Memory Traces in the Sand: Engrams and Reconsolidation

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Table of Contents

Summary

Memory engrams and memory reconsolidation are both important concepts that shed light on the physical substrate and fundamental processes of memory, respectively. In this paper, I argue that the methods used in the study of the former can help us to better understand the latter. Connecting the topics ensures that related phenomena in neuroscience do not remain isolated, but rather complement each other. For that purpose, after outlining the topics, they are combined on a fundamental and applied level. It was found that topics such as reconsolidation window and boundary conditions of reconsolidation are better understood with the molecular and cellular insights of engrams

Memory Traces in the Sand: Engrams and Reconsolidation

In the past decades, two major findings have become a mainstream of neuroscience research. First, there is more and more accumulating evidence that our memories are stored within the connections between neurons. These physical representations of individual memories in the brain are called memory engrams (Tonegawa et al., 2015). Second, contrary to our previous understanding, memories are not fixed after being consolidated. Rather, they can still undergo a process called memory reconsolidation, whereby the previous memory content can be modified (Nader, 2015). In this paper, I will review both of these concepts as well as how they relate to each other. The research question is to establish how the knowledge of memory engrams can inform us about memory reconsolidation. It is an important question to answer, since the accelerating pace of discoveries and the increasing amount of concepts and definitions in neuroscience may make it difficult to connect topics that may at first seem unrelated.

In order to sketch a connection between the two topics, I will first track the memory engrams and reconsolidation separately, from the first discoveries to the current research. Then, I will explore the utility of applying molecular and cellular techniques of studying engrams to better understand the phenomenological and behavioural changes caused by reconsolidation. Lastly, it will be explained how this connection of topics can be useful in the clinical practice.

What are memory engrams?

Despite the seeming novelty of biological memory traces, Richard Semon coined the term “engram” at the beginning of the last century (Schacter et al., 1978). His work is especially remarkable if we look at it in the context of his times. At a period when there was a serious debate about whether memory is a physical or a purely psychic phenomenon, he

proposed that engrams represent biological alterations to the brain. He also proposed that a partial reactivation of the activity taking place during encoding of an event can be sufficient to retrieve the memory (although terms different from encoding and retrieval were used). Furthermore, that retrieving activity could originate internally, not only as a result of re-encountering the stimulus. These ideas are not far off from the modern understanding of engrams developed on the basis of experimental evidence. Most importantly, Semon had already proposed that retrieval does not just bring back the memory, but also alters the engram, thus directly relating to the topic of the current paper being written over a hundred years later. However, his ideas did not resonate with his contemporaries, so for a long time they were left without much attention.

Although the theoretical underpinnings of memory traces existed for over a century, the research of those is relatively recent and it is only growing in popularity as seen in PubMed publications (Fig. 1). The initial lack of investigations is not surprising if we consider the limited methods available to the researchers of the day. In the middle of the last century, Karl Lashley, one of the pioneers in studying engrams, could only separate various brain areas from each other with a knife to observe the effects of those disruptions on learning (Eichenbaum, 2016). He has not been able to find a memory trace, but did not abandon his belief that engrams existed in the brain. Research methods have significantly advanced since then, focusing first on the localization of neurotransmitters in the brain, then on immediate early genes and their promoters to localize the recently activated cells (Sakaguchi & Hayashi, 2012). These efforts of location have further been aided by developing visualization techniques which do not require slicing the brain into thin slices as to not disrupt the existing connections and structures (Pavlova et al., 2018). Additionally, researchers can now control which cells become part of an engram through CREB expression, since it leads to higher excitability of those cells (Dong et al., 2006). Further, optogenetic techniques allow us to

accurately promote or hamper consolidation of individual memories (Sakaguchi & Hayashi, 2012). Overall, then, we are now able to locate, visualize and manipulate the memory engrams which were once only a theoretical construct with little empirical support.

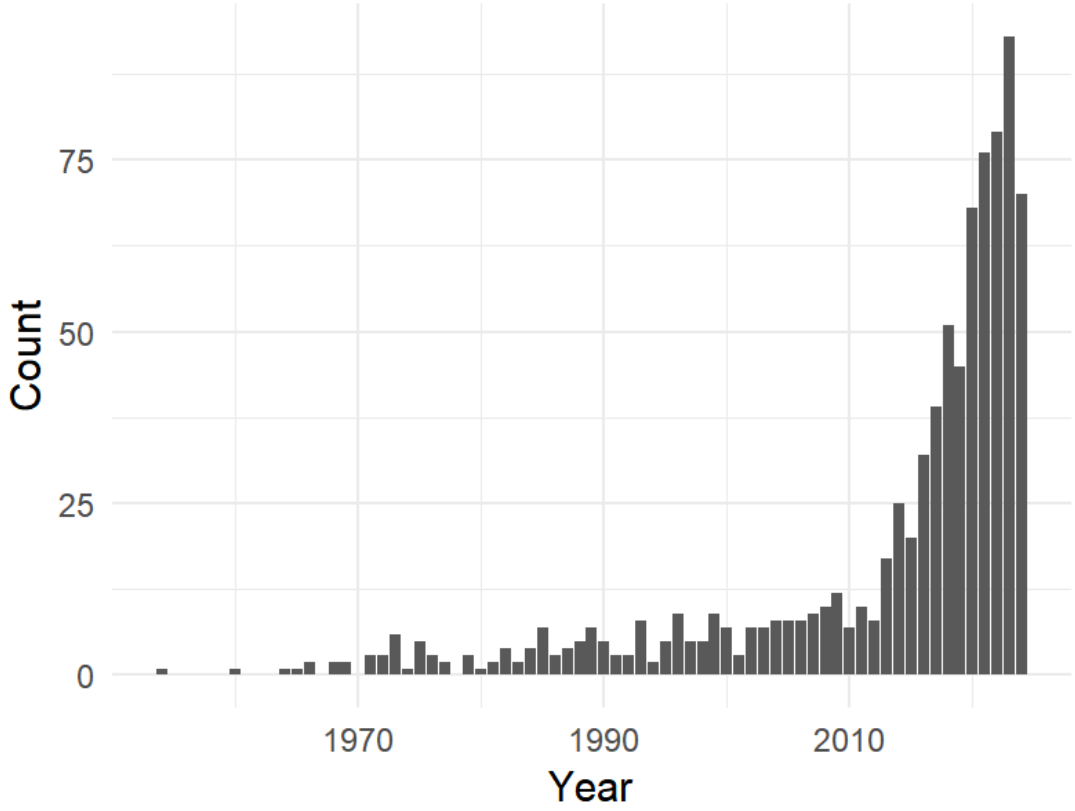

Figure 1. *The Number of Publications on PubMed on the Topic of "Memory Engrams"*

Before continuing the discussion of engrams, it is important to have a clear picture of what they are, according to our current knowledge. To start off, Tonegawa et al. (2015) define memory engrams as the "enduring physical or chemical changes that were elicited by learning and underlie the newly formed memory associations." They also provide three criteria to prove that a series of cells belongs to a memory engram: these cells should be activated during learning, they should be physically changed by that process and reactivating these cells recalls the encoded memory. It is interesting to note that the authors talk about *cells*, not *neurons* in particular. Currently, there is some evidence of microglia remodeling the synapses and thereby affecting memory decay (Wang et al., 2020). Chen et al. (2020) have even found

transcriptional alterations to microglia and astrocytes weeks after encoding a memory. However, since the reactivation of those non-neuronal cells does not retrieve the memory, they do not satisfy the third criterion mentioned above. Therefore, they would not currently be considered a part of an engram complex. While the definition is often repeated in the articles written on the topic, the first two criteria seem redundant - if a memory can be reliably brought to the awareness by activating a group of cells, then showing their activity during encoding or their physical alterations does not seem to contribute to the proof of these cells being part of an engram. Still, the first two criteria are informative of the process of memory trace formation and reflect the researchers' steps in confirming cells to be part of an engram. Other than the definition and criteria, it is important to know what allows a neuron to become part of an engram complex and what differentiates it from a non-engram neuron. Yiu et al. (2014), based on previous research, manipulated excitability in a random subset of lateral amygdala neurons. Using three different methods, they found that increasing excitability of neurons leads to their recruitment into a forming memory engram independent of the method applied. This particular characteristic is important to remember as it will help us explain the link between memory engrams and reconsolidation. Overall then, neurons can become engram cells through outcompeting their neighbors in excitability and we can prove their nature if the reactivation of those neurons recalls the encoded memory.

With that being said, where can we find these engrams? The answer to this trivial question is surprisingly complicated. While the engrams are usually studied in the hippocampus, due to its long-known involvement in forming memories and in the amygdala, owing to the popularity of fear conditioning paradigms, engrams do not only involve the subcortical regions. Rather, an engram complex is usually wide-spanning and also involves various cortical regions. As an example, Kitamura et al. (2017) found that activating a part of the prefrontal cortex receiving input from the hippocampus was enough to elicit freezing

behaviour in fear-conditioned mice even when they were in a non-conditioned environment. Moreover, contrary to some previous suggestions, memory engrams involve the cortex almost as soon as they begin to form. For instance, Brodt et al. (2016) instructed their participants to navigate a virtual maze while in an fMRI to investigate the dynamics of cortical engram formation. The maze was either static, allowing the participants to learn its layout or dynamic, such that it changed its layout when not directly observed. The researchers found that the posterior parietal cortex and the precuneus in particular were activated immediately upon learning a new spatial environment together with the hippocampus. Further, the activity of precuneus was immediately higher upon a subsequent re-encounter with the environment. Within a span of just two days, the hippocampus became less active in exploring this environment, whereas precuneus activity had only grown and was becoming more and more independent of hippocampal activation. Crucially, these findings were only true for the static maze group, meaning that the activity changes were dependent on learning. The findings overall suggest that the formation of an engram complex involving the cortex starts immediately upon learning and that the cortex representation increases in its importance over time. Still, there is no direct evidence that the precuneus was part of the engram, since it was not possible to reactivate it in human participants. Rather, its involvement in the engram is triangulated from all the correlational data. These and similar findings make part of the systems consolidation theories of memory, where the hippocampus acts to quickly learn patterns in the environment and assists the cortical areas in becoming part of this engram until both independently become sufficient to recall the memory (Brodt & Gais, 2021). Some systems consolidation theories speculate that the memory stored in the cortical regions could be phenomenologically different from the one in the hippocampus, whereby the hippocampus contains detailed information upon recall, whereas the cortex only encodes an abstract summary of the experience (Kumaran et al., 2016). These storage differences are explained in

terms of the different computational structures created by the neuronal connections in the two areas. Regardless, it should be clear that a single memory engram can encompass several distant brain regions and that the consolidation within those regions can occur almost simultaneously.

Memory Reconsolidation

When studying the concept of memory within both the psychological and biological sciences, it is common to start by describing the memory stages - encoding, consolidation, retrieval, and forgetting, like in the paper by Guskjolen and Cembrowski (2023). However, this may portray a wrong picture for the learners of the topic, where the stages are unidirectional and the memories can only be either stored and retrieved or forgotten - a picture too stable compared to reality. Rather, an already consolidated memory can be destabilized upon recall or reactivation and can be either maintained, forgotten or potentially altered by novel input (Alberini, 2013; Walker et al., 2003). The restabilization of the activated memory is termed reconsolidation and it was first discovered half a century ago by Schneider and Sherman (1968) and recently brought back to attention in a seminal study by Nader et al. (2000), who applied it in a fear conditioning paradigm. In this latter study, the authors first subjected all the rats once to an auditory stimulus (CS) and an electric shock (US). During test 1, which was 24 hours later, half of the rats were exposed to the CS again (Fig. 2a) and the other half was put in the test room without the CS (Fig. 2d). Each half was further divided into three groups depending on an injection that they received right after test 1. These injections were either a high or low dose of protein synthesis inhibitor anisomycin or a control solution mimicking cerebrospinal fluid. The injections were local to the basolateral amygdala in order to only affect fear memories. As seen in Figure 2b, all the rats exposed to CS at test 1 tended to freeze at about the same level. However, in test 2, taking place in another 24 hours, rats that received a high dose of anisomycin after test 1 tended to fear the CS less than the

other two subgroups (Fig. 2c), indicating forgetting. Importantly, if the CS was not presented during test 1, then the injections had no effect as can be seen by all the subgroups similarly freezing in fear during test 2. These findings indicate that if a memory is reactivated, but protein synthesis (important for consolidation) is blocked, then that memory tends to be forgotten. If there is either no protein inhibitor or no recall, then the memory is unaffected. Additionally, the low doses of anisomycin not being effective in preventing consolidation confirmed previous findings that a high dose is required to reach a threshold of at least 90% protein synthesis inhibition (Rosenblum et al., 1993). With this simple setup, Nader et al. (2000) provided strong support for the phenomenon of reconsolidation. Since then, various sources of evidence have further demonstrated the instability of stored memories and researchers are now investigating the various boundary conditions of memory reconsolidation, such as memory age and intensity (Alberini, 2013). However, the existence of the phenomenon itself is not in doubt.

A connected question often covered in the literature was the purpose of memory reconsolidation. In general, it was posited that it exists to allow for memory updating in order to be able to adapt to a changing environment (Alberini, 2011). Accordingly, the effect of reconsolidation varies depending on the conditions in which it is induced. Memories can be strengthened, exemplified by rehearsal of previous memories and by experiments pairing retrieval with negatively arousing events (Stickgold & Walker, 2005; Finn & Roediger, 2011). They can be weakened or extinguished when retrieved in a state of acute stress or when undergoing a specific therapy (Larrosa et al., 2017; Chen et al., 2021). The memories can also have their content altered, like in the common research paradigms that generate false memories in mice (Lau et al., 2020). Altered memories upon reconsolidation could also be connected to repressed memories and false witnesses in humans (Otgaar et al., 2022; Schacter

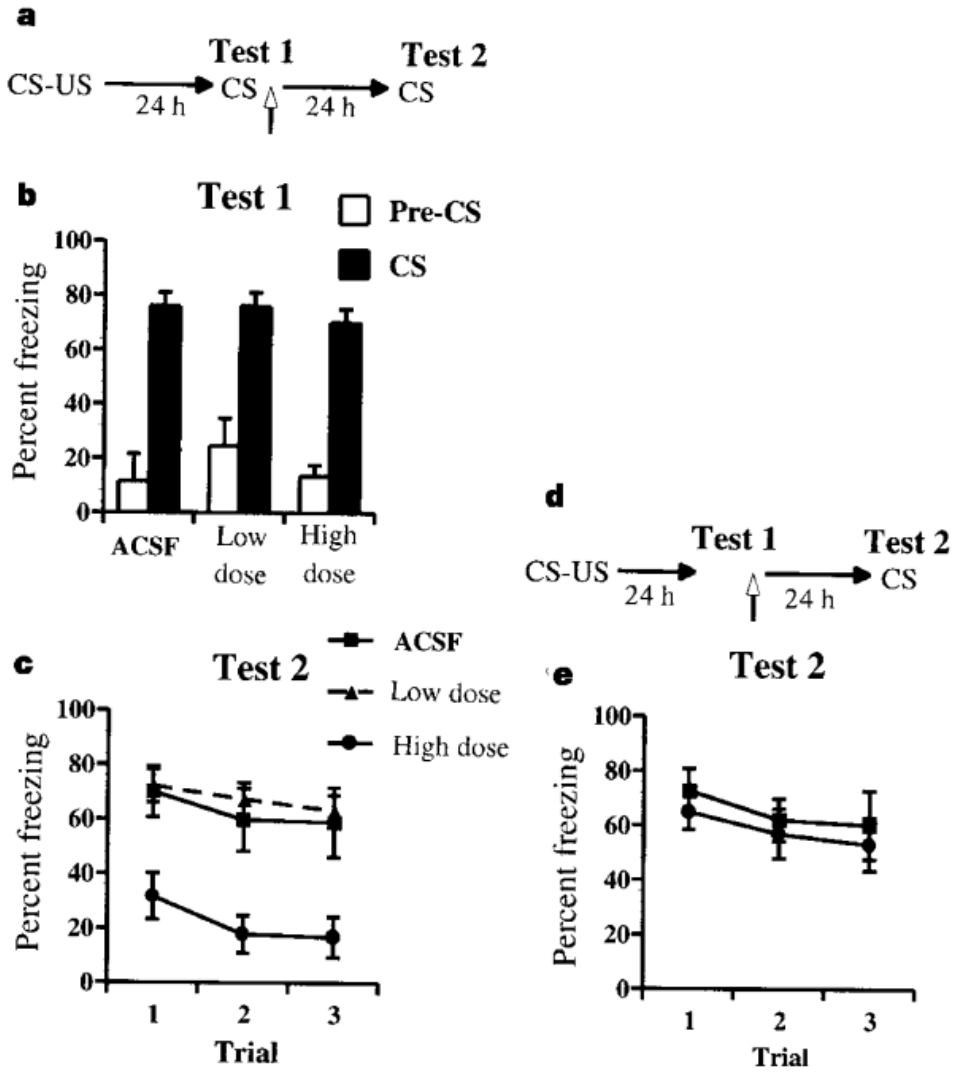

Figure 2. *Evidence for reconsolidation from a fear-conditioning paradigm (Nader et al., 2000). The mice that were re-exposed to CS1 after receiving a high dose of anisomycin did not exhibit fear when shown CS1 24 hours later.*

& Loftus, 2013). Additionally, older and stronger memories are often less malleable upon activation unless there is a significant mismatch between the predicted and actual outcomes (Alberini, 2013). Overall, the consequences of memory consolidation are variable, but in general they all promote a flexible adaptation to the environment.

Connecting memory reconsolidation and engrams

As mentioned above, memory reconsolidation can serve a variety of purposes. However, upon an organism recalling a situation from the past, can we predict what will happen to their memories? To help us answer this question, we can turn to memory engrams. In essence, researchers can use the newly established methods of engram studies to explore memory reconsolidation at the cellular or molecular level. Such studies have already been conducted by various research groups, so in this section I will review what engrams can teach us about memory reconsolidation. Specifically, I will investigate some of the first papers connecting the two topics to see the molecular mechanisms of reconsolidation as well as what happens to the memories after this process.

Motivated by the common occurrence of false memories in humans, Ramirez et al. (2013) investigated whether they could instill a false fear memory in mice. For this purpose, they created mice in which a promoter of *cFos*, an immediate early gene, would also lead to expression of Channelrhodopsin-2 (ChR2), an ion channel activated by light. In this way, any active neuron would express ChR2, thereby becoming available for a later artificial reactivation by an implanted light electrode. However, this pathway could only proceed when mice had no antibiotic doxycycline (Dox) in their diet, which inhibited the pathway. Therefore, by temporarily removing Dox from the mice diets, researchers could tag a subset of neurons that was active at that time and reactivate those neurons later using an artificial light. A virus containing ChR2 was injected into either CA1 or DG depending on the condition. Using the implanted constructs, the neurons that were highly active at the time of context A exploration were tagged with ChR2. When mice were fear conditioned in context B 24 hours later, the previously tagged memory of context A was optogenetically reactivated. When they were later re-exposed to the supposedly neutral context A, they froze for longer than the control mice or the mice who underwent similar treatment but were put in a novel context C (Fig. 3). Interestingly, if the mice had a false fear memory of context A implanted,

they showed less freezing when re-exposed to context B as compared to mice that were only fear conditioned to B without the optogenetic activation. The authors propose that it was due to the competition of the conditional stimuli. It is also important to note that, as can be seen in the figure, the false memory was implanted when DG, but not CA1 neurons were activated. The main findings were also confirmed in a conditioned place avoidance paradigm, such that one of the chambers served as a labeled CS instead of chamber A. Furthermore, optogenetically reactivating the context A engram in a novel context D led to mice freezing more than the control group. This served as additional evidence that the initially tagged engram did not just serve as a memory of context A, but also as a fear memory. Overall, the authors have managed to implant a false fear memory in an engram of a previously neutral context. While they do not call it such explicitly, this study used memory reconsolidation to implant the memory, since the reactivation of the memory A made it labile to change, which allowed the fear response to be applied to it as well.

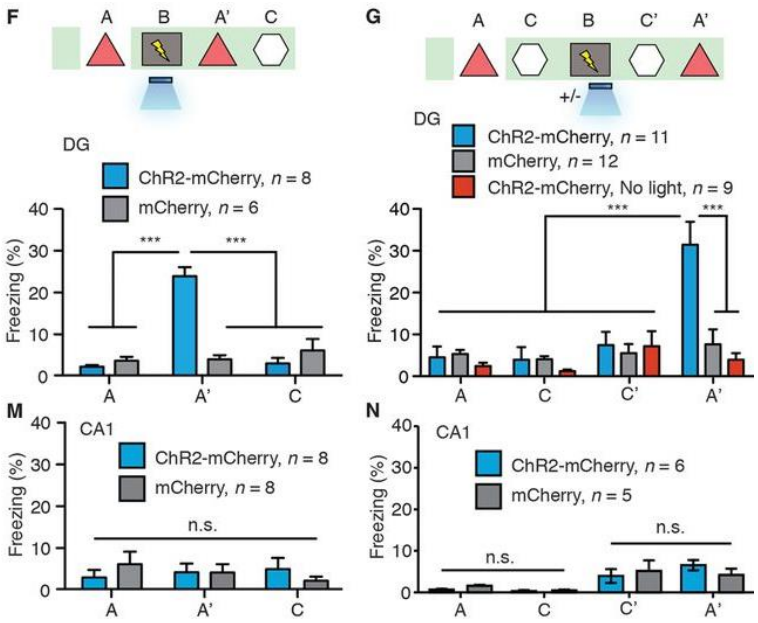

Figure 3. *Optogenetic activation of an engram for the previously neutral context A during fear conditioning in context B created a false memory (Ramirez et al., 2013). When mice were returned to context A, they exhibited fear, which did not generalize to an unrelated context C.*

Garner et al. (2012) were motivated by a different research question, but they employed experiments similar to Ramirez et al. (2013) with two major exceptions. First, instead of targeting either DG or CA1 like the latter, Garner and colleagues targeted most of the forebrain, which, based on the technique they used, likely incorporated the neocortex, the hippocampus, the amygdala, and the basal ganglia (Alexander et al., 2009; Mayford et al., 1996). Second, instead of optogenetically activating the memory of a neutral context A, they did so chemogenetically, which involved a stimulation of approximately 30 rather than 5 minutes. Besides, the temporal dynamics of neuronal firing were likely to differ between these two modes of activation, but Garner et al. (2012) did not measure these dynamics. Otherwise, they still tagged the neurons active during the exploration of context A and reactivated those during fear conditioning. This time, however, mice did not freeze when re-exposed to context A, meaning that a false memory was not formed, nor did they freeze when chemogenetically stimulated (Fig. 4). Furthermore, they showed less fear than the control group when in context B, where they were originally conditioned. However, being in context B and receiving chemogenetic activation led to a significant increase in the fear response. In other words, only a full reinstatement of the conditions at the training caused a fear response comparable to the controls. Therefore, in contrast to the previous study, instead of a false memory to a natural, but previously neutral stimulus, mice developed a synthetic memory, which required both a natural and an artificial stimulus to fully retrieve. Ramirez et al. (2013) propose that memory reconsolidation resulted in a synthetic rather than a false memory due to the temporal and spatial differences between the study designs as well as the unknown variation in the pattern of neuronal firing. Still, it is worth mentioning that when the researchers tagged neurons active in context B, rather than those in context A, their activation did not trigger a fear response in a novel environment. Therefore, seeing how the engram activation did not elicit the supposedly encoded fear memory, it begs the question whether the chemogenetic

procedure in question can even tag a specific memory engram, as Josselyn and Tonegawa (2020) seem to indicate in their review. Regardless, the two studies together show that the temporal characteristics of engram reactivation may lead to different results after reconsolidation - a false memory or a synthetic memory.

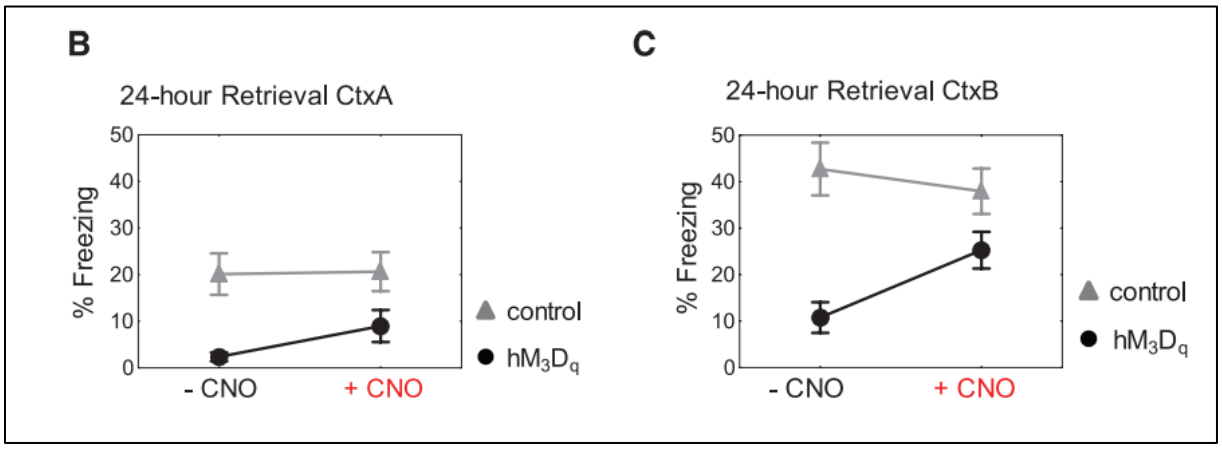

Figure 4. *Chemogenetic activation of an engram for the previously neutral context A during fear conditioning in context B created a synthetic memory (Garner et al. 2012).*

The question of how time interacts with memory reconsolidation is overall a popular topic of investigation. To determine the time window of reconsolidation, mice were put through an auditory fear paradigm (Rashid et al., 2016). After being fear conditioned to an audio cue CS1, they were conditioned to CS2 1.5, 3, 6, 18 or 24 hours later (Fig. 5). When tested for the reaction to CS2 24 hours after the last conditioning, the mice which had the two training sessions separated by less than 6 hours tended to freeze more. Therefore, it seems that fear conditioning to CS1 strengthened the memory for fear conditioning to CS2 if they occurred closely in time. The time window of around 6 hours was also corroborated by molecular analyses on cultured mice neurons. Stimulating those neurons led to an increase in CREB concentrations, but after 4 hours it returned to the baseline and instead the concentration of ICER, a natural inhibitor of CREB, increased – perhaps indicative of a refractory period afterwards (Mioduszewska et al., 2003). In order to confirm that the

reinforcement of memory CS2 was due to memory CS1 instead of the previously experienced sensory stimuli, the same experiment design was repeated but with either the cue CS1 or the electric shock administered alone. Without the corresponding conditioning to CS1, the memory for CS2 was not reinforced even if either the shock or the CS1 were administered within 6 hours of conditioning for CS2. On the contrary, the reinforcement still worked when CS1 was replaced with a light cue and paired with a shock, indicating that the heightened fear response for CS2 was not just due to an overgeneralized fear of audio cues. Further, it is likely that the reinforcement was due to reconsolidation, since gene expression tagging showed that there was a significant overlap between the neurons involved in two engrams, but only when the time interval was 6 rather than 24 hours. Additional proof of the engrams being linked comes from the fact that extinguishing CS2 resulted in not only reduced fear to this cue, but also in reduced fear to CS1. Curiously, despite always testing fear recall to CS2, the authors did not try to extinguish CS1 in order to see the effect on CS2. Still, this set of experiments further shows that linking of two memories can result in not only false or synthetic memories, but also in the reinforcement of the memory presented later in time while the engram cells of the first memory are still in an excited state.

There is a number of conclusions that can be made about reconsolidation on the basis of these experiments studying them at the engram level. First, we can briefly summarize the kinds of processes happening in the engrams during reconsolidation. It is clear that the engram cells are excited upon retrieval and produce high levels of CREB. This window of high excitability lasts for around 6 hours (although the reconsolidation window might not be linear, see Moyano, 2022), followed by a refractory period when those same cells are less active than their neighbours due to rising ICER concentrations. The timing of this excitability is important, since, as described before, activated neurons are more pliable and they are preferentially recruited for new memories. This coupling likely serves an adaptive role, since

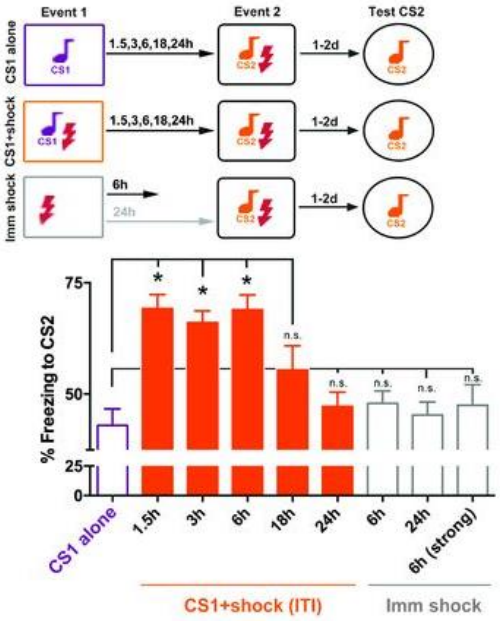

Figure 5. *Reinforcement of the Second Memory During the Reconsolidation Window (Rashid et al., 2016)*

events happening one after the other are likely to be connected. Crucially, the content of the memories does not play a key role as long as they are situated closely in time. This is what enables the old memory to be updated with the new information - it is the mechanism of memory reconsolidation at the engram level.

Second, memory reconsolidation can result in vastly different results based on the particular conditions - what conclusions can we make based on the commonalities and differences of the reviewed studies? A major distinction between the first two experiments of this section is that the former resulted in a false memory, whereas the latter created a synthetic memory not retrievable by natural stimuli. As the authors themselves noted, the latter study targeted a larger part of the brain and for a significantly longer period of time (Ramirez et al., 2013). While they did not provide a reason for why this difference led to different outcomes, it could be that the engram complexes merged together instead of simply being linked. A recent modelling study suggests that the overlap between engrams is a tradeoff - too few

engram cells in common means the memories are not connected, whereas too many result in one combined memory instead of containing two different memories (Gastaldi et al., 2021). Therefore, the extensive chemogenetic activation may have fused the two memories due to their co-activation. However, neither study measured the overlap between the engrams of two contexts, so this remains a question for further investigation.

Translation of the engram and reconsolidation knowledge to humans

For human application, reconsolidation is mainly important as a starting step of fear or anxiety therapy. It is often applied to PTSD and specific phobia patients, but also in cases of substance abuse (Chen et al., 2021). The therapy begins with the retrieval of the relevant stimulus either through direct or virtual exposure or through recall which destabilize the corresponding engram. Afterwards, the participants undergo either behavioural extinction or pharmacological inhibition of reconsolidation (Walsh et al., 2018). Reconsolidation therapies are more effective than those which only involve extinction, with behavioural and pharmacological methods both being effective depending on the diagnosis. However, the effectiveness of such interventions in the context of disorders such as mentioned above is currently limited, since they target strong and remote memories, which are both boundary conditions for reconsolidation (Bui & Milton, 2023). Considering that most of the experiments carried out on mice and humans modify recently encoded memories, their findings and effect sizes are hard to translate to the clinical populations (like the experiments reviewed in Kredlow et al., 2016). Therefore, while reconsolidation therapies are already promising for treating anxiety, fear and addiction, fundamental studies should target older memories to bridge the gap between the clinic and the laboratory.

Considering that memory age is a boundary condition for reconsolidation, Gräff et al. (2014) sought to assess its potential impact on reconsolidation therapies. First, the researchers verified whether there was a difference in the effectiveness of therapy between recent and

remote memories. They fear conditioned the mice and exposed them to reconsolidation therapy either 1 or 30 days later. While both groups initially showed a reduction in freezing upon re-exposure to the conditioned context or cue, a month after the intervention the mice with a remote memory exhibited spontaneous recovery, whereas those with a recent one still did not exhibit fear. Next, researchers compared the levels of histone acetylation in the hippocampi of the two groups, since this epigenetic marker plays an important role in neuronal plasticity. As expected, the remote memory group showed less acetylation after recall. To target this difference, they then peritoneally administered histone deacetylase inhibitors (HDACi) to the rodents after the recall that forms the first part of the therapy. Consequently, the mice with a remote fear memory that received HDACi did not relapse one month after the extinction procedure. Their freezing levels were now comparable to the recent memory group. Confirming the intended effect of the manipulation, the remote group with HDACi had a lower level of overall acetylation and had their *Arc*, *cFos* and *Igf2* genes upregulated, indicative of synaptic plasticity. In total, while remote memories are less susceptible to reconsolidation, administering HDACi may be beneficial for increasing therapy effectiveness. While the study analyzed molecular changes on the level of the whole hippocampus, it would have benefitted from focusing on the engram of the fear memory instead. Localizing the epigenetic differences to the engram could provide stronger support for the use of HDACi in the reconsolidation therapy.

Additionally, knowledge of engrams may help develop new interventions that are not reliant on extinction. For instance, Borgomaneri et al. (2020) induced a fear memory in the participants and later applied repeated TMS to the dorsolateral PFC in order to prevent the memory's reconsolidation. As predicted, participants showed less fear responses upon reencountering the stimuli. However, they still remembered the association between the pictures and the shock - it simply did not elicit fear. Therefore, it is possible that only a part of

the engram was overwritten. To completely overwrite the memory, perhaps some other areas need to be targeted. Additionally, there is a possibility that different kinds of memories will be distributed across differing regions. For these reasons, it could be helpful to not just overwrite the engrams, but also to be able to localize them in humans. Some recent research indicates that high frequency oscillations could reflect engram activity (Kucewicz et al., 2024). If so, combining these techniques could allow researchers to locate specific engrams in the brain and then weaken them, as is needed in therapy, or perhaps even reinforce or alter them in humans. Furthermore, since memories tend to become more dependent on cortex than on hippocampus in the process of systems consolidation, these techniques could prove to be effective for targeting remote memories.

Conclusion

Overall, engrams provide a different level of analysis for understanding memory reconsolidation. With the available tools for tagging individual engram cells, we can better understand the kinds of processes happening during reconsolidation. For instance, we have seen how the reconsolidation window of 6 hours is likely caused by the intracellular CREB cycle initiated by neuron activation. Additionally, some of the long-lasting questions regarding reconsolidation, such as boundary conditions, could be explained and manipulated through engrams. The remote memories that were previously resistant to change could be altered through the use of HDACi by altering the epigenetic markers on the neurons. Some other questions remaining concern the difference between consolidation and reconsolidation as well as examining the relationship between engram overlap and the memory characteristics. Lastly, tagging engrams either optogenetically or chemogenetically is a method of eliminating unnecessary variability in the study design, since the memories can be destabilized without exposure to the cues of the memory.

All of these findings will in the end contribute to not just the fundamental understanding of memory, but also to better treatment options for patients suffering from PTSD, specific phobias and substance abuse. As we have seen, there are real possibilities for engrams to be identified in humans and even manipulated using TMS. For all these reasons, it is important to study reconsolidation at the specific level of engrams.

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