THE MODULATORY INFLUENCES OF AMYGDALA-HIPPOCAMPAL INTERACTIONS ON EMOTIONAL MEMORY

by
AMAYA GRANT

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Approved: *J. Benjamin Hutchinson, Ph.D.*
Primary Thesis Advisor

This thesis is a literature review on the effects that emotion has on memory. The influences that emotion has on memory will be analyzed, specifically through the lens of amygdala-hippocampal interactions. Primary focus will be on the compilation and analysis of emotional memory studies, and how the enhancement of emotional memories is facilitated by amygdala-hippocampal modulation. By viewing brain activity and the direct or indirect projections to and from these specific brain regions, I will provide a cohesive, critical literature review of relevant cognitive neuroscience work on emotional memory and amygdala-hippocampus connections. By compiling relevant cognitive neuroscience findings in one thesis, this will make it easier to understand and comprehend the amygdala-hippocampal interconnection and its impact on emotional memory.

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Introduction

Over the last 20 years, the psychological and neuroscientific research community has become increasingly interested in the interactions between the amygdala and hippocampus. Much research has been conducted on these brain regions separately, but only recently have their interactions become a focal point of interest. Within the cognitive neuroscience field, researchers have sought to explain the connections between these brain regions and how they influence memory. It can be seen and demonstrated by these influences recorded effects on certain memory processes, like encoding, consolidation, and retrieval.

Amygdala and Hippocampus

To establish these brain regions, I will discuss their placement and role within the human brain. The amygdala and hippocampus are both part of the limbic and medial temporal lobe systems. The limbic system is involved with behavioral and emotional responses and includes certain structures of the brain which help in processing emotions. It also receives inputs from sensory systems around the body (Morgane et al., 2005). While the medial temporal lobe system handles distinct processes such as encoding, consolidation, and retrieval. (Cutsuridis & Yoshida, 2017) It is also crucial for processing episodic (recollection of memory from a specific time or place) and spatial (location of objects or occurrence of an event) memory.

It is well known that the amygdala, an almond-shaped brain region in the temporal lobe, has a central role in processing and responding to fearful or threatening stimuli (Baxter & Croxson, 2012). Some note that there has been a lot of research on the amygdala's modulation of fear in the brain (LeDoux, 2007). This means that findings and fear research regarding the human amygdala have previously focused on the whole region rather than looking deeper into

neuroanatomy, like nuclei or sub-nuclei. There is also less understanding of the amygdala's detailed circuits involved in emotional states, compared to the amygdala's circuits related to fear.

While the amygdala is well known for its role in fear conditioning, the hippocampus is critical for supporting the creation of new memories, or declarative memories. This information has been found through extensive research on the function of the hippocampus and conducting studies on participants with hippocampal lesions (Knierim, 2015). Declarative memories are memories that can be verbalized and brought to conscious awareness. Declarative memories consist of episodic and semantic (recollection of a concept, word, or number) memory. Hippocampal neuronal networks also encode events and places that are common across related episodes (Eichenbaum, 2001).

Recent research has revealed that there are many ways that these brain regions are connected, more so than previously thought. Although these two are independent brain regions, they become linked during the encoding and consolidation of emotional situations. The amygdala can also modulate the encoding and storage of hippocampal-dependent memories (LaLumiere et al., 2017; E. Phelps, 2004). The hippocampal complex, which forms episodic representations of the emotionally significant events, can also influence amygdala response when emotional stimuli is encountered (Phelps, 2004). These are just a few examples of how these brain regions work together when emotion is involved in memory.

How are the amygdala and hippocampus connected? How do they interact? What information has been contributed from animal studies to human research? What requirements are needed for memories to emotionally enhanced? My goal is to explore these questions and conduct a literature review on the relevant research related to the amygdala, hippocampus, and their interactions. I will critically analyze papers on this topic, and I will identify the major

findings, as well as identifying areas in need of more exploration or study. I will focus on connections between the supporting evidence (scientific, peer-reviewed articles or studies) and how these are related to amygdala-hippocampal interactions. The main goal is to ascertain how emotional memory is supported or modulated by amygdala-hippocampal interactions; and how and why certain information is prioritized over others.

Emotional Memory

Cognitive neuroscientists describe emotional memory from a perspective of how emotional events are learned and remembered in the human brain (LaBar & Cabeza, 2006). Other researchers say that the term 'emotional memory' describes how "emotion during an initial experience affects episodic memory" or "episodic memories for events that initially elicited a negative or positive affective responses" (Williams et al., 2022). Although there are many definitions for 'emotional memory', for the most part, researchers have agreed upon two dimensions of emotional memory. The first dimension is arousal (calm to excitement), and the second dimension is valence (unpleasant (negative) to pleasant (positive) with neutral as intermediate); and their impact on declarative (explicit; episodic memory) or non-declarative (implicit; fear conditioning) memory. The main goal for researchers who focus on emotional memory is to figure out what psychological or neural mechanisms underlie emotional retention in the human brain.

Methodology

For simplicity's sake, I won't be reviewing every single form of methodology or brain imaging studies used to examine emotional memory processes. I will include some of the most common methodology that researchers and cognitive psychologists have used to examine emotional memory in humans, from what I've read and researched on this topic.

Common Brain Imaging Techniques

Functional magnetic resonance imaging (fMRI) (Dolcos et al., 2004; Murty et al., 2010). The fMRI is, "an indirect measure of hemodynamic response by measuring changes in… blood oxygenation level dependent (BOLD) signal" (Tyng et al., 2017). It can be used to examine which brain regions are more active depending on the stimuli. MRIs also have higher spatial resolution than EEGs.

Event-related fMRI (Ritchey et al., 2008) is a form of fMRI that is used to detect changes in the BOLD hemodynamic responses to certain events.

Event-related fMRI dynamic causal modeling (DCM) of fMRI data (Fastenrath et al., 2014). This modeling is used to infer about "directed connectivity between brain regions based on imaging data such as… fMRIs" (Sadeghi et al., 2020).

Positron emission tomography (PET) measures glucose metabolism or region cerebral blood flow to identify the different neural networks involving pleasant, unpleasant, or neutral emotions (K. S. LaBar & Cabeza, 2006; Lane et al., 1997; Taylor et al., 1998; Tyng et al., 2017).

Electroencephalogram (EEG) (Kim & Choi, 2020). The EEG is used to obtain high temporal resolution records of electrical brain activity. It is used to map cognitive neuroscience cognitive and emotional processing (Tyng et al., 2017). This is a continuous measurement of brain activity.

Event-related brain potentials (ERP) (Dolcos & Cabeza, 2002). This technique can be used to assess how the brain functions in response to stimulation of the senses (touch, sound, sight, etc.). It helps capture neural activity related to both cognitive and sensory processes (Sur & Sinha, 2009). ERPs are short segments of EEG data that are time-locked to events of experimental interest.

Functional near-infrared spectroscopy (fNIRS) (Tseng et al., 2018). fNIRS can be used to map the hemodynamic responses associated with brain activation. The many studies that have used this technique are associated with task performance (Tyng et al., 2017; Villringer et al., 1993).

Subjects with **lesions, damage, or amnesia** in certain brain areas, like the amygdala, hippocampus, or medial temporal lobe (Adolphs et al., 2005; Anderson & Phelps, 2001; Buchanan & Adolphs, 2004; Phelps, 2004).

Animal Studies and Research

Research on rats has identified the amygdala as a critical structure which underlies the circuitry of fear conditioning (Janak & Tye, 2015; Kim & Jung, 2006). It has also been shown that the amygdala has specific synaptic connections that aid in the acquisition and storage of memories in fear conditioning (Rodrigues et al., 2004). Recent efforts have tried to find parallels in human studies compared with animal studies (Adolphs et al., 2005). An example of parallel findings is the studies which explored the role of positive emotions in animals (Baxter & Murray, 2002) as well as humans (Herbert et al., 2009). Both studies conclude that the amygdala's role in emotional processing is not limited to fear (E. A. Phelps & LeDoux, 2005).

Additionally, previous studies of rats and other mammals on emotional learning and memory (J. E. LeDoux, 2000), as well as fear conditioning studies have been helpful for researchers trying to understand human responses. For example, studies on rodents and arousal, wherein responses are measured after a trigger (shock or short-lived stressor), have revealed that these stressors ultimately increase the likelihood that those events are remembered (Williams et al., 2022).

Although, one of the main drawbacks from these animal studies is that the examined influence of the amygdala on the hippocampus was mainly studied within an emotionally aversive learning context (Fastenrath et al., 2014; E. Phelps, 2004); but this drawback is also animal studies' biggest strength. Since these animals' studies were mainly done within an emotionally aversive context, it can limit the context, information, and findings gleaned to a specific learning environment. When looking at human studies and ethics, these same studies can't be ethically replicated in humans. So, human studies can expand upon and build on the previous research from animal studies.

Previous animal studies on emotional arousal and its effect on the enhancement of memory consolidation, have revealed how consolidation is facilitated by the amygdala's influence on the hippocampus (E. Phelps, 2004; E. A. Phelps & LeDoux, 2005). While there is evidence on the memory consolidation of emotionally arousing memories in animals, evidence in humans has been more centered on encoding processes (LaLumiere et al., 2017).

Animal studies have revealed how the amygdala receives sensory information. They've found that it receives information via two routes: the rapid, but simplistic input from the sensory thalamus, and the slower, but more detailed representation from the sensory cortex (J. LeDoux, 2003). This gives human research a better understanding of how the amygdala receives different kinds of information.

Some researchers have found that common social scenarios often create similar patterns of neural activation between humans and non-human animals (NHA). (Zablocki-Thomas et al., 2022) For example, there are similar patterns of neural activation in the amygdala for emotions associated with variations of arousal, as there are for NHA. (Bliss-Moreau et al., 2020).

It seems that while there have been many findings from animal research that can be applicable to human studies, the most important research has been the animal studies related to fear conditioning. This research is important because most NHA on fear conditioning has been conducted with the inclusion of an emotionally aversive learning context, or aversive stimulus (shock). The involvement of ethical considerations and reinforcement in human studies means that researchers investigating fear conditioning in humans cannot learn about fear responses as critically as animal studies can. That is why NHA research is invaluable within the study of fear in psychology. Overall, NHA research has extended the basic findings from animals about the amygdala's role in emotional processing and fear.

Key Findings and Research on the Amygdala-Hippocampus Interactions in Emotional Memory Processes

This section will contain findings, studies, and research in relation to the impact that the amygdala and hippocampus have on emotional memory processes. This section will not contain each and every important finding on emotional memory, but it will include findings that I deem pertinent to create a general, comprehensive understanding of the topic.

Overall, emotion has a strong influence on attention, especially modulation of selective attention. This is closely linked to the learning processes concerning the limited capacity of attention and being able to focus on relevant information. We know that emotion can facilitate encoding and the retrieval of salient information more efficiently (Tyng et al., 2017). It's important to monitor the amygdala when emotional stimuli are involved because the amygdala has been proven to account for attentional differences in emotionally arousing stimuli versus neutral stimuli. This means that the amygdala contributes to emotional experience by increasing attention to salient events (Anderson, 2007).

Although the hippocampus has been recorded to work closely with the amygdala in the context of emotional memory, it has been specifically proven to be essential for "spatial contextual detection" in recognition memory (Gálvez-Márquez et al., 2022). Specifically, the dorsal hippocampus has been found to be involved in coding and storing of memory context (Maren & Hobin, 2007; Maren & Holt, 2000). This section will closely analyze how the amygdala and hippocampus work together to modulate certain memory processes when emotion is involved.

Valence/Arousal

When looking at human brain imaging studies, these have shown that greater amygdala activation is related to emotional events, compared to neutral events, in enhancing episodic memory (Anderson et al., 2006; Ritchey et al., 2008). Studies have been done to see if amygdala activation alone is sufficient to enhance recollection. Researchers have found that sufficient levels of systemic arousal must be required to alter memory consolidation. This alteration will ultimately result in enhanced recollection of emotional events (Anderson et al., 2006).

These findings on systemic arousal and memory consolidation were found when researchers compared stimulus types (scenes vs faces) and valence (negative vs neutral) within the remember-known paradigm (Anderson et al., 2006). Sympathetic arousal recordings were also compared with recognition memory (proportion correctly remembered, depending on stimulus type and valence). Their results revealed a parallel dissociation in memory and sympathetic arousal. This means that emotionally aversive scenes enhanced remembrance rather than familiarity, and that fearful faces did not enhance either remember of familiar responses. When sympathetic arousal was recorded, findings revealed that "aversive scenes but not fearful faces were associated with a significant increase in peripheral sympathetic arousal" (Anderson et al., 2006).

This evidence is suggestive that activation in the amygdala may be necessary but alone is *insufficient* to enhance episodic memory for emotional events (EEM). It seems that fearful faces don't activate EEM. Although stimuli is enough to increase amygdala activity, there is still an insufficient level of systemic arousal to activate EEM. In conclusion, present results suggest that enhanced memories of emotionally significant events arise from both amygdala activation and heightened systemic arousal (Anderson et al., 2006; Roesler et al., 2021), which also allows the

amygdala to influence the hippocampus. Because of this evidence, it is believed that emotional relevance of the information is the one of the most important factors for memory retrieval.

The shared amygdala-hippocampal activation for emotionally arousing events (Dolcos et al., 2004; Kilpatrick, 2003) depends on many neurochemical events, stress hormones and adrenergic receptors**,** which enhance hippocampal consolidation of new episodic memories (which will be further explained in the Pharmacology section) (J. L. McGaugh et al., 1996). Therefore, greater retention for emotional events is possible by shared input from both the systemic arousal and amygdala activation, and that amygdala activation requires other neuro-modulatory influences from brain regions (hippocampus) to support enhanced recollection (E. A. Phelps & LeDoux, 2005).

Many neuroimaging studies compared neutral, negative, or positively charged information and its effect on the amygdala and hippocampus connectivity. Findings support the enhancement effect of emotional arousal on episodic memory encoding (Fastenrath et al., 2014; Sommer et al., 2008; Wang, 2018).

Much of previous research has supportive evidence that emotionally valanced events are better remembered than neutral events. Even more specifically, researchers wanted to know whether positive or negative information has similar or different effects on amygdala-hippocampal connectivity. Results revealed that net connectivity between the two regions were similar for the two valences (Fastenrath et al., 2014). This means that there was a strong connection from the amygdala to the hippocampus, and that this connection increased when participants viewed both positive and negatively valence pictures, but not so much for neutral pictures. This demonstrates, along with other research, that valence, whether negative or

positive, has more influence on encoding than something with a neutral valence (Fastenrath et al., 2014; McIntyre & Roozendaal, 2007; Sergerie et al., 2008).

Results were found by running a dynamic-causal model (DCM) of fMRI data, which revealed a strong connection starting from the amygdala to the hippocampus while participants encoded neutral pictures with a positive or negative valence. This human research was based off the memory-modulation hypothesis and model, by James McGaugh, which was generated from animal research, in which the main idea is that the amygdala regulates information processing in the hippocampus (McGaugh, 2000). It appears that researchers have conducted human studies that support this hypothesis. Results also suggest that the influence of the amygdala on the hippocampus is 10 times stronger than the influence on the hippocampus on the amygdala (Fastenrath et al., 2014).

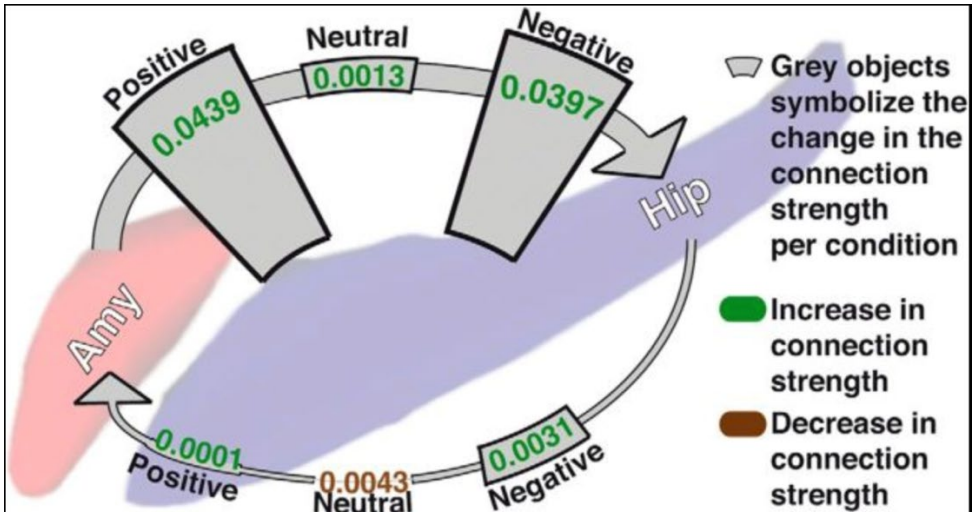

Figure 1: Depicting the change in connection strength between the amygdala and hippocampus during the encoding of positive, negative, and neutral pictures. (Accredited to Fastenrath et al., 2014).

Overall, differences of arousal and memory were smaller between positive and negative valence, than emotional or neutral stimuli (Fastenrath et al., 2014). This study demonstrates the

ways that the amygdala and hippocampus synchronously work together to encode positive, negative, or neutral images.

In a theoretical review, researchers point out that most of the research on emotional content within neuroscience and cognitive psychology have mainly focused on negative emotional content, not positive (Williams et al., 2022). This may be because researchers are trying to use stimuli that will provide the maximum effects of revealing emotion on memory. Since people typically attend to more negative information than positive, researchers were constrained to negative stimuli to get the biggest results (Baumeister et al., 2001). Additionally, most of the work in humans has been built on previous research which studied memory effects in rodents (Sazma et al., 2019; Woodson et al., 2003). This NHA research and literature predominantly used experiments in which the stimulus were shocks or other brief stressors. With the inclusion of a negative stimulus, it was thought that this would increase the likelihood for the participant to remember that event.

Important findings focusing on the power of negative episodic memories have revealed: negative content has a shallower forgetting curve than neutral content (Yonelinas & Ritchey, 2015); there are more specific and vivid recollection of a past negative event than of a past neutral event (Smith et al., 2004); and that these memories are durable. Although the enhanced durability of emotional memories has many memory models that have been thought to account for this. One model in particular, the memory-modulation model, (which was previously mentioned) is one of the first models to explain emotional enhancement of memory (McGaugh, 2000). Results consistent with this model support the idea that amygdala activity is enhanced when negative content is successfully encoded, and that the amygdala often interacts with the hippocampus in this process (Richardson et al., 2004).

But this is one model of many, each of which has sufficient research and evidence to support them. Although, as some researchers point out, these models are not mutually exclusive, as they focus on different characteristics or phases of memory (Williams et al., 2022); and there hasn't been a generalized consensus on which model is the most correct.

When looking at the hippocampal and amygdala binding systems, it seems that the hippocampus and amygdala may subserve different binding functions (Yonelinas & Ritchey, 2015). This concept supposes the amygdala and hippocampus binding systems work independently, as two separate systems with distinct function. There's the amygdala-based system, which prioritizes binding items to an emotion, and the hippocampal-based system which prioritizes binding items to its context (Yonelinas & Ritchey, 2015). So, when negative emotions are engaged, the theory supposes that negative emotion may create an imbalance between the engagement of the hippocampus and amygdala and may even cause a shift towards amygdala binding. While positive emotions would lead to an equal engagement of both systems, and a shift towards hippocampal binding (Williams et al., 2022).

Although, researchers still don't know how the balance of hippocampus and amygdala binding systems are determined, they've found promising evidence that neurofeedback is a crucial factor in this process (Williams et al., 2022).

For instance, neurofeedback can be used to enhance emotion regulation or to downregulate amygdala activity (Brühl et al., 2014; Linhartová et al., 2019). By providing participants with neurofeedback of their own amygdala activity using cognitive reappraisal, amygdala activity was significantly reduced (Herwig et al., 2019). Neurofeedback also increased connectivity between the amygdala and hippocampus. This example demonstrates how

neurofeedback may be used to achieve greater balance between the amygdala and hippocampus binding systems.

The memory-modulation model (McGaugh, 2000) and amygdala-hippocampus binding system (Williams et al., 2022; Yonelinas & Ritchey, 2015) are just a few of many interesting concepts that researchers have created within emotional memory research. These theories provide substantial points of reference for other neuroscientists who may try to understand how the valence of certain emotions can lead to better, or worse, encoding and amygdala-hippocampal connectivity.

Consolidation

Memory consolidation has been found to be dependent on the hippocampus. The hippocampus reorganizes information stored in the neocortex until that information becomes consolidated and is dependent of the hippocampus (Squire et al., 2015). Researchers have also found another brain region, the amygdala, that works with the hippocampus in the memory consolidation process. The amygdala and hippocampus have been found to interact, translate, and consolidate emotions. Brain structures are activated by an emotional event and "cross-talk" with each other in the process of consolidation (Richter-Levin & Akirav, 2000). Researchers have found that the amygdala and hippocampus act synergistically (in a cross-talk) to form long-term memories of significantly emotional events. The cross-talk occurs during the process of consolidation, and results in dual activation of both brain regions when emotion is involved in memory (Richter-Levin & Akirav, 2000).

For example, enhancement of consolidated memories, rather than initial encoding, comes from the amygdala's modulation of hippocampal-dependent memories (J. McGaugh, 2002;

Packard & Cahill, 2001). So, when the amygdala encounters emotionally reactive stimuli, it modulates consolidated memory (E. A. Phelps & LeDoux, 2005).

The selectivity of memory can be attributed to the effects of emotional arousal and attentional/sensory process, as discussed in the valence/arousal section. But within the process of consolidation, emotional arousal can also lead to preferential consolidation (J. L. McGaugh, 2000). One reason for this enhanced consolidation state is that the amygdala can engage other neuro-modulatory systems to "alter thresholds for synaptic modification" (Roozendaal et al., 2009). Through this systems-consolidation process, emotionally arousing experiences can prompt interaction between distant regions, like the hippocampal-neocortical circuits (Paz et al., 2006; Sirota & Buzsáki, 2005).

One study hypothesizes that functional connectivity between the amygdala and hippocampus would be increased during rest, following an emotionally arousing experience (de Voogd et al., 2016). Their findings revealed that amygdala-hippocampal connectivity did in fact increase during post-learning awake rest compared to baseline. For future implications, this means that this study could reveal a potential way that emotional memories are selectively consolidated. This could then explain why emotional memories are preferentially preserved in long-term memory (de Voogd et al., 2016).

Overall, the cross-talk between amygdala and hippocampus, as well as the amygdala's modulation of hippocampal-dependent memories, and emotional arousal can lead to enhanced or strengthened consolidation for emotionally charged events (at the moment of the event, or later during post-learning awake).

Retrieval/Recall

It is well known that emotionally salient events are often more vividly remembered than neutral events, which can improve the accuracy of recall. This process is facilitated by the amygdala, which influences attention and shifts through the present information to direct attention towards emotionally charged events (Buchanan, 2007; Kensinger, 2009). This attention can enhance retrieval of emotionally charged memories (Tyng et al., 2017). Both memory context and behavioral context can impact the underlying neural structures involved with emotional retrieval (Smith et al., 2006). Even specific factors of a task can influence connectivity between these two regions (Fastenrath et al., 2014). When examining the amygdala and hippocampus during a contextual retrieval task, in which emotional context and relevance of retrieved emotional information were manipulated by the researchers, results revealed that retrieval of "emotionally-valanced, contextual information" is associated with enhanced activity in the hippocampus and amygdala (Fastenrath et al., 2014; Smith et al., 2006). This means that when emotional information is relevant within behavioral contexts, retrieval ultimately increases connectivity between the hippocampus and amygdala bidirectionally.

As stated previously, emotional relevance of the information is the one of the most important factors for memory retrieval. Findings have revealed that an increase in connection strength from the hippocampus to the amygdala is reflected when negative items are retrieved, as opposed to items with a neutral context (Bisby & Burgess, 2017; Smith et al., 2006). Overall, this supports the idea that when information is retrieved within an emotionally valanced context, this retrieval is associated with increased connectivity between amygdala and hippocampus. Amygdala-hippocampal activity increases bidirectionally when retrieving emotional information, especially when that information is relevant to current behavior (Smith et al., 2006).

From a broader viewpoint, their findings show that both behavioral context and memory content are important for understanding the dynamics which underlie emotional retrieval. As discussed in the Valence/Arousal section, retrieval of information encoded in emotional contexts, compared to retrieval from neutral contexts, increases connection strength from the hippocampus to the amygdala. In this enhanced pattern of effective connectivity expressed bidirectionally**,** **(**moving from the hippocampus to amygdala and vice versa), processing differences in retrieval of items (negative vs neutral contexts) was primarily reflected in an increased connection strength between the hippocampus and amygdala (Smith et al., 2006).

Overall this means that retrieval of memories encoded within an emotionally charged context, is associated with an increased effective connectivity between the hippocampus and amygdala, bidirectionally (Buchanan, 2007; Smith et al., 2006). So, retrieval of emotional information or memories is facilitated by the connections that exist between the hippocampus and amygdala.

Fear Conditioning

The process of fear conditioning is mediated by several brain regions, including the amygdala and hippocampus. The amygdala itself is the key brain region involved in processing emotional information like fear. In the context of fear conditioning, the amygdala plays a key role in associating the neutral stimulus with a fear-inducing stimulus (Lanuza et al., 2008; Mahan & Ressler, 2012). It does this by detecting a fearful stimulus, and then sending those signals to other brain regions, which then initiates a physiological response. The hippocampus is also another important brain region involved in fear conditioning. Within the context of fear conditioning, the hippocampus plays a critical role in forming and consolidating memories of fearful stimulus, as well as its association with the neutral stimulus (Oh & Han, 2020; Raineki et

al., 2010). This process is thought to be achieved by something called synaptic plasticity. It does this by detecting a fearful stimulus, and then sending those signals to other brain regions, which then initiates a physiological response, in which neurons can modify the strength of their connection (Stampanoni Bassi et al., 2019)

More specifically, it is thought that these two brain regions work independently but collaborate on separate memory processes during fear conditioning. For instance, the hippocampus is involved with the initial encoding and consolidation, while the amygdala is involved with the retrieval of fear memory (Feng et al., 2014; Raber et al., 2019).

The amygdala and hippocampus have complex interactions between themselves, especially in the formation and expression of fear memories. For instance, amygdala damage means subjects fail to show physiological indication of conditioned fear, while hippocampus damage impairs subjects' ability to consciously report events of fear conditioning. So, amygdala damage predicts impaired fear conditioning, and hippocampal damage predicts impairment of the formation and retention of fear memories (Bechara et al., 1995; K. LaBar et al., 1995). Additional studies have also shown that the amygdala provides input to the hippocampus, and that the hippocampus modulates amygdala activity during fear conditioning (Ressler, 2010; Yang & Wang, 2017).

Evidence from fear conditioning research has shown yet another way in which these brain regions independently, but synergistically work together to facilitate fear learning and conditioning.

Downsides to the Emotional Enhancement of Memories

While it seems like the amygdala's involvement in encoding emotional memories is all positive, this also means that associative memory (the ability to link or associate two or more

pieces of information together) can become impaired (Wang & Cui, 2018). It's well known that emotional arousal can impair association memory (Madan et al., 2017). This is thought to be a result of when emotional arousal interferes with attention or focus, such as when arousal tends to narrow attention to emotionally salient events or pieces of information (to be later discussed in detail). Emotional arousal can also create interference during the encoding and consolidation of information. This is because cognitive resources may be focused on processing and reacting to emotional stimuli, thereby ignoring associative or neutral information (Šimić et al., 2021; Tyng et al., 2017).

Another important downside of emotionally enhanced memory is that it can lead to persisting negative emotions and memories (Bisby & Burgess, 2017; Tyng et al., 2017). Oftentimes, individuals who experience traumatic or stressful events may have accompanying vivid and detailed memories that are difficult to forget. This can lead to many mental disorders like post-traumatic stress disorder (PTSD), anxiety or depression. In some cases, emotionally enhanced memories can cause undue and unwanted stress, which can exacerbate negative emotions and psychological distress (Van Der Kolk, 2000). This may be explained by research that compares the power of negative emotions versus positive emotions. Researchers have seen that negative moods may process information and details in a more narrow and analytic way than people in positive or neutral moods (Albarracin & Hart, 2011; Wolf et al., 2021).

As mentioned earlier, another significant drawback for emotional memories is that the amygdala can differentially enhances details rather than gist or global representations (Adolphs et al., 2005). Emotional memories are thought to be mediated by the amygdala to create vividly detailed recollections of emotional events (Buchanan, 2007). The amygdala also sends signals to the hippocampus to strengthen the encoding and consolidation of emotions and memories.

However, this process can lead to the narrowing of attention, so much so that individuals only focus on the salient details on the emotional event, at the expense of the broader context of gist (K. S. LaBar, 2007; Šimić et al., 2021). There are several negative consequences of this attentional bias, like impairing one's ability to generalize information from one situation to another. For instance, if one fails to recognize similarities between other, less salient events, this could lead to failure to learn from experience or adapt to new situations.

It seems that while the emotional enhancement of memories, facilitated by amygdala-hippocampal interaction, may be useful for remembering details, improving long-term memory retention, and accuracy of memory recall, it also has several drawbacks. Such as impairment of associative memory, details at the sake of the global representations, and persisting negative memories.

Neuroanatomy and Projections

Knowledge of neuroanatomy is important because it gives a more in-depth understanding of how closely these two brain regions are and how they interact. By studying the neuroanatomy of these brain structures, we can see the underlying neuronal networks which connect these two together. For example, through tract tracing studies researchers have found evidence that the robust and complex interconnections exist between amygdala nuclei and layers of individual hippocampal/parahippocampal regions (McDonald & Mott, 2016). This means that there are many ways that these brain regions are connected, more so than previously thought.

Looking further into the anatomical organization of the amygdala, there has been some debate among researchers on how to divide the amygdala based on the various criteria and its internal subdivisions which relate to other brain regions (LeDoux, 2007; Sylvester et al., 2020). To clear up confusion, the term "basolateral" can mean both a specific nucleus and a larger region. Each nuclei can also be further divided into subnuclei. For instance, the amygdala nuclei are split into the basolateral (BLA) groups, which can be subdivided into the lateral nucleus (LA), basomedial nucleus (BM), basolateral nucleus (BL); cortical groups; and centromedial groups. It's important to understand even the subnuclei because there is interesting information to be found. For example, researchers have found that certain subnuclei of the amygdala modulate the consolidation of emotional memories (J. McGaugh, 2002).

Moving into the connections between the basolateral amygdala and hippocampus, the BLA and hippocampus are the two brain regions which can operate independently to exert their distinct functions in emotion and memory. Generally, the amygdala and hippocampus work synergistically, or work together to form long-term memory (Yang and Wang, 2017). The medial prefrontal cortex (mPFC) also bidirectionally connects with the amygdala and receives

projections from the hippocampus. It is a region that forms synapses with both the hippocampus and the BLA (Ghashghaei et al., 2007; Marek et al., 2013).

Similarly, researchers have found that the BLA and basolateral nucleus (BL) modulate the consolidation of memories of emotionally arousing experiences through projections to brain regions, like the hippocampus (McDonald & Mott, 2017). By examining rat studies, they've found evidence that suggests modulation effects on hippocampal-dependent memories which can depend on direct or indirect pathways connecting the BLA with the hippocampus and entorhinal cortex (Packard et al., 1994; Roesler et al., 2002). By looking at human studies they've also found that amygdala-hippocampal interactions can enhance declarative (explicit memories) of emotionally arousing events (Phelps, 2004). Finally, by viewing fMRIs of human brains, researchers can see that the formation of memories of emotional stimuli involves interactions of the basolateral amygdala with the entorhinal cortex and hippocampus, wherein the brain areas are activated by retrieval of emotional memories (McDonald and Mott, 2017; Dolcos et al., 2005). Activation of the BLA can also facilitate hippocampal long-term potentiation (Fastenroth et al., 2014; Roozendaal and McGaugh, 2011).

This research has provided significant evidence in support of the connections between the BLA and the hippocampus.

In terms of BLA-CA1(cornu ammonis-1) circuitry, anatomical projections from the BL to CA1 indicated that the BL may be a key subregion within the hippocampal formation to modulate different stages of information processing (Yang and Wang, 2017). Other researchers also support a monosynaptic connection between the BL and vCA1 (Chauhan et al., 2021). Although, there has been evidence that modulatory effects of the BL and Bm on memory are via separate pathways, and that this involves an increase in the "excitability of dorsal dentate gyrus

(dDG) neurons" (McDonald and Mott, 2017; Ikegaya et al., 1996). Since there haven't been any direction projections found from the BL and BM to the dDG (which is a cortical region, part of the larger brain systems called the hippocampal formation), this means that the modulatory pathways are polysynaptic. Meaning that the dDG, BL, and BM involve two or more synapses in the central nervous system to communicate.

There are other areas of the brain that the amygdala sends direct projections upon encountering emotional stimuli (McDonald & Mott, 2017). These areas include the ventral subiculum (vSub), ventral cornu ammonis-1(vCA1), entorhinal cortex, and perirhinal cortex. The vSub and vCA1 are areas within the hippocampal formation, which includes the hippocampus proper, containing the cornu ammonis, dentate gyrus, and subiculum. The vCA1 is important because it facilitates a reciprocal anatomical connectivity that exists between the anterior hippocampus and amygdala (Madan et al., 2017).

This research indicates that there are many intricate and subtle ways that the amygdala and hippocampus interact neuroanatomically, either directly or indirectly.

Of note, although the entorhinal cortex, perirhinal cortex, and subiculum are not major areas of focus, they are mentioned quite frequently within the context of amygdala-hippocampal interactions. An interesting study on afferents of the amygdala and the hippocampal formation in the rhesus monkey finds evidence for a pattern of "hippocampal and amygdaloid projections to the entorhinal and perirhinal cortices" that indicates that these regions can possibly hold broad interactions between the amygdala and the hippocampus (Saunders and Rosene, 1998). Also, studies on connectivity of the rat amygdaloid complex support evidence for strong projection from the BLA to the perirhinal and entorhinal cortices (Pitkanen, 2000). The rhinal cortices act as an "inhibitory gating mechanism" that regulates interactions. This mechanism is regulated by

the amygdala, through the BLA, to modulate emotional information (Paz and Pare, 2013). This demonstrates how many cortices, regions, and structures are actively sending direct, or indirect projections to and from each other, often involving the amygdala or hippocampus, to modulate emotional memory.

One limitation researchers Yang and Wang have noted is that further research into the monosynaptic BLA-hippocampus projection is needed to understand how BLA and hippocampus interact directly to account for emotion-regulated memories (2017). They suggest that although the BLA could modulate hippocampus-dependent behavior, via neural correlation, there isn't enough evidence to support a direct BLA-hippocampus projection. It's important that further research is done on this subject so that we know how this relationship accounts for emotionally regulated memories.

One thing to note is that hippocampal formation-BLA projections are glutamatergic (Richter-Levin and Akirav, 2000; Mello et al., 1992). Researchers McDonald and Mott (2017) discuss the neuroanatomy, neurotransmitters, glutamatergic pyramidal cells that mediate interconnections, and GABAergic projection neurons involved with the amygdala-hippocampal interactions (McDonald & Mott, 2017). These neurons are also involved in the amygdalar modulation of hippocampal-dependent mnemonic (any learning technique that aids information retention or retrieval in the human memory for better understanding) functions.

Diving further into the cells, researchers have found that the cortical amygdalar nuclei and the basolateral amygdala nuclear complex (BLC; lateral, basolateral, basomedial, amygdalohippocampal area) have cortex-like cell types: projection neurons (glutamatergic pyramidal); and GABAergic nonpyramidal neurons (many are interneurons and can be

distinguished) (McDonald & Mott, 2017). These cell types exist to mediate interconnections between the amygdala and hippocampus (Andjelic, 2009).

The glutamatergic pyramidal neurons (GPN) and a small subpopulation of GABAergic nonpyramidal neurons participate in amygdalohippocampal interconnections (McDonald and Mott, 2017; Tyzio, 1999). Furthermore, GPN are the main neuronal type associated with projections from the hippocampal/parahippocampal region to the amygdala, as well as projections from the cortical/basolateral amygdala nuclei to the hippocampal region (McDonald and Zaric, 2015). Amygdalohippocampal interconnections also involve long-range nonpyramidal projection neurons (LRNP) neurons which stand in as inhibitory GABAergic neurons. Overall, the interconnections between amygdala and hippocampal regions are mediated by inhibitory GABAergic LRNP neurons. The glutamatergic projections, which start in the entorhinal cortex, extend through the hippocampal formation and even pass through the trisynaptic circuit itself on its way to the amygdala as a mediator (McDonald and Mott, 2017; McDonald and Zaric, 2015). A figure of the MTL GABAergic network and its connections is displayed below.

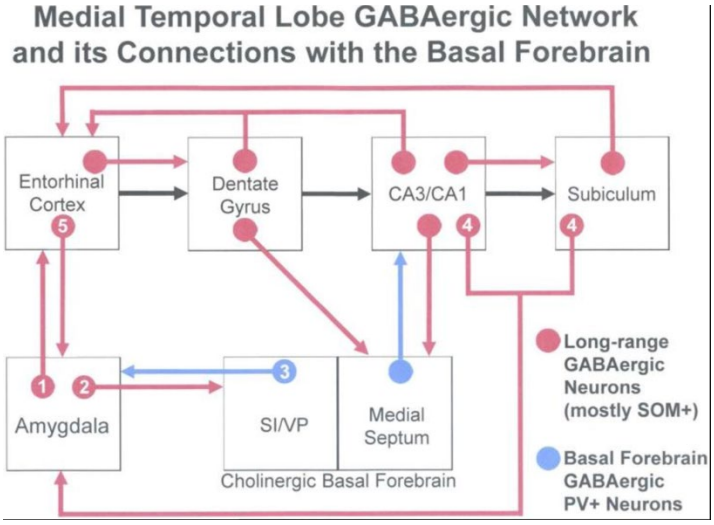

Figure 2: Medial Temporal Lobe GABAergic Network and its Connections with the Basal Forebrain (McDonald & Mott, 2017).

From a broader viewpoint, LRNP neurons contribute to connections between the neocortex to perirhinal cortex, then the perirhinal cortex projects to the entorhinal cortex, from there it goes to the hippocampus, and travels to the subicular region and finally ends in the entorhinal cortex. These connections have been dubbed the "temporal lobe GABAergic supernetwork" (McDonald and Mott, 2017; Buzsaki and Chrobak, 1995).

This research provides evidence of deep interconnections (neurons) between the amygdala and hippocampus which sends projections and mediates their interactions during emotionally regulated memories.

Pharmacology

Animal models suggest that the amygdala modulates the consolidation of hippocampus-dependent memories through stress hormones (Phelps, 2005). In the most basic terms, this is accomplished by, "the stress hormones which activate adrenergic receptors in the basolateral amygdala that then modulates the effect of these hormones on hippocampal consolidation" (Phelps, 2004; McGaugh and Roozendaal, 2002). This process can be pharmacologically blocked when B-adrenergic receptors are used to impair the enhancement of memories for emotionally charged events in humans. This suggests that amygdala modulation of consolidation is dependent on "neurohormonal changes that occur with arousal" (Cahill et al., 1994; Phelps and LeDoux, 2005). By looking at the administration of a B-adrenergic blocker in humans, results show that the blocker erases the emotional enhancement of episodic memory (Strange et al., 2003); a function that can be replicated by damaging the amygdala.

When looking into neurohormonal memory modulation, researchers have found that infusion of B-adrenergic receptor antagonists into the basolateral amygdala (BLA) blocks the memory-enhancing effects of adrenaline, and infusion of B-adrenergic receptor agonists facilitates memory consolidation (K. S. LaBar & Cabeza, 2006). Memory consolidation of learning tasks can be blocked by adrenocortical suppression and is enhanced by infusions of glucocorticoid receptor agonists into the BLA and hippocampus (Roozendale and McGaugh, 1997). Administration of B-adrenergic receptor agonists (propranolol) before encoding reduces long-term retention advantages that would typically occur when emotionally arousing stimuli is encountered (Cahill, 1994; McGaugh, 1998). Functional neuroimaging studies show that amygdala activity during encoding of emotional stimuli is reduced by propranolol.

Also, the similar studies on propranolol have shown that this beta-blocker disrupts the amygdala-hippocampal interactions that underlie emotional memory formation, particularly the consolidation of memories. This suggests that the beta-adrenergic activity in the amygdala and hippocampus is critical for emotional memory consolidation.

Research on rodents has shown that adrenal stress hormones modulate performance on various learning and memory tasks (J. McGaugh, 2002; J. L. McGaugh, 2000, 2004). Emotional events start complex interactions between adrenergic and glucocorticoid systems that are coordinated by the hypothalamic-pituitary-adrenal axis. Rodent evidence supports the memory-modulation hypothesis, that greater long-term memory (LTM) for more emotional than neutral events reflects the neuro-modulatory influences of the amygdala on consolidation in the MTL lobe by stress hormones (McGaugh, 2000).

An interesting topic that researchers have debated is the effect of emotional arousal on memory for preceding neutral events. Researchers conducted studies to see which mechanisms play a role in emotion induced enhancements or decrements in memory. In this series of experiments (psychological, psychopharmacological, and neuropsychological), the researchers examine the data that characterizes emotion-induced forgetting and enhancement (Strange et al., 2003).

They found that adrenergic release enhanced memories for emotional events. This is consistent with animal research indicating that enhanced memory is associated with emotional experiences and activation of the beta-adrenergic system (Van Stegeren et al., 1998). What they weren't sure of is how this process was mediated by the amygdala. Through more rigorous testing, they found that emotion-evoked B-adrenergic activity disrupts the encoding of items right before an emotional event. This is because emotional arousal can trigger a hormone called

norepinephrine which can disrupt memory encoding, especially for non-emotional information which precedes the emotional event (Strange et al., 2003; Tully & Bolshakov, 2010).

Pharmacology studies have been crucial for understanding the neurochemical and neurohormonal events that occur when an emotional event is encountered. Especially interesting is how the amygdala releases hormones which then effect hippocampal consolidation. The beta-adrenergic blocker and the beta-adrenergic receptor agonist (propranolol) have been key factors for understanding amygdala-hippocampus activity and interactions during emotional memory processes.

Conclusion

Coming back to the questions proposed in the introduction: What information has been contributed from animal studies to human research? How are the amygdala and hippocampus connected? How do they interact? What requirements are needed for memories to emotionally enhanced?

Animal findings and research have been instrumental to human research on emotional memory and amygdala-hippocampus interactions. Most importantly it has extended basic findings about fear and the amygdala's role in emotional processing. There have been many important human findings on the impact that amygdala-hippocampus interactions have on emotional memory processes (encoding, consolidation, retrieval) and how valence/arousal have a role in these processes. Fear conditioning and downsides to the emotional enhancement of memory are also important concepts to consider. It seems that through all these concepts and memory processes, the amygdala and hippocampus work together in many complex and intricate ways. Their influences are also heavily dependent upon sympathetic arousal, valence, and emotional context.

Although these are two independent brain regions, they collaborate and work synergistically within the human brain. Although there is no complete, 100% known answer that can explain all their functions and abilities, there is still much research about them that is known. Such as that these brain regions cross talk and connect bidirectionally, through a dynamic and mutual relationship to modulate emotional memory. Effects can be replicated or even blocked in the instance of pharmacological studies. The neuroanatomy of these two brain regions is extremely complex and demonstrates how closely interweaved the amygdala and hippocampus are.

As for how this thesis can apply to the world and its broader implications, I have concluded that the amygdala-hippocampus connection could be one of the many stepping stones researchers can take to fully understand emotional memory. If there is so much information and findings that can be gleaned from just two brain regions, then imagine how a review on all the brain regions could reveal how inter-connectedly they work together to modulate emotional memory. It would be amazing to fully understand the impact and influences that emotions have on the whole brain. The important findings that I stated in this thesis highlight one avenue of thought to ponder as the psychology and neuroscience research community continue to questions and understand the human brain.

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