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Memory circuits in dementia: The engram, hippocampal neurogenesis and Alzheimer's disease

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Abstract

Here, we provide an in-depth consideration of our current understanding of engrams, spanning from molecular to network levels, and hippocampal neurogenesis, in health and Alzheimer's disease (AD). This review highlights novel findings in these emerging research fields and future research directions for novel therapeutic avenues for memory failure in dementia. Engrams, memory in AD, and hippocampal neurogenesis have each been extensively studied. The integration of these topics, however, has been relatively less deliberated, and is the focus of this review. We primarily focus on the dentate gyrus (DG) of the hippocampus, which is a key area of episodic memory formation. Episodic memory is significantly impaired in AD, and is also the site of adult hippocampal neurogenesis. Advancements in technology, especially opto- and chemogenetics, have made sophisticated manipulations of engram cells possible. Furthermore, innovative methods have emerged for monitoring neurons, even specific neuronal populations, *in vivo* while animals engage in tasks, such as calcium imaging. *In vivo* calcium imaging contributes to a more comprehensive understanding of engram cells. Critically, studies of the engram in the DG using these technologies have shown the important contribution of hippocampal neurogenesis for memory in both health and AD. Together, the discussion of these topics provides a holistic perspective that motivates questions for future research.

Keywords

Alzheimer's disease and related dementia; Adult hippocampal neurogenesis; Engram; Hippocampus- dependent learning and memory

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1. Introduction

At the beginning of the 20th century, Richard Semon had established the term memory "engram" to define the physical substrate of memory storage (Semon, 1921). This concept was further articulated and empirically determined by Karl Lashley and Donald Hebb (Franz and Lashley, 1917; Hebb, 1949). However, the causative association between the activity of a discrete group of neurons and memory expression was shown experimentally a few decades later (Han et al., 2007, 2009a). An engram is a neuronal representation of a memory and is a dynamic ensemble (Josselyn et al., 2017; Semon, 1921). It is initially formed when organisms acquire new information, which is processed in the dentate gyrus of the hippocampus. This memory can then be consolidated, a process of converting short-term memory (STM), which lasts only minutes to hours, into long-term memory (LTM), which can persist a lifetime (Asok et al., 2019; Kandel, 2009; Kandel et al., 2014). There are two levels of consolidation complementing each other: 1) synaptic/cellular consolidation involves local changes to store new information with fast dynamics at the synaptic and cellular level; 2) systems consolidation pertains to the reorganization of multiple circuits to represent long-term memory, occurring over a more extended time scale, ranging from months to years (Dudai, 2004, 2012; Dudai et al., 2015). When necessary, or when primed, the memory is retrieved (Frankland et al., 2019). The memory has been demonstrated to be further modified with each retrieval event through a process of reconsolidation (Haubrich and Nader, 2018; Lee et al., 2017b; Nader, 2015). Each of these stages is crucial for proper and optimal formation of memories and their dynamic modulation. Insight into the molecular and cellular dynamics and profile of the engram was possible thanks to recent advancements in genetics, molecular biology and bioengineering, which enabled investigators to not only target a certain neuronal population, but also chemically and optically manipulate these cells and their synapses while the animals perform a learning and memory task (Choi and Kaang, 2022; Choi et al., 2018; Deisseroth, 2015; Kim et al., 2017; Roth, 2016; Urban and Roth, 2015). Further, advancements in omics approaches have allowed us to gain insight into the spatial and temporal molecular profiles of single cells (Clark et al., 2022; Grieco et al., 2023; Hampel et al., 2021; Mishra et al., 2022).

Dysfunction of any of these stages may affect the quality of the memory. For example, in Alzheimer's disease (AD), memory retrieval was shown to be impaired, manifested by inaccessible memories (Roy et al., 2016). AD is the most prevalent form of dementia. It is characterized by progressive memory loss and cognitive deterioration. While behavioral and cognitive impairments in AD and related dementia are well understood, very little is known about the neuronal substrate underlying these impairments. Brain areas affected in AD, e.g., the hippocampal formation, are critical for learning and memory. In the dentate gyrus of the hippocampus, the engram is composed of both mature and immature neurons. In fact, the high excitability and plasticity of immature neurons, make them preferential recruitees into the memory engram (Kee et al., 2007). Reduced number of immature neurons in the aging dentate gyrus is thought to underlie defective contextual discrimination, which is the ability of the animal to separate between two distinct but similar contexts (Wu et al., 2015). In AD, fewer immature neurons get recruited into memory engrams, which contributes to memory impairments (Mishra et al., 2022). In this Review, we will explore the intriguing

and latest understanding of the engram and the neuronal types that compose it, with a focus on mature and immature neurons of the dentate gyrus, and discuss the current understanding of engram alterations in AD. This information will shed light on an intricate set of processes of memory formation and its dysfunction, especially in the context of dementia.

1.1. The engram: neuronal ensembles of a memory

Insight into the molecular underpinning of engram cells, coupled with technological breakthroughs, have allowed neuroscientists to manipulate memories, implant false memories (Garner et al., 2012; Liu et al., 2014), and even retrieve lost memories in the diseased brain (Roy et al., 2016). Neurons are thought to get selectively activated by learning due to a relatively greater excitability state. Evidence suggests that increased expression of CREB may be the mechanism behind this selection during learning. Previous experiments have shown that activation of these neurons was necessary and sufficient to express memory (Han et al., 2007; Kim et al., 2016). Some evidence suggests that the relative excitability prior to memory acquisition may determine the probability of a neuron to get recruited into the acquisition phase and the memory engram (Yiu et al., 2014). This may be aligned with the finding that immature neurons in the dentate gyrus are preferentially recruited into the engram (Box 1) (Kee et al., 2007). However, more studies are warranted to understand the selection process by which neurons get recruited for a memory task. For example, it is yet to be shown that cells with higher *endogenous* levels of CREB would be more likely to get recruited into the memory engram. Further, studies have established that reactivation of hippocampal neurons that participated in a memory engram was sufficient to retrieve some aspects of the memory that were originally encoded (Han et al., 2009a; Josselyn et al., 2015; Liu et al., 2012). Notably, several studies suggest that the total number of neurons that get recruited into a specific memory engram is thought to be uniform, suggesting that either only a certain amount of neurons is needed for memory expression, or that there is a constraint on the overall size of the engram of a specific memory trace (Han et al., 2007; Mishra et al., 2022). One hypothesis that gained support recently is that somatostatin-expressing interneurons in the dentate gyrus govern the size of the neuronal ensemble that store a memory (Stefanelli et al., 2016). A recent study established that the ability to form precise episodic memories depends on the functional maturation of parvalbumin-expressing interneurons in the CA1 region of the hippocampus during early childhood, through assembly of extracellular perineuronal nets (Ramsaran et al., 2023).

1.2. From short- to long-term memory: states of the engram

Recent experimental evidence posits that memory engrams exist in multiple states: latent, silent, and active. The “latent” state indicates that the memory is present but not readily accessible during recall using natural cues. In the “silent” state, the memory is present but inaccessible through natural cues and can only be accessed through certain specific manipulations. The “active” state denotes a memory that is both present and accessible using natural cues (Josselyn and Tonegawa, 2020; Lei et al., 2022a; Tonegawa et al., 2018) . Experimentally, silent engrams can be induced by anisomycin treatment following training (Roy et al., 2017; Ryan et al., 2015) and have been observed in a familial Alzheimer’s disease model (Roy et al., 2016). In the healthy brain, silent engrams were assumed to play a role in memory transformation. Interestingly, there is a stark contrast between the

fate of engrams in the prefrontal cortex and hippocampus over time. The active engrams in the hippocampus become silent over time during post-consolidation period of 1–14 days, while in the prefrontal cortex, the stages of engrams progress in the reverse order of the hippocampal engram, which are silent during the same period (Kitamura et al., 2017). Besides optogenetics mediated-activation and artificial induction of engram stage, a recent study showed that physiological conditions could also transform a silent engram to a latent or active engram (Lei et al., 2022a). Silent engrams,-can only be accessed through artificial stimuli. Latent engrams can be retrieved by natural cues (Josselyn and Tonegawa, 2020; Tonegawa et al., 2018). Recent findings challenge the idea that memories not transformed from STM to LTM are lost. Instead, they can become silent engrams. Further exposure or activation of the silent engram can facilitate its conversion into LTM. This discovery revolutionizes our understanding of memory processes and highlights the potential for reactivating and consolidating dormant memories.

Investigating the triggers and mechanisms involved in silent engram activation may lead to advancements in memory-related disorders (Wally et al., 2022). Studies monitoring the use of cerebral glucose (Bontempi et al., 1999) immediate early gene activation (Frankland et al., 2004; Maviel et al., 2004), and dendritic spine formation (Lesburgueres et al., 2011; Restivo et al., 2009) have indicated that rapid encoding of episodic memory in the hippocampus can be followed by temporally graded neural changes in the medial prefrontal (mPFC), orbitofrontal, anterior cingulate, or retrosplenial cortices. The memory progressively becomes dependent on the cortical structure and independent of the hippocampus, possibly indicating the cross-talk between the cortical and hippocampal memory engram for remote memory formation. Visualization and manipulation of neuronal ensembles over prolonged periods of time requires a stable or permanent tag in activated neurons. A TetTag transgenic mouse line was used by Tayler et al. (2013) to express a stable form of green fluorescent protein (GFP) in activated neurons during contextual fear conditioning (CFC) (Tayler et al., 2013). They observed that context-dependent reactivation of tagged neurons occurred 2 days after conditioning in hippocampal and cortical regions, whereas reactivation selectively occurred 2 weeks later in several cortical regions upon retrieval. Recently, Kitamura et al. (2017) reported that CFC-activated neurons in the mPFC are sufficient and necessary for memory expression 12–14 days after conditioning using the TetTag mouse with optogenetic manipulation (Kitamura et al., 2017). Matos et al. (2019) reported that CFC-activated mPFC neurons are required for remote memory expression up to at least 1 month after learning using a viral-TRAP (Targeted Recombination in Active Populations) in combination with a chemogenetic approach (Matos et al., 2019). Noteworthy in both studies, mPFC engram cells were not involved in recent memory, indicating their time-dependent engagement through systems consolidation. The temporal role of mPFC engram cells was further confirmed in a study by DeNardo et al. (2019) that tagged these cells during memory retrieval at different timepoints after fear conditioning using a TRAP2 transgenic mouse (DeNardo et al., 2019). Interestingly, the involvement of CFC-activated mPFC neurons in remote memory appears to be contingent upon training intensity, with strong fear conditioning resulting in a disengagement of the learning-activated mPFC ensemble (Matos et al., 2019). It has been speculated that the encoding of highly aversive experiences depends on more evolutionary primordial emotional brain systems,

consequently leading to a lack of top-down control by the mPFC. The persistent nature of memory encoding by mPFC neurons was also demonstrated in a mouse model following alcohol self-administration paradigm (Visser et al., 2020). mPFC neurons that are activated during alcohol self-administration drive cue-induced relapse to alcohol seeking following 1 month of abstinence. Thus, even though investigations into engram cell stability gained attention only recently, it is evident that the mPFC can serve as a critical network hub, harboring persistent engram cells that encode aversive and appetitive types of memory.

Retrieval of previously encoded and consolidated information, or ecphory, is thought to be a collaboration of stored past information and new data available at the time of the memory retrieval attempt. Memory retrieval could vary in its level of accuracy or faithfulness to the originally encoded information. Previous studies showed that high similarity between encoding and retrieval information contributes to greater faithfulness of the memory recall. These observations encompass the encoding specificity hypothesis. However, it was not clear whether the relationship between encoding and test conditions is correlational or causative. A recent study by Jung et al. (2023) sheds important light on this issue and shows that the interaction between stored information and cues available at memory retrieval is critical, and that for maximal engram reactivation and memory recall to occur, retrieval conditions should closely match training conditions. This study provides a biological basis for the encoding specificity hypothesis (Jung et al., 2023).

1.3. Inhibitory engrams

The current experimental toolbox only allows for labeling and manipulation of a subset of cells, mainly excitatory, glutamatergic neurons. However, there are multiple cell types, including inhibitory, GABAergic neurons, and non-neuronal cells that have been reported to play a role in memory formation (Giorgi and Marinelli, 2021; Kol et al., 2020; Raven and Aton, 2021). Parvalbumin- (PV+) and somatostatin-expressing (SST+) inhibitory neurons have been studied. The role of inhibitory engrams was proposed to have at least two main purposes: 1) to keep the excitatory neuron engram in check, and 2) to keep memory from interfering with other memory traces. Specifically, inhibiting central amygdala interneurons disinhibit its excitatory engram and increase the expression of fear memory (Hou et al., 2022). Inhibitory neuron engrams facilitate memory formation and possibly separate two overlapping memories (Koolschijn et al., 2019). In one study, evidence suggested that PV+ interneurons regulate the number of neurons recruited into the memory engrams (Morrison et al., 2016), while another study reported a similar role to SST+ interneurons (Stefanelli et al., 2016). PV+ and SST+ interneurons form broad, but occasionally overlapping, subtypes of interneurons in the hippocampus and cortex (Udakis et al., 2020). PV+ interneurons preferentially target perisomatic regions of pyramidal neurons and regulate spiking and network oscillations through feedforward and feedback inhibition (Varga et al., 2012). In contrast, SST+ interneurons target mainly distal dendritic regions and regulate pyramidal neurons mainly via feedback inhibition (Chiu et al., 2013; Schulz et al., 2018). Being active on a different phase of the theta cycle (Klausberger and Somogyi, 2008; Varga et al., 2012) provides PV+ and SST+ interneurons with unique capabilities to modulate the response of pyramidal neurons to excitatory inputs. Some or all these differences may account for the unique characteristics of the two putatively distinct ensembles.

The inhibitory engram has been proposed as one mechanism of forgetting, as it exerts inhibitory tone onto excitatory engrams via GABAergic signaling (Barron et al., 2017; Ryan and Frankland, 2022). However, there has been no direct evidence to support this theory. In fact, using optogenetic, chemogenetic and Cal-Light methods (Lee et al., 2017a), investigators found that both CCK+ and PV+ inhibitory neurons did not have an effect on the consolidation or retrieval of contextual fear memory. Interestingly, when CCK+ interneurons were inhibited, the animals were unable to distinguish between a familiar context and a novel one. This may suggest a role in context specificity, rather than in forgetting. Further research involving the tagging and manipulation of inhibitory engrams during memory tasks is needed to better understand their role in memory formation. Notably, engram activity is necessary for interference to occur. Examination of interference-based forgetting revealed that although retroactive interference leads to decreased engram cell reactivation during recall, optogenetic stimulation of the engram cells is sufficient to induce memory retrieval. This suggests that forgotten engrams can be reinstated by the appearance of similar or related information, and that retroactive interference regulates the engram to be reversible and updatable (Autore et al., 2023).

1.4. Immature and adult-born dentate neurons in the engram

The hippocampus is uniquely characterized by the continuous formation of new neurons from neural stem cells and their integration in the dentate gyrus. A full description of the molecular and cellular characteristics of hippocampal neurogenesis is provided elsewhere (Disouky and Lazarov, 2021; Gage, 2019). Here we briefly discuss a few aspects that are relevant to this review.

As neurons mature, they migrate into the granule cell layer of the hippocampus and integrate into the hippocampal circuitry. Initially, they are connected primarily with local interneurons (Alvarez et al., 2016; Hainmueller and Bartos, 2020; Yeh et al., 2018). At this stage, newborn neurons begin to sprout dendrites and synapse with CA3 mossy fibers as well as other mature granule cells and interneurons in the hippocampus (Denoth-Lippuner and Jessberger, 2021; Luna et al., 2019; Vivar et al., 2012, 2013). While initially high expression of the Na+−KH+−Cl– transporter NKCC1 causes GABA to have initially a depolarizing effect on membrane potential of immature neurons, in later stages of neuronal maturation, reduced expression of NKCC1 and increased expression of KCC2 occurs, causing GABA signaling to become inhibitory (Denoth-Lippuner and Jessberger, 2021). Dendritic spines further extend and develop into mushroom shapes in the outer molecular layer, and strengthen synapses with neurons in layer II of the entorhinal cortex (Vivar et al., 2013). Thus, clearly, in addition to cell autonomous signaling, the local network activity of the hippocampus is critical for the development of neurogenesis. Adult-born neurons specifically synapse with perineuronal net (PNN)-containing PV^+ interneurons (Briones et al., 2021). PNNs have been implicated in dendritic spine stabilization and synaptic plasticity, and thus could have downstream effects on circuit activity (Cope and Gould, 2019; Song et al., 2013; Yamada et al., 2018). While still not fully understood, enzymatic removal of PNNs has been shown to lead to increased plasticity and reduced PV^+ inhibitory interneuron activity (Briones et al., 2021; Lensjo et al., 2017). This change in PV^+ interneuron activity affects gamma oscillation (30–100 Hz) activity within the hippocampus (Lensjo et al.,

2017). Thus, the interaction between PNN-containing PV^+ interneurons and new neurons is important for the stability of circuit synchrony and excitation-inhibition balance. Excitation-inhibition balance is a crucial part of healthy brain function (Marin-Burgin et al., 2012; Topolnik and Tamboli, 2022). In the hippocampus, inhibitory interneurons facilitate proper neuronal oscillation activity. Increased inhibitory activity in the hippocampal network leads to disruption of adult-born neuron maturation timeline, particularly along the septo-temporal axis of the hippocampus (Piatti et al., 2011). Namely, reduced network activity results in delayed neuronal maturation period, and vice-versa for increased network activity. Thus, not only does the local network activity influence adult-born neurons, but adult-born neurons can affect the existing network. For example, recent studies have shown that increased neurogenesis affects the number and morphology of dendritic spines on mature neurons (Adlaf et al., 2017; Mishra et al., 2022). The high firing rate of newly mature neurons during their increased activity phase (occurring at approximately 4 weeks) influences population firing rates that lead to increased sparsity and alterations in hippocampal oscillations (McHugh et al., 2022). At the population level, this is notable as the DG has approximately an order of magnitude more cells compared to the upstream entorhinal cortex (EC) or downstream CA3 (Goncalves et al., 2016; Jinno, 2011). Given that adult-born granule cells form synapses with and can inhibit existing mature GCs (Luna et al., 2019), taken together this could lead to increased sparsity within the DG specifically that is important for learning and memory functions such as pattern separation (Chawla et al., 2005; Yassa et al., 2011).

Immature newborn granule cells in the dentate gyrus are thought to be key players in learning and memory due to their high excitability and enhanced synaptic plasticity (Fig. 1). One could speculate that immature neurons primed during learning as they mature influence the neural representation by being more excitable, in part due to reduced feedback inhibition (Danielson et al., 2016; Marin-Burgin et al., 2012). They receive decreased inhibition and show more overlapping activity and less discriminative spatial tuning in response to perforant path stimulation (Danielson et al., 2016; Dieni et al., 2013; Kheirbek et al., 2012; Marin-Burgin et al., 2012). Indeed, immature neurons are preferentially recruited into memory engrams (Kee et al., 2007). Two hypotheses have been postulated to define the role of immature neurons in memory processing, i.e., the “integrator” hypothesis and the “inhibition” hypothesis. According to the integrator hypothesis, immature neurons are more likely to indiscriminately encode new information and consequently associate the events that happened close in time (Aimone et al., 2010; Deng et al., 2010). They are found to encode new information in a familiar context as well as separately encoding information about new contexts separated by time (Aimone et al., 2009; Rangel et al., 2014, 2013). These neurons are also found to be important for encoding in a novel context under conditions of higher interference. Alternatively, according to the inhibition hypothesis, these neurons orchestrate inhibition of mature neurons to sparse memory representations. They display synaptically driven action potential while their firing rate is lower than that of mature neurons (Heigele et al., 2016; Sultan et al., 2010). Furthermore, using *in vivo* calcium imaging, it was shown that immature neurons ranging from 3 to 6 weeks are more active and excitable than the older ones (Miller and Sahay, 2019). Decreased excitability of mature neurons is observed after optogenetic activation of immature neurons, while increased excitability in the DG network is observed after silencing or ablating immature neurons (Anacker et al., 2018; Burghardt

et al., 2012; Drew et al., 2016; Ikrar et al., 2013; Lacefield et al., 2012; Park et al., 2015; Sahay et al., 2011). Combining functional imaging, retroviral birth dating, and chemogenetic silencing, Lods et al. (2021) examined the role of different generations of adult-born neurons in spatially memory reconsolidation. They found that memory retrieval activates both 1–2-week-old immature neurons and 6-week-old mature neurons during learning (Lods et al., 2021). Specifically, chemogenetic silencing of these populations during remote retrieval-induced reconsolidation demonstrated that the neuronal population that was immature at the time of learning was critical for both maintenance and memory update after its reactivation, i.e., remote memory stabilization. Li et al. (2012) reported that development of GABAergic inputs controls the contribution of maturing neurons to the adult hippocampal network and define the memory representations (Li et al., 2012). Simonova et al. (2022) proposed that potentiation-based non-associative plasticity of GABAergic transmission might help to counter-balance an increase of excitatory drive that is facilitated by enhanced LTP at the glutamatergic synapses in maturing granule cells (Simonova et al., 2022). The selective regulation of the plasticity potential of the granule cells of different ages determines how the hippocampal network stores and maintains memories. For instance, GABA depolarizes immature granule cells via Na^{+}-K^{+}-$2CL^{-}$ co-carriers because of their higher chloride reverse potential. GABA-related depolarization is mediated by CREB. The development of GABA inhibitory synapses onto immature granule cells is timed such that young neurons are more responsive to novel cortical inputs that are less capable of activating mature granule cells. Therefore, immature granule cells can integrate across multiple cortical inputs, whereas mature counterparts remain selective. This rapid response of the immature adult-born neurons might be susceptible to available hippocampal BDNF levels. Ablation of the BDNF receptor, tropomyosin receptor kinase B (TrkB), in progenitor cells indicated that the BDNF-TrkB pathway is involved in immature neuron-driven synaptic plasticity and behavior with CREB levels as the downstream effectors. BDNF expression might therefore be needed for coding of similar presentations in the DG. Another study implied that N-methyl-D-aspartic acid-mediated plasticity was also involved in pattern separation (Fig. 2) (McHugh et al., 2007).

The cholinergic system has also been shown to be important in learning and memory function. Cholinergic innervation originating from the septum regulates hippocampal theta rhythm necessary for proper hippocampal function (Jeong et al., 2014). Additionally, deficiency of cholinergic neurons in the basal forebrain reduced the number of immature neurons in the subgranular region of the DG. Alvarez et al. (2016) showed that an accelerated integration of immature neurons is dependent on PV+ neurons, which might speed up the functional significance of immature neurons by expanding their connectivity (Alvarez et al., 2016). A decrease or an increase in neurogenesis delayed or sped up the recovery of memory capacity, respectively, suggesting that hippocampal adult neurogenesis plays a critical role in reducing LTP saturation and keeps the gate open for new memories by clearing out the old memories from the hippocampal memory circuit (Alam et al., 2018). Various computational models have suggested that adult-born neurons minimize memory interference when similar items are presented (Becker, 2005; Wiskott et al., 2006). Clearance of old memories might be accelerated by enhancing neurogenesis. Neurogenesis is required for the formation of new memories, especially during higher hippocampal

network activity (Deisseroth et al., 2004). Together, this suggests that the levels of excitatory network activity and neurogenesis is critical for maintaining the balance between old memory storage and new memory formation. Various computational models postulated that encoding new information will not only remodel neural networks but also weaken the existing neural connections that have been established for storing old memories (Fusi et al., 2005). A competitive interplay between immature granule cells and mature neurons might be one hypothesis underlying increased neurogenesis-induced loss of old memories. A study by Akers et al. (2014) reported that functional integration of new neurons may result in circuit modifications that compete with preexisting circuits that contribute to forgetting of existing memories (Akers et al., 2014). Toni et al. (2007) suggested that competitive interaction between new and mature neurons for inputs from the entorhinal cortex imparts survival advantage to new neurons for the formation of new memories (Toni et al., 2007). Similarly, McAvoy et al. (2016) suggested that selectively reducing the dendritic spines in mature dentate granule cells allows for the efficient integration of new neurons into hippocampal circuitry (McAvoy et al., 2016). Furthermore, spatial and temporal integration dynamics of the GABAergic and glutamatergic inputs is required to elicit action potentials in new granule neurons. Further, hippocampal neurogenesis has been implicated in regulating the acquisition of new memories (Kee et al., 2007), their temporal storage and organization (Aimone et al., 2006), in encoding (Bernier et al., 2017), consolidation (Kitamura and Inokuchi, 2014), and their retrieval (Bernier et al., 2017). Other evidence suggests that hippocampal neurogenesis modulates the time that memory remains in the hippocampus before being transferred to the cortices. Feng et al. (2001) suggested that impairments in hippocampal neurogenesis may impair the clearance of 2-week-old contextual memory traces, while not affecting cued fear memory (which primarily involves the amygdala). The consequence of this impaired clearance of contextual memory traces was better retention of that memory two weeks post training, as compared to the control group (Feng et al., 2001). Taken together, these observations suggest that hippocampal neurogenesis plays a crucial role in hippocampal-dependent cognitive tasks like pattern separation, spatial navigation learning and long-term spatial memory retention, spatial pattern discrimination, trace conditioning, contextual fear conditioning and clearance of hippocampal memory. A study by Kirwan and Stark (2007) used the Stark test, a mnemonic similarity resembling the rodent pattern separation task, which involves discriminating the visual similarities of two different, but similar, images. An improved performance in pattern separation Stark test in humans was found to be associated with increased blood oxygen level-dependent (BOLD) fMRI signal, selectively in the DG (Kirwan and Stark, 2007). More studies specifically detecting the activity of immature neurons in the human brain are warranted.

Nevertheless, the significant drop in levels of neurogenesis in the adult brain compared to the juvenile and postnatal in rodents (Akers et al., 2014; Demars et al., 2013a) have led investigators to hypothesize either stage-specific roles, or a prospective function. In the latter, neurogenesis shapes the hippocampus to allow successful processing of future memory events (Cushman et al., 2021). A similar controversy exists concerning the level of neurogenesis in the adult primate and human brain and its function. Some studies failed to detect new neurons in the adult hippocampus (Cipriani et al., 2018; Franjic et al., 2022; Sorrells et al., 2018, 2021), while others have described the presence of

hippocampal neurogenesis even in elderly primates and humans (Boldrini et al., 2018; Eriksson et al., 1998; Li et al., 2023; Spalding et al., 2013; Tobin et al., 2019; Zhou et al., 2022). Evidence clearly suggests that levels of neurogenesis are significantly reduced in Alzheimer's disease (Moreno-Jimenez et al., 2019; Tobin et al., 2019; Zhou et al., 2022). Differences in detection level of cells in the human brain can stem from postmortem tissue quality, histological qualification (for example, postmortem delay (PMD), fixation), immunohistochemical methodology and sequencing approaches (for example, sequence depth, proxy identification). For detailed discussion of these matters please see (Flor-Garcia et al., 2020; Gallardo-Caballero et al., 2023; Lucassen et al., 2020; Terreros-Roncal et al., 2023; Tosoni et al., 2023). However, like in the rodent, levels of hippocampal neurogenesis drop in the juvenile and adult brain, and further drops in aging-linked Alzheimer's disease and related dementia. Future technologies allowing the detection of new neurons in live humans may help resolve this dispute and provide important insight into the functional significance of hippocampal neurogenesis in learning and memory in the human brain.

1.5. The cellular compartments of the engram

What are the cellular compartments that store memory traces in neurons? The Hebbian law proposed that memory strength lies at the synapse, thus where memory traces are stored (Hebb, 1949). Hebb's postulation was later supported by long-term potentiation and long-term depression as molecular correlates of memory formation. Synaptic plasticity was established as the mechanism of the physiological stress responses may translate into time-dependent effects on learning and memory (Wiegert et al., 2006). Stressful events provoke an orientation of attentional and memory processes towards threat-related stimuli (de Kloet et al., 2005; Hermans et al., 2014). Recently, Lesuis et al. (2021) studied the effects of corticosterone, the primary glucocorticoid in mice, on the generalization of fear expression and how glucocorticoids affect the engram (Lesuis et al., 2021). Using pharmacological, electro-physical, DREADD technology approaches, the authors demonstrated that generalization of fear expression occurred due to the increased size of the DG engram. Two recent studies have demonstrated the role of social reward and stress on memory engram. Lei et al. (2022c) investigated the role of social reward, social stress, and adult-born granule cells (abGCs) on the engram by employing several approaches such as pharmacological, chemogenetics and *in vivo* calcium imaging to demonstrate that social reward activates more abGC engram neurons, while social stress involves fewer engram neurons, suggesting that social stress involves more non-engram abGCs (Lei et al., 2022c). Together, their studies show that socially rewarding and socially stressful situations modulate memory retrieval, use different populations of abGCs, and have distinct effects on neuronal activity in the DG. Finkelstein et al. (2022) examined the effect that social interactions have on memory. They focused on the hippocampus and amygdala, which are both involved in memory formation and social behavior learning and memory formation (Bliss and Lomo, 1973; Kandel and Tauc, 1965). Further support came from the observations of structural changes at the dendritic spine level during learning events (Hofer et al., 2009; Matsuzaki et al., 2004). Interestingly, experiments using fear conditioning paradigms showed that the structural outcome depends on the phase of memory formation. Specifically, spine elimination was observed in the case of auditory fear conditioning, while memory extinction promoted spine formation (Lai et al., 2012). Seminal studies

developed a synaptic optoprobe, AS-PaRac1 (activated synapse targeting photoactivatable Rac1), which allowed the labeling of potentiated spines while facilitating the shrinkage of AS-PaRac1-positive spines. With this approach, only the potentiated synapses in the motor cortex were optically erased, causing deficits in rotarod learning behaviors, which suggested that memory traces were stored at the synapses (Hayashi-Takagi et al., 2015; Poo et al., 2016). Previous studies have implied that upon learning and memory tasks the synapses undergo multiple rounds of synaptic scaling to adjust for information storage in dendritic spines (Redondo and Morris, 2011; Redondo et al., 2010). According to the synaptic tag and capture theory, only synapses that made connections with other synapses during memory acquisition (synaptic engrams) will be strengthened over time, while the non-connected synapses (non-synaptic engrams) will not be strengthened (Frey and Morris, 1997, 1998). A recent study used a dual eGRASP (green fluorescent protein reconstitution across synaptic partners) approach. eGRASP allowed investigators to visualize two colors distinguishing the engram vs. non-engram synapse from presynaptic neurons (CA3) to postsynaptic neurons (CA1) (Choi et al., 2018). Using eGRASP, the authors illustrated that only synapses between engram cells (E-E) would show an increase in spine head diameter, volume, and density, but not the other variations (N-N, N-E, or E-N). They further demonstrated that these structural changes correspond to the intensity of the stimulus (Choi and Kaang, 2022; Choi et al., 2018). In the auditory cortex and the lateral amygdala, the morphologies of activated synapses were shown to increase following contextual fear conditioning (CFC), but surprisingly, the same activated synapses decreased following fear extinction learning, as revealed by the dual-GRASP approach (Choi and Kaang, 2022). This supports the idea of memory extinction as an “unlearning” process rather than a process of new learning. Nevertheless, the authors could not exclude the possibility that new learning can occur independently through a parallel process The same conclusion was further supported by experiments that used real-time two-photon imaging of the hippocampal engram network (Lee and Han, 2023). Lastly, Lee et al. (2023) studied the synapses between engram and non-engram neurons between the CA1 and CA3. They used dual eGRASP system to label both (non-) engram cells and (non-) engram synapses before and after fear conditioning and after extinction. After CFC, there was an increased number of existing and newly formed synapses between the CA1 and CA3. Conversely, extinction reduced the number of engram synapses. Further investigation showed that dendritic spines were preferentially located near areas with previously low spine density (Lee et al., 2023). These data provide detailed evidence on the synaptic alterations that occur after learning and extinction in the context of the engram (Fig. 3).

2. Environmental effects on engrams

The formation, modification and re-modification of the dynamic engram is subject to many external influences and environmental factors. Stress and emotional arousal are prominent modulators of the memory engram (Christianson and Mjorndal, 1985; Diamond et al., 2007; Joels et al., 2011; Schwabe and Wolf, 2012). Social experiences or stressful events switch memory engram states among active, latent or silent states. Lei *et al.* showed that acute social reward experiences switch the silent memory engram into the latent state (Lei et al., 2022b). Conversely, an acute social stress causes transient forgetting via

turning a latent memory engram to silent one. Stressful events result in the fine-tuned and orchestrated physiological response involving numerous hormones, neurotransmitters and neuropeptides (Henckens et al., 2009). Stress mediators including catecholamines such as adrenaline and nor adrenaline (NA), neuropeptides like corticotropin-releasing factor (CRF), glucocorticoids, corticosteroids, endocannabinoids act in timely fashion to affect neural networks and alter memory (Joels and Baram, 2009; Lesuis et al., 2021). Neurophysiological studies targeting hippocampal plasticity provided the first evidence that different waves of circuits. They found that (1) social interactions improved fear memory and (2) this was exclusive to male mice. Their study shows that social interactions can shape memory in sex-specific ways. At the cellular level, social interaction can reactivate fear-induced engrams in the DG to strengthen memory (Finkelstein et al., 2022). Ramirez et al. (2015) showed that the stress-induced, depression-related behaviors acutely rescued by optogenetically reactivating DG cells that were previously active during a positive experience indicated that activation of positive memory engrams suppresses depression-like behavior. A brain-wide histological investigation, along with pharmacological and projection-specific optogenetic blockade experiments, identified glutamatergic activity in the hippocampus-amygdala-nucleus accumbens pathway as a key pathway that underlies this acute rescue. Moreover, the rescue of stress-induced behavioral impairments and neurogenesis happened at time points beyond the light stimulation (Ramirez et al., 2015). The activation of positive memory engrams has been shown to alleviate depression-related behaviors; conversely, negative memory hippocampal engrams contribute to the susceptibility to developing depression-related behavior after chronic social defeat stress (Zhang et al., 2019).

Adult hippocampal neurogenesis is intensely regulated by environmental and behavioral factors (Dranovsky et al., 2011; van Praag et al., 2000). Spatial learning promotes neural progenitor cell differentiation and the survival of newborn neurons (Ambrogini et al., 2000). Running increases the proliferation of neural progenitor cells and environmental enrichment increases the survival of newborn neurons, leading to enhanced neurogenesis (Kempermann et al., 1997; van Praag et al., 1999). Social reward increases neurogenesis by modulating stress-related hormones. On the other hand, optogenetically activation of memory engram cells in the hippocampus can restore chronic stress-induced decline of neurogenesis (Gould and Tanapat, 1999; Ramirez et al., 2015). As such, adult hippocampal neurogenesis may link emotional experiences and memory (Anacker and Hen, 2017; Opendak and Gould, 2015). In agreement with this notion is a recent study showing that acute social reward and acute social stress exert differential impacts on memory retrieval of contextual fear memory by modulating the reactivation of engram cells, including distinct populations of new neurons (Lei et al., 2022a).

3. The engram and memory dysfunction: aging and brain pathology

Memory loss takes place during aging. Dementia, a cluster of disorders characterized by loss of memory and cognitive decline, is strongly linked to aging. Alzheimer’s disease (AD) is the most prevalent form of dementia and characterized by progressive memory loss and cognitive deterioration. The pathological hallmarks of AD are amyloid β (Aβ) deposition and tau neurofibrillary tangles (NFTs). The pathology originates in the entorhinal cortex, after which it spreads throughout the rest of the hippocampal formation and the cortex

(Braak et al., 1996). Most AD patients have the sporadic form of the disease (late onset AD, LOAD), for which there is no known cause, and aging is the greatest risk factor. A multitude of environmental and genetic factors increase the risk of AD, the former includes stress, type-2 diabetes, cardiovascular disease, obesity (Caruso et al., 2018; Justice, 2018; Mattson and Magnus, 2006; Santiago and Potashkin, 2021; Swerdlow, 2007), and the latter Apolipoprotein E ε4 (*APOE4*), PICALM, CLU, TREM2 and others (Hampel et al., 2021; Lambert et al., 2013). About 5% of AD patients have an early onset, autosomal dominant (EOAD) form of AD, also known as familial AD (FAD). FAD is caused by genetic mutations in amyloid precursor protein (*APP*) and presenilin 1,2 (*PSEN1*, *PSEN2*) (Lazarov and Marr, 2010). The mechanism of neuronal vulnerability in AD, leading to their death, is not fully understood. Neuronal vulnerability, manifested by amyloid deposition and neurofibrillary tangles originates in a critical region of memory formation and processing, namely, the hippocampal formation. Neuronal cell loss starts in the entorhinal cortex, continues in the CA1 and subiculum, and propagates into other cortical areas (Braak et al., 2006a, 2006b; Roussarie et al., 2020). If neurons that are likely to participate in an engram are vulnerable to AD pathology in the hippocampus, which is crucial for episodic memory, this may lead to deficits in memory. Spatial transcriptomics reveals that accumulation of and proximity to amyloid plaques leads to plaque-induced altered gene expression in astrocytes, microglia, and oligodendrocytes (Chen et al., 2020). However, the mechanism by which vulnerability affects engram neurons, and the nature of alterations in neuronal function are largely unknown. Early vulnerability of neurons in AD is manifested by the degeneration of synaptic terminals, which are crucial for memory formation and retrieval, as discussed above. Further, engram dynamics are mediated in part by modifications of dendritic spines. Preservation of dendritic spines has been linked to preservation of memory in AD (Boros et al., 2017; Mishra et al., 2022). Microglia are known to regulate dendritic spines. Dysfunctional microglia activity can lead to abnormal spine elimination has been correlated with reduced memory performance in AD (Cornell et al., 2022; Merlini et al., 2019). Further, reduction of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which is a key component for neuronal survival and synaptic plasticity and maintenance, has been shown in AD. Similarly, nerve growth factor (NGF) is also key for neuronal growth, survival, and maintenance, and is known to regulate the amyloidogenic pathway (Sampaio and Wang, 2017). In addition to molecular factors, disruption of sleep and circadian rhythm, a process which is critical for learning and memory [for a comprehensive review see (Smarr et al., 2014)], has been shown in AD (Harper et al., 2004; Webster et al., 2014), and has been related to reduced clearance of Aβ (Xie et al., 2013). Numerous studies have shown that hippocampal neurogenesis is reduced with age in rodents and primates (Demars et al., 2013b; Kase et al., 2020; Leuner et al., 2007; Tobin et al., 2019). This has been associated with a decline in cognitive function and attributed, among other factors, to alterations in the systemic milieu (Villeda et al., 2011). Improvements in neurogenesis and spatial memory performances were observed in senescent or middle-aged mice raised in an enriched environment, suggesting that age-related processes may be reversible, at least in part (Kempermann et al., 2002, 1998). Along the same line, physical activity, whether voluntary running wheel or forced treadmill, were found to restore the levels of neurogenesis from old mice to those of young sedentary ones (Kronenberg et al., 2006; van Praag et al.,

2005). Increased neurogenesis in old, exercised animals was found to be associated with improved spatial learning and memory (van Praag et al., 2005).

Human neurogenesis was first described by Eriksson and colleagues in 1998 (Eriksson et al., 1998), with subsequent reports citing evidence for and against its existence (discussed in detail in (Kempermann et al., 2018). Studying human hippocampal neurogenesis is made more difficult by technical complications such as varying PMD times, fixation methods and duration, disease stage of the subject, potential confounds from the dying process, and other environmental factors (Kempermann et al., 2018). Further, there may be different time scales in the maturation of ABNs in humans compared to mice; thus, experiments with human tissue using known proxies from mice, namely, DCX and PSA-NCAM, may be difficult to interpret (Kempermann et al., 2018).

Controversy notwithstanding, reduced hippocampal neurogenesis was observed in the human aging and Alzheimer's disease (AD) brain and was correlated with cognitive decline (Boldrini et al., 2018; Moreno-Jimenez et al., 2019; Tobin et al., 2019; Zhou et al., 2022). Further, non-demented with AD neuropathology (NDAN) patients had higher levels of SOX2+ cells, suggesting that ABNs may be protective against cognitive decline (Briley et al., 2016; Salta et al., 2023). Finally, patients with elevated numbers of DCX+ cells had higher levels of synaptic proteins, together suggesting that increased neurogenesis is correlated with better cognitive performance and synaptic integrity in the context of AD (Salta et al., 2023; Tobin et al., 2019).

In that regard, APP, PS1 and APOE were shown to regulate hippocampal neurogenesis (Demars et al., 2013a; Gadadhar et al., 2011; Lazarov and Demars, 2012; Matsushita et al., 2023; Rijpma et al., 2013). Numerous mouse models of AD have shown alterations in hippocampal neurogenesis (reviewed elsewhere (Disouky and Lazarov, 2021; Lazarov and Hollands, 2016)). However, very little information is available on the state of the engram in AD. If the connectivity between engram neurons is reduced by pathologies, such as Aβ or hyperphosphorylated tau accumulation in AD, the efficiency of memory may be affected. Recent studies in AD mouse models suggest that fewer immature neurons in the dentate gyrus get recruited into the engram during learning and memory and that their molecular profile is distinct compared to the healthy brain, which is manifested by memory impairments (Fig. 4) (Mishra et al., 2022). Another study suggests that memories are successfully formed in an AD mouse model but cannot be retrieved (Roy et al., 2016). It has been proposed that engram cells can be the emerging therapeutic target to retrieve lost memory in the early stage of AD. Thus far, translational experiments pursuing the manipulation of the engram have been promising. For example, optogenetics has been safely and effectively applied to awake non-human primate rhesus macaques (Han et al., 2011, 2009b). In addition, viral transfection in transgenic mice can also be a strategy to specifically activate memory cells. For this purpose, more studies examining the engram in AD are warranted.

4. Summary and future directions

Research on manipulating memory engram cells is a relatively recent and emerging field, which can be classified into three categories: (1) implanting false memories, (2) retrieving inaccessible ones, (3) altering the emotional valence associated with specific memories. An engram-centric memory hypothesis explains the requirements of an efficient neuronal network with synapse function and connectivity for the efficient memory retrieval by engram cells. Studies to this effect in AD mouse models can provide novel information that would provide new information on the molecular and cellular constituents underlying memory deficits in AD and related dementia.

Many questions concerning the fate of the engram in aging and dementia remain. Future studies should investigate the memory substrate along its behavioral manifestation in health and disease (Box 2).

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Data Availability

No data was used for the research described in the article.

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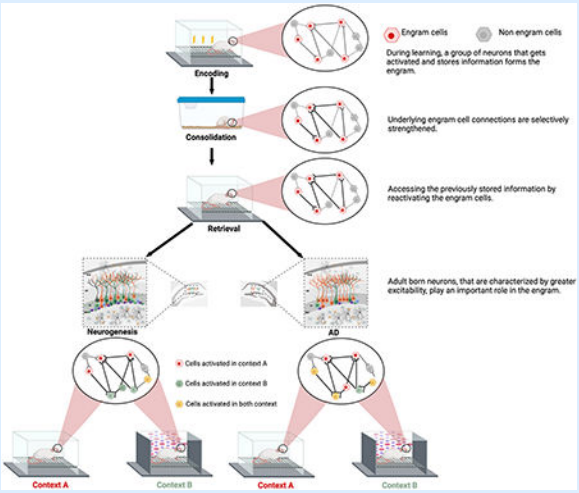
Box 1

What is an engram.



Box 2

The toolbox of engram identification.

The use of IEGs to identify the neuronal substrate of the engram may not encapsulate the memory in its entirety. Memories involve multimodal, salient experiences. While IEGs have been useful tools for studying the engram, they also have limitations. Previous studies suggest that there is a large, but not complete, overlap in neuronal ensembles expressing various IEGs (Minatohara et al., 2015), raising the question of whether different IEGs capture different subsets of the engram ensemble, and whether different IEGs may have different physiological roles (Gallo et al., 2018). Furthermore, IEGs are expressed minutes after an experience and remain expressed for some hours afterwards. While this is useful as an experimental tool, it is not known what fraction of the memory is captured by IEGs. It may be possible that IEGs capture some but not all neurons critical for a memory. Further tools should also be developed in the context of pathology, such as AD, where IEGs may be dysregulated. A deeper understanding of the neuronal substrate of memory traces is critical to advance the field.

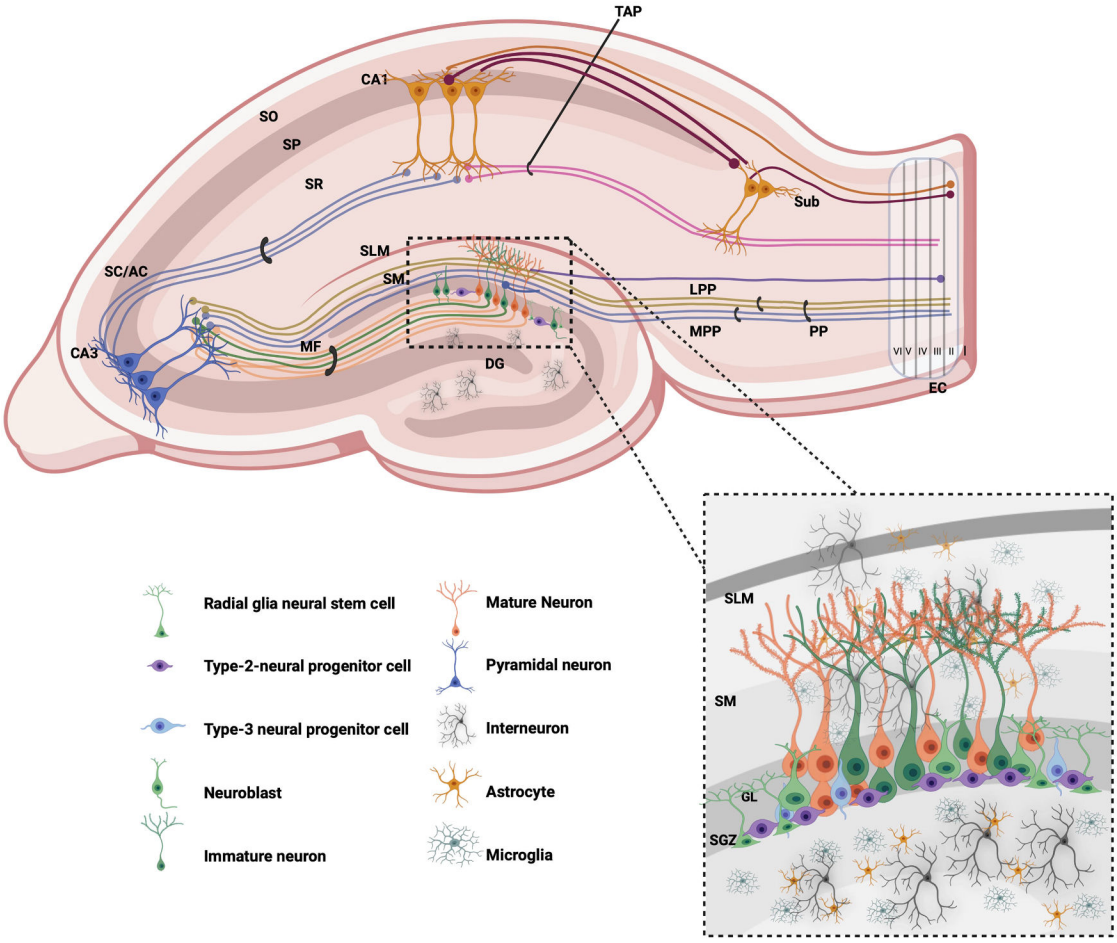


Fig. 1.

Neurogenesis is a part of the gateway to memory formation. New neurons are continuously added to the dentate gyrus and play a role in the function of the hippocampal formation circuitry. SO: *stratum oriens*, SP: *stratum pyramidale*; SR: *stratum radiatum*; SLM: *stratum lacunosum moleculare*, GCL: granular cell layer; CA: *cornu Ammonis*; MF: mossy fibers; SA/AC: Schaffer collateral pathway; LPP: lateral perforant pathway; MPP: medial perforant pathway; PP: perforant pathway; Sub: *subiculum*; EC: entorhinal cortex.

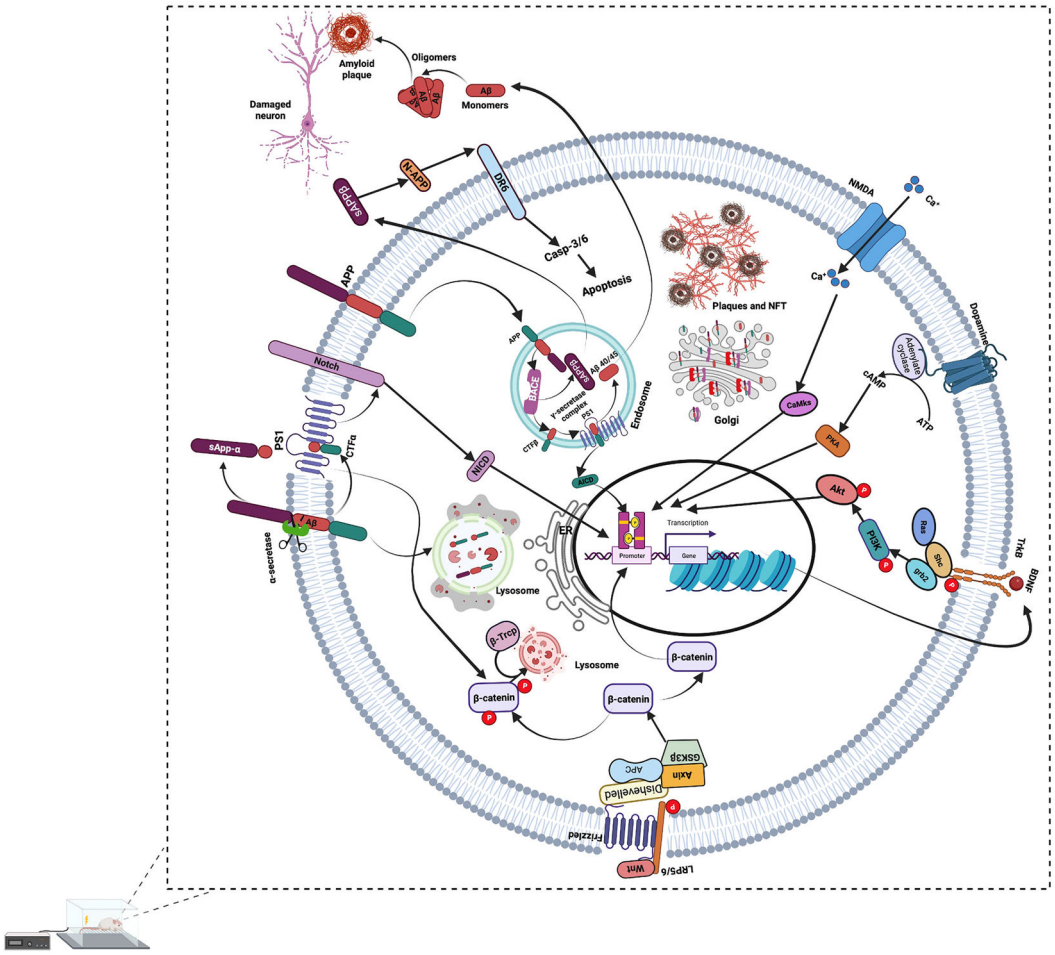


Fig. 2.

Molecular signals underlying memory formation. Signaling pathways regulating learning and memory, including signals that play central roles in Alzheimer's disease, e.g., amyloid precursor protein (APP). sAPPα: soluble amyloid precursor protein alpha, NMDA: N-methyl-D-aspartate, NICD: notch intracellular domain, CAMKs: Ca^{2+}/calmodulin-dependent protein kinase, PKA: protein kinase A, PI3K: phosphoinositide 3-kinase, grb2: Growth Factor Receptor Bound Protein 2, Ras: Rat sarcoma virus, shc: Src homology and Collagen, BDNF: brain derived neurotrophic factor, ATP: Adenosine triphosphate, TrkB: tyrosine receptor kinase B, NFT: neurofibrillary tangles, GSK3β: Glycogen synthase kinase-3 beta, APC: adenomatous polyposis coli, Aβ: beta-amyloid, PS1: presenilin 1, cAMP: Cyclic adenosine 3′,5′-monophosphate, AICD: APP intracellular domain.

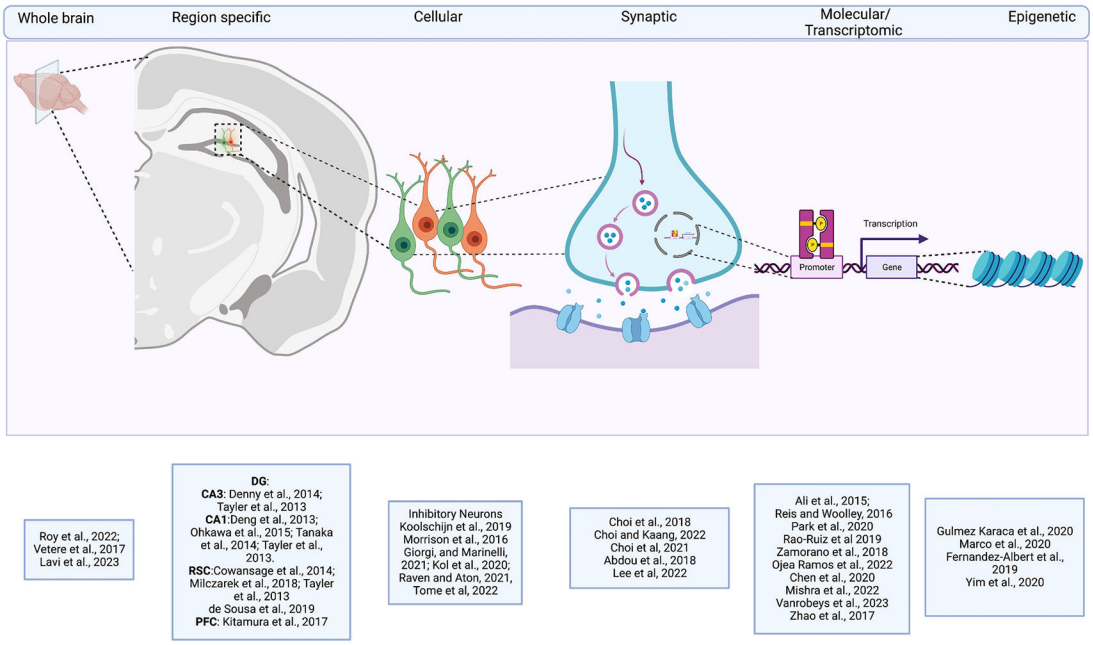


Fig. 3.

The multifaceted levels of memory engrams. The engram is manifested at the circuitry and cellular levels and has synaptic, transcriptomic and epigenetic fingerprints.

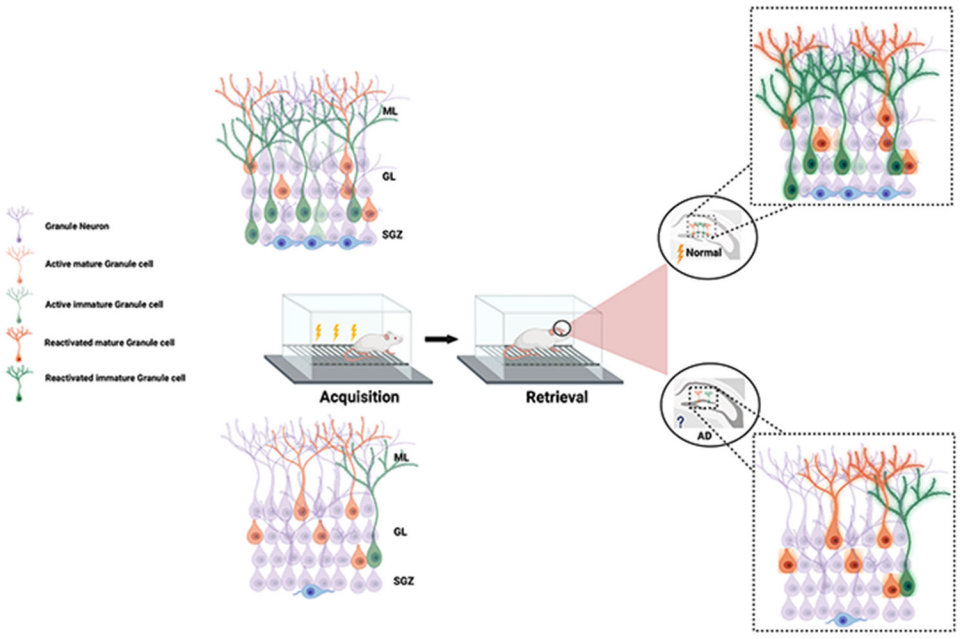


Fig. 4.

Neurogenesis in the engram in health and in Alzheimer's disease. Immature neurons in the dentate gyrus get recruited into memory engram during memory acquisition and reactivated during retrieval. In Alzheimer's disease (AD), deficits in neurogenesis are manifested by impaired recruitment of immature neurons. SGZ: subgranular zone, GL: granular cell layer, ML: outer molecular layer.