Allocation of the Memory Engram: Miniature Review

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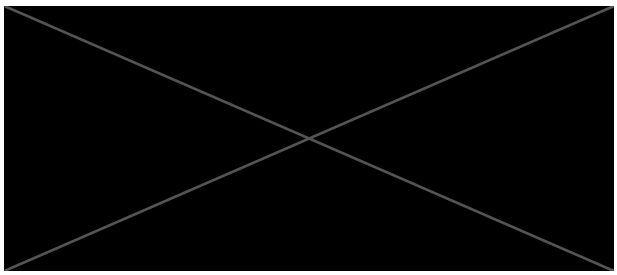

SUMMARY

The formation of memories has been a long-standing mystery in the field of neuroscience. The engram theory postulated by Richard Semon in 1904 sought to explain this phenomenon, that engram cells store memories via long-term physical changes. Only in recent decades do we have the technology to study them. Tools like optogenetics and viral vectors allow us to tag and detect engram neurons during behavioural paradigms. Despite these advancements, many questions about memory formation remain.

1.0 BACKGROUND

1.1 History of the Memory Engram

One of the most complicated questions in neuroscience research is how memories are encoded, consolidated, stored, and recalled. To answer this question, the German memory researcher and zoologist, Richard Semon, introduced a new term known as the memory engram in 1904 to describe the phenomenon of memory formation, storage, and recall (1). The memory engram describes how memories are stored as long-term physical changes in the brain. He proposed that different networks of cells are activated for different experiences to create a long-lasting change and when presented with the right stimuli they can be reactivated, thereby triggering memory recall (2). Though his theory was largely ignored, the American psychologist, Karl Lashley, dedicated a significant part of his career to localize Semon's engram in the brain (1). Due to the lack of success in localizing the engram, in 1949, Lashley's student and Canadian neuroscientist, Donald Hebb developed his own theory that was quite reminiscent of Semon's "memory engram" (2). He theorized that memories can not be isolated to one specific region of the brain. They are stored throughout the brain in interconnected networks as "cell assemblies" or "memory traces". He further added that the entire network of assembly cells does not need to be reactivated necessarily to trigger memory recall, nor does partial damage to the network delete the memory in its entirety (1). Still at this time diving into the neurobiological mechanisms to prove the existence of memory engrams was an incredibly challenging task. However, in more recent years with the progression and development of modern technologies and experimental methods, there is a resurgence of memory engram research.

1.2 Where are we today?

Presently, our knowledge of memory allocation seems to support memory engram theory, in particular, Hebb's theory of interconnected networks of cell assemblies where "cells wired together, fire together". We have several types of memories that can activate different brain regions during recall, memory encoding cannot be isolated to one specific region (3). For example, the hippocampus is often thought of in popular science to be our main memory storage log, evidence of memory engrams show consolidation and recall in other brain regions such as the amygdala (3). However, the major current belief in memory engram research suggests that there is a competition between neurons to be recruited as engram cells and that this competition is dependent on the relative excitability of each neuron (1). It also appears that the size and strength of an engram is not reflected in the number of neurons recruited to be engram cells but in the number of synapses connecting them (1). Thus, the size and strength of a memory engram relates well with forms of long-term synaptic plasticity mechanisms such as long-term potentiation (LTP) and depression (LTD) (4, 5). However, while synaptic plasticity and memory engram formation have clear similarities, their linkage continues to be controversial in the field (4, 5).

The formation of memory engrams has also been connected to the expression of immediate early genes (IEGs). IEGs are well-known to quickly respond to various changes that occur in cells and have high selective expression in neural populations undergoing learning and memory formation (6). However, the molecular and cellular mechanisms of IEGs in memory engram formation remain to be elucidated. Overall, the purpose of this miniature review is to provide a detailed account of engram theory and types of experimental design used to study mechanisms of the engram. Additionally, this paper aims to present possible mechanisms of different stages of memory formation and questions about the engram that remain unanswerable at this time.

2.0 METHODS

2.1 Literature Search

The study was performed following systematic review guidelines for a mini review on theories and experimental design on the allocation of the memory engram. The literature search was conducted using the international database, Pubmed, for articles published over the last 5 years between 2019 and 2024. Key original articles and reviews were identified using 9 different keywords and phrases. The keywords and phrases included in the searches were: memory engram, memory allocation, engram cells, engram excitability, engram cellular mechanisms, hippocampal memory engrams, amygdala memory engrams, memory consolidation theories, and immediate early genes. All stages and results of the literature search and article selection process are outlined in Table 1.

2.2 Article Eligibility Criteria and Data Compilation

Articles included in this study were required to meet the following criteria:

1. Review or original research article.
2. All keywords or similar within each search term in the title.
3. Either related to theory or experiments relating to memory engrams.
4. Published within the last 5 years (2019 – 2024).

Article exclusion criteria:

1. Editorials and other articles that were not a review or original research.
2. Not a freely accessible article.
3. If the article had a focus on memory engrams relating to a specific neurological disease or psychiatric disorder.

3.0 RESULTS

3.1 A Total of 6 Articles Identified in Pubmed

In the international database, Pubmed, a total of 4 search phrases were used to identify key articles describing the memory engram theory and experiments with current evidence to support this theory. A total of 6 articles were selected for the review and were published in the last 5 years between 2019 and 2024, a free source, had key words from search phrases in the title and/or abstract, and were either reviews or original research articles. An overview of the search results can be found in Table 1.

Table 1: Literature search results. Overview of the literature search conducted in Pubmed for key phrases for research and theoretical knowledge of the memory engram. Each stage of the selection process narrowed to the most relevant articles available and carefully chosen. *In the final selection those with an Asterix indicate a repeated article.

	Primary Database: PubMed	**Stage 1**	**Stage 2**	**Stage 3**	**Final Selection***
Key Phrases	*Search Volume*	*2019 - 2024*	*Free Source*	*Title or Abstract*	*Total*
Memory engram	720	345	250	61	4*
Engram excitability	69	34	25	2	1*
Engram mechanisms	179	91	69	5	1*
Engram theory	102	42	28	5	1

Of the 6 selected articles:

1. 1 gives a thorough overview of the history of memory formation and consolidation theories before Richard Semon.
2. 1 describes the debate between describing engrams as cellular or synaptic along with evidence supporting both schools of thought.
3. 1 gives an overview of modern engram experiment types.
4. 1 is a study on memory engrams in the hippocampus and amygdala.
5. 1 is a study on how a false memory can be generated in the amygdala by co-allocation of a memory engram.
6. 1 is a review on the molecular mechanisms of the memory engram.

4.0 DISCUSSION

4.1 The Engram Before Richard Semon

As described in the introduction, the search for the memory engram has existed for the last century and only with the advancement of modern technology and methods do we have evidence to back up Semon's theory. However, Semon did not come up with the memory engram theory out of nothing; in fact, in the last 150 years, there has been significant advancement in our understanding of the nervous system and how it functions (7). Terms such as "neuron", "axon", "dendrite", "synapse", and "neurotransmitter" are very modern and our ability to easily define them now is important for the development of memory engram theory and our current evidence to support it. Many scientists before Semon laid the groundwork and some had similar ideas about memory allocation as well (7).

In the middle to late 1800s, the popular theory at the time for neural communication was that neurons were connected as one giant electrical network as a continuous reticulum. Italian pathologist, Camillo Golgi, invented his "black reaction" Golgi staining to observe and describe the layers of neurons under a microscope to lay foundation for his Reticular Theory (7). The invention of the Golgi stain eventually led to Spanish neuroscientist, Santiago Ramon y Cajal, to discover contradictory evidence to Golgi. Cajal's work was the first evidence of what we now know

today as the synapse and that the nervous system is made of discrete cells rather than a continuous reticulum (7). From his discovery, he described two theories (7). The first was that nerve cells secreted chemotactic substances to attract each other. The second was that the nervous system and brain was constantly changing and had plasticity which was a huge progression for neuroscience and connects well with Semon's engram theory that our memories are stored as physical changes in the brain.

In the 1890s, Italian psychiatrist, Eugenio Tanzi, and Austrian neurologist, Sigmund Freud, also proposed theories that are of similar ideology to Semon's memory engram (7). Tanzi postulated that transmission via the junction between neurons in the formation of associative memories was dependent on localization facilitation. He argued that repeated activation of a neural pathway when learning would increase the number of neurons in the pathway to reduce the distance between each other which would then improve and strengthen transmission (7). While we know today that this is not completely correct, it is an early potential description of a physical change in the brain for memory formation. In congruence with Semon, Freud also theorized that learning creates long-term changes in the efficacy of neuronal connectivity which could be a possible mechanism for memory (7).

Finally, just a few years before Semon came up with the term "engram", and very long before Hebb described memories being stored as interconnected neuronal networks, English psychologist, William McDougall, presented his synaptic theory to describe a physical foundation for memory formation (7). He sought to describe synaptic plasticity as a mechanism for various mental processes and that neurons are functionally grouped together. He further explained that stimulation of one neuron in the group would lead to activation of the rest of the group which sounds a lot like Hebb's "cells that fire together, wire together" (7). Overall, it does not seem right to only credit Semon and Hebb with engram and cell assembly theories when several scientists made significant contributions and very similar theories prior.

4.2 Engram Experiments

4.2.1 Summary of the Past and Present

In the beginning of the experimental work for searching for the existence of the memory engram, Karl Lashley first made an attempt at the seemingly impossible task with the resources available at the time. He spent decades of his work trying to localize the engram only to discover that it was impossible to localize and concluded that the engram was very ambiguous (1). For his experiment he had a maze with a specific path for several rats to learn in order to obtain a reward at the end. Lashley's assumption was that when the rats had memorized the maze route that the engram for the maze route would localize in the cortex (1). He then proceeded to remove different parts of the cortex and different sizes and have the rats attempt to find their way through the maze again. While the size of lesions in the cortex were correlated with the degree of memory impairment in the rats, the location of the lesion did not matter. These experiments are what led to Hebb theorizing that memory cannot be localized, it is distributed across the brain.

While Lashley's experiments were not fruitful in the end, today we have more advanced technology and methods that have allowed us to identify evidence of engrams. There are four main types of study: observational, loss-of-function, gain-of-function, and mimicry studies. For example, observational studies often use viral vector methods like optogenetics or chemogenetics to tag cells active during training that express IEGs (1). Additionally for memory testing, observational studies will use immunohistochemistry staining to identify IEG expressing cells. The

purpose of this is to compare the two cell populations and if there is an overlap between them, this is thought to be indicative of an engram. The purpose of loss-of-function studies is to disturb an already identified engram by inhibition or ablation before memory testing to observe how it impacts memory and behaviour (1). Gain-of-function studies do the opposite where engram cells are artificially activated to trigger memory retrieval which also utilizes optogenetics or chemogenetics (1). Finally, mimicry studies attempt to induce an artificial memory which can also influence behaviour (1). Each of these studies are important for increasing our understanding of memory encoding and how it works.

4.2.2 Mixed Engram Study in the Hippocampus and Amygdala

The most common and well-studied structures in memory engram research are by far the hippocampus and amygdala. This is because both structures have well established easily constructable paradigms. In the hippocampus, spatial and navigation memory can be studied in rodents using maze tasks, while in both the amygdala and hippocampus, emotional memory can be studied using fear conditioning. In the study *Zaki et. al. 2022*, they investigated if re-instating a fear would re-engage the original engram cell representation in the basolateral amygdala (BLA), dentate gyrus (DG), and CA1 in the hippocampus or if fear re-instatement would give rise to a new engram cell representation (8). The purpose of their investigation was because it is often seen clinically that patients who receive exposure therapy remain prone to fear relapse. Additionally, this study is a good example of an engram study that utilizes several ways to investigate engrams as mentioned above: observational, loss-of-function, and gain-of-function.

To investigate this, they performed contextual fear conditioning on male C57BL/6 mice using a foot shock stimulus and two rounds of extinction training the day after (8). To reinstate the memory, they would place the mice in the original context and a novel environment with the conditioned stimulus. Overall, freezing responses were much higher in the original fear conditioning environment compared to a new environment. To identify fear memory engrams, they performed an observational study using viral vectors to tag neurons with yellow fluorescent protein (eYFP) and c-Fos, a commonly used IEG for engram studies (8). To determine which cells became memory engrams, they counted cells expressing eYFP and c-Fos during the contextual fear conditioning paradigm and during recall to determine which cells overlap. Between the BLA, CA1, and DG, the DG had the most significant overlap between cells in fear conditioning and recall. During extinction protocol, the overlap in cells decreased in the DG, but increased again when the mice were reinstated in the original environment. The BLA and CA1 had roughly the same activity throughout, however, the expression of c-Fos significantly increased in the BLA after reinstatement (8). Overall, the result indicated that engram cells originally active in the DG during contextual fear conditioning are reactivated when fear is reinstated. Additionally, the increased expression of c-Fos in the BLA after fear reinstatement may also indicate that same engram cells that were initially active during fear conditioning are reactivated.

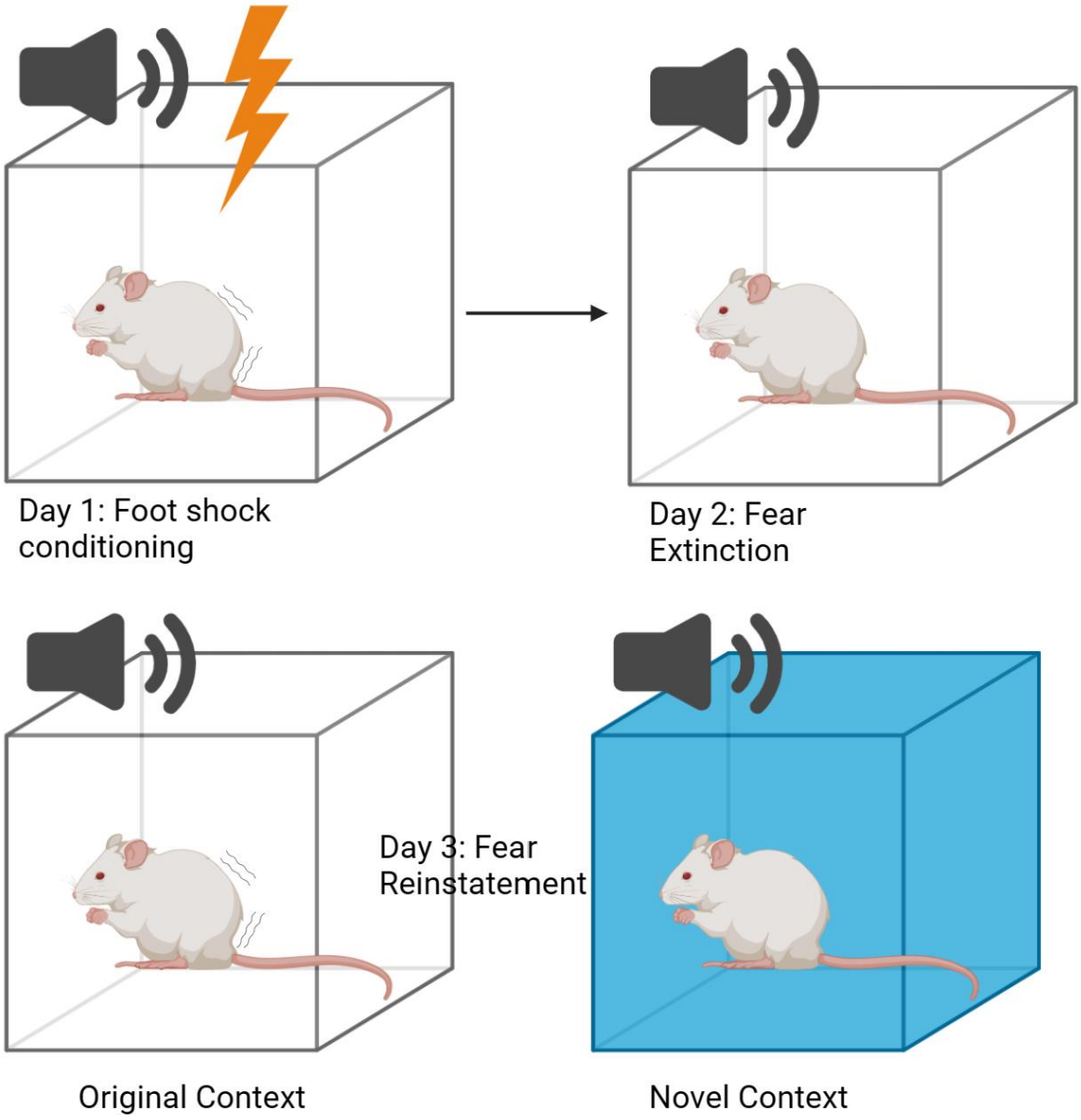

Figure 1: Fear reinstatement paradigm for *Zaki et. al. 2022*. This figure was created using Biorender.com.

Once *Zaki et. al. 2022* had observed fear engrams in the DG, BLA, and CA1, they continued with a loss-of-function study to determine if the neuronal activity in fear conditioning was required for reinstated fear expression (8). To investigate this, they used optogenetics by injecting a light-sensitive neuronal silencer called ArchT, c-Fos, and eYFP with a viral vector to tag DG, BLA, and CA1 neurons. When mice were subjected to reinstatement recall, they exhibited significantly less freezing behaviour when neurons were optically inhibited with light. Interestingly, this behaviour was reversed when the light was switched off for the DG and the BLA, but freezing did not increase once again for the CA1 (8). This indicates that the engram cells active during initial fear conditioning are required for fear reinstatement since their inhibition during reinstatement resulted in decreased freezing behaviour in the mice. However, it appears that this inhibitory effect has a more long-term impact in the CA1 compared to the BLA and DG (8).

Finally, *Zaki et. al. 2022* performed a gain-of-function study to determine if they could trigger fear reinstatement by artificially activating the engram cells instead of using a foot shock (8). To do this they optogenetically expressed channel rhodopsin (ChR2) in the fear engram cells in the BLA, DG, and CA1 and performed the contextual fear conditioning and extinction as normal. Then, to reinstate the fear memory, the mice were placed back in the original fear conditioning environment and ChR2 tagged engram cells were stimulated for 60 seconds. Overall, there were no significant differences in freezing compared to controls and it was concluded that activity in these neurons is not enough on its own to trigger fear reinstatement (8). This suggests that reinstating fear is more complex than simply reactivating associated engram neurons. This could possibly mean there is a specific firing pattern in how the engram neurons communicate and/or other brain region connections are involved and are required to activate the engram neurons or be active in tandem. Overall, the experiments used in this study are just one example of how engrams can be studied and understood. It also highlights the importance of investigating how memory engrams function in fear-based memory because understanding such mechanisms will help in the future for finding better treatment for those who have suffered traumatic events.

4.2.3 Mimicry Study on Neuronal Excitability in Memory Allocation and Generation of Behaviour

Another interesting way to experimentally investigate engrams are mimicry studies. As previously described, mimicry studies create a false memory that can be retrieved and observed through behaviour. Often times this involves the use of a neutral stimulus in one context and an aversive stimulus in a different context. The stimuli should technically not be associated with each other, but end up producing a freeze response when the animal is placed back in the neutral stimulus context and not in a novel context with the neutral stimulus (1). This is considered a false fear memory. In general, false memory formation is important for understanding why witness testimony can sometimes be unreliable in front of the law and why certain details of our memories can sometimes get muddled and mixed together with other events (9).

In the study *Lau et. al. 2020* they hypothesized that a false fear memory could be generated in mice using knowledge of how engram cells compete for memory allocation based on their relative excitability and that they remain more excitable for several hours post-event (9). Because of this, their thought was that there would be an overlap memory allocation if they presented mice with a neutral stimulus at a close enough timepoint after fear conditioning. In the study they trained male and female C57BL/6NTac and 129S6/SvEvTac mice with tone cued and light cued fear conditioning with a foot shock. Then at 3 hours or 24 hours they placed the mice in a new environment and played a different tone without foot shock. They used both tone and light cued paradigms to eliminate the possibility that even if they used a different sound, that it could be generalized for the fear response for the same sensory modality. What they found was that when mice were first exposed to the second neutral stimulus 3 hours after or 24 hours after did not make a difference in the freezing responses. However, the next day, the 24-hour group froze no more than the control group while the 3-hour group froze significantly more than the 24-hour group and control to the neutral stimulus in the same context. This result was an indication that a false fear memory had been created, however, further investigation was required to verify that there was an overlap in engram cell memory allocation.

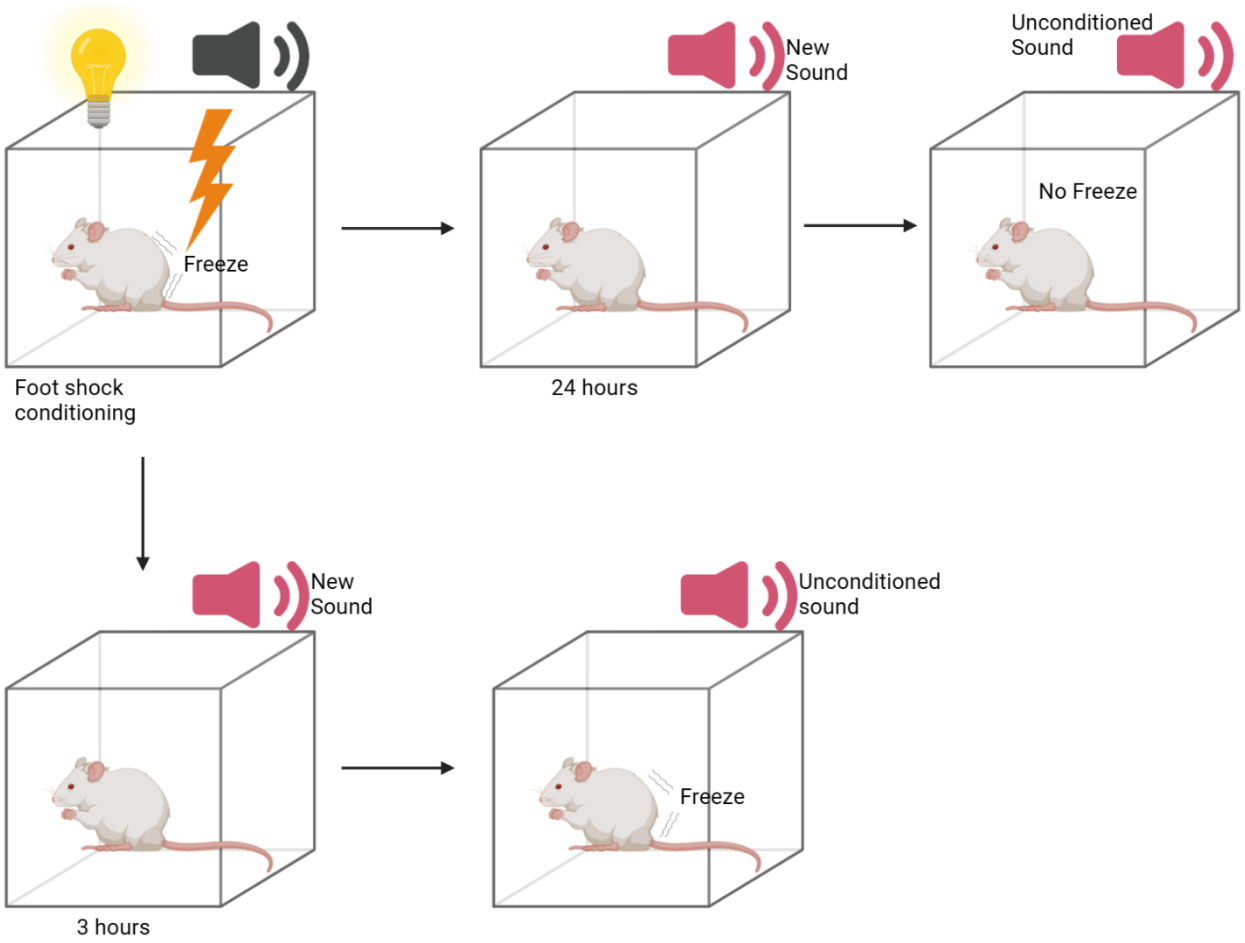

Figure 2: False fear memory allocation paradigm from *Lau et. al. 2020*. This figure was created using Biorender.com.

To verify their result, they also used optogenetics to determine that the temporarily continued hyperexcitability of engram neurons post-memory formation was in fact the mechanism of the behaviourally observed false memory (9). Additionally, because their experiments were time sensitive, they attempted to manipulate the allocation of engram cells rather than tagging cells that express IEGs because of the slower dynamics compared to neuronal activity (9). Therefore, rather than waiting to see which cells become engram cells, one can stimulate neurons to increase excitability prior to fear conditioning to create a bias for those cells to become an engram cell population. This is quite an interesting way to investigate memory engram allocation since it is more common to tag cells with IEG promoters to identify engrams post-allocation. However, while memory engram allocation has been well associated with IEG expression (10), biasing engram cells by increasing excitability before a learning task also helps to confirm this as a direct mechanism in memory formation.

To bias the allocation of engram cells, they optogenetically infected neurons in the lateral amygdala with NpACY which expresses an excitatory blue light activated ChR2 and a red light activated halo rhodopsin (9). Before fear conditioning, they stimulated neurons tagged with NpACY with blue light. When mice were presented with the conditioned stimulus once again, they inhibited the same neurons with red light and saw a decrease in the freeze responses compared to controls where red light was shone on random neuronal populations (9). Then at 3 hours and

24 hours, the mice were presented with a neutral stimulus along with red light inhibition to see if it would interrupt false memory formation. When presented with the neutral stimulus the following day, they found that there was no difference in freeze response between the two groups and that only those who did not receive red light inhibition had freeze responses. Furthermore, upon statistical analysis they were able to determine that there was an overlap in the neuronal populations involved in the fear conditioned engram and the neutral stimulus false fear memory engram (9).

Overall, the results of this study indicate that the relative excitability of engram neurons primes them for memory allocation. This is because their continued hyperexcitability shortly after a learned experience increases the likelihood of false memory formation by associating with a similar experience (9). These results are not only important for understanding mechanisms of memory engrams but also for understanding why humans can also develop false memories and their impact in recollection of traumatic events, legal cases, childhood, and more.

4.3 Mechanisms of the Memory Engram and Remaining Questions

While we now have several studies with evidence to support the existence of the memory engram and cell assemblies several questions still remain. One of these questions is: are engrams best described as cellular, synaptic, or somewhere in between (11)? The description of a cellular engram refers to a group of cells that are activated when learning something new. This group of cells then becomes functionally connected and for there to be memory recall of what was learned, some or all of the cells must be activated again (11). While engrams are commonly described in terms of engram cells, the synaptic connections among these cells are just as important. Synaptic engrams are described as the change in synaptic strength between engram cells in which these connections are what account for memory formation (11). Overall, there appears to be evidence supporting and discrediting both which indicates that a complete memory engram may require both cellular and synaptic mechanisms or something else entirely. Not all cells that fire at the same time are necessarily engram cells, and not all synaptic connections lead to memory formation (10, 11).

As described in the introduction, there has been some debate as to what degree is LTP and synaptic plasticity involved in memory formation. This is because there are a few stages to memory formation: encoding, consolidation, storage, and recall (10). While by definition an engram requires some level of plasticity for there to be a physical change, for it to be a long-lasting change, this mat not be explained by synaptic plasticity alone. Furthermore, many studies have also shown that inhibiting the mechanism of LTP in amnesic mice does not prevent the encoding and storage of memory (10). Artificial engram activation still continued to produce a behaviour that indicated a memory had been formed. However, other studies have shown that differences in dendritic spine shape and structure may be important plastic changes for memory formation. Memory storage has been connected to dendritic spines with a mushroom-like shape while learning has been connected with thin dendritic spines (10). For example, in the DG there was a notable increase in mushroom-like dendritic spines between 1 to 5 days after memory encoding (10). Another reason for LTPs involvement in the memory engram has to do with the expression of IEGs. When LTP occurs, there is a large influx of Ca^{2+} which is important for several signalling cascades that activate transcription factors. This then increases the expression of IEGs like Arc, c-Fos, and Zif268 (10). As indicated in the previously described study, *Zaki et. al. 2022*, tagging neurons with IEGs to identify engram cells is quite common in engram studies (1, 8). This is because IEG expression is very rapid and indicative of active cells which as shown in *Lau et.*

al. 2020, increased excitability and activity of an engram cell preferentially allocates it to the engram during memory formation (9). Overall, it appears that both synaptic and cellular mechanisms are important for memory engram formation, however, additional mechanisms may also be at play.

Another major question when it comes to memory, is that if the nervous system is so plastic and subject to constant changes, how are memories stabilized between engram cells? How do already existing engrams not get changed or affected? One possibility is that engrams store memory in stable connectivity patterns or that synaptic connections between neurons are stabilized by neural cell adhesion molecules and perineuronal nets (PNNs) (10). Neural cell adhesion molecules are known to provide stability, strength, and help with the maturation of synapses. They are also important for transcription and protein synthesis. PNNs are also important for neuronal and synaptic stability, but they are a specific type of extracellular matrix (10). Interestingly, PNNs are known to restrict synaptic plasticity which could be an indication of how neurons hold onto memories (10). While it is currently unknown how PNNs restrict synaptic plasticity, they are thought to have some kind of restraining effect on neurons and limit the diffusion of AMPA receptors (10). Finally, there is additional possibility that glial cells also have an important role in memory formation. While microglia are typically thought of as the immune cells of the nervous system, they also have an important role in synaptic pruning and continue their house keeping in the healthy adult brain (10). Therefore, microglia may also have a role in modifying connections between neurons in memory formation. Astrocytes also release gliotransmitters such as D-serine which is important for LTP. There is also evidence that increased activation of astrocytes enhances memory recall (10). Finally, oligodendrocyte proliferation and myelination increases when there is an increase in neuronal excitability which can of course be attributed to the need for increased transmission. However, the increased excitability of the neurons is also important for engram cell selection (10). Together, neural cell adhesion molecules, PNNs, and glial cells are alternative mechanisms that may facilitate memory formation in engram cells and not only synaptic plasticity.

4.4 Conclusions

In conclusion, memory engram research has increased significantly in the last few decades since the conception of the theory over a century ago. While we have come a long way in developing methods that can be used to study engrams such as with optogenetics and behavioural paradigms like fear conditioning, we still have a long way to go in elucidating the mechanisms of memory formation. For example, while it is great that we have some understanding on what kind of changes may occur for an engram to form, it remains unclear how engrams are stabilized long-term.

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