. & Bustos, E. M. The role of the amygdala in the perception of positive emotions: an "intensity detector". *Frontiers in Behavioral Neuroscience* **9**, 178 (2015). https://doi.org/10.3389/fnbeh.2015.00178

Diano, M., Celeghin, A., Bagnis, Arianna. & Tamietto, M. Amygdala Response to Emotional Stimuli without Awareness: Facts and Interpretations. *Frontiers in Psychology* **7**, 2029 (2016). https://doi.org/10.3389/fpsyg.2016.02029

Gold, P. E., Hankins, L., Edwards, R. M., Chester, J. & McGaugh, J. L. Memory interference and facilitation with posttrial amygdala stimulation: effect on memory varies with footshock level. *Brain Research* **86**, 509-13 (1975). https://doi.org/10.1016/0006-8993(75)90905-1

Galvez, R., Mesches, M. H. & McGaugh, J. L. Norepinephrine release in the amygdala in response to footshock stimulation. *Neurobiology of Learning and Memory* **66**, 253-7 (1996) https://doi.org/10.1016/s0006-8993(98)00795-1

Quirarte, G. L., Galvez, R., Roozendaal, B. & McGaugh, J. L. Norepinephrine release in the amygdala in response to footshock and opioid peptidergic drugs. *Brain Research* **808**, 134-40 (1998). https://doi.org/10.1016/s0006-8993(98)00795-1

Bass, D. I., Partain, K. N. & Manns, J. R. Event-Specific Enhancement of Memory via Brief Electrical Stimulation to the Basolateral Complex of the Amygdala in Rats. *Behavioral Neuroscience* **126**, 204-208 (2012). https://doi.org/10.1037/a0026462

Hatfield, T. & McGaugh, J. L. Norepinephrine infused into the basolateral amygdala posttraining enhances retention in a spatial water maze task. *Neurobiology of Learning and Memory* **71**, 232-9 (1999). https://doi.org/10.1006/nlme.1998.3875

Liang, K. C., McGaugh, J. L. & Yao, H. Y. Involvement of amygdala pathways in the influence of post-training intra-amygdala norepinephrine and peripheral epinephrine on memory storage. *Brain Research* **508**, 225-33 (1990) McIntyre, C. K., Hatfield, T. & McGaugh, J. L. Amygdala norepinephrine levels after training predict inhibitory avoidance retention performance in rats. *European Journal of Neuroscience* **16**, 1223-6 (2002). https://doi.org/10.1016/0006-8993(90)90400-6

Mongeau, R., Miller, G. A., Chiang, E. & Anderson, D. J. Neural Correlates of Competing Fear Behaviors Evoked by an Innately Aversive Stimulus. *Journal of Neuroscience* **23**, 3855-3868 (2003). https://doi.org/10.1523/JNEUROSCI.23-09-03855.2003

Lanuza, E., Moncho-Bogani, J. & LeDoux, J. E. Unconditioned Stimulus Pathways to the Amygdala: Effects of Lesions of the Posterior Intralaminar Thalamus on Footshock-Induced c-Fos Expression in the Subdivisions of the Lateral Amygdala. *Neuroscience* **155**, 959-968 (2008). https://doi.org/10.1016/j.neuroscience.2008.06.028

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J. & McGaugh, J. L. Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceeds of the National Academy of Sciences of the United States of America* **93**, 8016-21 (1996). https://doi.org/10.1073/pnas.93.15.8016

Nielson, K. A. & Powless, M. Positive and negative sources of emotional arousal enhance long-term word-list retention when induced as long as 30 min after learning. *Neurobiology of Learning and Memory* **88**, 40-7 (2007). https://doi.org/10.1016/j.nlm.2007.03.005

Liu, D. L. J., Graham S. & Zorawski, M. Enhanced selective memory consolidation following post-learning pleasant and aversive arousal. *Neurobiology of Learning and Memory* **89**, 36-46 (2008). https://doi.org/10.1016/j.nlm.2007.09.001

Steidl, S., Razik, F. & Anderson, A. K. Emotion enhanced retention of cognitive skill learning. *Emotion* **11**, 12-9 (2011). https://doi.org/10.1037/a0020288

Nielson, K. A. & Arentsen, T. J. Memory modulation in the classroom: selective enhancement of college examination performance by arousal induced after lecture. *Neurobiology of Learning and Memory* **98**, 12-6 (2012). https://doi.org/10.1016/j.nlm.2012.04.002

Siebert, M., Markowitsch H. J. & Bartel, P. Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. *Brain* **126**, 2627-37 (2003). https://doi.org/10.1093/brain/awg271

Cahill, L., Babinsky, R., Markowitsch, H. J. & McGaugh, J. L. The amygdala and emotional memory. *Nature* **377**, 295-6 (1995). https://doi.org/10.1038/377295a0

Markowitsch H. J., Calabrese, P., Würker, M., Durwen, H. F., Kessler, J., Babinsky, R., Brechtelsbauer, D., Heuser, L. & Gehlen, W. The amygdala's contribution to memory--a study on two patients with Urbach-Wiethe disease. *NeuroReport* **5**, 1349-52 (1994). https://doi.org/10.1097/00001756-199406270-00013

Shin, L. M., Rauch, S. L. & Pitman, R. K. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences* **1071**, 67-79 (2006). https://doi.org/10.1196/annals.1364.007

Herringa, R. J. Trauma, PTSD and the Developing Brain. *Current Psychiatry Reports* **19**, 69 (2017). https://doi.org/10.1007/s11920-017-0825-3

Hussain, L. S., Reddy, V. & Maani, C. V. Physiology, Noradrenergic Synapse. *StatsPearls Publishing*, Treasure Island (FL) (2020).

Tank, A. W. & Wong, D. L. Peripheral and central effects of circulating catecholamines. *Comprehensive Physiology* **5**, 1-15 (2015). https://doi.org/10.1002/cphy.c140007

Fung, M. M., Viveros, O. H. & O'Connor, D. T. Diseases of the adrenal medulla. *Acta Physiologica* **192**, 325-335 (2008). https://doi.org/10.1111/j.1748-1716.2007.01809.x

Myers, B., McKlveen, J. M. & Herman, J. P. Glucocorticoid actions on synapses, circuits, and behavior: Implications for the energetics of stress. *Frontiers in Neuroendocrinology* **35**, 180-196 (2014). https://doi.org/10.1016/j.yfrne.2013.12.003

McIntyre, C. K., McGaugh, J. L. & Williams, C. L. Interacting Brain Systems Modulate Memory Consolidation. *Neuroscience & Biobehavioral Reviews* **36**, 1750-1762 (2012). https://doi.org/10.1016/j.neubiorev.2011.11.001

Reul, J. M. & de Kloet, E. R. Anatomical resolution of two types of corticosterone receptor site in rat brain with in vitro autoradiography and computerized image analysis. *The Journal of Steroid Biochemistry and Molecular Biology* **24**, 269-72 (1986). https://doi.org/10.1016/0022-4731(86)90063-4

Meaney, M. J., Sapolsky, R. M. & McEwen, B. S. The development of the glucocorticoid receptor system in the rat limbic brain. II. An autoradiography study. *Brain Research* **350**, 165-8 (1985). https://doi.org/10.1016/0165-3806(85)90261-5

Wang, Q., Verweij, E. W. E., Krugers, H. J., Joels, M., Swaab, D. F. & Lucassen, P. J. Distribution of the glucocorticoid receptor in the human amygdala; changes in mood disorder patients. *Brain Structure & Function* **219**, 1615-26 (2014). https://doi.org/10.1007/s00429-013-0589-4

Jurado-Berbel, P., Costa-Miserachs, D., Torras-Garcia, M., Coll-Andreu, M. & Portell-Cortés, I. Standard object recognition memory and "what" and "where" components: Improvement by post-training epinephrine in highly habituated rats. *Behavioural Brain Research* **207**, 44-50 (2010). https://doi.org/10.1016/j.bbr.2009.09.036

O King II, S. & Williams, C. L. Novelty-induced arousal enhances memory for cued classical fear conditioning: interactions between peripheral adrenergic and brainstem glutamatergic systems. *Neurobiology of Learning and Memory* **16**, 625-34 (2009). https://doi.org/10.1101/lm.1513109

Roozendaal, B., Barsegyan, A. & Lee, S. Adrenal stress hormones, amygdala activation, and memory for emotionally arousing experiences. *Progress in Brain Research* **167**, 79-97 (2008). https://doi.org/10.1016/S0079-6123(07)67006-X

Rasch, B., Spalek, K., Buholzer, S., Luechinger, R., Boesiger, P., de Quervain, D. J-F. & Papassotiropoulos, A. Aversive stimuli lead to differential amygdala activation and connectivity patterns depending on catechol-O-methyltransferase Val158Met genotype. *NeuroImage* **52**, 1712-9 (2010). https://doi.org/10.1016/j.neuroimage.2010.05.054

McGaugh, J. L. Consolidating memories. *Annual Review of Clinical Psychology* **66**, 1-24 (2015). https://doi.org/10.1146/annurev-psych-010814-014954

Barsegyan, A., Mirone, G., Ronzoni, G., Guo, C., Song, Q., van Kuppeveld, D., Schut, E. H. S., Atsak, P., Teurlings, S., McGaugh, J. L., Schubert, D. & Roozendaal B. Glucocorticoid enhancement of recognition memory

via basolateral amygdala-driven facilitation of prelimbic cortex interactions. *Proceeds of the National Academy of Sciences of the United States of America* **116**, 7077-7082 (2019). https://doi.org/10.1073/pnas.1901513116

Kim, E. J. & Kim, J. J. Amygdala, Medial Prefrontal Cortex and Glucocorticoid Interactions Produce Stress-Like Effects on Memory. *Frontiers in Behavioral Neuroscience* **13**, 210 (2019). https://doi.org/10.3389/fnbeh.2019.00210

Shoshan N. & Akirav, I. The effects of cannabinoid receptors activation and glucocorticoid receptors deactivation in the amygdala and hippocampus on the consolidation of a traumatic event. *Neurobiology of Learning and Memory* **144**, 248-258 (2017). https://doi.org/10.1016/j.nlm.2017.08.004

Morris, K. A., Chang, Q., Mohler, E. G. & Gold, P. E. Age-related memory impairments due to reduced blood glucose responses to epinephrine. *Neurobiology of Aging* **31**, 2136-2145 (2009). https://doi.org/10.1016/j.neurobiolaging.2008.12.003

Cahill, L. & Alkire, M. T. Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding. *Neurobiology of Learning and Memory* **79**, 194-8 (2003). https://doi.org/10.1016/S1074-7427(02)00036-9

van Stegeren, A. H. The role of the noradrenergic system in emotional memory. *Acta Psychologica* **127**, 532-41 (2008). https://doi.org/10.1016/j.actpsy.2007.10.004

Roozendaal, B., McEwen, B. S. & Chattarji, S. Stress, memory and the amygdala. *Natural Reviews Neuroscience* **10**, 423-33 (2009). https://doi.org/10.1038/nrn2651

Kuhlmann, S. & Wolf, O. T. Arousal and cortisol interact in modulating memory consolidation in healthy young men. *Behavioral Neuroscience* **120**, 217-23 (2006). https://doi.org/10.1037/0735-7044.120.1.217

Zoladz, P. R., Clark, B., Warnecke, A., Smith, L., Tabar, J. & Talbot, J. N. Pre-learning stress differentially affects long-term memory for emotional words, depending on temporal proximity to the learning experience. *Physiology and Behavior* **103**, 467-76 (2011). https://doi.org/10.1016/j.physbeh.2011.01.016

Adelson, R. Stimulating the vagus nerve: memories are made of this. *American Psychological Association* **35**, 36 (2004).

Arai, T., Watanabe, T., Nagaro, T. & Matsuo, S. Blood-brain barrier impairment after cardiac resuscitation. *Critical Care Medicine* **9**, 444-8, (1981). https://doi.org/10.1097/00003246-198106000-00002

Pluta, R., Lossinsky, A. S., Wiśniewski, H. M. & Mossakowski, M. J. Early blood-brain barrier changes in the rat following transient complete cerebral ischemia induced by cardiac arrest. *Brain Research* **633**, 41-52 (1994). https://doi.org/10.1016/0006-8993(94)91520-2

Giustino, T. F., Ramanathan, K. R., Totty, M. S., Miles, O. W. & Maren, S. Locus Coeruleus Norepinephrine Drives Stress-Induced Increases in Basolateral AMygdala Firing and Impaires Extinction Learning. *Journal of Neuroscience* **40**, 907-916 (2020). https://doi.org/10.1523/JNEUROSCI.1092-19.2019

Quirarte, G. L., Roozendaal, B. & McGaugh, J. L. Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. *Proceeds of the National Academy of Sciences of the United States of America* **94**, 14048-14053 (1997). https://doi.org/10.1073/pnas.94.25.14048

Ferry, B., Roozendaal, B. & McGaugh, J. L. Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between beta- and α_1-adrenoceptors. *Journal of Neuroscience* **19**, 5119-23 (1999). https://doi.org/10.1523/JNEUROSCI.19-12-05119.1999

Ferry B. & McGaugh, J. L. Clenbuterol administration into the basolateral amygdala post-training enhances retention in an inhibitory avoidance task. *Neurobiology of Learning and Memory* **72**, 8-12 (1999). https://doi.org/10.1006/nlme.1998.3904

LaLumiere, R. T., Buen, T-V. & McGaugh, J. L. Post-training intra-basolateral amygdala infusions of norepinephrine enhance consolidation of memory for contextual fear conditioning. *Journal of Neuroscience* **23**, 6754-8 (2003). https://doi.org/10.1523/JNEUROSCI.23-17-06754.2003

Liang, K. C., Chen, L. L. & Huang, T. E. The role of amygdala norepinephrine in memory formation: involvement in the memory enhancing effect of peripheral epinephrine. *Chinese Journal of Physiology* **38**, 81-91 (1995).

Liang, K. C., Juler, R. G. & McGaugh, J. L. Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. *Brain Research* **368**, 125-33 (1986). https://doi.org/10.1016/0006-8993(86)91049-8

Miyashita, T., Williams, C. L. Epinephrine administration increases neural impulses propagated along the vagus nerve: Role of peripheral beta-adrenergic receptors. *Neurobiology of Learning and Memory* **85**, 116-24 (2006). https://doi.org/10.1016/j.nlm.2005.08.013

Chen, C. C. & Williams, C. L. Interactions between epinephrine, ascending vagal fibers, and central noradrenergic systems in modulating memory for emotionally arousing events. *Frontiers in Behavioral Neuroscience* **6**, 35 (2012). https://doi.org/10.3389/fnbeh.2012.00035

Sun, L., Peräkylä, J., Holm, K., Haapasalo, J., Lehtimäki, K., Ogawa, K. H., Peltola, J. & Hartikainen, K. M. Vagus nerve stimulation improves working memory performance. *Journal of Clinical and Experimental Neuropsychology* **39**, 954-964 (2017). https://doi.org/10.1080/13803395.2017.1285869

Huffman, W. J., Subramaniyan, S., Rodriguiz, R. M., Wetsel, W. C., Grill, W. M. & Terrando, N. Modulation of neuroinflammation and memory dysfunction using percutaneous vagus nerve stimulation in mice. *Brain Stimulation* **12**, 19-29 (2019). https://doi.org/10.1016/j.brs.2018.10.005

Ekmekçi, H. & Kaptan, H. Vagus Nerve Stimulation. *Open Access Macedonian Journal of Medical Sciences* **6**, 391-394 (2017). https://doi.org/10.3889/oamjms.2017.056

Noble, L. J., Souza, R. R. & McIntyre, C. K. Vagus nerve stimulation as a tool for enhancing extinction in exposure-based therapies. *Psychopharmacology* **236**, 355-367 (2019). https://doi.org/10.1007/s00213-018-4994-5

Vázquez-Oliver, A., Brambilla-Pisoni, C., Domingo-Gainza, M., Maldonado, R., Ivorra, A. & Ozaita, A. Auricular transcutaneous vagus nerve stimulation improves memory persistence in naïve mice and in an intellectual disability mouse model. *Brain Stimulation* **13**, 494-498 (2020). https://doi.org/10.1016/j.brs.2019.12.024

Jacobs, H. I. L., Riphagen, J. M., Razat, C. M., Wiese, S. & Sack, A. T. Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. *Neurobiology of Aging* **36**, 1860-7 (2015). https://doi.org/10.1016/j.neurobiolaging.2015.02.023

Roozendaal B., Okuda, S., de Quervain, D. J-F. & McGaugh, J. L. Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience* **138**, 901-10 (2006). https://doi.org/10.1016/j.neuroscience.2005.07.049

Roozendaal B., Okuda, S., Van der Zee, E. E. & McGaugh, J. L. Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proceeds of the National Academy of Sciences of the United States of America* **103**, 6741-6746 (2006). https://doi.org/10.1073/pnas.0601874103

Roozendaal, B., Quirarte, G. L. & McGaugh, J. L. Glucocorticoids interact with the basolateral amygdala β-adrenoceptor--cAMP/cAMP/PKA system in influencing memory consolidation. *European Journal of Neuroscience* **15**, 553-60 (2002). https://doi.org/10.1046/j.0953-816x.2001.01876.x

Ferry, B., Rozendaal, B. & McGaugh, J. L. Involvement of α_1-adrenoceptors in the basolateral amygdala in modulation of memory storage. *European Journal of Pharmacology* **372**, 9-16 (1999). https://doi.org/10.1016/s0014-2999(99)00169-7

Saha, S. & Datta, S. Two-way active avoidance training-specific increases in phosphorylated cAMP response element-binding protein in the dorsal hippocampus, amygdala, and hypothalamus. *European Journal of Neuroscience* **21**, 3403-14 (2005). https://doi.org/10.1111/j.1460-9568.2005.04166.x

Davis, M. F., Tsui, J., Flannery, J. A., Li, X., DeLorey, T. M. & Hoffman, B. B. Activation of alpha2 adrenergic receptors suppresses fear conditioning: expression of c-Fos and phosphorylated CREB in mous amygdala. *Neuropsychopharmacology* **29**, 229-39 (2004). https://doi.org/10.1038/sj.npp.1300324

Attardo, A., Lu, J., Kawashima, T., Okuno, H., Fitzgerald, J. E., Bito H. & Schnitzer, M. J. Long-Term Consolidation of Ensemble Neural Plasticity Patterns in Hippocampal Area CA1. *Cell Reports* **25**, 640-650 (2018). https://doi.org/10.1016/j.celrep.2018.09.064

Navarrete, M., Cuartero, M. I., Palenzuela, R., Draffin, J. E., Konomi, A., Serra, I., Colié, S., Castaño-Castaño, S., Hasan, M. T., Nebreda, A. R. & Esteban, J. A. Astrocytic p38alpha MAPK drives NMDA receptor-dependent long-term depression and modulates long-term memory. *Nature Communications* **10**, 2968 (2019). https://doi.org/10.1038/s41467-019-10830-9

Izquierdo, I., Furini, C. R. G. & Myskiw, J. C. Fear Memory. *Physiological Reviews* **96**, 695-750 (2016). https://doi.org/10.1152/physrev.00018.2015

Squire, L. R., Stark, C. E. L. & Clark, R. E. The medial temporal lobe. *Annual Review of Neuroscience* **27**, 279-306 (2004). https://doi.org/10.1146/annurev.neuro.27.070203.144130

Dong, Z., Han, H., Li, H., Bai, Y., Wang, W., Tu, M., Peng, Y., Zhou, L., He, W., Wu, X., Tan, T., Liu, M., Wu, X., Zhou, W., Jin, W., Zhang, S., Sacktor, T. C., Li, T., Song, W. & Wang, Y. T. Long-term potentiation decay and memory loss are mediated by AMPAR endocytosis. *Journal of Clinical Investigation* **125**, 234-247 (2015). https://doi.org/10.1172/JCI77888

Abraham, W. C., Jones, O. D. & Glanzman, D. L. Is plasticity of synapses the mechanism of long-term memory storage? *Nature* **4**, 9 (2019). https://doi.org/10.1038/s41539-019-0048-y

Wynne, C. D. L. Dogs in Pavlov's laboratory. *Behavioral Processes* **81**, 355-7 (2009). https://doi.org/10.1016/j.beproc.2009.04.007

VanElzakker, M. B., Dahlgren, M. K., Davis, F. C., Dubois, S. & Shin, L. M. From Pavlov to PTSD: the extinction of conditioned fear in rodents, humans, and anxiety disorders. *Neurobiology of Learning and Memory* **113**, 3-18 (2014). https://doi.org/10.1016/j.nlm.2013.11.014

Abe, K. Modulation of hippocampal long-term potentiation by the amygdala: a synaptic mechanism linking emotion and memory. **86**, 18-22 (2001). https://doi.org/10.1254/jjp.86.18

Ikegaya, Y., Saito, H. & Abe, K. Dentate gyrus field potentials evoked by stimulation of the basolateral amygdaloid nucleus in anesthetized rats. *Brain Research* **718**, 53-60 (1996). https://doi.org/10.1016/0006-8993(95)01465-9

Akirav, I. & Richter-Levin, G. Priming stimulation in the basolateral amygdala modulates synaptic plasticity in the rat dentate gyrus. *Neuroscience Letters* **270**, 83-86 (1999). https://doi.org/10.1016/s0304-3940(99)00488-7

Akirav, I. & Richter-Levin, G. Biphasic Modulation of Hippocampal Plasticity by Behavioral Stress and Basolateral Amygdala Stimulation in the Rat. *Journal of Neuroscience* **19**, 10530-10535 (1999). https://doi.org/10.1523/JNEUROSCI.19-23-10530.1999

Ikegaya, Y., Nakanishi, K., Saito, H. & Abe, K. Amygdala beta-noradrenergic influence on hippocampal long-term potentiation in vivo. *NeuroReport* **8**, 3143-6 (1997). https://doi.org/10.1097/00001756-199709290-00027

Frey, S., Bergado-Rosado, J., Seidenbecher, T., Pape, H-C. & Frey, J. U. Reinforcement of Early Long-Term Potentiation (Early-LTP) in Dentate Gyrus by Stimulation of the Basolateral Amygdala: Heterosynaptic Induction Mechanisms of Late-LTP. *Journal of Neuroscience* **21**, 3697-3703 (2001). https://doi.org/10.1523/JNEUROSCI.21-10-03697.2001

Bass, D. I., Nizam, Z. G., Partain, AK. N., Wang, A. & Manns, J. R. Amygdala-Mediated Enhancement of Memory for Specific Events Depends on the Hippocampus. *Neurobiology of Learning and Memory* **107**, 37-41 (2014). https://doi.org/10.1016/j.nlm.2013.10.020

Bergao, J. A., Lucas, M. & Richter-Levin, G. Emotional tagging--a simple hypothesis in a complex reality. *Progress in Neurobiology* **94**, 64-76 (2011). https://doi.org/10.1016/j.pneurobio.2011.03.004

McGaugh, J. L. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience* **27**, 1-28 (2004). https://doi.org/10.1146/annurev.neuro.27.070203.144157

Paré, D. Role of the basolateral amygdala in memory consolidation. *Progress in Neurobiology* **70**, 409-20 (2003). https://doi.org/10.1016/s0301-0082(03)00104-7

Kim, E. J., Kim, E. S., Park, M., Cho, J. & Kim, J. J. Amygdalar stimulation produces alterations on firing properties of hippocampal place cells. *Journal of Neuroscience* **32**, 11424-34 (2012). https://doi.org/10.1523/JNEUROSCI.1108-12.2012

Hopkins, W. F. & Johnston, D. Frequency-dependent noradrenergic modulation of long-term potentiation in the hippocampus. *Science* **226**, 350-2 (1984). https://doi.org/10.1126/science.6091272

Seidenbecher, T., Reymann, K. G. & Balschun, D. A post-tetanic time window for the reinforcement of long-term potentiation by appetitive and aversive stimuli. *Proceeds of the National Academy of Sciences of the United States of America* **94**, 1494-1499 (1997). https://doi.org/10.1073/pnas.94.4.1494

Diamond, D. M., Bennett, M. C., Engstrom, D. A., Fleshner, M. & Rose, G. M. Adrenalectomy reduces the threshold for hippocampal primed burst potentiation in the anesthetized rat. *Brain Research* **492**, 356-60 (1989). https://doi.org/10.1016/0006-8993(89)90919-0

Diamond, D. M., Bennet, M. C., Fleshner, M. & Rose, G. M. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus* **2**, 421-30 (1992). https://doi.org/10.1002/hipo.450020409

Rey, M., Carlier, E., Talmi, M. & Soumireu-Mourat, B. Corticosterone effects on long-term potentiation in mouse hippocampal slices. *Neuroendocrinology* **60**, 36-41 (1994). https://doi.org/10.1159/000126717

Pavlides, C., Watanabe, Y. & McEwen, B. S. Effects of glucocorticoids on hippocampal long-term potentiation. *Hippocampus* **3**, 183-92 (1993). https://doi.org/10.1002/hipo.450030210

Kerr, D. S., Huggett, A. M. & Abraham, W. C. Modulation of hippocampal long-term potentiation and long-term depression by corticosteroid receptor activation. *Psychobiology* **22**, 123-133 (1994).

Akirav, I. & Richter-Levin, G. Mechanisms of Amygdala Modulation of Hippocampal Plasticity. *Journal of Neuroscience* **22**, 9912-9921 (2002). https://doi.org/10.1523/JNEUROSCI.22-22-09912.2002

Conrad, C. D. The Relationship Between Acute Glucocorticoid Levels and Hippocampal Function Depends Upon Task Aversiveness and Memory Processing Stage. *Nonlinearity in Biology, Toxicology, and Medicine* **3**, 57-78 (2005). https://doi.org/10.2201/nonlin.003.01.004

Careaga, M. B. L., Tiba, P. A., Ota, S. M. & Suchecki, D. Pre-test metyrapone impairs memory recall in fear conditioning tasks: lack of interaction with beta-adrenergic activity. *Frontiers in Behavioral Neuroscience* **9**, 51 (2015). https://doi.org/10.3389/fnbeh.2015.00051

Hansen, N. & Manahan-Vaughan, D. Hippocampal long-term potentiation that is elicited by perforant path stimulation or that occurs in conjunction with spatial learning is tightly controlled by beta-adrenoreceptors and the locus coeruleus. *Hippocampus* **25**, 1285-98 (2015). https://doi.org/10.1002/hipo.22436

Buzsáki, G. & Draguhn, A. Neuronal oscillations in cortical networks. *Science* **304**, 1926-9 (2004). https://doi.org/10.1126/science.1099745

Jutras, M. J. & Buffalo, E. A. Synchronous Neural Activity and Memory Formation. *Current Opinion in Neurobiology* **20**, 150-155 (2010). https://doi.org/10.1016/j.conb.2010.02.006

Caporale, N. & Dan, Y. Spike timing-dependent plasticity: a Hebbian learning rule. *Annual Review of Neuroscience* **31**, 25-46 (2008). https://doi.org/10.1146/annurev.neuro.31.060407.125639

Bass, D. I. & Manns, J. R. Memory-Enhancing Amygdala Stimulation Elicits Gamma Synchrony in the Hippocampus. *Behavioral Neuroscience* **129**, 244-256 (2015). https://doi.org/10.1037/bne0000052

Belluscio, M. A., Mizuseki, K., Schmidt, R., Kempter, R. & Buzsáki, G. Cross-Frequency Phase-Phase Coupling between Theta and Gamma Oscillations in the Hippocampus. *Journal of Neuroscience* **32**, 423-435 (2012). https://doi.org/10.1523/JNEUROSCI.4122-11.2012

Bragin, A., Jando, G., Nadasdy, Z., Hetke, J., Wise, K. & Buzsáki, G. Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. *Journal of Neuroscience* **15**, 47-60 (1995). https://doi.org/10.1523/JNEUROSCI.15-01-00047.1995

Trimper, J. B., Galloway, C. R., Jones, A. C., Mandi, K. & Manns, J. R. Gamma oscillations in rat hippocampal subregions dentate gyrus, CA3, CA1, and subiculum underlie associative memory encoding. *Cell Reports* **21**, 2419-2432 (2017). https://doi.org/10.1016/j.celrep.2017.10.123

Trimper, J. B., Stefanescu, R. A. & Manns, J. R. Recognition memory and theta-gamma interactions in the hippocampus. *Hippocampus* **24**, 341-353 (2014). https://doi.org/10.1002/hipo.22228

Csicsvari, J., Jamieson, B., Wise, K. D. & Buzsáki, G. Mechanisms of gamma oscillations in the hippocampus of the behaving rat. *Neuron* **37**, 311-22 (2003). https://doi.org/10.1016/s0896-6273(02)01169-8

Colgin, L. L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M-B. & Moser, E. I. Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* **462**, 353-7 (2009). https://doi.org/10.1038/nature08573

Shirvalkar, P. R., Rapp, P. R. & Shapiro, M. L. Bidirectional changes to hippocampal theta-gamma comodulation predict memory for recent spatial episodes. *Proceeds of the National Academy of Sciences of the United States of America* **107**, 7054-7059 (2010). https://doi.org/10.1073/pnas.0911184107

Fell, J., Klaver, P., Lehnertz, K., Grunwald, T., Shcaller, C., Elger, C. E. & Fernández, G. Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. *Nature Neuroscience* **4**, 1259-64 (2001). https://doi.org/10.1038/nn759

Sederberg, P. B., Kahana, M. J., Howard, M. W., Donner, E. J. & Madsen, J. R. Theta and Gamma OScillations during Encoding Predict Subsequent Recall. *Journal of Neuroscience* **23**, 10809-10814 (2003). https://doi.org/10.1523/JNEUROSCI.23-34-10809.2003

Jutras, M. J., Fries, P. & Buffalo, E. A. Gamma-Band Synchronization in the Macaque Hippocampus and Memory Formation. *Journal of Neuroscience* **29**, 12521-12531 (2009). https://doi.org/10.1523/JNEUROSCI.0640-09.2009

Carr, M. F., Karlsson, M. P. & Frank, L. M. Transient slow gamma synchrony underlies hippocampal memory replay. *Neuron* **75**, 700-713 (2012). https://doi.org/10.1016/j.neuron.2012.06.014

Buzsáki, G., Buhl, D. L., Harris, K. D., Csicsvari, J., Czéh, B. & Morozov, A. Hippocampal network patterns of activity in the mouse. *Neuroscience* **116**, 201-11 (2003). https://doi.org/10.1016/s0306-4522(02)00669-3

Tort, A. B. L., Komorowski, R. W., Manns, J. R., Kopell, N. J. & Eichenbaum, H. Theta-gamma coupling increases during the learning of item-context associations. *Proceeds of the National Academy of Sciences of the United States of America* **106**, 20942-20947 (2009). https://doi.org/10.1073/pnas.0911331106

Lisman, J. E. & Jensen, O. The Theta-Gamma Neural Code. *Neuron* **77**, 1002-1016 (2013). https://doi.org/10.1016/j.neuron.2013.03.007

Inman, C. S., Manns, J. R., Bijanki, K. R., Bass, D. I., Hamann, S., Drane, D. L., Fasano, R. E., Kovach, C. K., Gross, R. E. & Willie, J. T. Direct electrical stimulation of the amygdala enhances declarative memory in humans. *Proceeds of the National Academy of Sciences of the United States of America* **115**, 98-103 (2018). https://doi.org/10.1073/pnas.1714058114

Lesting, J., Narayanan, R. T., Kluge, C., Sangha, S., Seidenbecher, T. & Pape, H-C. Patterns of Coupled Theta Activity in Amygdala-Hippocampus-Prefrontal Cortical Circuits during Fear Extinction. *PLoS One* **6**, e21714 (2011). https://doi.org/10.1371/journal.pone.0021714

Narayanan, R. T., Seidenbecher, T., Kluge, C., Bergado, J., Stork, O. & Pape, H-C. Dissociated theta phase synchronization in amygdalo-hippocampal circuits during various stages of fear memory. *European Journal of Neuroscience* **25**, 1823-31 (2007). https://doi.org/10.1111/j.1460-9568.2007.05437.x

Popa, D., Duvarci, S., Popescu, A. T., Léna C. & Paré, D. Coherent amygdalo-cortical theta promotes fear memory consolidation during paradoxical sleep. *Proceeds of the National Academy of Sciences of the United States of America* **107**, 6516-9 (2010). https://doi.org/10.1073/pnas.0913016107

Terada, S., Takahashi, S. & Sakurai, Y. Oscillatory interaction between amygdala and hippocampus coordinates behavioral modulation based on reward expectation. *Frontiers in Behavioral Neuroscience* **7**, 177 (2013). https://doi.org/10.3389/fnbeh.2013.00177

Ahlgrim, N. S. & Manns, J. R. Optogenetic Stimulation of the Basolateral Amygdala Increased Theta-Modulated Gamma Oscillations in the Hippocampus. *Frontiers in Behavioral Neuroscience* **13**, 87 (2019). https://doi.org/10.3389/fnbeh.2019.00087

Almaguer, W., Capdevila, V., Ramírez, M., Vallejo, A., Rosillo, J. C. & Bergado, J. A. Post-training stimulation of the basolateral amygdala improves spatial learning in rats with lesion of the fimbria-fornix. *Restorative Neurology and Neuroscience* **23**, 43-50 (2005).

Dahmani, L., Courcot, B., Near, J., Patel, R., Amaral, R. S. C., Chakravarty, M. M. & Bohbot, V. D. Fimbria-Fornix Volume Is Associated With Spatial Memory and Olfactory Identification in Humans. *Frontiers in Systems Neuroscience* **13**, 97 (2020). https://doi.org/10.3389/fnsys.2019.00087