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Dynamic memory enqrams: Unveiling the celular mechanisms of memory encoding, consolidation, generalizaton, and updating in the brain

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One of the fundamental questions of neuroscience is how the brain can store, generalize, and update memories. Memories are believed to be stored through biophysical and molecular changes in neuronal ensembles called engrams, which are distributed across different brain regions. The dynamic changes that occur in engram cells during the encoding, consolidation, generalization, and updating of memory are still not fully understood. However, recent advancements in techniques for labeling and manipulating neural activity have allowed for investigation of the dynamic changes of memory engrams across different memory processes. Understanding engram dynamics may inform interventions for posttraumatic stress disorder and memory disorders. In this review, we summarize the recent progress in dynamic memory engrams across memory encoding, consolidation, generalization, and updating, shedding new light on the mechanisms underlying engram formation and maturation.

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Introduction

One of the fundamental questions of neuroscience is how the brain can store, generalize, and update memories. The search for the mechanistic substrates of memory, what Richard Semon called the "engram" has continued into the present day. Hebb pioneered the idea of neuronal ensembles, which is small populations of sparsely distributed neurons, are active in response to a specific salient stimulus and the synaptic connections between them are strengthened. The explosion of research that is beginning to uncover the dynamic cellular and molecular mechanisms by which memories are encoded, consolidated, and updated. Recent advancements in techniques for labeling and manipulating neural activity have facilitated the study of engram cells throughout memory acquisition, retrieval, generalization, and updating.

Engram Storage of Memory

Memory is a vital cognitive function, allowing organisms to encode, store, and retrieve information. The concept of memory engrams, discrete physical traces that represent stored memories in the brain, dates back to early theoretical models but has recently gained empirical traction with modern neurobiological techniques. Recent advances in memory engram technology, combining immediate early gene (IEG)-based tagging and optogenetic manipulation, have enabled the identification and control of neuronal ensembles encoding specific memories. Studies by Mayford and Tonegawa demonstrated that reactivating tagged engram cells can induce memory retrieval, even in novel contexts, while inhibiting these cells impairs recall. These findings confirm that engrams are sparsely distributed, functionally linked neuronal populations that undergo enduring changes during learning and reactivate during retrieval. Engram formation is driven by intrinsic excitability and CREB-mediated transcriptional regulation, with hyperexcitable neurons preferentially recruited into memory-encoding ensembles. During consolidation, synaptic stabilization and systems-level reorganization transition memories from hippocampal to cortical storage, enabling long-term persistence. Retrieval involves the reactivation of original encoding ensembles, with artificial stimulation of engram cells bypassing natural cues to induce memory recall. Collectively, these insights reveal engrams as dynamic, distributed networks that encode, consolidate, and retrieve memories through coordinated neural activity. This framework not only advances our understanding of memory mechanisms but also holds promise for addressing memory-related disorders.

Defining the Engram: From Theoretical Abstraction to Biological Reality

The term engram raised by Richard Semon in 1904 as the "mnemic trace" encoding memory which has evolved from a philosophical construct into a cornerstone of modern neuroscience (1, 2). Despite its conceptual simplicity, defining the engram with biological precision remains a challenge, requiring integration across molecular, cellular, and systems-level perspectives. Semon's original formulation posited the engram as a latent neural modification persisting after learning, capable of being reactivated to reproduce conscious memory. However, early 20th-century neuroscience lacked tools to empirically validate this idea. Karl Lashley, a geneticist turned psychologist tried to find an engram but failed. In his experiments, he trained the rat to learned maze memory task by giving the reward. However, the size, but not the location, of lesion in cortex correlated with the memory deficits (3). After more than 30 years of searching, Lashley concluded that memory is not localized to a particular brain area (4).

As the next leap of engram, Hebb raised a concept that "neurons that fire together, wire together" (5, 6). It was hypothesized by Hebb that a cell assembly is formed through reciprocal connections between cells that are simultaneously active during an experience. Furthermore, reactivation of a subset of these assembly cells was proposed to trigger the reactivation of the entire assembly.

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Despite these scientists have defined and described the engram, there remains a paucity of studies investigating its biological basis. The growing interest in engram research has been significantly driven by innovations in memory engram technology, which facilitates the identification and controlled modulation of neuronal ensembles encoding specific memories. This methodology integrates IEG-based cellular identification with optogenetic control mechanisms. Neuronal activation during memory retrieval is visualized through IEG immunohistochemical markers, while cells engaged during initial encoding are selectively tagged via temporally regulated IEG promoters that induce stable fluorescent reporter expression. A brain region (or global network) is considered to harbor an engram when the overlap between training-activated (tagged) and retrieval-activated (IEG-expressing) neurons exceeds stochastic expectations. Mayford and colleagues targeted amygdala neurons activated during auditory fear conditioning—a behavioral paradigm where a neutral auditory cue (conditioned stimulus, CS) becomes associated with an aversive footshock (unconditioned stimulus, US) (7). Posttraining re-exposure to either the CS or context elicits freezing behavior in rodents, reflecting robust associative memory. Their experimental design involved reintroducing mice to the conditioning context 3 days posttraining, with zif268 immunohistochemistry identifying retrieval-activated neurons. Strikingly, the observed overlap between tagged (training-active) and zif268+ (retrieval-active) neuronal populations in the amygdala nucleus surpassed chance levels, with ~11% of sampled neurons exhibiting dual activation—a finding consistent with the existence of an engram supporting this conditioned fear memory. Comparable findings have been replicated across diverse neuroanatomical regions—such as the dorsal hippocampus (8–12), amygdala (7, 9, 11, 13–15), and cortical areas (9, 14, 16, 17)—using varied activity-dependent labeling techniques in multiple memory paradigms. Collectively, these investigations corroborate the widespread existence of engram-associated neuronal ensembles. Nevertheless, functional validation remains critical to confirm whether reactivated candidate engram cells genuinely constitute the neural substrate of experiential memory.

Tonegawa and colleagues provide the first causal evidence through a gain-of-function approach, tagging dentate gyrus (DG) neurons activated during contextual fear conditioning (pairing a specific environment with footshock) to express the light-sensitive cation channel channelrhodopsin-2 (ChR2) via activity-dependent promoters (7, 18). In a novel, nonconditioned context where mice exhibited no spontaneous freezing, optogenetic stimulation of these labeled DG neurons elicited robust freezing behavior—the learned adaptive response (10)—despite the absence of prior aversive experiences in this setting. Crucially, this effect was memory-specific: photoactivation failed to induce freezing when downstream CA1 neurons were silenced during initial training, thereby blocking memory formation (19). Subsequent studies employing optogenetic or chemogenetic activation protocols demonstrated that in the absence of natural sensory cues, targeted reactivation of engram cells in various brain regions reliably evokes memory-associated behaviors across multiple tasks (20–25). These findings align with Semon's concept of ecphory—the process by which latent engrams transition to active memory states. Complementing these gain-of-function results, loss-of-function experiments reveal that subsequent ablation or inhibition of engram neurons consistently impairs memory retrieval, further solidifying their necessity in mnemonic processes.

Together, engrams are sparsely distributed populations of neurons that undergo enduring physical or chemical changes during learning from different levels, thereby storing specific memory information (Figure 1). Following memory consolidation, these cells are functionally linked through strengthened synaptic connections and reactivate during memory retrieval. Critically, engram cells are not confined to a single brain region but form interconnected engram complexes across the hippocampus, amygdala, prefrontal cortex, and other circuits, depending on memory type (e.g., episodic, emotional, or procedural).

Engram in Memory Encoding

The engram represents enduring neurobiological modifications induced by learning experiences, which subsequently enable the retrieval of corresponding memories. Engram neurons are operationally defined as cellular subpopulations selectively engaged in the encoding, consolidation, and retrieval of specific mnemonic information.

A central question in memory research concerns the mechanisms underlying selective neuronal recruitment during encoding. Emerging evidence implicates cell-autonomous properties, particularly intrinsic excitability (the propensity of neurons to generate action potentials in response to synaptic input), as a critical determinant of engram allocation. Neurons with elevated baseline excitability exhibit preferential activation during learning and are disproportionately incorporated into memory-encoding ensembles (26–28). This excitability bias aligns with observations that neurons overexpressing CREB—a transcriptional regulator known to enhance both intrinsic excitability (29–31) and dendritic spine density (30, 32)—are selectively recruited into engrams, whereas CREB-deficient neurons are excluded from encoding processes (33–35). Notably, transient CREB upregulation immediately prior to learning enhances memory formation, demonstrating its capacity to regulate mnemonic allocation on behaviorally relevant timescales (35).

The prevailing model posits that CREB-driven engram recruitment operates via excitability modulation. Empirical support for this mechanism includes: Excitability Suppression: Pharmacogenetic inhibition of CREB-overexpressing neurons abolishes their preferential engram integration. Excitability Enhancement: Artificially increasing neuronal excitability (independent of CREB manipulation) promotes engram membership. These findings establish a direct causal link between cellular excitability states and competitive engram allocation during memory encoding. While traditional models posit memory storage at the level of individual neurons, contemporary frameworks emphasize encoding through neuronal ensembles—functionally coordinated cell assemblies that exhibit stimulus-, task-, or state-dependent synchronous activity. A critical unresolved question centers on whether these ensembles merely aggregate independent neurons or emerge from specialized intercellular relationships. Holographic optogenetic techniques, particularly two-photon precision stimulation, have provided mechanistic insights into this issue (36, 37). Repeated photostimulation of defined neuronal groups enhances their spontaneous coactivation probability, even in the absence of external cues—a hallmark of ensemble formation (37). Strikingly, such assemblies self-organize through cell-autonomous mechanisms: unexpected strong and persistent increased intrinsic excitability within stimulated neurons showing their correlated activity, with an initial depression followed by a potentiation after a recovery period in presynaptic plasticity (38). These observations align with theoretical models proposing that memory encoding involves the preferential recruitment of hyperexcitable neurons into temporally coordinated activity patterns (39). Collectively, these findings challenge synaptic plasticity-centric paradigms, suggesting intrinsic excitability states—rather than synaptic rewiring—serve as primary drivers of ensemble-level memory representation.

Engram in Memory Consolidation

Newly acquired memories are initially sustained by transient, experience-dependent neuronal activation (26, 38, 40–43). However, such memories remain labile and prone to rapid decay unless stabilized through subsequent molecular processes. The conversion of transient memory traces into enduring forms necessitates transcriptional activation and de novo protein synthesis. These molecular cascades drive synaptic stabilization, characterized by strengthened connectivity among coactivated neuronal ensembles engaged during encoding (44, 45). Crucially, interventions disrupting these molecular pathways—termed synaptic consolidation—abrogate long-term memory persistence. Pharmacological or genetic disruption of these pathways blocks the transition to long-term memory storage (29, 46). For instance, inhibition of CREB-mediated transcriptional activation—a key regulator of synaptic plasticity—impairs mnemonic persistence (30, 45). Similarly, postlearning administration of protein synthesis antagonists abolishes long-term memory formation (44, 45). Thus, synaptic stabilization constitutes a pivotal bottleneck: memories undergoing this process attain persistence and future retrievability, whereas unstabilized traces are subject to decay.

Long-term hippocampal memory formation is enhanced through repeated behavioral or internal reactivation of the learning event.

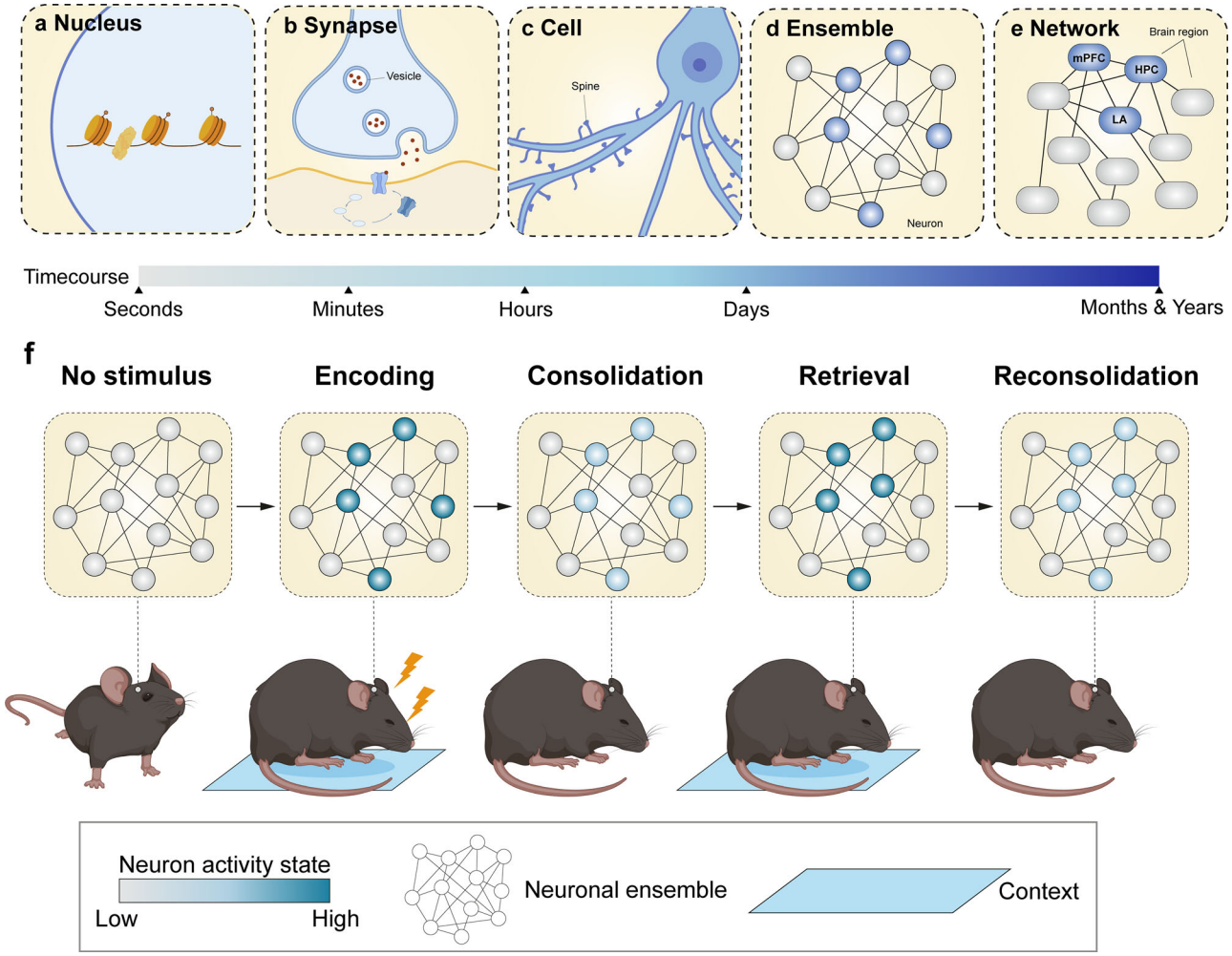

Figure 1. Hierarchical organization and dynamic states of fear engrams. (A–E) Multiscale engram representations: (A) Nuclear level of epigenetic/transcriptional remodeling; (B) Synaptic level change of neurotransmitter release; (C) Cell level of neuronal connectivity reconfiguration and plasticity change; (D) Regional ensemble coactivation; (E) Network-level engagement (blue = learning activation); (F) Mnemonic state transitions: Engrams (highlighted in dark blue) emerge through activity-dependent synchronization of neuronal ensembles during contextual fear memory acquisition (encoding). During subsequent consolidation processes, these engrams undergo gradual transition into a dormant state characterized by stabilized synaptic connectivity. Notably, memory retrieval triggers transient reactivation of consolidated engrams, temporarily destabilizing their established neural activity patterns while simultaneously manifesting as context-specific freezing behavior. Crucially, this reactivation phase initiates reconsolidation mechanisms that restabilize modified engram configurations, ultimately restoring them to a quiescent storage state with updated mnemonic information. HPC, hippocampus; LA, lateral amygdala; mPFC, medial prefrontal cortex.

Notably, such reactivation occurs not only during active engagement but also during offline states (e.g., sleep or quiet wakefulness), where spontaneous replay of activity patterns emerges among recently activated hippocampal neurons. These replay events are temporally coupled to sharp-wave ripples (SWRs)—high-frequency network oscillations—and critically facilitate memory stabilization. Experimental interventions demonstrate that optogenetic reactivation of lateral amygdala engram cells during fear conditioning consolidation enhances subsequent memory robustness (24), with analogous findings observed in the retrosplenial cortex (47). Furthermore, fear memory engram neurons exhibit sleep-preferential reactivation, and suppressing their activity during sleep (but not wakefulness) abolishes consolidation (48–50), underscoring the role of endogenous replay in memory reinforcement.

Following initial synaptic stabilization, memories undergo system consolidation, transitioning from hippocampal dependence to medial prefrontal cortex (mPFC)-dependent storage over days to years. This process, termed systems consolidation, allows coexistence of hippocampal and mPFC engrams representing the same experience (51, 52). However, memory phenomenology diverges based on activated ensembles: hippocampal engrams retain episodic, context-specific details, whereas mPFC ensembles encode schematic, generalized representations post-consolidation (52–56). Mechanistically, mPFC-dependent consolidation unfolds over weeks, marked by delayed structural plasticity: dendritic spine density increases and strengthened engram-to-engram connectivity emerge weeks postencoding (11, 57). A prevailing model posits that hippocampal indexing—where hippocampal SWRs reactivate neocortical activity patterns from initial encoding—drives mPFC maturation (36, 58). According to this framework, repeated hippocampal-mPFC replay during sleep promotes neocortical stabilization, ultimately enabling hippocampus-independent recall. Disrupting hippocampal engram activity during this critical window prevents mPFC plasticity (e.g., spine remodeling, synaptic strengthening) and retrieval-related reactivation (11, 57, 59, 60), validating the hippocampus's instructive role in systems consolidation.

Engram in Memory Retrieval

Once an engram has been consolidated and stored, it can be activated to induce memory retrieval. Consolidated engrams mediate memory

retrieval, a process governed by the similarity between retrieval cues and the original encoding context. Successful retrieval recapitulates neural activity patterns present during encoding. Seminal studies employing Arc RNA catFISH revealed that contextual memory retrieval preferentially reactivates hippocampal CA1 neurons active during initial encoding (61). Subsequent work in TetTag mice demonstrated that fear memory retrieval reactivates basolateral amygdala (BLA) engram cells, with reactivation rates predicting memory strength (7). These findings established that retrieval engages original encoding ensembles—a principle replicated across diverse paradigms and brain regions (12, 57, 62).

Crucially, engram neurons are necessary for retrieval. Pretraining amplification of excitability in select lateral amygdala or hippocampal neurons enables memory allocation to these cells. Their targeted ablation (34) or inhibition (63–65) disrupts specific memory retrieval without impairing new learning, a phenomenon generalizable across DG, CA1, insular cortex, nucleus accumbens, and mPFC (8, 11, 16, 33, 66). Artificial engram reactivation bypasses natural cues to induce memory retrieval (10, 19, 67–69). Multiregional co-activation enhances retrieval efficacy compared to single-region stimulation (69), replicating across fear conditioning, place preference, and social memory tasks (6, 22, 36, 70, 71). Retrieval itself transiently boosts engram excitability via Kir2.1 channel modulation, improving behavioral discrimination and pattern separation (72). Notably, minimal stimulation suffices: activating two visual cortex engram neurons drives ensemble-wide pattern completion and memory retrieval (37). Hippocampal engram stimulation further recruits downstream amygdala and cortical ensembles (59, 73), illustrating system-level coordination. This capacity for activity pattern completion from sparse inputs underlies artificial engram-driven retrieval.

Engram and Memory Generalization

Fear overgeneralization represents a maladaptive behavioral response to nonthreatening stimuli or neutral environments. This phenomenon, a hallmark feature of anxiety spectrum disorders such as generalized anxiety disorder, panic disorder, and posttraumatic stress disorder (PTSD) (74, 75), demonstrates significant clinical relevance. This section synthesizes current understanding of hippocampal and extrahippocampal engram contributions to fear generalization, with particular emphasis on neural circuit mechanisms driving this pathological memory process.

Hippocampal Engrams and Fear Generalization

Engram cells within the dorsal dentate gyrus (dDG) critically support memory precision through pattern separation—a computational process essential for discriminative memory retrieval (76, 77). The temporal degradation of memory specificity correlates with dynamic hippocampal-cortical network reorganization during systems consolidation (78). Hippocampus plays an important role in maintaining the specificity of memories over time through the hippocampal–cortical interactions that underlie memory consolidation (79, 80). Recent mechanistic studies reveal DG circuit regulation of memory precision: (1) DG-CA3 connectivity via stratum lucidum inhibitory interneurons (SLINs) modulates recent memory specificity (81); (2) Mossy fiber terminal filopodia contacting SLINs mediate feedforward CA3 inhibition (82, 83); (3) DG-driven inhibitory control shapes CA3 activation patterns and memory precision (81, 84). Notably, the actin-binding protein ABLIM3 emerges as a learning-sensitive regulator of DG-SLIN connectivity. ABLIM3 downregulation enhances context-specific engram reactivation in hippocampal-cortical networks while reducing remote fear generalization (85), positioning it as a molecular brake on memory specificity.

Neuronal competition analyses demonstrate that generalized fear expression in novel contexts arises from fear engram dominance over non-engram dDG populations. Complementary findings reveal ventral DG mossy cell (vMC) suppression correlates with context-generalized fear, while vMC-dDG pathway activation selectively attenuates generalized fear responses without affecting conditioned fear (86).

Stress constitutes a homeostatic challenge critically involved in PTSD pathogenesis and fear memory generalization (87). Stress exposure during memory encoding/processing induces maladaptive fear generalization characterized by context-inappropriate memory expression (88). Stressors activate the hypothalamic-pituitary-adrenal axis, triggering adrenal glucocorticoid release that potentiates memory generalization (89, 90). Engram formation follows sparse encoding principles, preferentially recruiting hyperexcitable principal neurons while suppressing incorporation of less responsive cells (65, 91). Through activity-dependent TetTag labeling of footshock-activated ventral CA1 neurons, researchers demonstrated that chronic aversive engram activation drives fear generalization, directly linking stress exposure to maladaptive memory expression (92). Postconditioning glucocorticoid elevation induces contextual fear generalization, correlating with enhanced excitability and expansion of DG engram populations. Notably, chemogenetic silencing of these activated DG engrams blocks stress hormone–mediated generalization (93). Engram expansion occurs through training-phase disruption of inhibitory networks, particularly parvalbumin-positive (PV^+) interneurons (94). Targeted PV^+ interneuron suppression in dorsal CA1 during threat conditioning produces hyperdense engrams and generalized fear memories (95). These findings support a mechanistic framework where stress-induced PV^+ dysregulation alters engram/non-engram competitive dynamics, potentially enabling context-independent fear retrieval.

Engrams in Other Brain Areas and Memory Generalization

Emerging evidence suggests that stress-mediated corticosterone signaling enhances fear engram ensemble density within the lateral amygdala, thereby promoting fear generalization (96). Mechanistic investigations revealed that pharmacological interventions targeting glucocorticoid receptors (antagonists) and endocannabinoid systems (synthesis inhibitors), combined with neuromodulatory approaches enhancing PV^+ neuronal activity or suppressing cannabinoid receptor expression in lateral amygdala PV^+ neurons, effectively restored threat memory specificity and normalized engram sparsity in stressed mice. These findings establish a critical retrograde signaling mechanism through which endocannabinoids modulate PV^+ interneuron activity to mediate stress-induced memory generalization (96).

Current theoretical frameworks propose three potential mechanisms for memory generalization: (1) encoding-phase modifications, (2) retrieval-phase manifestations, and (3) temporally dynamic recruitment of distinct neural networks (97, 98). Recent advances in neuronal tagging technology, particularly the scFLARE2 system (single-chain fast light- and activity-regulated expression 2), have enabled precise temporal tracking of amygdala neuronal ensembles during threat conditioning. These studies demonstrate that temporally proximate threat experiences become neurobiologically linked through coallocation to overlapping engram ensembles, establishing this as a fundamental mechanism of memory generalization (99).

The neural substrates of memory generalization extend beyond canonical hippocampal-amygdala circuits. The retrosplenial cortex (RSC) demonstrates multimodal involvement in cognitive processes ranging from spatial navigation (58) to prospective cognition (100) and contextual memory retrieval (101). Postacquisition reactivation of memory engrams facilitates neocortical ensemble maturation through activity-dependent synaptic plasticity, a critical process in systems consolidation (11). Notably, high-frequency stimulation of RSC engrams 24 hours postlearning induces fear generalization and shifts recent memory retrieval dominance to the anterior cingulate cortex (ACC), bypassing hippocampal involvement (47). This neural reorganization exhibits state-dependent specificity, occurring exclusively during offline brain states (sleep/anesthesia) rather than active wakefulness (47). Complementary findings reveal regulatory mechanisms in prefrontal circuitry. Chemogenetic silencing of infralimbic (IL) cortical ensembles established during learning exacerbates generalization, whereas their activation enhances memory specificity, indicating IL-mediated inhibitory control over fear generalization (102). Furthermore, molecular investigations identify insulin-like growth factor 2 receptors (IGF-2R) in auditory cortex layer 2/3 as critical modulators of engram precision. Reduced IGF-2R expression correlates with fear generalization, while exogenous IGF-2 administration directly into auditory cortex preserves remote fear memory specificity, suggesting IGF-2 signaling maintains engram fidelity over time (103).

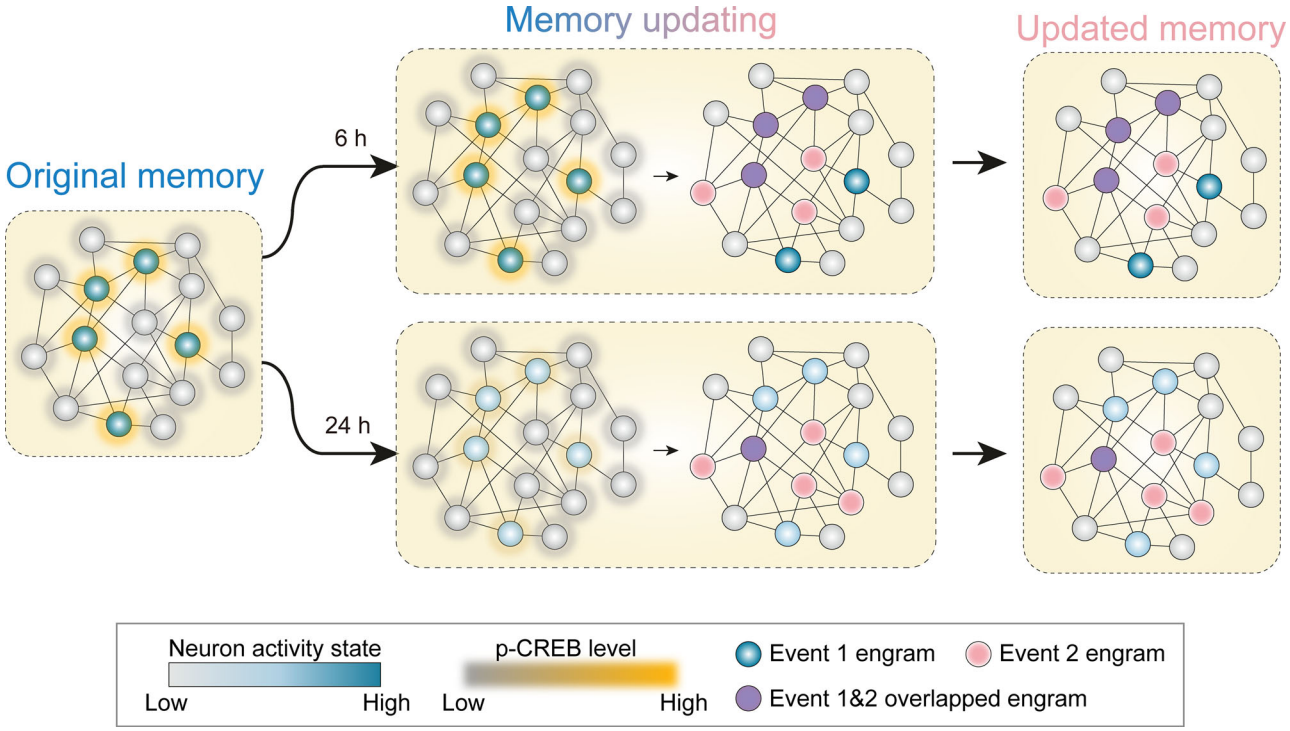

Figure 2. Engram competition in memory updating. During memory consolidation processes, engrams initially encoded by event 1 (blue) maintain a state of heightened excitability and p-CREB level relative to adjacent neuronal populations for ~6 h postencoding. When a similar event 2 (pink) occurs within this temporal window, the hyperexcitable event 1 engram neurons demonstrate preferential recruitment during event 2 encoding, resulting in overlapping engram (purple) formation and subsequent memory trace updating from event 1 to event 2. Following extended temporal intervals (24 h), event 1 engrams undergo intrinsic excitability reduction. Subsequent event 2 encoding under these conditions engages a novel population of hyperexcitable neurons achieve preferential recruitment for event 2 engram formation. This temporal-dependent segregation of memory traces enables memory updating.

Engram and Memory Updating

Memory updating is a fundamental process that allows organisms to adapt to new information, modify existing knowledge, and integrate novel experiences with pre-existing memories. Memory linking is one of the most extensively studied examples of memory updating in current research. The neural representation of memories, or engrams, is central to this process. Recent advances in neuroscience have shown that memory engrams are not static but are instead malleable, subject to modification or updating through mechanisms such as reconsolidation, synaptic plasticity, and cellular reorganization. In this section, we summarize the dynamic engram overlap in memory updating and how to switch the valence of engrams.

Engram Overlap in Memory Updating

The hypothesis that overlapping neuronal ensembles mediate memory traces originated from Pavlovian conditioning paradigms, wherein animals learn to link a CS (e.g., tone/light) with an US (e.g., shock/food) to elicit conditioned responses (e.g., freezing) (104). While not strictly reflecting memory linkage, this process necessitates stimulus association (Figure 2).

Early work visualized CS–US convergence using Arc—an IEG dynamically redistributed between nucleus (0–5 min postactivation) and cytoplasm (5–30 min) (61). By temporally separating CS/US presentations by ~25 min, amygdalar neurons coactivated during associative learning were identified (105–107), with their convergence proving essential for taste memory formation (108). However, these static snapshots lacked temporal resolution to resolve ensemble dynamics during association. To address this, subsequent studies employed in vivo real-time calcium imaging in freely behaving mice to record ensemble activity during the presentation of the CS and US, as well as during the following periods. One study demonstrated that the neuronal ensemble in the amygdala responding to the CS changed to resemble that of the US after successful association, suggesting cross-talk between subensembles of the same memory (109). A second study revealed another form of neuronal cross-talk in the hippocampal area CA1 (110). During the presentation of the CS and US, their respective ensembles responded independently to each input. However, after the presentation of both stimuli, a phase of network reverberation occurred, during which the two ensembles exhibited synchronized activity, facilitating the successful CS–US association. This finding indicates that, in addition to cellular overlap, a temporal overlap in the activity of distinct ensembles may also link different aspects of a memory.

Signals related to the CS and US converge on the same neurons within seconds or minutes to generate associations within a single episodic memory. Similarly, studies have demonstrated that different memories, encoded hours apart, may (under specific conditions) be stored within the same neuronal population, facilitating memory linking. One study illustrated how neuronal coallocation, defined as overlap between neuronal ensembles, can naturally link contextual memories encoded in close temporal proximity within the hippocampus (111). In this study, mice exposed to two different contexts within a short temporal window (5 h) showed that the memories of these contexts were linked. Specifically, a foot shock in one chamber caused the mice to freeze significantly in the other chamber. This response was not merely due to generalization, as the mice were able to distinguish between the two linked contexts and a neutral context that had never been associated with the prior two, demonstrating that the memory linkage was specific and the identity of each memory was preserved. Calcium imaging and engram labeling, using genetic and immunohistochemical techniques, revealed a higher degree of overlap between the active ensembles encoding each context when the memories were linked, as compared to when they were separated by a longer temporal window, in which case no linkage occurred. A similar study, using

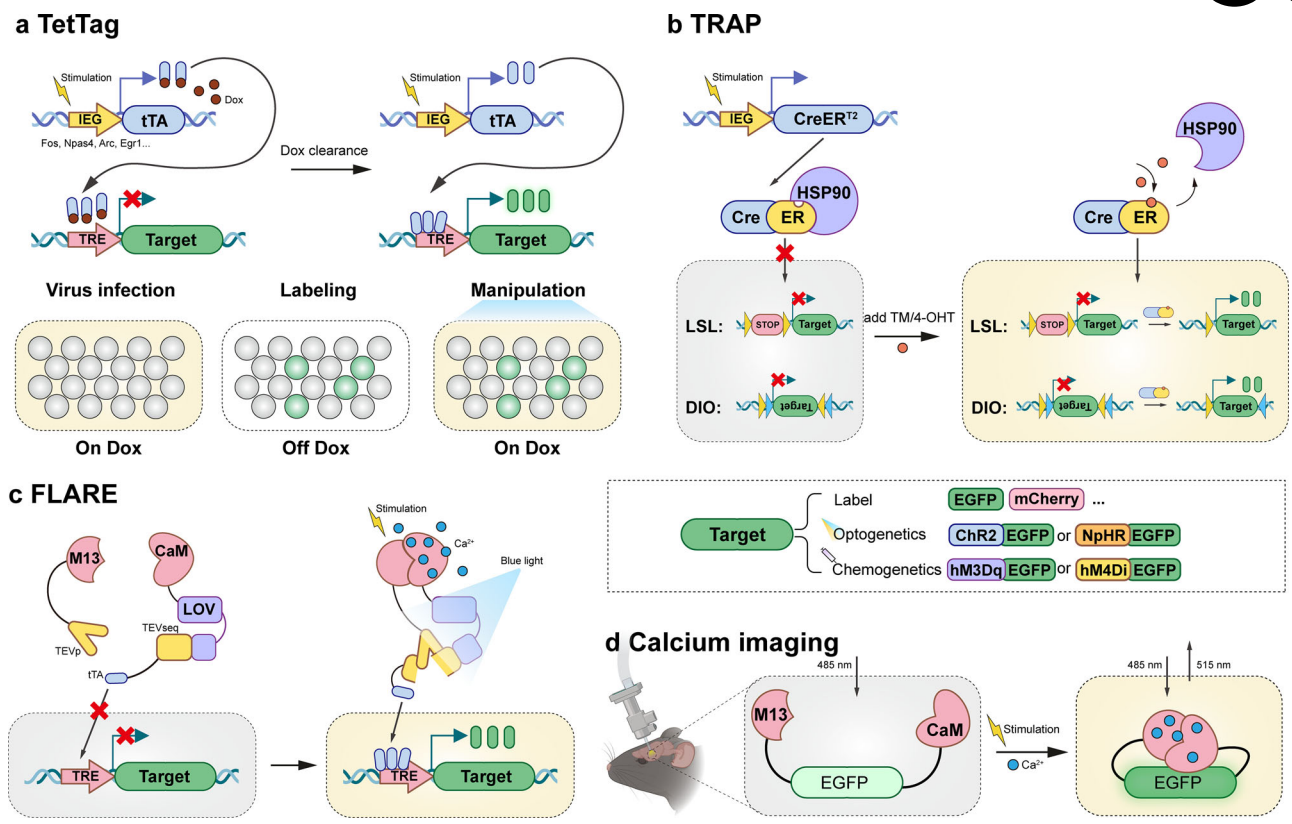

Figure 3. Neuronal activity–dependent tools for labeling, manipulating, and recording neurons. (A–D) Diagram of activity-dependent tools for neuronal labeling and manipulating, TetTag (A); TRAP (targeted recombination in active populations (B); FLARE (Fast Light and Activity-Regulated Expression system) (C); (D) Diagram of GCaMP-based calcium imaging technology.

auditory fear conditioning (AFC) with two separate tones, showed comparable coallocation and memory linking in the mouse amygdala when the tones were presented in close temporal proximity (65). This research further demonstrated that engram overlap and memory linking can also be induced by the mere recall (rather than initial learning) of an event shortly before the encoding of a second memory. In addition to linking memories of the same type, there are also reports of linking between different types of memories. It has been reported that two amygdala-dependent emotional memories—conditioned taste aversion (CTA) and AFC—were linked through repeated coretrieval sessions (112). This linkage was demonstrated by the observation that mice froze (the behavioral response to AFC) upon receiving saccharin, the conditioned taste aversion stimulus. Labeling and optogenetically inhibiting the overlapping ensemble shared between both paradigms preserved both memories but disrupted the link between them. This finding illustrates that memories can be specifically linked without altering the individual memories, providing valuable insights into the content encoded within the overlapping engrams. Memories to be linked across long periods such as days are poorly understood. A recent study found that two memory ensembles separated two days apart is overlapped during the offline period after learning (113), which suggested that offline periods after learning may be important for memory integration as well. In addition, ensembles coreactivation occurs more during wake than during sleep.

Above researches have primarily focused on memory linking through engram manipulation without altering the original memory engrams. While this approach constitutes a form of memory updating, real-world memory updating often involves modifications to memory content—such as the transformation of a positive memory into a negative one. A critical unanswered question remains: does engram overlap occur during such content-modifying memory updating processes? A previous study reported that the original memory engram of fear contributes to remote fear attenuation via high overlap with extinction ensembles which have been reported distinct with fear ensembles in the fear extinction paradigm (114). However, these prior investigations relied on IEG-dependent tagging approaches, which lack the temporal resolution to resolve dynamic engram interactions during active behavioral states. The development and application of genetically encoded calcium indicators (GECIs) have established the monitoring of cytosolic calcium ion concentration dynamics as a prominent methodology for real-time detection of neuronal activity (Figure 3) (115). In addition to monitoring neuronal activity, FLARE, developed from GECI, enables high temporal resolution labeling and manipulation of neurons by using 10 min of blue light stimulation to drive the specific expression of any target protein (116). Nonetheless, due to the inherent limitations of optogenetics, the potential for artificial effects remains an inherent drawback of both optogenetic and chemogenetic approaches. Furthermore, while hippocampal engram overlap has been characterized, the existence and mechanisms of engram overlap in prefrontal circuits remained unexplored. Our lab was the first to identify a high overlap between fear and extinction engrams during a postretrieval paradigm, using in vivo calcium imaging at the single-cell level in the prefrontal cortex (PrL) (23). Fear extinction memory has been previously reported as a newly formed reward memory (23). These findings support the concept of engram overlap in memory updating, suggesting that memory updating is mediated by the rewriting of the original memory trace through significant engram overlap.

Switch of Valence Associated with Engram

Engram overlap has been observed in various memory updating scenarios, and experiments manipulating engrams have shown that the information encoded in the original engram can be either enhanced or attenuated. However, it remains unclear whether the value encoded by the original engram can undergo a revise. The reactivation of engram cells

by natural cue, or optogenetic manipulation could be a prerequisite for memory malleability to integrate the new information outside the original memory trace and orchestrated to constitute an updated memory. It has been reported that the valence associated with the hippocampal DG memory engram could be bidirectionally reversed (22); however, the BLA engrams were not able to reverse the valence of the memory. Consistent with this report, our previous study found that the reactivation of BLA engram cells is not sufficient for the memory valence updating; however, US stimulus, which triggers a more generalized BLA activation, could induce the BLA engram encoding updating (23). While we demonstrated that memory updating is specific to learning-associated memory encoding as the valence of innate fear engrams (shock labeled) was unchanged. In addition, the valence associated with engram in PrL could also be revised by increased overlap with another engram which encode opposite valence (23). Only a part of original engram showed increased activity during memory updating, suggesting that a part of cell activation pattern alteration might be sufficient for switching the function of original engram.

What is the underlying mechanism through which engrams contribute to memory updating? As proposed by Morris and colleagues (117), the modification of synaptic connection patterns, mediated by synaptic plasticity, is the fundamental mechanism by which the brain stores memory. Using synaptic optoprobe techniques, Kasai and colleagues demonstrated that acquired motor learning was disrupted by optical shrinkage of potentiated spines, but this manipulation had no effect on spines activated by a distinct motor task in the same cortical region (118). This suggests that acquired motor memory depends on the formation of a task-specific, dense synaptic ensemble. Furthermore, optogenetic manipulation of synaptic plasticity specific to one memory was shown to affect the recall of only that memory, without altering a linked fear memory encoded in the shared ensemble (25), indicating that synapse-specific connectivity of engram cells preserves the identity and storage of individual memories. Additionally, using the dual-eGRASP (GFP reconstitution across synaptic partners) technique, it was reported that fear conditioning enhanced connectivity and increased spine morphology between engram cells, while extinction weakened the connectivity between these cells. We hypothesize that memory information is stored in the specific pattern of connections among engram cells, and that memory updating may alter the original engram encoding by modifying its connections with other engrams.

Dynamic of Engram Cells Maturation

Memory formation involves experience-responsive neuronal ensembles that constitute both the necessary and sufficient substrate for recall. A fundamental question in neurobiology concerns the temporal progression of engram states following initial encoding. Current models propose that engrams undergo molecular and circuit-level refinement during consolidation, with encoding-activated cells playing essential roles in successful retrieval (6). Notably, prefrontal circuitry demonstrates time-dependent functional specialization in memory processing. Chemogenetic silencing experiments reveal that mPFC engram cells activated during acquisition become indispensable for remote memory recall (typically 2–4 weeks postencoding), yet remain nonessential for recent memory retrieval. Intriguingly, these mPFC ensembles exhibit natural cue-induced reactivation specifically during remote timepoints, suggesting their progressive integration into cortical memory networks (11). Conversely, hippocampal engram cells display inverse temporal dynamics. Calcium imaging studies demonstrate complete absence of natural cue reactivation in CA1 engram populations 15 days postconditioned fear consolidation (CFC) (11, 119). Longitudinal monitoring of synaptic reorganization in hippocampal pyramidal neurons revealed rapid turnover of basal dendritic spines, with learning-associated connectivity patterns dissipating within 15 days postacquisition (11, 119). This synaptic reorganization was corroborated by quantitative analysis demonstrating 38.7% reduction in dendritic spine density within DG engram cells at 14 days post-training (11). These complementary observations collectively demonstrate bidirectional engram state transitions: Cortical engrams transition from latent to functionally dominant states across a ~2-week consolidation window. Hippocampal engrams paradoxically maintain stable synaptic connectivity during recent memory phases but undergo progressive functional silencing (Figure 4).

Transcriptional and Epigenetic Mechanisms Underlying the Dynamic Change in Engrams

Emerging evidence reveals that dynamic transformations in memory engram cells are governed by multifaceted molecular and epigenetic mechanisms. Chromatin plasticity emerges as a critical regulator, with enhanced nuclear flexibility increasing neuronal excitability to prime cellular recruitment into engram networks (120). Longitudinal analyses further demonstrate experience-dependent chromatin reorganization during memory formation and retrieval phases, suggesting structural genomic adaptations underlie engram functionality (121). DNA methylation patterns exhibit spatiotemporal specificity in memory processing. Cortical hypermethylation persists in the mPFC following CFC, with pharmacological inhibition of methyltransferases at remote timepoints impairing retrieval—a mechanistic demonstration of epigenetic maintenance of long-term memories (122). The differential DNA methylation alternations in hippocampus and mPFC at 1 h and 4 weeks after CFC correlates strongly with the dynamic temporal spatial location of associative memory (123), which could alter the expression and splicing of genes involved in functional plasticity and synaptic wiring. Increased DNA 5-hydroxy methylation levels have also been reported in mPFC for remote contextual fear memories (124). Using neuronal activity-dependent promoter to drive de novo DNA methyltransferase 3a2 (Dnmt3a2) overexpression within DG memory engram cells specifically during consolidation was sufficient to strengthen contextual fear memory, which suggests DNA methylation selectively within memory engrams as a mechanism of stabilizing engrams during consolidation that supports successful memory retrieval (125).

Histone modification during learning has also been shown to be important for the memory dynamic. The increases in histone H3 acetylation in the orbitofrontal cortex (OFC) were observed after social transmission of food preference learning, and interference with this cascade during the early postacquisition period could bidirectionally regulate remote memory retrieval (126). Histone H2A.Z, a variant of histone H2A, is actively exchanged in response to fear conditioning in the hippocampus and the mPFC, where it mediates gene expression and restrains the formation of recent and remote memory (127). How does synaptic transmission trigger transcriptional changes in engram cells to contribute to memory consolidation? DG engram neurons exhibit prominent CREB-dependent transcription features which are required for recent CFC memory consolidation (128). CREB-mediated transcription in mPFC engram cells has been reported to be required for remote memory consolidation (129).

Neuronal Excitability and Engram Dynamic

Neuronal excitability is an intrinsic property that determines the threshold for spike generation and regulates signal transmission (130). Studies have shown that neurons with inherently higher excitability during memory encoding are more likely to become part of the engram (28, 64). Patch-clamp recordings have revealed that synapses connecting hippocampal engram cells are selectively strengthened compared to those linking non-engram cells, as evidenced by increased excitatory postsynaptic current amplitude, enhanced spontaneous excitatory postsynaptic current amplitude, and an elevated AMPA-to-NMDA receptor ratio (19). Moreover, DG engram cells exhibit a transient increase in excitability following memory reactivation, a phenomenon mediated by NMDA receptor activation and a subsequent cascade leading to the downregulation of Kir2.1 channels (72). This rapid yet temporary modulation enhances the precision and efficacy of subsequent memory retrieval (72). In the context of social associative olfactory memory, the reorganization of GluN2B-containing NMDA receptors acts as a critical tuning mechanism, determining the fate and malleability of cortical memory engrams (131).

Dynamic maturation of memory engrams also depends on neuronal circuit activity. It has been demonstrated that the maturation of mPFC engram cells requires postlearning input from hippocampal engram cells (11). For example, chronic inhibition of hippocampal DG engram cell output via selective tetanus toxin (TeTX) expression initiated one-day post-training abolished the reactivation of mPFC engram cells during remote

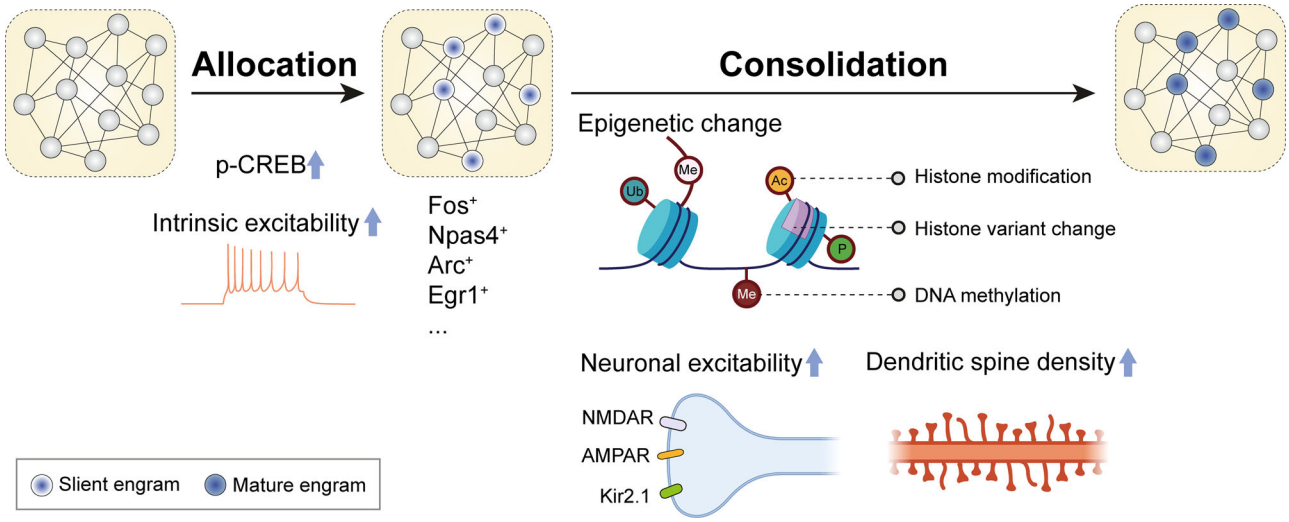

Figure 4. Dynamic mechanisms of engram maturation. During the allocation, engram allocation is primarily governed by enhancements in intrinsic neuronal excitability, driven primarily by increased phosphorylation of CREB, which primes these cells for selective recruitment. Following allocation, engram formation is molecularly marked by the expression of IEGs including Fos, Npas4, Arc, and Egr1. The consolidation phase is characterized by epigenetic reprogramming, such as DNA methylation, histone posttranslational modifications (e.g., acetylation, phosphorylation), and histone variant exchange. Concurrently, neuronal excitability is further modulated through synaptic recruitment of NMDA receptors, AMPA receptors, and inwardly rectifying potassium channels (Kir), while dendritic spine density increases to reinforce synaptic connectivity. Throughout this maturation process, engrams transition from a silent state to a functionally mature configuration, marked by enduring structural and molecular adaptations that support long-term memory storage.

exposure to a conditioned context and prevented the associated increase in dendritic spine density observed in control subjects. Furthermore, pharmacologically silencing hippocampal activity during early phases impaired remote social transmission of food preference (STFP) memory, stored in the OFC, indicating that early hippocampal activity is crucial for the subsequent maturation and stabilization of mnemonic traces (126). Disruption of hippocampal engram activity during recent recall at remote timepoints, or interference with CA1-to-ACC projections postlearning, impairs remote CFC memory, suggesting that functional connectivity between engrams is vital for their maturation during the transition from recent to remote memory (132). Additionally, overexpression of hippocampal Dnmt3a2 promotes the transfer of fear memory traces from the hippocampus to the cortex and facilitates the maturation of mPFC engrams, further supporting the role of DNA methylation–mediated hippocampal activity in cortical memory engram maturation (133). Finally, the consolidation of remote contextual fear memories has been linked to progressive strengthening of excitatory connections between PFC engram neurons active during learning, a plasticity process that is CREB-dependent and relies on sustained hippocampal signals (57).

Dynamic Components of Engrams

Several questions remain regarding the dynamic changes in engram cells. Engram neurons are typically defined as those activated during both memory encoding and retrieval. One common method for identifying activated neurons involves detecting the expression of IEGs such as Fos, Npas4, Arc, and Egr1, which serve as markers of neuronal activity (134). Notably, functional heterogeneity within memory engrams can be delineated by the differential expression of these IEGs. For instance, it has been reported that the Fos ensemble promotes the generalization of contextual fear memory, whereas the Npas4 ensemble is essential for its discrimination (135). Furthermore, developmentally distinct subpopulations of hippocampal neurons are differentially recruited into memory traces over time. Specifically, late-born neurons are preferentially recruited for retrieval shortly after CFC acquisition, while early-born neurons become more prominent at later stages (136). This divergent recruitment underlies the gradual reorganization of memory ensembles, thereby influencing memory persistence and plasticity. Computational models using spiking neural networks have revealed that neurons can both drop out of and join engrams during memory consolidation, with inhibitory synaptic plasticity playing a critical role in refining engram selectivity (137). In addition, long-term potentiation (LTP), an activity-dependent and sustained increase in synaptic strength, is suspected to contribute to engram maturation via LTP-like mechanisms. Notably, inducing optical LTP shortly after fear conditioning has been shown to preferentially enhance memory encoding (42, 138). Moreover, the use of dual-enhanced green fluorescent protein reconstitution across synaptic partners (dual-eGRASP) has allowed researchers to monitor synaptic dynamics, revealing that changes at CA3-to-CA1 engram synapses are key modulators during fear memory states (139, 140). Despite these advances, how functionally distinct memory engrams are defined within a memory trace and how they dynamically evolve during consolidation and updating remain open questions. Numerous studies have demonstrated that reactivation of memory engrams during offline periods following learning is critical for both memory consolidation and updating (113, 141). For example, after a fearful event, memory encoding ensembles are reactivated and strengthened during post-conditioning sleep, and disrupting this engram reactivation during sleep impairs the consolidation of fear memory (49, 142). The intrinsic mechanisms driving offline engram activation warrant further investigation.

Questions to be Answered

The study of dynamic change of engrams across different memory processes such as encoding, consolidation, generalization, and updating has significantly contributed to our understanding of memory. However, there are still numerous fundamental questions that remain unanswered. For example, we now know that memory engrams undergo epigenetic changes related to their activation state during learning, which will subsequently influence both immediate and long-term transcriptional responses. However, there are significant gaps in our understanding of the crucial steps that connect these nuclear changes to the reinforcement of specific synaptic connections. Furthermore, across different memory processes such as consolidation, retrieval, generalization, and updating, mechanisms that drive neurons drop out of and drop into engrams network to modify our memory remains unknown. The neural ensemble fluidity in engram composition confers our memory stability and flexibility, which mechanism need further investigation. Finally, our knowledge of the intrinsic mechanism underlying the offline activation of memory engrams in an unconscious state is totally lacking, which might shed light on the understanding of our memory representations drift over time

depend on our experience and internal states. The ongoing development and optimization of new technologies for studying engram cells hold great promise for addressing these fundamental questions, which have the potential to revolutionize our understanding and treatment of memory-related disorders.

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Author Contributions

Z.Y.C. and S.W.T. conceptualized, wrote, and revised the manuscript and figures. X.L.C. contributed to the figure art.

Author Disclosures

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