

# The 21st century engram

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## Abstract

The search for the *engram*—the neural mechanism of memory—has been a guiding research project for neuroscience since its emergence as a distinct scientific field. Recent developments in the tools and techniques available for investigating the mechanisms of memory have allowed researchers to proclaim the search is over. While there is ongoing debate about the justification for that claim, renewed interest in the engram is clear. This attention highlights the impoverished status of the engram concept. As research accelerates, the simple characterization of the engram as an enduring physical change is stretched thin. Now that the engram commitment has been made more explicit, it must also be made more precise. If the project of 20th century neurobiology was finding the engram, the project of the 21st must be supplying a richer account of what's been found. This paper sketches a history of the engram, and a way forward.

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## KEY WORDS

engram, memory, memory trace, optogenetics

“Engrams” is a word psychologists use frequently although what they mean by it neither they nor the physiologists have, as yet, quite decided.

(Penfield, 1968, p 831)

## 1 | INTRODUCTION

The search for the *engram*—the neural mechanism of memory—has been a guiding research project for neuroscience since its emergence as a distinct scientific field. Characterizing this inquiry as a search is apt. The investigation is guided by some sense of what is being looked for. That is, there is a commitment to the idea that there is an engram, which is prior to any discoveries *about* the engram. The commitment often goes unnoticed. As Dudai (2002) once noted, most memory scientists are focused less on whether there are engrams than on how they work. Still, one occasionally finds remarks like the following:

As a scientist I am compelled to the conclusion—not postulation, not assumption, but conclusion—that there must exist certain physical-chemical changes in the nervous tissue that correspond to the storage of information, or to the engram, changes that constitute the necessary conditions of remembering. The alternative stance... is sheer mysticism (Endel Tulving, as quoted in Gazzaniga, 1997).

As Tulving's comment illustrates, even when the commitment is made explicit, it remains highly general. Belief in the engram is simply a belief that memories are enduring physical changes in the brain. This modest, inchoate idea of an engram has long sufficed because it complements the level of precision available with the tools and techniques of neuroscience—while incredible progress has been made in understanding the mechanisms of memory storage, identifying the nature and location of particular engrams has not been possible. The search for the engram has thus gone forward without much pressure to render the commitment more explicit or precise.

Until now. As the result of recent developments in the tools and techniques available for investigating the mechanisms of memory, researchers have recently proclaimed that “not only can contemporary rodent studies claim to have found the engram, but also to have identified means to control it” (Josselyn et al., 2015, p. 531). Many concur with Josselyn and colleagues on this point and are excited for what these results reveal about the basic mechanisms of memory and possible connections with broader areas of memory science. But there are also many who disagree, arguing that such proclamations overstate the significance of this work and fail to engage with a substantive conception of memory (e.g., Ranganath, 2022).

Whether or how these disputes will be resolved remains unclear. What is clear is that these findings have reinvigorated talk about the engram. There is increasing interest in exploring the historical and theoretical roots of this concept, as demonstrated by the recent rise in review pieces on the engram (e.g., Josselyn et al., 2017; Josselyn & Tonegawa, 2020; Poo, 2016) and newfound attention to Richard Semon, who coined the term in the early 20th century. Two decades ago, Schacter's (2001) intellectual biography of Semon aptly characterized him as a “neglected pioneer.” Now, thanks to these new lines of research, reference to Semon is becoming a standard feature of papers on the mechanisms of memory.

This attention highlights the impoverished status of the engram concept. As research accelerates, the simple characterization of the engram as an enduring physical change is stretched thin. Now that the engram commitment has been made more explicit, it must also be made more precise. If the project of 20th century neurobiology was finding the engram, the project of the 21st must be supplying a richer account of what's been found. This paper sketches a way forward.

## 2 | SEMON'S ENGRAM

The “engram” is the memory trace, scientized. Contemporary neurobiologists often use the terms “memory trace” and “engram” interchangeably (e.g., Denny et al., 2017; Poll et al., 2020), but of course the idea of a memory trace long predates neuroscience. Memory traces have featured in accounts of remembering since there were such accounts. The trace is generally understood to be the mechanism or process by which information, ideas, and experiences are preserved across time—making possible memory's diachronic nature. It is difficult to say much beyond this; the memory trace remains as elusive as it is enduring. Arguments for traces are rare; appeals to metaphor are common (Robins, 2017).

Semon coined the term *engram* in the early 20th century, in his book *Die Mneme* (1904/1921). Semon had a host of reasons for carving out this new term. A student of Ernst Haeckel, he appears to have shared his mentor's interest in crafting neologisms to draw attention to key ideas and theories. Semon was also intentionally avoiding use of more familiar terms like “memory image,” as he wanted to characterize a potentially broader range of phenomena and avoid anything that would “invariably suggest phenomena in consciousness” (Semon, 1921, p. 24). “Engram” was meant to pick out a mechanism of retention that could be found across a range of biological organisms.

Semon was agnostic as to the nature of the engram. At times, he even expressed skepticism that it would ever be identified. His interest was in postulating the existence of some such mechanism—that is, a physical and/or chemical change to the brain as a result of learning, sustained over time to support remembering. He selected the term *engram* in particular to convey that “a permanent record has been written or engraved” (Semon, 1921, p. 24).<sup>1</sup>

Even from this general characterization, the engram precisifies the commitment to memory traces in at least three ways. First, it is a commitment to memory retention via a *physical* mechanism. While there have long been accounts of memory traces in physical terms, there are also many psychical, or at least not explicitly physicalist accounts on offer.

Seamon was aware of psychical accounts amongst his contemporaries and actively resisted them (see Schacter, 2001). Second, the engram is a commitment to a particular type of physical mechanism, one housed in the brain—or as Seamon referred to it, the “irritable substance” of biological organisms.<sup>2</sup> Third, it is intended to be a general mechanism of retention, including but not exclusive to human memory. It is this final feature that caused trouble for Seamon and fueled the dismissal of him and his work. Seamon was searching for a way to articulate the mechanism by which biological organisms acquire and retain information—and transmit that information to future generations. Operating prior to the discovery of DNA and our current understanding of genetics, he saw promise in thinking of the mechanisms of memory transmission and reproductive transmission as similar. This Lamarckian approach did not endear him to biologists and geneticists of the mid-20th century.<sup>3</sup>

Even as a minimal commitment, Seamon's conception of the engram provides a methodology that has long sufficed for productive investigation of the mechanisms of memory. If the retention of information from experience requires a persistent change to the underlying neural system, then the aim of a neurobiological account of memory is to identify and isolate the neural mechanism(s) responsible for that change.

### 3 | THE SEARCH FOR THE ENGRAM

The methodology that guides the search for the engram may derive from Seamon, but its deployment has traditionally been associated with Karl Lashley. Lashley's scientific reputation is that of a “nihilist”, “demolition expert”, and “quintessential outsider” (as quoted in Nadel & Maurer, 2018). This reputation was earned, in large part, through his exhaustive—and unsuccessful—search for the engram. Working primarily with rats, Lashley trained them to navigate mazes. Following their training, he lesioned a distinct, small section of cortex in each rat to determine whether any particular section of cortex was necessary for maze navigation (Lashley, 1929, 1933, 1950). Lashley failed to identify any such necessary part of the cortex. Instead, a lesion's impact on a rat's performance was positively correlated to the amount of cortex removed, irrespective of location. Lashley proclaimed that there was no engram, no memory-specific sections of the brain. He advocated instead for a view of the brain's *equipotentiality*, according to which all areas of the brain are capable of performing any given cognitive task.

Lashley's work did not bring about wholesale endorsement of equipotentiality, nor did it stop the search for the brain's memory-specific mechanisms. Lashley's allegedly exhaustive investigations were restricted almost entirely to the cortex. Other lines of research would soon reveal that a set of subcortical structures—most notably, the hippocampus—play a critical role in memory (e.g., Milner, 1962; Scoville & Milner, 1957). Lashley's work did, however, quell interest in the engram and the framing of the study of memory in the brain as a search for this elusive particular. That is, research into where and how the brain stores memories continued, even accelerated, after Lashley, but talk of the engram did not.

Subsequent decades produced a steady stream of research into the specific brain regions that support memory, as well as the cellular and molecular mechanisms by which the neurons in these regions make retention possible. As a result, there are now broad areas of consensus amid ongoing debates and new discoveries. For example, it is widely recognized that there are several distinct forms of memory, each of which engages different brain regions and/or processes. The Multiple Memory Systems view (Squire, 2004) operates as the default, but there are challenges to the divisions it proposes (e.g., Cabeza & Moscovitch, 2013; De Brigard, 2019) as well as taxonomic alternatives on offer (e.g., Murray et al., 2017). Across these territorial disputes, there is nonetheless general agreement that the hippocampal formation, which includes the hippocampus as well as the dentate gyrus, subiculum complex, and entorhinal cortex (Schultz & Engelhart, 2014), is critical for memory processing.

There is, similarly, broad consensus that memory retention involves changes in the strength of synaptic connections between neurons. This commitment reflects both the general neuron doctrine that guides contemporary neuroscience, as well as specific discoveries about Long-Term Potentiation (Bliss & Lømo, 1973) and Long-Term Depression (Lynch et al., 1977), the processes by which connections between neurons are strengthened and weakened, respectively, and are thought to mediate the encoding of information. Additional discoveries have helped to fill in the details about how this information is stored over time, including discoveries about synaptic consolidation (Frey & Morris, 1997) that provide a mechanism for stabilizing a memory after these connective changes, preventing further encoding, and discoveries about sparse coding (Han et al., 2007) that offer a framework for storing multiple memories in a neural region by allowing individual memories to be stored each across a small set of neurons. The extensive study of these phenomena

has yielded some results that challenge the synaptic view (Gold & Glanzman, 2021) and there is a small but vocal minority who advocate for a molecular view of memory storage (e.g., Gaito, 1976; Gallistel, 2017).

Alongside this agreement about where to look and what to look for, there is a shared sense of the standards required for establishing that any brain region, neural process, or subcellular activity is directly involved in retention. Investigations are guided by the principles of *necessity* and *sufficiency*—as demonstrated through interference and stimulation experiments, respectively. Necessity is established by identifying a feature of the system whose loss, inhibition, or degradation prevents the organism from remembering. Sufficiency is established by demonstrating how the activation of a feature of the system produces remembering.<sup>4</sup>

This general method has thus remained largely unchanged since Lashley, as neuroscientists have used it to investigate many forms of memory at many distinct levels. What has changed, accelerating discovery along the way, are the tools and techniques available for researchers to use when inhibiting and activating the underlying neural system. As Josselyn et al. (2015) express this point, “progress in finding the engram is directly linked to tool evolution” (p. 528).

The impact of tools can be seen by comparing what was available to Lashley with what is available now. To inhibit neural activity, Lashley had to use thermocautery to lesion brain tissue, which impacted not only a wide swath of neurons, but also glial cells like astrocytes and oligodendrocytes, across multiple brain regions. The techniques available for inhibition and ablation have expanded since, allowing researchers a progressively narrower focus on the specific cells of interest—that is, the engram. Thompson and colleagues were able to perform increasingly precise lesions in the cerebellum, identifying particular regions in the anterior interpositus nucleus that are necessary for eyeblink condition in rabbits (Bao et al., 2002; Chapman et al., 1988; Thompson & Kim, 1996). In similarly pioneering work, Josselyn and colleagues were able to extend this level of precision to the mechanism of auditory fear conditioning in the rat amygdala (Han et al., 2009). In previous work the group established that, in the lateral amygdala, neurons that have increased levels of the transcription factor CREB compared with their neighbors were the most likely to be recruited to the formation of an engram for an auditory fear memory. They were then able to artificially induce increased CREB in selective neurons, effectively predetermining which ones would become the engram. Once the fear memory was formed, they selectively deleted the neurons with increased CREB—and demonstrated that the loss of these specific neurons resulted in erasure of the acquired fear memory.

These results illustrate improved tools for demonstrating *necessity*. The development of tools and methods for demonstrating *sufficiency* has proven more difficult. Techniques for stimulating particular neurons in living, behaving organisms have been slower to emerge. Penfield conducted extensive neurosurgical work in the mid-20th century. He showed, inadvertently, that electrical stimulation of the lateral superior temporal lobe could elicit memories, or at least mental states that felt memory-like (Penfield & Perot, 1963).<sup>5</sup> While this work suggested engram activation might be possible, it did not offer any means for stimulating engrams in systematic and selective ways. The standards for demonstrating sufficiency have thus sometimes been lowered. For example, Thompson and colleagues argued for observation of changes to particular neurons as a result of conditioning, settling for *recording* changes in neural activity rather than *inducing* them (Steinmetz et al., 1992). Recording techniques have reached impressive levels of precision. Recent advances like activity-dependent cell-labeling (Mayford, 2014) and in vivo calcium imagining (Yang & Yuste, 2017) allow for enhanced tagging and tracking of engram cells.

This brief review is intended to make clear that many tools have contributed to progress in understanding the basic mechanisms of memory—and also to set the stage for optogenetics as the most significant tool innovation in the search for the engram. *Optogenetics* allows for the control of neural activity with light (Deisseroth, 2010). This method makes it possible, for the first time, to demonstrate the sufficiency of a particular set of neurons for a particular engram.<sup>6</sup> The next section elaborates on the method and significance of creating light-responsive engrams in more detail.

#### 4 | LIGHT-RESPONSIVE ENGRAMS

Prior to the development of optogenetics, the direct activation of engrams faced two significant challenges. The first it shared with neural mechanisms more generally and was identified above: there was no tool available that allowed for systematic in vivo intervention into neural activity. The second challenge is memory specific. Robins (2018) characterizes it as the *methodological challenge*: the stored engram and the process by which it is retrieved can be distinguished in principle, but not in practice. Retrieval is the only route by which storage can be investigated. In studies with non-human animals, where retrieval requires returning the animal to the original learning context and/or reinstating the original learning conditions, this significantly limits what can be investigated experimentally. The use of optogenetics

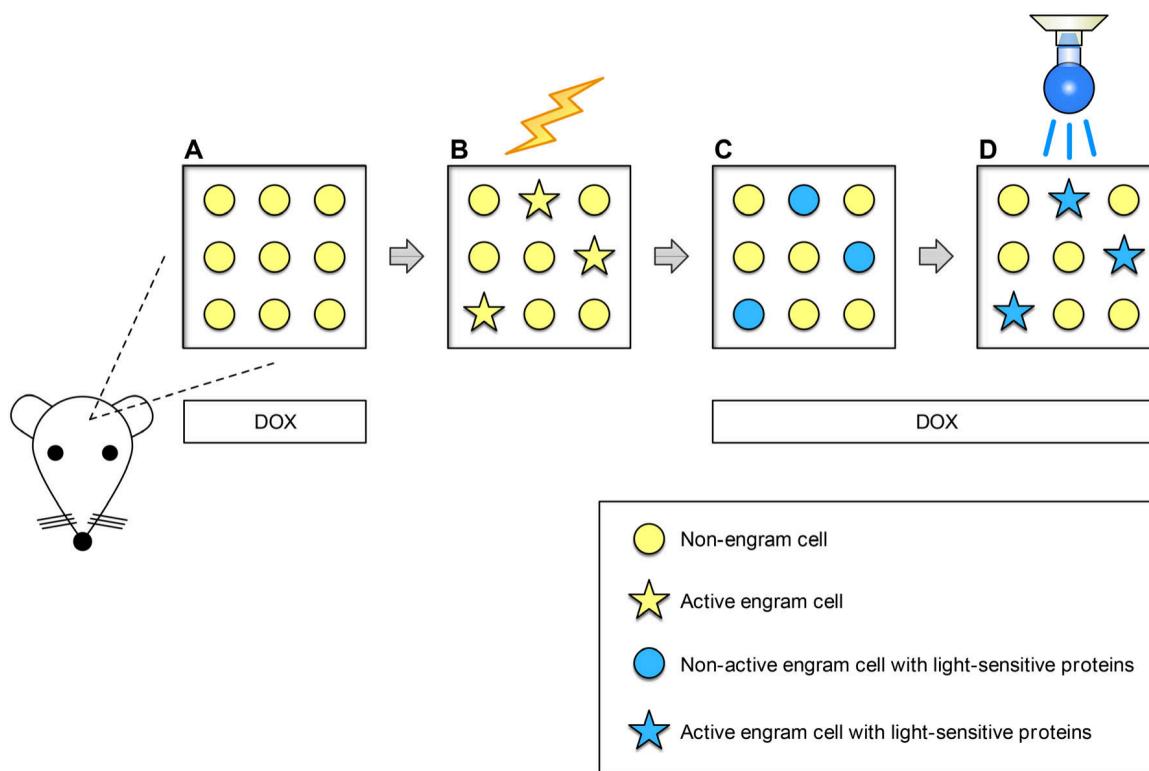
to produce light-responsive engrams was thus exciting not only as an instance of the general revolution in techniques for investigating neural mechanisms (Häusser, 2014), but as a specific advance in how studies of memory in non-human animals could be conducted.

Tonegawa and colleagues conducted the initial “proof of concept” experiments for producing light-responsive engrams (Liu et al., 2012, 2014). These experiments involved mice, contextually conditioned to fear and reward stimuli while exploring a novel conditioning chamber. Either during or immediately after the initial exploration, the mouse is given a positive (food, social engagement) or negative (foot shocks) stimulus. The encounter instills an associative memory, pairing the mouse’s memory of the environment with a positive or negative valence from the stimulus. When the mouse is later returned to the chamber, its behavior indicates memory of the previous (positive or negative) experience in this context. Mice that received a positive stimulus will now actively explore the chamber, whereas mice that received a negative stimulus will now freeze (i.e., refrain from voluntary movement).

The neurons active during this exploration encode the mouse’s experience of the environment—they constitute the engram for the spatial memory. The aim of these studies is to use optogenetic techniques to make this engram light-sensitive—that is, getting the neurons involved in the engram, and only those cells, to express the opsin (a light-sensitive protein). If this can be done, then the engram can be reactivated by exposing those neurons to light.

Previous research has established that these engrams are encoded by neurons in the dentate gyrus (DG), a portion of the hippocampal formation. The Tonegawa group used transgenic mice engineered to possess the ChR2 transgene in all DG neurons, so that the light-responsive Channelrhodopsin-2 (ChR2) protein will be expressed whenever its DG neuron is activated. To ensure that light-responsive DG neurons are only activated during the experimental condition where the engram is formed, the mice are also engineered to be sensitive to doxycycline—*dox*, an antibiotic given through the animal’s water supply. *Dox* controls transgene expression, so the mice will only express the light-sensitive protein when they are *not* being treated with *dox*.

Figure 1 offers an illustration of the basic technique used for creating light-activated memory engrams. The boxes (A)-(D) offer a schematic representation of neurons in the mouse’s DG. Both before (A) and after (C-D) training the animal is given *dox*, so that the only neurons that will express the light-sensitive protein are those active during exploration of the conditioning chamber (B). During (B), the mouse enters the chamber, and while exploring, receives a set of foot



**FIGURE 1** Illustration of the activity-dependent cell labeling process by which engram cells are made to express light-sensitive proteins. Boxes A–D depict the state of neurons in the mouse’s dentate gyrus.

shocks. The exploration activates a set of DG neurons that encode a spatial memory for that context. Since all of the animal's DG neurons have the ChR2 transgene and the animal is no longer taking dox, whichever of these neurons are recruited to form the resultant engram will express the light-responsive opsin (as depicted in C). The engram formed in (B) can now be activated by shining blue light onto the DG, as shown in (D). That is, when the mouse's DG is exposed to blue light (via the insertion of a fiber optic cable), the DG neurons that encoded the spatial memory are reactivated, causing the mouse to engage in the freezing behavior characteristic of remembering the prior experience.

The ability to create and then reinstate a memory via a light-responsive engram is, in and of itself, a remarkable breakthrough. Results of these initial studies offer an effective response to both challenges identified above, allowing researchers straightforward ways to sidestep what had previously appeared to be intractable problems. The significance of this innovation becomes more apparent as this basic technique is coupled with further interventions. I briefly characterize two such lines of research below.

#### 4.1 | Manipulating engram content

Once light-responsive engrams are formed, they can be reactivated without returning the organism to the original context. This opens up the possibility of pairing the reactivated engram with additional information from other contexts. Ramirez et al. (2013) and Redondo et al. (2014) used this to produce false memories in mice. In these experiments, mice first formed light-responsive engrams via the basic technique outlined above. Then, mice were taken to a new conditioning chamber. Once in the chamber, the optical implant was turned on, activating the light-responsive engram formed in the previous context. While the light-responsive engram is active, the mouse is given a new stimulus, distinct from what occurred in the prior context.<sup>7</sup>

Mice with this manipulated engram were then exposed to one of three test conditions: they were returned to the original chamber, returned to the second chamber, or taken to a third, novel conditioning chamber. When returned to the second chamber, they responded in ways consistent with the stimulus received in that context. When taken to the third, novel chamber, the mice display standard exploratory behavior, suggesting that whatever manipulations occurred while the light-responsive engram was reactivated did not have an overall effect on behavior. The condition of interest is the first: when mice are returned to the original chamber where the light-responsive engram (which has now been manipulated) was formed. In this context, mice display the behavior associated with the stimulus received in the second chamber, even when it is distinct from what originally occurred in this context.

#### 4.2 | Activating engrams without retrieval

Light-responsive engrams can also be used to assess whether engrams are still present in cases where standard forms of retrieval are not possible. The Tonegawa research group garnered a lot of attention for a set of studies showing that memories which appeared, on the basis of behavior, to be lost could be reinstated via the application of light. Previously, it was generally assumed that retrieval failure meant that the memory had been lost. These results were exciting because they challenged the standard view of synaptic consolidation (Knight, 2015; Ryan et al., 2015) and provided a new way of conceiving of early-stage Alzheimer's Disease (Roy et al., 2016). The Josselyn Frankland Lab (Guskjolen et al., 2018) extended this research further into mouse models of infant/childhood amnesia. Together, these findings offered the first clear experimental demonstration of a way to distinguish storage from retrieval (Robins, 2018) and reignited debate between synaptic and molecular views of the engram (Han et al., 2021). Optogenetic intervention provided a way to activate engrams that had otherwise become silent.

These results provided researchers with a new way to use optogenetic intervention to shine a light, quite literally, on the neural mechanisms of memory. The method can be used to track engrams over time, exploring the possibility that some engrams transition into a silent state endogenously during the lifetime of a memory.

*Systems consolidation* is an intriguing process within which to look for such silent engrams. Consolidation is the process by which information moves from temporary to longer-term memory storage. Within contemporary neurobiology, most distinguish between two forms of consolidation, each with a distinct timescale. First, there is *synaptic consolidation*, which is the initial stabilization of the engram that occurs directly after learning (i.e., within the first few minutes or hours). *Systems consolidation* is the long-term process of stabilizing a memory. The precise timescale for systems consolidation is a matter of some debate; it is thought to occur anywhere from a few weeks or months to possibly

even years or decades after the initial engram formation (McGaugh, 2000). The precise nature of systems consolidation is also a matter of debate—most notably between proponents of the Standard Model, who proposes that this process involves the transfer of a memory from the DG neurons of the hippocampal formation to the prefrontal cortex (PFC) (Dudai & Morris, 2000) and proponents of Multiple Trace Theory (Nadel & Moscovitch, 1997) who argue that both hippocampal and PFC neurons are actively involved throughout the consolidation process.

The application of optogenetic techniques to systems consolidation offers a new route to understanding how neurons in these two regions are involved in the long-term storage of memory and how their involvement changes over time (Frankland & Bontempi 2015). In Kitamura et al. (2017), the researchers again designed a set of experiments creating light-responsive engrams in mice—this time, creating light-responsive engrams in both the hippocampus *and* in the PFC, and tracking them over an extended 6-week period.

The activity of the hippocampal cells, in the days directly after the learning event, is familiar from and consistent with the previous studies. These cells form an engram of the event, which can be reactivated optogenetically or by standard retrieval methods—that is, by placing the animal back in the original context. Kitamura et al. (2017) continued to track and reactivate this engram over time and showed that, over the course of 6 weeks, the engram changed, eventually reaching a point where it could be reactivated optogenetically but not contextually. That is, the mouse no longer activated the memory when returned to the original context, but the memory could still be reactivated optogenetically. This change in behavior was accompanied by changes in the engram neurons. The density of dendritic spines decreased over time, as the hippocampal engram went from a mature state to a silent one.

The light-responsive engram cells in the PFC exhibited a similar transformation, but in the opposite direction. In the days immediately following training, the PFC engram cells could be reactivated optogenetically, but could not be activated contextually. Across the 6 weeks the engram changed into a state whereby it could be activated both optogenetically *and* contextually. Much as the hippocampal engram went from mature to silent, the PFC engram went from silent to mature.

The discovery of silent engrams is exciting, for what it suggests about systems consolidation and the nature of the engram more generally. Systems consolidation presupposes that engrams persist over time and thus can be tracked from one point to another. There are competing accounts of this process, the Standard Model and Multiple Trace Theory. The evidence to adjudicate between them has been mixed. Now, with optogenetics, researchers have a more fine-grained tool at their disposal, allowing them to track specific engrams through this process. The Kitamura et al. (2017) study showed that, over the lifetime of a memory, hippocampal engrams transition from active to silent, while engrams in frontal cortex transition from silent to active (Kitamura et al., 2017). We can now ask: how do these findings bear on the debate between the standard model of systems consolidation and multiple trace theory?

In the original paper, Kitamura et al. (2017) depict their results as supporting Multiple Trace Theory. Interestingly, however, in a review paper published by the same research group the following year (Tonegawa et al. 2018), the researchers portrayed their results as supporting the Standard Model.

This reversal need not be seen as a limitation of the research, or confusion on the part of the researchers. What it suggests instead is that the results of this research could be interpreted either way, depending on how one defines the engram and tracks it over time. Researchers have to decide whether they want to consider the neurons involved in the hippocampus and PFC as two parts of a single engram or as two separate engrams. If considered a single engram, the results support the Standard Model. If considered two distinct engrams, then the results are more in line with Multiple Trace Theory. Further experiments may help to illuminate these possibilities more clearly, but the question of which way to define the engram is a theoretical, not empirical, one.

Adding engram-level work thus illuminates a previously neglected dimension along which these views disagree: over the feature by which they track the engram over time. The engram can be individuated in terms of its underlying vehicle or its content. The engram is also dynamic; tracking it over time requires sensitivity to the ways that both of its features can change – and in ways that are not necessarily complementary or synchronized. To track an engram over time, a researcher must select one of these features—its vehicle or its content—as the one by which the engram will be re-identified. Given the accompanying dynamics, this opens up the possibility for the two ways of tracking to diverge. This gives us a way to contextualize the systems consolidation debate. The Standard Model tracks the content of an engram. Multiple Trace Theory, in contrast, tracks its physical structure. Recognizing these differences does not tell us that one approach is preferable to the other. But simply recognizing this theoretical difference and its influence on the debate is a step forward.

Even aside from the issue of how these results bear on theories of systems consolidation, the discovery of silent engrams has implications for our understanding of the engram more generally. Silent engrams are characterized as

engrams that are *only* accessible via optogenetics, not by standard retrieval processes. As defined, they are a *tool-dependent phenomenon*: defined in terms of the investigative tool (i.e., optogenetics) that is used to detect them (Kitamura et al., 2017). The aim, however, is to go beyond our understanding of them in this limited experimental context. Josselyn and Tonegawa (2020) illustrate this in their recent review, where they connect studies of the silent engram to established features of memory processes and suggest that “engram silencing may represent a continuum of a natural state of an engram” (p. 9). To explore this possibility, we must ask: what role do silent engrams play in endogenous memory processing? In other words, how does what we are able to do to engrams, via optogenetics and the like, relate to what the engram does on its own in the process of remembering?

## 5 | THE 21ST CENTURY ENGRAM

Above I offered a brief review of why and how optogenetics, in concert with a host of complementary techniques, has reinvigorated memory research that is directly and explicitly focused on the engram. In order to support this research and foster its further development, conceptual work on the nature of the engram must likewise be resuscitated.

Josselyn et al. (2015) have initiated this work. They have gone back to Semon to extract the properties of the engram, one that has quickly become, quite literally, a textbook account:

1. An engram is a persistent change in the brain that results from a specific experience or event.
2. An engram has the potential for *ecphory*—that is, an engram may be expressed behaviorally through interactions with retrieval cues, which could be sensory input, ongoing behavior, or voluntary goals. The term ecphory can be thought of as roughly equivalent to retrieval.
3. The *content* of an engram reflects what transpired at encoding and predicts what can be recovered during subsequent retrieval.
4. An engram may exist in a *dormant state* between the two active processes of encoding and retrieval (ecphory)—that is, an engram exists beyond the operations and processes required to form and recover it.

(Rudy, 2021, p. 260)

This is not a particularly illuminating account of the engram. It's a stretch to call these *properties*. The four features listed offer ways of elaborating on the idea of an engram. At best, they give us a sense of the engram at its margins—what it does during encoding and retrieval—but little sense of the engram itself. These features may be helpful in guiding the search for the engram but offer little guidance on how to understand the engram once we have found it. I do not say this to further malign Semon, nor to criticize any of the contemporary neuroscientists who are re-engaging with him. Quite the opposite.

I propose that Semon's work be seen as a starting point from which a richer conception of the engram can be built. To guide this construction, I identify a lesson that can be drawn from recent engram research: the integration of optogenetics provides a tool-driven return to the engram as a *token-level commitment*. As stated at the paper's outset, the engram commitment has long been able to persist in an implicit and highly general form. Perhaps as a lesson learned from Lashley, memory scientists have tailored their commitments about the underlying mechanisms of retention to the precision afforded by available tools. The approach has long allowed for principled avoidance of any commitment one way or the other about engrams. Researchers instead make claims about where and how particular *types* of retention occur. They may claim, for example, that episodic memory is supported by the dorsal hippocampus or that fear conditioning is supported by the amygdala. The types may become more specific as research develops—e.g., evidence could indicate that auditory fear conditioning is amygdala specific, whereas multimodal contextual fear conditioning also involves the hippocampus (Kim & Fanselow, 1992). Still, the claims remain at type level. They do not claim, for example, that episodic memory *A* is supported by a sparse code across dorsal hippocampal neurons  $X_1-X_N$  or that the fear of tone *B* is supported by amygdalar neurons  $Y_1-Y_N$ . Such token-level claims may be consistent with or even implied by the type-level investigations that researchers are engaged in, but there has not been any theoretical or methodological impetus for such proclamations.

Indeed, the token-level engram commitment has always felt artificial and simplistic. Even as he argued it must be the case, Semon was skeptical any future science would be able to identify it. Lashley made a spectacle out of taking the commitment seriously. Viewed from one perspective, Lashley's work can be seen as a *reductio ad absurdum* of the idea that the memory can be studied with this fineness of grain.

Against this skeptical backdrop, optogenetics provides the necessary precision and renders the token-level commitment to the engram plausible. The technique allows for the tagging of engram cells for a *specific* learning event, identified in terms of both its underlying mechanism and its content. At least for simple memories like those involved in contextual fear conditioning, researchers can now say precisely which neurons were activated in response to a particular application of an aversive stimulus. Josselyn and Tonegawa's (2020) recent review of contemporary engram research has a single image on its opening page: an up-close depiction of two adjacent neurons in the dentate gyrus, a non- engram cell, stained white, and an engram cell, stained pink.<sup>8</sup>

Acknowledging this point gives us a way to refocus the engram concept. The key feature of Semon's view, articulated by Josselyn and colleagues, is the first, defining feature: the engram is a "persistent change in the brain that results from a specific experience or event" (p. 521).<sup>9</sup> This is the core of the engram concept. It may at first seem too straightforward to be significant. It is, however, an essential first step in building out a richer conception. It provides an understanding of the engram's explanatory role: the engram explains the retention of information from particular past events. From here, we can go on to ask: what features must an engram have in order to play this role?

A complete answer to this question would require far more space than I have available here. In what follows, I briefly sketch two key features of the engram: (1) discrete retention that is (2) information-bearing/content-supporting.

## 5.1 | Discrete retention

The engram commitment is not simply a commitment to the claim that memory involves the retention of information. Framed as a general commitment to retention, it is difficult to identify any contemporary memory scientists who dissent.<sup>10</sup> Even those who think that memory is future oriented (Schacter & Addis, 2007) or focused on prediction (Vecchi & Gatti, 2020) still believe that thinking about and predicting the future rely on the acquisition and storage of information. The difference between engram and non- engram views concerns *how* information is stored. Commitment to the engram involves a commitment to specific form of information retention. It is a claim that information from specific experiences is retained in that experience-specific form. This retention could be imperfect; some engrams may be lost, degraded, or overwritten. For those that are retained, however, the underlying vehicle must be capable of supporting retention from that particular past experience—and must be capable of doing so amongst a multitude of other such engrams.

This places a constraint on the engram's underlying neural vehicle. The vehicle must support *discrete* retention. This commitment is both less and more onerous than has standardly been assumed. The token-level commitment to engrams with identifiably distinct mechanisms has often been interpreted as a commitment to *localism*—that is, that the engram must be housed in a particular neuron(s) or area of the brain. Semon's critics often characterized his view in this way, despite his clear denial of the view.<sup>11</sup> Lashley's search for the engram was framed around this localist conception. Others have expressed worries that a demand for localization would "dictate to science what to discover in the human brain" (Zemach, 1983).

A commitment to discrete storage is not, however, a commitment to local storage. Local storage is one form of discrete storage, but not the only one. An engram could be distributed across a distributed network of neurons, even across multiple brain regions, and still be discrete, so long as the distributed pattern is unique or catalogued in an accompanying index (Robins, 2016).

This does not mean that a supporter of engrams can be entirely ecumenical about the mechanisms of storage. Some forms of distributed processing, where the neural changes due to a particular experience are incorporated into a network in ways that allow them to be overlaid on one another, blending changes due to this experience into the changes from previous experiences, fail to be discrete in the sense required. In such a superpositional, blended system the neural changes owing to any particular experience would wash out over time, precluding the sustained retention of particulars that the engram commitment involves. Hebb (1949) himself advocated for a *structural* constraint on the engram that is aligned with the emphasis on discrete storage proposed here. Along this line, he argued that proposals of diffuse storage across dynamic patterns of brain activity, as defended by Lashley and Köhler, were unable to account for the continued retention of specific memories. More recently, some have begun to advocate for increased attention to accounts of *mnemonic structure* which allow ways of generalizing from multiple, similar events while retaining the distinctness of the individual memories involved (de Sousa et al., 2019). Such proposals are meant as an alternative to the more traditional approach involving schematic structures, where the abstraction process erases distinctions owing to particular events.

The commitment to discrete retention does not demand particular results. It cannot straightforwardly adjudicate the debate between synaptic and molecular views of engram storage, for example. It does, however, impose a constraint that each view must meet in order to be viable, which may provide productive ways to move the debate forward. It could then participate in the “demise” of the synaptic view built upon the principles of Hebbian learning, as some are predicting (Trettenbrein, 2016). Either way, Hebb’s lasting impact on the engram would persist in his defense of discrete, structural retention.

## 5.2 | Information-bearing/content-supporting

The commitment to the existence of an engram is not merely a commitment to a physical mechanism. Given the long-standing emphasis on a search for the underlying mechanisms of memory, it is often understood in this way. For example, a recent textbook defines the engram as “a physical change in the brain that forms the basis of a memory” (Gluck et al., 2020: p. 59). Philosophers, too, have tended to overemphasize the causal features of the memory trace/engram commitment. The most prominent defense of memory traces, from Martin and Deutscher (1966), has been labeled the *causal theory of memory*. Many have defended versions of this commitment as exclusively causal (Rosen, 1975) or content free (Hutto & Peeters, 2018; Werning, 2020).

But, as emphasized at the outset of this paper, the identification of the engram is the result of a *search*. In order for a candidate neural mechanism or process to be identified as an engram, it must play a particular explanatory role. That role is causal: we are looking for neural changes that result from experience and that are involved in subsequent re-expression of what was learned or acquired from that prior experience. The role is not, however, merely causal. There are numerous causal connections between experiences and states of the brain. The ones of interest for identifying the engram are the ones that support the retention of information from the past experience and the reactivation of what’s retained in relevant contexts. The precision allowed by contemporary engram research makes it possible to sort between candidate mechanisms and processes with the requisite fineness of grain.

The engram commitment thus comes with the understanding of the engram as information-bearing/content-supporting built in. The commitment is in the portrayal of Semon’s initial proposal, as indicated in the list of properties outlined above, but the connection between the causal role and the engram’s content is not made explicit. Consider property (2), the potential for ecphory. This is a critical component of the engram’s causal role—determining the set of relevant contexts in which the engram should be reactivated, if it exists. This set of contexts will be determined in ways that are content or information-specific. That is, we would expect an engram to be reactivated not only by return to the original context or re-exposure to the original stimulus, but also by similar contexts and stimuli.

Whether the engram is viewed as a *representation* may still be an open question, depending on one’s views of what representation requires. Even as debates over whether or how to understand neural representation (e.g., Baker et al., 2022), it is still a significant step forward to emphasize that the token-level commitment to the engram involves a commitment to token-level content. Discussions of memory content have tended to be highly general. The traditional distinction between declarative and nondeclarative forms of memory in the Multiple Memory Systems approach encourages a linguistic approach to memory content, difficult to apply in work with non-human animals. Similarly, work on episodic memory tends, on one end, to emphasize its phenomenological features—how content is represented in autonoetic consciousness rather than *what* is represented. On the other end, discussions of episodic memory concern whether the hippocampal system that supports it are fundamentally spatial (O’Keefe & Nadel, 1978) or some combination of space and time (Howard & Eichenbaum, 2015).

The precision afforded by recent engram research, which allows targeting and tracking of specific engrams, encourages more specific proposals about the token memory content. So far, the engrams tracked via optogenetic methods are instances of associative conditioning. It is a matter of some dispute whether such behavioral linkages should be construed as content-bearing. Establishing their candidacy requires demonstrating that the learned association can be flexibly deployed across a range of relevant contexts. Cao (2022), for example, argues that the engrams formed in the initial Lui et al. (2014) study appear too simplistic to meet this standard. The alleged engram is either on or off; active or not. It is reasonable to expect that full-blown representational states would have “more articulated components, ones that ought to be individually manipulable” (Cao, 2022, p. 151). Subsequent studies of light-responsive engrams, like those outlined in Sections 4.1 and 4.2, go further in this direction and may surpass the threshold. At the very least, they demonstrate how future work can use subtle distinctions in retrieval context and engram manipulation to disambiguate between similar ways of construing memory content.

Josselyn and colleagues (Park et al., 2022) have taken a significant step toward demonstrating that optogenetically identifiable engrams can be flexibly employed in behavior. They do so by investigating fear extinction, where associative fear conditioning to a particular stimulus is overridden by repeated exposure to the stimulus without the accompanying aversive stimulus. They demonstrated the ability to tag the extinction engram, using the same general methodology by which associative engrams are made light-responsive. They then sketch how further exploration of this light-responsive extinction engram could be used to adjudicate between alternative conceptions of its content. Is extinction better understood as learning new information or unlearning previously acquired information?

### 5.3 | The future of the engram

The engram is a persistent change in the brain that results from a specific experience or event. It is a neural mechanism or process that allows discrete retention of the information or content acquired from the prior experience. Understanding these features is especially important as engram research moves forward.

Optogenetics has brought the search for the engram to a close—at least for basic, associative engrams. This achievement does not mark the end of engram research. Instead, it presents an opportunity for work to move in new directions. Optogenetics and its complementary suite of tools allow not only for the tagging of particular engrams, but for their tracking and manipulation over time. This allows researchers to go beyond questions about where and how engrams are formed, asking questions about the engram across its lifespan. This is a significant advance, and change in how the engram is understood. The prior conception of the engram characterized it exclusively in terms of its activity during encoding and retrieval. The time between these two stages, constituting the majority of its existence, was understood loosely at best and characterized by a single term: dormant. The ability to track the engram across this so-called dormant period has shown it to be anything but. Studies like those outlined in Section 4.2 illustrate ways the engram changes over time, from silent to accessible. In the same vein, Ryan and Frankland (2022) propose that contemporary engram research offers a new view of forgetting—as continual changes to an engram cell's plasticity and availability, rather than the simpler binary distinction between remembered or forgotten.

Such work raises the stakes for the engram concept. We now must not only think about the engram's features at encoding or at retrieval, but as features that persist, and change, over time. Their fluctuation raises challenges for reidentifying the engram that must be acknowledged. As proposed above, engrams have two key features—structure and content. It is difficult already to articulate how these features relate in the engram at a particular time. The problem is magnified as the engram is tracked over time. Both features are dynamic, changing over the lifetime of the engram, and doing so in ways that are not necessarily complementary or synchronized. Tracking an engram over time requires selecting one of these features to use in reidentification. A researcher could tag a particular set of neurons and track their activity over time, observing whether or how the associated content changes each time these neurons are reactivated. Conversely, a researcher could track the content over time, investigating changes in which neurons are associated with its expression. Each approach is fruitful and worth pursuing. It is possible, however, that the two routes of inquiry will lead to different conclusions about the nature of the engram under investigation. Recognizing this difference and the possibility of conflict does not yet offer any grounds for determining that one approach is preferable to the other—for a particular engram, or more generally. Simply recognizing it and its potential influence on debates about the engram, encouraging researchers to reflect on which method they are using and why, would be a step forward.

## 6 | CONCLUSION

Neuroscientists have long searched for the engram. The availability of new tools and techniques has rapidly accelerated the search, allowing researchers to make a host of exciting and significant discoveries about where and how engrams are formed. These tools are now changing how neuroscientists ask, and answer, questions about the basic mechanisms of memory. The goal is no longer simply to find the engram, but to explore its dynamics—tagging, tracking, and manipulating engrams over time and across a range of conditions. To support these exciting new avenues of inquiry, a richer conception of the engram is required. In this paper, I have sketched such an account, attempting along the way to draw lessons from the concept's historical roots and from features of contemporary research.

The engram matters because memory matters. It is a central, significant cognitive capacity. The importance of remembering is often made most apparent by its disruptions—from everyday misremembering, to PTSD, to the onset of

Alzheimer's. Explaining, treating, and possibly ameliorating these memory malfunctions requires an understanding of how particular experiences, skills, and pieces of information are retained over time. The research surveyed here has produced a clearer and more fine-grained understanding of this retention than ever before, and deserves to be accompanied by a similarly refined engram concept. Together, these developments may allow us to someday make good on Squire and Kandel's proclamation that "memory promises to be the first mental faculty to be understandable in a language that makes a bridge from molecules to mind" (Squire & Kandel, 1999, p. 3).

## AUTHOR CONTRIBUTIONS

**Sarah Robins:** Conceptualization (lead); formal analysis (lead); investigation (lead); project administration (lead).

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## ENDNOTES

<sup>1</sup> In this way, Semon's account fits well with many writing-focused ways of characterizing memory traces (see Draaisma, 2000).

<sup>2</sup> Deference to this sense of engram can be seen in the use of the term *exogram* for physical memory traces outside of the brain (Donald, 1991; Sutton, 2010).

<sup>3</sup> It is worth noting that recent work, particularly in epigenetics, has led to renewed interest in the inheritance of acquired characteristics in general and Semon's work in particular (e.g., Jablonka & Lamb, 2020).

<sup>4</sup> Najenson (2021) discusses these as loss of function and gain of function experiments, respectively.

<sup>5</sup> Penfield's discovery came along with his invention of the "Montreal Procedure" for neurosurgery, during which patients remained awake and conversant. Penfield used this technique to help ensure that interventions made to address epilepsy would be as selective as possible, and avoid areas of cognitive and personal importance. Use of this procedure allowed him to develop a preliminary map of many functional areas of the brain, including the role of the temporal lobes in memory (see Kumar & Yeragana, 2011 for a more extensive history).

<sup>6</sup> For a more extensive discussion of this point, see Goshen, 2014.

<sup>7</sup> In the Ramirez et al. (2013) study, the initial context involved only exploration and the subsequent context involved footshocks. In the Redondo et al. (2014) study, the original context involved either a positive or a negative stimulus and the stimulus valence was reversed in the second context.

<sup>8</sup> The neurons in the image are from a transgenically modified mouse. The neurons in the dentate gyrus were filled with biocytin in order to examine morphology, which renders them white. The engram cell was expressing express the red fluorescent protein mCherry as a result of activation, which appears pink in combination with the biocytin.

<sup>9</sup> Semon's commitment to this token-level view of the engram is evident throughout *Die Mneme*, where he continually refers to them as "individually acquired engrams" (Semon, 1921, p. 120). At times, he appears to endorse a view akin to Multiple Trace Theory, where in each reactivation of an engram involves the creation of a new engram (see Schacter, 2001 for discussion of this point).

<sup>10</sup> Possibly Buszaki (2019).

<sup>11</sup> See Schacter, 2001, ch. 8 on this point.

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