Emotional memory and hippocampal-amygdala dynamism in context of Post-Traumatic Stress Disorder (PTSD).

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Abstract

Proper communication between hippocampus and amygdala is essential in the formation of emotional memory. In Post-Traumatic Stress Disorder (PTSD) patients, the hippocampal-amygdala dynamism is compromised leading to various psychological and physical symptoms. Current methods of PTSD treatment carry a myopic vision by focus on alleviating specific symptoms alone limiting scope of treatment. The development of effective treatment methods for PTSD patients requires a holistic understanding of the role of hippocampus-amygdala complex by expanding on the current understanding of encoding, consolidation and retrieval of emotional memory.

Keywords: Emotional memory, Post-traumatic stress disorder, Hippocampal-amygdala complex, Encoding.

Introduction

Memories make up our everyday lives. Some memories are pleasant and we want to cherish their presence while other memories are traumatic and we struggle to forget them. Victims of social violence, survivors of wars and like and individuals with other life-threatening experiences undergo a revamping of their response to aversive stimuli. This is because of the scar that such traumatic experiences leave on individuals' cognitive representation. Memories of emotional significance vary in the degree of their intensity and how they affect different individuals. When it comes to individuals with Post-Traumatic Stress Disorder (PTSD), these memories have a huge impact on individuals' day to day lives. PTSD is a condition where patients suffer from a pathological replay of memory formed in response to painful, life-threatening or horrifying events. Currently, the two treatment methods used for PTSD are trauma-based psychotherapies and drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs). A combination of these treatment methods is effective for some individuals but the relative efficacy of these treatments for patients across the spectrum has not been validated. Numerous studies based on PTSD suggest a specific association between the extreme stress of trauma and alterations in memory functioning. Memories of negative emotional significance are at the constant replay in the patients with PTSD and understanding the neural and cognitive basis of these memories will pave the way for designing new drugs or therapeutic methods to treat PTSD related mental disorders. PTSD patients constantly suffer from anxiety and pain as a result of the stressors that evoke traumatic memories. What brain regions are responsible for the vulnerability in the brains of these patients that associate stressors to memories? What kind of relationship do brain structures have with each other? How are memories of emotional significance encoded and prioritized? In this paper, I take a fresh look at traumatic memories in examining the role of respective brain regions hippocampus in memory declaration and amygdala in adding emotional significance to the memories [1].

Literature Review

I also delveloped deeper to investigate how the modulation of memories of emotional significance by the amygdala hippocampal complex might be error-prone in patients with PTSD. In upcoming sections, I outline the neural mechanisms of memories of emotional significance and interaction between the hippocampus and the amygdala in modulating emotional memories. Subsequently, I investigate how the neural mechanisms and hippocampal-amygdala interactions are affected in various ways in PTSD patients. Finally, I conclude that the study of the interactions between the amygdala and hippocampus, in relation to memories of emotional significance, is integral in devising more effective treatment methods to help PTSD patients across the spectrum [2].

Working of different memory system

On the surface level, workings of memory can be divided into explicit and implicit memory systems. The implicit memory system, also called the non-declarative memory system, can be understood by the unconscious ability to demonstrate prowess in a certain skill or recognition related activity without having to consciously recollect the previous memory of being involved in these activities. Implicit memory includes skill learning, habit formation, emotional learning and the phenomenon of priming and classical conditioning. The explicit memory system, also called the declarative memory system, deals with the conscious recollection of past experiences and information. Explicit memory includes episodic memory-the conscious recollection of life events, semantic memory-factual or general world knowledge and spatial memory-recorded information and spatial orientation of the one's environment [3,4].

The distinction between explicit and implicit memory is particularly useful for research in PTSD because implicit and explicit memory processes are affected in different ways in PTSD patients. Implicit memory processes may automatically facilitate access to information about the traumatic event leading to fear conditioning and trauma re-experiencing phenomena in PTSD. Explicit memory deficits are common in PTSD patients leading to the patients being unable to remember certain facts or instances of traumatic events accurately. Though the distinction between implicit and explicit systems is important in understanding how PTSD affects these systems separately, the line between implicit memory and explicit memory quickly weakens as we delve deep into the mechanisms of formation and retrieval of memories that have emotional significance.

The mechanism of formation of emotionally significant memory relates to both implicit and explicit memory systems. Memories of emotional experiences have been understood to have adaptive functions. For example, fearful memories of predators if prioritized in the memory bank can help identify predators and help mediate quicker response to the sight of predators. These memories that have an emotional association attached to them are termed emotional memories. Emotional memories that are mediated by explicit memory systems are related to workings of the medial temporal lobe structures mainly the hippocampus. Emotional memory mediated by implicit memory systems is related to the amygdala. The implicit activation of the amygdala has been shown to modulate explicit memory storage. Explicit memory in PTSD is related to declarative memories of the trauma that contain explicit information about the sensory features of the situation, the emotional and physiological reactions experienced and the perceived meaning of the event [5].

The process of memory consolidation and retrieval is mediated by hippocampal formation as supported by empirical evidence collected from patients with medial temporal lobe damage. Further, hippocampal volume reduction and activity dysfunction are an integral part of the maintenance of PTSD. The amygdala has been repeatedly studied as a brain structure that modulates emotional response. Ongoing research on emotional memory has elucidated that the amygdala plays an important role in the emotional processing of memory by sending inputs to the entorhinal cortex which further projects to the hippocampal formation. The relationship between the hippocampus and the amygdala is a two way dynamic process because there is strong evidence that reinforces the constant cross-talk between the amygdala and the hippocampus during memory encoding or retrieval process. In PTSD patients, the amygdala and the hippocampus are affected differently, thus, affecting the communication between these systems to form and maintain emotional memory [6].

Emotional memory neural mechanisms and modulatory agents: Emotions play an integral role in how we remember different memories. Certain memories are enhanced more than others in the memory bank because of the associations that emotions play in the formation and recall process of these memories. Different mechanisms underlying the formation of the memory have been studied over many years to understand the emotional aspect of various memories and how different memory systems incorporate the mechanisms to keep the interaction between emotions and memories alive throughout the lifespan of these memories [7,8].

Various hypotheses regarding the concept of emotional tagging. Cellular basis of memory identifies the process of Long Term Potentiation (LTP) as the basic cellular block of memory. LTP is a cellular mechanism whereby neurons learn to increase the synaptic strength between two or more neurons over time with the repeated high frequency stimulation of the neurons in succession. One of the internal mechanisms by which the emotional aspect of an event gets incorporated into the memory is by using the molecular tags which modulate the state of LTP. The role of CaMK II as the molecular tag for LTP in apical dendrites of the CA1 region in mice. Their research suggests that LTP can exist in two different states: Short lasting LTP (E-LTP) and Long-lasting LTP (L-LTP) [9-11].

Emotional tagging is a concept that is related to emotional and affective factors facilitating the transition from E-LTP to L-LTP. Tetanic stimulation is a sequence of stimulations of an individual neuron caused by the successive stimulation of connecting neurons. Successive tetanic stimulations over time lead to a high-frequency burst of the presynaptic action potential which is termed tetanus. The transition from E-LTP to L-LTP happens when a weak tetanic stimulation is converted to strong tetanus. In an experiment conducted in mice, E-LTP induced by a weak tetanic stimulus to one afferent set was converted into L-LTP by applying strong tetanus to a separate set of afferents within a given time window as shown by *in vitro* experiments carried out in the CA1 hippocampal subfield [12-14].

Neurohormonal modulation during different memory stages is an important mechanism of modulation of memory formation and storage. Memory systems including emotional memory undergo four memory stages: Encoding, consolidation, storage and retrieval. These stages distinctly require neurohormonal and neuronal interaction between different circuits to modulate different stages. Hypothalamic-Pituitary Adrenal (HPA) axis acts as an important neurohormonal modulatory feedback mechanism to alter these different stages. Emotional situations initiate complex interactions between adrenergic and glucocorticoid systems that are coordinated by the HPA axis. Various studies on rodents have shown that memory consolidation for both appetitively and an aversively motivated learning task are blocked by adrenocortical suppression and are enhanced by infusions of glucocorticoid receptor agonists into the basolateral amygdala and the hippocampus. Beta-adrenergic receptor blockade in healthy adults during encoding produces similar deficits to the amygdala damage on a test of emotional memory. The inference derived to show that the amygdala is involved in encoding of emotional memory [15].

Emotional events usually acquire a higher degree of priority during the recall process of the memory associated with the event. These memories can be accessed or evoked by the use of emotions that are associated with the memory encoding

process. A reductionist approach to understand the mechanisms of emotional memory has inspired cognitive neuroscience to study lesioned patients. Urbach-Wiethe Syndrome is a rare condition characterized by Systemic deposition of hyaline material, prominent in the skin, oral mucosa and pharynx. In patients with UrbachWiethe syndrome, severe long-term recall and recognition of emotional words, pictures and stories occur. From studies done on various patients with Urbach-Wiethe syndrome, conclusions that relate to impairments in emotion-cognition interactions have been stated rather than problems with emotion evaluation. The evaluation suggests that even after the amygdala has been damaged to a certain extent some aspects of emotional memory are still preserved generating questions regarding amygdala's role in emotional memory retrieval. In order to probe this further, understanding the functioning of the emotional memory system to emotion and emotion-cognition dynamics is essential [16].

In order to delve deeper into the investigation of emotional memory, we consider the study that proposes two different routes to emotional memory. Deriving from the two dimensions of emotion, study outlines that there exist distinct neural processes for valence and arousal aspects of emotional memory. In general, emotional information can be characterized by two dimensions: Arousal and valence. Arousal dimension has to do with the exciting and calming response that the emotional information carries whereas the valence dimension relates to the positive and negative aspects of the emotional information. It has been suggested in the studies that examined the effect of the emotional content of long-term memory that the amygdala's role in emotional memory is related to arousal dimension. The hedonic hypothesis outlined by the states that when the amygdala processes information, a central hedonic state result which accompanies dual activation of the amygdala and the hippocampus. The results from study rest on the concluding remarks regarding simultaneous activation of the amygdala and the hippocampus during the memory encoding process reinforcing the idea of crosstalk between the amygdala and the hippocampus study outlines that "memory enhancement for arousing items is mediated by the amygdalar-hippocampal network which may reflect relatively automatic effects of emotion on memory and might be specifically engaged when emotional stimuli elicit an arousal effect" [17].

Amygdala-hippocampus interaction in the modulation of emotional memory: The medial temporal lobe structures, the amygdala and the hippocampus have independent functionality. The amygdala is associated with emotional regulation and specializes in the processing of fear and emotional correspondence between aversive stimulus. The memory system that relates to the amygdala is an implicit memory system that facilitates information storage related to emotions. The hippocampal complex, on the other hand, is responsible for explicit memory encoding and retrieval. Independent functioning of these two memory systems has been established from the evidence derived from focal lesion patients. It was discovered that when testing the fear conditioning paradigm in patients with the amygdala damage that even though the patients report that the particular percept for stimulus resulted in the fear, they do not show any physiological response to the precept of the stimulus. A similar study performed on patients with hippocampal lesioning showed opposite results stating that the patients showed a physiological response to the percept of stimulus, but they were unable to address whether the percept was responsible for their physiological response to the percept of the stimulus. The dissociation in the physiological response to the percept of stimulus and the memory of the association of the percept show that these two responses are handled by independent memory systems [18].

Despite the independence of the memory systems in the amygdala and the hippocampus, numerous studies have shown that there exist interactions between the amygdala and the hippocampus when emotion and memory are intertwined. Memories that have an emotional context usually tend to be more persistent and vivid than memories that lack emotional context. The amygdala-hippocampus interaction is responsible for the persistence and vividness of memories that have an emotional context. How do memories become more persistent and vivid with the presence of emotional context?

The first line of evidence suggests that the amygdala can modulate the encoding and storage of hippocampaldependent memories. During the process of memory encoding, the ability to perceive and attend to the stimulus is integral to how the representation of the stimulus is stored. Emotion can influence the perception and attendance to the stimulus by modulating the degree of attention put forth during the process. A Functional Magnetic Resonance Imaging (FMRI) study done on testing the attentional blink paradigm has shown that damage to amygdala impairs the normal facilitation of attention for emotional stimuli. The amygdala also plays a huge role in influencing memory during the consolidation period. After the memory has been successfully encoded, the memories are in an intermediate state where they are susceptible to disruption. During the period of consolidation, the amygdala modulates the memories through the action of stress hormones. Throughout the life cycle of the memory, the amygdala constantly modulates the memories by using different modulatory influences which include neurohormonal and molecular mechanisms.

The hippocampal complex can influence the amygdala response when emotional stimuli are encountered by forming episodic representations of the emotional significance and interpretation of events. Evidence drawn from testing the fear conditioning paradigm suggests that the recollection of emotional stimulus properties and strategies acquired through instruction requires the formation of hippocampal-dependent memories. The processes underlying episodic memory encoding and retrieval in time can influence the emotional reaction to a certain stimulus in the future. The prediction in part is possible because of the modulatory interaction of the hippocampal complex on the amygdala [19].

A reductionist approach to investigate the cooperativity of the amygdala-hippocampal complex studied patients with different

levels of left medial temporal pathology. Researchers studying the amygdala-hippocampal cooperativity discovered that the ipsilateral hippocampus and the amygdala are codependent during the encoding of emotional items. The codependency predicts a reciprocal modulation of the amygdala activity by the hippocampus for the successful encoding of emotional items. A model based on the same study also found a significant correlation between the left hippocampal volume and encoding activity. As part of a similar investigation, a similar correlation between the amygdala activity and subsequent memory for emotional materials on normal subjects has been established. An observation supporting the idea that the effects of the amygdala activation on encoding are expressed in the modulation of the hippocampal activity in regions involved in verbal encoding operations has been outlined. On the other side, a prediction based on the severity of the hippocampal pathology suggests that the magnitude of encoding-related neuronal activity for emotional items is dependent on the left and the right amygdala. A more-severe left the hippocampal volume loss has shown to predict less activity in the left amygdala and more in the right amygdala whereas the less-severe left hippocampal volume loss has shown to predict more activity in the left amygdala and less activity in the right amygdala. These findings have provided ample evidence regarding the crosstalk between the amygdala and the hippocampus. How does the interaction between the amygdala and hippocampus play a role in the context of emotional memory [20] ?

Every emotional memory is unique because there is a different level of correspondence between the hippocampus and the amygdala during the formation of that particular emotional memory. Examining neural plasticity in the hippocampus and the amygdala has been suggested as a method to gauge the functionality of overall learning and memory mechanisms which elicit required levels of response from both the amygdala and the hippocampus to form emotional memories. The changes in neural plasticity level in the amygdala is a piece of clinical evidence based on structural and functional brain imaging that suggests the amygdala function may be disordered in patients with affective illness. As a result of the amygdala's dysfunctionality, the hippocampus might not receive the same level of inputs to maintain the emotional memory, giving rise to various emotional memory related problems. Through the process of sending inputs to the hippocampus, the amygdala has a critical role in regulating neural plasticity and neurogenesis in the hippocampus. For example, the amygdala after discharges, even short of inducing a full-blown seizure, are capable of inducing neuronal sprouting in dentate granule cells and also induce apoptosis in distant structures of the dentate Gyrus in the Hilar region of the hippocampus. The proper functioning of the independent systems of the hippocampus and the amygdala and the communication between both the systems in various levels of correspondence (i.e. cellular to cognitive) is paramount in the context of the lifespan of any emotional memory.

PTSD in the context of emotional memory: In PTSD patients, intrusive memory and impoverished memory functioning are severely compromised. Other various memory related alterations are also common in PTSD. Analyzing these complex memory alterations outline an integral relationship between mind and brain. Various psychological theories presented emphasize that the psychological alterations could find other domains and quickly turn into social and cognitive deficits. The information processing ability is equally affected as the cognitive representations are conjured up from the memories and analyzing memory related deficits might help us understand cognitive deficits in PTSD patients. The memory-enhancing effects of emotional events are mediated by the activation of beta-adrenergic activity within the amygdala complex. In neuronal level within the amygdala complex, the memory enhancing effects of adrenaline are accentuated in PTSD patients and the action of noradrenergic system adding to the adrenaline effects during encoding makes the traumatic memories prioritized in the memory bank. During retrieval of the memory, the adrenaline release further strengthens the traumatic memory trace by creating a positive feedback loop. The creation of such a feedback loop which strengthens over time explains the deep-seated attribute memories of traumatic events after a traumatic event. Drugs pertaining to the current treatment for PTSD are limited to SSRI's that primarily act on the serotonergic system in the brain. Emphasizing the design of new drugs that regulate beta-adrenergic activity in the amygdala might help relieve various problems associated with recurring traumatic memories as the positive feedback loop can be broken by blocking the beta-adrenergic hyperactivity within the amygdala complex. By changing the hyperactive adrenergic action during encoding and retrieval, the emotional tag attached to the memory can be dampened, thus, decreasing the overall effect of the traumatic memory on the brain. The changes in emotional tag related to memory might also help change the cognitive representation associated with the memory. The required changes in cognitive representation might help lessen the impact of cognitive deficits operating in PTSD patients [21].

Discussion

The beta-adrenergic activity in the amygdala is not the only mechanism affected in PTSD related neuronal changes. Hippocampus related sensitivity to stress is equally responsible for memory-related effects. Stress as a result of traumatic memory has a direct impact on the HPA axis. The exposure to stress for long periods of time is related to a marked increase in cortisol from the adrenal gland. The cortisol, which is further regulated by Adreno Cortico Tropin releasing Hormone (ACTH) released by the pituitary gland, is important in regulating the HPA axis. The Corticotropin-Releasing Factor (CRF) released by the hypothalamus is in turn responsible for regulating the ACTH levels. These cascades of regulatory mechanisms are provoked by the initial increase in cortisol. As the cortisol level rises, the inhibitory feedback systems are activated, reducing the release of CRF and ACTH. The role of the hippocampus in this process is to keep cortisol within the physiological range by altering the primary feedback of the Glucocorticoid (GC) receptor sites present within the hippocampus. The presence of GC sites within the

hippocampus makes the hippocampus sensitive to stress which further relates to the changes in the HPA axis. The work confirms that the impairment of the hippocampus, a loss of neurons and dendritic connections in the hippocampal network, are caused by excessive GC release.

In neuronal level, loss of neurons and loss of dendritic connections in the hippocampus relates to alterations in LTP related mechanisms. High GC levels not only produce deficits in learning but also affect memory directly by preventing the strengthening of the connection between neurons. Additionally, memory deficits in PTSD patients is the result of hippocampal atrophy initiated by stress-induced high cortisol levels. GC mediated hippocampal toxicity and memory dysfunction are areas of major concern when it comes to treatment for PTSD patients. Using therapy-based techniques or mindfulness to lessen the severity of stress on PTSD patients is a great way to reduce stress-related damage to the hippocampus. In patients where therapy is less effective, using drugs that counteract the high level of cortisol might help prevent the deleterious cascade of the GC-mediated hippocampal damage that a high level of cortisol motivates.

Conclusion

The processes that underline the communication between the hippocampus and the amygdala are of prime important in context of emotional memory formation and maintenance. During emotional memory-related processing, the amygdala attaches a molecular tag as input to the memory so that the particular memory can be accessed later more easily by using the emotional tag to prioritize the memory. In the context of emotional memory formation, the interactions between the amygdala and the hippocampus are particularly important when the memory has an emotional response attached to it. The amygdala modulates encoding and the storage of the hippocampal dependent memories. On the other end, the hippocampal complex guides the amygdala response when emotional stimuli are encountered by forming episodic representations based on the emotional significance derived from the interpretation of the event. The correspondence between the hippocampus and the amygdala essentially happens through the neural plasticity that these brain regions evoke on each other. The regulation of proper communication between these two systems is integral in preserving emotional memories and their tags such that the memories are not pathological to the brain. Further, preserving physical elements of communication of the system and its functionality is important in ensuring that the learning process is not disrupted. In PTSD, there exist functional changes in the hippocampus and the amygdala and as a result of specific changes in these systems, the correspondence between the two systems is severely compromised leading to a pathological replay of emotional memories. Thus, the treatment regarding PTSD should take into account the independent functionality of the hippocampal and the amygdalar systems as well as the collaborative work of these systems on the maintenance of emotional memory to discover treatment mechanisms that can work across the spectrum for patients with PTSD.

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