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Review

Synaptic Plasticity, Engrams, and Network Oscillations in Amygdala Circuits for Storage and Retrieval of Emotional Memories

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The neuronal circuits of the basolateral amygdala (BLA) are crucial for acquisition, consolidation, retrieval, and extinction of associative emotional memories. Synaptic plasticity in BLA neurons is essential for associative emotional learning and is a candidate mechanism through which subsets of BLA neurons (commonly termed "engram") are recruited during learning and reactivated during memory retrieval. In parallel, synchronous oscillations in the theta and gamma bands between the BLA and interconnected structures have been shown to occur during consolidation and retrieval of emotional memories. Understanding how these cellular and network phenomena interact is vital to decipher the roles of emotional memory formation and storage in the healthy and pathological brain. Here, we review data on synaptic plasticity, engrams, and network oscillations in the rodent BLA. We explore mechanisms through which synaptic plasticity, engrams, and long-range synchrony might be interconnected.

The neuronal circuits of the amygdala orchestrate emotional learning and memory via complex mechanisms that occur at multiple levels. Three phenomena that received particular attention are synaptic plasticity, the recruitment of engrams, and network oscillations. These events have largely been examined independently, but they are likely to interact to shape memory encoding and retrieval. Here, we review data demonstrating that the amygdala and connected brain areas of rodents coordinate acquisition, consolidation, retrieval, and extinction of emotional memories. We provide an original perspective linking plasticity, engram, and oscillations, highlighting unresolved questions that could push the field toward a more integrated understanding of emotional memory storage and retrieval.

The amygdala is a brain structure located in the medial temporal lobe that regulates emotional behavior in rodents, as well as non-human and human primates (Phelps and LeDoux, 2005). Moreover, the amygdala can function as the site for formation and storage of associative memories (Blair et al., 2005; Fanselow and LeDoux, 1999). Among different associative learning paradigms, fear conditioning is the most studied. Most amygdala nuclei have been shown to regulate various stages of fear learning. Among these, two nuclei play a pivotal role: the BLA, (which includes the lateral amygdala, LA and the basal amygdala, BA, nuclei) and the central amygdala (CeA, which is composed of lateral, CeL, and medial, CeM, sectors) (e.g., LeDoux et al., 1990; Wilensky et al., 2006). In addition to regulating negative emotions such as fear, BLA neurons are also important for reward-based learning and memory (Beyeler et al., 2016; Gore et al., 2015; Namburi et al., 2015; Tye and Janak, 2007; Tye et al., 2008). These data provided novel demonstration to the classical idea that the BLA is one of the sites in which positive and negative valences are assigned to sensory stimuli (Everitt et al., 1989; LeDoux et al., 1988).

The idea that memory is physically stored in specific brain circuits goes back to the "engram theory" of Semon (1921) and early attempts to test this theory experimentally (e.g., Lashley, 1950; Olds et al., 1972; reviewed by Tonegawa et al., 2015). Recent developments in genetics and optogenetics have provided useful tools to establish a causal relation between neuronal engrams and fear memory and to assign specific roles to neuron types (Tonegawa et al., 2015). Namely, neurons activated during a particular behavior can be genetically tagged (Reijmers et al., 2007) and subsequently activated/silenced using optogenenetics (Liu et al., 2012) or chemogenetics (Yiu et al., 2014). These approaches have revealed that associative memory acquisition and expression rely on the activation of specific groups of neurons (commonly termed "ensembles" or "engrams"; Josselyn et al., 2015; Tonegawa et al., 2015). Importantly, activation of specific engrams in the BLA has been shown to be involved in the encoding of either aversive or appetitive memories (Gore et al., 2015; Redondo et al., 2014).

Experiments in rodents have unveiled that synaptic plasticity in BLA neurons is critical for associative aversive learning (e.g., Nabavi et al., 2014; Rogan et al., 1997). Extracellular potentials commonly termed "network oscillations" detected in the BLA are another critical factor governing emotional memory storage

and retrieval. In particular, theta and gamma oscillations synchronize the BLA with interconnected areas during fear and reward memory retrieval (Bauer et al., 2007; Seidenbecher et al., 2003). Although synaptic plasticity, engrams, and network oscillations are clearly involved in emotional memory storage and retrieval, a key challenge is to understand how these three phenomena are related.

Long-term changes in synaptic strength between ensembles of neurons could be the primary basis of engram formation (Poo et al., 2016). BLA neuronal excitability is a key determinant of synaptic plasticity induction (Motanis et al., 2014) and engram formation (Han et al., 2007; for a discussion on this topic, also see Holtmaat and Caroni, 2016). During long-range synchrony, the excitability of BLA neurons is modulated by oscillations in other structures, such as the medial prefrontal cortex (mPFC) (Karalis et al., 2016; Likhtik et al., 2014). This indicates that long-range synchrony could play an important role in plasticity induction and selection of BLA engrams.

Synaptic Plasticity in Amygdala Circuits

It is thought that memories are formed and stored by long-term changes in the strength of synaptic connections between neurons, a process known as synaptic plasticity (Citri and Malenka, 2008). Long-term increases or decreases of synaptic strength lasting for hours, days, and perhaps even longer periods of time have been termed long-term potentiation (LTP) and long-term depression (LTD), respectively. These phenomena were discovered in the hippocampus (Bliss and Lømo, 1973; Dudek and Bear, 1992; Mulkey and Malenka, 1992), but they have been subsequently described also in the amygdala (for an exhaustive review, see Pape and Paré, 2010).

The majority of the studies that examined the mechanisms of LTP and LTD in the amygdala focused on the LA, where NMDA receptors are expressed in principal neurons (PNs) at both cortical and thalamic synapses (Farb and LeDoux, 1997, 1999). GABAergic interneurons are gatekeepers of synaptic plasticity because depression of GABA release promotes LTP induction in the BLA (Bazelot et al., 2015; Bissière et al., 2003; Tully et al., 2007). This can be achieved, for example, by release of neuromodulators such as noradrenaline and dopamine (Bissière et al., 2003; Tully et al., 2007).

Investigating the mechanisms of synaptic plasticity induction in the amygdala is crucial because, as we will describe later, LTP and LTD are cellular substrates of emotional learning and memory. Learning a CS-US association (e.g., auditory tone-footshock or auditory tone-reward) increases synaptic efficacy at synapses of the CS pathway in BLA neurons (McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997; Tye et al., 2008).

Network Oscillations in Amygdala Circuits

It is important to acknowledge that the majority of the studies investigating the induction of LTP and LTD in amygdala circuits employed artificial stimulation protocols. These involve firing synchronously large numbers of axons as well as stimulating at high frequency in a prolonged or regular fashion. It is therefore unlikely that these protocols accurately simulate what occurs under normal physiological circumstances. Thus, it is essential to establish how long-term synaptic plasticity is physiologically induced in BLA neurons in vivo.

As we will review below, network oscillations are associated with the synchronization of BLA PNs, creating ensembles of PNs that fire in sync with each other and with distant afferent neurons. Thus, oscillations could play an important role in the induction of synaptic plasticity in the BLA via precise coordination of presynaptic and postsynaptic activity.

Network oscillations are rhythmic voltage deflections revealed by local field potential (LFP) recordings. These oscillations occur in various frequency bands and are thought to be caused by the synchronous synaptic activity of large numbers of neurons (Buzsáki et al., 2012). The oscillatory activity in the BLA occurs in different frequency bands, such as delta (0.5–4 Hz), theta (4–12 Hz), beta (12–30 Hz), and gamma (30–120 Hz), with changes in both frequency and amplitude depending on behavioral state, as in other brain areas (Buzsáki, 2009).

It is still not clear whether LFPs are intrinsically generated within the BLA, are triggered by synaptic interplay from various inputs, or they merely reflect activity that passively propagates from nearby sources; e.g., the hippocampus (Pape and Paré, 2010). Yet several lines of evidence suggest that rhythmic activity in the BLA is unlikely to be volume conducted from neighboring areas. Specifically, BLA neurons display intrinsic membrane oscillations at theta frequency range (Pape and Driesang, 1998; Paré et al., 1995a). Furthermore, the firing of BLA neurons fluctuates rhythmically with local theta and gamma oscillations (Karalis et al., 2016; Popescu et al., 2009; Stujenske et al., 2014). Finally, theta synchrony between the LA and CA1 hippocampus is observed during fear memory retrieval, but not during exploratory behavior when CA1 displays strong theta activity (Narayanan et al., 2007; Seidenbecher et al., 2003).

Simultaneous multi-site LFP recordings have been employed to assess whether oscillatory patterns in the BLA and interconnected structures change in a coordinated fashion during behavior. Synchrony of distant LFPs is measured by either power correlation or phase coherence (alignment of peaks and troughs). Additionally, Granger causality analysis tests whether one time series predicts another, enabling to assess the directionality of rhythmic activity between regions (e.g., whether it is the hippocampus that drives BLA oscillations or vice versa).

A very important theoretical and clinical aspect is that abnormal network oscillations have been often detected in several brain diseases, such as neuropsychiatric disorders in humans (e.g., Uhlhaas et al., 2006) and in animal models (e.g., Ghosh et al., 2013). This crucial topic, however, will be not examined here. This is because of our specific focus on fundamental cellular mechanisms and because this translational aspect has been already discussed by some excellent reviews (Buzsáki and Watson, 2012; Uhlhaas and Singer, 2006).

In this section, we introduce the main oscillatory rhythms that have been recorded from the BLA and interconnected areas of rodents and cats (Figure 1), focusing on their cellular mechanisms. We will subsequently review their involvement in various phases of emotional learning.

Delta Oscillations

Slow oscillations in the delta frequency range (0.5–4 Hz) have been observed in the BLA, primarily, but not exclusively during

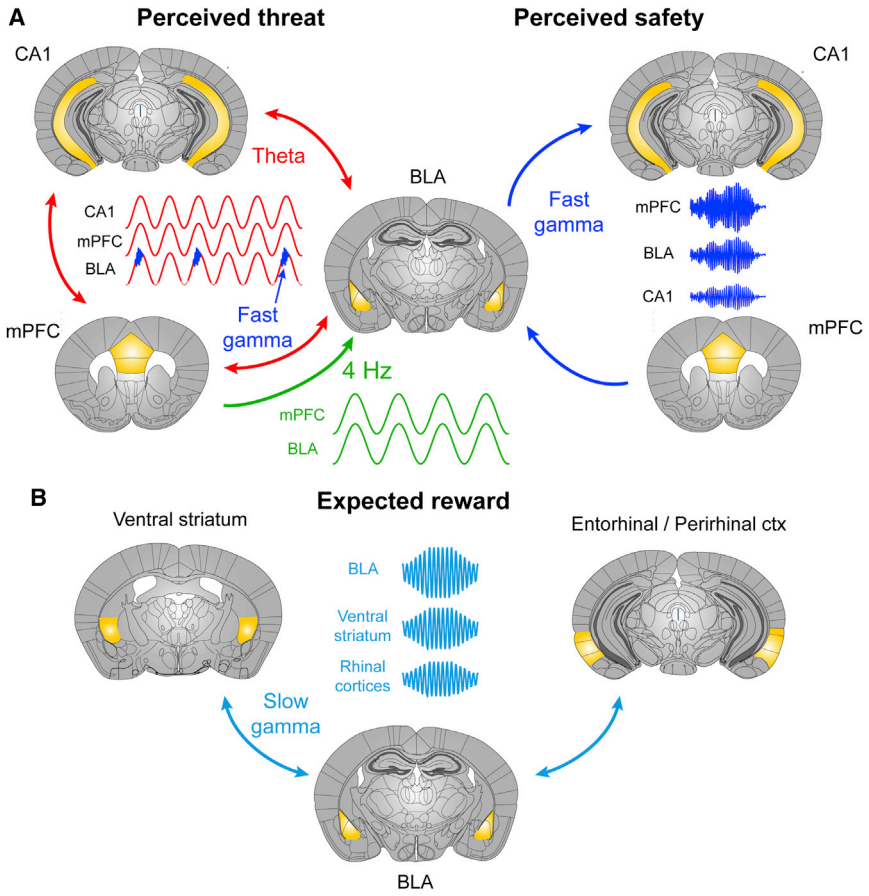

Figure 1. Oscillations in the BLA and Interconnected Structures

(A) Oscillatory interactions between BLA, mPFC, and hippocampus (CA1 region) underlying fear memory retrieval. A perceived threat (a CS+ predicting a footshock) enhances theta power and coherence in BLA, mPFC, and CA1 (left) (Lesting et al., 2011; Likhtik et al., 2014; Narayanan et al., 2007; Seidenbecher et al., 2003). In this behavioral situation, BLA fast gamma (70–120 Hz) power is low, but fast gamma bouts are phase locked to theta oscillations (Stujenske et al., 2014). A 4 Hz oscillation originating from the mPFC synchronizes this structure with the BLA during freezing episodes (Karalis et al., 2016). A situation of perceived safety (a CS− predicting the absence of a footshock) leads to a synchronized increase in fast gamma power in mPFC, BLA, and CA1 (right) (Stujenske et al., 2014). Note that fast gamma follows an mPFC→BLA→CA1 directionality.

(B) Presentation of a CS+ predicting a reward leads to increased slow gamma (30–45 Hz) power and coherence between the BLA and cortical and subcortical structures (Bauer et al., 2007; Popescu et al., 2009).

both slow-wave sleep in cats (Paré and Gaudreau, 1996) and urethane anesthesia in mice (Bazelot et al., 2015). This oscillatory pattern occurs during cortical synchronization and slow-wave activity. Delta oscillations appear to coordinate the timing of BLA neuron firing. In the BA, PNs and putative INs fire at opposite phases of delta oscillations recorded from rhinal cortices: the former cell type at the peak of delta, the latter at the trough (Paré and Gaudreau, 1996).

Theta Oscillations

Rhythmic BLA network activity at slow theta frequency (4–8 Hz) has been recorded in rodents and cats during defined brain states and behaviors (Karalis et al., 2016; Likhtik et al., 2014; Paré and Collins, 2000; Seidenbecher et al., 2003). Notably, BLA theta oscillations appear to be distinct from locomotion-driven hippocampal theta (8–12 Hz) because they do not occur during locomotion (Seidenbecher et al., 2003) and are not affected by inactivation of the medial septum (Karalis et al., 2016). Thus, pathways and neuronal dynamics that generate this oscillation are different from the ones that produce classic hippocampal theta, suggesting that BLA slow theta is linked to different information encoding and behavioral output.

The transmembrane currents giving rise to BLA theta oscillations are likely generated by synaptic inputs, mostly glutamatergic, from afferent regions (such as the hippocampus or the mPFC). Additionally, PN membranes display intrinsic resonance at theta frequency (Pape and Driesang, 1998; Paré et al., 1995a), suggesting that synchronous theta fluctuations of PN membrane potentials might contribute to theta oscillations in the LFP, even independently from synaptic potentials. Similarly to the hippocampus, current sources provided by rhythmic inhibitory postsynaptic potentials (IPSPs) from interneurons (INs) innervating the perisomatic domain of PNs, particularly parvalbumin (PV)-expressing INs could play a critical role in BLA theta generation (Buzsáki, 2002).

Gamma Oscillations

Higher frequency oscillatory activity in the gamma band (30–120 Hz) has also been detected in the BLA of rodents. Compared to hippocampus and neocortex, experimental evidence of the cellular mechanisms generating gamma oscillation in the BLA is scant. However, kainate receptors, gap junctions, and acetylcholine appear to be critical (Randall et al., 2011; Sinfield and Collins, 2006), potentially by regulating reciprocal synaptic interactions between PNs and INs (particularly fast-spiking PV+ INs).

Two gamma frequency bands have been described for the BLA in vivo: a slow gamma (30–70 Hz or 35–45 Hz, depending on the study) and a fast gamma (70–120 Hz) (Bauer et al., 2007; Popescu et al., 2009; Stujenske et al., 2014). Furthermore, the power of BLA fast gamma oscillations can be modulated by the phase of local or mPFC theta oscillations (Stujenske et al., 2014). This phenomenon is generally referred to as theta-gamma cross-frequency coupling (for review Lisman and Jensen, 2013).

In summary, delta, theta, and gamma oscillations occur in the rodent BLA in vivo. Similar to other brain structures, these network oscillations likely originate from rhythmic excitatory postsynaptic potentials (EPSPs) and IPSPs and from synchronous membrane fluctuations in PNs. However, the non-laminar

arrangement of BLA cells and of axons carrying external inputs does not favor the occurrence of current sources and sinks that have been suggested to account for oscillations in the hippocampus (Buzsáki, 2002).

In the next sections, we will explore the synaptic and oscillatory mechanisms underlying acquisition, consolidation, retrieval, and extinction of emotional memories, with a particular focus on fear conditioning. We will illustrate that emotional memories are stored by changes in synaptic weights and formation of neuronal engrams in the amygdala. These memories are then retrieved by long-range oscillatory synchrony, temporal coordination of spikes, and reactivation of these engrams.

Emotional Memory Acquisition Increases Synaptic Efficacy and Forms Engrams in the BLA

Fear Conditioning Triggers LTP at Cortical and Thalamic Synapses in the LA

In this section, we will illustrate that synaptic plasticity in amygdala circuits is essential for the retrieval of associative fear memories (Johansen et al., 2011; Pape and Paré, 2010). This does not mean that the amygdala is the sole neuronal structure responsible for this process. In fact, auditory fear conditioning induces widespread synaptic plasticity in many other brain areas, such as the auditory thalamus and cortex (reviewed in Tovote et al., 2015). For example, new synaptic contacts have been observed after the acquisition of a fear memory at excitatory synapses between the LA and neurons of the auditory cortex (Yang et al., 2016).

Within the basolateral complex, the LA has been identified as a crucial site for emotional memory acquisition. Indeed, lesions of the LA before cued fear conditioning abolished conditioned responses (LeDoux et al., 1990). A similar disruption of fear conditioning was obtained by infusion of an NMDA receptor antagonist into the BLA before conditioning (Campeau et al., 1992). Since NMDA receptor antagonists block the induction of LTP in the LA (Bauer et al., 2002; Huang and Kandel, 1998), these experiments altogether pointed at LTP at LA synapses as a cellular substrate for emotional learning.

The LA receives projections from thalamic and cortical regions involved in auditory processing (CS) as well as somatosensory inputs (US) (LeDoux, 2000). Importantly, the CS and US inputs converge on the same population of neurons in the LA (Romanski et al., 1993). According to the synaptic plasticity model for fear learning, the CS alone cannot trigger the fear response because its synaptic input is too weak to activate the downstream fear circuits. However, the conditioning causes potentiation of CS-relaying synapses onto LA PNs to access downstream circuits for fear expression and to activate them. This model predicts that fear conditioning causes a lasting increase in the LA response to the CS inputs, and this increase is required for the fear memory formation (Johansen et al., 2011; Pape and Paré, 2010; Sigurdsson et al., 2007).

More recently, it has been shown that a conditioned fear memory can be inactivated by depotentiating the synapses using an NMDA-dependent LTD induction protocol (Nabavi et al., 2014). Importantly, the subsequent LTP induction reactivates fear memory (Nabavi et al., 2014). This demonstrates the necessity of potentiation of auditory synaptic inputs in the LA in fear conditioning. However, LTP induction on naive animal fails to induce a detectable fear response (Nabavi et al., 2014). There could be multiple non-mutually exclusive reasons for this observation. The LA is composed of neurons with opposing valences for reward and aversion (see below). Non-selective potentiation of neurons of opposing valences could result in negligible behavioral responses. Indeed, inhibition of neurons encoding for a negative valence in the amygdala not only impairs fear learning, but also enhances reward seeking behavior and vice versa (Kim et al., 2016; Namburi et al., 2015).

Alternatively, it may be that LTP induction in the LA is necessary, but not sufficient for fear conditioning. Consistent with the necessity of Hebbian LTP (which requires the pairing of presynaptic release and postsynaptic depolarization), hyperpolarization of LA neurons interfered with the conditioning (Johansen et al., 2014). Conversely, optical depolarization of LA PNs paired with an auditory CS during training evoked freezing to the CS during the retrieval session (Johansen et al., 2010). However, freezing remained dramatically lower than following footshock-tone pairings (Johansen et al., 2010, 2014). Further investigation pointed to the complementary role of the neuromodulator noradrenaline: the local infusion of β-adrenergic receptor antagonist before the aversive conditioning significantly reduced the fear learning (Johansen et al., 2014). In this regard, it is not known whether this neuromodulator functions by lowering the threshold for the plasticity or by stabilizing it. Nonetheless, noradrenaline is thought to enhance contextual fear learning by lowering the threshold for LTP induction in the hippocampus (Hu et al., 2007).

Taken together, these data demonstrate that an aversive stimulus contributes to fear memory formation by depolarizing postsynaptic cells, and thereby inducing Hebbian plasticity, as well as by evoking the release of neuromodulators from subcortical inputs which target the amygdala and other limbic areas. Therefore, neuromodulator release, triggered by aversive stimuli during the conditioning procedure, may be essential for fear conditioning.

Although early models depicted the LA as the major site for the plasticity, later studies demonstrated that in addition to the LA, the CeA is necessary for fear learning. Functional inactivation of the CeA by local infusion of the $GABA_A$ agonist muscimol prior to the conditioning impaired fear memory retrieval (Wilensky et al., 2006). This result suggests that synaptic plasticity of inhibitory neurons of the CeA may be required for fear learning. Two subpopulations of inhibitory neurons with reciprocal inhibitory connections within the CeL have been identified. One group expresses protein kinase C-δ (PKC-δ), but predominantly lacks somatostatin (SOM) expression (Ciocchi et al., 2010; Haubensak et al., 2010; Li et al., 2013). These PKC-δ+ CeL neurons inhibit CeM neurons and are silenced during CS presentation by activation of CeL PKC-δ-negative neurons (Ciocchi et al., 2010; Haubensak et al., 2010). Since CeM neurons trigger fear responses via their projection to the periacqueductal gray (Ciocchi et al., 2010; Tovote et al., 2016), activation of CeL PKC-δ-negative cells triggers disinhibition of the CeM, thereby facilitating fear expression (i.e., freezing).

In addition to this CeL-CeM disinhibitory circuit, CeL SOM+ neurons undergo potentiation of glutamatergic synaptic inputs

upon fear conditioning (Li et al., 2013). Selective suppression of SOM+ neurons during the conditioning blocks the conditioning-induced plasticity in the CeL and impairs formation of the fear memory (Li et al., 2013). Interestingly, SOM+ cells are long-range projection neurons that avoid the CeM and instead target the periacqueductal gray (Penzo et al., 2014). In summary, fear conditioning triggers LTP at CS-relaying synapses onto LA neurons, a phenomenon involving the release of noradrenaline, but it also induces multiple changes in synaptic strength in CeA circuits.

Appetitive Conditioning Activates a Population of BLA Neurons

In addition to aversive memories, evidence suggests that the BLA orchestrates reward conditioning (Cador et al., 1989; Everitt et al., 1989; Hatfield et al., 1996). Similar to fear conditioning, an increase in excitatory synaptic inputs to the LA underlies the formation of associative reward memories (Tye et al., 2008). In vivo electrophysiological recordings together with activity-dependent tagging demonstrated that, despite statistical similarity in population activity during positive and negative stimuli (Muramoto et al., 1993; Shabel and Janak, 2009), there are distinct BLA neurons that encode associative fear and reward memories (Beyeler et al., 2016; Namburi et al., 2015; Redondo et al., 2014) and affective value in general (Beyeler et al., 2016; Schoenbaum et al., 1998; Shabel and Janak, 2009).

Available data suggest that there is no clear topographical segregation between neurons encoding aversive and reward memories, suggesting that these populations are intermingled (Gore et al., 2015; Namburi et al., 2015; Shabel and Janak, 2009; Zhang et al., 2013). This raises the intriguing question of how the same region encodes contrasting emotional values (Namburi et al., 2016). One possibility is that the neurons encoding the reward and aversive learning are connected to corresponding regions that elicit different behavioral responses. In an alternative scenario, BLA neurons are not assigned to any intrinsic valence prior to conditioning, but only after the conditioning they acquire the appropriate valence. This possibility implies that each neuron is connected to both aversive and reward centers.

However, a recent report identified two genetically and anatomically segregated populations of BLA excitatory neurons involved in valence-specific behaviors and connected through reciprocal inhibition (Kim et al., 2016). These two populations are *Rspo2*$^{+}$ BLA neurons, magnocellular neurons of the anterior BLA, that are activated by aversive stimuli, and *Ppp1r1b*$^{+}$ BLA neurons, parvocellular neurons of the posterior BLA, that are activated by appetitive stimuli. The analysis of the projections of these two neuronal populations reveals that positive valence neurons comprise cells projecting extensively to CeL, CeM, nucleus accumbens, and ventral hippocampus, a result consistent with non-fixed valence value data based on projection-defined cell populations (Beyeler et al., 2016). Future research using in vivo recordings or calcium imaging from animals that undergo conditioning of opposing valences may identify non-overlapping neurons and/or neurons which over time switch their specificity for a particular valence.

From a network perspective, studies by Paré's group have shown that during appetitive learning the power and synchrony of slow gamma oscillations (35–45 Hz) increases in BLA, rhinal cortices, and striatum (Bauer et al., 2007; Popescu et al., 2009; Figure 1B). The firing of ~50% of BLA neurons was modulated by this slow gamma rhythm. However, it remains unclear whether gamma oscillations are involved in the selection of BLA neurons encoding the CS-reward association or, by contrast, interconnected BLA-striatal-rhinal cortex neurons encoding this are the generators of this oscillation.

Emotional Memory Acquisition Leads to the Formation of Engrams in the BLA

How are neurons in the BLA recruited for memory formation during the conditioning? Although the majority of neurons receive convergent CS and US inputs, only about 20%–30% of them develop an increased response to the CS after the conditioning (Repa et al., 2001; Rumpel et al., 2005). This is explained by the findings that after auditory fear conditioning 20%–30% of neurons in the LA express activated cyclic (c)AMP response element-binding protein (CREB), a hallmark of neuronal excitability (Han et al., 2007). This suggests that a subpopulation of the neurons have a lower threshold for plasticity, possibly due to their higher intrinsic excitability and their stronger excitatory interconnections (Kim et al., 2013). Supporting this hypothesis, neurons randomly overexpressing CREB in the LA are more likely to be recruited to the memory traces and targeted deletion of neurons overexpressing CREB after the conditioning permanently eliminates fear expression (Han et al., 2009). It is important to consider, however, that such random nature of engram neuron distribution is at odds with data showing that certain neuron populations are assigned to specific behavioral outputs. For example, BLA neurons projecting to the prelimbic mPFC promote fear expression ("fear neurons"), whereas the ones projecting to the infralimbic region promote fear extinction ("extinction neurons", see section on fear extinction below for further details; Senn et al., 2014). Future work should resolve these questions, potentially by combining activity-based genetic tagging of engram cells and viral tracers to map their inputs and outputs.

In summary, current evidence suggests that associative emotional learning leads to the formation of an engram in the BLA, likely via synaptic plasticity induction at CS-relaying synapses on subsets of BLA PNs (Figure 2). The most excitable PNs appear to be the ones that are more likely to undergo LTP. Induction of LTP at CS-relaying synapses is thought to trigger increased PN firing at CS presentation following fear conditioning, thereby leading to stronger recruitment of downstream circuits (e.g., CeA neurons).

An outstanding question is what mechanisms determine the excitability of LA PNs that undergo LTP. Is the threshold for plasticity reached due to intrinsic membrane properties, synaptic inputs, slow depolarization caused by neuromodulators, or all factors combined? Are network oscillations involved?

Emotional Memory Consolidation Requires Protein Synthesis and Release of Neuromodulators in the BLA

In order to be retrieved after days, months, or even years, a short-term memory must be converted into long-term memory, a process known as memory consolidation (McGaugh, 2000). Consolidation is easily achieved following acquisition of associative, emotionally arousing experiences, particularly for fearful ones that are vital for survival. Many studies examined the

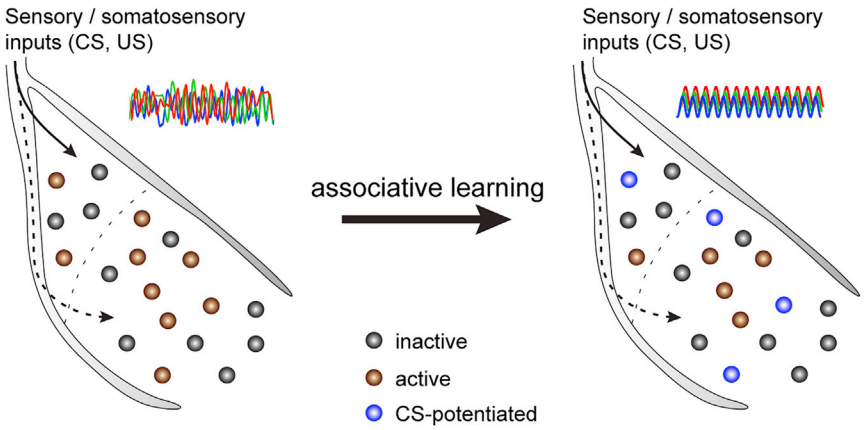

Figure 2. Synaptic Plasticity and Network Oscillation Gate Memory Engram Formation in the BLA

Before learning, some BLA neurons (gray balls) display low excitability and others (brown balls) higher excitability (by intrinsic factors and/or synaptic inputs). At the population level, poorly synchronized rhythms can be detected among BLA and connected brain areas. Learning promotes Hebbian synaptic plasticity of the CS pathway on neurons that were more active during conditioning. This plastic process results in CS-potentiated neurons that form an engram (blue balls). Memory retrieval triggers synchronization of rhythmic activity between the BLA and some interconnected structures, as well as reactivation of engram cells.

mechanisms through which the BLA modulates the consolidation of various types of memory via action on other brain areas (McGaugh, 2004). However, relatively little is known about the cellular and network mechanisms orchestrating the consolidation of fear memory.

A putative mechanism through which emotional memories are consolidated is the conversion from early LTP to late LTP, which is RNA dependent and protein synthesis dependent (Huang et al., 1994; Huang and Kandel, 1998; Nguyen and Kandel, 1996; but see Canal et al., 2007). In support of this theory, posttraining infusion of a protein synthesis inhibitor in the BLA reduces freezing during retrieval (Schafe and LeDoux, 2000).

In addition, the release of neuromodulators in the BLA appears to be important for fear memory consolidation (LaLumiere et al., 2003; Vazdarjanova and McGaugh, 1999). Specifically, infusion of noradrenaline in the BLA enhanced contextual fear conditioning consolidation (LaLumiere et al., 2003), although noradrenergic blockade in the BLA disrupted reconsolidation, but not consolidation (Dębiec and Ledoux, 2004). Cholinergic blockade in the BLA impaired contextual fear memory consolidation (Vazdarjanova and McGaugh, 1999). Finally, stress can promote the consolidation of a weak fear memory via serotonin release and 5-HT_{2C} receptors in the BLA (Baratta et al., 2016).

Oscillatory communication between the hippocampus, the thalamus, and the neocortex during both slow-wave sleep and rapid eye movement (REM) sleep is thought to be important for memory consolidation (for review, see Diekelmann and Born, 2010). Evidence suggests that BLA oscillatory patterns taking place during sleep could be important for the consolidation of emotional memories. In particular, during REM sleep following fear conditioning, the strength of fear memory retrieval positively correlates with directional theta synchronization from CA1 hippocampus to the BLA and from the BLA to the mPFC (Popa et al., 2010). A critical unanswered question is whether oscillations occurring during slow-wave sleep that follows emotional learning are also important for subsequent retrieval.

In the hippocampus, firing patterns occurring during exploration of a novel environment are reactivated in the same order during subsequent slow-wave sleep and mostly during oscillatory complexes called sharp-wave ripples (Wilson and McNaughton, 1994). This temporally coordinated reactivation is believed to promote the redistribution of memories to neocortical sites. In line with this, a recent study showed that reinforcing the temporal coordination of hippocampal sharp-wave ripples and cortical delta oscillations and spindles boosted memory consolidation (Maingret et al., 2016).

We propose that similar mechanisms could occur in the BLA. During slow-wave sleep and under anesthesia, synchronized population bursts from BLA neurons give rise to large amplitude potentials (termed "sharp potentials") and synchronized firing in the entorhinal cortex and in the dentate gyrus (Collins et al., 1999; Paré et al., 1995b). These dynamics may redistribute information to the rhinal cortices following emotional memory acquisition. Another important open question is whether sequences of BLA engrams that are recruited during acquisition are subsequently reactivated during sleep to stabilize synaptic strengthening. Thus, protein synthesis and neuromodulators are critical for emotional memory consolidation in the BLA, whereas the involvement of BLA oscillations and long-range synchrony remains to be largely dissected.

Reactivation of BLA Engrams and BLA Slow Theta Synchronization Underlie Emotional Memory Retrieval

Current views suggest that BLA neurons that were strongly activated during emotional memory acquisition and formed an engram via LTP induction are then reactivated during fear memory retrieval (Redondo et al., 2014; Yiu et al., 2014; Figures 2 and 3). Recently, this has been elegantly demonstrated using chemogenetic and optogenetic approaches. In one study, LA neurons that were activated immediately before fear conditioning using DREADDs were then reactivated days after training in a different context, and this produced freezing (Yiu et al., 2014). In another study, optogenetic activation of BLA neurons originally activated in a context where footshocks were presented drove conditioned place avoidance of the training context (Redondo et al., 2014). In the same study, optogenetic activation of BLA neurons originally activated in a context where a reward was presented drove conditioned place preference for the training context (Redondo et al., 2014).

Evidence suggests that reactivation of these cells is driven by stronger synaptic drive. First, fear and reward conditioning enhance field potentials or neuronal firing recorded from the

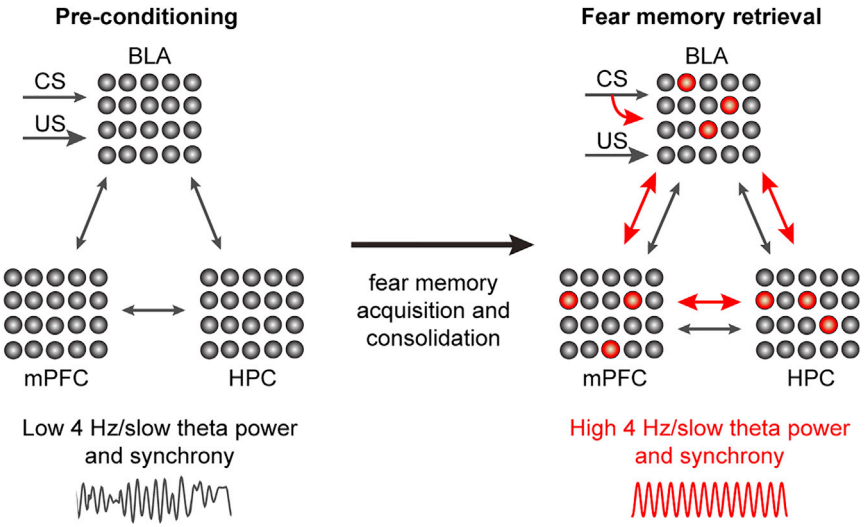

Figure 3. Hypothetical Mechanism of Slow Theta/4 Hz Synchronization via Engram Cells

Before fear conditioning (left), US synapses onto BLA neurons have a stronger weight than CS synapses. No engram encodes the CS/US association. Power and synchrony of slow theta/4 Hz oscillations are low. With fear conditioning, the CS pathway gains stronger synaptic weight onto BLA engram cells due to LTP induction (right). The power and synchrony of slow theta/4 Hz oscillations between BLA, mPFC, and hippocampus (HPC) are high. Additional engram neurons are present in mPFC and HPC. We propose that these neurons are strongly interconnected with BLA engram cells via LTP. Additionally, we speculate that rhythmic firing of these reciprocally interconnected engrams could be a mechanism of generation of slow theta/4 Hz oscillations.

LA in vivo and evoked by either CS presentation or stimulation of the auditory thalamus (Goosens et al., 2003; McKernan and Shinnick-Gallagher, 1997; Quirk et al., 1995; Rogan et al., 1997; Tye et al., 2008). Second, fear and reward conditioning induce LTP in LA neurons (McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997; Tye et al., 2008). Third, a more direct demonstration of this theory has been provided by showing that release of glutamate is enhanced in BLA engrams in acute slices (Nonaka et al., 2014).

Thus, reactivation of BLA engrams that associate an auditory cue with a positive or negative stimulus appears to be driven by LTP at auditory pathways. It remains unclear what pathways are instead potentiated for engram cells that associate a stimulus with a particular context, but some evidence suggests that one of these could be the projection from the ventral hippocampus (Xu et al., 2016).

In addition to changes in synaptic strength, a large body of evidence suggests that fear memory retrieval is achieved via temporal coordination between the BLA and other areas involved in memory processing. Seminal work from Pape's group revealed that the LFPs recorded from the mouse LA, dorsal CA1 (dCA1) hippocampus, and mPFC synchronize at theta frequency during contextual and cued fear memory retrieval (involving both power correlation and phase synchronization; Seidenbecher et al., 2003; Narayanan et al., 2007; Lesting et al., 2011; Figure 1A). Since the dCA1 and the LA do not appear to be reciprocally connected in rodents, theta coupling might arise from relay from rhinal cortices. A recent study demonstrated that the temporal association cortex, a prominent source of higher-order auditory information to the BLA, also synchronizes at theta frequency with the BLA during fear memory retrieval (Cambiaghi et al., 2016).

How do BLA, mPFC, and hippocampus interact to discriminate between aversive and safety signals in a fear conditioning paradigm? Likhtik et al. (2014) showed that a situation of perceived safety (presentation of a CS−, namely an auditory cue signaling absence of footshock) triggered stronger phase locking of BLA neuron firing to mPFC theta oscillations compared to presentation of a CS+ (a situation of perceived danger). These data suggest that synchronous rhythmic activity of mPFC and BLA neurons is crucial for successful fear discrimination. Furthermore, the mPFC appears to temporally coordinate BLA neuron firing at theta frequency to signal safety; i.e., that a tone is not predicting a shock.

In line with the involvement of mPFC-BLA theta synchrony in fear memory retrieval and appropriate defensive responses, Karalis et al. (2016) reported that 4 Hz synchronous activity between the mPFC and the BLA occurs during freezing (and predicts freezing episodes). Using Granger causality analysis, the authors showed that this 4 Hz synchrony was driven by the mPFC. The majority of putative PNs and INs of the BLA and the mPFC fire phase locked to this 4 Hz oscillation. During freezing, mPFC and BLA PNs phase locked to the 4 Hz oscillation display higher co-firing compared to PNs that are not phase locked (Karalis et al., 2016). These results suggest that 4 Hz oscillations reflect temporal coordination of mPFC-BLA PNs firing. This coordination is likely to involve the activity of GABAergic INs innervating the perisomatic region of PNs. Surprisingly, PV+ basket or axo-axonic cells, analyzed as groups, do not fire significantly phase locked to hippocampal slow theta in anesthetized rats (Bienvenu et al., 2012). Consistently, optogenetic activation of PV+ INs of the mPFC—but not of the BLA—triggered freezing behavior, as well as 4 Hz oscillations in mPFC and BLA (Karalis et al., 2016). However, other BLA interneuron types that have been shown to fire phase locked to hippocampal slow theta might be involved (Bienvenu et al., 2012; Mańko et al., 2012). These data indicate that 4 Hz oscillations trigger freezing responses. In the BLA, this rhythm does not seem to be locally generated, but instead driven by rhythmic synaptic inputs from mPFC PNs.

This 4 Hz oscillation appears to be distinct from sensory-evoked mPFC theta oscillations described by Courtin et al. (2014) for various reasons. First, mPFC theta is a transient phenomenon lasting a few hundreds of milliseconds, whereas the 4 Hz/slow theta rhythm described by Seidenbecher et al. (2003) and Karalis et al. (2016) lasts several seconds. Second, 4 Hz oscillations occur during freezing even without CS presentation (Karalis et al., 2016). Third, CS presentation resets the phase

of ≥6 Hz theta oscillations in the mPFC, but not of 4 Hz oscillations in mPFC and BLA (Karalis et al., 2016). Thus, the picture that emerges is that 4 Hz oscillations in mPFC and BLA signal threat and mediate freezing, whereas theta oscillations ≥6 Hz could be involved in sensory perception. Further studies will hopefully assign a more precise role to these oscillatory bands.

Thus, theta power and synchrony are involved in aversive learning and defense responses. Given the data linking the BLA with reward learning (e.g., Beyeler et al., 2016; Everitt et al., 1989; Gore et al., 2015; LeDoux et al., 1988; Namburi et al., 2015), it is possible that slow theta/4 Hz oscillations could contribute more generally to the encoding of valence, but this possibility still awaits empirical verification.

As in the case of theta rhythms, gamma oscillations appear to be important for emotional memory retrieval. The power of fast gamma (70–120 Hz) decreases when an animal successfully discriminates an auditory cue predicting a footshock and increases when a cue not paired with the shock (thereby signaling safety) is presented (Stujenske et al., 2014; Figure 1A). Theta-BLA gamma phase-amplitude coupling recorded in the mPFC increases upon successful fear discrimination that leads to freezing. In contrast, fear discrimination does not appear to cause changes in the power of the slow gamma (40–70 Hz) or in the phase amplitude cross-frequency coupling between theta and slow gamma (Stujenske et al., 2014).

Emotional Memory Extinction Involves Changes in BLA Synaptic Weights and Long-Range Synchrony

Fear responses can undergo extinction, especially after reexposure of the CS in the absence of the predicted US; extinguished fear responses tend to spontaneously return with time (Myers and Davis, 2007). The main synaptic mechanisms that have been proposed to be responsible for fear memory extinction are (1) depotentiation or LTD of previously potentiated synapses on PNs, (2) induction of LTP at CS afferents on INs, and (3) LTP of inhibitory synaptic transmission (Maren, 2015).

First, learning-induced LTP can be depotentiated and extinction training occludes this phenomenon (Hong et al., 2009; Kim et al., 2007). Second, LTP of excitatory synapses has been reported at either cortical or thalamic input onto LA INs (Bauer and LeDoux, 2004; Mahanty and Sah, 1998). Third, GABAergic intercalated cells have been suggested to be essential for extinction (Amano et al., 2010). These neurons receive excitatory inputs that exhibit both NMDA receptor-dependent LTP and LTD (Royer and Paré, 2002). Fourth, heterosynaptic LTP at IN-PN synapses mediated by retrograde release of nitric oxide has been reported (Lange et al., 2012).

Overall, potentiation of inhibitory neurotransmission, and not depotentiation of synapses that have undergone LTP during fear conditioning, is an attractive cellular mechanism supporting the notion that extinction does not erase the conditioning memory, but promotes a parallel memory that dampens the expression of the original fear memory (Bouton et al., 2006; Maren, 2011). However, the identity of the GABAergic neuron types involved in this process, in addition to intercalated cells, remains to be ascertained.

Notably, fear extinction involves a marked change in the responsiveness of BLA neurons to the CS (Herry et al., 2008; Senn et al., 2014). Specifically, fear neurons acquire excitatory responses to the CS after conditioning, but lose them with extinction training (Herry et al., 2008). "Extinction-resistant neurons" remain CS responsive even after extinction, whereas extinction neurons acquire CS responsiveness with extinction (Herry et al., 2008). Interestingly, fear and extinction neurons modulate the expression and the extinction of fear memories via complementary projections to the prelimbic and infralimbic regions of the mPFC (Senn et al., 2014). While synaptic plasticity is likely to contribute to these rearrangements, its involvement has not been directly demonstrated. Besides changes in synaptic plasticity and CS responses, a study showed that extinction is associated with remodeling of GABAergic synapses of two interneuron populations (Trouche et al., 2013).

Network oscillations have also been suggested to be involved in fear extinction (Pape and Paré, 2010). Theta synchrony between CA1 hippocampus and LA decreases during fear memory extinction (Lesting et al., 2011). Additionally, fear memory extinction is characterized by theta directionality from the mPFC to the LA (Lesting et al., 2013). Finally, BLA gamma power increases with extinction and BLA gamma oscillations couple to mPFC theta (Stujenske et al., 2014), strengthening the theory that a stronger input from the mPFC to the BLA signals extinction and, more in general, safety. We speculate that synaptic plasticity at the mPFC glutamatergic pathway to BLA neurons is involved in this directional theta signal from the mPFC. However, current synaptic evidence is counterintuitive because fear extinction does not increase, but instead decreases synaptic drive from mPFC pyramidal cells to BLA PNs (Cho et al., 2013).

In summary, both long-term synaptic plasticity and network oscillations are involved in fear memory extinction, likely via multiple mechanisms involving several pathways and GABAergic cell types. In the future, optical activation of specific pathways, particularly the mPFC-BLA projection, could draw a link between synaptic plasticity, mPFC-BLA oscillations, and the extinction of aversive memories.

Bridging Synaptic Plasticity, Engram, and Oscillations in the Amygdala

In summary, acquisition of an emotional memory forms an engram of neurons in the BLA, likely by inducing LTP at pathways relaying associative cues (auditory thalamus and cortex for an auditory CS and potentially the hippocampus for a context) to BLA PNs. The selection of the engram and the induction of LTP are critically regulated by the excitability of BLA PNs. Excitability is controlled by several factors including GABAergic interneuron activity, strength of local excitatory connections, release of neuromodulators, and intrinsic cell membrane properties. Retrieval of emotional memories occurs, at least in part, via reactivation of the engram formed during acquisition and stabilized during consolidation via protein synthesis and, potentially, oscillatory mechanisms occurring during slow-wave and REM sleep. For fear memories, slow theta synchronization between the BLA, the mPFC, and CA1 hippocampus is involved in the retrieval to drive defense responses. For appetitive memories, gamma synchrony between the BLA, the striatum, and rhinal cortices appears to be important (Figure 1). Finally, the extinction of fear memories involves changes in plasticity at multiple pathways

and remodeling of IN-PN connections. At the network level, extinction reduces CA1-BLA theta synchrony, but increases mPFC to BLA theta directionality.

On balance, evidence suggests that engram formation and LTP are directly linked phenomena for the storage of associative memories in amygdala circuits. Specifically, LTP induction is the mechanism (or one of the mechanisms) that generates engram cells (Ryan et al., 2015). This is corroborated by experiments showing that expression of immediate-early genes such as CREB and Zif268 occurs in cells that have undergone LTP (Minatohara et al., 2016). Although the role of c-Fos in synaptic plasticity remains unclear, engram cells tagged with the c-Fos promoter in the dentate gyrus display stronger synaptic potentials evoked by stimulation of the entorhinal cortex (as well as higher AMPA/NMDA ratio) compared to non-tagged cells (Ryan et al., 2015).

A crucial question in neuroscience is whether the brain encodes sensory information using a rate code or a spike temporal code (Brette, 2015). In other words, does the spike timing matter or the vast majority of computation can be performed using the firing rates with which individual neurons respond to a particular stimulus? In the amygdala, initial studies focused on the rate coding properties of BLA neurons (e.g., changes in firing rates and synaptic weights in response to an auditory CS: Quirk et al., 1995; Tye et al., 2008). However, recent work suggests that the BLA can also encode information via temporal coding, particularly via long-range synchrony (e.g., Popescu et al., 2009; Seidenbecher et al., 2003) or via the timing of spikes with respect of an ongoing oscillation (e.g., Karalis et al., 2016; Popescu et al., 2009; Stujenske et al., 2014).

So far, these two computational aspects have been examined independently. However, dissecting the relation between synaptic plasticity (influencing rate coding) and network oscillations (influencing temporal coding) in the BLA is essential to understand the mechanisms of emotional memory formation and storage. An outstanding question is whether the induction of synaptic plasticity is shaped by network oscillations and synchrony, or, by contrast, long-range synchrony between the BLA and interconnected areas (namely mPFC and hippocampus) is a result of LTP induction across these structures.

It is important to acknowledge that network oscillations in the amygdala have been mostly examined together with rhythms detected in the mPFC or the hippocampus. In contrast, most of the synaptic plasticity data at amygdala synapses resulted from the activation of intra-amygdaloid circuits or from the stimulation of thalamic or cortical afferents. This discrepancy in anatomical areas further complicates the attempts to bridge network oscillations and synaptic plasticity in amygdala circuits. Short-term or long-term synaptic plasticity can be induced at hippocampal (Bazelot et al., 2015; Maren and Fanselow, 1995) and mPFC synapses (Cho et al., 2013). Additionally, a recent study has shown that the auditory cortex also undergoes theta synchronization with the BLA (Cambiaghi et al., 2016). Further investigation of the auditory pathways from an oscillation perspective, as well as of the mPFC and CA1 pathways from the plasticity perspective, could provide unprecedented knowledge on how BLA circuits store and retrieve information.

Theta oscillations have been linked with plasticity induction in the hippocampus. Electrical tetanic stimulation induces LTP in the hippocampus when delivered at the peak of theta, but LTD when delivered at the trough of theta (Hölscher et al., 1997; Huerta and Lisman, 1996; Pavlides et al., 1988). In line with this, optogenetic stimulation of PV+ cells in dCA1 enhances encoding when delivered at the peak of theta and retrieval when delivered at the trough (Siegle and Wilson, 2014). In the BLA, Bazelot et al. (2015) demonstrated that a theta frequency input from ventral CA1 pyramidal cells depresses feedforward inhibition onto PNs via activation of presynaptic $GABA_B$ receptors located on the axon terminals of INs. Notably, this depression of feedforward inhibition favors the induction of LTP at another theta rhythmic excitatory pathway, namely the projection from LA PNs.

Yet, it is important to consider that the slow frequency of theta oscillations might not be able to recruit known Hebbian plasticity. Additionally, the power of slow theta/4 Hz oscillations is low during fear memory acquisition, when LTP is induced in the BLA (Seidenbecher et al., 2003). Thus, 4 Hz oscillations could be crucial for retrieval by organizing mPFC, BLA, and hippocampal cells into cell assemblies (Dejean et al., 2016) and therefore by transmitting information to downstream cells in the fear circuit with high fidelity.

In contrast, gamma oscillations are more easily linkable to synaptic plasticity because a gamma cycle matches several biophysical factors regulating excitatory input integration in BLA PNs: (1) the time constant of $GABA_A$ receptor-mediated IPSPs and AMPA-receptor-mediated EPSPs (Johnston and Wu, 1995), (2) the membrane time constant of PNs (Faber et al., 2001), and (3) the time window for the induction of spike-timing-dependent plasticity (STDP; Magee and Johnston, 1997; Markram et al., 1997). Consistent with this view, synapses of the rodent visual cortex display LTP when EPSPs coincide with the peaks of the gamma oscillations, but exhibited LTD when EPSPs coincided with the troughs (Wespatat et al., 2004). Moreover, in the rodent auditory cortex, the power of CS-induced gamma oscillations predicted the acquisition of an auditory fear memory (Headley and Weinberger, 2011).

Gamma oscillations can modulate the firing of BLA neurons (Popescu et al., 2009; Stujenske et al., 2014). Consequently, gamma synchrony between the BLA and interconnected structures could coordinate pre- and postsynaptic spiking and induction of STDP. This could underlie the formation of neuronal ensembles encoding emotionally salient cues. Ultimately, recruitment of ensembles of BLA PNs within a gamma cycle could increase the chances of discharging postsynaptic neurons via EPSP summation (Harris et al., 2003).

Instead, slow theta/4 Hz synchronization between the BLA, the mPFC, and CA1 hippocampus, which is known to occur during successful fear discrimination and freezing behavior, could be the effect and not the cause of synaptic strengthening across these regions. Learning of an emotionally relevant experience has been shown to generate engrams in various brain regions (Tonegawa et al., 2015). Additionally, a recent study has shown that engram cells display high functional connectivity across regions (Ryan et al., 2015). Thus, we speculate that synchronous activity of strongly interconnected mPFC-BLA-ventral CA1 engrams could contribute, at least partially, to enhanced network synchronization across these areas (Figure 3).

Recent methods enabling the genetic tagging of engram cells could resolve these important questions. Tagging of neurons

using transcription factors such as c-Fos and CREB could be an effective strategy to unravel the link between network oscillations and plasticity in the BLA. For example, optogenetic tagging of BLA neurons in which emotional memory acquisition induces c-Fos expression could be combined with LFP recordings to examine the modulation of engram cell firing by local or distant oscillations. In addition, optogenetic manipulation of BLA, mPFC, and CA1 engram cells could clarify (1) whether these neurons are preferentially connected via synaptic strengthening and (2) whether these neurons are sufficient and necessary for network synchronization across mPFC-BLA-CA1 axis.

Finally, neuromodulators such as noradrenaline, dopamine, acetylcholine, and serotonin could provide another key to disentangle the relationship between oscillations, synaptic plasticity, and emotional learning and memory. These neurotransmitters have been shown to control the power and synchrony of various brain rhythms (Benchenane et al., 2010; Kocsis et al., 2007; Sörman et al., 2011; Vandecasteele et al., 2014) and in the case of dopamine, the formation and reactivation of cell assemblies (Benchenane et al., 2011; McNamara et al., 2014). Release of these neuromodulators in the BLA has been shown to facilitate the induction of synaptic plasticity (Bissière et al., 2003; Chen et al., 2003; Jiang et al., 2016; Tully et al., 2007) and to be crucial for fear learning (Fadok et al., 2009; Hu et al., 2007; Jiang et al., 2016; Johnson et al., 2015).

In conclusion, understanding the relationship between synaptic plasticity and network oscillations in BLA circuits and uncovering how these phenomena lead to the formation of engrams represent an important goal to enable a deeper understanding of emotional memory formation.

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