Chapter 13

The Key Amygdala-Hippocampal Dialogue for *Adaptive* Fear Memory

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Additional information is available at the end of the chapter

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Abstract

For centuries, philosophical and clinical studies have emphasized a fundamental dichotomy between emotion and cognition, for instance between implicit/emotional memory and explicit/representative memory. However, in the last few decades, cognitive neuroscience has highlighted data indicating that emotion and cognition are in fact in close interaction and that reciprocal amygdalar-hippocampal influences underlie their mutual regulation. While supporting this view, the present chapter discusses experimental data indicating that the hippocampal and amygdalar systems not only regulate each other and their functional outcomes but also qualify specific emotional memory representations through specific activations and interactions. Specifically, we review consistent data unveiling a direct contribution of both the amygdala and septo-hippocampal system to the identification of the predictor of a threat in different situations of fear conditioning. Our suggestion is that these two brain systems and their interplay determine the selection of relevant emotional stimuli, thereby contributing to the adaptive value of emotional memory. Hence, beyond the mutual *quantitative* regulation of these two brain systems described so far, we propose that different configurations of the hippocampal-amygdalar network qualitatively impact the formation of memory representations, thereby producing either adaptive or maladaptive (e.g., PTSD-like) fear memories.

Keywords: memory representation, cognition, emotion, amygdala, hippocampus

1. From dissociation to interaction of emotion and cognition

From the antiquity until the last 50 years, it was commonly held that emotion, and more generally, all somatic (body-related)/physiological processes disrupted cognition, seen as "pure representation" and more recently as "information processing" whose investigation was supposed to avoid all "interfering" body-related processes [1, 2]. This view was particularly

emphasized by the cognitive revolution, which was inspired by the computer metaphor and thus considered that analyses of cognition had to be expurgated of all emotional/physiological, potentially disruptive, processes. As Damasio wrote 20 years ago, we all grew up with the wide common view "that emotions and reason did not mix any more than oil and water (…) that the mechanisms of reason existed in a separate province of the mind, where emotion should not be allowed to intrude," and when thinking about the brain behind that mind, we "envisioned separate neural systems for reason and emotion" [3].

In the field of memory research, the essential dissociation between sensory/emotional memory and representation-based memory can for instance be found in Aristote (De memoria et reminiscentia, see in Ref. [4]) in the form of "simple memory" that would be directly related to sensory perception and shared by all species, *vs*. "voluntary memory retrieval" that would be unique to humans. In the XIXth century, Maine de Biran was the first philosopher who explicitly referred to different forms of memory as a function of the information processing involved. An automatic "mechanical memory" involved in the acquisition of habits and a "sensory memory" would both operate at an unconscious level and differ from a "representative memory" allowing the "conscious recollection of ideas and events" [5]. Finally, it is Henri Bergson who offered the most detailed discussion regarding this dissociation between a behavioral/procedural/implicit memory *vs*. a representative/explicit memory in his monography entitled "Matter and memory" [6]. According to Bergson, "The past survives under two distinct forms: first, in motor mechanisms; second, in independent recollections." Regarding the first, "Habit rather than memory, it acts our past experience but does not call up its image." "The other is the true memory, (…) leaving to each fact its place and consequently marking its date, truly moving in the past and not, like the first, in an ever renewed present." Strikingly, this description directly echos a distinction between nondeclarative and declarative memory systems referring to knowing how and knowing what, respectively, and proposed almost a century later by Cohen and Squire [7].

In support of this dissociation are the observations of patients with specific brain lesions who display a deficit for one type of memory leaving intact the other one. For instance, a clear double dissociation was found between fear conditioning and declarative memories, which were shown to be respectively dependent on the amygdala and the hippocampus [8]. Patients with bilateral lesion to the amygdala, an almond-shape brain structure adjacent to the hippocampus in the medial temporal lobe, could not acquire a conditioned fear response (measured as a change in skin conductance) to a conditional stimulus (CS+) previously paired with an aversive event (an unconditional stimulus, US), whereas they could acquire the explicit knowledge about the contingency between the CS+ and the aversive US. Thus, although these patients knew and could declare what they previously learned, they could not display any physiological expression of conditioned fear. In contrast, patients with selective bilateral lesion of the hippocampus showed an opposite pattern of results, that is, a normal conditioned fear response to the CS+ but no explicit knowledge of the past CS+/US association. This study first supports previous data obtained in nonhuman animals indicating a critical role for the amygdala in emotional learning [9–13]; second, it indicates that the hippocampus may underlie a factual representation of emotionally laden memory; and third, it points out the existence of two different neural substrates underlying representative and emotional/sensory memories that may not overlap.

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This fundamental dichotomy between emotion and cognition, and more specifically between behavioral/emotional memory and explicit/representative memory, has been recurrent for several centuries both in philosophical and neuropsychological studies more recently. However, the last few decades have highlighted clinical and experimental data indicating that emotion and cognition, as well as their underlying neural networks, are in close interaction. Overall, these findings even suggest that the understanding of natural cognition requires the consideration of emotion.

First, on the basis of several consistent observations of brain-lesioned patients who combined normal intellect but profound deficit in decision making together with compromised ability to express emotion and to experience feelings, Damasio [3] developed an elegant theory supporting the idea that "reason may not be as pure as most of us think it is or wish it were, that emotions and feelings may not be intruders in the bastion of reason at all (…)," but on the contrary "indispensable for rationality." The somatic marker hypothesis he developed [3, 14] is an alternative to the pure reasoning, which cannot explain by itself the normal decision making that generally takes a few minutes or seconds. In brief, this hypothesis suggests that when confronted with a situation that requires an effective choice, biological markers, which relate to emotion-related physiological body-states or representation of them, automatically qualify or connote, positively or negatively, some particular options or images (as a function of previous experiences of such a situation). This emotional connotation leads thereby individuals to immediately reject some negative outcome-related options and thus to choose a particular action among the remaining more positive alternatives. In this view, emotions, and more generally body-related physiological mechanisms, directly contribute to normal cognition, which guides adaptive behaviors.

Second, in the specific field of memory research, a growing body of evidence consistently shows that emotion contributes to the enhancement of episodic/representative/declarative memory. Thus, patients with amygdala damage do not show the normal enhancement of episodic memory for emotionally laden events when compared to memory for neutral events [15–17]. It is classically assumed that such memory enhancement may be due to amygdala's influence on the encoding and/or consolidation of hippocampal-dependent memories [13, 18–22]. In accordance with the last assumption, manipulation of the amygdala after encoding alters memory enhancement classically observed with physiological arousal [23].

Although most of studies examining hippocampal-amygdalar interactions focused on the amygdalar influence on episodic memory, several observations indicate that hippocampal-dependent representative memory can also reciprocally influence amygdala-dependent emotional memory. For instance, in the paradigm called "instructed fear," the actual CS+/aversive US conditioned association is replaced by an explicit oral communication about the CS-US contingency. This learning thus requires the hippocampus for acquisition of an episodic representation of the emotional significance of the fearful stimulus. Interestingly, it has been shown that such paradigm results in robust physiological fear responses to the CS+ that are correlated to the activation of the left amygdala [24] and specifically dependent on this brain structure [25]. These results indicate that a hippocampus-dependent instructed representation of the emotional significance of a stimulus can lead to the amygdala-dependent expression of

conditioned fear in situations in which fear is anticipated but the aversive event never actually experienced [26]. Another example of this hippocampal influence comes from studies devoted to emotion regulation. These studies emphasize the impact of cognition on emotion by showing that reasoning and conscious strategies of reappraisal of emotional scenes can diminish both experience of fear and related amygdalar activation [27, 28].

Altogether, these cognitive neuroscience studies first indicate that contrary to what has been claimed for centuries, emotion can serve cognition, as exemplified by its critical contribution to decision making or to the enhancement and persistence of episodic memory. Second, they also reveal that, reciprocally, cognitive processes as reasoning, conscious appraisal, or explicit representation of events can modulate emotional responses, either promoting or reducing fear. Third, they emphasize the idea that reciprocal amygdalar-hippocampal influences might underlie such mutual regulation of emotion and cognition. While supporting this view, the present chapter discusses experimental data, obtained in rodents, indicating that the hippocampal and amygdalar systems not only regulate each other and their functional outcomes but also qualify specific emotional memory representations through specific activations and interactions. Hence, beyond the mutual quantitative regulation of these two brain systems described so far, we propose that different activations of the hippocampus and amygdala leading to specific neural configurations qualitatively impact the formation of emotional memory, thereby producing either adaptive or maladaptive fear memories.

2. Adaptive versus maladaptive fear memories

Classical fear conditioning is one of the most used paradigms to study emotional memory. Depending on the CS-US contingency, the predictive CS can be either the discrete (i.e., phasic) salient CS or the surrounding background context (i.e., tonic contextual cues). If the discrete CS is systematically *paired* with the aversive US, it becomes the right predictor of the US and overshadows tonic contextual cues which are thus consigned in the background. In contrast, if the discrete/salient CS is presented but explicitly unpaired with the US (pseudo-random distribution of the discrete CS and US), then, although salient, it is not predictive of the footshock. Consequently, contextual cues that are continuously present during the aversive experience become the primary stimuli that enter into association with the footshock and thus constitute the right predictor of the US [12, 29–32].

The two fear conditioning procedures described above allows the assessment of adaptive *vs*. maladaptive conditioned fear responses. Typically, animals submitted to the CS-US pairing procedure (predicting-discrete CS situation) will normally express more conditioned freezing when re-exposed to the discrete CS (e.g., tone) than animals submitted to the CS-US unpairing procedure (predicting-context situation). In contrast, when the same animals are re-exposed to the conditioning context, those previously submitted to the predicting-context situation express more conditioned freezing than animals submitted to the predicting-discrete CS situation. These results indicate that with the pairing procedure, animals normally form a preferential discrete CS-US association, identifying the tone CS as the right predictor of the threat

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to the expense of the background context. In contrast, under the unpairing procedure, the context is identified as the right predictor, and this is attested by the expression of an adaptive high fear response to contextual cues but not to the discrete CS.

Compared to these adaptive fear responses, a significant fear response to the discrete salient CS instead of the context in a predicting-context situation or an increased fear response to the conditioning context to the expense of the discrete CS in a predicting-discrete CS situation is the behavioral expression of maladaptive fear memories. In both cases, animals take the wrong predictor of the threat.

3. The amygdala directly contributes to the formation of *adaptive* fear memory

In the traditional model describing the amygdala function in emotional learning [12], the lateral (LA) amygdaloid nucleus is required for the acquisition of discrete CS-US associations, while the basolateral (BLA) nucleus, which receives projections from the hippocampus [33], is thought to mediate context–US association. Using reversible inactivation of either LA or BLA, one of our studies first confirmed the critical role of the LA in the formation of discrete CS-US association and also revealed that the BLA is specifically required for conditioning to contextual cues but not to a discrete tone CS [34]. These data, together with consistent electrophysiological findings showing that thalamic but not polymodal cortical stimulation induces LTP in LA, whereas polymodal cortical but not thalamic stimulation induces LTP in BLA strongly suggest that LA activation is a sensory interface underlying simple, unimodal CS/US association, whereas the BLA may serve as an amygdaloid sensory interface for more complex information, thus underlying associations between the US and configural/contextual cues. As this complexity dimension is observed both for input and output pathways of the amygdala, it would constitute a common organizing factor in the functional anatomy of this brain structure [35]. Second, our study also revealed that the LA enhances or reduces BLA-mediated conditioning to the context depending on whether the context (CS-US unpairing) or the discrete CS (CS-US pairing) best predicts the footshock US. Thus, refining the classical model of amygdala function in fear learning, these findings indicate that depending on the CS-US contingency, LA-BLA interaction (through a competing or synergistic mode) promotes the selection of the best predictor of the aversive US, leading thereby to adaptive fear responses [34].

Now, to what extent hippocampal-dependent representative memory can be dissociated from amygdala-based emotional memory? Several studies from our laboratory obtained in mice provide evidence for a dissociation between the behavioral expression (freezing behavior) of fear conditioning and hippocampal neurophysiological coding (changes in hippocampal–septal synaptic transmission) involved in this emotional learning [29, 31]. In one of these studies, we showed that while lesions of the amygdala dramatically reduced the behavioral expression of fear conditioning, they did not prevent the hippocampal neurophysiological changes associated with different types of fear conditioning previously experienced but alter their direction. Thus, despite the absence of conditioned freezing, different changes in hippocam-

pal–septal excitability were specifically associated with a predicting-context and predicting-discrete CS learning situation [29]. Our suggestion is that these neurophysiological changes contribute to a form of knowledge about the conditioning situation encountered by subject the day before that would be dissociated from the behavioral expression of this aversive experience. Nevertheless, while sparing specific hippocampal neurophysiological changes as a function of the type of learning, amygdala lesions also clearly interfered with these synaptic changes, as they produced opposite changes with respect to nonlesioned controls. Strikingly, this observation strongly suggests that the amygdala-dependent and hippocampal-dependent forms of knowledge involved are not independent but interactive. Specifically, the content of hippocampal-dependent representations about relations among various sensory exteroceptive stimuli [36, 37] might be altered if fear conditioning is prevented by amygdala lesions.

In another series of studies, it was shown that the amygdala can indeed modulate synaptic plasticity in the hippocampus [38, 39]. Priming the amygdala just prior to an attempt to induce long-term potentiation (LTP) in the hippocampus (e.g., by stimulating the BLA 1 hour before high-frequency stimulation to the perforant path) modulates the level of plasticity in a region-specific manner [40–42], much like the effects of exposure to stress [38, 43]. It was later found that this modulation was specifically mediated by the basal amygdala [44]. Furthermore, stress and amygdala modulation of hippocampal plasticity were shown to be dependent on the exact way the amygdala was activated [45, 46], indicating that such modulation involves a dynamic interaction between these two structures, as predicted before [47].

Hence, from an initial emphasis on the dissociation between representative memory and emotional/behavioral memory, several findings come to indicate that the underlying neural systems of these two types of memory are interactive. It turns out that the hippocampal system is modulated by the amygdala, and that such modulation is even dependent on the type of learning situation [29]. This last observation led us to propose that the amygdalar influence of the hippocampal system might contribute to the selection of relevant emotional information and thus to the formation of adaptive fear memory.

4. The septo-hippocampal system is critically required for adaptive fear memory

Beyond the classical "restricted" role of the hippocampus in fear memory: a direct contribution to the selection of predictor of threat.

Lesion and electrophysiological studies indicate that the hippocampus is involved in relational memory. This theory postulates that the hippocampus is engaged in the encoding of events, episodes as sequences of events, and importantly, in linking these episodes by common features into relational representations in declarative memory. These hippocampus-dependent relational representations are required for the subject to compare different events and contribute to memory flexibility [48–50].

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On these bases, studies dedicated to identify the role of the hippocampus in fear memory, and more specifically in fear conditioning, overall indicate a requirement of this brain structure in contextual fear conditioning [51, 52]. Indeed, lesion of the hippocampus was shown to disrupt conditioned fear responses to the context in which fear conditioning occurs. The current neurobiological model of fear conditioning postulates that the hippocampus is required for forming an integrated representation of contextual cues. Then, this representation is subsequently associated with the US within the amygdala. Experiments from our laboratory contributed to confirm the current view of the role of the hippocampus in contextual conditioning. Nevertheless, they also unveiled a more extended role for the hippocampus in fear conditioning. Indeed, our data repeatedly and consistently showed that the hippocampus is differentially engaged in fear conditioning depending on the predictive value of CSs and contributes to the selection of the right predictor of threat [29, 30, 34, 53–55]. As written above, subjects adaptively select among environmental stimuli those that best predict an aversive event, either a discrete CS when it is paired with, and thus predictive of the aversive US or the context when a CS-US unpairing procedure is used.

Comparing these two conditioning procedures (CS-US pairing *vs*. unpairing), one of our studies revealed that a long-lasting strengthening of CA1 synaptic efficacy is specifically observed when the context, but not the discrete CS, is the right predictor of the US [56]. At the molecular level, a biphasic pattern of ERK1/2 CREB activation in the CA1 is specifically associated with a predicting-context situation, whereas only early monophasic activation is observed in a predicting-discrete CS situation [56]. Moreover, blockade of ERK1/2 activation with intra-hippocampal infusion of MEK inhibitor severely disrupted conditioned fear to the context, when the context, but not the discrete CS, was the right predictor of the US [56]. Altogether, these findings show that the hippocampus is differentially engaged in fear conditioning depending on the relative predictive value of the discrete CS *vs.* context for the occurrence of an aversive event. Specifically, they also indicate that hippocampal activation is critically required for contextual conditioning when the context, but not the discrete CS, is the right predictor of a threat.

In another set of experiments, we found that changes in the hippocampal-septal glutamatergic neurotransmission directly contribute to the identification of either the discrete CS or the context as predictor of the footshock US. First, a decrease in the hippocampal-lateral septal (HPC-LS) synaptic transmission was found to be associated with a predicting-context situation, whereas no change or even an increase in this neurotransmission was observed in predicting-discrete CS situations [29, 31, 57]. On the basis of these data, we have assessed the behavioral consequences of pharmacological manipulation of this glutamatergic neurotransmission. In accordance with previous electrophysiological data, we showed that pretraining infusion of glutamic acid into the lateral septum, which mimics an increase in the HPC-LS neurotransmission, promotes the selection of a discrete tone CS to the detriment of the context as predictor of a footshock US. In contrast, infusion of glutamatergic antagonist (Kynurenate), which inhibits this neurotransmission, promotes the selection of the context as major predictor of the US, while blocking the identification of the discrete tone CS as predictor [55]. In full accordance with these data, we have previously shown that pretraining infusion of arginine vasopressine (AVP) or its antagonist into the lateral septum, which is known to increase and

decrease the HPC-LS glutamatergic neurotransmission, respectively, could also promote the selection of the discrete tone CS or the context, respectively, as predictor of the US [30].

Altogether, these findings indicate that the role of the hippocampal system is not restricted to the processing of contextual information in fear conditioning. Beyond this classic role, consistent data unveil a direct contribution of the hippocampal-septal system to the acquisition of adaptive fear responses as a function of the learning situation. Our suggestion is that this system plays a key role in the selection of relevant stimuli, which are the right predictors of threat (i.e., discrete CS *vs*. contextual cues), thereby contributing to the adaptive value of emotional memory.

How can changes in the HPC-LS glutamatergic neurotransmission favor the selection of either a discrete tone CS or contextual cues as predictor of a threat? Previous experiments have emphasized the functional importance of changes in HPC-LS excitability for feedback regulation of hippocampal activity [58]. Based on these findings, we postulate that glutamatergic receptors localized into the LS would exert, *via* an increase in GABAergic cells excitability, an inhibitory effect on cholinergic cells in the medial septum [59, 60], which projects to the hippocampus. This means that in a predicting-discrete CS situation (CS-US pairing), the observed increase in HPC-LS glutamatergic neurotransmission would result in a GABA-mediated decrease in the activity of cholinergic neurons in the medial septum. This negative feedback would thus down regulate the hippocampal cholinergic activity, reducing thereby the hippocampal-dependent processing of contextual cues to the benefit of the discrete CS. By an opposite mechanism, in a predicting-context situation (CS-US unpairing), the observed decrease in the HPC-LS glutamatergic neurotransmission would result in a stronger hippocampal cholinergic activity, thereby enhancing the hippocampal-dependent processing of contextual cues, which would finally be selected as predictor of the footshock US to the detriment of the discrete CS [30].

The hippocampal processing is thought to be powerfully modulated by cholinergic projections originating in the medial septum/vertical limb nucleus of the diagonal band of Broca (MS/VDB). The hippocampal cholinergic neurotransmission has been previously involved in various CSs processing [61–66] and is thought to play a critical role in the coordination between different memory systems leading to the selection of appropriate behavioral strategies [67–69]. Specifically, increasing cholinergic activity in the hippocampus increases the selection of a place strategy to the detriment of cue-based strategy [70, 71]. We thus reasoned that changes in this cholinergic neurotransmission might also contribute to the adaptive selection of amygdala-mediated CS-US or context-US associations as a function of the type of procedure used. First, we showed that the magnitude of the hippocampal cholinergic release is dependent on the conditioning procedure used. In a predicting-context situation, that is, when the context is the right predictor of the US, Acetylcholine (Ach) release is stronger than in a predicting-discrete tone CS situation. Second, increasing the hippocampal cholinergic transmission with pretraining intra-hippocampal infusion of physostigmine (acetylcholinesterase inhibitor) results in the selection of the context as best predictor of US occurrence at the expense of the discrete tone CS. Conversely, decreasing the hippocampal cholinergic transmission with intra-hippocampal infusion of muscarinic antagonist scopolamine results in the selection of the tone CS instead of the context as main predictor

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of the US, thus mimicking tone fear conditioning to the detriment of contextual conditioning. These results demonstrate that level of hippocampal cholinergic transmission determines the selection among the context and the discrete CS that one that best predicts the aversive US [53]. Interestingly, the pharmacologically induced increase (physostigmine) and decrease (scopolamine) in hippocampal cholinergic neurotransmission is respectively associated, at the molecular level, with increase and decrease in ERK1/2 activation in both CA1 and Dentate Gyrus. Although previous studies have suggested that decreasing hippocampal cholinergic neurotransmission may prevent animals from forming an integrated representation of the context Gale [62], our findings reveal a more extended role for this neurotransmission in fear conditioning. It turns out that hippocampal cholinergic neurotransmission regulates the hippocampal recruitment in fear conditioning as a function of the procedure used (CS-US pairing *vs*. unpairing), thereby contributing to the selection of relevant emotional information (predicting- discrete CS or context) and thus to the expression of adaptive fear responses [53].

Overall, our findings have led us to propose an additional function of the septo-hippocampal system in fear conditioning. Beyond to the classical role of this system [49], in the processing of CSs as configural representation, we assume that the hippocampal engagement would result in a relational representation of the learning situation including the relative predictive value of all CSs (discrete CS and tonic context). When the context is the main predictor of the occurrence of an aversive event, the recruitment of the septo-hippocampal system would be stronger when a discrete cue best predicts the occurrence of the aversive US. Importantly, this differential engagement of the hippocampal system may causally contribute to the attribution process of different predictive values to the various emotionally laden CSs (i.e., phasic/discrete CS *vs*. tonic context).

5. A hippocampal-amygdalar dialogue *qualifies* emotional memory representation

The current neurobiological model of fear conditioning postulates that the only way the hippocampus can influence the amygdalar function is by conveying the representation of the context where conditioning has occurred to the amygdala. Then, this hippocampus-dependent representation of the context is supposed to be associated with the US in the amygdala. According to this model, the hippocampus has almost no critical role in conditioning to a discrete tone CS, while the amygdala is critically required for forming the discrete CS-US association.

According to our proposition, the hippocampus is engaged in the processing of a relational representation of CSs and directly contributes to the formation of adaptive fear memories. It would thus be involved in both auditory and contextual fear conditioning. Its differential engagement as a function of the conditioning procedure would causally contribute to the selection of one or another CS as predictor of the threat. As it was previously shown that the amygdala also directly contributes to adaptive fear memory, our findings suggest a more complex

relationship between the hippocampus and the amygdala in fear conditioning. In order to specify the hippocampal-amygdalar relationship, we reasoned that because changes in the hippocampal cholinergic neurotransmission could determine the selection of either the discrete CS or the context as predictor of an aversive US, these changes should also qualitatively constrain the amygdalar activation. As described above, decreasing the hippocampal cholinergic transmission by intra-hippocampal infusions of scopolamine prior to fear conditioning promotes the selection of the discrete tone CS as predictor of the US at the expense of the context. As expected, our study further showed that this hippocampal manipulation not only *mimics* tone fear conditioning but also produces a pattern of phosphorylated-ERK (p-ERK1/2) expression within the lateral (LA) and basolateral (BLA) amygdala similar to the one observed in control mice for which the discrete tone CS is objectively the right predictor. Conversely, increasing the hippocampal cholinergic transmission with intra-hippocampal infusion of physostigmine results in the selection of the context as predictor of US. In that case, and in a very consistent manner, physostigmine infusion produces a pattern of p-ERK1/2 expression in the LA/BLA similar to that one observed in mice for which the context objectively best predicts the US [53]. These findings reveal that the hippocampal cholinergic neurotransmission constrains the amygdala function: depending on its level, it produces two different patterns of amygdalar activation, which specifically underlie either context or discrete CS-US association, thereby leading to predominant conditioned fear responses either to the context or to the discrete CS. Hence, depending on the objective predictive value of the CSs for the occurrence of an aversive event, changes in the hippocampal cholinergic neurotransmission determine the relative engagement of the LA and BLA nuclei in bringing about the adaptive selection of either the discrete CS or the context as valid predictor. These findings are in accordance with the view supporting a role for Ach in regulating the relative contribution of different neural systems for learning [67, 68, 72]. These findings are also congruent with previous clinical studies indicating that having a hippocampal dependent episodic representation of the predictive value of CSs influences amygdala-based memory [24, 27, 28].

Altogether, these findings have led us to propose a modified version of the neurobiological model of fear conditioning. When the discrete tone CS is the main predictor of US, an increased HPC-LS glutamatergic neurotransmission would result in a GABA-mediated decrease in the activity of cholinergic neurons located in the medial septum, which projects to the hippocampus. Under this predicting-discrete CS situation, the low hippocampal cholinergic activity constrains the LA/BLA functioning in such a way (competition) that the discrete CS, and not the context, is ultimately selected as valid predictor. Conversely, when the context is the best predictor, a decrease in the glutamatergic hippocampal-septal neurotransmission would result in an increased release of acetylcholine in the hippocampus. This high level of Ach release contributes to a synergistic functioning of LA and BLA nuclei necessary for the selection of the context as the main predictor of the threat [34, 53]. Finally, different but specific engagements of the septo-hippocampal-amygdalar network appear to underlie the selection of relevant information, thereby contributing to the formation of adaptive emotional memories. The hippocampal and amygdalar systems not only regulate each other and their functional outcomes but also *qualify* specific emotional memory representations through specific activations and interactions [73].

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6. Dysfunction in the hippocampal-amygdalar dialogue might contribute to PTSD-related memory

Experimental studies just described above indicate that direct [53] or indirect manipulation [30, 55] of the hippocampal cholinergic neurotransmission can result in maladaptive fear memories. The identification of the discrete CS instead of the context in a predicting-context situation, or conversely, the selection of the context instead of the discrete CS in a predicting-tone CS situation reflects the formation of false memory that leads to the expression of inappropriate fear responses to the wrong predictor of a threat.

Specifically, these studies consistently show that all manipulations that aim at blocking or decreasing the hippocampal cholinergic transmission lead to the selection of an irrelevant but salient discrete CS instead of the background contextual cues as predictor of the footshock US. This striking formation of a prevalent discrete CS-US association to the detriment of the context-US association in a situation in which the discrete CS does not yet predict the occurrence of the threat is reminiscent of some critical aspects of traumatic memory as observed in posttraumatic stress disorder (PTSD). Indeed, one of the cardinal features of PTSD-related memory is a paradoxical qualitative alteration of memory including both memory intensification for the core traumatic event and a memory deficit for the traumatic environment. In other words, *hypermnesia* for some salient trauma-related cues that received the full attention of the subject during the traumatic event would co-exist with *amnesia* for peri-traumatic contextual stimuli that were too briefly apprehended to receive enough conscious attention [74–78]. Of particular relevance with the PTSD-related memory profile are the studies indicating that an increase in emotional arousal can promote the use of cue-based memory, but that such bias could result from an impairing effect of emotion on hippocampus-dependent cognitive memory [79].

Most of animal models of PTSD-related memory have exclusively focused on the quantitative alteration of memory, that is, the persistence of a strong fear memory, neglecting the qualitative alteration of traumatic memory. Yet, for over a century, clinical studies have consistently described the underrepresentation of the trauma in the context-based hippocampal-dependent memory system in favor of its overrepresentation in a cue-based sensory/emotional/implicit amygdala-dependent memory system [74, 76, 77]. In full accordance with the data presented above, these studies strongly suggest that a hippocampal-dependent deficit in contextual processing of stressful situations might contribute to the development of PTSD-related paradoxical memory.

In order to explain this hypermnesia/amnesia paradoxical profile, Layton and Krikorian [77] proposed an interesting neurobiological model in which PTSD-related memory would be the result of an increasing amygdalar inhibition of the hippocampus along with situations of increasing stress intensity. In low-to-mild stressful situations, the amygdala, weakly activated, would stimulate the hippocampus, promoting thereby the consolidation of hippocampal-dependent declarative information that would culminate in the formation of long-term "flashbulb" memory. As discussed above, this hypothesis is supported by considerable data indicating that the

amygdala modulates hippocampal activity and positively contributes to the consolidation of autobiographical information that are emotionally connoted [26, 29, 80]. In contrast, in intense or extreme stressful situations, the amygdala would be more and more recruited and would increasingly inhibit the hippocampus. As a consequence, trauma-related stimuli could not be consolidated anymore in the declarative memory system and thus would be susceptible to amnesia. Nevertheless, because the amygdala would directly contribute to the consolidation of the trauma, this one could be retrieved. The memory of the trauma, however, would be mostly implicit and would only correspond to what the amygdala can encode and store, that is the core of the trauma as well as certain details like the most salient simple cues and associated emotional feelings. This hypothesis is extremely congruent with the idea developed here that hippocampal disruption and dysfunction in hippocampal-amygdalar interaction can produce a switch from normal to abnormal fear memory-like PTSD-related paradoxical memory.

In line with this idea, we recently demonstrated a key role for the hippocampus in PTSD-like fear memory in mice under high-stressful situation. Because corticosterone (CORT), the main stress hormone in rodents, was shown to enhance the consolidation of adaptive fear memory in some stressful situations [26, 81–84], but also to impair the hippocampal function and disrupt context-based memory in others [85–87], we hypothesized that injection of CORT into the hippocampus, its main brain target, immediately after fear conditioning might either promote adaptive or produce PTSD-like fear memory as a function of the intensity of the stressful event. In order to observe a putative experimental bias toward a cue-based memory at the expense of a hippocampal-dependent context-based memory of the trauma, we used a predicting-context condition in which a discrete (tone) CS is present but irrelevant (not predictive of the US). In that case, the erroneous selection of the discrete CS as predictor of the footshock US reflects the expression of a maladaptive (PTSD-like) fear memory. As expected, we first showed that in a predicting-context situation using low footshock intensity, CORT injection in the hippocampus enhances adaptive conditioned fear to the context. In contrast, after a high-stress condition, the same CORT injection produces PTSD-like memory with the induction of a fear response to the most salient but irrelevant cue (a discrete tone) together with a decreased fear response to the right predictor (the conditioning context). Second, as in humans [88–91], compared to normal fear memory, PTSD-like memory induced in mice was found to be associated with hyperactivation of the right amygdala together with hypoactivation of the hippocampus [92].

Altogether these studies unveil a key role for the hippocampal-amygdalar network in the appraisal of emotional information and the formation of adaptive fear memories. As attested by behavioral and brain imaging outcomes of experimental manipulations of this network, dysfunction in this neural circuit, especially mediated by disruption of the hippocampal activation, turns out to be at the core of the development of abnormal/maladaptive fear memory, as observed in stress-related disorders like PTSD.

7. Conclusion: co-determined emotion and cognition

Although emotion can impair cognitive processes in certain extreme circumstances leading to maladaptive fear memory like in PTSD, it can also serve cognition. A growing body of

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evidence indicates that in contrast to artificial cognition, our natural cognition implies emotional experience with all its underlying somatic/physiological mechanisms. The fact that emotion can serve cognition, as illustrated by its critical contribution to decision making and to the enhancement of episodic memory, has been associated for a few decades to this other fact that, reciprocally, cognitive processes regulate emotional states. In addition, numerous data now indicate that this mutual regulation is mediated, at least in part, by a reciprocal modulation of the amygdalar and hippocampal systems.

Beyond the mutual quantitative regulation of these two brain systems described so far, the present chapter developed the idea that different recruitments of the hippocampus and the amygdala lead to specific neural configurations that qualitatively impact the formation of emotional memory, thereby producing different memory representations of an aversive experience. First, showing that the amygdala differentially modulates the hippocampal-septal excitability depending on whether a discrete CS or a complex background context is identified as predictor of a threat (i) indicates that a brain structure traditionally involved in the attribution of an affective value to neutral stimuli interact with another brain system that is supposed to underlie the "cognitive" processing of factual information and (ii) suggests that the hippocampal-dependent appraisal of such information may thus be dependent on the amygdala-dependent emotional experience encountered. Second, showing reciprocally that manipulating the hippocampal system during the acquisition of an aversive experience dramatically alters, and in fact can even lead to the switch from adaptive to maladaptive conditioned fear responses, indicates that a brain system known to underlie factual/representative memory directly contributes to the formation of specific emotional memory representations. Third, the systematic comparison of two different fear-conditioning situations, that is, predicting-context *vs*. predicting-discrete CS situation, revealed that the hippocampal system and amygdala both contribute to each learning situation. Importantly, their contribution to these two different learnings implies different patterns of activation and thus different recruitments of the hippocampal-amygdalar network as a function of the predictor of the threat. Hence, the main implication of this observation is that two neural systems known to underlie two well-known dissociable forms of memory turn out to be closely interactive when normal individuals form adaptive emotional memory.

While this chapter started with the idea of a fundamental dissociation between behavioral/emotional memory *vs*. representative memory, it comes to the idea that, except in some extent in pathological states, any of these two forms of memory can be conceived as isolated from the other. As proposed by Varela et al. 20 years ago [2], while all formal representations or cognitive processes are fundamentally embodied and "emerge from recurrent sensory-motor patterns," reciprocally all behavioral expressions of a past experience are necessarily constraint and guided by the cognitive structure of the individual concerned. In other words, our cognition would be "a creative form of enacting significance on the basis of the animal's embodied history."

In line with both the somatic markers hypothesis proposed by Damasio [3, 14] and the concept of "enaction" proposed by Varela et al. [2], the studies reviewed here support the general idea that "cognitive representation" and "emotional experience" should be conceived as co-determined entities, while factual representation takes its roots in somato-visceral

experiences, reciprocally, emotional experience depends on a more or less sophisticated guiding factual representation, such mutual dependency serves the expression of adaptive behaviors.

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