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Chapter 10

Amygdala and Emotional Modulation of Multiple Memory Systems

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Abstract

Stress and anxiety can either enhance or impair memory, and the direction of the effect partially depends on the type of memory being affected. Behavioral or pharmacological stressors typically impair cognitive memory mediated by the hippocampus, but enhance stimulus-response habit memory mediated by the dorsolateral striatum. Evidence also indicates that the effect of emotion on different kinds of memory critically depends on a modulatory role of the basolateral amygdala (BLA). BLA modulation of multiple memory systems may be achieved through its glutamatergic projections to other brain regions, which may enhance stress hormone activity, modulate competition between memory systems, and alter synaptic plasticity. The neurobiology underlying the emotional modulation of multiple memory systems may be relevant to understand the impact of emotional arousal on the development and expression of human psychopathologies characterized by maladaptive habitual behaviors (e.g., drug addiction and relapse).

Keywords: memory, stress, emotional modulation, basolateral amygdala, hippocampus, dorsolateral striatum, habit, post-traumatic stress disorder.

1. Introduction

The amygdala of the mammalian brain has been historically associated with emotional behavior (e.g., Ref. [1]), and studies conducted over the past several decades have indicated that this structure also modulates the storage of long-term memories (for review, see Ref. [2]). In particular, the amygdala confers the influence of emotional arousal on learning and memory processes occurring in other brain regions, such as the hippocampus and dorsal striatum [3, 4].

Within the context of a "multiple systems" approach to memory organization, the hippocampus is a critical part of a neural system mediating what are broadly defined as "cognitive" memories involving explicit, declarative information, such as facts and past experiences [5]. Cognitive memory function of the hippocampus also includes acquisition of spatial cognitive maps, i.e., learned mental representations of space which may be used for allocentric navigation [6]. In contrast, the dorsal striatum mediates associations between stimuli and responses and thus encodes memories broadly defined as procedural, stimulus-response (S-R), or habitual (i.e., perseverative responding following devaluation of the reinforcer) [7]. For instance, the dorsolateral striatum (DLS) mediates habitual lever pressing behavior in instrumental learning situations [8], as well as acquisition and expression of a consistently reinforced egocentric turning response in the plus-maze [9].

The hippocampus and dorsal striatum differ not only in terms of their anatomical loci and mnemonic functions, but also these brain regions are differentially influenced by parametric factors, including amount of training, reinforcement schedules, and stress/anxiety [10]. As noted above, the emotional modulation of memory systems is mediated by the amygdala, which becomes active during states of emotional arousal and sends glutamatergic projections to other structures to influence the consolidation of memory [2]. The impact of emotional arousal on memory conferred by the amygdala appears to influence hippocampus- and dorsal striatum-dependent memory differently. For instance, high levels of stress or anxiety typically impair learning and memory functions of the hippocampus and enhance learning and memory functions of the dorsolateral striatum [3, 4].

The present chapter provides an updated review of the emotional modulation of multiple memory systems with a focus on the role of the basolateral amygdala. The review begins by describing evidence for the existence of multiple memory systems in the mammalian brain, and this is followed by a review of the influence of stress and anxiety on hippocampus and dorsal striatum-dependent memory processes. Although emotional arousal potentially influences memory formation in several brain regions, we focus on the hippocampus and dorsal striatum. Potential mechanisms through which the amygdala modulates multiple memory systems are also discussed, including the role of memory system interactions, stress hormones, and synaptic plasticity. The relevance of these findings to understanding and treating some human psychopathologies is also considered.

2. Multiple memory systems in the mammalian brain

The mammalian brain is composed of anatomically distinct memory systems [11, 12]. An understanding of the relative contributions of these distinct systems to memory is based upon studies dissociating their involvement in specific memory tasks. Carefully designed behavioral tasks can be used to parse the unique roles of multiple memory systems by keeping sensory, motor, and motivational factors constant, but changing the learning and memory requirements from one task to another. When manipulations of one brain region affect task "A," but not task "B," and lesions of another brain region affect task "B," but not task "A," we can determine that these two brain systems play distinct and somewhat independent roles in memory processing [12].

The first studies demonstrating a double dissociation between hippocampus- and dorsal striatum-dependent memory systems employed an eight-arm radial maze [13, 14]. Two distinct versions of the eight-arm radial maze were used: a cognitive spatial version and an S-R habit version. In the spatial version (also called the win-shift task), a rat was given the opportunity to explore the maze and retrieve food contained at the end of each arm. Multiple extra-maze cues surrounded the maze, allowing rats to acquire a cognitive map of the learning environment, which they could use to seek the spatial locations containing food and avoid the spatial locations from which food was already retrieved. Rats given lesions to the hippocampal system made more re-entries into the unbaited arms, indicating an impairment in spatially guided memory performance, whereas rats given lesions to the dorsal striatum were not impaired [13, 14].

In the S-R habit version of the radial maze (also called the win-stay version), a light cue at each arm signaled whether food was available there. An error was recorded if the animal entered an arm which was not currently signaled with a light cue. This task involves S-R habit memory to the extent that successful performance requires animals to associate the light cue (S) with approach behavior (R) [15]. Lesion of the dorsal striatum impaired memory performance in this S-R habit version of the radial maze, whereas hippocampal lesions actually enhanced performance [13]. A later study indicated that lesions confined to the dorsolateral striatum (DLS) were sufficient to impair memory in the S-R radial maze [16]. Taken together, these findings indicate that the hippocampus but not the DLS mediates spatial memory, whereas the DLS but not the hippocampus mediates S-R habit memory. Considering that the spatial and S-R versions of the radial maze depend on similar motivational, motoric, and sensory requirements, the differential role of the hippocampus and DLS may be attributed to the distinct mnemonic requirements in each task. The observation that hippocampal lesions *enhanced* memory performance in the S-R habit task may be attributed to a competitive interaction between memory systems, which will be described later.

A plus-maze apparatus has also been extensively employed to examine multiple memory systems in rats. The plus-maze consists of four arms arranged in a cross-shaped (+) orientation. Three slightly different procedures can be carried out to dissociate multiple memory systems using the plus-maze. Rats trained in a dual-solution task were released from a consistent start arm (e.g., North arm) with a palatable food reinforcer located in a consistent goal arm (e.g., West arm). Two distinct learning strategies could lead to a food reward: 1) rats could learn the spatial location of the reinforcer and spatially guide behavior to the reinforced location or 2) rats could acquire a consistent body-turn response at the intersection of the maze (e.g., turn right), regardless of the spatial location of the reinforcer. The strategy was assayed using a subsequent probe trial in which the animal was released from the opposite starting position (e.g., South arm). If rats went to the same spatial location (i.e., making the opposite turn at the choice point), they were identified as place learners. If rats continued to make the same turn at the maze intersection as they did during training, they were identified as response learners.

One of the interesting features of the dual-solution plus-maze task is that early in training animals usually display place learning during the probe trial, whereas after extended training, animals predominantly display response learning, potentially indicating the gradual formation of a motor habit [9, 17, 18]. In addition to the training parameters, the expression of

place and response learning may also be influenced following temporary inactivation of the hippocampus or DLS. Early in training, when control animals displayed place learning, temporary inactivation of the hippocampus before the probe trial eliminated preferential use of either place or response learning, whereas DLS inactivation had no effect [9]. Later in training, when control animals mostly displayed response learning, temporary inactivation of the DLS before the probe trial shifted animals back to the predominant use of place learning, whereas hippocampal inactivation had no effect [9].

The role of the hippocampus in place learning and DLS in response learning has also been demonstrated using single-solution versions of the plus-maze. In a place learning version of the plus-maze, animals are released from alternating start arms (e.g., North and South), whereas the food reinforcer remains in a consistent spatial location (e.g., the West arm). Thus, in order for animals to be successful in this task, they presumably need to acquire a spatial cognitive map of the learning environment using extra-maze cues so that they may accurately guide behavior from different starting positions to the same spatial location. In the response learning version of the plus-maze, the animal is reinforced to make a consistent body-turn response (e.g., right turn) at the maze intersection, regardless of the animal's starting position. For instance, if the animal is started from the North arm, the food reward may be located in the West arm; if the animal is started from the South arm, the food reward is located in the East arm. In this particular example, regardless of the animal's starting position, a right body-turn will consistently lead to the reinforcer. Extensive evidence using these tasks indicates that learning and memory in the place version of the plus-maze requires hippocampal function, whereas learning and memory in the response version requires DLS function [19–22].

The radial maze and plus-maze experiments, as well as other experiments using a Morris water maze [23–25], have been critical in demonstrating the differential mnemonic functions of the hippocampus and DLS. These studies have provided strong converging evidence that the hippocampus mediates spatial cognitive memory, whereas the DLS mediates S-R habit memory. Additional studies have been conducted primarily using the plus-maze tasks to demonstrate that these different kinds of memory are differentially influenced by parametric factors, such as exposure to stress and anxiety [4, 10, 26].

3. Emotional modulation of memory systems in rodents

The influence of emotion on memory has been well known since ancient times. The *Rhetorica ad Herennium*, an ancient handbook on rhetoric written sometime in the late 80s BCE, emphasized the importance of associating to-be-remembered information with emotionally arousing images to facilitate later recall. Also, in medieval times, in order to commemorate important events, such as weddings, a child was thrown into a river, helping the child and spectators form a lifelong memory of the event. In addition to the well-known enhancing effects of emotion, there is evidence that high levels of emotional arousal may also cause memory impairments. Whether emotion enhances or impairs memory depends partly on the type of memory being affected.

Extensive experimental evidence from rodents and humans indicates that emotional arousal modulates hippocampus- and DLS-dependent forms of memory differently. In an initial demonstration of the emotional modulation of multiple memory systems, investigators employed two versions of the Morris water maze, a spatial version dependent on hippocampal function and a cued version dependent on DLS function. In the spatial version, animals were released into a large circular pool of water over the course of training from multiple starting positions. In order to escape the water, the animals could mount an invisible escape platform located in a consistent spatial location. Thus, learning to quickly find the platform over the course of training may require acquisition of a cognitive map of the learning environment. In the cued version of the Morris water maze, animals were also released from different starting positions, however the platform remained visible throughout training, enabling animals to form an S-R association between the visibly cued platform (S) and swimming approach behavior (R). Evidence indicates that spatial learning in the Morris water maze depends on hippocampal function [27], whereas cued learning depends on dorsal striatal function [24, 25, 28–30].

Consistent with the hypothesis that emotion differentially influences multiple memory systems, a stress regimen involving chronic restraint and tail shock impairs memory in the hippocampus-dependent spatial version of the Morris water maze, but enhances memory in the DLS-dependent cued version [31]. Similarly, in a dual-solution version of the plus-maze, a chronic variable stress regimen that includes chronic restraint and forced swim among other potent stressors leads to the preferential use of response learning over place learning during the probe trial [32]. This chronic variable stress regimen is also associated with increased changes in dendritic morphology in the DLS [32]. In a circular hole-board task that can also be solved adequately using either a place strategy or S-R strategy, chronic restraint stress also increases the use of an S-R strategy [33].

The effects of chronic stress regimens on memory systems may also be observed with acute behavioral stressors. One hour of restraint stress is sufficient to impair acquisition in a place learning version of the plus-maze and enhance acquisition in a response learning version of the plus-maze [34]. Acute restraint stress is also associated with an increase in the use of a response learning strategy in the circular hole-board task [35]. Similar effects may be observed with an ecologically valid stressor. Pre-training exposure to predator odor enhances acquisition of response learning in a plus-maze task and leads to the preferential use of response learning in a dual-solution version of the plus-maze [36]. Aside from acute or chronic behavioral stressors, hypertension and trait anxiety have also been associated with the use of a response learning strategy in dual-solution versions of the plus-maze and Morris water maze [37–40].

The majority of studies using chronic or acute behavioral stressors have employed procedures with an innate ability to induce emotional arousal (e.g., restraint stress, exposure to predator odor, etc.). However, some studies have also indicated that a previously neutral stimulus that has acquired the ability to induce emotional arousal can also modulate memory. In these studies, animals are initially trained in a standard fear conditioning paradigm, in which a tone is repeatedly paired with a footshock, encouraging the acquisition of a tone-shock association. Later, when the tone is played alone, the animal demonstrates freezing behavior, indicating emotional arousal or, more specifically, fear to the tone. Post-training exposure to

a tone previously paired with shock enhances consolidation of response learning in the plus-maze and produces a response learning bias in a dual-solution version of the task [41, 42]. In addition, exposure to a fear-conditioned tone is also associated with greater response learning over place learning in a dual-solution version of the Morris water maze [43].

The influence of behavioral stressors on multiple memory systems is mimicked by anxiogenic drugs. Systemic administration of anxiogenic α-2 adrenoreceptor antagonists yohimbine or RS 79948-197 produces a response learning bias in the dual-solution plus-maze [44, 45]. In addition, systemic administration of RS 79948-197 enhances memory in a response learning task and impairs memory in a place learning task [46, 47]. Administration of the stress hormone corticosterone also enhances response learning in the plus-maze and increases the use of response learning in a circular hole-board task [35, 48]; see also Ref. [34].

Thus, robust emotional arousal induced by behavioral stressors or anxiogenic drug injections appears to favor DLS-dependent S-R habit memory, while impairing hippocampus-dependent cognitive memory. It should be noted, however, that there is also evidence that emotional arousal may sometimes facilitate hippocampus-dependent memory (for review, see Ref. [2]). It is possible that the influence of emotional arousal on hippocampus-dependent memory follows an inverted U-shaped curve, in which high and low levels of emotional arousal impair and moderate levels enhance cognitive memory [49–51].

4. Emotional modulation of memory systems in humans

The majority of studies examining the influence of emotional arousal on multiple memory systems have employed lower animals, such as rats and mice. However, there is also evidence that emotional arousal may influence human memory in a similar manner. In one experiment, participants were instructed to select one of four cards, which were positioned face-down in a 3-D model of a room, with the goal of picking the "win card." During training, the win card remained in the same spatial location relative to the distal room cues and was also consistently located next to a proximal cue (i.e., a potted plant). During a subsequent probe trial, the plant was moved to a different spatial location. If participants selected the card next to the plant, they were considered to be using an S-R strategy. If participants selected the card from the original spatial location, they were considered to be using a place strategy. Pre-training psychosocial stress (i.e., public speaking) increased the use of an S-R strategy [52]. Likewise, in a 2-D version of the win-card task, chronic stress was associated with greater use of a response learning strategy over a place learning strategy [33].

The finding that stress and anxiety enhance dorsal striatum-dependent, S-R habit memory has also been observed using an instrumental learning task. Subjects were first trained to perform two instrumental responses, each resulting in the delivery of a distinct food outcome. Later, one of the food outcomes was devalued by freely providing the participant with the food until satiety. Participants subjected to the socially evaluated cold pressor test, which promotes high levels of emotional arousal, continued to make the instrumental response for the devalued outcome, indicating habitual behavior, whereas control subjects decreased responding for the devalued outcome, indicating goal-directed behavior [53, 54].

Another task employed to examine the influence of emotional arousal on multiple memory systems is the probabilistic classification task, also known as the weather prediction task. This task involves presenting participants with a random series of cards covertly associated with distinct weather outcomes (rain or sunshine), and the participant is instructed to predict the weather based on the cards presented for a given trial. Over the course of training, participants are provided with trial-by-trial feedback indicating whether their prediction was correct, allowing participants to gradually learn what series of cards are most likely associated with rain or sunshine. Neuroimaging evidence suggests that either the hippocampus or dorsal striatum may be recruited for learning in this task [55–58], and the relative use of these systems may also be determined behaviorally using mathematical models [59–61]. Emotional arousal elicited using the socially evaluated cold pressor test biases subjects toward the use of a dorsal striatum-dependent strategy in the weather prediction task, whereas non-stressed control subjects show a preference for using a hippocampus-dependent strategy [61]. Moreover, functional magnetic residence imaging (fMRI) indicates that performance in this task is positively correlated with dorsal striatal activation in stressed subjects, whereas performance is positively correlated with hippocampal activation in non-stressed subjects [61].

Thus, converging evidence from humans and lower animals indicates that high levels of emotional arousal, in particular stress and anxiety, promote a shift from hippocampus-dependent cognitive strategies toward dorsal striatum-dependent habit strategies. The following sections consider some of the mechanisms that may be implicated, including a modulatory role of the amygdala, competition between memory systems, stress hormones, and plasticity.

5. Emotional modulation of memory systems: role of the amygdala

Early evidence indicated a clear role for the amygdala in learning and memory [1, 62, 63]; however, it took several decades of subsequent research before this brain region was considered one of the principal learning and memory structures of the brain (for review, see Ref. [2]). As mentioned above, the amygdala mediates emotional memories, such as stimulus-affect associations and emotionally charged CS-US associations underlying Pavlovian fear conditioning [64]. In addition to mediating emotional memories, the amygdala also has a prominent role in allowing emotional arousal to influence memory formation in other brain regions, such as the hippocampus and dorsal striatum. Presumably, during high levels of emotional arousal, the amygdala becomes active and modulates memory function of other brain regions either directly through glutamatergic projections to these brain regions or indirectly through activation of the hypothalamic-pituitary-adrenal (HPA) axis, which in turn leads to the release of adrenal stress hormones that directly stimulate memory structures of the brain [2].

Consistent with the view that the amygdala confers the effects of emotional arousal on memory, there is extensive evidence that the influence of stress and anxiety on hippocampus- and DLS-dependent memory depends on amygdala function. In one study, animals with amygdala lesions or sham lesions were subjected to chronic restraint/tail shock stress and were subsequently trained in a hippocampus-dependent version of the Morris water maze [31]. Stressed animals with sham lesions showed impaired hippocampus-dependent memory,

relative to non-stressed controls, whereas stressed animals with amygdala lesions were not impaired. Thus, the impairing effect of emotional arousal on hippocampal memory function depends on the integrity of the amygdala.

Whereas the study cited above employed permanent lesions of the amygdala, similar effects may be observed with temporary inactivation of the basolateral portion of the amygdala (BLA). In one study, animals were trained in either a hippocampus-dependent place learning or DLS-dependent response learning version of the water plus-maze and received post-training systemic infusions of the anxiogenic drug RS 79948-197 [46]. Post-training drug infusions target the consolidation phase of memory processing, i.e., when the short-term memory is consolidated into a long-term memory trace [65]. Post-training anxiogenic drug infusions impaired consolidation in the place learning task and enhanced consolidation in the response learning task, and both of these effects were blocked by temporary inactivation of the BLA with the sodium channel blocker bupivacaine [46]. Likewise, in the dual-solution plus-maze task, exposure to predator odor biased animals toward the use of response learning over place learning, whereas temporary inactivation of the BLA with bupivacaine eliminated the response learning bias produced by predator odor [36].

Additional evidence implicating a role for the amygdala in the emotional modulation of multiple memory systems comes from studies employing intra-BLA administration of anxiogenic drugs. Administration of the anxiogenic drugs RS 79948-197 or yohimbine directly into the BLA mimics the effects of systemic administrations. In a dual-solution plus-maze task, intra-BLA administration of RS 79948-197 or yohimbine leads to the preferential use of response learning over place learning [44, 45]. In addition, intra-BLA administration of RS 79948-197 enhances memory in the response learning version of the plus-maze and impairs memory in the place learning version of the task [66].

Finally, the critical role of the amygdala in the emotional modulation of multiple memory systems has also been demonstrated in humans. In one study, human participants were subjected to the socially evaluated cold pressor test, which stimulates emotional arousal, and subsequently performed the weather prediction task while undergoing fMRI [67]. Stressed subjects, relative to non-stressed controls, were more likely to use habit-based strategies over cognitive strategies, and this was accompanied by increased activation of the dorsal striatum and decreased activation of the hippocampus [67]. In addition, stressed subjects showed increased functional connectivity between the amygdala and dorsal striatum and decreased connectivity between the amygdala and hippocampus, relative to non-stressed control subjects [67]. Thus, the amygdala appears to be implicated in the emotional modulation of multiple memory systems in both lower animals and human subjects.

6. Mechanisms underlying amygdala modulation of multiple memory systems

The studies reviewed above clearly indicate that the amygdala, in particular the basolateral complex of the amygdala, is critically implicated in the emotional modulation of hippocampus

and DLS-dependent memory. However, the potential mechanisms through which the BLA modulates these systems have yet to be adequately addressed in this chapter. One possibility, as mentioned briefly above, is that the BLA modulates memory through direct glutamatergic projections to other brain regions. Indeed, the BLA strongly innervates the hippocampus [68], making it possible that a direct BLA-hippocampus pathway underlies the influence of emotional arousal on cognitive spatial memory. In contrast, the BLA does not innervate the dorsolateral region of the striatum implicated in habit memory. It is possible that the BLA could modulate DLS-dependent memory through its projections to the posteroventral region [69, 70], which may also be associated with habit memory function [29, 30]. In addition, the BLA projects to the ventromedial region of the striatum, which could possibly influence the DLS indirectly through an ascending spiral (see Ref. [71]). However, the potential roles of these amygdalostriatal projections in the emotional modulation of habit memory have yet to be explored.

Regarding the mechanisms that potentially underlie amygdala modulation of memory systems, evidence has indicated a role of stress hormones and competitive interactions between memory systems. There is also evidence that the amygdala may directly modulate synaptic plasticity in the hippocampus, which may be a neural mechanism underlying the emotional modulation of spatial memory.

6.1. Stress hormones

The influence of emotional arousal on memory formation has been attributed in part to stress hormones, including catecholamines (e.g., noradrenaline) and glucocorticoids (corticosterone in rodents; cortisol in humans). During an emotionally arousing event, stress hormones released via the HPA axis may influence memory by stimulating noradrenergic, glucocorticoid, or mineralocorticoid receptors in the brain [2, 72]. Following release from the periphery, corticosterone readily crosses the blood brain barrier and thus may modulate brain function directly. In contrast, adrenaline cannot cross the blood brain barrier and instead influences brain function by activating the vagus nerve, which enters the brain and innervates the nucleus of the solitary tract [73]. The nucleus of the solitary tract then projects to the locus coeruleus, which releases noradrenaline in multiple brain areas, including the amygdala [74].

Consistent with a potential role of stress hormones in the emotional modulation of memory, the effects of stress/anxiety on hippocampus- and DLS-dependent memory may be mimicked following systemic or intra-cerebral injections of drugs that increase stress hormone activity [44, 66, 75–78]. For instance, as mentioned above, systemic or intra-BLA injection of α_2-adrenoreceptor antagonist RS 79948-197, which increases noradrenaline release, leads to an enhancement of DLS-dependent habit memory and impairment of hippocampus-dependent spatial memory [44–47, 66]. In addition, systemic or intra-DLS glucocorticoid administration enhances habit memory [48, 77–82; but, see also Ref. 83], whereas systemic or intra-hippocampal glucocorticoids may either enhance or impair cognitive memory [75, 76, 84, 85].

The influence of emotional arousal on hippocampus- and DLS-dependent memory may be prevented via blockade of noradrenergic, glucocorticoid, or mineralocorticoid receptors [35, 67, 86–88]. For instance, the enhancement of DLS-dependent habit memory produced by

exposure to a fear conditioned stimulus may be blocked by systemic or intra-BLA administration of the β_2-adrenoreceptor antagonist propranolol [42].

Evidence suggests that glucocorticoid and noradrenergic mechanisms also interact to influence memory. The enhancing and impairing effects of intra-hippocampal glucocorticoids on cognitive memory depend on noradrenergic activity in the BLA [89, 90]. In addition, whereas systemic corticosterone administration enhances DLS-dependent habit memory in the water plus-maze, this enhancement is blocked by concurrent administration of propranolol [48].

It is possible that both glucocorticoid and noradrenergic mechanisms must be onboard in order for emotional arousal to influence memory. Whereas concurrent administration of hydrocortisone and α_2-adrenoreceptor antagonist yohimbine enhances DLS-dependent habit memory, administration of either drug alone has no effect [91]. This seems to contradict other evidence reviewed above suggesting that administration of either corticosterone or RS 79948-197 alone may enhance habit memory in the water plus-maze. However, it is possible that the aversive nature of the water maze may be sufficient to promote the endogenous release of glucocorticoids and noradrenaline in the brain, and since both stress hormones are onboard, subsequent administration of either corticosterone or RS 79948-197 alone may be capable of influencing memory. Indeed, previous evidence indicates that corticosterone administration may only be capable of modulating object recognition memory when the learning situation is sufficiently arousing and thus increases noradrenergic activity in the BLA [92].

6.2. Competition between memory systems

In addition to the role of stress hormones, there is also evidence that following BLA modulation of memory systems, the hippocampus and DLS potentially interact with each other in a competitive fashion to influence memory. Competition between two memory systems becomes evident when disrupting function of one memory system enhances function of the other system [57]. For instance, in some learning situations, lesions or temporary inactivation of the hippocampal system enhances memory in DLS-dependent habit memory tasks [13, 14, 93]. Likewise, disrupting dorsal striatal function facilitates memory in some hippocampus-dependent spatial memory tasks [94–96]. Moreover, consistent with a competitive interaction between memory systems, enhancing the function of one system through intra-cerebral injection of memory enhancing drugs sometimes impairs function of the other memory system. For instance, hippocampus-dependent spatial memory is impaired following intra-DLS administration of either glucose or a drug that increases CREB activity [28, 97].

Some investigators have suggested that the influence of emotional arousal on multiple memory systems may be partially explained by a competitive interaction between systems [10, 26]. As reviewed above, there is evidence that very high levels of emotional arousal impair hippocampus-dependent spatial memory. Consistent with a competitive interaction between memory systems, this stress-induced impairment of hippocampus-dependent memory may be similar to a hippocampal lesion, to the extent that it may indirectly enhance DLS-dependent habit memory. Indeed, the same anxiogenic drug doses that impair hippocampus-dependent place learning also enhance DLS-dependent response learning in the water plus-maze [34, 46, 66].

On the other hand, it is possible that stress or anxiety may indirectly impair hippocampus-dependent memory in part by increasing dorsal striatal function. As mentioned above, intra-DLS administration of corticosterone facilitates DLS-dependent habit memory. This suggests that stress hormones released following activation of the HPA axis may be able to directly enhance DLS-dependent habit memory through stimulation of dorsal striatal glucocorticoid receptors. Consistent with evidence that in some learning situations, augmenting dorsal striatal function indirectly impairs hippocampus-dependent spatial memory [28, 97], it is possible that an increase in dorsal striatal memory function is partially responsible for the impairment in hippocampus-dependent memory observed following stress or anxiety. This hypothesis has yet to be examined. Likewise, the precise neural mechanisms that mediate competition between memory systems have not been elucidated.

6.3. Synaptic plasticity

There is evidence to suggest that the emotional modulation of memory may be partially attributed to BLA efferents altering synaptic plasticity in multiple memory systems. Synaptic plasticity refers to experience-dependent changes in brain function and is often considered as a candidate neural substrate of learning and memory [98–101]. BLA stimulation may either enhance or impair long-term potentiation (LTP) in the hippocampus [102], a form of plasticity associated with spatial memory formation (for review, see Ref. [100]). Chronic restraint and tail shock have also been associated with impaired LTP in the hippocampus, and this impairment was blocked by amygdala lesions [31]. In the same study, the stress-induced impairment of hippocampal LTP mediated by the amygdala was also associated with impaired spatial memory and enhanced DLS-dependent memory in the water maze [31].

In addition to modulating hippocampal plasticity, BLA stimulation also facilitates induction of LTP in the ventral striatum [103]. Whether BLA facilitation of ventral striatal plasticity indirectly influences memory function of the dorsal striatum has not been examined.

7. Relevance to psychopathology

Amygdala modulation of multiple memory systems may be relevant to understanding the role of learning and memory processes in some human psychopathologies. Dorsal striatum-dependent memory processes have been linked to the habit-like behavioral symptoms in numerous psychiatric disorders, such as Tourette syndrome, post-traumatic stress disorder (PTSD), autism spectrum disorders, obsessive-compulsive disorder, drug addiction and relapse, and others [104–109]. Interestingly, stress and anxiety may have an important role in each of these disorders by promoting development, expression, or exacerbation of habit-like symptoms. For instance, one of the characteristic symptoms of PTSD involves avoidance behaviors, which are automatically evoked by trauma-related cues (e.g., jumping away from a loud noise). Some investigators have suggested that such symptoms may reflect heightened DLS-dependent habit memory due to the high levels of emotional arousal during and after the traumatic event

[3, 110, 111]. Indeed, neuroimaging evidence indicates differences in amygdala and dorsal striatal structure and function, as well as malformation of the hippocampus and impaired cognitive memory, in individuals with PTSD (for review, see Ref. [110]). Drug abuse may also be viewed as a manifestation of overactive habit memory, which may be exacerbated by stress [109]. In light of evidence in lower animals discussed above, it is likely that the stress-induced enhancement of habit-like symptoms in PTSD, drug addiction, and other disorders may be partially mediated by the amygdala and its connections to multiple memory systems.

8. Conclusion

Emotional arousal induced by stress and anxiety influences distinct memory systems in different ways. Behavioral and pharmacological stressors enhance S-R habit memory mediated by the DLS and impair cognitive spatial memory mediated by the hippocampus in both lower animals and humans. The BLA is the chief neural substrate implicated in the emotional modulation of hippocampus- and DLS-dependent memory. The BLA potentially influences spatial memory via its glutamatergic projections to the hippocampus and also alters synaptic plasticity in this brain region. Stress hormones (i.e., adrenaline and corticosterone/cortisol) are also involved in the emotional modulation of memory via activation of noradrenergic, glucocorticoid, and mineralocorticoid receptors across the BLA, hippocampus, and DLS. The BLA may also influence memory via modulating the competitive interaction between hippocampus- and DLS-dependent memory systems. These experimental findings may provide insight into the neural mechanisms underlying some clinical psychiatric disorders in which high levels of stress or anxiety are associated with impaired cognitive memory and enhanced habit-like symptoms.

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