**What Have We Learned About the Engram?**

**Jonathan Najenson**

Penultimate Version, Forthcoming in *Synthese*

**Abstract** The discovery of the engram, the physical substrate of memory, is a central challenge for the sciences of memory. Following the application of optogenetics to the neurobiological study of memory, scientists and philosophers claim that the engram has been found. In this paper, I evaluate the implications of applying optogenetic tools to the localization of the engram. I argue that conceptions of engram localization need to be revised to be made consistent with optogenetic studies of the engram. I distinguish between challenges to vehicle and content localization. First, I consider the silent engram hypothesis. According to this hypothesis, optogenetic studies indicate that synaptic efficacy, the traditional engram-bearing vehicle, is important merely for retrieval. I argue that this interpretation rests upon a misunderstanding of accessibility. Second, I argue that optogenetic-based strategies and findings conflict with preservationist and constructivist views on memory storage. There is an enduring trace, but stored content may change over time and experience, resulting in doubt about what constitutes a single engram.

1. **Introduction**

The question of the nature of memory traces has accompanied the study of memory from its inception. Plato describes memory as leaving traces on the soul as do impressions on a block of wax - “Whatever is so imprinted we remember and know so long as the image remains; whatever is rubbed out or has not succeeded in leaving an impression we have forgotten and do not know” (Plato, Theaetetus, 191d–e). Not so different from the Platonic idea, the analogy to a library where memories are put down in our minds as books, kept in specific locations for future reading, still seems to be a guiding metaphor for thinking about how memories are retained.

The existence of a remaining trace has traditionally been taken as an assumption that representational theories of memory must postulate (De Brigard 2014a). The underlying assumption is that without certain physical changes in a system that corresponds to the storage of information, learning is impossible. A mediating trace is meant to explain how retention of past information enables an individual to have experiences of the kind that would not have been possible in the absence of retained information. Consequently, the medium in which information is held has always been the linchpin of the sciences of memory.

The term ‘engram’ was coined by Richard Semon in his detailed analysis of memory (1921) and has since been adopted by neuroscientists to signify the medium in which information is held in the nervous system. Neuroscientists define the engram as equivalent to the physical substrate of memory, a neural process that physically preserves learned information (Tonegawa et al. 2015). The search after the engram in neuroscience has involved attempts to find where and how this process occurs and to characterize the information retained in this medium.

Despite its central role in theories of memory, the attempt to empirically observe the engram has historically been met with skepticism regarding its localization to a specific place. Summarizing his decades-long work using ablation of specific neural areas after a learning experience, Karl Lashley concluded that “there are no special cells reserved for special memories” (1950, p.26). The discovery of specific neural vehicles preserving learned information, ‘special cells reserved for special memories’, has been considered since Lashley’s time to be a unique methodological challenge faced by the memory sciences.[[1]](#footnote-1)

Lashley’s failure to locate the engram, however, might result from the limitations of the tools available in his time (Josselyn et al. 2015). New tools, so-called engram technology, are believed to have provided a principled way to look inside the brain and locate the engram. There is now a growing consensus among neuroscientists that optogenetic tools permit interventions, at a level of specificity, which enables the tracking and manipulation of engrams from acquisition to retrieval. As Sarah Robins has recently argued, optogenetics is a particularly powerful tool since “an engram can be tracked from its formation and then reactivated (via optogenetic intervention) to induce remembering” (2016, p.18).

The advancement made possible by optogenetics produced results that cast new light on the localization of engrams. Localization, the process of assigning an operation to a specific component, is a major step in mechanistic discovery (Bechtel 2007). Localization of the engram involves the assignment of memory storage to specific and persistent neural vehicles. Two aspects of engram localization can be distinguished. The first aspect concerns the localization of the information-carrying vehicle, like looking for a book in a library. The second aspect concerns the localization of information retained by a vehicle, analogous to locating the content retained by, potentially different, copies of a book.

While optogenetics allows to track and manipulate engrams it raises new challenges, thereby overturning neuroscientific and philosophical conceptions of engram localization. The first challenge concerns the neural vehicle where engrams are stored. On a traditional neurobiological conception of memory storage, engrams are stored as alterations in the strength of synaptic connections following a consolidation process (Martin et al. 2000). Results from optogenetic studies appear to be at odds with this traditional view. Although synaptic consolidation is disrupted, the engram can be artificially retrieved through optogenetic activation. In place of the traditional view, Tonegawa and colleagues (Roy et al. 2017; Josselyn & Tonegawa 2020) propose that engrams are stored independently from alterations in the strength of synaptic connections.

An additional challenge concerning content localization arises for philosophical views of memory traces. A standing question in philosophical discussions about the engram concerns whether the capacity for information storage involves persistent and discrete memory representations. Given the prevalence of memory errors, views such as constructivism take it that memory content depends on reconstructing representations from a general information store. According to De Brigard (2014b), representations are reconstructed when similar patterns of activation encoded during past events are re-activated from neural structures which other capacities may share. Optogenetic studies of the engram, however, have been interpreted as standing in tension with the constructivist rejection of persistent and discrete memory traces, primarily due to the key role engrams play in producing false memories (Robins 2016). Optogenetics studies of the engram, in turn, can be seen as supporting a more traditional ‘storehouse’ view, according to which preserved and persistent representations are retrieved from memory storage.

The purpose of this paper is to evaluate what has been learned about the engram, and its localization, following the application of optogenetics. Specifically, I aim to argue that neuroscientific and philosophical conceptions of engram localization need to be revised to be made consistent with optogenetic studies of the engram. Optogenetic tools may permit direct activation of stored information but leave open where such information is stored and the role that changes to synaptic strength play during encoding to retrieval. Additionally, although optogenetic studies provide evidence about the existence of an engram, such stored information is altered and modified over time, thereby conflicting with both preservationist and constructivist conceptions of memory storage.

I begin in section 2 by examining how optogenetic tools are used to find the engram. I present the criteria given for engram discovery and describe the strategies used to confirm them. I intend to show the ways in which the application of optogenetics is used to localize engrams, thus constraining the possible responses to the challenges that will be discussed in subsequent sections. Section 3 revolves around the issue of vehicle localization. In this section, I examine the proposal that a silent engram, an inaccessible engram that may only be retrieved artificially, through optogenetic activation, indicates that memories are stored independently from changes to synaptic plasticity. I argue that such claims rest upon an unnecessary conflation of accessibility and retrievability. In section 4, I deal with questions concerning content localization. I argue that optogenetic studies reveal that engrams do persist but the information they carry changes over time and experience. The upshot is that although a causal link to the past has been identified it raises new challenges to philosophical views about the nature of engrams.

1. **Engram Discovery - Criteria and Strategy**

In this part, I look at how the use of optogenetic tools to answer questions about memory involves the application of different strategies to confirm the discovery of the engram. Although some of these strategies have been used to study the engram before, the novel significance of optogenetic interventions is in providing the means to track, manipulate and artificially create specific engrams. Focusing on how these strategies are used to confirm such criteria is crucial for understanding claims made by neuroscientists about finding the engram.

Neuroscientists rely on three criteria to evaluate the discovery of an engram.[[2]](#footnote-2) The first discovery criterion is *contiguity*. There is an enduring physical change in the nervous system that results from a learning experience. The second discovery criterion is *specificity.* The information stored in an engram is retained in a specific neural vehicle that can be tracked and distinguished from other engram and non-engram vehicles. The last discovery criterion is *similarity.* The vehicles carrying an engram bear a structural resemblance to the informational link that is remembered, such that by intervening on the engram’s structure, researchers may predict what can be remembered. When these three criteria are met, the neural process under investigation counts as an engram.[[3]](#footnote-3)

The development of optogenetics, a new technology that enables the manipulation of neurons with light, is believed to have provided a principled way to locate the engram. So-called engram technology grants the ability to label and manipulate components of specific memory engrams, by fusing immediate early gene labeling and optogenetics (Tonegawa et al. 2015). The way optogenetics works is by piecing together genetic constructs of light-sensitive proteins (opsins) and either virally inserting them into target neurons or genetically engineering an animal to express these light-sensitive proteins in a designated area. Optical fibers are inserted, and specific neurons can be labeled, activated, and silenced by light manipulation. In particular, optogenetics allows both tracking and on/off switching of neural activity.

Optogenetics is believed to have provided the means to find the engram because it allows the combination of experimental strategies. These strategies concern a kind of experiment examining a causal hypothesis in different neuroscientific levels, e.g., modulating a molecular variable A and measuring the effect on a behavioral variable B. I follow Silva, Landreth and Bickle (2013) in dividing these strategies into positive and negative manipulations. Manipulation experiments are positive when they involve an increase in variable A, and negative when they involve a decrease in variable A. For instance, in a positive manipulation experiment, researchers measure the effect of A on B by increasing the probability of receptor’s A activity and using a behavioral task to examine the effect of this change on memory phenomenon B. Optogenetic tools are used to localize engrams by combining positive and negative manipulation experiments.

I evaluate three types of such strategies: loss-of-function, gain-of-function, and mimicry. The novel advantage of optogenetics in applying these strategies comes from two reasons. First, optogenetics makes it possible to combine both loss-of-function and gain-of-function in one experimental setting using a similar tool. The combination of these strategies in tandem allows to inhibit and induce the formation of a specific engram. Second, in contrast to loss-of-function studies which can be conducted with various methods (examples include natural or initiated ablation, genetic engineering, and application of chemical agents), the ability to perform gain-of-function experiments is an important methodological advantage gained from optogenetic tools. Optogenetic-based strategies, thus, are unique in providing *novel* evidence for the existence of the engram.[[4]](#footnote-4)

Let us examine these strategies to see how they are used to localize engrams. The first discovery criterion is contiguity. Following the acquisition of a memory, persistent physical changes resulting from the retention of learned information are expected to occur. To determine this, researchers employ a loss-of-function strategy. In loss-of-function experiments, a biological structure’s capacity to perform a certain activity is disabled. By analyzing the deficiencies resulting from this non-functional state, researchers can inquire into the structure’s original functional role.

Abdou et al. (2018) inquired into whether individual memories might be eliminated by preventing the physical changes resulting from a learning experience.[[5]](#footnote-5) Mice were subjected to auditory fear conditioning, in which two different tones, at 2 and 7 Hz, were associated with a foot shock. By labeling cells that were activated with a fluorescent protein, they observed that the association is formed in the synaptic connections between neuron terminals of the auditory cortex (AC) and neurons of the lateral amygdala (LA).

After tracking the formation of an associative trace, the researchers applied optical long-term depression (LTD) only to the synaptic connections that were activated by the 7Hz tone association. Optical LTD reverses the synaptic consolidation process responsible for retaining encoded information, making these neurons unable to express their newly gained state. Exposing the animals to a retrieval cue (i.e., the auditory stimuli) revealed that they lacked any fear of the 7Hz tone but still responded to the 2Hz tone.[[6]](#footnote-6) The animals appear to forget what the 7Hz tone signals.

When amnesia results from such manipulation, researchers conclude that without the relevant vehicle the memory cannot be retrieved. By reversing the consolidation process, Abdou et al. (2018) could confirm that the fear memory requires that an enduring physical change must persist in these neurons for the behavior to be recovered. In this case, the animals were made to lose a certain functional response by optically initiating a process that eliminates the neural vehicle responsible for retaining information about one of the tones.

The second discovery criterion is specificity. A memory is believed to have a specific neural vehicle where it is retained. To determine if a neural vehicle is specific to a memory, researchers employ a gain-of-function strategy. By creating the supposed function artificially, one could determine whether the causal structure manipulated could accomplish the functional role sought after.

To determine whether the 7Hz tone association had a specific neural vehicle, Abdou et al. (2018) induced optical long-term potentiation (LTP) in the specific cells that were labeled in the auditory fear conditioning task. First, the researchers induced amnesia by inhibiting synaptic consolidation, thus eliminating the response to both tones. Subsequently, the researchers applied optical LTP only to the specific synapses that previously retained information about the 7Hz tone.

In contrast to LTD, optically inducing LTP “turns on” the memory by artificially initiating synaptic consolidation. By applying optical LTP to the synapses mediating the response to the 7Hz tone and not to the synapses mediating the 2Hz tone response, it was found that mice displayed a fear response only to the 7Hz tone — the tone whose relevant synapses were optically activated — thereby confirming their specificity.

The loss-of-function and gain-of-function strategies employed in this study are examples of negative and positive manipulations, respectively. In the negative manipulation experiment, researchers measure the effect of a cellular variable A, i.e., LTD, on a behavioral variable B, i.e., fear response. By inhibiting variable A and using a behavioral task, in the form of exposure to a retrieval cue, researchers examine the effect of this change on variable B, the manifestation of fear memory. In the positive manipulation experiment, researchers evaluate the effect of increasing a cellular variable, i.e., activating LTP, on a behavioral variable, i.e., fear response. By inducing the cellular process, researchers examine the effect of this manipulation on memory retrieval. In this study, the animals gained a functional response by positively manipulating LTP.

The last discovery criterion is similarity. The vehicles carrying an engram are expected to be structurally similar to the informational link that is remembered. The strategy employed here, termed Mimicry, uses optogenetic tools to create an ‘apparent’ memory for some past experience that did not in practice occur or to alter the information retained in an engram by manipulating the structure of its neural vehicles (Martin et al. 2000). The underlying idea is that the engram preserves information in virtue of its underlying vehicles being organized in a certain way. Altering this structure artificially should result in a different behavioral expression.

In these cases, researchers generate one or more engrams and examine whether combining or omitting certain parts of the neural vehicle would alter the behavioral response. For example, memories may be artificially created by associating them with learning episodes from another context, or their retained information might be changed by altering parts of the underlying neural vehicle. By optically altering an existing memory in order to create an artificial one, researchers examine how changes to the structure of a neural vehicle alter the information retained in an engram (See, e.g., Robins 2016 for elaboration on this optogenetic false memory technique).

Ramirez et al. (2013) examined memory implementation by creating an artificial fear memory in mice, thereby mimicking the neural vehicle which preserves the learned experience. First, they introduced mice to a chamber and labeled neurons that were responsive to that location (context A). At the second stage of the experiment, the animals were placed in a second chamber where they received shocks, leading the animals to fear the chamber (context B). While the shock stimulus was administered in context B, the labeled neurons from context A were artificially reactivated. After the animals were reintroduced to context A, they displayed fear behavior despite never having received foot shocks in that chamber. The co-activation results in an artificial creation of a memory, connecting the original memory to the artificially activated context.[[7]](#footnote-7) Information from one context was transferred to another context by linking it to another engram. In this case, a false memory is generated by an association of neural vehicles representing a location with neural vehicles representing a frightening tone.

Mimicry experiments may also be considered positive manipulation experiments. In contrast to gain-of-function experiments, however, mimicry experiments may go beyond an increase in variable A, such as activating LTP and examining the effect on behavior. By performing interventions that *alter* the spatial or temporal distribution of the neural vehicle resulting from a prior learning experience, thereby altering the animal’s memory of that experience, researchers are able to learn about how the original memory is retained and predict what will be retrieved.

The three strategies complement each other, and it is by their combined use that an engram may be said to be discovered. Loss-of-function experiments are used to determine whether a neural process is required for memory retention. As optically halting consolidation in specific synapses eliminates a learned response, it can be inferred that without these synapses the memory might not be retained or retrieved. This inference, however, does not tell whether these synapses are sufficient for retaining that memory as there might be other neural vehicles involved. This evidence is gained by gain-of-function experiments. By employing this strategy, it is determined whether activation of specific synapses, would result in the expression of the same learned behavior.

This inference establishes, nevertheless, only that learning does or does not occur. It does not tell much about the content being retained in the engram’s latent state. Establishing what content is being retained is accomplished by similarity-focused strategies such as mimicry. The reference to changes in internal representations as a result of changes to neural vehicles is used to infer what has been learned and not merely that learning occurred. Together, these optogenetically-driven interventions indicate that there is an enduring physical change with a specific neural vehicle that is structurally similar to learned information. Such strategies underlie neuroscientists’ claims to have found the engram.

In the following sections, I evaluate whether optogenetic-based strategies and findings are at odds with neuroscientific and philosophical conceptions of engram localization. In the next section, I discuss the conflicting evidence regarding the localization of the engram-bearing vehicle. In section 4, I consider the implications of optogenetic studies to preservationist and constructivist views of content localization.

1. **Between Storage and Retrieval**

So, does optogenetics allow us to see where memories go? Despite the ability to manipulate the engram, the evidence gained from optogenetic studies presents a conflicting picture about the neural vehicles storing information. The leading hypothesis of memory storage in neuroscience is the synaptic plasticity hypothesis, according to which memories are stored as alterations in the strength of synaptic connections between neurons. Optogenetic-based results, however, have been taken to show that the traditional conception of memory storage is mistaken.

In this section, I focus on the implications of optogenetics for questions concerning the engram’s vehicle localization. Specifically, I examine whether the traditional conception of vehicle localization, according to which memory storage is localized to changes in synaptic strength, is compatible with optogenetic findings. I present a recent argument that optogenetic studies of the engram reveal that memories are not stored by changes in synaptic strength, which are important merely for retrieval. I argue that this interpretation of the evidence rests upon an unnecessary conflation of accessibility and retrievability. Consequently, both traditional and revisionary views of the engram-bearing vehicle do not accommodate the optogenetic findings.

Neuroscientists widely believe that memories are stored as alterations in the strength of synaptic connections. According to the broadly accepted model, the formation of an engram occurs through a process known as synaptic consolidation. Consolidation refers to the process by which stabilization of a memory involves gene expression and protein synthesis necessary to strengthen synapses. In this process, newly acquired information which is initially sensitive to interference, comes over time to be encoded in a format that is dependent on enduring synaptic changes in the nervous system. Underlying this process are the mechanisms of LTP and LTD, which modify the synaptic strength of pre-existing connections.

Evidence for the synaptic consolidation model comes from studies of experimental amnesia. In these studies, a treatment is administered that disrupts processes required for the consolidation process. The treatment usually administered is an amnesiac agent, anisomycin, whose application inhibits protein synthesis in the postsynaptic neuron. Inhibiting protein synthesis before or immediately after a learning experience blocks synaptic consolidation and results in amnesia of the information learned.

According to the synaptic consolidation model of memory storage, disrupting the consolidation process weakens the synaptic link, thereby preventing the formation of the engram. As described in the previous section, optically inducing LTP or LTD reinstates or blocks the formation of an engram, respectively. So, artificially activating or inhibiting synaptic consolidation may change the mnemic state of the animal, switching it from remembering the learning experience to forgetting it. Moreover, fluorescent protein labeled cells that are activated in the acquisition of that memory, exhibit substantially greater synaptic strength and higher dendritic spine density than non-engram cells, i.e., proximal but non-learning related cells (Ryan et al. 2015). These two states of neurons are correlated with different levels of synaptic efficacy: If synapses are strengthened the animal remembers; if they are weakened the animal forgets. Prima facie, optogenetic tools appear to offer an additional vindication of the synaptic consolidation model of memory storage.

Some inconsistencies, however, make it difficult to accept the conclusion that memories are stored in synapses. A surprising dissociation between synaptic strength and the engram was discovered. Ryan et al. (2015) found that engram cells retain information even in the absence of cell-speciﬁc increases in synaptic strength. After mice were treated with anisomycin, the amnesiac agent, direct optogenetic activation was applied to the engram cells which, surprisingly, resulted in successful retrieval of the memory. Natural cues, i.e., the learned stimuli, could not retrieve the memory but artificial optogenetic activation could. A memory could be retrieved in the absence of synaptic strengthening.

These findings present a puzzling inconsistency. On the one hand, information could be retrieved in the absence of synaptic strengthening but only by an artificial retrieval cue in the form of direct optogenetic activation. On the other hand, it is apparent that memory could not be retrieved with the original natural retrieval cues without a change in synaptic efficacy. What should we make of this?

Neuroscientists have interpreted these findings as indicating that the engram is stored independently from synaptic strength. Josselyn and Tonegawa argue, in contrast to the traditional model of synaptic storage, that disrupting protein synthesis consolidation does not disrupt memory storage but places the engram in a state of *silence*. Synaptic consolidation is not important for storage but, instead, plays a role in retrieval:

“The finding that optogenetically stimulating a silent engram in an otherwise amnestic mouse, even 1 week after training, induces memory retrieval challenges the view that protein synthesis-dependent cellular consolidation is important for memory storage. Instead, these findings suggest that the role of cellular consolidation is to enhance subsequent retrievability of an engram” (Josselyn & Tonegawa 2020, p.8)

To capture these different states of retrievability, memory theorists such as Tonegawa and Josselyn draw on Tulving's distinction between engram accessibility versus availability. Tulving argued that forgetting an event does not amount to the trace of that event being lost (Tulving et al. 1966). It could also mean that the engram is currently inaccessible but can be accessed given the right retrieval cues. Tulving’s distinction stemmed from experiments in which more words from a list could be remembered if retrieval was cued rather than free. That is, participants that were presented with cues that aid in recovering the information, such as the membership of the words in specific categories, could retrieve much more words than participants who were instructed to freely recall words without any guiding cues. So, availability does not entail accessibility. One may retain a memory without being able to access it.

Using this distinction, memory theorists argue that different states of accessibility to an engram may exist: (i) it can be dormant such that natural retrieval cues could access the engram and elicit the memory. This is the normal state of the engram. (ii) An engram may also be unavailable such that neither natural nor artificial reactivation results in memory retrieval. In this case, it could be said to be lost and its content forgotten. (iii) An additional state is situated between unavailable and a dormant engram. Engrams in this state are termed *silent* engrams. Silent engrams are available but may only be accessible by artificially reactivating engram cells producing an artificial retrieval cue.[[8]](#footnote-8)

Silent engrams are, thus, engrams that cannot be retrieved by natural retrieval cues but can be retrieved via direct optogenetic stimulation. The idea of a silent engram challenges the localization of the engram-bearing vehicle to changes in synaptic efficacy. Localization of the engram to synaptic links has been the result of manipulations that prevent synaptic consolidation. If, however, inhibiting synaptic consolidation prevents only subsequent retrieval then optogenetics leads to an alternate conception of where engrams are stored. As Robins says - “memory theorists have long supposed that disrupting the consolidation process produces forgetting by erasing the original engram. Ryan et al. show that, at least in mice, traces are not erased during consolidation; they merely become inaccessible” (2018, p.1088).

So how is the fact that synaptic strengthening is crucial for natural accessibility accommodated? Synaptic strength is taken to be a mechanism for memory retrieval rather than memory storage. The synapses that are activated during acquisition guide the eventual pattern of cellular connectivity controlling information retrieval, whereas memory is stored in engram ensembles, a collection of engram cells localized within a brain region. Strong synaptic connections, on this model, are access points to the information retained in engram cells, not a medium where information is held. Hence, the notion of a silent engram can be seen as a way to resolve the tension between optogenetics-based results and the traditional synaptic view of vehicle localization.

There are several objections that can be made to the notion of a silent engram. I will focus on two issues concerning the dissociation of the engram-bearing vehicle from synaptic efficacy. First, assigning to synaptic consolidation a role for retrieval depicts this process as unidirectional. By unidirectional I mean that information may only be extracted through strong synaptic links, but it cannot enter the engram. There is reason to think, however, that information may also go in through such synaptic access points. It is in this sense that the process could be said to be bidirectional. Stored information requires synaptic efficacy to be retrieved from the engram, but synaptic efficacy might also be required for forming the engram.

Consider the phenomenon of reconsolidation. Synaptic consolidation, a state of increased cellular sensitivity to amnesiac agents following the acquisition of information, occurs not only following the acquisition of a memory but continues to happen when a memory is reactivated and recalled. This phase is termed *Re*-consolidation and describes a state where a stable engram returns to a labile mode following reactivation. That is, applying amnesiac agents to relevant neurons after retrieval causes amnesia of the retained information. Reconsolidation has been found to occur only in cases of mismatch between retained and novel information (Winters et al. 2011) and it is thought that the function of reconsolidation is to *update* learned information (McKenzie & Eichenbaum 2011).

If updating information stored in an engram requires that engram cells have strong synaptic links, then it cannot be that synaptic efficacy is merely a retrieval mechanism. Synapses have a role beyond extracting information. If information in the engram is updated through synaptic consolidation, then information is not only retrieved through synapses but rather it is also acquired through synapses. Strong synapses are not only points of access to a preexisting and stable engram. They are also points of “entry” to stored engrams.

One could maintain that the process of reconsolidation produces a new memory trace and thus reject that synaptic efficacy is responsible for updating information in the same preexisting engram. According to multiple trace theory, reactivation of memory traces can lead to the formation of a new cortical engram that qualitatively overlaps with an existing hippocampal engram (Winocur et al. 2007; Hardt & Nadel 2018). So, synaptic efficacy would play such a role only if a new engram-bearing vehicle is not formed during reconsolidation.

Although this is conceptual possibility, there are two reasons to question its plausibility.[[9]](#footnote-9) First, the formation of a new engram does not exclude the possibility that information in the preexisting engram is updated. Reconsolidation may lead to the formation of a new engram alongside the strengthening or weakening of the preexisting engram (Nadel et al. 2007). Second, it is unclear to what extent the newly formed engram is distinguished from the previous one. It could be that cortical and hippocampal vehicles are different components of the same engram expressed in behavior according to the contextual demands of a given situation. Whatever is the case, the silent engram model does not account for these possibilities.

To be clear, the relation between reconsolidation and accessibility does not entail that synapses are the vehicles of memory storage. It does mean, however, that synapses are not responsible only for retrieval. If we understand accessibility to be the property of whether the engram may be retrieved, then synaptic strength is not related exclusively to accessibility. But, if we understand accessibility to additionally involve modifications to the content retained in an engram, then the role of synaptic strength involves more than mere retrieval. Accessibility involves *extraction* of information, but it also involves *insertion* of information.

The second issue concerns whether accessibility should be interpreted as concerning a retrieval deficit rather than a storage deficit. On one understanding of accessibility, it involves a problem in *retrieving* a memory. Changes in accessibility refer to how hard it is to retrieve an engram. Access to silent engrams might be possible only through specific forms of retrieval, such as artificial retrieval cues produced by optically reactivating engram cells. On this view, the silent engram could be depicted as a book that is present in a library, but whose call number is currently misplaced and so the book cannot be found. The right recall cue, direct optogenetic activation in this case, could retrieve the memory.

It is not necessary, however, to understand accessibility deficits as a retrieval deficit. Another way to interpret deficits in accessibility is to conceive them as a *storage* problem. In this case, changes in accessibility refer to the strength of the engram itself rather than to its potential retrievability. On this understanding, accessibility amounts to how *much* there is to access in a given engram rather than *how* it could be accessed. In other words, accessibility involves the integrity of the engram, not its retrievability. Continuing the previous analogy, the book is found in the library, but it is in a degenerate condition, where parts of the text are illegible or lost. In this case, much of the information could not be retrieved because the memory is weaker and contains less information about the remembered event.

The classical model in which memories are stored through synaptic efficacy is consistent with an interpretation of inaccessibility as a storage deficit. Recall that according to synaptic consolidation theory, engrams are stored following a protein-synthesis dependent process that modifies the strength of synaptic connections. Direct optogenetic activation of an engram in the absence of synaptic efficacy is seen as evidence that the engram is not synapse-dependent, thereby supporting a retrieval view of accessibility. In contrast, on a storage view of accessibility direct optogenetic activation of engram cells is successful because it may artificially *augment* a weak engram. While the book cannot be read in its natural condition, it might be restored to its original state, discerning words from incomplete fragments of text. Direct optogenetic activation amounts then to something more like memory reconstruction than memory retrieval.

I do not assume that *empirically* distinguishing between these two alternatives is an easy task. In studies of experimental amnesia, retrieval is measured by comparing the difference in behavioral responses between the experimental group of animals receiving an amnesiac agent and the control group (usually administered with Saline). For example, in the studies of auditory fear memory reviewed, the measure used to tell whether the animal remembers the tone is the amount of time the animal freezes for, upon hearing it. Researchers conclude that the experimental group forgot when the duration of freezing in the experimental group is significantly lower (statistically) than the control group. Experimental amnesia does not mean that there is no recollection at all but just that the retrieval cue elicited a considerably lower response rate. Hence, the way forgetting is measured is ambiguous between a storage and retrieval deficit. Deciding between these competing interpretations may require different measures of evaluating behavioral amnesia.

That said, several empirical implications follow if direct optogenetic activation has a reconstructive role. First, selective optogenetic activation of engram cells might prevent the deterioration of a memory. If direct optogenetic activation reconstructs a memory, then reinstating a memory may lead to change in the information retained by the engram. We should not expect any change to the information retained if direct optogenetic activation merely retrieves a memory. Second, a more informative procedure would involve comparing the experimental group’s performance to a group of animals that have not acquired the association at all. Sufficiently strong retrieval cues should elicit a weak memory. Natural retrieval cues, however, should not have any effect if the engram is simply irretrievable. In this case, animals would be expected to perform as if they have not learned at all.

To summarize, this section focused on the localization of the engram to a neural vehicle. On the traditional view of vehicle localization, engrams are stored as alterations in the strength of synaptic connections. Despite progress in tracking and manipulation of engrams, optogenetic findings raise new questions about the localization of engram-bearing vehicles. While the engram cannot be retrieved by natural retrieval cues, a fact correlated with low synaptic strength, optogenetic activation of engram cells has been interpreted as directly activating the engram. In this state the engram is conceived as silent, i.e., stored but inaccessible by natural retrieval cues. The silent engram is seen as providing evidence for a dissociation of synaptic strength from its presumed role as a vehicle for memory storage. Consequently, the engram is argued to be independent of synaptic strength which is taken to be important for retrieval but not for storage.

I argued that the silent engram hypothesis unnecessarily conflates accessibility with the retrievability of the engram. First, if updating a memory might require synaptic reconsolidation then the function of synaptic strength involves acquisition alongside retrieval. Accessibility may include inserting information, not merely extracting it. Second, direct optogenetic activation might be seen as augmenting a weak memory trace rather than artificially bypassing a currently inaccessible memory trace. Deficits in accessibility might be the result of the engram’s integrity, not its retrievability. Accordingly, the traditional view may not be accommodated by the silent engram hypothesis. Whether engrams are stored as alterations in synaptic strength is thereby left unresolved by optogenetic evidence. Where memories are stored, therefore, remains an open question following the application of optogenetics.

1. **What Is in an Engram?**

Alongside questions concerning where a memory trace may be stored, optogenetic-based engram studies have provided findings that are relevant to the philosophical discussion surrounding memory retention, specifically concerning how to single out engrams over time. In contrast to the previous section which focused on the localization of the engram to a storing vehicle, this section focuses on the localization of content that is, supposedly, stored in engrams. If, in fact, there are engrams, what kind of information do they retain? Optogenetic findings on the engram, I claim, are in tension with the answers philosophical views provide to this question.

It is generally believed that memory refers to the past. Consequently, contemporary philosophical accounts of memory have been dominated by discussions about the implications of findings of memory errors for the concept of a memory trace. Research into false memory has found that memories of past experiences can be systematically distorted, and the prevalence of memory errors has driven calls for a reconsideration of the belief that positing memory traces is necessary for explaining the capacity to remember past events. Two ways to understand the retention of memory have developed from these discussions. Following others, I shall call the first constructivism and the opposing view preservationism.

On the constructivist view, memory is a capacity for constructing representations of past events from a general information store. Representations are reconstructed from neural structures which other capacities, such as counterfactual reasoning and imagining the future, may share. There are several versions of the constructivist idea, but I will focus here on De Brigard’s view as it is closest to the way the engram is understood in neuroscientific contexts.

According to De Brigard, in contrast to traditional “storehouse” views, memory does not involve the storage of discrete traces of past events - “‘Storing’ is a rather misleading term. What seems to occur when we encode information is the strengthening of neural connections due to the co-activation of different regions of the brain” (2014b, p.170). At first glance, it might appear that this is the standard synaptic storage model already discussed. A crucial difference, however, is that on a constructivist view there is no *persisting* physical change in the nervous system that corresponds to a memory. Engrams, in De Brigard’s view, “do not preserve the structure of the representational vehicle from the moment of encoding to the moment of retrieval” (2014a, p.406). They are the *dispositional* properties of neural networks to re-activate similar patterns of activation encoded during the original perceptual event.

As the capacity to remember the past is reconstructive in nature, constructivists deny that engrams are memory traces of particular past events. There is, of course, retention of information but the form in which information is stored does not involve representations of particular past events but “a schematic representation of relevantly similar situations” (De Brigard 2014b, p.170). Memory traces retain gist-like representations, and the schematic nature of these representations is what explains the tendency for pervasive errors in remembering.

The second view about the nature of memory involves a more traditional ‘storehouse’ conception according to which past events are preserved in memory and retrieved from a specific store. Again, there are several strands of the preservationist view, but I will assume here that the following two commitments are shared by most of its proponents (Michaelian and Robins 2018).

First, preservationists are committed to the existence of persistent traces which play a causal role in remembering a past event. It is in virtue of preserving information from encoding to the act of retrieval that these persistent traces are able to play this role. The second commitment has to do with the information retained in engrams. Engrams, on the preservationist view, carry information about a *particular* past event. So, for every memory trace there is a unique original event to which it is causally linked. Retrieval of a memory trace causes a memory about past events because it carries information originally encoded in a particular event.

To draw out the distinction between these two views more clearly, it is vital to highlight their points of disagreement. We can characterize the disagreement between these two views as involving the following assumptions:

*Transmissibility* - remembering must involve a trace preserving information from encoding to retrieval.

*Stability* - A representation similar to the particular past event encoded is retained from encoding to retrieval.

Preservationists are committed to these assumptions while constructivists deny these assumptions.[[10]](#footnote-10) More specifically, preservationists are committed to the *Transmissibility* assumption, while constructivists deny that information-bearing trace is preserved from encoding to retrieval.[[11]](#footnote-11) Another point of contention involves the *Stability* assumption. Again, Preservationists are committed to this assumption while constructivists deny this, offering instead a view on which memory traces are schematic and gist-like representations.

Optogenetic intervention into the engram results in tension with the constructivist’s rejection of *Transmissibility*. The constructivist may argue that engrams are dispositions of neural networks, denying that there is a specific memory trace persisting from encoding to retrieval. The application of loss-and-gain of function strategies, however, suggests that engrams are retained by specific neural vehicles that may be tracked through the acquisition of a memory to its retrieval. The persistence of certain *actual* cellular changes is what determines whether a memory would be retrieved.

In particular, engrams are not entirely dependent on the stimulus conditions required to evoke memory retrieval. Preventing the relevant cellular or molecular changes from occurring would result in forgetting even if stimulus conditions in the form of retrieval cues are present. Moreover, artificially inducing these cellular or molecular changes results in retrieval of a memory even if these stimulus conditions are absent. It seems thus that engrams do not behave in the way we would expect of a dispositional property.[[12]](#footnote-12) The predictions of engram theory hold true because there is a persistent neural vehicle corresponding to a memory that is being tracked and manipulated. Contra constructivism, then, optogenetic studies seem to vindicate the *Transmissibility* assumption.

For *Stability*, the opposite holds true. Optogenetic studies of the engram actually suggest that the information stored in engrams does not correspond to a particular past event in a *fixed* way. Engrams are constantly changing, making it difficult to attribute to the engram any stable content. Due to changes in the neural vehicles retaining the memory, the encoded information in an engram may undergo continuous updating and modification (see, e.g., De Brigard 2017; Robins 2020). This tells against the *Stability* assumption because there are changes to stored information that keep occurring throughout the “life” of an engram. So, the dynamic character of engrams appears to be in tension with the preservationist commitment that memories are similar to the original event in which they were encoded. Let me elaborate on this point.

A central way in which engrams are dynamically transformed involves changes to the information retained in an engram. I have already mentioned that the information retained in an engram may be updated following a reconsolidation process. An additional way in which the content of an engram may change involves another form of consolidation, termed systems consolidation (McClelland et al. 1995; Winocur et al. 2007). Consolidation between neural systems, such as the hippocampus and neocortex, may lead to a change in the format of retained information. As Henke describes it - “Most encoded episodes succumb to abstraction and loss of detail over time and undergo semanticization, which occurs when regularities are extracted from several experienced episodes” (2010, p.528).

Optogenetic studies of reconsolidation and systems consolidation provide evidence that the information retained in an engram may change over time and experience. Optogenetic studies of reconsolidation indicate that optogenetically deactivating engram cells prevents the update of information (Lux et al. 2016). Preventing reconsolidation from occurring results in the loss of information gained following reexposure. Furthermore, optogenetic studies of systems consolidation have found that optogenetic activation of engram cells in the retrosplenial cortex produces context generalization. Mice that underwent optogenetic stimulation showed a fear response that is generalized to new contexts, while mice that did not, exhibited a generalized fear response over time (De Sousa et al. 2019). Artificially inducing systems consolidation transforms the trace into a schematic representation. Optogenetics studies, thus, further support the claim that reconsolidation and system consolidation processes alter the engram, either by updating it with novel information or by transforming it to a gist-like representation.

Changes in the stored content indicate that the engram might not be as stable as the preservationist assumes. The information retained may transform, such that it becomes more abstract or contains fewer details about the original experience. With time and recurrent exposure to similar events, corresponding changes would occur in the neural representation of a memory, thereby making it less determinate in regard to a particular past experience. This evidence tells against the *Stability* assumption, suggesting that over time the information retained in an engram may become more schematic, as constructivists claim.

Most philosophers that subscribe to a preservationist view accept that the content of a memory can change over time (Michaelian and Robins 2018). Details, of course, may be forgotten and lost. However, they consider the addition of new information to be incompatible with remembering. Positions closer to constructivism accept the generation of new content between experience and retrieval. But, as I interpret these hybrid views, the source of novel information does not come from the engram but from the act of reconstruction. Specifically, generation of new content occurs at the stage of retrieval and does not involve any distortion of the trace itself.

These findings are in tension with even weaker forms of preservationism. Consolidation processes may not only “subtract” information included in the original engram experience, but they may also “add” new information between encoding and retrieval. Moreover, as I have argued, the information in the engram itself is transformed over time. Memory errors may result from changes to what information is stored rather than to the way it is retrieved. During the stage of storage, new content is generated.

Optogenetic studies of the engram depict a conflicting picture. On the one hand, these studies suggest a view of the engram in which there is a persistent trace that lasts from the moment of acquisition to its behavioral expression. On the other hand, there is considerable evidence that the content of the engram is dynamically transformed. It, therefore, seems that we should accept *Transmissibility* but reject *Stability*. A resulting view is that memory traces persist but do so dynamically, namely, they continue from encoding to retrieval but their content changes over time and experience. Needless to say, such findings are in tension with the commitments of both constructivist and preservationist views.

Prima facie, constructivist and preservationist views appear to be package deals, i.e., positions whose commitments we must jointly accept or reject. Such an impression results from the fact that accepting only one of the assumptions appears to undermine the causal connection of memory to the past. On a view that adopts *Transmissibility* but rejects *Stability*, specifying what exactly remains the same throughout the existence of an engram is a mystery. What makes something an individual engram?

Note that the existence of a single and specific engram is fundamental to the experimental logic of engram theory. The criteria for the discovery of the engram depend on the fact that the same object is being tracked and manipulated. Furthermore, there is an underlying assumption that the engram’s individuality is not transient. Although these paradigms may fall short of capturing the complete dynamics of memory, this characteristic is not taken to preclude the possibility of going beyond a snapshot moment and accessing the lasting content stored in an engram.

Constructivist and preservationist views each face their own challenge in reconciling their commitments with optogenetic studies. The optogenetic intervention into the engram should lead constructivists to rethink their rejection of the *transmissibility* assumption. The preservationist’s commitment to *stability* should be abandoned or accommodated given present optogenetic evidence. The ability of these views to meet these challenges involves revising their commitments regarding how engrams persist through acquisition to retrieval and the extent to which they preserve information similar to the encoded event.

Since questions about the cognitive architecture of memory are empirical questions, optogenetic tools can be used to determine which of the assumptions underlying memory storage should be rejected. A natural way involves a hypothetical experiment in which optogenetic tools are applied to more complex mediums of information such as schemas. What would an animal remember in case a schema is optogenetically deactivated?

If engrams are assimilated over time to a general information store, then we would expect that an animal would be able to remember only those items that share the least in common with the erased schema. If that were the case, engrams would not persist as individual representations but would merge into schemas over time. The preservationist’s commitment to *transmissibility* would no longer be tenable. Alternatively, if the original engram is preserved for as long as the memory is considered to be retained, then we would expect that an animal would remember all items at the same level. If that were the case, it could be said that engrams preserve their individuality from encoding to retrieval. The constructivist would then need to accommodate the *stability* assumption. Hence, the outcome of such manipulation entails different things for constructivist and preservationist views of memory storage.

1. **Conclusions**

Let us take stock. What have we learned? Has the elusive engram been found? Despite considerable progress in manipulating and tracking engrams, optogenetics raises new challenges concerning engram localization, the assignment of memory storage to specific and persistent neural vehicles. I argued that neuroscientific and philosophical conceptions of engram localization need to be revised in light of optogenetic studies of the engram.

I first described how researchers use optogenetics to localize the engram. Optogenetic tools allow researchers to employ key strategies, thereby meeting criteria for engram discovery. By applying optogenetic-based strategies such as loss-of-function, gain-of-function, and mimicry, neuroscientists have found an enduring neural vehicle preserving information from learned experience.

I claimed that optogenetic-based strategies and findings impact two aspects of engram localization: vehicle and content. Optogenetics allows the direct manipulation of engrams but, as a result, partly dissociates the capacity for information storage from synaptic efficacy, the neural vehicle to which this capacity was traditionally attributed. I argued that the silent engram hypothesis does not accommodate the traditional view due to conflating accessibility and retrievability. Consequently, optogenetic studies do not give a clear picture of the engram-bearing vehicle.

The second aspect of engram localization concerns content localization. What information has been localized in engrams following optogenetics? I argued that the two philosophical views about memory storage, preservationism and constructivism, embody commitments that conflict with optogenetic-based findings. There is an enduring trace but the content it stores may change over time and experience. The result of such conflict is uncertainty regarding what constitutes a single engram. To reconcile optogenetic studies, these philosophical views may need to accommodate or even abandon their commitments. Despite immense progress in controlling engrams, it seems we are still confronted with Lashley’s doubt; Are there special cells reserved for special memories?

**Acknowledgments**

I would like to thank Colin Allen, Aya Evron, J.P. Gamboa, Topaz Halperin, Arnon Levy, Sarah Robins, Oron Shagrir, Filippo Vindrola, and three anonymous reviewers for their thoughtful comments and suggestions on this article. This work was supported by the Interuniversity Ph.D. Program in the History and Philosophy of the Life Sciences, supported by the Humanities Fund of the Israeli Council of Higher Education; The Sidney M. Edelstein Center for History and Philosophy of Technology and Medicine at the Hebrew University of Jerusalem; The Jack, Joseph and Morton Mandel School for Advanced Studies in the Humanities at the Hebrew University of Jerusalem.

**References**

Abdou, K., Shehata, M., Choko, K., Nishizono, H., Matsuo, M., Muramatsu, S. I., & Inokuchi, K. (2018). Synapse-specific representation of the identity of overlapping memory engrams. *Science*, *360*, 1227-1231.

Bechtel, W. (2008). *Mental mechanisms: Philosophical perspectives on cognitive neuroscience*. New York, NY: Routledge.

Colaço, D. (2020). Recharacterizing scientific phenomena. *European Journal for Philosophy of Science*, *10*, 1-19.

Cooper, J. M. (Ed.). (1997). *Plato: complete works*. Indianapolis, IN: Hackett.

De Brigard, F. (2014a). The nature of memory traces. *Philosophy Compass*, *9*, 402-414.

— (2014b). Is memory for remembering? Recollection as a form of episodic hypothetical thinking. *Synthese*, *191*, 155–185.

— (2017). Cognitive systems and the changing brain. *Philosophical Exploration*s, *20*, 224-241.

De Sousa, A. F., Cowansage, K. K., Zutshi, I., Cardozo, L. M., Yoo, E. J., Leutgeb, S., & Mayford, M. (2019). Optogenetic reactivation of memory ensembles in the retrosplenial cortex induces systems consolidation. *Proceedings of the National Academy of Sciences*, *116*, 8576-8581.

Feest, U. (2017). Phenomena and objects of research in the cognitive and behavioral sciences. *Philosophy of Science*, *84*, 1165-1176.

Hardt, O., & Nadel, L. (2018). Systems consolidation revisited, but not revised: the promise and limits of optogenetics in the study of memory. *Neuroscience letters*, *680*, 54-59.

Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nature Reviews Neuroscience*, *11*, 523.

Josselyn, S. A., Köhler, S., & Frankland, P. W. (2015). Finding the engram. *Nature Reviews Neuroscience*, *16*, 521.

— (2017). Heroes of the engram. *Journal of Neuroscience*, *37*, 4647-4657.

Josselyn, S. A., & Tonegawa, S. (2020). Memory engrams: Recalling the past and imagining the future. *Science*, *367*(6473).

Lashley, K. S. (1950). In search of the engram. *Society for Experimental Biology No. 4:* *Physiological mechanisms in animal behavior,* 454–482. Cambridge: Cambridge University Press.

Lux, V., Masseck, O. A., Herlitze, S., & Sauvage, M. M. (2017). Optogenetic destabilization of the memory trace in CA1: insights into reconsolidation and retrieval processes. *Cerebral Cortex*, *27*, 841-851.

Martin, S. J., Grimwood, P. D., & Morris, R. G. (2000). Synaptic plasticity and memory: an evaluation of the hypothesis. *Annual review of neuroscience*, *23*, 649-711.

McClelland JL, McNaughton BL, O’Reilly RC. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychological Review,* *102*, 419–57

McKenzie, S., & Eichenbaum, H. (2011). Consolidation and reconsolidation: two lives of memories?, *Neuron*, *71*, 224-233.

Michaelian, Kourken & Robins, Sarah (2018). Beyond the causal theory? Fifty years after Martin and Deutscher. In Kourken Michaelian, Dorothea Debus & Denis Perrin (eds.), *New Directions in the Philosophy of Memory* (pp.13-32). New York, NY: Routledge.

Nadel, L., Winocur, G., Ryan, L., & Moscovitch, M. (2007). Systems consolidation and hippocampus: two views. *Debates in Neuroscience*, *1*, 55-66.

Ramirez, S., Liu, X., Lin, P. A., Suh, J., Pignatelli, M., Redondo, R, Ryan T. & Tonegawa, S. (2013). Creating a false memory in the hippocampus. *Science*, *341*, 387-391.

Robins, S. K. (2016). Optogenetics and the mechanism of false memory. *Synthese*, *193*, 1561-1583.

— (2018). Memory and Optogenetic Intervention: Separating the Engram from the Ecphory. *Philosophy of Science,* 85, 1078-1089.

— (2020). Stable Engrams and Neural Dynamics. *Philosophy of Science*, *87*, 1130-1139.

Roy, D. S., Muralidhar, S., Smith, L. M., & Tonegawa, S. (2017). Silent memory engrams as the basis for retrograde amnesia. *Proceedings of the National Academy of Sciences*, *114*, 9972-9979.

Ryan, T. J., Roy, D. S., Pignatelli, M., Arons, A., & Tonegawa, S. (2015). Engram cells retain memory under retrograde amnesia. *Science*, *348*, 1007-1013.

Semon, R. (1921). *The Mneme*. London: George Allen & Unwin.

Silva, A. J., Landreth, A., & Bickle, J. (2013). *Engineering the next revolution in neuroscience: the new science of experiment planning*. Oxford: Oxford University Press.

Sullivan, J. A. (2018). Optogenetics, pluralism, and progress. *Philosophy of Science*, *85*, 1090-1101.

Tonegawa, S., Liu, X., Ramirez, S., & Redondo, R. (2015). Memory engram cells have come of age. *Neuron*, *87*, 918-931.

Tulving, E., & Pearlstone, Z. (1966). Availability versus accessibility of information in memory for words. *Journal of Verbal Learning and Verbal Behavior*, *5*, 381-391.

Winocur G, Moscovitch M, Sekeres M. (2007). Memory consolidation or transformation: context manipulation and hippocampal representations of memory. *Nature Neuroscience,* *10*, 555–557

Winters, B. D., Tucci, M. C., Jacklin, D. L., Reid, J. M., & Newsome, J. (2011). On the dynamic nature of the engram: evidence for circuit-level reorganization of object memory traces following reactivation. *Journal of Neuroscience*, *31*, 17719-17728.

Yokose J, Okubo-Suzuki R, Nomoto M, Ohkawa N, Nishizono H, Suzuki A, Matsuo M, Tsujimura S, Takahashi Y, Nagase M, Watabe AM, Sasahara M, Kato F & Inokuchi K. (2017). Overlapping memory trace indispensable for linking, but not recalling, individual memories. *Science*, *355*, 398-403.

1. Lashley marks a skeptical point in the search after the engram, but several important historical landmarks have occurred since his time. For a more detailed account of the history see, e.g., Josselyn, Köhler and Frankland (2017). [↑](#footnote-ref-1)
2. Neuroscientists refer to these criteria in various ways. Josselyn, Köhler and Frankland claim that the criteria for finding the engram include a persistence criterion - “a persistent change in the brain that results from a specific experience” and a content-bearing criterion - “the content of an engram reflects what transpired at encoding and predicts what can be recovered during subsequent retrieval” (2015, p.521). I have called these criteria *contiguity* and *similarity*, respectively. *Specificity*, for example, is invoked by Inokuchi and colleagues who take it as a basic assumption that “memory is encoded in a specific cell ensemble that is activated during learning... individual memories are generally represented by different cell ensembles” (Yokose et al. 2017, p,1). Philosophers apply roughly similar criteria, see e.g., (De Brigard 2014a). [↑](#footnote-ref-2)
3. These criteria are meant to delineate the properties that researchers assume to characterize the engram. If vindicated, the characterization would provide evidence in favor of a certain descriptive account of the engram. These properties do not necessarily constitute the engram. The characterization of the phenomenon may still be revised in light of new or conflicting evidence (See, e.g., Feest 2017, Colaço 2020). [↑](#footnote-ref-3)
4. This advantage should not distract us from Jackie Sullivan’s important remark on the need to “recognize the value of methodological and perspectival pluralism for identifying the beneﬁts and limitations of novel experimental techniques” (2018, p.1100) when it comes to optogenetics. Optogenetics may have off-target effects, behavioral effects that occur due to the transient inhibition of a neural area and alternative tools may be used to circumvent such limitations. [↑](#footnote-ref-4)
5. While Abdou et al. (2018) is not the first study to show the application of optogenetics to the study of the engram (See, e.g., Robins 2018 for several examples), this study is notable for establishing the specificity of the engram and its intimate relation to synaptic efficacy which will be discussed in the next section. [↑](#footnote-ref-5)
6. Fear, in mice, is manifested in freezing behavior. [↑](#footnote-ref-6)
7. Such memories might be more accurately described as distorted rather than newly created memories. Nevertheless, the ability to induce such memories supports the idea that optogenetics is used to evaluate the similarity of a retrieved memory to the event encoded by altering the underlying vehicles, thus constituting a form of mimicking natural memory formation and retrieval. [↑](#footnote-ref-7)
8. An ensuing impression might be that the silent state of the engram is an artifact of using optogenetic tools. Although this is a possible interpretation, the fact that direct optogenetic activation of non-engram cells does not cause a similar behavioral expression tells against it. [↑](#footnote-ref-8)
9. Nevertheless, reconsolidation does raise several difficulties regarding the stability of the engram’s content over time. I touch upon this issue in the next section. [↑](#footnote-ref-9)
10. Preservationists assume that a causal condition is necessary and sufficient for remembering but usually do not make a distinction between the way a memory is casually transmitted and the transmitted content. [↑](#footnote-ref-10)
11. The trace is the same entity persisting through time although its informational properties may vary. [↑](#footnote-ref-11)
12. One may object that a constructivist view is not committed to engrams being dispositional. An alternative option is to think of them as distributed neural connections where information is stored holistically. Accepting a distributed trace, however, assumes a form of *Transmissibility*, which constructivists deny. In the last part of this section, I consider a hypothetical experiment whose results constructivists could use to answer this challenge without accepting *Transmissibility*. I thank an anonymous reviewer for raising this point. [↑](#footnote-ref-12)