

Imperial College London
Department of Bioengineering

Role of intrinsic neural properties in memory formation and maintenance

Geoffroy Yannick G  rald Delamare

Thesis submitted for the degree of Doctor of Philosophy
October 2024

Statement of Originality: I hereby declare that all work presented in this thesis was performed by me or was referenced otherwise.

Copyright Declaration: The copyright of this thesis rests with the author. Unless otherwise indicated, its contents are licensed under a Creative Commons Attribution-Non Commercial 4.0 International Licence (CC BY-NC). Under this licence, you may copy and redistribute the material in any medium or format. You may also create and distribute modified versions of the work. This is on the condition that: you credit the author and do not use it, or any derivative works, for a commercial purpose. When reusing or sharing this work, ensure you make the licence terms clear to others by naming the licence and linking to the licence text. Where a work has been adapted, you should indicate that the work has been changed and describe those changes. Please seek permission from the copyright holder for uses of this work that are not included in this licence or permitted under UK Copyright Law.

Contents

Abstract	4
Acknowledgments	5
Introduction	6
Historical background of memory research	6
Theoretical models of memory	7
Role of intrinsic neural properties in memory circuits	9
Further challenges to the synaptic memory paradigm	11
Overview of the thesis	12
References	14
Chapter 1 - From intrinsic excitability to memory linking	20
Chapter 2 - A mechanism underlying representational drift	33
Chapter 3 - Towards an epigenetic memory	58
Conclusion	78
Summary	78
Discussion about the model	79
Future directions	81
References	83

*How happy is the blameless vestal's lot!
The world forgetting, by the world forgot.
Eternal sunshine of the spotless mind!
Each pray'r accepted, and each wish resign'd?*

Alexander Pope

Abstract

While the mechanisms of synaptic plasticity underlying memory dynamics are well understood, the role of intrinsic neural properties has been largely unexplored, so far. Recent works studying memory dynamics over long timescales have unveiled mechanisms that synaptic models of memories have been unable to explain. First, neural ensembles representing individual memories of temporally close events tend to overlap in multiple brain regions. Moreover, memory representations are not static in time, and the neurons taking part of memory ensembles change over timescales of hours to days. Finally, the transcription of learning-related genes is altered in neurons taking part of memory ensembles, long after learning. Based on these recent findings, this thesis explores the role of intrinsic neural properties in memory dynamics, using a computational model. Overall, it provides predictions on the interplay between synaptic and intrinsic plasticity in memory formation and maintenance.

Acknowledgments

First of all, I would like to thank my PhD supervisor Claudia Clopath. Claudia has been an important mentor in these past years of my life, both scientifically and for my career in general, and I am very grateful for her support. I would like to thank the members of the Clopath lab, past and present, for the great discussions and support. Thank you to all the researchers with whom I had the chance to collaborate: Douglas who worked with me on my first project when I joined the lab, Denise and Joe from the Icahn School of Medicine at Mount Sinai in New York for the collaboration on the second project, and Johannes from the École Polytechnique Fédérale de Lausanne for the collaboration on the epigenetics project. I am grateful to have had the chance to work with all these brilliant researchers. I would also like to thank my friends from Paris, London, Brussels, and around the world, as well as the friends I had the chance to meet through conferences and the summer schools. Finally, I would like to thank my family, who has supported me during my PhD and all along my studies.

Introduction

Historical background of memory research

The presence of neural structures as basis for encoding individual memories has long been hypothesised by the scientific community. In 1904, Richard Semon suggested that memories take the form of a non-physical, physiochemical trace that he named "en-gram" (Schacter, Eich, and Tulving, [1978](#)). In today's view, engrams cells are defined as subset of neurons which are activated when experiencing an event, *i.e.* during memory encoding, and that can be specifically reactivated afterwards, inducing recall of the associated memory (Josselyn and Tonegawa, [2020](#)). For a long time however, the presence of such structure has remained unproven. Indeed, observing a memory engram requires to measure neural activity *in vivo*, or tag neurons genetically for a restraint time window, while the subject is performing a memory task. For a long time, this technological challenge has been is a significant limitation in memory studies. In the recent years however, scientific advances such as in genetic tagging, optical imaging and optogenetics have now made possible the study of memory engrams.

In 2009 and 2012, two major studies respectively showed that activity of the engram following learning is necessary and sufficient to trigger memory recall. The behavioral paradigm used in these studies, and in most of the following ones in the field of engram research, is the fear conditioning protocol. Animals (usually mice) are placed in a conditioning chamber where they learn to associate the context of the chamber to an

electric shock (memory encoding). The mouse is later placed in the same chamber with no foot shock and the strength of memory recall is measured by reading how much the mouse spends "freezing" (memory recall). Throughout the behavioral protocol, active neurons can be tagged at different time windows using immediate early genes such as c-Fos. Those active during memory encoding and recall can be defined as being part of the memory engram (Josselyn and Tonegawa, 2020). In the first loss-of-function experiment, ablating neurons belonging to the memory engram in the lateral amygdala was sufficient to suppress a fear memory (Han et al., 2009). This first study proved that the activity of the engram is necessary for memory recall. Three years after this study, the first gain-of-function experiment found that optogenetic reactivation of the engram in the hippocampal dentate gyrus was sufficient to recall the memory (Liu et al., 2012). By artificially activating the engram, the mouse showed freezing behavior, suggesting that its activity is sufficient for triggering memory recall.

Overall, these recent studies have shown causal relations between neural activity of engrams and behavioral read-out of individual memories, laying the foundations for a model of memory circuits: memories are now largely assumed to take the form of specific ensembles of neurons that are reactivated during recall. However, the engram paradigm still lacks an answer to a fundamental question: How are memory engrams formed and maintained across long timescale?

Theoretical models of memory

To understand how memories of past events are encoded in the brain, we must understand the basis of learning, beyond the engram literature. Since the second part of the 20th century, neuroscientists have assumed that learning is induced by synaptic plasticity. While patterns of neural spiking activity are known to be correlated with behavioral output (as mentioned in the previous section), it is natural to hypothesize that long-term information is maintained in the synapses connecting individual neu-

rons and brain regions to each other. As such, learning can be defined as a correlated change between synaptic connectivity pattern, neural activity and behavior. Research for the mechanisms underlying learning and synaptic plasticity has benefited from an interesting interplay between both experimental and theoretical works. First, in 1949, Donald Hebb proposed a mathematical framework for synaptic plasticity and learning (Hebb, 1949). The idea behind this framework is that the synapse linking two neurons is reinforced if the neurons have correlated activity. This model can be summarised behind the idea that neurons that "fire together wire together". A large corpus of experimental works have since proven this theory (Kandel and Tauc, 1965; Bliss and Lømo, 1973), which is now the mainly adopted framework in computational studies (Markram, Gerstner, and Sjöström, 2011; Zenke, Agnes, and Gerstner, 2015; Tomé, Sadeh, and Clopath, 2022).

These initial works have laid the foundations for models of learning at the synaptic level. However, at the network level, it is still unclear where and how neurons are organised to encode individual memories. Indeed, a major challenge in memory research is to understand how local neural plasticity can give rise to memory engrams. In 1982, John J. Hopfield formalised mathematically the idea that individual memories can be stored in networks of neurons that are recurrently connected (Hopfield, 1982). This seminal study gave rise to the theory of attractor networks (Amit, 1989) as potential mathematical models for memory circuits: individual memories take the form of assemblies of highly recurrently connected neurons, that can be reactivated for memory recall (Gastaldi et al., 2021; Rennó-Costa, Lisman, and Verschure, 2014; Wills et al., 2005; Van De Ven et al., 2016). These types of models have since then been used to specifically model memory ensembles (Zenke, Agnes, and Gerstner, 2015; Gallinaro, Gašparović, and Rotter, 2022; Manz and Memmesheimer, 2023; Kastellakis, Silva, and Poirazi, 2016) and have successfully explained different brain processes such as pattern completion and separation (Chavlis and Poirazi, 2017; Gastaldi et al., 2021; Amit, 1989). Experimentally, this theoretical framework is consistent with experimental re-

sults on engrams which link structural changes with learning. Indeed, spine growth and decrease have been associated with long-term potentiation and depression of synapses, in turn linked to an increase or decrease and the memory strength, respectively (Joselyn and Tonegawa, 2020).

Role of intrinsic neural properties in memory circuits

While the memory research community has been focused on synapses, it has largely omitted to consider the intrinsic properties of neurons (Fig. 1). In the recent years, neurons' membrane and nucleus properties have been shown to undergo continual changes and to be strongly affected by learning. In particular, the intrinsic excitability of neurons, defined as the magnitude of the activity in response to a given input current, is dynamic (Mau, Hasselmo, and Cai, 2020; Chen et al., 2020). Moreover, excitability of

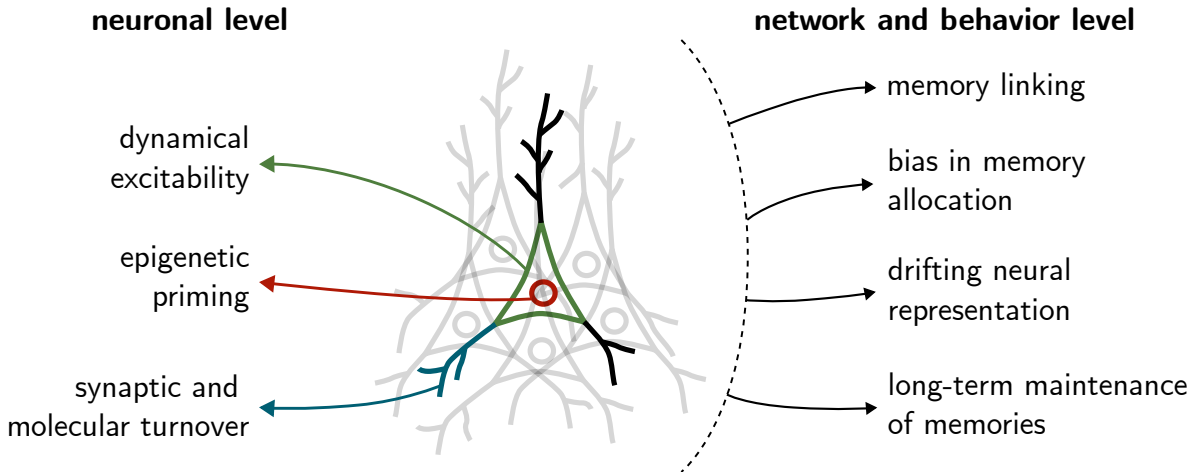


Figure 1: **Summary of the recent findings that challenge the traditional synaptic-based models of memory circuits.** Left: At the nucleus, membrane and synaptic levels, some experimental observations are generally disregarded by computational studies. Right: At the network and behavioral level, some properties of the memory dynamics that are yet to be understood.

neurons taking part in memory ensemble is known to increase on a timescale of a few hours after learning Moyer, Thompson, and Disterhoft, 1996; Rashid et al., 2016; Chen et al., 2020), before decreasing (Shen et al., 2022). Finally, other lines of research have shown that learning is linked with large changes in the transcription of genes associated to learning-related proteins (Gräff et al., 2011).

The role of these intrinsic neural changes is not yet understood and has been poorly explored so far. Epigenetic changes are known to be involved in all stages of memory (Coda and Gräff, 2024). For example, a recent work has shed light on the role of histone acetylation - a type of epigenetic mechanism - in regulating memory allocation in the amygdala (Santoni et al., 2024). However, these intrinsic changes to the neuron’s nucleus have not been integrated in computational models of memories. Moreover, intrinsic excitability has been shown to play a key role in memory formation and recall. Neurons with elevated excitability have been shown to be preferentially allocated to the memory trace (Rogerson et al., 2014; Silva et al., 2009; Zhou et al., 2016). This is an important result because it gives - at least partially - an explanation to how neurons become part of a specific memory ensemble. Based on this idea, further works have shown that two memories of events that happen close in time tend to be linked. At the neural activity level, the associated memory engrams tend to overlap due to an increase in excitability following learning (Cai et al., 2016; Rashid et al., 2016; Yokose et al., 2017). Moreover, elevated excitability has also been shown to help performing better pattern separation and completion during memory recall (Pignatelli et al., 2019). These recent works have speculated a role for intrinsic neural properties in memory circuits, and raise limitations to the existing memory paradigm (Fig. 1).

Further challenges to the synaptic memory paradigm

Recent works have demonstrated that memory ensembles are not static and undergo constant dynamical changes. The neurons representing a given feature or event tend to change across time, despite stable behavior, in a process known as representational drift (Khatib et al., 2023; Sadeh and Clopath, 2022; Driscoll, Duncker, and Harvey, 2022). Similar effects have been observed in place cells, which are neurons representing specific locations in space. The specific correlation between physical location and neural activity changes across time, in a process known as remapping (Ziv et al., 2013; Rubin et al., 2015). In both cases, the dynamical nature of neural representations challenges the widely accepted view that memories take the form of very stable neural structures. Therefore, two questions arise from these recent observations: why would the brain constantly change neural representations and what are the underlying mechanisms? An answer to the first question is that drifting ensembles allow for encoding temporal information, along with information of the memory itself, in a process known as "time-stamping" (Rubin et al., 2015; Khatib et al., 2023; Clopath et al., 2017). The underlying mechanisms are not yet known but several ideas have emerged. Theories suggested that it could arise from behavioral variability (Sadeh and Clopath, 2022), exercise (Snou et al., 2023) or fluctuations of excitability (Mau, Hasselmo, and Cai, 2020).

Moreover, a more general challenge to the synaptic-based memory paradigm has not been discussed yet. Synapses are known for a long time to undergo molecular turnover, which challenges the idea that all the information is encoded in the synapses. Indeed, for long-term memories, external mechanisms should be required to maintain synapses across very long timescales (Crick, 1984). So far, this problem has been largely ignored by the memory research community, despite some works going in that direction (Mongillo, Rumpel, and Loewenstein, 2017; Lisman, 1985). One key solution to this problem could be that part of the information is encoded as an intrinsic change in the neuron's nucleus (Titley, Brunel, and Hansel, 2017), for example as an alteration of

the epigenome (Coda and Gräff, 2024). Overall, this question gives another reason to considering intrinsic neural changes when studying memory, going beyond the idea that information is solely encoded at the synapse level (Fig. 1).

Overview of the thesis

In light of these recent experimental results, we propose to investigate the role of neural intrinsic parameters in memory formation and maintenance. To that end, we developed a model for memory formation and maintenance using a rate-based recurrent neural network. The network is composed of neurons which receive input from an external stimulus and which are all recurrently connected. As detailed in the following chapters, stimulation of the network leads to formation of neural ensembles, which are associated to specific memories (Fig. 2a). All synapses are plastic and follow a Hebbian rule, meaning that the synaptic weights are increased when connected neurons fire together. Importantly, the model is equipped with intrinsic excitability: the response of each neuron to a given stimulus is modulated by an intrinsic dynamical variable (Fig. 2b). Memory encoding is modelled by an initial stimulation of the network, which lead to the formation of an ensemble. Subsequent stimulations of the network induce the reactivation of the ensemble, therefore modelling memory recall.

This model has been adapted differently to the three chapters of this thesis (see Methods for each section), and the modelling choice is discussed at the end of the thesis. Using this theoretical framework, we approach the questions raised in this introduction under three different angles. These approaches are based on different hypothesis backed by experimental results, and lead to testable predictions.

- The first chapter of this thesis aims at understanding how increase in excitability following learning can give rise to engram overlap and memory linking. This work is based on recent experimental results showing that increased level of intrinsic excitabil-

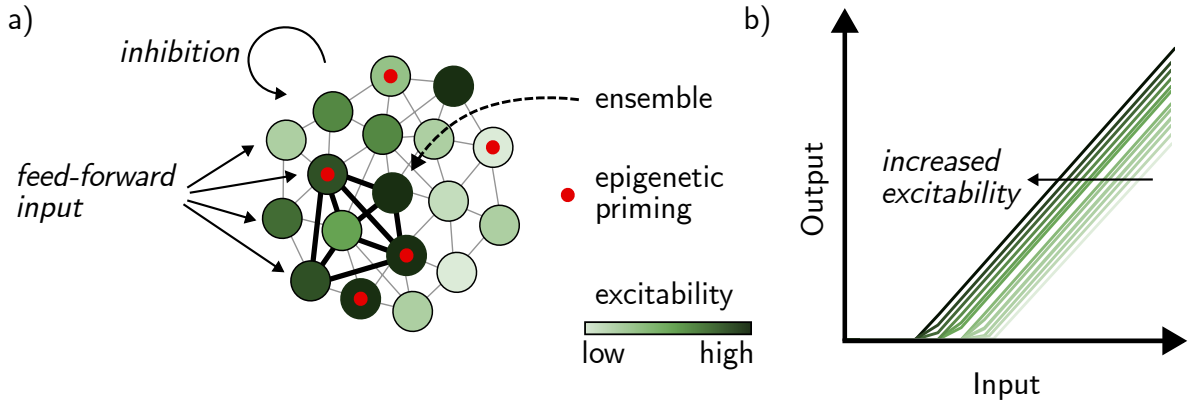


Figure 2: **General schematic of the model developed in this thesis** a) Network of all-to-all recurrently connected neurons, receiving feed-forward input stimulation and activity-dependent inhibition. Each neuron has a unique, dynamical excitability and can be epigenetically primed (third chapter). Individual memories take the form of highly recurrently connected neurons. b) Excitability of each neuron is given by a unique threshold of its input-output function: a high excitability leads to a high firing rate for a given input current.

ity lead to memory linking and bias memory allocation. The main hypothesis of this work is that these results can be explained by the interplay between intrinsic excitability and synaptic plasticity gives. The results serve as predictions regarding the neural dynamics underlying memory allocation and linking.

- In the second chapter, we propose a new mechanism to explain representational drift. We hypothesised that slow fluctuations of intrinsic excitability is a motor for drift, most likely among others, which has not been experimentally proven yet. This framework allows us to predict the conditions that allow excitability to encode temporal information in memory ensembles.

- The third and last chapter focuses on exploring the role of epigenetics in memory circuits. Backed by recent experiments, we developed a hypothetical model which

introduces epigenetics in a memory circuit, challenging the traditional models of synaptic memories. This work predicts mechanisms for long-term maintenance of memories through modifications of the epigenome.

References

- Schacter, Daniel L., James Eric Eich, and Endel Tulving (Dec. 1978). “Richard Semon’s theory of memory”. In: *Journal of Verbal Learning and Verbal Behavior* 17.6, pp. 721–743. DOI: [10.1016/S0022-5371\(78\)90443-7](https://doi.org/10.1016/S0022-5371(78)90443-7).
- Josselyn, Sheena A. and Susumu Tonegawa (Jan. 2020). “Memory engrams: Recalling the past and imagining the future”. In: *Science* 367.6473, eaaw4325. DOI: [10.1126/science.aaw4325](https://doi.org/10.1126/science.aaw4325).
- Han, Jin-Hee et al. (Mar. 2009). “Selective Erasure of a Fear Memory”. In: *Science* 323.5920, pp. 1492–1496. DOI: [10.1126/science.1164139](https://doi.org/10.1126/science.1164139).
- Liu, Xu et al. (Apr. 2012). “Optogenetic stimulation of a hippocampal engram activates fear memory recall”. In: *Nature* 484.7394, pp. 381–385. DOI: [10.1038/nature11028](https://doi.org/10.1038/nature11028).
- Hebb, D. O. (1949). *The organization of behavior: a neuropsychological theory*. Mahwah, N.J: L. Erlbaum Associates.
- Kandel, E R and L Tauc (Nov. 1965). “Heterosynaptic facilitation in neurones of the abdominal ganglion of *Aplysia depilans*.” In: *The Journal of Physiology* 181.1, pp. 1–27.
- Bliss, T. V. P. and T. Lømo (1973). “Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path”. In: *The Journal of Physiology* 232.2, pp. 331–356. DOI: [10.1113/jphysiol.1973.sp010273](https://doi.org/10.1113/jphysiol.1973.sp010273).
- Markram, Henry, Wulfram Gerstner, and Per Jesper Sjöström (Aug. 2011). “A History of Spike-Timing-Dependent Plasticity”. In: *Frontiers in Synaptic Neuroscience* 3. DOI: [10.3389/fnsyn.2011.00004](https://doi.org/10.3389/fnsyn.2011.00004).

- Zenke, Friedemann, Everton J. Agnes, and Wulfram Gerstner (Nov. 2015). “Diverse synaptic plasticity mechanisms orchestrated to form and retrieve memories in spiking neural networks”. In: *Nature Communications* 6.1, p. 6922. DOI: [10.1038/ncomms7922](https://doi.org/10.1038/ncomms7922).
- Tomé, Douglas Feitosa, Sadra Sadeh, and Claudia Clopath (Feb. 2022). “Coordinated hippocampal-thalamic-cortical communication crucial for engram dynamics underneath systems consolidation”. In: *Nature Communications* 13.1, p. 840. DOI: [10.1038/s41467-022-28339-z](https://doi.org/10.1038/s41467-022-28339-z).
- Hopfield, J J (Apr. 1982). “Neural networks and physical systems with emergent collective computational abilities.” In: *Proceedings of the National Academy of Sciences* 79.8, pp. 2554–2558. DOI: [10.1073/pnas.79.8.2554](https://doi.org/10.1073/pnas.79.8.2554).
- Amit, Daniel J. (1989). *Modeling Brain Function: The World of Attractor Neural Networks*. Cambridge: Cambridge University Press. DOI: [10.1017/CB09780511623257](https://doi.org/10.1017/CB09780511623257).
- Gastaldi, Chiara et al. (Dec. 2021). “When shared concept cells support associations: Theory of overlapping memory engrams”. In: *PLOS Computational Biology* 17.12, e1009691. DOI: [10.1371/journal.pcbi.1009691](https://doi.org/10.1371/journal.pcbi.1009691).
- Rennó-Costa, César, John E. Lisman, and Paul F. M. J. Verschure (May 2014). “A Signature of Attractor Dynamics in the CA3 Region of the Hippocampus”. In: *PLOS Computational Biology* 10.5, e1003641. DOI: [10.1371/journal.pcbi.1003641](https://doi.org/10.1371/journal.pcbi.1003641).
- Wills, Tom J. et al. (May 2005). “Attractor Dynamics in the Hippocampal Representation of the Local Environment”. In: *Science* 308.5723, pp. 873–876. DOI: [10.1126/science.1108905](https://doi.org/10.1126/science.1108905).
- Van De Ven, Guido M. et al. (Dec. 2016). “Hippocampal Offline Reactivation Consolidates Recently Formed Cell Assembly Patterns during Sharp Wave-Ripples”. In: *Neuron* 92.5, pp. 968–974. DOI: [10.1016/j.neuron.2016.10.020](https://doi.org/10.1016/j.neuron.2016.10.020).
- Gallinaro, Júlia V., Nebojša Gašparović, and Stefan Rotter (Feb. 2022). “Homeostatic control of synaptic rewiring in recurrent networks induces the formation of stable memory engrams”. In: *PLOS Computational Biology* 18.2, e1009836. DOI: [10.1371/journal.pcbi.1009836](https://doi.org/10.1371/journal.pcbi.1009836).

- Manz, Paul and Raoul-Martin Memmesheimer (Apr. 2023). “Purely STDP-based assembly dynamics: Stability, learning, overlaps, drift and aging”. In: *PLOS Computational Biology* 19.4, e1011006. DOI: [10.1371/journal.pcbi.1011006](https://doi.org/10.1371/journal.pcbi.1011006).
- Kastellakis, George, Alcino J. Silva, and Panayiota Poirazi (Nov. 2016). “Linking Memories across Time via Neuronal and Dendritic Overlaps in Model Neurons with Active Dendrites”. In: *Cell Reports* 17.6, pp. 1491–1504. DOI: [10.1016/j.celrep.2016.10.015](https://doi.org/10.1016/j.celrep.2016.10.015).
- Chavlis, Spyridon and Panayiota Poirazi (2017). “Pattern separation in the hippocampus through the eyes of computational modeling”. In: *Synapse* 71.6, e21972. DOI: [10.1002/syn.21972](https://doi.org/10.1002/syn.21972).
- Mau, William, Michael E Hasselmo, and Denise J Cai (Dec. 2020). “The brain in motion: How ensemble fluidity drives memory-updating and flexibility”. In: *eLife* 9, e63550. DOI: [10.7554/eLife.63550](https://doi.org/10.7554/eLife.63550).
- Chen, Lingxuan et al. (Sept. 2020). “The role of intrinsic excitability in the evolution of memory: Significance in memory allocation, consolidation, and updating”. In: *Neurobiology of Learning and Memory* 173, p. 107266. DOI: [10.1016/j.nlm.2020.107266](https://doi.org/10.1016/j.nlm.2020.107266).
- Moyer, James R., Lucien T. Thompson, and John F. Disterhoft (Sept. 1996). “Trace Eyeblick Conditioning Increases CA1 Excitability in a Transient and Learning-Specific Manner”. In: *Journal of Neuroscience* 16.17, pp. 5536–5546. DOI: [10.1523/JNEUROSCI.16-17-05536.1996](https://doi.org/10.1523/JNEUROSCI.16-17-05536.1996).
- Rashid, A. J. et al. (July 2016). “Competition between engrams influences fear memory formation and recall”. In: *Science* 353.6297, pp. 383–387. DOI: [10.1126/science.aaf0594](https://doi.org/10.1126/science.aaf0594).
- Shen, Yang et al. (June 2022). “CCR5 closes the temporal window for memory linking”. In: *Nature* 606.7912, pp. 146–152. DOI: [10.1038/s41586-022-04783-1](https://doi.org/10.1038/s41586-022-04783-1).
- Gräff, Johannes et al. (Apr. 2011). “Epigenetic Regulation of Gene Expression in Physiological and Pathological Brain Processes”. In: *Physiological Reviews* 91.2, pp. 603–649. DOI: [10.1152/physrev.00012.2010](https://doi.org/10.1152/physrev.00012.2010).

- Coda, Davide Martino and Johannes Gräff (Feb. 2024). “From cellular to fear memory: An epigenetic toolbox to remember”. In: *Current Opinion in Neurobiology* 84, p. 102829. DOI: [10.1016/j.conb.2023.102829](https://doi.org/10.1016/j.conb.2023.102829).
- Santoni, Giulia et al. (July 2024). “Chromatin plasticity predetermines neuronal eligibility for memory trace formation”. In: *Science* 385.6707, eadg9982. DOI: [10.1126/science.adg9982](https://doi.org/10.1126/science.adg9982).
- Rogerson, Thomas et al. (Mar. 2014). “Synaptic tagging during memory allocation”. In: *Nature Reviews Neuroscience* 15.3, pp. 157–169. DOI: [10.1038/nrn3667](https://doi.org/10.1038/nrn3667).
- Silva, Alcino J. et al. (Oct. 2009). “Molecular and Cellular Approaches to Memory Allocation in Neural Circuits”. In: *Science* 326.5951, pp. 391–395. DOI: [10.1126/science.1174519](https://doi.org/10.1126/science.1174519).
- Zhou, Miou et al. (Dec. 2016). “CCR5 is a suppressor for cortical plasticity and hippocampal learning and memory”. In: *eLife* 5, e20985. DOI: [10.7554/eLife.20985](https://doi.org/10.7554/eLife.20985).
- Cai, Denise J. et al. (June 2016). “A shared neural ensemble links distinct contextual memories encoded close in time”. In: *Nature* 534.7605, pp. 115–118. DOI: [10.1038/nature17955](https://doi.org/10.1038/nature17955).
- Yokose, Jun et al. (Jan. 2017). “Overlapping memory trace indispensable for linking, but not recalling, individual memories”. In: *Science* 355.6323, pp. 398–403. DOI: [10.1126/science.aal2690](https://doi.org/10.1126/science.aal2690).
- Pignatelli, Michele et al. (Jan. 2019). “Engram Cell Excitability State Determines the Efficacy of Memory Retrieval”. In: *Neuron* 101.2, 274–284.e5. DOI: [10.1016/j.neuron.2018.11.029](https://doi.org/10.1016/j.neuron.2018.11.029).
- Khatib, Dorgham et al. (Aug. 2023). “Active experience, not time, determines within-day representational drift in dorsal CA1”. In: *Neuron* 111.15, 2348–2356.e5. DOI: [10.1016/j.neuron.2023.05.014](https://doi.org/10.1016/j.neuron.2023.05.014).
- Sadeh, Sadra and Claudia Clopath (Aug. 2022). “Contribution of behavioural variability to representational drift”. In: *eLife* 11. Ed. by Stephanie E Palmer, Michael J Frank, and Yaniv Ziv, e77907. DOI: [10.7554/eLife.77907](https://doi.org/10.7554/eLife.77907).

- Driscoll, Laura N., Lea Duncker, and Christopher D. Harvey (Oct. 2022). “Representational drift: Emerging theories for continual learning and experimental future directions”. In: *Current Opinion in Neurobiology* 76, p. 102609. DOI: [10.1016/j.conb.2022.102609](https://doi.org/10.1016/j.conb.2022.102609).
- Ziv, Yaniv et al. (Mar. 2013). “Long-term dynamics of CA1 hippocampal place codes”. In: *Nature Neuroscience* 16.3, pp. 264–266. DOI: [10.1038/nn.3329](https://doi.org/10.1038/nn.3329).
- Rubin, Alon et al. (Dec. 2015). “Hippocampal ensemble dynamics timestamp events in long-term memory”. In: *eLife* 4. Ed. by Howard Eichenbaum, e12247. DOI: [10.7554/eLife.12247](https://doi.org/10.7554/eLife.12247).
- Clopath, Claudia et al. (Mar. 2017). “Variance and invariance of neuronal long-term representations”. In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 372.1715, p. 20160161. DOI: [10.1098/rstb.2016.0161](https://doi.org/10.1098/rstb.2016.0161).
- Snou, Mitchell L. de et al. (Feb. 2023). “Exercise accelerates place cell representational drift”. In: *Current Biology* 33.3, R96–R97. DOI: [10.1016/j.cub.2022.12.033](https://doi.org/10.1016/j.cub.2022.12.033).
- Crick, Francis (Nov. 1984). “Neurobiology: Memory and molecular turnover”. In: *Nature* 312.5990, pp. 101–101. DOI: [10.1038/312101a0](https://doi.org/10.1038/312101a0).
- Mongillo, Gianluigi, Simon Rumpel, and Yonatan Loewenstein (Oct. 2017). “Intrinsic volatility of synaptic connections — a challenge to the synaptic trace theory of memory”. In: *Current Opinion in Neurobiology*. Computational Neuroscience 46, pp. 7–13. DOI: [10.1016/j.conb.2017.06.006](https://doi.org/10.1016/j.conb.2017.06.006).
- Lisman, John E. (May 1985). “A mechanism for memory storage insensitive to molecular turnover: a bistable autophosphorylating kinase.” In: *Proceedings of the National Academy of Sciences* 82.9, pp. 3055–3057. DOI: [10.1073/pnas.82.9.3055](https://doi.org/10.1073/pnas.82.9.3055).
- Titley, Heather K., Nicolas Brunel, and Christian Hansel (July 2017). “Toward a Neurocentric View of Learning”. In: *Neuron* 95.1, pp. 19–32. DOI: [10.1016/j.neuron.2017.05.021](https://doi.org/10.1016/j.neuron.2017.05.021).
- Dong, Yan et al. (Apr. 2006). “CREB modulates excitability of nucleus accumbens neurons”. In: *Nature Neuroscience* 9.4, pp. 475–477. DOI: [10.1038/nn1661](https://doi.org/10.1038/nn1661).

Geva, Nitzan et al. (June 2023). “Time and experience differentially affect distinct aspects of hippocampal representational drift”. In: *Neuron*. DOI: [10.1016/j.neuron.2023.05.005](https://doi.org/10.1016/j.neuron.2023.05.005).

Chapter 1 - From intrinsic excitability to memory linking

The interplay between intrinsic excitability and synaptic plasticity in memory circuits has been largely disregarded in computational studies. However, recent advances in memory engram research have highlighted the important role of excitability in memory formation (Cai et al., 2016; Rashid et al., 2016) and recall (Pignatelli et al., 2019). In 2016, two major studies have shown temporal linking of memory engrams, in the amygdala (Rashid et al., 2016) and the hippocampus (Cai et al., 2016). In both studies, two memories of events that happened close in time tend to have overlapping neural representation. By tagging neurons during encoding and recall of different memories, some neurons can be shared among temporally linked memory engrams inducing memory linking (Cai et al., 2016). The linking of memory engrams has been associated to increase in excitability following learning (Dong et al., 2006), although the mechanisms underlying it are unknown. In this first chapter, we introduce a model of dynamical intrinsic excitability in a memory network to understand its role in memory allocation and linking. The following work was published in the *Journal of Neuroscience* in April 2024.

Intrinsic Neural Excitability Biases Allocation and Overlap of Memory Engrams.

Geoffroy Delamare, Douglas Feitosa Tomé, Claudia Clopath. 2024. Journal of Neuroscience 44 (21) e0846232024. doi:[10.1523/ jneurosci.0846-23.2024](https://doi.org/10.1523/JNEUROSCI.0846-23.2024)

Authors contribution Conceptualisation: GD, DFT, CC; Development of methodology: GD, DFT, CC; Simulations: GD; Data analysis and visualisation: GD; Writing original draft: GD; Reviewing and editing: GD, DFT, CC

Intrinsic Neural Excitability Biases Allocation and Overlap of Memory Engrams

 Geoffroy Delamare,¹  Douglas Feitosa Tomé,^{1,2} and  Claudia Clopath¹

¹Department of Bioengineering, Imperial College London, London SW7 2AZ, UK and ²Institute of Science and Technology Austria, Klosterneuburg 3400, Austria

Memories are thought to be stored in neural ensembles known as engrams that are specifically reactivated during memory recall. Recent studies have found that memory engrams of two events that happened close in time tend to overlap in the hippocampus and the amygdala, and these overlaps have been shown to support memory linking. It has been hypothesized that engram overlaps arise from the mechanisms that regulate memory allocation itself, involving neural excitability, but the exact process remains unclear. Indeed, most theoretical studies focus on synaptic plasticity and little is known about the role of intrinsic plasticity, which could be mediated by neural excitability and serve as a complementary mechanism for forming memory engrams. Here, we developed a rate-based recurrent neural network that includes both synaptic plasticity and neural excitability. We obtained structural and functional overlap of memory engrams for contexts that are presented close in time, consistent with experimental and computational studies. We then investigated the role of excitability in memory allocation at the network level and unveiled competitive mechanisms driven by inhibition. This work suggests mechanisms underlying the role of intrinsic excitability in memory allocation and linking, and yields predictions regarding the formation and the overlap of memory engrams.

Key words: engram; excitability; memory; memory allocation; memory linking; plasticity

Significance Statement

In the brain, memories are not formed in isolation from each other. For example, two memories of events that happened close in time tend to be linked, so that recalling one memory leads to recall of the second one. Although memories are thought to be formed by strengthening synapses among neurons, understanding memory linking requires us to consider intrinsic properties of the neurons themselves. In this study, we modeled a neural network aiming at explaining how memories are formed and linked in the brain. This model is able to reproduce experimental results and allows us to make predictions about how to link or dissociate memories.

Introduction

Neural circuits have the ability to form and retain memories that last from hours to years. In particular, pioneering anatomical studies (Scoville and Milner, 1957) have suggested that such

circuits are located in the hippocampus, although they had long remained unobserved. Over the past decades, technological advances such as neural imaging and optogenetics allowed for the discovery of engram cells in multiple brain regions as the neural substrate for memory storage and retrieval (Josselyn and Tonegawa, 2020). They are defined as a subpopulation of neurons that is initially activated during presentation of a stimulus, followed by transient physical and/or chemical changes that lead to its specific reactivation during memory recall (Josselyn and Tonegawa, 2020). Engram cells have been observed in the hippocampus (Liu et al., 2012), in the amygdala (Morrison et al., 2016; Rashid et al., 2016), and the neocortex (Tonegawa et al., 2015; Kitamura et al., 2017). These studies have shed lights on the ability of neural populations to store and retrieve memories but the exact mechanisms responsible for the formation of memory engrams are not yet fully clear.

The mechanistic understanding of the formation and long-term stability of memory engrams has long been dominated by Hebbian learning (Hebb, 1949). Indeed, most computational

Received May 5, 2023; revised March 25, 2024; accepted March 25, 2024.

Author Contributions: G.D., D.F.T., and C.C. designed research; G.D., D.F.T., and C.C. performed research; G.D. analyzed data; G.D. wrote the first draft of the paper; G.D., D.F.T., and C.C. edited the paper; G.D., D.F.T., and C.C. wrote the paper.

We thank Sadra Sadeh and Inês Completo Guerreiro for helpful comments on the manuscript, Yosif Zaki and Denise J. Cai for useful feedback and members of the Clopath lab for discussion and support. This work was supported by Biotechnology and Biological Sciences Research Council (BB/N013956/1 awarded to C.C.), Wellcome Trust (200790/Z/16/Z awarded to C.C.), the Simons Foundation (564408 awarded to C.C.), and Engineering and Physical Sciences Research Council (EP/R035806/1 awarded to C.C.).

Competing Interest Statement: The authors declare no competing financial interests.

Correspondence should be addressed to Claudia Clopath at c.clopath@imperial.ac.uk.

<https://doi.org/10.1523/JNEUROSCI.0846-23.2024>

Copyright © 2024 Delamare et al.

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license, which permits unrestricted use, distribution and reproduction in any medium provided that the original work is properly attributed.

models have focused on synaptic mechanisms, such as long-term potentiation or depression (Bliss and Collingridge, 1993; Josselyn and Tonegawa, 2020) that have been able to provide insight into the formation and stability of neural assemblies (Litwin-Kumar and Doiron, 2014; Zenke et al., 2015). As a result, the contribution of other important mechanisms, like intrinsic excitability (Titley et al., 2017), has remained underexplored. Indeed, previous experimental works have shown that neurons with high excitability are preferentially allocated to memory engrams (Han et al., 2007; Silva et al., 2009; Zhou et al., 2009). Interestingly, learning is known to transiently increase neural excitability, reducing the afterhyperpolarization of neurons over several hours (Thompson et al., 1996; Oh et al., 2003). This transient increase is likely due to the learning-induced expression of the transcription factor cAMP Response Element-Binding Protein (CREB) (Han et al., 2007; Silva et al., 2009; Rashid et al., 2016), which is known to play a role in regulating neural excitability (Dong et al., 2006). As a result, time-varying excitability may account for overlapping neural ensembles encoding memories of events that are temporally linked (Sehgal et al., 2018), namely events spaced by a short temporal delay, as observed in the lateral amygdala (Rashid et al., 2016), the hippocampal dorsal CA1 (Cai et al., 2016; Shen et al., 2022), and the retrosplenial cortex (Sehgal et al., 2021).

Attractor networks (Amit, 1989) have been previously used to describe the recurrent network properties of overlapping memory engrams (Gastaldi et al., 2021) but without taking excitability into account. Previous theoretical works have described how the dynamics of plasticity-related proteins and excitability can lead to co-allocation of memories at the dendritic level (Kastellakis et al., 2016; Sehgal et al., 2021; Chowdhury et al., 2022). Here, we extend these computational works to focus on the role of excitability in the recurrent neural network dynamics and its link with behavioral output. Combining synaptic plasticity and activity-dependent intrinsic excitability, our model is able to explain—at the mechanistic level—experimental findings regarding overlapping neural ensembles and memory linking. Moreover, we uncover the potential mechanisms allowing neurons to compete for allocation to memory engrams, as observed experimentally. Our results suggest that the temporal linking of memory engrams arises from co-activation of different neural ensembles, mediated by the interaction of time-varying excitability and synaptic plasticity. Finally, our model makes testable predictions about how the balance among inhibition, feed-forward inputs, and excitability is crucial for determining the extent of overlap among engrams of temporally close events.

Methods

Rate model. Our rate-based model consists of a single recurrent neural network of N neurons (with firing rate r_i , $1 \leq i \leq N$) which receives inputs from an external region of N^{in} neurons (with firing rate r_i^{in} , $1 \leq i \leq N^{\text{in}}$). The weights between the input region and the network are given by the matrix W^{FF} (Fig. 1b). Recurrent connections are given by the weight matrix W . Inhibition is introduced as $I = I_0 + I_1 \sum_{j=1}^N r_j$, where I_0 sets a baseline inhibition level and I_1 scales an inhibition term proportional to the sum of the firing rates of the N neurons. Finally, excitability is added as a time-varying threshold $\epsilon_i(t)$ of the input–output function. The rate dynamics of a neuron i is therefore given by

$$\tau_r \frac{dr_i}{dt} + r_i = \text{ReLU} \left(\sum_{j=1}^N W_{ij} r_j + \sum_{j=1}^{N^{\text{in}}} W_{ij}^{\text{FF}} r_j^{\text{in}} - I + \epsilon_i(t) \right), \quad (1)$$

where τ_r is the decay time of the rates and ReLU is the rectified linear activation function. In Figure 5, the dashed lines correspond to the case

where inhibition is reduced, i.e., I_1 is set to a lower value I_1^- (see Table of parameters).

In Figure 7d, noise is applied as random variable sampled at each integration step from a uniform distribution centered around 0 and of amplitude 4 (a.u.).

Weights dynamics. The feed-forward weights W^{FF} are static and define three receptive fields (RFs) that model three different contexts (Fig. 1b). Neurons 1–15 respond preferentially to the first context, neurons 16–30 to the second context, and neurons 31–45 to the third context. All-to-all recurrent connections W are plastic and the weights W_{ij} between each presynaptic neuron i and postsynaptic neuron j follow a Hebbian rule given by

$$\tau_W \frac{dW_{ij}}{dt} = (1 + \text{US}(t)) * \tanh(r_i * (r_j - r_j^0(t))), \quad (2)$$

where τ_W is the learning time constant and $\text{US}(t)$ is the unconditioned stimulus (US) which is equal to US^+ when US is applied (synchronously with stimulation of the context) and 0 otherwise. r_j^0 is the temporal mean over a time window δ of the firing rate of neuron j , given by

$$r_j^0(t) = \frac{1}{\delta} \int_{t-\delta}^t r_j(t') dt'. \quad (3)$$

An upper cap W_{max} and a lower cap W_{min} are applied to the recurrent weights W to prevent them from being negative or too high.

Intrinsic neural excitability. Intrinsic neural excitability follows dynamics that have been previously hypothesized to be due to the increase in the CREB transcription factor following learning (Silva et al., 2009). Each neuron's initial excitability ϵ_i^0 is sampled from a half-normal distribution of mean 0 and standard deviation 0.5. If the firing rate of a given neuron i reaches a set active threshold θ , its excitability ϵ_i moves from its initial value ϵ_i^0 to a higher value E , 2.9 s after neurons are tagged. Excitability then decays to ϵ_i^0 with a time scale τ_e :

$$\tau_e \frac{d\epsilon_i}{dt} + \epsilon_i = \epsilon_i^0. \quad (4)$$

Note that we did not consider any increase in excitability following recall in all figures but Figure 7c. In the latter, neurons are tagged during recall of the first memory and excitability of the active neurons is increased between 300 ms and 500 ms after recall onset, before decaying to baseline.

Stimulation protocol. During training, either the first, second, or last third of the N^{in} neurons from the input region are activated, namely their firing rates are set to a fixed value r_{CS} . This activation is repeated N_{stim} times for a duration ΔT , with an interstimulus delay ΔS . During the recall period, one of the three contexts is presented for a duration ΔT . During training in all figures (except Fig. 3), shock is applied synchronously with the context, namely the value US in the learning rule (Eq. 2) is set to a non-zero value US^+ . In Figure 3, shock is applied during the last presentation of the blue context (when specified).

During the simulations where excitability is manipulated (Figs. 4 and 5), the first N_{e^+} neurons received an enhanced excitability $\epsilon^{\text{increase}}$, that is added to their initial excitability ϵ_i^0 during presentation of the first context. Then, when inhibition is applied (i^+), the first N_{i^+} neurons receive an external negative current i .

Behavioral read-out. We introduced a read-out variable of the memory strength in order to compare it with the freezing levels measured in experiments. To that end, we modeled this memory strength using an ideal observer defined as

$$F = \sum_{i \in \Omega} \int_{t_r}^{t_r + \Delta T'} r_i(t) dt, \quad (5)$$

where t_r is the onset of the recall stimulation and $\Delta T = 100$ ms is the integration time, corresponding to the temporal window during which the neuron is active. Ω denotes the ensemble of neurons belonging to the engram, namely the set of neurons crossing the active threshold θ during the recall time window.

The engram overlap (Figs. 6 and 7) is computed as the number of neurons responding to both recall of the first context and another context (either the same context, a novel context, or a context that was presented with a 6 h or 24 h delay) divided by the number of neurons responding to the first context.

Exclusion criteria. During some simulations, the firing rates of some neurons increased and reached non-realistic values. We defined a threshold of 100 Hz and decided to exclude any trials where the firing rate of any neuron reached 100 Hz at any time point. Around 10% of the trials were typically excluded.

Integration. Integration was done using Euler's method on Python. A time step of 0.5 ms was used during and 3 s after training sessions, and during and 300 ms after recall sessions. Between training and recall, a time step of 20 s was used. Firing rates of neurons below 10^{-5} were set to 0.

Table of parameters. An initial set of parameters was used in most of the figures except in Figure 3. This initial configuration was chosen to match previous experimental results in the lateral amygdala (Rashid et al., 2016). In Figure 3, a second set of parameters was used to match engrams overlap measures observed in the hippocampal dCA1 (Cai et al., 2016).

Results

Formation of a single memory engram in a recurrent network with excitability

In order to study the effect of excitability in memory allocation and linking, we built a rate-based model with feed-forward and

recurrent connections, equipped with excitability and Hebbian plasticity. Excitability of each neuron i is modeled as a time-varying threshold ϵ_i of the input–output function (Methods, Eq. 1). This excitability is initially sampled from a random distribution (Methods) and changes to a higher value when the neuron's firing rate reaches a threshold θ before decaying to its initial value (Methods, Eq. 4). Feed-forward inputs are defined as a single layer divided in three subpopulations corresponding to different contexts. Feed-forward weights are set as a diagonal block structure to define three receptive fields (RFs, Methods, Fig. 1a and b), such that presenting a context increases the input current to a subpopulation of neurons in the main region. Recurrent connections are assumed to be all-to-all and plastic, according to a Hebbian learning rule (Methods, Eq. 2), and initialized at 0. We then stimulated the network by presenting different contexts (training phase, Methods).

We first observed that, after presenting the first context, the firing rates of neurons responding preferentially to this context (Fig. 1d, left) are above the “active” threshold θ , which we defined as the threshold above which neurons are classified as active. This was not the case for the other neurons in the network (Fig. 1d, left). Analyzing the recurrent weights matrix revealed that learning led to the formation of an assembly of neurons strongly connected to each other (Fig. 1c). The weights between neurons outside the assembly, however, have not significantly changed from their initial value equal to zero. We then sought to test the ability of the network to perform pattern completion. To this end, we stimulated the network with a partial cue and measured memory retrieval. We observed that stimulating four out of the seven neurons composing the assembly, namely those that were tagged as active during training (Methods), is enough to activate all the neurons in the assembly (Fig. 1e, right). This result shows that stimulating a subset of neurons of the assembly is sufficient to activate other neurons in the same assembly through strong intra-assembly connections.

Intrinsic neural excitability induces overlap among memory engrams of temporally close events

Next, we investigated the effect of presenting a second context to the network either 6 h or 24 h after the first one (Methods, Fig. 2a), inspired by previous experiments (Rashid et al., 2016). We designed our model in such a way that, after learning, excitability of neurons taking part in the newly formed assembly is increased, before slowly decaying to their baseline level (Methods, Eq. 4). Specifically, there is a transient increase in excitability after stimulating the network by the first context (Fig. 2b, red triangle) and the second context (Fig. 2b, blue triangle). We then measured memory recall for both contexts successively (Fig. 2a). Presenting a second context after a 24 h delay led to the formation of a second neural assembly in the recurrent weights matrix, distinct from the first one (Fig. 2c, top, and e). This second assembly is composed of neurons that are responsive to only the second context. As in the previous section, neurons that are part of both assemblies are reactivated independently during memory recall (Fig. 2d, top). Interestingly, we found that if the second context is presented after a 6 h delay, some off-diagonal weights are also reinforced for neurons responding preferentially to the second context (Fig. 2c, bottom). This suggests that the two memories are encoded by overlapping neural representations in the case where the contexts are presented 6 h apart but not 24 h apart. Indeed, when recalling the second memory, we observed a co-activation of neurons that take part in the first assembly in the case of a 6 h delay (Fig. 2d, bottom). We can

Parameter	Description	Figures 1, 2, and 4–7	Figure 3
N	Number of neurons in the main region	60	
N^{in}	Number of neurons in the input layer	30	
τ_{ϵ}	Excitability decay time constant	24 h 12 h	
E	Excitability increase	3.5	4
τ_r	Rate decay time constant	15 ms	
θ	Active threshold	6 Hz	4 Hz
I_0	Inhibition baseline	6	
I_1	Inhibition multiplicative factor	0.9	
I_1^-	Reduced inhibition multiplicative factor	0.88	
ΔT	Stimulation duration	40 ms	
N_{stim}	Number of stimulation per training sessions	20	15
ΔS	Interstimulus delay	150 ms	
$W_{\text{RF}}^{\text{FF}}$	Feed-forward weights corresponding to the RF neurons	0.3	
$W_{\text{non-RF}}^{\text{FF}}$	Feed-forward weights corresponding to the non-RF neurons	0.2	
τ_w	Hebbian rule time constant	750 ms	500 ms
W_{max}	Upper cap for plastic recurrent weights	1	
W_{min}	Lower cap for plastic recurrent weights	0	
US^+	Unconditioned stimulus strength	1	0.5
r_{CS}	Firing rate of the neurons from the input layer when activated	4 Hz	
δ	Averaging time of firing rates	15 s	
N_{ϵ^+}	Number of neurons that receive enhanced excitability	8	–
$\epsilon^{\text{increased}}$	Increase in excitability	5	–
N_{i^+}	Number of neurons that are inhibited	6	–
i	Inhibition strength	0.5	–

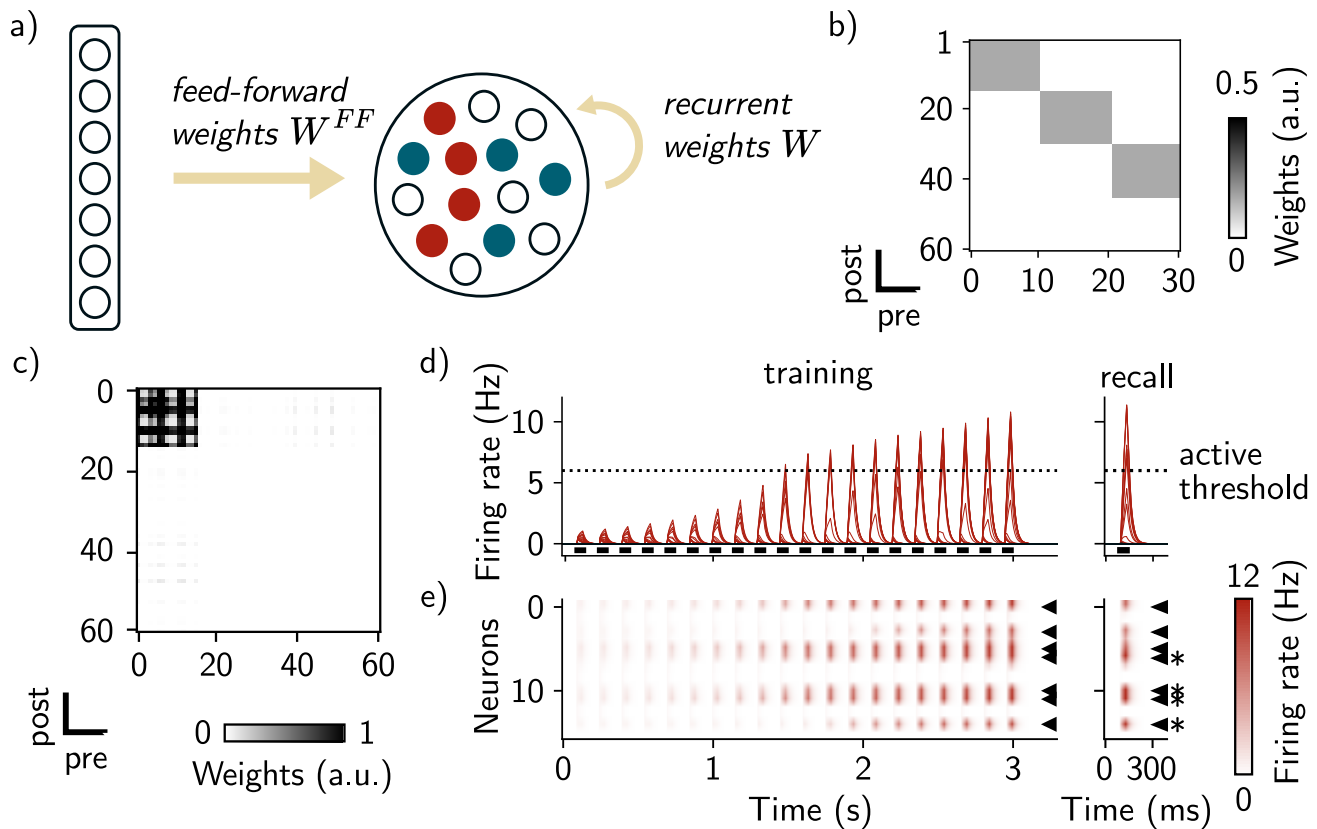


Figure 1. Encoding a single memory engram in a recurrent network equipped with intrinsic neural excitability. **a**, Diagram of the network architecture. Neurons in the input layer (left) project to the network with feed-forward connections W^{FF} (right). The feed-forward weights are defined such that neurons in the main layer have RFs (only two are shown here, red and blue neurons). **b**, Fixed, feed-forward synaptic weights matrix W^{FF} . RFs are defined by strong weights in a block-diagonal structure. When presenting the first context for example, the first 10 neurons of the input region are activated which in turn stimulate preferentially the first 15 neurons in the main region. **c**, Recurrent weights matrix after training. The block structure shows a neural assembly with stronger connections between neurons responding to the red context (0–15). **d**, Firing rates of all the neurons across time during training (left) and recall (right). Neurons responding preferentially to the context are shown in red while the other neurons are shown in black and do not respond to the stimulus. Black bars show presentations of the stimulus to the network. The dashed line is the “active” threshold, i.e., the threshold above which neurons are classified as active. **e**, Firing rate of each neuron responding preferentially to the first context during training (left) and recall (right). Black arrows indicate seven neurons that were tagged as “active” during training and that were reactivated during recall. During the recall phase, four of these seven neurons (black stars) were stimulated.

therefore quantify the overlap between the two assemblies, namely the number of neurons that were active during recall of both contexts, and found that it is higher in the case where the events were separated by 6 h relative to 24 h (Figs. 6 and 7). This overlap seems to be independent of the engram size (Fig. 7b). We also observed similar results when excitability was increased following recall or when the activation threshold during training was heterogeneous (Methods, Fig. 7c). The presence of ongoing noise throughout the simulation did not affect the results (Methods, Fig. 7d). In contrast, no overlap was observed when excitability was kept fixed (Fig. 7c).

Linking memories at the behavioral level in a fear conditioning simulation

We then asked whether this structural overlap among memory engrams could lead to memory linking. To that end, we modeled a fear conditioning experiment (Cai et al., 2016). We measured the strength of the memory recall as an ideal observer, namely a read-out value that is proportional to the sum of the neurons' firing rate, integrated over the duration of the recall stimulus (Methods, Eq. 5). The US was introduced as a multiplicative term in the Hebbian learning rule (Methods, Eq. 2) such that the recurrent weights are preferentially increased when the US is applied.

We presented three distinct contexts to the network, separated by 7 d and 5 h (Fig. 3a). In order to test memory linking, we presented the last context a second time, now paired with the US (Fig. 3a, in blue) and measured the memory strength of each of the three contexts. We observed that the memory strength was high when presenting either the blue context, which was paired with the US, or the yellow context, which was not paired with the US but was initially separated by 5 h relative to the shocked context (Fig. 3b). Conversely, presenting the red context, delayed by 7 d, elicited a level of memory recall comparable to the control case when no US was applied (Fig. 3b). Similarly to previous results (Fig. 2), the memory ensemble associated to the yellow contexts overlaps with the one associated to the blue context, but not the red one (Fig. 3c–e). Our model was then able to show that two memories encoded close in time tend to be linked in such a way that recalling either memory can lead to a similar behavioral output, as shown experimentally (Cai et al., 2016; Shen et al., 2022).

Manipulating initial excitability biases neural allocation of memories

Given that excitability is a key mechanism for linking memory engrams, we then asked to what extent excitability could also play a role in biasing memory allocation. To that end, and inspired by previous experiments (Rashid et al., 2016), we

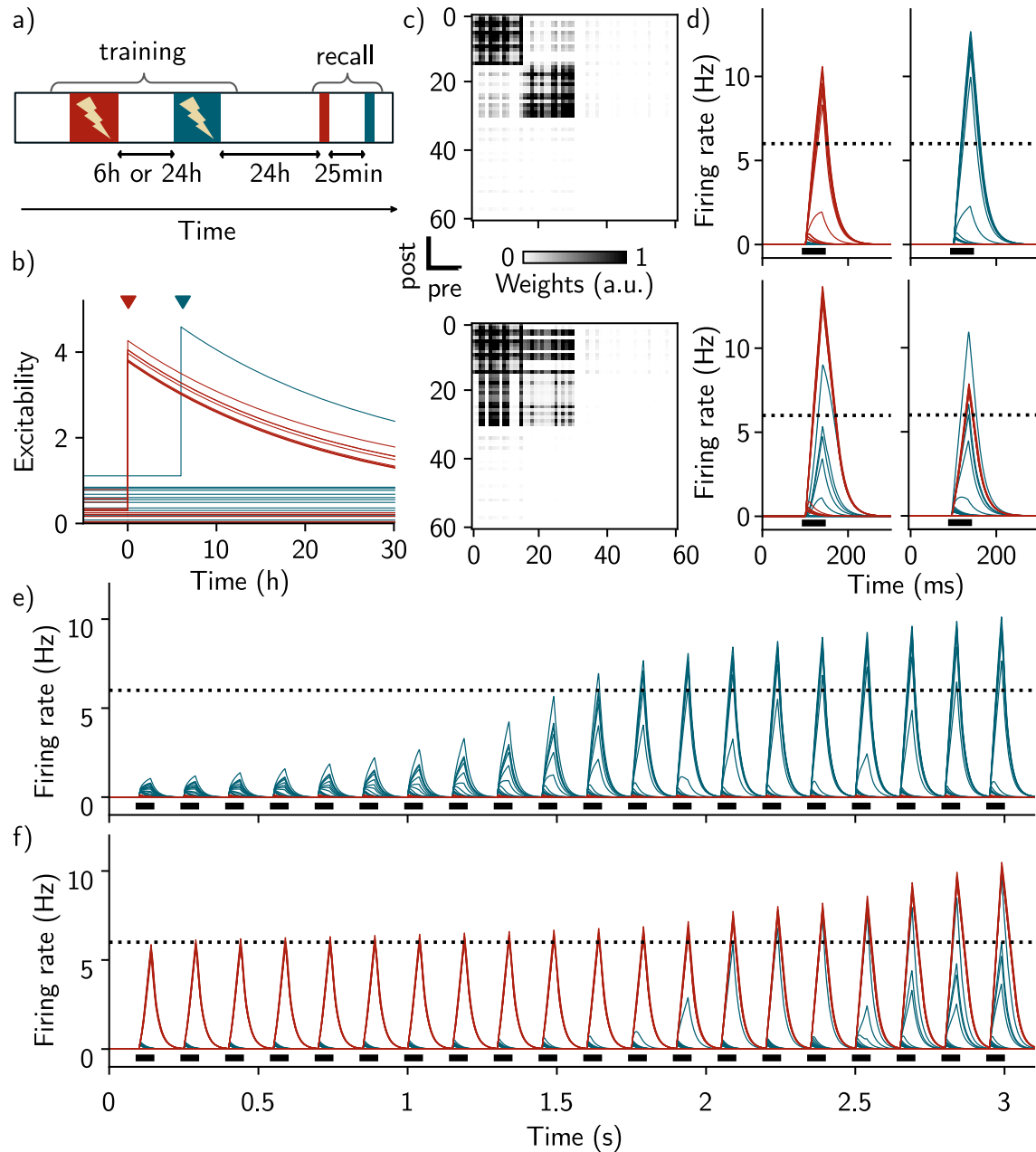


Figure 2. Training-induced increase in excitability induces overlap among memory engrams of temporally close events. **a**, Simulation protocol for studying the effect of forming two memories, spaced by different temporal delays. During the training phase, two contexts are presented 6 h or 24 h apart. After 24 h, both contexts are recalled, separated by 25 min. **b**, Time course of excitability for each neuron of the network. Whenever the firing rate of a neuron crosses the active threshold, its excitability moves to a higher value (red and blue triangles corresponding to training on the first and second contexts, respectively), before decreasing to their initial value on a time scale of 24 h (Methods). Red and blue traces correspond to neurons responding preferentially to the first and second contexts, respectively. **c**, Recurrent weights matrix immediately after training, in the case where the contexts are presented 24 h apart (top) and 6 h apart (bottom). **d**, Firing rates of individual neurons during recall of the first context (left) and the second context (right), in the case where the events are separated by 24 h (top) and 6 h (bottom). Neurons 1–15 respond preferentially to the first context (red) and neurons 16–30 respond preferentially to the second context (blue). The dashed line corresponds to the active threshold and the black bars to the stimulation. **e**, Time course of the firing rate of all the neurons during presentation of the second context, when presented 24 h after the first context (same protocol as Fig. 2). **f**, Same as **e**, when the second context is presented 6 h after the first one.

increased the initial excitability of a subset of the neurons that respond preferentially to the first context (ϵ^+ , Methods, Fig. 4a) during training of the first context. We then inhibited this subpopulation during memory recall (i^+ , Methods, Fig. 4c) and measured the strength of memory recall. We found that inhibiting the subpopulation whose excitability was enhanced reduced the memory strength during recall relative to the control case without manipulation of excitability (Fig. 4d and f, top). This suggests that neurons with enhanced

excitability are preferentially allocated to memory engrams (Fig. 4g, left).

Next, we presented two different contexts to the network, separated by 6 h or 24 h, and tested how increasing excitability to a subset of neurons during formation of the first memory could bias the overlap between the two memory engrams. We inhibited the subpopulation that received enhanced excitability during recall of the second context and we measured the memory strength of the second context (Fig. 4b and f, bottom). In the

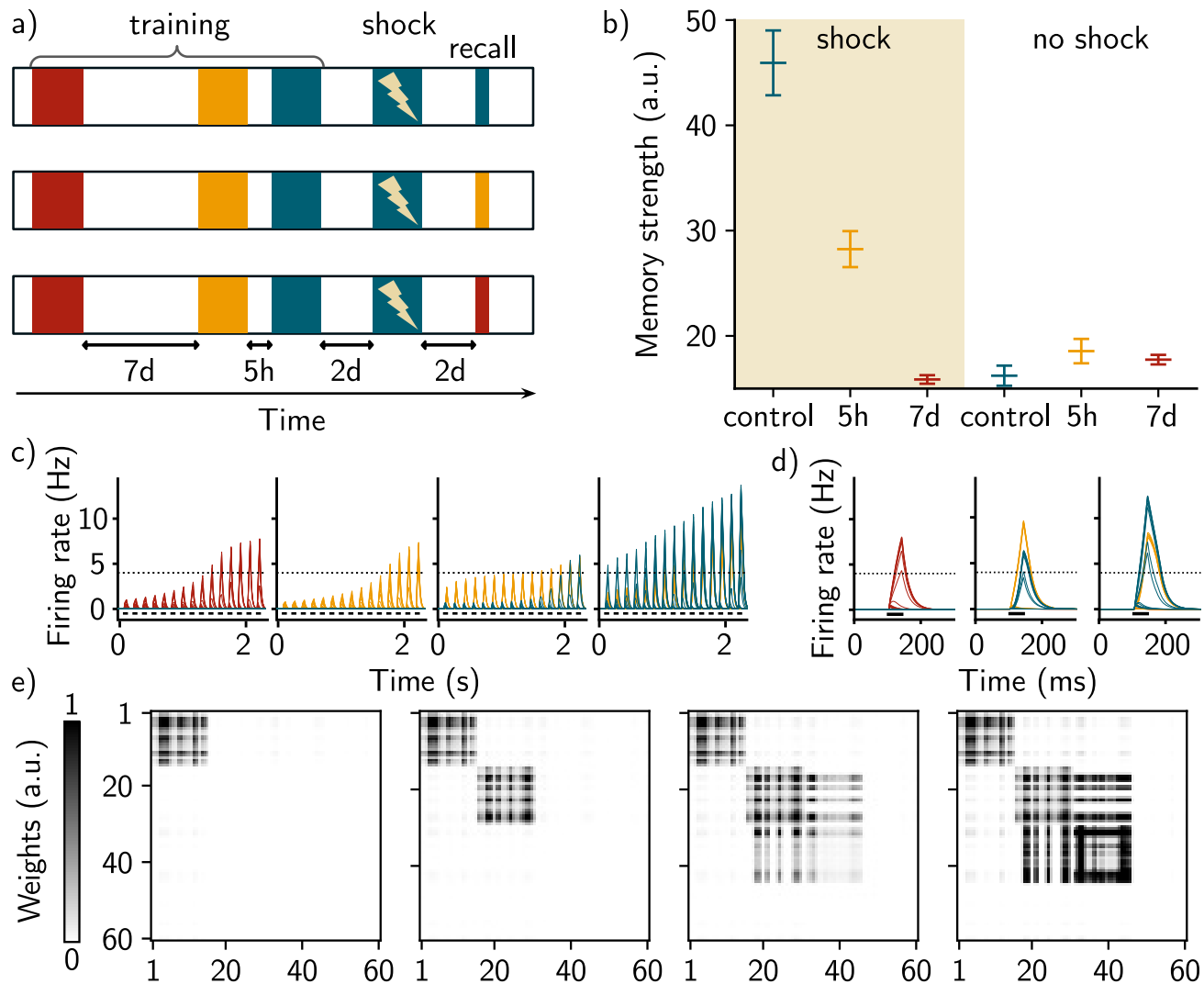


Figure 3. Memory linking in a fear conditioning simulation. *a*, Simulation protocol of fear conditioning. Three contexts are used and are delayed by either 7 d (red and yellow) or 5 h (yellow and blue). Shock is then applied 2 d later in the blue context by pairing the context with an unconditioned stimulus (Methods). Memories are then recalled independently for each of the three contexts. *b*, Memory strength read-out upon recalling the three memories, when shock is applied (left) or not (right). $n = 10$ simulations and data are shown as mean $\pm$ s.e.m. *c*, Firing rates of all the neurons across time during training in the fear conditioning protocol depicted in *a*. Each color represents a population of neurons that receives high input current when one of the contexts is presented. The first, second, and third panels correspond, respectively, to the presentation of the first, second, and third contexts, with a delay of 7 d (between the first and the second one) and 5 h (between the second and the third one). Shock is applied 2 d after the first presentation of the third context (rightmost panel). The dashed line corresponds to the active threshold and the black bars to the stimulation. *d*, Firing rate of the neurons during recall of the first, second, and third memory, respectively, 2 d after the shock. *e*, Corresponding recurrent weights matrices after presentation of each of the three contexts (first three panels) and after the second presentation of the third context paired with the shock (rightmost panel).

case where the events were separated by 6 h, inhibiting the subpopulation resulted in a reduction of the memory strength as compared to the case where the events were delayed by 24 h (Fig. 4*e* and *f*, bottom). Given that the subpopulation ϵ^+ is composed of neurons responding preferentially to the first context, this suggests that this subpopulation preferentially took part in the overlap between the two memory engrams (Fig. 4*g*, right).

Inhibition-induced competition among neurons crucially regulate memory allocation for temporally close events

Finally, we sought to evaluate how much neurons compete for memory allocation. To that end, we repeated the same protocol as in the previous section, but inhibiting the subpopulation (i^+) during presentation of the second context, instead of during recall (Fig. 5*a*). We observed that the formation of the second memory was impaired when the contexts were presented 6 h apart compared to the 24 h delay (Fig. 5*b*, solid lines). Note

that this is the case whether or not the subpopulation (ϵ^+) is inhibited (i^+) during recall (Fig. 5*b*, solid lines).

We then hypothesized that this memory impairment was driven by inhibition. We repeated the simulation as above while reducing the amount of inhibition in the network (Methods) during presentation of the second context, as inspired by previous experiments (Rashid et al., 2016). We observed that the memory strength was less impaired by inhibition of the subpopulation (i^+) when the network inhibition was reduced (Fig. 5*b*, dashed lines). Indeed, the memory strength of the second context increased more for a delay of 6 h compared to 24 h, relative to the case with baseline inhibition (Fig. 5*b*, dashed lines).

The balance among inhibition, feed-forward inputs, and excitability is crucial for forming overlaps

Overall, we found that excitability can induce overlap between memory engrams. This overlap is dependent on the temporal

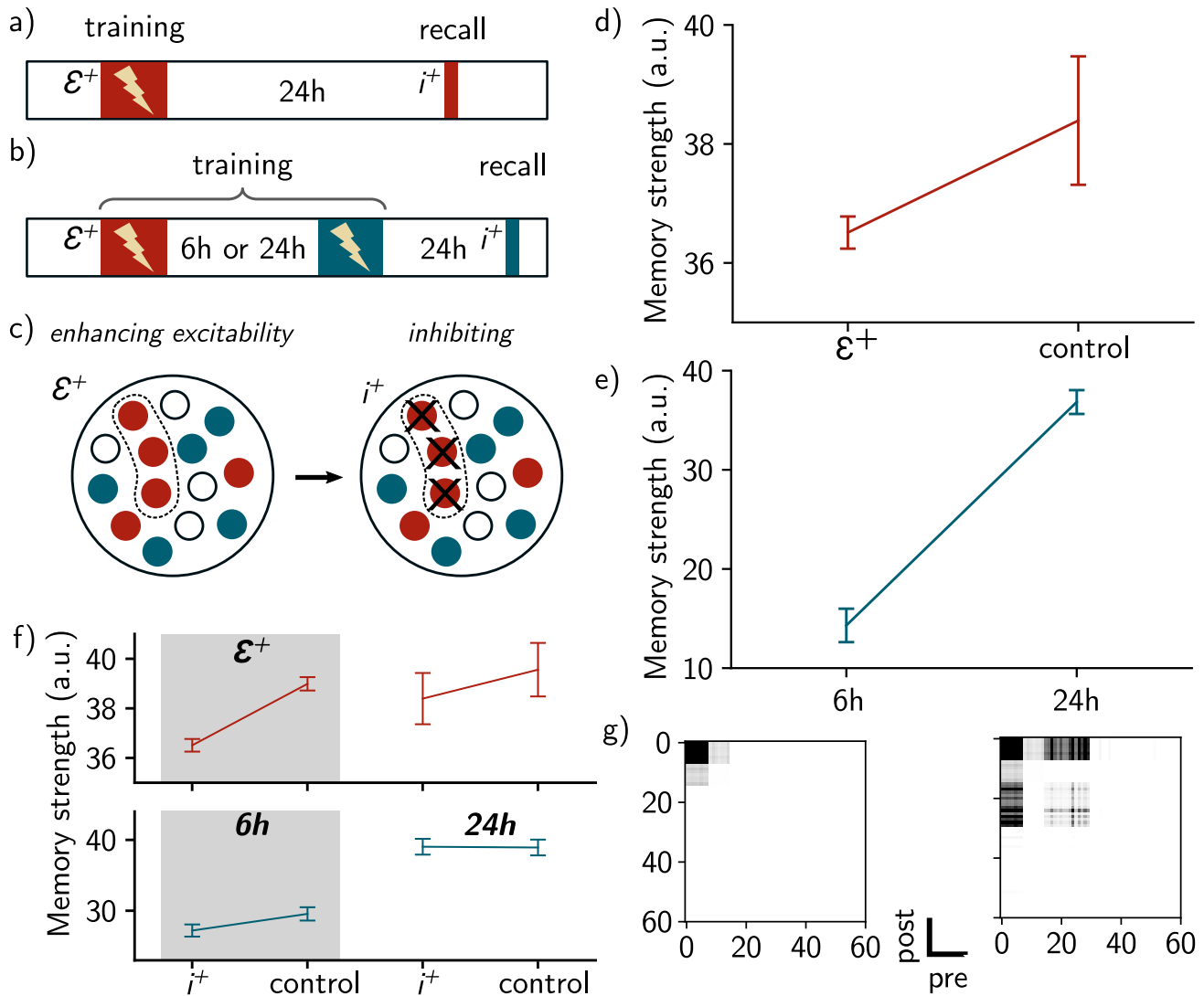


Figure 4. Neurons with enhanced excitability are preferentially allocated to memory engrams and overlapping ensembles. **a**, Protocol for biasing memory allocation to a subpopulation of neurons. Excitability of a subset of neurons is enhanced during training (ϵ^+ , top). During recall, this subpopulation is blocked (i^+ , Methods). In the control case, excitability is not manipulated. **b**, Protocol for biasing the overlap to a subset of neurons. Again, excitability is enhanced (ϵ^+) for a subset of neurons during presentation of the first context (red). Then, a second context is presented (blue) after 6 h or 24 h, and the memory strength of the second context is measured while blocking the subpopulation that received enhanced excitability (i^+). **c**, Spatial representation of the protocol: a subset of N_{ϵ^+} neurons receives an enhanced excitability ϵ^+ , that is added to their initial excitability. During inhibition, N_{i^+} neurons from this subset are inhibited, receiving a negative current i^+ (Methods). **d**, Memory strength of the context while blocking the subset of neurons, in the case where excitability is enhanced (ϵ^+) or not (control). **e**, Memory strength when recalling the second memory in **b**, when the two contexts are separated by either 6 h or 24 h. For all simulations, $n = 50$ simulations and data are shown as mean $\pm$ s.e.m. **f**, Same as **d** and **e**, when the subset is either inhibited (i^+) or not (control) during recall. For each conditions, $n = 50$ simulations and data are shown as mean $\pm$ s.e.m. **g**, Recurrent weight matrix after presentation of the first context (left) and the second context (right) for a 6 h delay.

delay between the two contexts in a manner consistent with experimental findings in the lateral amygdala (Rashid et al., 2016) and in the hippocampal dorsal CA1 (Cai et al., 2016). Our result predicts that the engram overlap arises from reactivation of the first ensemble when forming the second memory (Fig. 2f). Indeed, co-activation of neurons encoding the first memory (red traces) along with neurons responding preferentially to the second context (blue traces) lead to strengthening of the weights between these two ensembles, due to Hebbian plasticity (Fig. 2c and f). We varied the temporal delay between the two contexts and found that the amount of overlap decreases when this delay increases (Fig. 6b).

We also predict that increasing the level of inhibition I_0 leads to a decrease in the overlap between the two ensembles. Indeed, if the two events are separated by 6 h, increasing I_0 leads to a

decrease in the overlap as compared to the control case (Fig. 6c, I_0^+). We found that decreasing the excitability decay timescale τ_ϵ also leads to a decrease in the overlap (Fig. 6c, τ_ϵ^-). Indeed, the excitability increase following learning needs to be above a threshold otherwise the first ensemble cannot be reactivated even if the second context is presented after 6 h (Fig. 7j). Similarly, the overlap among memory engrams decreases with the active threshold set during training (Fig. 7a).

Finally, we predict that the network can only form overlapping memory engrams if the feed-forward weights that do not form RFs ($W_{\text{non-RF}}^{FF}$) are within a defined range (Fig. 7i). If these weights are too low, neurons that are not preferentially activated by the second context cannot be reactivated when presenting this context after 6 h. On the other hand, if they are too high, the ensembles overlap independently of the temporal delay between

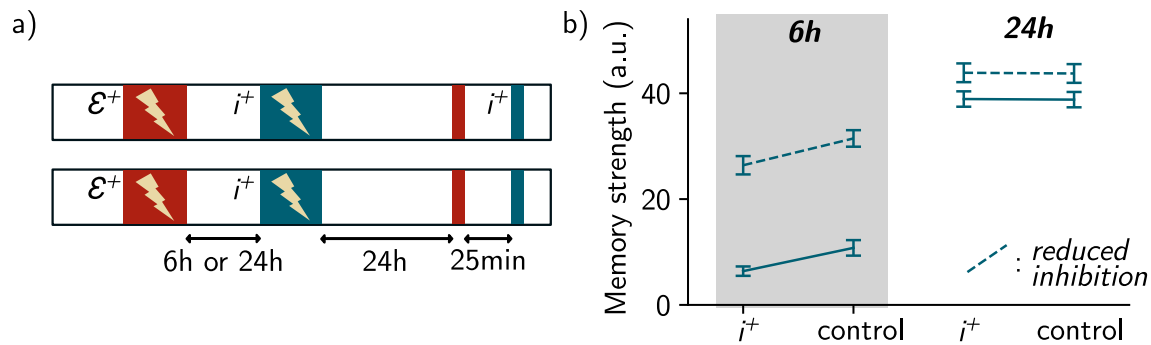


Figure 5. Neurons compete for allocation to memory engrams. *a*, Same protocol as Figure 4*b* but with the inhibition of the subset (I^+) applied during presentation of the second context. The subset is then either inhibited (I^+) or not (control) during recall. *b*, Fear measurement when recalling the second memory when the events are separated by either 6 h or 24 h. The dashed line corresponds to the case where global inhibition I_1 is reduced (Methods). For all simulations, $n = 50$ simulations and data are shown as mean $\pm$ s.e.m. (nine trials were excluded, Methods).

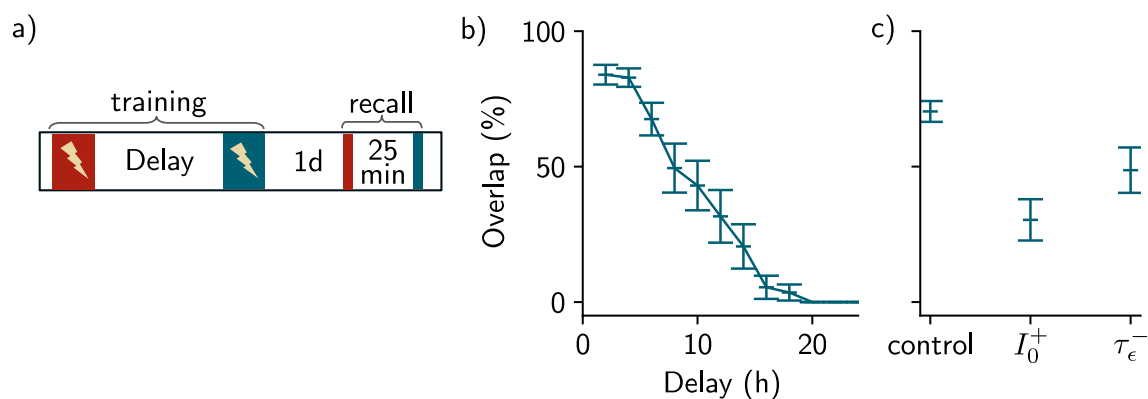


Figure 6. Predictions regarding the overlap among memory engrams. *a*, Protocol for forming overlap among memory engrams. During training, two contexts were presented, separated by a given temporal delay. The recall protocol allows for measuring the amount of overlap between engrams associated to the first context (red) and the second context (blue). *b*, Overlap among engrams against the temporal delay between the contexts. For each temporal delay, $n = 20$ simulations (three were excluded, Methods). Results are shown as mean $\pm$ s.e.m. *c*, Overlap obtained for a 6 h delay in the control case, the case where inhibition was increased I_0^+ and the case where the excitability decay time was decreased τ_e^- . For the control case, $n = 50$ simulations (five were excluded, Methods) and for I_0^+ and τ_e^- , $n = 20$ simulations. Data are shown as mean $\pm$ s.e.m.

the two contexts. In that case, we even observed an overlap with the novel context (Fig. 7*i*, yellow line).

Discussion

Learning a single memory

We first showed that our network is able to form memories when stimulated by a feed-forward input. We attributed this formation to synaptic plasticity, independently from the dynamics of neural excitability. Indeed, the time scale of excitability is much slower than the time scale of Hebbian plasticity in our model, suggesting that the initial activation of the neurons by feed-forward inputs leads to strengthening of the synaptic weights through Hebbian learning. The structure of the neural assembly holding the formed memory is similar to previous theoretical works that have used attractor networks (Amit, 1989; Gastaldi et al., 2021). These neural assemblies are formed during the learning phase and are reactivated during memory recall. Importantly, memories can be recalled even when stimulated by a partial cue, suggesting that the neural activity is driven by recurrent connections. In particular, the structural change that leads to the formation of neural assemblies leads to the formation of a memory, as suggested in previous definitions of engram cells (Josselyn and Tonegawa, 2020).

The ability of the network to perform pattern completion is complemented by its ability to perform pattern separation.

However, we did not evaluate pattern separation in our model. This would be interesting in particular because a recent study has shown that increased neural excitability in dentate gyrus improves pattern completion and separation (Pignatelli et al., 2019). The role of the recall-induced increase in excitability could explain this improvement. This could be directly tested in our model, for example by presenting a conflicting cue to the network and measuring pattern separation after recall of the memory.

In our model, the range of the firing rates of neurons during stimulations is consistent with electrophysiological recordings during fear conditioning in the amygdala (Lee et al., 2021) and in CA1 (Cohen et al., 2017). Here, we did not consider spontaneous firing rate apart from when introducing background noise in Figure 7*d*. Finally, our model does not take into account the evolution of memory engrams across time. Indeed, when the network is not stimulated, the recurrent weights are kept static. In this framework, the delay between the training phase and the recall phase has no impact on the recurrent weights.

Overlap between memory engrams of temporally close events

Here, we built a model that is able to reproduce the overlap among memory engrams of events that are temporally linked. These overlaps have been observed in the amygdala (Rashid et al., 2016), the hippocampus (Cai et al., 2016), and the retrosplenial cortex (Sehgal et al., 2021) while it has been reported

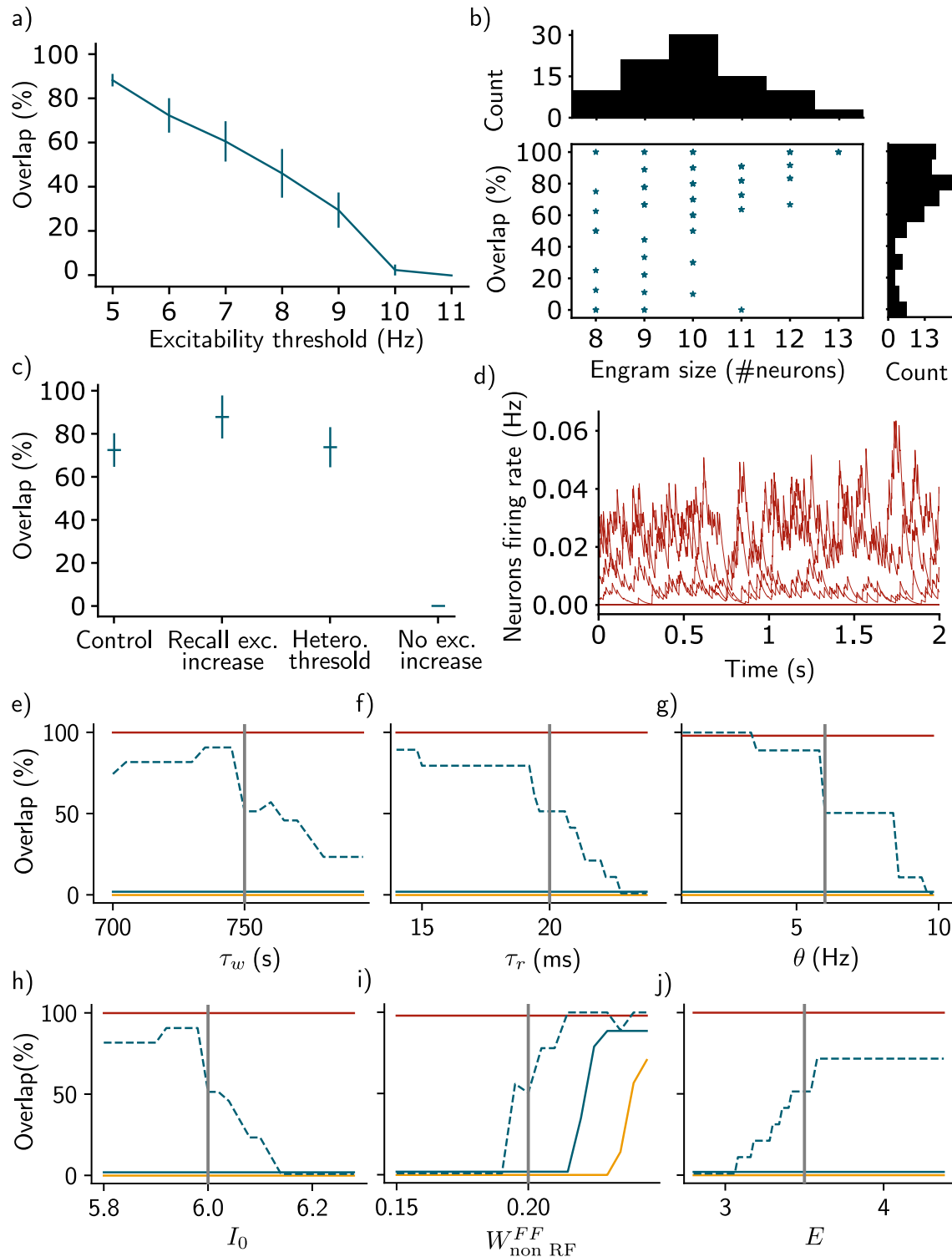


Figure 7. Further model analysis. **a**, Overlap among two engrams when the contexts are separated by 6 h (same protocol as Fig. 2, Methods) against the activation threshold during training. Here, the activation threshold during recall remains fixed (6 Hz). $n = 10$ simulations (one was excluded, Methods) and data are shown as mean $\pm$ s.e.m. **b**, Overlap among two engrams when the contexts are separated by 6 h against the size of the first engram. Each dot shows one simulation. The top and right histograms show the distribution of engram sizes and overlaps, respectively. $n = 100$ simulations (11 were excluded, Methods). **c**, Overlap among two engrams when the contexts are separated by 6 h in four scenarios: (1) control case (as in Fig. 2), (2) excitability is increased following recall of the memories, (3) activation threshold during training is sample from a half-normal distribution of mean 6 Hz and standard deviation 1 Hz, and (4) excitability is left at baseline during the entire simulation. $n = 10$ simulations (one was excluded, Methods) and data are shown as mean $\pm$ s.e.m. **d**, Neurons firing rate 1 h after learning the first memory in the presence of ongoing noise throughout the whole simulation, when two contexts are presented 6 h apart. Traces in red correspond to neurons responding preferentially to the first context, other neurons' firing rate is at baseline. **e**, Overlap measured during the same protocol as Figure 2 as a function of the main parameters of the model (Methods, Table of parameters). The dashed blue line and the solid blue line correspond to the 6 h delay and the 24 h delay, respectively. The red line corresponds to the case where the same context is presented and the yellow to the case where a novel context is presented. $n = 50$ simulations (five were excluded, Methods) and data are shown as mean $\pm$ s.e.m. Each gray line corresponds to the parameter that has been selected for the simulations in the main figures.

that these three regions are involved in a memory consolidation process known as systems consolidation (Kitamura et al., 2017; Tonegawa et al., 2018). However, it remains unclear what information is transferred from one region to another and investigating a potential transfer of overlap between brain regions would help understand how temporal memory linking evolves over the course of systems consolidation.

Structural overlap of memory engrams induces memory linking

Here, we reproduced a fear conditioning experiment by modeling the US as a three-factor learning rule. We reasoned that an aversive event (e.g., foot shock) would increase some neuromodulators that in turn modulate plasticity. On the other hand, our measure of memory strength (averaged firing rates of the neurons belonging to the engram) is comparable to the fear read-out in experimental works on rodents (freezing response), which is also a proxy for memory strength.

After showing that memories of temporally close events are structurally linked in overlapping neural ensembles, we showed that this overlapping structure can induce memory linking. In line with recent experimental studies (Cai et al., 2016; Yokose et al., 2017), we observed in our model that this overlap supports memory linking as the fear associated with one context can be transferred to another context (Fig. 3).

We also note that this memory linking is a result of the short temporal delay between contexts. Indeed, in contrast to previous studies (de Sousa et al., 2021; Gastaldi et al., 2021), the overlap between two memory engrams is independent from the conceptual relation between the contexts in question, which we did not consider here. However, it is possible that this overlap supports the formation of mnemonic structures, as they have been observed in the hippocampus for instance (Deuker et al., 2016; Barron et al., 2020). Further work could be done to investigate the importance of overlapping memory engrams for more complex cognitive processes such as inferential reasoning (Zeithamova et al., 2012; Barron et al., 2020).

Manipulating excitability biases neural allocation of memories

In our model, memory allocation is determined by two main factors. On the one hand, engrams are preferentially allocated to neurons that receive increased feed-forward inputs, as defined in the feed-forward weights (Fig. 1). On the other hand, we showed that memory allocation is also biased toward neurons with high excitability (Fig. 4), consistent with previous studies (Zhou et al., 2009; Rashid et al., 2016). However, for the sake of simplicity, we did not explicitly probe the relative importance of the feed-forward weights compared to intrinsic excitability. To that end, it would be necessary to introduce some variability in the structure of the RFs, and subsequently investigate how neuronal memory allocation is impacted by feed-forward inputs versus excitability dynamics.

Here, we considered that excitability is mainly governed by the transcription factor CREB. We modeled its dynamics by increasing excitability instantaneously after learning and then allowing it to decay over a time scale of a few hours, as motivated by several experimental studies (Moyer et al., 1996; Thompson et al., 1996; Oh et al., 2003; Kitagawa et al., 2017). Although the results might be similar, it is important to note that these dynamics are conceptualized and that other mechanisms that are not considered here are also known to regulate neural excitability. For instance, internalization of Kir2.1 channel increases neural excitability during memory recall (Pignatelli et al., 2019)

while the expression of the C-C chemokine receptor type 5 is known to decrease excitability (Zhou et al., 2016; Shen et al., 2022). Adult-born neurons are also known to be more excitable than their counterparts (Silva et al., 2009). Overall, the exact relationship between firing rate and change in excitability is not known. For this reason, we abstracted the dynamics of excitability by only considering the increase of excitability following learning and a slow decay over a timescale of several hours. Finally, memory allocation may also be influenced by other mechanisms beyond the scope of the present study such as synaptic tagging and spine clustering (Rogerson et al., 2014; Kastellakis et al., 2016).

We also showed that artificially increasing excitability in an ensemble of neurons could also bias co-allocation of this ensemble to further memories as shown in previous experimental findings (Rashid et al., 2016). This result arose naturally in our model because neurons with enhanced excitability are preferentially allocated to the first memory, and will then overlap with the second engram (Fig. 4g).

Role of inhibition in memory allocation and linking

Finally, we showed that neurons can compete for memory allocation and that the outcome of this competition is determined by both the initial excitability of neurons and the amount of inhibition in the network. We first showed that blocking neurons which received enhanced excitability during presentation of the first context impaired learning of a second context presented shortly after, suggesting that these neurons have a competitive advantage over the others for memory allocation. Second, we showed that reducing inhibition restored the ability of the network to learn the second memory, suggesting that competition is driven by inhibition.

In our model, neurons with a higher initial excitability are favored for memory allocation and inhibit the remaining neurons, preventing them from taking part in a memory engram. This process has been previously shown experimentally (Han et al., 2007; Rashid et al., 2016) and this study provides a computational model that sheds light on the underlying competitive mechanism. Finally, we use a homogeneous global inhibition model, but further studies could explore the effect of populations of different inhibitory cell types on engram overlap and memory linking.

Conclusion

In summary, we have built a recurrent neural network model that can reproduce the experimentally observed neuronal overlap between temporally linked memory engrams by combining both synaptic plasticity and neural excitability. Our results suggest that engram overlaps are crucially determined by the balance among inhibition, feed-forward inputs, and excitability.

References

- Amit DJ (1989) *Modeling brain function: the world of attractor neural networks*. Cambridge: Cambridge University Press. <https://www.cambridge.org/core/books/modeling-brain-function/2EA95FDABF616D187220A6B9596091B7>
- Barron HC, et al. (2020) Neuronal computation underlying inferential reasoning in humans and mice. *Cell* 183:228–243.e21.
- Bliss TVP, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361:31–39.
- Cai DJ, et al. (2016) A shared neural ensemble links distinct contextual memories encoded close in time. *Nature* 534:115–118.
- Chowdhury A, Luchetti A, Fernandes G, Filho DA, Kastellakis G, Tzilivaki A, Ramirez EM, Tran MY, Poirazi P, Silva AJ (2022) A locus coeruleus-

- dorsal CA1 dopaminergic circuit modulates memory linking. *Neuron* 110:3374–3388.e8.
- Cohen JD, Bolstad M, Lee AK (2017) Experience-dependent shaping of hippocampal CA1 intracellular activity in novel and familiar environments. *eLife* 6:e23040.
- de Sousa AF, Chowdhury A, Silva AJ (2021) Dimensions and mechanisms of memory organization. *Neuron* 109:2649–2662.
- Deuker L, Bellmund JL, Navarro Schröder T, Doeller CF (2016) An event map of memory space in the hippocampus. *eLife* 5:e16534.
- Dong Y, Green T, Saal D, Marie H, Neve R, Nestler EJ, Malenka RC (2006) CREB modulates excitability of nucleus accumbens neurons. *Nat Neurosci* 9:475–477.
- Gastaldi C, Schwalger T, Falco ED, Quiroga RQ, Gerstner W (2021) When shared concept cells support associations: theory of overlapping memory engrams. *PLoS Comput Biol* 17:e1009691.
- Han J-H, Kushner SA, Yiu AP, Cole CJ, Matynia A, Brown RA, Neve RL, Guzowski JF, Silva AJ, Josselyn SA (2007) Neuronal competition and selection during memory formation. *Science* 316:457–460.
- Hebb DO (1949) *The organization of behavior: a neuropsychological theory*. Mahwah, NJ: L. Erlbaum Associates.
- Josselyn SA, Tonegawa S (2020) Memory engrams: recalling the past and imagining the future. *Science* 367:eaaw4325.
- Kastellakis G, Silva AJ, Poirazi P (2016) Linking memories across time via neuronal and dendritic overlaps in model neurons with active dendrites. *Cell Rep* 17:1491–1504.
- Kitagawa H, Sugo N, Morimatsu M, Arai Y, Yanagida T, Yamamoto N (2017) Activity-dependent dynamics of the transcription factor of cAMP-response element binding protein in cortical neurons revealed by single-molecule imaging. *J Neurosci* 37:1–10.
- Kitamura T, Ogawa SK, Roy DS, Okuyama T, Morrissey MD, Smith LM, Redondo RL, Tonegawa S (2017) Engrams and circuits crucial for systems consolidation of a memory. *Science* 356:73–78.
- Lee J, An B, Choi S (2021) Longitudinal recordings of single units in the basal amygdala during fear conditioning and extinction. *Sci Rep* 11:11177.
- Litwin-Kumar A, Doiron B (2014) Formation and maintenance of neuronal assemblies through synaptic plasticity. *Nat Commun* 5:5319.
- Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K, Tonegawa S (2012) Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 484:381–385.
- Morrison DJ, Rashid AJ, Yiu AP, Yan C, Frankland PW, Josselyn SA (2016) Parvalbumin interneurons constrain the size of the lateral amygdala engram. *Neurobiol Learn Mem* 135:91–99.
- Moyer JR, Thompson LT, Disterhoft JF (1996) Trace eyeblink conditioning increases CA1 excitability in a transient and learning-specific manner. *J Neurosci* 16:5536–5546.
- Oh MM, Kuo AG, Wu WW, Sametsky EA, Disterhoft JF (2003) Watermaze learning enhances excitability of CA1 pyramidal neurons. *J Neurosci* 90:2171–2179.
- Pignatelli M, Ryan TJ, Roy DS, Lovett C, Smith LM, Muralidhar S, Tonegawa S (2019) Engram cell excitability state determines the efficacy of memory retrieval. *Neuron* 101:274–284.e5.
- Rashid AJ, et al. (2016) Competition between engrams influences fear memory formation and recall. *Science* 353:383–387.
- Rogerson T, Cai DJ, Frank A, Sano Y, Shobe J, Lopez-Aranda MF, Silva AJ (2014) Synaptic tagging during memory allocation. *Nat Rev Neurosci* 15:157–169.
- Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11–21.
- Sehgal M, et al. (2021) Co-allocation to overlapping dendritic branches in the retrosplenial cortex integrates memories across time. Pages: 2021.10.28.466343. Section: New Results.
- Sehgal M, Zhou M, Lavi A, Huang S, Zhou Y, Silva A (2018) Memory allocation mechanisms underlie memory linking across time. *Neurobiol Learn Mem* 153:21–25.
- Shen Y, et al. (2022) CCR5 closes the temporal window for memory linking. *Nature* 606:146–152.
- Silva AJ, Zhou Y, Rogerson T, Shobe J, Balaji J (2009) Molecular and cellular approaches to memory allocation in neural circuits. *Science* 326:391–395.
- Thompson LT, Moyer JR, Disterhoft JF (1996) Transient changes in excitability of rabbit CA3 neurons with a time course appropriate to support memory consolidation. *J Neurophysiol* 76:1836–1849.
- Titley HK, Brunel N, Hansel C (2017) Toward a neurocentric view of learning. *Neuron* 95:19–32.
- Tonegawa S, Liu X, Ramirez S, Redondo R (2015) Memory engram cells have come of age. *Neuron* 87:918–931.
- Tonegawa S, Morrissey MD, Kitamura T (2018) The role of engram cells in the systems consolidation of memory. *Nat Rev Neurosci* 19:485–498.
- Yokose J, et al. (2017) Overlapping memory trace indispensable for linking, but not recalling, individual memories. *Science* 355:398–403.
- Zeithamova D, Schlichting ML, Preston AR (2012) The hippocampus and inferential reasoning: building memories to navigate future decisions. *Front Hum Neurosci* 6:70.
- Zenke F, Agnes EJ, Gerstner W (2015) Diverse synaptic plasticity mechanisms orchestrated to form and retrieve memories in spiking neural networks. *Nat Commun* 6:6922.
- Zhou M, et al. (2016) CCR5 is a suppressor for cortical plasticity and hippocampal learning and memory. *eLife* 5:e20985.
- Zhou Y, Won J, Karlsson MG, Zhou M, Rogerson T, Balaji J, Neve R, Poirazi P, Silva AJ (2009) CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala. *Nat Neurosci* 12:1438–1443.

Chapter 2 - A mechanism underlying representational drift

A key result of the previous study is that the dynamics of intrinsic excitability can temporally correlate memory ensembles. In a sense, excitability can be seen as a marker for temporal information by modulating allocation at different time points. The idea that temporal information can be encoded in the dynamics of neural ensembles has been recently explored in the context of representational drift (Geva et al., [2023](#); Mau, Hasselmo, and Cai, [2020](#); Clopath et al., [2017](#)). An important result showed that drift can allow for time-stamping memories (Rubin et al., [2015](#)), meaning that drifting memory ensembles contain information about their temporal history. Combining ideas from both the excitability and the drift literature, we suggest that fluctuations of intrinsic neural excitability can be a motor for drift. The following work was published in *eLife* in June 2023 (Version of Record published in May 2024) and was realised in collaboration with Dr. Denise J Cai and Yosif Zaki at the Icahn School of Medicine at Mount Sinai (New York, United States).

Drift of neural ensembles driven by slow fluctuations of intrinsic excitability.

Geoffroy Delamare, Yosif Zaki, Denise J Cai, Claudia Clopath. 2024. *eLife* 12:RP88053.
doi:[10.7554/eLife.88053.3](https://doi.org/10.7554/eLife.88053.3)

Authors contribution Conceptualisation: GD, YZ, DJC, CC; Development of methodology: GD, CC; Simulations: GD; Data analysis and visualisation: GD; Writing original draft: GD; Reviewing and editing: GD, YZ, DJC, CC

Drift of neural ensembles driven by slow fluctuations of intrinsic excitability

Geoffroy Delamare^{1*}, Yosif Zaki², Denise J Cai², Claudia Clopath^{1*}

¹Department of Bioengineering, Imperial College London, London, United Kingdom;

²Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, United States

Abstract Representational drift refers to the dynamic nature of neural representations in the brain despite the behavior being seemingly stable. Although drift has been observed in many different brain regions, the mechanisms underlying it are not known. Since intrinsic neural excitability is suggested to play a key role in regulating memory allocation, fluctuations of excitability could bias the reactivation of previously stored memory ensembles and therefore act as a motor for drift. Here, we propose a rate-based plastic recurrent neural network with slow fluctuations of intrinsic excitability. We first show that subsequent reactivations of a neural ensemble can lead to drift of this ensemble. The model predicts that drift is induced by co-activation of previously active neurons along with neurons with high excitability which leads to remodeling of the recurrent weights. Consistent with previous experimental works, the drifting ensemble is informative about its temporal history. Crucially, we show that the gradual nature of the drift is necessary for decoding temporal information from the activity of the ensemble. Finally, we show that the memory is preserved and can be decoded by an output neuron having plastic synapses with the main region.

*For correspondence:

g.delamare21@imperial.ac.uk (GD);

c.clopath@imperial.ac.uk (CC)

Competing interest: See page 10

Funding: See page 10

Preprint posted

17 March 2023

Sent for Review

07 April 2023

Reviewed preprint posted

08 June 2023

Reviewed preprint revised

15 December 2023

Version of Record published

07 May 2024

Reviewing Editor: Lisa M

Giocomo, Stanford School of Medicine, United States

© Copyright Delamare et al. This article is distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use and redistribution provided that the original author and source are credited.

eLife assessment

This is an **important** theoretical study providing insight into how fluctuations in excitability can contribute to gradual changes in the mapping between population activity and stimulus, commonly referred to as representational drift. The authors provide **convincing** evidence that fluctuations can contribute to drift. Overall, this is a well-presented study that explores the question of how changes in intrinsic excitability can influence distinct memory representations.

Introduction

In various brain regions, the neural code tends to be dynamic although behavioral outputs remain stable. Representational drift refers to the dynamic nature of internal representations as they have been observed in sensory cortical areas ([Driscoll et al., 2017](#); [Sadeh and Clopath, 2022](#); [Driscoll et al., 2022](#)) or the hippocampus ([Ziv et al., 2013](#); [Hainmueller and Bartos, 2018](#)) despite stable behavior. It has even been suggested that pyramidal neurons from the CA1 and CA3 regions form dynamic rather than static memory engrams ([Hainmueller and Bartos, 2018](#); [Spalla et al., 2021](#)), namely that the set of neurons encoding specific memories varies across days. In the amygdala, retraining of a fear memory task induces a turnover of the memory engram ([Cho et al., 2021](#)). Additionally, plasticity mechanisms have been proposed to compensate for drift and to provide a stable read-out of the neural code ([Rule and O'Leary, 2022](#)), suggesting that information is maintained. Altogether, this line of evidence suggests that drift might be a general mechanism with dynamical representations observed in various brain regions.

However, the mechanisms underlying the emergence of drift and its relevance for the neural computation are not known. Drift is often thought to arise from variability of internal states (*Sadeh and Clopath, 2022*), neurogenesis (*Rechavi et al., 2022; Driscoll et al., 2017*) or synaptic turnover (*Attardo et al., 2015*) combined with noise (*Kossio et al., 2021; Manz and Memmesheimer, 2023*). On the other hand, excitability might also play a role in memory allocation (*Zhou et al., 2009; Mau et al., 2020; Rogerson et al., 2014; Silva et al., 2009*), so that neurons having high excitability are preferentially allocated to memory ensembles (*Cai et al., 2016; Rashid et al., 2016; Silva et al., 2009*). Moreover, excitability is known to fluctuate over timescales from hours to days, in the amygdala (*Rashid et al., 2016*), the hippocampus (*Cai et al., 2016; Grosmark and Buzsáki, 2016*), or the cortex (*Huber et al., 2013; Levenstein et al., 2019*). Subsequent reactivations of a neural ensemble at different time points could therefore be biased by excitability (*Mau et al., 2022*), which varies at similar timescales than drift (*Mau et al., 2018*). Altogether, this evidence suggest that fluctuations of excitability could act as a cellular mechanism for drift (*Mau et al., 2020*).

In this short communication, we aimed at proposing how excitability could indeed induce a drift of neural ensembles at the mechanistic level. We simulated a recurrent neural network (*Delamare et al., 2022*) equipped with intrinsic neural excitability and Hebbian learning. As a proof of principle, we first show that slow fluctuations of excitability can induce neural ensembles to drift in the network. We then explore the functional implications of such drift. Consistent with previous works (*Rubin et al., 2015; Clopath et al., 2017; Mau et al., 2018; Miller et al., 2018*), we show that neural activity of the drifting ensemble is informative about the temporal structure of the memory. This suggest that fluctuations of excitability can be useful for time-stamping memories (i.e. for making the neural ensemble informative about the time at which it was formed). Finally, we confirmed that the content of the memory itself can be steadily maintained using a read-out neuron and local plasticity rule, consistently with previous computational works (*Rule and O'Leary, 2022*). The goal of this study is to show one possible mechanistic implementation of how excitability can drive drift.

Results

Many studies have shown that memories are encoded in sparse neural ensembles that are activated during learning and many of the same cells are reactivated during recall, underlying a stable neural representation (*Josselyn and Tonegawa, 2020; Poo et al., 2016; Mau et al., 2020*). After learning, subsequent reactivations of the ensemble can happen spontaneously during replay, retraining or during a memory recall task (e.g. following presentation of a cue *Josselyn and Tonegawa, 2020; Káli and Dayan, 2004*). Here, we directly tested the hypothesis that slow fluctuations of excitability can change the structure of a newly-formed neural ensemble, through subsequent reactivations of this ensemble.

To that end, we designed a rate-based, recurrent neural network, equipped with intrinsic neural excitability (Methods). We considered that the recurrent weights are all-to-all and plastic, following a Hebbian rule (Methods). The network was then stimulated following a 4day protocol: the first day corresponds to the initial encoding of a memory and the other days correspond to spontaneous or cue-induced reactivations of the neural ensemble (Methods). Finally, we considered that excitability of each neuron can vary on a day long timescale: each day, a different subset of neurons has increased excitability (*Figure 1a*, Methods).

Fluctuations of intrinsic excitability induce drifting of neural ensembles

While stimulating the naive network on the first day, we observed the formation of a neural ensemble: some neurons gradually increase their firing rate (*Figure 1b and c*, neurons 10–20, time steps 1000–3000) during the stimulation. We observed that these neurons are highly recurrently connected (*Figure 1d*, leftmost matrix) suggesting that they form an assembly. This assembly is composed of neurons that have a high excitability (*Figure 1a*, neurons 10–20 have increased excitability) at the time of the stimulation. We then show that further stimulations of the network induce a remodeling of the synaptic weights. During the second stimulation for instance (*Figure 1b and c*, time steps 4000–6000), neurons from the previous assembly (10–20) are reactivated along with neurons having high excitability at the time of the second stimulation (*Figure 1a*, neurons 20–30). Moreover, across several days, recurrent weights from previous assemblies tend to decrease while others increase (*Figure 1d*).

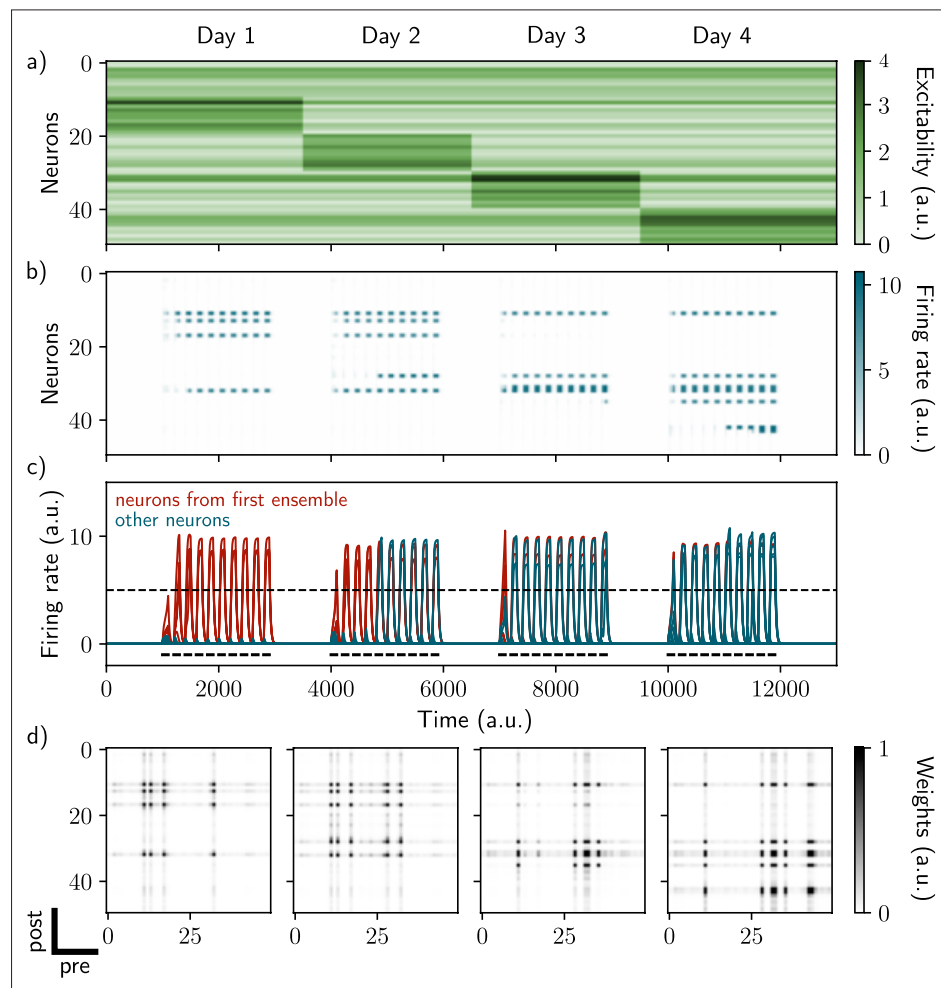


Figure 1. Excitability-induced drift of memory ensembles. **(a)** Distribution of excitability ϵ_i for each neuron i , fluctuating over time. During each stimulation, a different pool of neurons has a high excitability (Methods). **(b, c)** Firing rates of the neurons across time. The red traces in panel **(c)** correspond to neurons belonging to the first assembly, namely that have a firing rate higher than the active threshold after the first stimulation. The black bars show the stimulation and the dashed line shows the active threshold. **(d)** Recurrent weights matrices after each of the four stimuli show the drifting assembly.

The online version of this article includes the following figure supplement(s) for figure 1:

Figure supplement 1. Comparison of drifting behavior for different values of excitability amplitude.

Figure supplement 2. The rate of the drift does not depend on the size of the initial engram.

Indeed, neurons from the original assembly (**Figure 1c**, red traces) tend to be replaced by other neurons, either from the latest assembly or from the pool of neurons having high excitability. This is translated at the synaptic level, where weights from previous assemblies tend to decay and be replaced by new ones. Overall, each new stimulation updates the ensemble according to the current distribution of excitability, inducing a drift towards neurons with high excitability. Finally, in our model, the drift rate does not depend on the size of the original ensemble (**Figure 1—figure supplement 2**, Methods).

Activity of the drifting ensemble is informative about the temporal structure of the past experience

After showing that fluctuations of excitability can induce a drift among neural ensembles, we tested whether the drifting ensemble could contain temporal information about its past experiences, as suggested in previous works (**Rubin et al., 2015**).

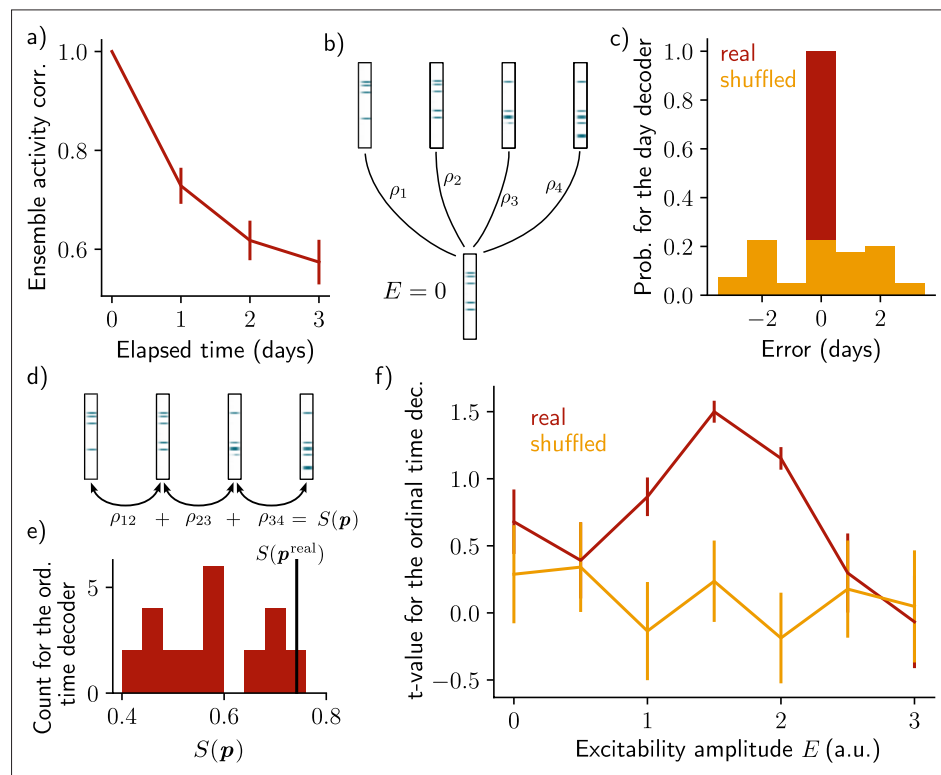


Figure 2. Neuronal activity is informative about the temporal structure of the reactivations. (a) Correlation of the patterns of activity between the first day and every other days, for $n=10$ simulations. Data are shown as mean $\pm$ s.e.m. (b) Schema of the day decoder. The day decoder maximises correlation between the patterns of each day with the pattern from the simulation with no increase in excitability. (c) Results of the day decoder for the real data (red) and the shuffled data (orange). Shuffled data consist of the same activity pattern for which the label of each cell for every seed has been shuffled randomly. For each simulation, the error is measured for each day as the difference between the decoded and the real day. Data are shown for $n=10$ simulations and for each of the 4 days. (d) Schema of the ordinal time decoder. This decoder output the permutation p that maximises the sum $S(p)$ of the correlations of the patterns for each pairs of days. (e) Distribution of the value $S(p)$ for each permutation of days p . The value for the real permutation $S(p_{\text{real}})$ is shown in black. (f) Student's test t-value for $n=10$ simulations, for the real (red) and shuffled (orange) data and for different amplitudes of excitability E . Data are shown as mean $\pm$ s.e.m. for $n=10$ simulations.

The online version of this article includes the following figure supplement(s) for figure 2:

Figure supplement 1. Sparse recurrent connectivity shows similar drifting behavior as all-to-all connectivity.

Figure supplement 2. Change of excitability as a variable slope of the input-output function shows similar drifting behavior as considering a change in the threshold.

Figure supplement 3. Two distinct ensembles can be encoded and drift independently.

Figure supplement 4. The two ensembles are informative about their temporal history and can be decoded using two output neurons.

Inspired by these works, we asked whether it was possible to decode relevant temporal information from the patterns of activity of the neural ensemble. We first observed that the correlation between patterns of activity after just after encoding decreases across days (Figure 2a, Methods), indicating that after each day, the newly formed ensemble resembles less the original one. Because the patterns of activity differ across days, they should be informative about the absolute day from which they were recorded. To test this hypothesis, we designed a day decoder (Figure 2b, Methods), following the work of Rubin et al., 2015. This decoder aims at inferring the reactivation day of a given activity pattern by comparing the activity of this pattern during training and the activity just after memory encoding without increase in excitability (Figure 2b, Methods). We found that the day decoder perfectly outputs the reactivation day as compared to using shuffled data (Figure 2c).

After showing that the patterns of activity are informative about the reactivation day, we took a step further by asking whether the activity of the neurons is also informative about the order in which the memory evolved. To that end, we used an ordinal time decoder (Methods, as in [Rubin et al., 2015](#)) that uses the correlations between activity patterns for pairs of successive days, and for each possible permutation of days p ([Figure 2d](#), Methods). The sum of these correlations $S(p)$ differs from each permutation p and we assumed that the neurons are informative about the order at which the reactivations of the ensemble happened if the permutation maximising $S(p)$ corresponds to the real permutation p^{real} ([Figure 2e](#), Methods). We found that $S(p^{\text{real}})$ was indeed statistically higher than $S(p)$ for the other permutations p ([Figure 2f](#), Student's t-test, Methods). However, this was only true when the amplitude of the fluctuations of excitability E was in a certain range. Indeed, when the amplitude of the fluctuations is null, that is when excitability is not increased ($E = 0$), the ensemble does not drift ([Figure 1—figure supplement 1a](#)). In this case, the patterns of activity are not informative about the order of reactivations. On the other hand, if the excitability amplitude is too high ($E = 3$), each new ensemble is fully determined by the distribution of excitability, regardless of any previously formed ensemble ([Figure 1—figure supplement 1c](#)). In this regime, the patterns of activity are not informative about the order of the reactivations either. In the intermediate regime ($E = 1.5$), the decoder is able to correctly infer the order at which the reactivations happened, better than using the shuffled data ([Figure 2f](#), [Figure 1—figure supplement 1b](#)).

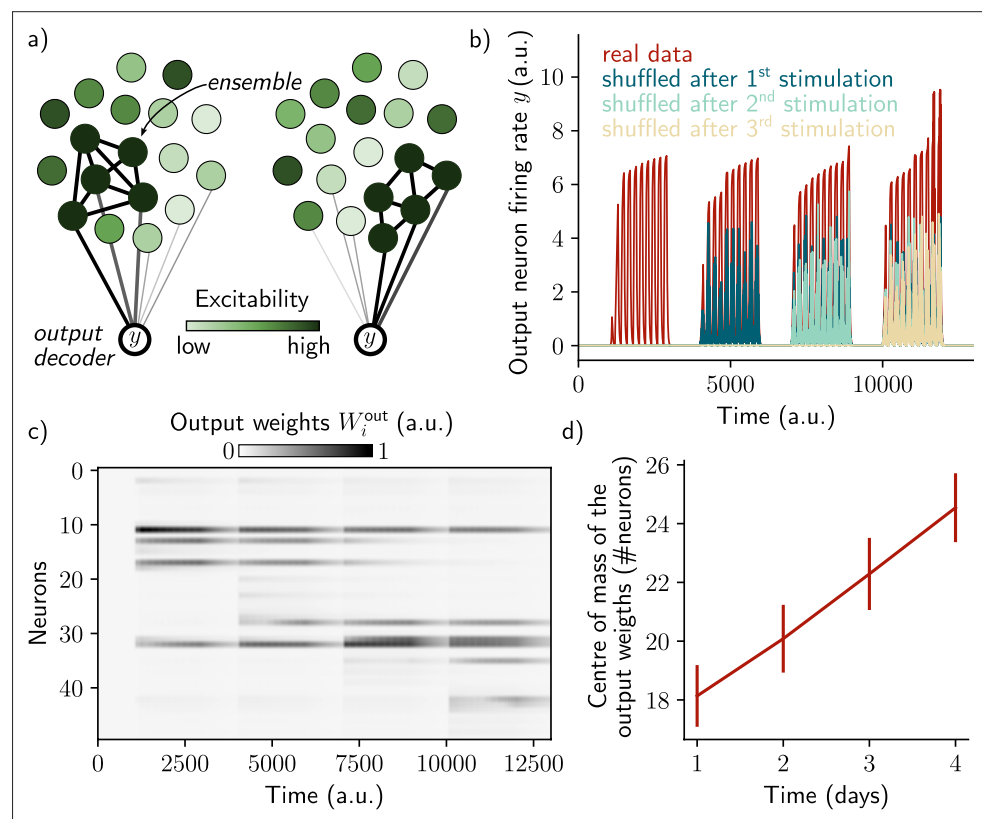


Figure 3. A single output neuron can track the memory ensemble through Hebbian plasticity. **(a)** Conceptual architecture of the network: the read-out neuron y in red 'tracks' the ensemble by decreasing synapses linked to the previous ensemble and increasing new ones to be linked to the new assembly. **(b)** Output neuron's firing rate across time. The red trace corresponds to the real output. The dark blue, light blue and yellow traces correspond to the cases where the output weights were randomly shuffled for every time points after presentation of the first, second and third stimulus, respectively. **(c)** Output weights for each neuron across time. **(d)** Center of mass of the distribution of the output weights (Methods) across days. The output weights are centered around the neurons that belong to the assembly at each day. Data are shown as mean $\pm$ s.e.m. for $n=10$ simulations.

The online version of this article includes the following figure supplement(s) for figure 3:

Figure supplement 1. The quality of the read-out decreases with the rate of the drift.

Finally, we sought to test whether the results are independent on the specific architecture of the model. To that end, we defined a change of excitability as a change in the slope of the activation function, rather than of the threshold (**Figure 2—figure supplement 2**, Methods). We also used sparse recurrent synaptic weights instead of the original all-to-all connectivity matrix (**Figure 2—figure supplement 1**, Methods). In both cases, we observed a similar drifting behavior and were able to decode the temporal order in which the memory evolved.

A read-out neuron can track the drifting ensemble

So far, we showed that the drifting ensemble contains information about its history, namely about the days and the order at which the subsequent reactivations of the memory happened.

However, we have not shown that we could use the neural ensemble to actually decode the memory itself, in addition to its temporal structure. To that end, we introduced a decoding output neuron connected to the recurrent neural network, with plastic weights following a Hebbian rule (Methods). As shown by **Rule and O’Leary, 2022**, the goal was to make sure that the output neuron can track the ensemble even if it is drifting. This can be done by constantly decreasing weights from neurons that are no longer in the ensemble and increasing those associated with neurons joining the ensemble (**Figure 3a**). We found that the output neuron could steadily decode the memory (i.e. it has a higher firing than in the case where the output weights are randomly shuffled; **Figure 3b**). This is due to the fact that weights are plastic under Hebbian learning, as shown by **Rule and O’Leary, 2022**. We confirmed that this was induced by a change in the output weights across time (**Figure 3c**). In particular, the weights from neurons that no longer belong to the ensemble are decreased while weights from newly recruited neurons are increased, so that the center of mass of the weights distribution drifts across time (**Figure 3d**). Finally, we found that the quality of the read-out decreases with the rate of the drift (**Figure 3—figure supplement 1**, Methods).

Two memories drift independently

Finally, we tested whether the network is able to encode two different memories and whether excitability could make two ensembles drift. On each day, we stimulated a random half of the neurons (context A) and the other half (context B) sequentially (Methods). We found that, day after day, the two ensembles show a similar drift than when only one ensemble was formed (**Figure 2—figure supplement 3**). In particular, the correlation between the patterns activity on the first day and the other days decay in a similar way (**Figure 2—figure supplement 4a**). For both contexts, the temporal order of the reactivations can be decoded for a certain range of excitability amplitude (**Figure 2—figure supplement 4b**). Finally, we found that using two output decoders allowed us to decode both memories independently. The output weights associated to both ensembles are remodeled to follow the drifting ensembles, but are not affected by the reactivation of the other ensemble (**Figure 2—figure supplement 4c**). Indeed, both neurons are able to ‘track’ the reactivation of their associated ensemble while not responding to the other ensemble (**Figure 2—figure supplement 4d**).

Discussion

Overall, our model suggests a potential cellular mechanisms for the emergence of drift that can serve a computational purpose by ‘time-stamping’ memories while still being able to decode the memory across time. Although the high performance of the day decoder was expected, the performance of the ordinal time decoder is not trivial. Indeed, the patterns of activity of each day are informative about the distribution of excitability and therefore about the day at which the reactivation happened. However, the ability for the neural ensemble to encode the order of past reactivations requires drift to be gradual (i.e. requires consecutive patterns of activity to remain correlated across days). Indeed, if the amplitude of excitability is too low ($E = 0$) or too high ($E = 3$), it is not possible to decode the order at which the successive reactivations happened. This result is consistent with the previous works showing gradual change in neural representations, that allows for decoding temporal information of the ensemble (**Rubin et al., 2015**). Moreover, such gradual drifts could support complex cognitive mechanisms like mental time-travel during memory recall (**Rubin et al., 2015**).

In our model, drift is induced by co-activation of the previously formed ensemble and neurons with high excitability at the time of the reactivation. The pool of neurons having high excitability can

therefore ‘time-stamps’ memory ensembles by biasing allocation of these ensembles (Clopath et al., 2017; Mau et al., 2018; Rubin et al., 2015). We suggest that such time-stamping mechanism could also help link memories that are temporally close and dissociate those which are spaced by longer time (Driscoll et al., 2022; Mau et al., 2020; Aimone et al., 2006). Indeed, the pool of neurons with high excitability varies across time so that any new memory ensemble is allocated to neurons which are shared with other ensembles formed around the same time. This mechanism could be complementary to the learning-induced increase in excitability observed in amygdala (Rashid et al., 2016), hippocampal CA1 (Cai et al., 2016) and dentate gyrus (Pignatelli et al., 2019).

Finally, we intended to model drift in the firing rates, as opposed to a drift in the turning curve, of the neurons. Recent studies suggest that drifts in the mean firing rate and tuning curve arise from two different mechanisms (Geva et al., 2023; Khatib et al., 2023). Experience drives a drift in neurons turning curve while the passage of time drives a drift in neurons firing rate. In this sense, our study is consistent with these findings by providing a possible mechanism for a drift in the mean firing rates of the neurons driven a dynamical excitability. Our work suggests that drift can depend on any experience having an impact on excitability dynamics such as exercise as previously shown experimentally (Rechavi et al., 2022; de Snoo et al., 2023) but also neurogenesis (Aimone et al., 2006; Tran et al., 2022; Rechavi et al., 2022), sleep (Levenstein et al., 2017) or increase in dopamine level (Chowdhury et al., 2022).

Overall, our work is a proof of principle which highlights the importance of considering excitability when studying drift, although further work would be needed to test this link experimentally.

Methods

Recurrent neural network with excitability

Our rate-based model consists of a single region of N neurons (with firing rate r_i , $1 \leq i \leq N$). All-to-all recurrent connections W are plastic and follow a Hebbian rule given by:

$$\frac{dW_{ij}}{dt} = r_i * r_j / \tau_W - W_{ij} / \tau_{\text{decay}} \quad (1)$$

where i and j correspond to the pre- and post-synaptic neuron respectively. τ_W and τ_{decay} are the learning and the decay time constants of the weights, respectively.

A hard bound of $[0, c]$ was applied to these weights. We also introduced a global inhibition term dependent on the activity of the neurons:

$$I = I_0 + I_1 \sum_{i=1}^N r_i + I_2 \sum_{i=1}^N r_i^2 \quad (2)$$

here I_0 , I_1 and I_2 are positive constants. All neurons receive the same input, $\Delta(t)$, during stimulation of the network (Figure 1c, black bars). Finally, excitability is modeled as a time-varying threshold ϵ_i of the input-output function of each neuron i . The rate dynamics of a neuron i is given by:

$$\tau_r \frac{dr_i}{dt} + r_i = \text{ReLU} \left(\Delta(t) + \sum_{j=1}^N W_{ij} r_j - I + \epsilon_i(t) \right) \quad (3)$$

where τ_r is the decay time of the rates and ReLU is the rectified linear activation function. We considered that a neurons is active when its firing rate reaches the active threshold θ .

In Figure 2—figure supplement 1, we applied a random binary mask to the recurrent weights in order to set 50% of the synapses at 0. A new mask was randomly sampled for each simulation.

In Figure 2—figure supplement 2, we modeled excitability as a change of the slope of the activation function (ReLU) instead of a change of the threshold as previously used (Figure 2—figure supplement 2a):

$$\tau_r \frac{dr_i}{dt} + r_i = \epsilon_i(t) * \text{ReLU} \left(\Delta(t) + \sum_{j=1}^N W_{ij} r_j - I \right) \quad (4)$$

Protocol

We designed a 4-day protocol, corresponding to the initial encoding of a memory (first day) and subsequent random or cue-induced reactivations of the ensemble (Josselyn and Tonegawa, 2020; Káli and Dayan, 2004) (second, third, and fourth day). Each stimulation consists of N_{rep} repetitions of interval T spaced by a inter-repetition delay IR . $\Delta(t)$ takes the value δ during these repetitions and is set to 0 otherwise. The stimulation is repeated four times, modeling four days of reactivation, spaced by an inter-day delay ID . Excitability ϵ_i of each neuron i is sampled from the absolute value of a normal distribution of mean 0 and standard deviation 1. In **Figure 2—figure supplement 2**, excitability ϵ_i is sampled from the absolute value of a normal distribution of mean 0.4 and standard deviation 0.2. Neurons 10–20, 20–30, 30–40, and 40–50 then receive an increase of excitability of amplitude E , respectively on days 1, 2, 3, and 4 (**Figure 1a**). A different random seed is used for each repetition of the simulation. When two memories were modeled (**Figure 2—figure supplements 3 and 4**), we stimulated a random half of the neurons (context A) and the other half (context B) successively (**Figure 2—figure supplement 3a**), every day.

Decoders

For each day d , we recorded the activity pattern V_d , which is a vector composed of the firing rate of the neurons at the end of the last repetition of stimulation. To test the decoder, we also stimulated the network while setting the excitability at baseline ($E = 0$), and recorded the resulted pattern of activity V_d^0 for each day d . We then designed two types of decoders, inspired by previous works (Rubin et al., 2015): (1) a day decoder which infers the day at which each stimulation happened and (2) an ordinal time decoder which infers the order at which the reactivations occurred. For both decoders, the shuffled data was obtained by randomly shuffling the day label of each neuron. When two memories were modeled (**Figure 2—figure supplements 3 and 4**), the patterns of activity were taken at the end of the stimulations by context A and B, and the decoders were used independently on each memory.

1. The day decoder aims at inferring the day at which a specific pattern of activity occurred. To that end, we computed the Pearson correlation between the pattern with no excitability V_d^0 of the day d and the patterns of all days d' from the first simulation $V_{d'}$. Then, the decoder outputs the day d_{inf} that maximises the correlation:

$$d_{\text{inf}} = \arg \max_{d'} \{ \text{corr}(V_d^0, V_{d'}) \} \quad (5)$$

The error was defined as the difference between the inferred and the real day $d_{\text{inf}} - d$.

2. The ordinal time decoder aims at inferring the order at which the reactivations happened from the patterns of activity V_d of every day d . To that end, we computed the pairwise correlations of each pair of consecutive days, for the 4! possible permutations of days p . The real permutation is called $p^{\text{real}} = (1, 2, 3, 4)$ and corresponds to the real order of reactivations: day 1 → day 2 → day 3 → day 4. The sum of these correlations over the 3 pairs of consecutive days is expressed as:

$$S(p) = \sum_{i=1}^3 \text{corr}(V_{p_i}, V_{p_{i+1}}) \quad (6)$$

We then compared the distribution of these quantities for each permutation p to that of the real permutation $S(p^{\text{real}})$ (**Figure 2**). The patterns of activity are informative about the order of reactivations if $S(p^{\text{real}})$ corresponds to the maximal value of $S(p)$. To compare $S(p^{\text{real}})$ with the distribution $S(p)$, we performed a Student's t-test, where the t-value is defined as:

$$t = \frac{S(p^{\text{real}}) - \mu}{\sigma / \sqrt{N}} \quad (7)$$

where μ and σ correspond to the mean and standard deviation of the distribution $S(p)$, respectively.

The drift rate Δ (**Figure 1—figure supplement 2** and **Figure 3—figure supplement 1**) was computed as:

$$\Delta = \sum_{i=2}^4 (1 - \text{corr}(V_1, V_i)) \quad (8)$$

Memory read-out

To test if the network is able to decode the memory at any time point, we introduced a read-out neuron with plastic synapses to neurons from the recurrent network, inspired by previous computational works ([Rule and O’Leary, 2022](#)). The weights of these synapses are named $\mathbf{W}^{\text{out}} = (W_i^{\text{out}})_{1 \leq i \leq N}$ and follow the Hebbian rule defined as:

$$\frac{dW_{ij}^{\text{out}}}{dt} = h(\mathbf{W}^{\text{out}}) * r_i * y / \tau_{\text{out}}^+ - W_i^{\text{out}} / \tau_{\text{out}}^- \quad (9)$$

where τ_{out}^+ and τ_{out}^- corresponds to the learning time and decay time constant, respectively. $h(\mathbf{W}^{\text{out}})$ is a homeostatic term defined as $h(\mathbf{W}^{\text{out}}) = 1 - \sum_{j=1}^N W_j^{\text{out}}$ which decreases to 0 throughout learning. h takes the value 1 before learning and 0 when the sum of the weights reaches the value 1. y is the firing rate of the output neuron defined y as:

$$y = \sum_{i=1}^N W_i^{\text{out}} r_i \quad (10)$$

The read-out quality index Q ([Figure 3—figure supplement 1](#)) was defined as:

$$Q = \langle \sum_{d=2}^4 y_d / y_d^{\text{shuffle}} \rangle_{N_{\text{shuffle}}} \quad (11)$$

where y_d corresponds to the value of y taken at the end of the last repetition of day d , and y_d^{shuffle} the equivalent with shuffled outputs weights. $\langle \dots \rangle_{N_{\text{shuffle}}}$ indicates the average over $N_{\text{shuffle}} = 10$ simulations.

In [Figure 2—figure supplements 3 and 4](#), two output decoders y_k , $k \in \{1, 2\}$, with corresponding weights $\mathbf{W}_k^{\text{out}} = (W_{i,k}^{\text{out}})_{1 \leq i \leq N}$ are defined as:

$$y_k = \sum_{i=1}^N W_{i,k}^{\text{out}} r_i + \beta_k \quad (12)$$

and follow the Hebbian rule defined as:

$$\frac{dW_{i,k}^{\text{out}}}{dt} = h(\mathbf{W}_{i,k}^{\text{out}}) * r_i * y_k / \tau_{\text{out}}^+ - W_{i,k}^{\text{out}} / \tau_{\text{out}}^- \quad (13)$$

Then, we aimed at allocating y_1 and y_2 to the first and the second ensemble (context A and B), respectively. To that end, we used supervised learning on the first day by adding a current β_k to the output neurons which is positive when the corresponding context is on:

$$\begin{aligned} \beta_0 &= 0.1 \text{ if } 1000 < t < 3000, 0 \text{ otherwise} \\ \beta_1 &= 0.1 \text{ if } 4000 < t < 6000, 0 \text{ otherwise} \end{aligned} \quad (14)$$

The shuffled traces were obtained by randomly shuffling the output weights $\mathbf{W}^{\text{out}}$ or $\mathbf{W}_k^{\text{out}}$ for each ensemble k .

Table of parameters

The following parameters have been used for the simulations. When unspecified, the defaults values were used. All except N are in arbitrary unit. [Figure 2—figure supplement 2](#) corresponds to the change from a threshold-based to a slope-based excitability. [Figure 2—figure supplements 3 and 4](#) corresponds to the stimulation of two ensembles. [Figure 2—figure supplement 1](#) corresponds to the sparsity simulation.

Param.	Description	Default	Figure 2—figure supplement 2	Figure 2—figure supplements 3 and 4	Figure 2—figure supplement 1
N	Number of neurons	50	-	-	-

Continued on next page

Continued

Param.	Description	Default	Figure 2—figure supplement 2	Figure 2—figure supplements 3 and 4	Figure 2—figure supplement 1
τ_W	Learning time constant of the recurrent weights	800	700	-	-
τ_{decay}	Decay time constant of the recurrent weights	1000	800	4000	-
τ_r	Decay time constant of the firing rates	20	-	-	-
τ_{out}^+	Learning time constant of the output weights	200	-	-	-
τ_{out}^-	Decay time constant of the output weights	1000	-	-	-
I_0	First inhibition parameter	12	4	8	7
I_1	Second inhibition parameter	0.5	0.7	0.8	0.8
I_2	Third inhibition parameter	0.05	-	-	-
δ	Input current during stimulation	15	-	12	20
E	Amplitude of the fluctuations of excitability	1.5	0.5	-	-
N_{rep}	Number of repetitions	10	-	-	-
T	Duration of each repetition	100	-	-	-
IR	Inter-repetition delay	100	-	-	-
ID	Inter-stimulation delay	1000	-	-	-
θ	Active threshold	5	1	-	-
c	Cap on the recurrent weights	1	.5	-	-

Additional information

Competing interests

Denise J Cai: Reviewing editor, eLife. The other authors declare that no competing interests exist.

Funding

Funder	Grant reference number	Author
Biotechnology and Biological Sciences Research Council	BB/N013956/1	Claudia Clopath
Wellcome Trust	10.35802/200790	Claudia Clopath
Simons Foundation	564408	Claudia Clopath
Engineering and Physical Sciences Research Council	EP/R035806/1	Claudia Clopath

The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication. For the purpose of Open Access, the authors have applied a CC BY public copyright license to any Author Accepted Manuscript version arising from this submission.

Author contributions

Geoffroy Delamare, Conceptualization, Data curation, Software, Formal analysis, Visualization, Methodology, Writing - original draft, Writing - review and editing; Yosif Zaki, Conceptualization, Writing - review and editing; Denise J Cai, Conceptualization, Project administration, Writing - review and

editing; Claudia Clopath, Conceptualization, Resources, Supervision, Funding acquisition, Validation, Investigation, Methodology, Project administration, Writing - review and editing

Author ORCIDs

Geoffroy Delamare  <http://orcid.org/0000-0001-6217-4370>

Denise J Cai  <http://orcid.org/0000-0002-7729-0523>

Claudia Clopath  <http://orcid.org/0000-0003-4507-8648>

Peer review material

Reviewer #3 (Public Review): <https://doi.org/10.7554/eLife.88053.3.sa1>

Author response <https://doi.org/10.7554/eLife.88053.3.sa2>

Additional files

Supplementary files

- MDAR checklist

Data availability

The code for simulations and figures is available at [GitHub](#) (copy archived at [Delamare, 2024](#)).

References

- Aimone JB**, Wiles J, Gage FH. 2006. Potential role for adult neurogenesis in the encoding of time in new memories. *Nature Neuroscience* **9**:723–727. DOI: <https://doi.org/10.1038/nn1707>, PMID: 16732202
- Attardo A**, Fitzgerald JE, Schnitzer MJ. 2015. Impermanence of dendritic spines in live adult CA1 hippocampus. *Nature* **523**:592–596. DOI: <https://doi.org/10.1038/nature14467>, PMID: 26098371
- Cai DJ**, Aharoni D, Shuman T, Shobe J, Biane J, Song W, Wei B, Veshkini M, La-Vu M, Lou J, Flores SE, Kim I, Sano Y, Zhou M, Baumgaertel K, Lavi A, Kamata M, Tuszyński M, Mayford M, Golshani P, et al. 2016. A shared neural ensemble links distinct contextual memories encoded close in time. *Nature* **534**:115–118. DOI: <https://doi.org/10.1038/nature17955>, PMID: 27251287
- Cho HY**, Shin W, Lee HS, Lee Y, Kim M, Oh JP, Han J, Jeong Y, Suh B, Kim E, Han JH. 2021. Turnover of fear engram cells by repeated experience. *Current Biology* **31**:5450–5461. DOI: <https://doi.org/10.1016/j.cub.2021.10.004>, PMID: 34687608
- Chowdhury A**, Luchetti A, Fernandes G, Filho DA, Kastellakis G, Tzivilaki A, Ramirez EM, Tran MY, Poirazi P, Silva AJ. 2022. A locus coeruleus-dorsal CA1 dopaminergic circuit modulates memory linking. *Neuron* **110**:3374–3388. DOI: <https://doi.org/10.1016/j.neuron.2022.08.001>, PMID: 36041433
- Clopath C**, Bonhoeffer T, Hübener M, Rose T. 2017. Variance and invariance of neuronal long-term representations. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **372**:20160161. DOI: <https://doi.org/10.1098/rstb.2016.0161>, PMID: 28093555
- Delamare G**, Feitosa Tomé D, Clopath C. 2022. Intrinsic Neural Excitability Induces Time-Dependent Overlap of Memory Engrams. *bioRxiv*. DOI: <https://doi.org/10.1101/2022.08.27.505441>
- Delamare G**. 2024. Drift. swb:1:rev:c79e1baeff8e3c3294ef794c77287827e3af9cec. Software Heritage. <https://archive.softwareheritage.org/swb:1:dir:50f44c9d73aa82fd3cd38347b9b6ed5c9af43a53;origin=https://github.com/gdelamar/drift;visit=swb:1:snp:d7c0ec941cf4282bc25b00df0862de834b7e1ed1;anchor=swb:1:rev:c79e1baeff8e3c3294ef794c77287827e3af9cec>
- de Snoo ML**, Miller AMP, Ramsaran AI, Josselyn SA, Frankland PW. 2023. Exercise accelerates place cell representational drift. *Current Biology* **33**:R96–R97. DOI: <https://doi.org/10.1016/j.cub.2022.12.033>, PMID: 36750030
- Driscoll LN**, Pettit NL, Minderer M, Chetih SN, Harvey CD. 2017. Dynamic reorganization of neuronal activity patterns in parietal cortex. *Cell* **170**:986–999. DOI: <https://doi.org/10.1016/j.cell.2017.07.021>, PMID: 28823559
- Driscoll LN**, Duncker L, Harvey CD. 2022. Representational drift: Emerging theories for continual learning and experimental future directions. *Current Opinion in Neurobiology* **76**:102609. DOI: <https://doi.org/10.1016/j.conb.2022.102609>, PMID: 35939861
- Geva N**, Deitch D, Rubin A, Ziv Y. 2023. Time and experience differentially affect distinct aspects of hippocampal representational drift. *Neuron* **111**:2357–2366. DOI: <https://doi.org/10.1016/j.neuron.2023.05.005>, PMID: 37315556
- Grosmark AD**, Buzsáki G. 2016. Diversity in neural firing dynamics supports both rigid and learned hippocampal sequences. *Science* **351**:1440–1443. DOI: <https://doi.org/10.1126/science.aad1935>, PMID: 27013730
- Hainmueller T**, Bartos M. 2018. Parallel emergence of stable and dynamic memory engrams in the hippocampus. *Nature* **558**:292–296. DOI: <https://doi.org/10.1038/s41586-018-0191-2>, PMID: 29875406
- Huber R**, Mäki H, Rosanova M, Casarotto S, Canali P, Casali AG, Tononi G, Massimini M. 2013. Human cortical excitability increases with time awake. *Cerebral Cortex* **23**:332–338. DOI: <https://doi.org/10.1093/cercor/bhs014>, PMID: 22314045

- Josselyn SA**, Tonegawa S. 2020. Memory engrams: Recalling the past and imagining the future. *Science* **367**:eaaw4325. DOI: <https://doi.org/10.1126/science.aaw4325>, PMID: 31896692
- Káli S**, Dayan P. 2004. Off-line replay maintains declarative memories in a model of hippocampal-neocortical interactions. *Nature Neuroscience* **7**:286–294. DOI: <https://doi.org/10.1038/nn1202>, PMID: 14983183
- Khatib D**, Ratzon A, Sellevoll M, Barak O, Morris G, Derdikman D. 2023. Active experience, not time, determines within-day representational drift in dorsal CA1. *Neuron* **111**:2348–2356. DOI: <https://doi.org/10.1016/j.neuron.2023.05.014>, PMID: 37315557
- Kossio YFK**, Goedeke S, Klos C, Memmesheimer R-M. 2021. Drifting assemblies for persistent memory: Neuron transitions and unsupervised compensation. *PNAS* **118**:e2023832118. DOI: <https://doi.org/10.1073/pnas.2023832118>, PMID: 34772802
- Levenstein D**, Watson BO, Rinzel J, Buzsáki G. 2017. Sleep regulation of the distribution of cortical firing rates. *Current Opinion in Neurobiology* **44**:34–42. DOI: <https://doi.org/10.1016/j.conb.2017.02.013>, PMID: 28288386
- Levenstein D**, Buzsáki G, Rinzel J. 2019. NREM sleep in the rodent neocortex and hippocampus reflects excitable dynamics. *Nature Communications* **10**:2478. DOI: <https://doi.org/10.1038/s41467-019-10327-5>, PMID: 31171779
- Manz P**, Memmesheimer RM. 2023. Purely STDP-based assembly dynamics: Stability, learning, overlaps, drift and aging. *PLOS Computational Biology* **19**:e1011006. DOI: <https://doi.org/10.1371/journal.pcbi.1011006>, PMID: 37043481
- Mau W**, Sullivan DW, Kinsky NR, Hasselmo ME, Howard MW, Eichenbaum H. 2018. The Same Hippocampal CA1 population simultaneously codes temporal information over multiple timescales. *Current Biology* **28**:1499–1508. DOI: <https://doi.org/10.1016/j.cub.2018.03.051>, PMID: 29706516
- Mau W**, Hasselmo ME, Cai DJ. 2020. The brain in motion: How ensemble fluidity drives memory-updating and flexibility. *eLife* **9**:e63550. DOI: <https://doi.org/10.7554/eLife.63550>, PMID: 33372892
- Mau W**, Morales-Rodriguez D, Dong Z, Pennington ZT, Francisco T, Baxter MG, Shuman T, Cai DJ. 2022. Ensemble Remodeling Supports Memory-Updating. *bioRxiv*. DOI: <https://doi.org/10.1101/2022.06.02.494530>
- Miller AMP**, Frankland PW, Josselyn SA. 2018. Memory: Ironing out a wrinkle in time. *Current Biology* **28**:R599–R601. DOI: <https://doi.org/10.1016/j.cub.2018.03.053>, PMID: 29787721
- Pignatelli M**, Ryan TJ, Roy DS, Lovett C, Smith LM, Muralidhar S, Tonegawa S. 2019. Engram cell excitability state determines the efficacy of memory retrieval. *Neuron* **101**:274–284. DOI: <https://doi.org/10.1016/j.neuron.2018.11.029>, PMID: 30551997
- Poo MM**, Pignatelli M, Ryan TJ, Tonegawa S, Bonhoeffer T, Martin KC, Rudenko A, Tsai LH, Tsien RW, Fishell G, Mullins C, Gonçalves JT, Shtrahman M, Johnston ST, Gage FH, Dan Y, Long J, Buzsáki G, Stevens C. 2016. What is memory? The present state of the engram. *BMC Biology* **14**:6. DOI: <https://doi.org/10.1186/s12915-016-0261-6>
- Rashid AJ**, Yan C, Mercaldo V, Hsiang H-LL, Park S, Cole CJ, De Cristofaro A, Yu J, Ramakrishnan C, Lee SY, Deisseroth K, Frankland PW, Josselyn SA. 2016. Competition between engrams influences fear memory formation and recall. *Science* **353**:383–387. DOI: <https://doi.org/10.1126/science.aaf0594>, PMID: 27463673
- Rechavi Y**, Rubin A, Yizhar O, Ziv Y. 2022. Exercise increases information content and affects long-term stability of hippocampal place codes. *Cell Reports* **41**:111695. DOI: <https://doi.org/10.1016/j.celrep.2022.111695>, PMID: 36417871
- Rogerson T**, Cai DJ, Frank A, Sano Y, Shobe J, Lopez-Aranda MF, Silva AJ. 2014. Synaptic tagging during memory allocation. *Nature Reviews. Neuroscience* **15**:157–169. DOI: <https://doi.org/10.1038/nrn3667>, PMID: 24496410
- Rubin A**, Geva N, Sheintuch L, Ziv Y. 2015. Hippocampal ensemble dynamics timestamp events in long-term memory. *eLife* **4**:e12247. DOI: <https://doi.org/10.7554/eLife.12247>, PMID: 26682652
- Rule ME**, O'Leary T. 2022. Self-healing codes: How stable neural populations can track continually reconfiguring neural representations. *PNAS* **119**:e2106692119. DOI: <https://doi.org/10.1073/pnas.2106692119>, PMID: 35145024
- Sadeh S**, Clopath C. 2022. Contribution of behavioural variability to representational drift. *eLife* **11**:e77907. DOI: <https://doi.org/10.7554/eLife.77907>, PMID: 36040010
- Silva AJ**, Zhou Y, Rogerson T, Shobe J, Balaji J. 2009. Molecular and cellular approaches to memory allocation in neural circuits. *Science* **326**:391–395. DOI: <https://doi.org/10.1126/science.1174519>, PMID: 19833959
- Spalla D**, Cornacchia IM, Treves A. 2021. Continuous attractors for dynamic memories. *eLife* **10**:e69499. DOI: <https://doi.org/10.7554/eLife.69499>, PMID: 34520345
- Tran LM**, Santoro A, Liu L, Josselyn SA, Richards BA, Frankland PW. 2022. Adult neurogenesis acts as a neural regularizer. *PNAS* **119**:e2206704119. DOI: <https://doi.org/10.1073/pnas.2206704119>, PMID: 36322739
- Zhou Y**, Won J, Karlsson MG, Zhou M, Rogerson T, Balaji J, Neve R, Poirazi P, Silva AJ. 2009. CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala. *Nature Neuroscience* **12**:1438–1443. DOI: <https://doi.org/10.1038/nn.2405>, PMID: 19783993
- Ziv Y**, Burns LD, Cocker ED, Hamel EO, Ghosh KK, Kitch LJ, El Gamal A, Schnitzer MJ. 2013. Long-term dynamics of CA1 hippocampal place codes. *Nature Neuroscience* **16**:264–266. DOI: <https://doi.org/10.1038/nn.3329>, PMID: 23396101

Figures and figure supplements

Drift of neural ensembles driven by slow fluctuations of intrinsic excitability

Geoffroy Delamare et al.

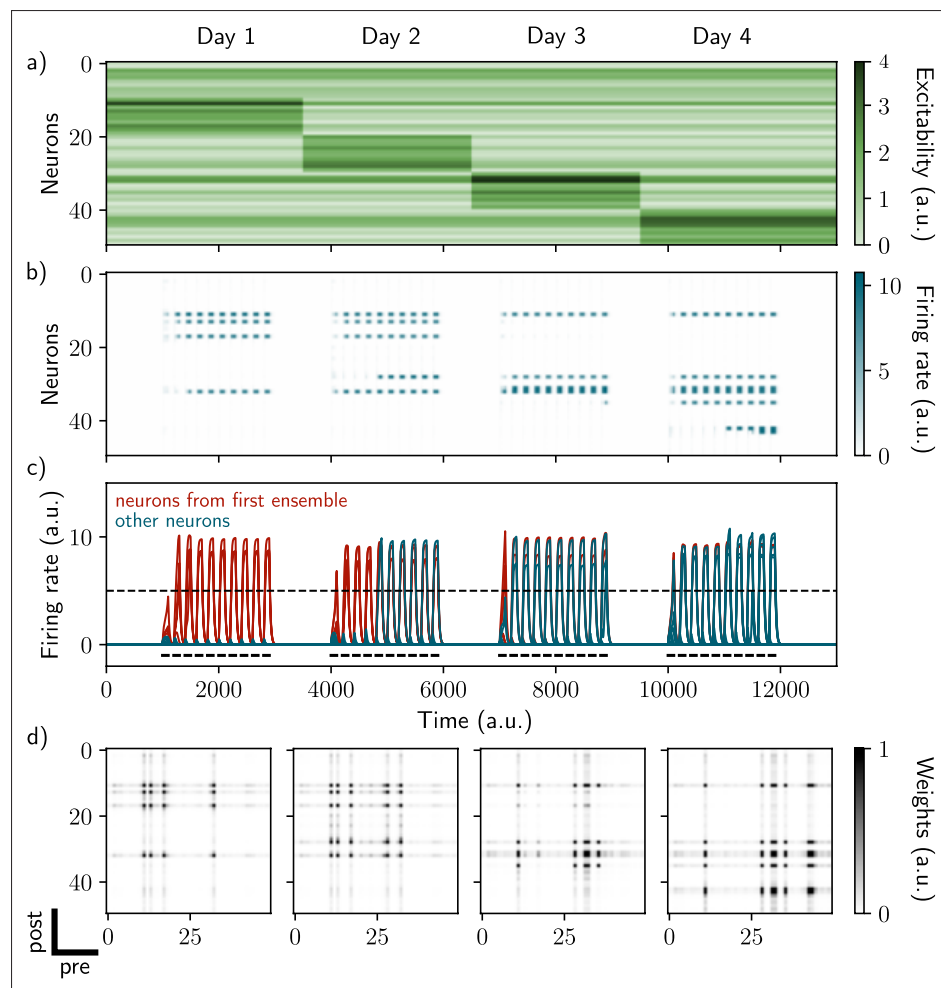


Figure 1. Excitability-induced drift of memory ensembles. **(a)** Distribution of excitability ϵ_i for each neuron i , fluctuating over time. During each stimulation, a different pool of neurons has a high excitability (Methods). **(b, c)** Firing rates of the neurons across time. The red traces in panel **(c)** correspond to neurons belonging to the first assembly, namely that have a firing rate higher than the active threshold after the first stimulation. The black bars show the stimulation and the dashed line shows the active threshold. **(d)** Recurrent weights matrices after each of the four stimuli show the drifting assembly.

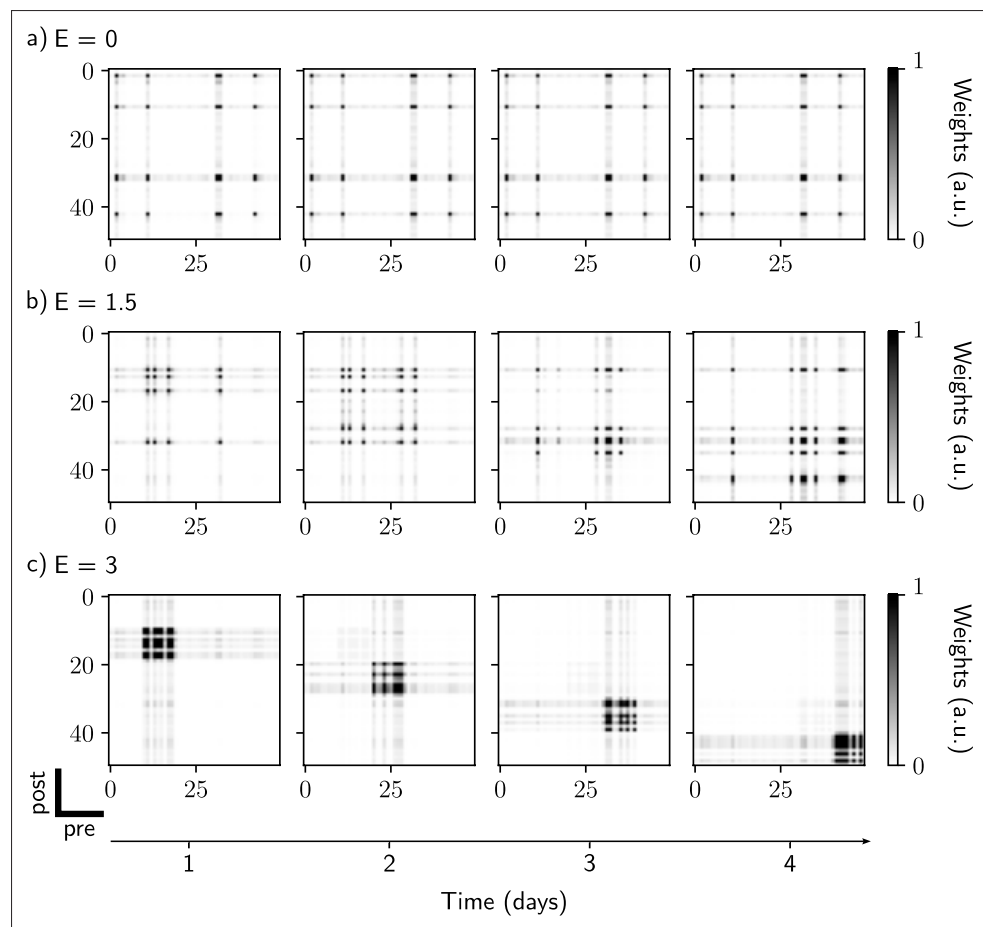


Figure 1—figure supplement 1. Comparison of drifting behavior for different values of excitability amplitude. (a) $E = 0$, no drift. A neural assembly is initially formed during the first stimulation and later reactivated every subsequent day. (b) $E = 1.5$, partial drift. The ensemble is gradually modified during each new stimulation. (c) $E = 3$, full drift. Each new stimulation leads to formation of a new ensemble, containing neurons that have high excitability during this time.

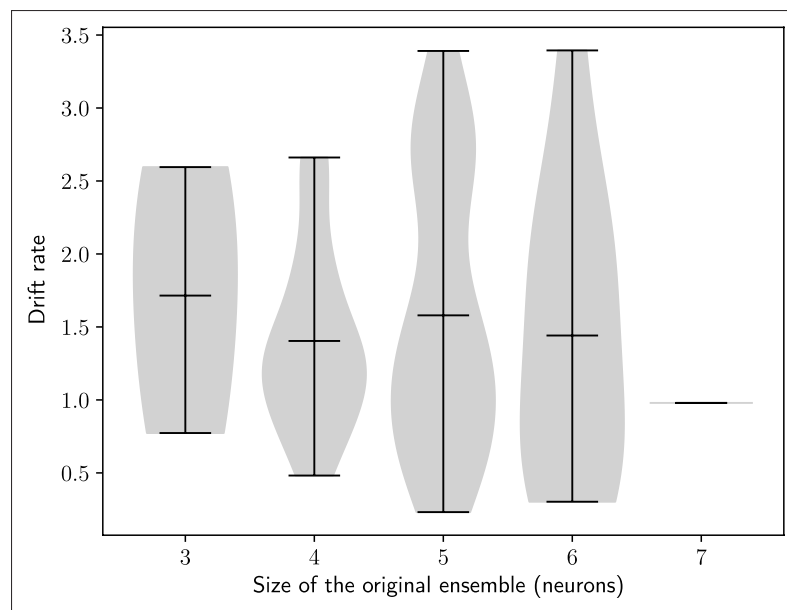


Figure 1—figure supplement 2. The rate of the drift does not depend on the size of the initial engram. Drift rate against the size of the original engram. Bars show minimum, mean and maximum values. $n=100$ simulations.

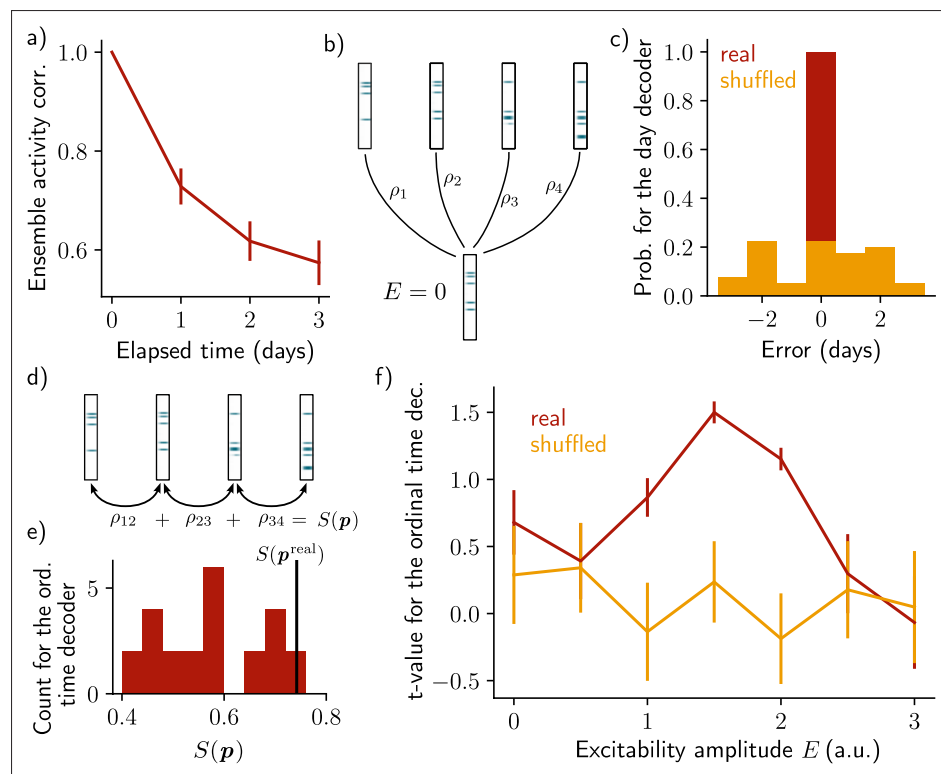


Figure 2. Neuronal activity is informative about the temporal structure of the reactivations. **(a)** Correlation of the patterns of activity between the first day and every other days, for $n=10$ simulations. Data are shown as mean $\pm$ s.e.m. **(b)** Schema of the day decoder. The day decoder maximises correlation between the patterns of each day with the pattern from the simulation with no increase in excitability. **(c)** Results of the day decoder for the real data (red) and the shuffled data (orange). Shuffled data consist of the same activity pattern for which the label of each cell for every seed has been shuffled randomly. For each simulation, the error is measured for each day as the difference between the decoded and the real day. Data are shown for $n=10$ simulations and for each of the 4 days. **(d)** Schema of the ordinal time decoder. This decoder output the permutation p that maximises the sum $S(p)$ of the correlations of the patterns for each pairs of days. **(e)** Distribution of the value $S(p)$ for each permutation of days p . The value for the real permutation $S(p_{\text{real}})$ is shown in black. **(f)** Student's test t-value for $n=10$ simulations, for the real (red) and shuffled (orange) data and for different amplitudes of excitability E . Data are shown as mean $\pm$ s.e.m. for $n=10$ simulations.

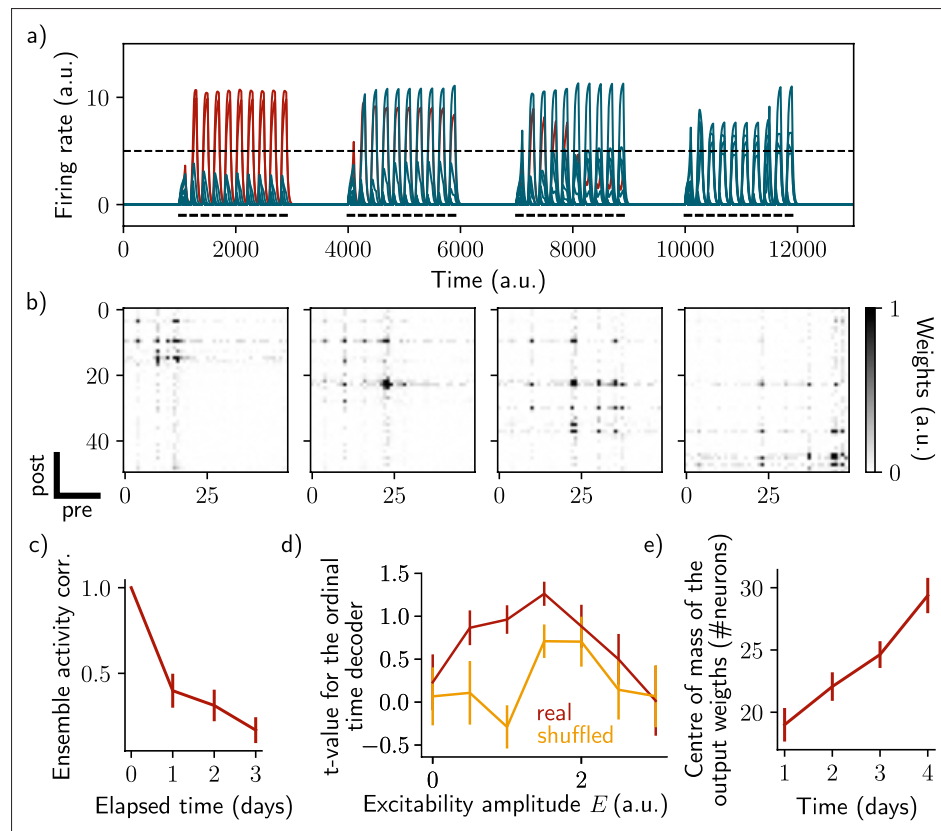


Figure 2—figure supplement 1. Sparse recurrent connectivity shows similar drifting behavior as all-to-all connectivity. The same simulation protocol as **Figure 1** was used while the recurrent weights matrix was made 50% sparse (Methods). **(a)** Firing rates of the neurons across time. The red traces correspond to neurons belonging to the first assembly, namely that have a firing rate higher than the active threshold after the first stimulation. The black bars show the stimulation and the dashed line shows the active threshold. **(b)** Recurrent weights matrices after each of the four stimuli show the drifting assembly. **(c)** Correlation of the patterns of activity between the first day and every other days. **(d)** Student's test t-value of the ordinal time decoder, for the real (red) and shuffled (orange) data and for different amplitudes of excitability E . **(e)** Center of mass of the distribution of the output weights (Methods) across days. **(c–e)** Data are shown as mean $\pm$ s.e.m. for $n=10$ simulations.

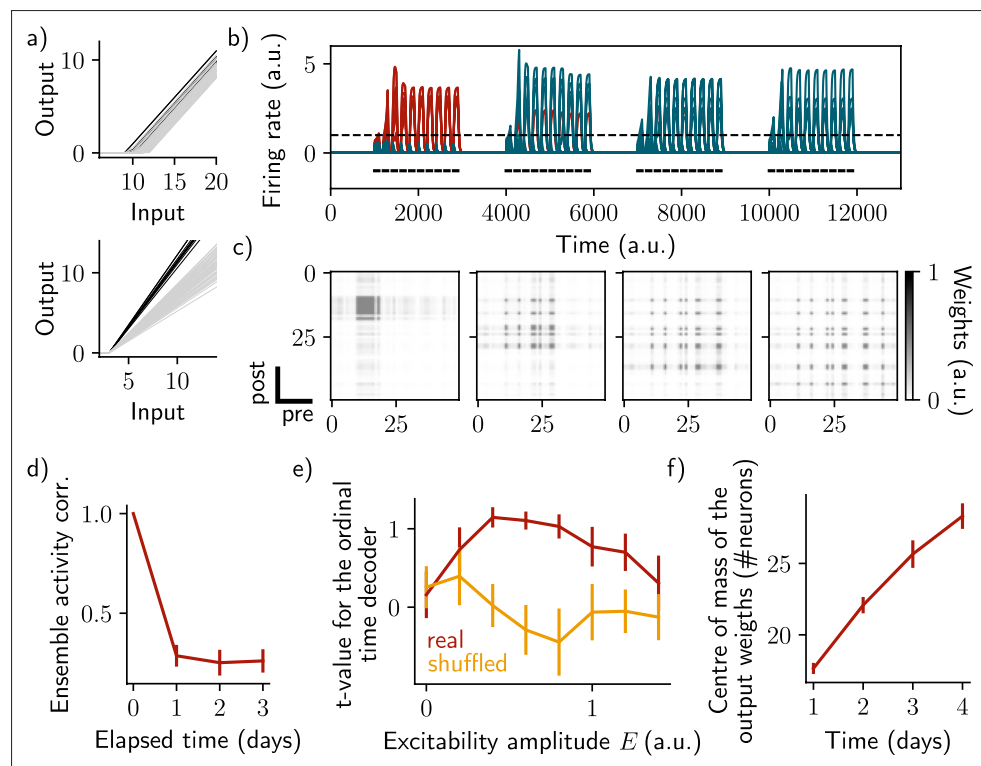


Figure 2—figure supplement 2. Change of excitability as a variable slope of the input-output function shows similar drifting behavior as considering a change in the threshold. The same simulation protocol as **Figure 1** was used while the excitability changes were modeled as a change in the slope of the activation function (Methods). (a) Schema showing two different ways of defining excitability, as a threshold (top) or slope (bottom) of the activation function. Each line shows one neuron and darker lines correspond to neurons with increased excitability. (b) Firing rates of the neurons across time. The red traces correspond to neurons belonging to the first assembly, namely that have a firing rate higher than the active threshold after the first stimulation. The black bars show the stimulation and the dashed line shows the active threshold. (c) Recurrent weights matrices after each of the four stimuli show the drifting assembly. (d) Correlation of the patterns of activity between the first day and every other days. (e) Student's test t-value of the ordinal time decoder, for the real (red) and shuffled (orange) data and for different amplitudes of excitability E . (f) Center of mass of the distribution of the output weights (Methods) across days. (d-f) Data are shown as mean $\pm$ s.e.m. for $n=10$ simulations.

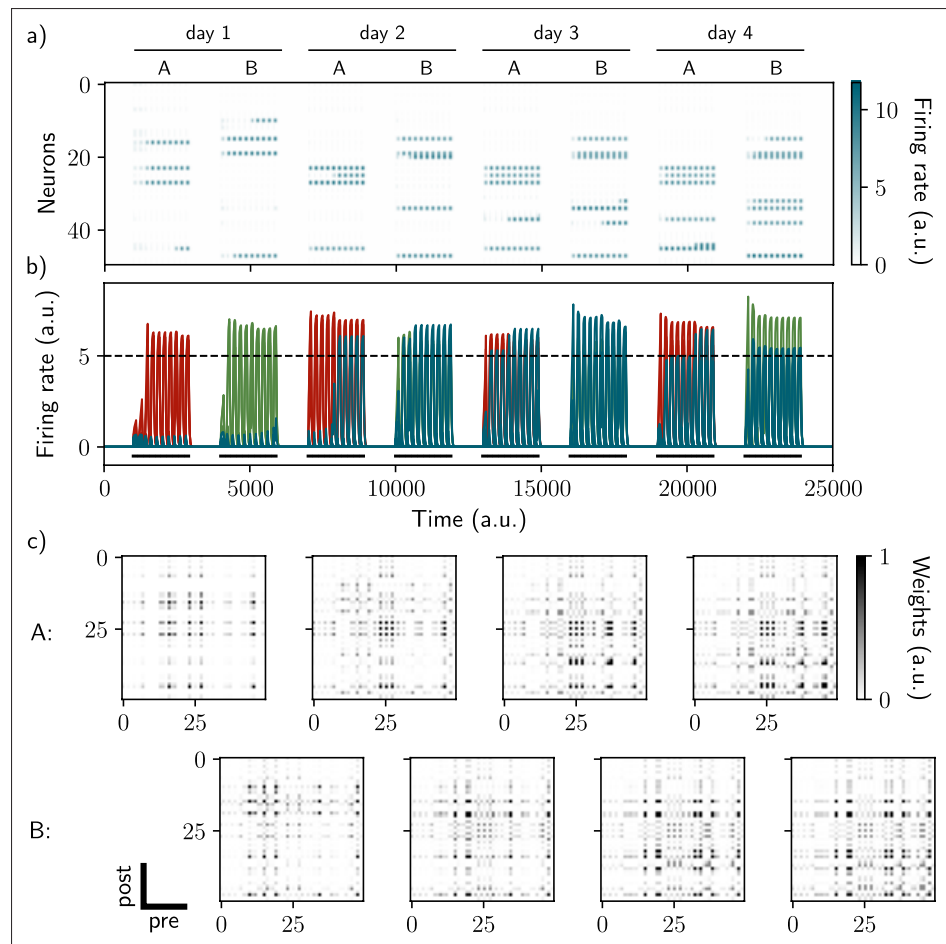


Figure 2—figure supplement 3. Two distinct ensembles can be encoded and drift independently. (a, b) Firing rates of the neurons across time. The red traces in panel (b) correspond to neurons belonging to the first assembly and the green traces to the second assembly on the first day. They correspond to neurons having a firing rate higher than the active threshold after the first stimulation of each assembly. The black bars show the stimulation and the dashed line shows the active threshold. (c) Recurrent weights matrices after each of the eight stimuli showing the drifting of the first (top) and second (bottom) assembly.

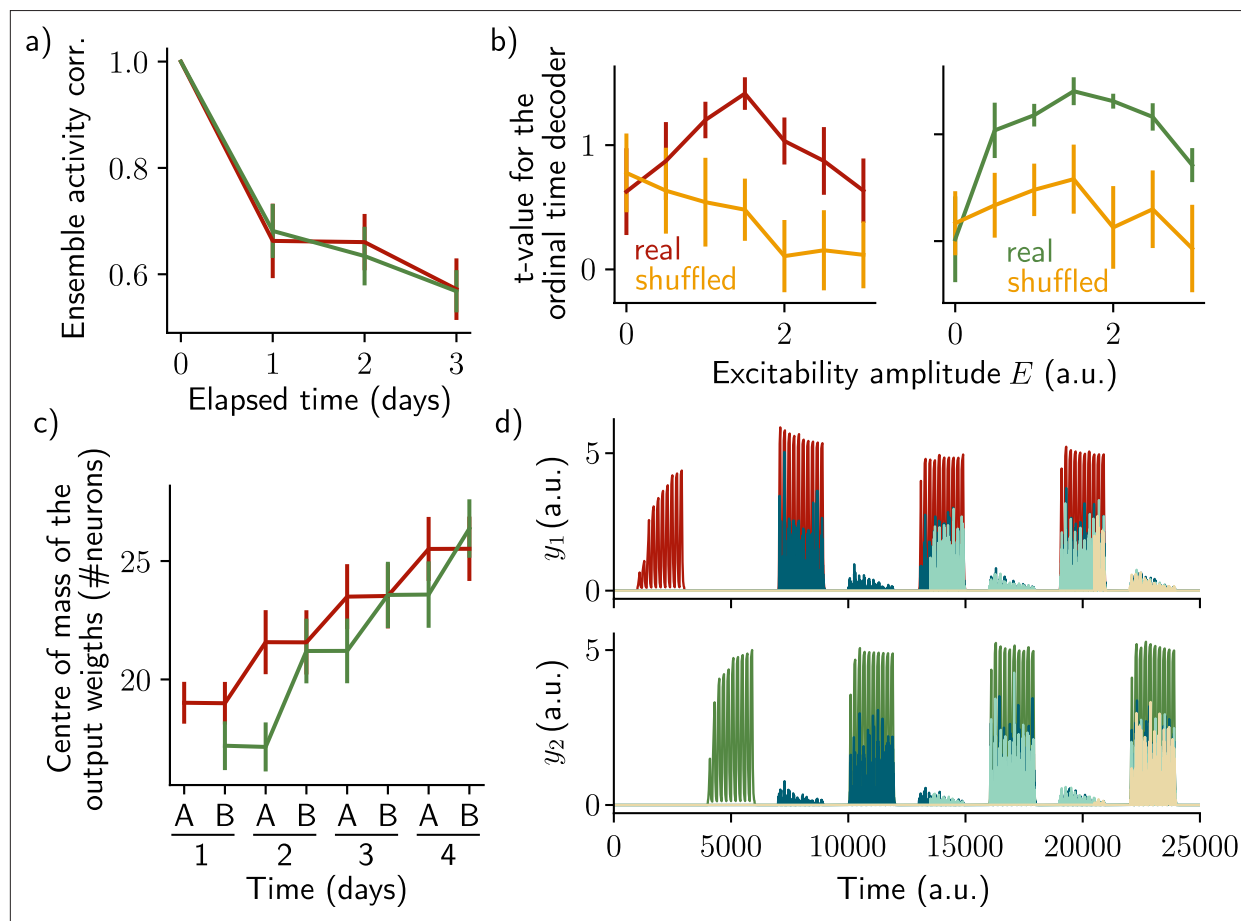


Figure 2—figure supplement 4. The two ensembles are informative about their temporal history and can be decoded using two output neurons. (a) Correlation of the patterns of activity between the first day and every other days, for the first assembly (red) and the second assembly (green). (b) Student's test t-value of the ordinal time decoder, for the first (red, left) and second ensemble (green, right) for different amplitudes of excitability E . Shuffled data are shown in orange. (c) Center of mass of the distribution of the output weights (Methods) across days for the first (W_1^{out} , red) and second (W_2^{out} , green) ensemble. (a–c) Data are shown as mean $\pm$ s.e.m. for $n=10$ simulations. (d) Output neurons firing rate across time for the first ensemble (y_1 , top) and the second ensemble (y_2 , bottom). The red and green traces correspond to the real output. The dark blue, light blue and yellow traces correspond to the cases where the output weights were randomly shuffled for every time points after presentation of the first, second and third stimulus, respectively.

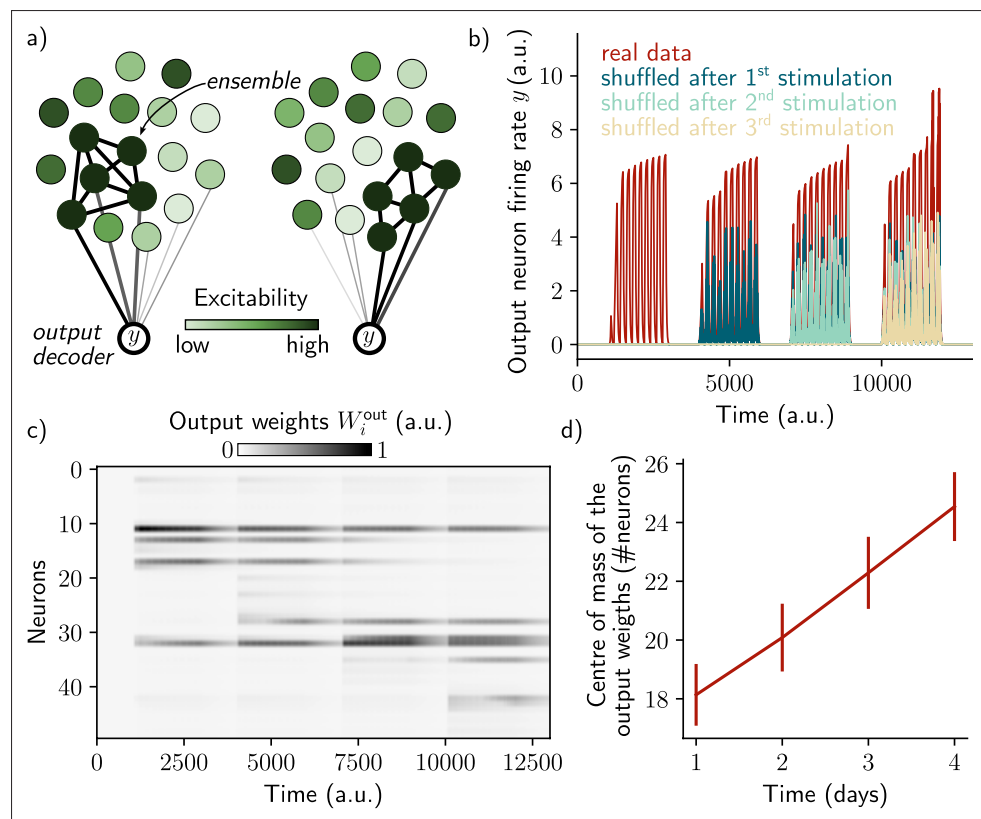


Figure 3. A single output neuron can track the memory ensemble through Hebbian plasticity. **(a)** Conceptual architecture of the network: the read-out neuron y in red ‘tracks’ the ensemble by decreasing synapses linked to the previous ensemble and increasing new ones to linked to the new assembly. **(b)** Output neuron’s firing rate across time. The red trace corresponds to the real output. The dark blue, light blue and yellow traces correspond to the cases where the output weights were randomly shuffled for every time points after presentation of the first, second and third stimulus, respectively. **(c)** Output weights for each neuron across time. **(d)** Center of mass of the distribution of the output weights (Methods) across days. The output weights are centered around the neurons that belong to the assembly at each day. Data are shown as mean $\pm$ s.e.m. for $n=10$ simulations.

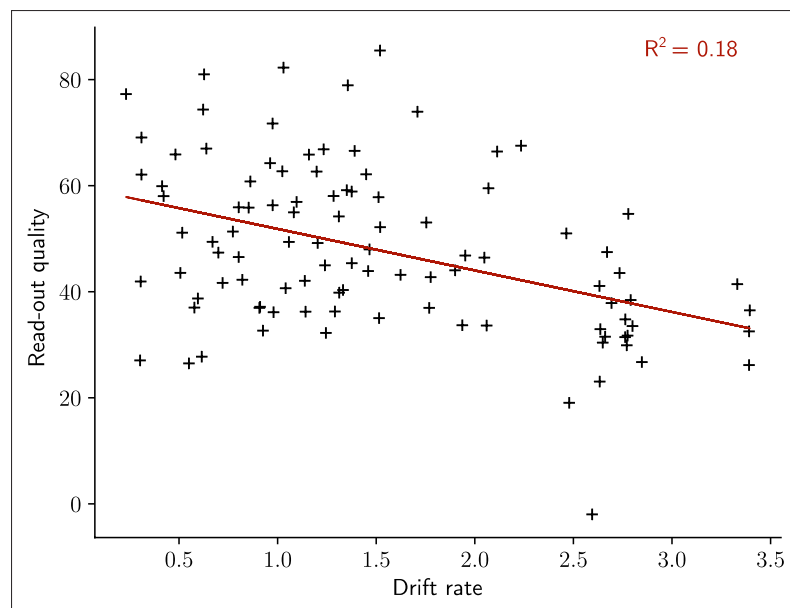


Figure 3—figure supplement 1. The quality of the read-out decreases with the rate of the drift. Read-out quality computed on the firing rate of the output neuron against the rate of the drift (Methods). Each dot shows one simulation. $n=100$ simulations.

Chapter 3 - Towards an epigenetic memory

So far, the focus of this thesis was on understanding how the dynamics of intrinsic excitability influences memory formation and maintenance. In particular, we modelled fluctuations of excitability - induced by learning or spontaneous - on the timescale of a few hours. However, learning has also been shown to be followed by intrinsic changes in how the nucleus of neurons transcript genes associated to learning-related proteins (Coda and Gräff, [2024](#)). These epigenetic changes may play a crucial role in memory dynamics, and could in principle help maintaining memories over a life time. So far however, epigenetics has largely been omitted in computational models of memory. In this last chapter, we introduced a model for epigenetics in a memory network and study the role and implication of epigenetic priming in memory formation and maintenance. This work is a result of a collaboration with Prof. Johannes Gräff (École Polytechnique Fédérale de Lausanne, Switzerland) and a preprint has been submitted to *Neuron* as a Viewpoint in October 2024.

A computational framework for epigenetic plasticity in memory. Geoffroy Delamare, Johannes Gräff*, Claudia Clopath*. 2024. Submitted to *Neuron*.

Authors contribution Conceptualisation: GD, JG, CC; Development of methodology: GD, CC; Simulations: GD; Data analysis and visualisation: GD; Writing original draft: GD; Reviewing and editing: GD, JG, CC

A computational framework for epigenetic plasticity in memory

Geoffroy Delamare¹, Johannes Gräff^{2*}, Claudia Clopath^{1*}

¹ Bioengineering Department, Imperial College London, London SW7 2AZ, United Kingdom

² Laboratory of Neuroepigenetics, Brain Mind Institute, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland

* co-last author

Abstract

Individual memories are thought to be encoded in synaptic connections forming assemblies of neurons that are specifically reactivated during memory recall. However, this widely accepted paradigm for memory cannot explain how individual ensembles are maintained over (life-) long timescales. Experimentally, learning has not only been associated with synaptic modifications among neurons, but also with epigenetic alterations of learning-related gene transcription within neurons. Although these epigenetic changes are known to be involved in all stages of memory dynamics, they have been largely omitted in computational studies. In this perspective, we advocate for the integration of epigenetics in computational models of memory. We first explore the role of epigenetic priming in the maintenance of memories across long timescales. We then investigate the implication of epigenetic modifications for memory allocation. Finally, we predict several computational advantages of including epigenetics over traditional models of synaptic memories. Overall, this paper stands as a first step towards an integration of epigenetics in computational models of memory circuits.

Introduction

Understanding memory circuits in the brain requires to answer two fundamental questions: How can memories on the one hand be rapidly encoded and on the other hand be stably maintained over timescales that can reach a lifetime? The main approach to answer these question from a neuroscience perspective has been to consider that information is encoded at the synapse level. Indeed, when experiencing an event, rapid changes among synapses give rise to specific connectivity structures among neurons. The corresponding activity patterns are reactivated when memory is retrieved, resulting in a neural code that correlates with the memory read-out [1]. Correspondingly, most computational models of memory circuits have assumed that information is encoded at the level of synapses. In particular, Hebbian learning rules have been successful to reproduce long-term potentiation (LTP) of synapses [2, 3]. Furthermore, memories can be modeled as neural ensembles formed through Hebbian associations, which are stable across time [4–7]. These ensembles are able to perform pattern separation and completion, making them particularly powerful to model memory engrams [8, 9]. Although this paradigm seems to explain well how memory is formed and retrieved, it also requires that synapses are maintained over very long timescales. For lifelong memories for example, this stability requirement implies that synapses are stable across several decades, although no experiment to date has directly proven synaptic stability over such extended timescales. This last point thus represents a fundamental stability problem: If memories are solely maintained in the synapses, how can long-lasting memories be resilient to ongoing molecular changes such as synaptic and protein turnover that happen at much shorter time scales [10, 11]?

Only few synaptic-based models of memory circuits have tackled this question so far [9, 12–14] and memory models have been largely agnostic to intrinsic changes within individual neurons following learning. In the past two decades, several experimental studies have shown that learning is associated with changes to the neuron’s epigenetic state [15–17]. In a way similar to cellular memory [16], for which epigenetic modifications in terms of posttranslational histone modifications or DNA methylation stably dictate gene expression changes during development and differentiation [18], epigenetic mechanisms have been proposed to potentially play a role in maintaining behavioral memory over very long timescales [19–21]. Indeed, epigenetic mechanisms have so far been shown to be implicated in all phases of a memory, from its encoding [22], to its consolidation [15, 23], retrieval [24] and extinction [25]. Their role has been associated with stimulus-specific increases in the transcription of genes related both to synaptic and intrinsic plasticity, thereby permitting a bidirectional dialogue between synapses and genes. However, computational models have largely omitted the role of epigenetics in memory dynamics.

Here, we provide a novel framework which includes the role of epigenetics in a computational model of memory. In a neural circuit model that incorporates recent experimental evidence, we consider that epigenetic mechanisms can regulate intrinsic neuronal properties such as their learning rate and excitability. We further integrate the concept of cognitive epigenetic priming by considering that neurons tagged during memory encoding are later more prone to transcribe excitability- and plasticity-related genes than non-tagged neurons. We first show that, after acquisition, a neural ensemble subject to molecular turnover leads to loss of memory. Then, we ask to what extent including epigenetics can lead to better maintenance of memory, as well as to memory allocation. Finally, we investigate the advantages of epigenetic regulation of excitability and synaptic plasticity over direct regulation of these factors, in particular regarding memory specificity. Together, this model stipulates that memory is not be solely encoded in the synaptic weights, but could rather be co-encoded in epigenetic patterns within the nucleus.

Results

Synaptic instability leads to loss of memory

Memories are thought to be encoded in neural ensembles, which are characterised by a strengthening of synaptic weights among neurons composing the assembly [6, 7]. However, it is not clear how such synapse-based memories are maintained across long timescales. Indeed, synapses are subject to molecular turnover, which can lead to the decay of synaptic strength, and thus to the loss of the memory [10, 26, 27].

To better understand the effect of synaptic decay over memory maintenance, we have designed a new model of memory encoding and recall using a recurrent neural network. Our network is composed of rate-based neurons that are recurrently connected. The synaptic weights follow a Hebbian rule and are subject to decay over a longer timescale (Methods). When we first stimulated our network, we observed the formation of a neural assembly: During encoding, a subset of neurons have firing rates above the active threshold, and the same subset is reactivated during recall (Fig. 1a). At the synaptic level, neurons from these subsets are recurrently connected (Fig. 1b).

We also observed that also subsequent reactivations of the ensemble induced an increase of the synaptic weights, they were not enough to maintain the ensemble across time (Fig. 1a,b). Indeed, firing rates of the tagged neurons went below the active threshold after a few reactivations. Therefore, we may now ask how it is possible to maintain memory across time despite such synaptic decay.

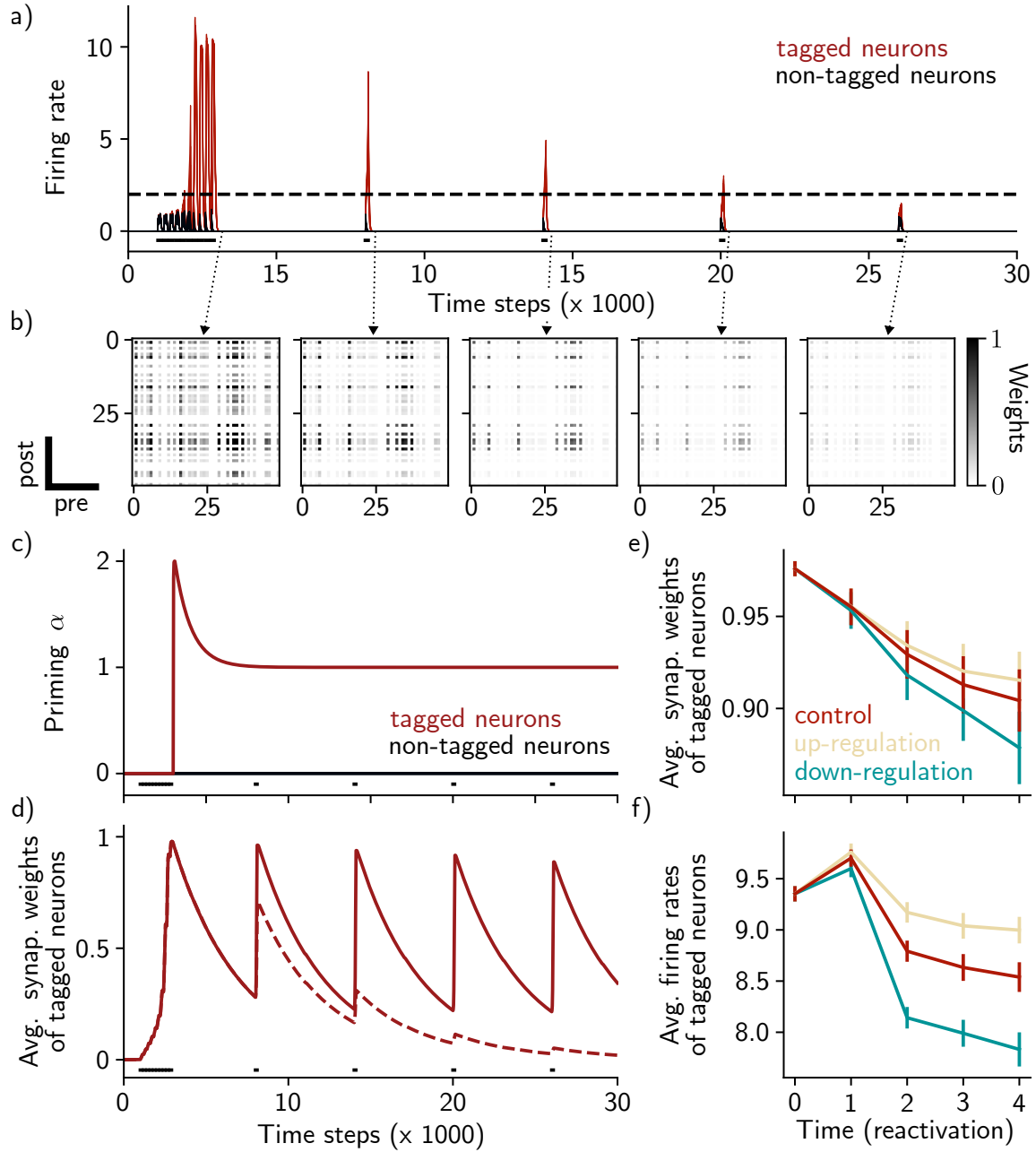


Figure 1: Epigenetic mechanisms can compensate for memory loss associated to synaptic decay. a) Firing rates of all neurons across time. Neurons tagged during encoding are shown in red, other neurons are shown in black. Black bars show stimulation of the network, the first one corresponding to encoding and the last four to recall. The dashed line corresponds to the active threshold. b) Synaptic weights right after encoding (1st panel) and right after each of the four reactivations (2nd to 5th panel). c) Dynamics of the priming variable: Tagged neurons are shown in red and non-tagged neurons in black. The priming variable of tagged neurons increases to 2 after encoding before decreasing to 1, its steady-state value. d) Averaged synaptic weights of tagged neurons across time when epigenetic modifications are considered (solid line) and when not (dashed line). Average over $n = 10$ simulations. e) and f) Recurrent synaptic weights and firing rates of tagged neurons in three different scenarios: When epigenetics is kept at control value (black), down-regulated, thereby preventing transcription (light blue), and up-regulated, thereby increasing transcription (yellow). Data is shown as mean $\pm$ s.e.m., $n = 100$ simulations.

Epigenetic priming of tagged neurons improves memory retention

We hypothesized that following encoding, intrinsic changes to the epigenome of individual neurons could help maintaining memories across much longer timescales. This hypothesis is based on recent findings suggesting that learning is followed by epigenetic changes [22]: Neurons tagged during encoding have been shown to have an altered epigenome over a timescale of at least a few days after learning, with both excitability- and plasticity-related genes being modulated by epigenetic mechanisms [24, 28]. In our model, we introduced epigenetic regulation of two neural factors: Intrinsic excitability and learning rate. During encoding, each neuron is attributed a epigenetic priming variable. If the neuron is active during encoding, this variable is set to increase before decreasing to a steady value (1c Methods), akin to what has been observed in vivo [24, 28]. Neurons in this state are now "primed" and ready to trigger transcription following neural activity, in particular during the successive reactivations of the ensemble. With this configuration, increase of intrinsic excitability and learning rate only happens if a given neuron is primed and if its firing rate is above a given threshold θ_α (Methods). We observed that the recurrent weights of neurons tagged during encoding were maintained across a longer time scale as compared to when the epigenetic priming variable was not introduced (1d). Therefore, epigenetic mechanisms greatly improved memory stability in the model.

We then asked what would be the effect of down- or up-regulating epigenetics in silico. We hypothesised that the manipulation of epigenetic factors that favour chromatin accessibility and therefore the transcription of excitability- and plasticity-related genes (such as histone acetylation, although our model remains agnostic to the specific type of epigenetic modification per se) would lead to a change in the maintainance of synaptic weights across time [21]. To test this, we varied the scale to which epigenetic priming affects the neuronal parameters: Changes in the epigenome alter the scaling factors associated to intrinsic excitability and synaptic plasticity (Methods). We found that down- and up-regulating epigenetics led to a decrease and increase in both firing rates and synaptic weights of tagged neurons (1. 1e, f), respectively.

Taken together, these results indicate that the loss of memories associated with synaptic decay in a neural circuit model can be greatly compensated when considering epigenetic regulation of internal nuclear factors. Tagged neurons during encoding are more easily reinforced during recall due to a better ability to transcribe excitability- and plasticity-related genes. In that sense, part of the memory is now encoded in the nucleus itself, and is therefore resilient to synaptic decay.

Epigenetics does not necessarily affect memory allocation

We then tested to what extent an epigenetic manipulation before learning has occurred might affect neuronal functioning, and thus tested its effect on memory allocation. Memory allocation is the process that determines which specific neurons in a neural network will become recruited to store a given memory [30]. Initially thought of as a stochastic process, such neuronal selection into the memory trace does not happen randomly, but rather depends on the individual state of a neuron at any given time. On the one hand, increased intrinsic excitability of neurons in the lateral amygdala (LA) was found to favor their allocation into the memory ensemble [31–33]; on the other hand, overexpression of the transcription factor Ca²⁺/cAMP response element-binding protein (CREB) not only instated a similar enhancement of intrinsic excitability, but also increased the chance to be selected into the memory trace [34–36].

In our model, we propose to directly test the extent to which priming a subset of neurons before memory encoding can bias these neurons for allocation. In our model, 20% of the neurons were primed just before memory encoding (Methods) such that the priming variable of these neurons is higher during memory encoding. During the last encoding stimulation, we measured the proportion of neurons that belong to the primed subset and that are tagged, *i.e.* that have had a firing rate above the active threshold during encoding. We found that the proportion of neurons both from the subset and tagged was similar to the control case, where all priming variables were kept at 0 (Fig. 2a), which indicates that memory allocation is not affected by epigenetic priming.

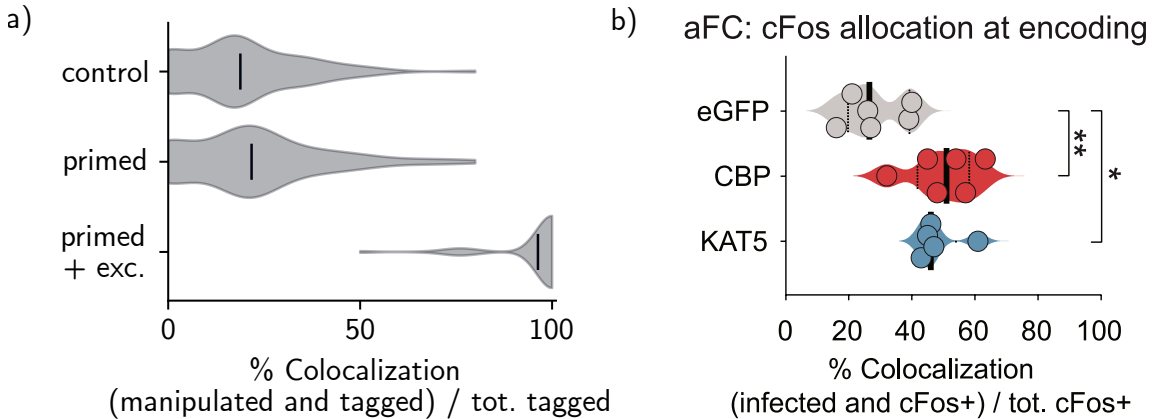


Figure 2: Primed neurons are preferentially allocated to the memory ensemble only when their excitability is concurrently increased. a) Colocalization of neurons in three different scenarios: when no neuron is primed during encoding (control), when a subset of neurons is primed (primed) and when primed neurons also have increased excitability (primed + exc.). $n = 1000$ simulations. b) Figure redrawn from Santoni et al., 2024 [29], showing that neurons with enhanced histone acetylation (mediated by the histone acetyltransferases CBP and KAT5) are preferentially allocated to the memory trace in lateral amygdala.

However, in our model, we did not observe any change in excitability prior to learning. This is because epigenetic priming was set to play a role only when neurons have a firing rate above the active threshold, which is not the case before learning here. Yet, experimentally, histone acetylation was recently found to be cell-intrinsically linked to neural excitability [29], prompting us to associate epigenetic priming with direct increases of neural excitability. When doing so, we found that primed neurons show a bias towards allocation (Fig. 2a) *i.e.* most neurons that were primed during encoding were also allocated to the assembly. This is consistent with a recent study showing that neurons with enhanced histone acetylation show increased excitability and are preferentially allocated to the memory trace in the lateral amygdala (Fig. 2b) [29]. Overall, our model provides predictions on how memory allocation can be biased when manipulating neural epigenetic states, and highlights the role of intrinsic excitability in this allocation.

Advantages of epigenetics over direct modulation of internal variables

So far, we have introduced epigenetics using a priming variable, meaning that increases in excitability and learning rate only happens with further reactivation of the neuron. In that sense, epigenetics may act as a "meta-learning" process, which is silent and has no effect while neurons firing rates remain below the activation threshold. This is in line with recent findings showing that inhibiting histone deacetylases (HDACs) increases long-term potentiation only when paired with learning and had no effect on its own [37]. Alternatively, we could expect similar memory consolidation with a simpler model, for example if the neurons learning rate and excitability were directly increased following encoding of the ensemble. Hence the following question is asked: What are the computational advantages of epigenetic priming over direct modulation of internal variables?

A first answer to that question is that, as a silent process, epigenetic priming is more energy efficient. In our model, the synapses and firing rates are not affected between reactivations, as neurons are silent during these time windows. The silent nature of such epigenetic priming is therefore better in terms of metabolic efficiency over direct regulation of intrinsic factors. A second answer may be found in the possibility that the silent nature of this process can prevent multiple memories from interfering with each other. Indeed, both experimental [38–40] and computational [6, 41] studies have shown that increased excitability can cause memory interference, or linking. Here again, because excitability of tagged neurons is not directly increased, we hypothesised that different ensembles should be reactivated and consolidated independently, with epigenetic mechanisms playing a role during the time window of reactivation.

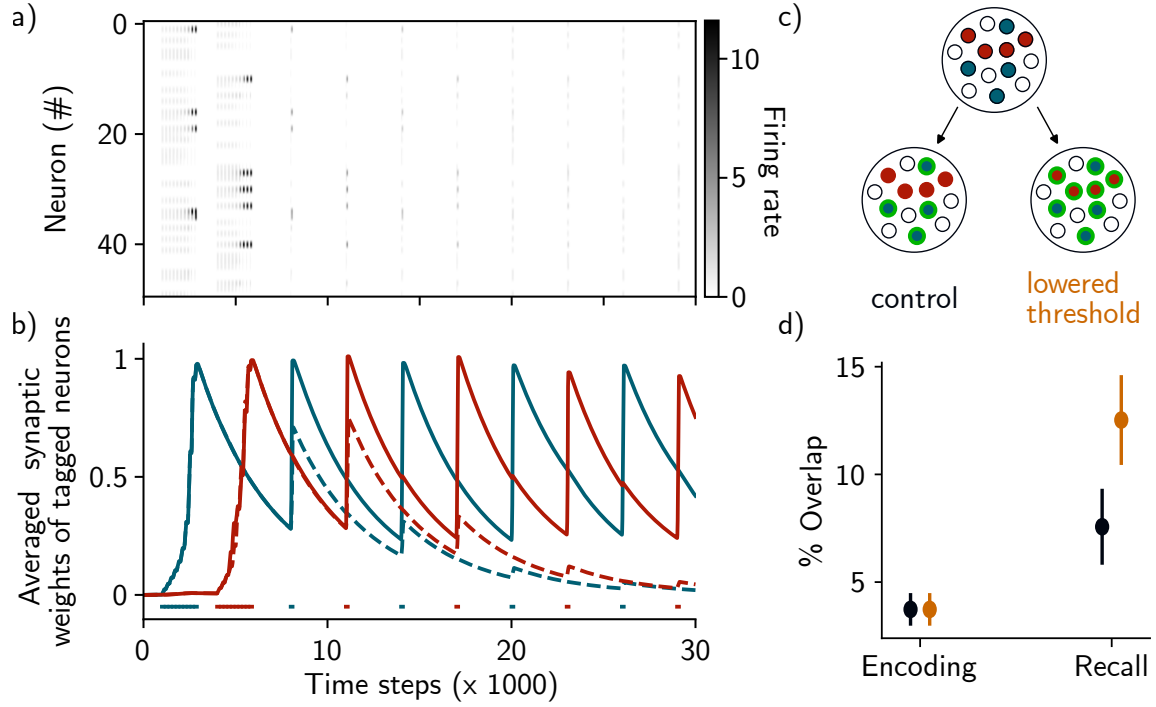


Figure 3: Epigenetic mechanisms help consolidating ensembles individually and is better at preventing memory interference. a) Firing rate of neurons across time without epigenetics. Two ensembles are formed by initial stimulation of subsets of neurons (Methods). As in the previous case with a single ensemble, firing rates of neurons from these ensembles decrease across time indicating memory loss. b) Averaged synaptic weights of tagged neurons across time when epigenetics is applied (solid line) and absent (dashed line), for neurons tagged in context A (red) and in B (blue). Average over $n = 10$ simulations. c) Epigenetics is added in the model in two different ways. Transcription of plasticity- and excitability-related proteins increases either when neurons are primed and active during recall (control) or only if they are primed regardless of further activation (lowered threshold). In our model, this corresponds to lowering the threshold for increase of excitability and learning rate. Epigenetic changes are shown in green. d) Overlap among the two ensembles in these two scenarios, during encoding and recall. Data is shown as mean $\pm$ s.e.m., $n = 100$ simulations.

To test this hypothesis, we modeled two memories, by stimulating different subsets of neurons in an alternate manner (Methods, Fig. 3a). We observed the formation of two distinct ensembles that are successively maintained through epigenetics regulation (Fig. 3b). We then measured the overlap among the ensembles, both during encoding and during the last recall in two different conditions: Either when transcription of excitability- and plasticity-related genes happens only in active neurons, or when transcription happens in all primed neurons (Methods). We found that the overlap during recall was high when transcription was not contingent on neural activity (Fig. 3c, Recall). In other words, conditioning the transcription of learning-related genes on neural activity allows for reinforcing ensembles independently, while protecting them from interfering.

Discussion

Overall, our study highlights the role of epigenetic mechanisms in a plastic recurrent neural network. Thereby, it challenges the traditional view that memories are solely encoded as a strengthening of the synaptic weights. Instead, part of the memory is encoded in the nucleus itself, through an alteration of the epigenome. These results thus serve as a springboard for further computational and theoretical predictions on how memory maintenance would be affected by epigenetic changes in memory circuits.

We have shown that epigenetic-based up-regulation of intrinsic excitability and synaptic plasticity can compensate for memory loss associated with molecular turnover. These results are consistent with recent experimental studies highlighting the role of epigenetics in memory maintenance [15, 16, 23, 42]. Nevertheless, our model generalises multiple epigenetics mechanisms, such as DNA methylation or histone acetylation, into a single variable that we name "epigenetic priming". In reality, epigenetic mechanisms are diverse and multi-faceted in nature: In addition to the long-known histone modifications of acetylation, methylation, phosphorylation, sumoylation and ubiquitination, recent studies have also identified that histones can be dopaminylated [43] or serotonylated [44], which provides an intriguing link to neurotransmitter signaling directly affecting the epigenome. Multiple such epigenetic priming variables should thus be considered in future models, either individually, or rather in combination [45], to start to fully apprehend epigenetic codes of learning and memory. Considering that every nucleus contains around 30'000 nucleosomes, each composed of eight core histone proteins, of which each contains around 30 modifiable amino acids, this poses a formidable computational challenge. Furthermore, our model remains thus far agnostic to the locus specificity of the epigenetic changes, both in terms of which genes they regulate and on which genetic element – promoter, enhancer or other – they fall. Moreover, as epigenetic mechanisms regulate the transcription of a large number of genes simultaneously, the computational challenge becomes even more interesting.

In our model, we considered epigenetic priming as stable during the entire duration of the simulation, and especially over the multiple reactivations of the ensemble. Experimentally, epigenetic priming of engram cells in mice has been shown to last for up to 5 days following learning [24], and that of excitatory neurons more generally speaking for up to 30 days post-encoding [22]. However, it could in principle last over a lifetime, as it does for epigenetic mechanisms regulating cell differentiation [16, 20], for early life stress-induced epigenetic markers [46] and for disease-associated cellular memories following inflammation in astrocytes [47]. How such stability in memory-bearing cell assemblies can be achieved remains unclear, but is a topic of great interest in the field of cellular epigenetic memories in development and differentiation [48, 49]. There, three factors have recently been identified as crucial for

the persistence of epigenetic memories: 1) There is a substantial density difference between chromatin compartments; 2) epigenetic marks spread in three dimensions thanks to the joint interplay between “reader” and “writer” enzymes; 3) the enzymes are limited in abundance relative to their histone substrates. In post-mitotic engram neurons, all three conditions are met: 1) Chromatin compartmentalization varies within engram nuclei [24, 29, 50]; both “reader” (the ones that recognize epigenetic marks) as well as “writer” (the ones that put the epigenetic marks in place) enzymes are at play in these neurons [29, 50, 51]; and these enzymes are by default limited compared to the histone proteins. Nevertheless, further work would also need to combine cell-intrinsic epigenetic mechanisms with existing models of long-term memory such as systems consolidation that explain memory maintenance over long timescales [52–54]. Indeed, as memory consolidation likely involves multiple brain areas at once, it would be particularly interesting to decipher brain region-specific epigenetic effects and whether and the extent to which they vary spatiotemporally during this process.

It is important to note that in our model synaptic recurrent weights are still needed to encode the information. As such, they highlight an intricate interplay between synapse-based and chromatin-templated plasticity. Epigenetic priming serves as a complementary mechanism that helps to maintain memories across time, and differs from a direct regulation of excitability and plasticity-related proteins. In our model, primed neurons remain in a silent mode until further reactivation. In other words, epigenetics acts as a secondary or “meta-learning” mechanism that impacts the network dynamics only for neurons that are part of an ensemble. This characteristic is based on studies showing that epigenetic priming primarily reduces the threshold for neural activity to trigger transcription [55] and does not, on its own, affect the neuron’s dynamic such as its firing [37]. As shown in this study, this feature leads to interesting results regarding memory allocation and selectivity. For example, epigenetic manipulation does not seem to bias allocation *a priori* unless it involves a direct increase in excitability.

Regarding memory selectivity, our model predicts that the silent nature of memory retention in the nucleus allows for protecting ensembles from interfering. In contrast, a direct increase of excitability- and plasticity-related proteins would lead to memory interference, as shown in the last section. This alternative scenario corresponds to experimental studies showing that learning-induced increase of excitability leads to memory linking [6, 38–40]. And although we speculate that epigenetic priming is more energetically efficient than, for example, a sustained increased excitability, it should be noted that epigenetic priming also comes with a metabolic cost [56, 57].

Finally, the current model focuses only on the memory engram paradigm. In particular, other cell

types and tasks could require more complex weight profiles than a neural assembly. Further work would also be needed to understand how epigenetic mechanisms could help maintaining more complex forms of memory, or lead to aberrant memory performance in neurological disorders such as Alzheimer’s disease, for which epigenetic aberrations have been documented [58–60]. Since the neuronal epigenome is also known to be affected by the environment [16, 20, 61] future studies should also explore how much environmental circumstances affect the epigenome, and thereby memory consolidation. Similarly to epigenetic codes laid down during cell differentiation in development, such acquired epigenetic information could in principle last for the lifetime of a cell, while being largely resilient to molecular turnover [16], and thus encode behavioral memories in stable manner.

Methods

Recurrent neural network with excitability

Our network is composed of $N = 50$ neurons, with firing rate r_i , $1 \leq i \leq N$, that follow a rate-based dynamics given by

$$\tau_r \frac{dr_i}{dt} + r_i = \text{ReLU} \left(\Delta_i^{(k)}(t) + \sum_{j=1}^N W_{ij} r_j - I + \varepsilon_i(t) \right) \quad (1)$$

where $\tau_r = 20$ is the decay time of the rates and ReLU is the rectified linear activation function. Recurrent connections $\mathbf{W}$ are all-to-all and plastic, and follow a Hebbian rule given by:

$$\frac{dW_{ij}}{dt} = \frac{r_i r_j}{\tau_i^+(t)} - \frac{W_{ij}}{\tau^-} \quad (2)$$

where i and j correspond to the pre- and post-synaptic neuron respectively. $\tau_i^+(t)$ and $\tau^- = 4000$ are the learning and the decay time constants of the weights, respectively. The dynamics of $\tau_i^+(t)$ is described in the next section. A hard bound of $[0, 1]$ was applied to these weights. Inhibition I is given by:

$$I = I_0 + I_1 \sum_{i=1}^N r_i + I_2 \sum_{i=1}^N r_i^2 \quad (3)$$

where $I_0 = 7$, $I_1 = 0.5$ and $I_2 = 0.05$. $\Delta^{(k)}(t)$ denotes the input from context $k \in \{1, 2\}$, with a dynamics explained in the protocol section below. Finally, excitability is modeled as a time-varying threshold $\varepsilon_i(t)$ of the input-output function of each neuron i , with a dynamics described in the next section.

Epigenetic priming

All neurons i are attributed a priming variable α_i which is initially set to 0. During encoding, if a neuron i reaches the firing threshold $\theta = 2$, the priming variable rapidly increases to 2 in a time scale $\tau_\alpha^+ = 10$,

for a duration of 100 time steps:

$$\frac{d\alpha_i}{dt} = (2 - \alpha_i)/\tau_\alpha^+ \quad (4)$$

Then, this priming variable decays to its steady state value of 1, in a time scale $\tau_\alpha^- = 1000$ for the rest of the simulation:

$$\frac{d\alpha_i}{dt} = (1 - \alpha_i)/\tau_\alpha^- \quad (5)$$

Finally, we assume that intrinsic excitability and learning rate are varying based on this epigenetic modification. In our model, the learning time constant of the Hebbian rule τ_i^+ and excitability ε_i^+ of neuron i are subject to the following dynamics:

$$\tau_i^+(t) = \frac{\tau_0^+}{1 + \beta_W \alpha_i(t)}, \text{ if } r_i > \theta_\alpha \quad (6)$$

$$\varepsilon_i^+(t) = \varepsilon_i^0(1 + \beta_\varepsilon \alpha_i(t)), \text{ if } r_i > \theta_\alpha \quad (7)$$

where $\tau_0^+ = 2500$ and ε_i^0 is randomly sampled from a chi-squared distribution of parameter 1 at each time step. When excitability is increased concurrently with epigenetic priming (Fig. 2a), 0.1 is added to $\varepsilon_i^+(t)$, for every primed neurons i , during memory encoding. Note that transcription only happens if neurons reach the firing rate θ_α . β_W and β_ε are scaling factors that are tuned for down- or up-regulation of epigenetics:

Parameter	Control	Down-regulation	Up-regulation
β_W	0.9	0.8	1.0
β_ε	0.9	0.8	1.0

Simulation protocol

We consider that the memory is initially encoded and later reactivated during memory recall, at different time points. The encoding stimulation consists of 10 repetitions of interval 100 time steps (ts) spaced by a inter-repetition delay of 100 ts. A random half of the neurons correspond to the first context. The second context corresponds to 95% of the other half and 5% of the neurons from the first context. When a context is presented, $\Delta_i^{(k)}(t)$ takes the value $\delta = 16$ if i belong to the corresponding context ensemble, and $\delta/10$ otherwise. The first context and second one (if any) are presented at $t = 1000$ and $t = 4000$. Recall consist of a single stimulation of duration of 100 ts, starting at $t = 8000$ and $t = 11000$ for the first and second context, respectively. Recall is repeated 4 times, with inter-repetition delay of duration of 6000 ts. The overlap between two ensembles was computed as the number of neurons being active

during presentation of both contexts, divided by the number of neurons active during the first one, It was computed during the last repetition of the encoding stimulation (encoding overlap) and during the last recall stimulation (recall overlap).

Acknowledgment

This work was supported by Wellcome Trust (200790/Z/16/Z awarded to CC), the Simons Foundation (564408 awarded to CC) and EPSRC (EP/R035806/1 awarded to CC). Research in the lab of Johannes Gräff is sponsored by the Synapsis Foundation (grant 2022-PI01); the Secrétariat d’Etat à la formation, à la recherche et à l’innovation (SEFRI M822.00049); the Swiss National Science Foundation (310030_219342; 310030_197752) and the Carigest Foundation.

References

1. Josselyn, S. A. & Tonegawa, S. Memory engrams: Recalling the past and imagining the future. *Science* **367**, eaaw4325. doi:10.1126/science.aaw4325 (Jan. 2020).
2. Hebb, D. O. *The organization of behavior: a neuropsychological theory* (L. Erlbaum Associates, Mahwah, N.J., 1949).
3. Bliss, T. V. P. & Collingridge, G. L. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **361**, 31–39. doi:10.1038/361031a0 (Jan. 1993).
4. Litwin-Kumar, A. & Doiron, B. Formation and maintenance of neuronal assemblies through synaptic plasticity. *Nature Communications* **5**, 5319. doi:10.1038/ncomms6319 (Dec. 2014).
5. Zenke, F., Agnes, E. J. & Gerstner, W. Diverse synaptic plasticity mechanisms orchestrated to form and retrieve memories in spiking neural networks. *Nature Communications* **6**, 6922. doi:10.1038/ncomms7922 (Nov. 2015).
6. Delamare, G., Tomé, D. F. & Clopath, C. Intrinsic Neural Excitability Biases Allocation and Overlap of Memory Engrams. *Journal of Neuroscience* **44**. doi:10.1523/JNEUROSCI.0846-23.2024 (May 2024).
7. Manz, P. & Memmesheimer, R.-M. Purely STDP-based assembly dynamics: Stability, learning, overlaps, drift and aging. *PLOS Computational Biology* **19**, e1011006. doi:10.1371/journal.pcbi.1011006 (Apr. 2023).
8. Spalla, D., Cornacchia, I. M. & Treves, A. Continuous attractors for dynamic memories. *eLife* **10**, e69499. doi:10.7554/eLife.69499 (Sept. 2021).

9. Gallinaro, J. V., Gašparović, N. & Rotter, S. Homeostatic control of synaptic rewiring in recurrent networks induces the formation of stable memory engrams. *PLOS Computational Biology* **18**, e1009836. doi:10.1371/journal.pcbi.1009836 (Feb. 2022).
10. Crick, F. Neurobiology: Memory and molecular turnover. *Nature* **312**, 101–101. doi:10.1038/312101a0 (Nov. 1984).
11. Albo, Z. & Gräff, J. The mysteries of remote memory. *Philosophical Transactions of the Royal Society B: Biological Sciences* **373**, 20170029. doi:10.1098/rstb.2017.0029 (Jan. 2018).
12. Fauth, M., Wörgötter, F. & Tetzlaff, C. Formation and Maintenance of Robust Long-Term Information Storage in the Presence of Synaptic Turnover. *PLOS Computational Biology* **11**, e1004684. doi:10.1371/journal.pcbi.1004684 (Dec. 2015).
13. Fauth, M. J. & van Rossum, M. C. Self-organized reactivation maintains and reinforces memories despite synaptic turnover. *eLife* **8** (eds Skinner, F. K. & Marder, E.) e43717. doi:10.7554/eLife.43717 (May 2019).
14. Lisman, J. E. A mechanism for memory storage insensitive to molecular turnover: a bistable autophosphorylating kinase. *Proceedings of the National Academy of Sciences* **82**, 3055–3057. doi:10.1073/pnas.82.9.3055 (May 1985).
15. Jarome, T. J. & Lubin, F. D. Epigenetic mechanisms of memory formation and reconsolidation. *Neurobiology of Learning and Memory. MCCA 2014* **115**, 116–127. doi:10.1016/j.nlm.2014.08.002 (Nov. 2014).
16. Coda, D. M. & Gräff, J. From cellular to fear memory: An epigenetic toolbox to remember. *Current Opinion in Neurobiology* **84**, 102829. doi:10.1016/j.conb.2023.102829 (Feb. 2024).
17. Campbell, R. R. & Wood, M. A. How the epigenome integrates information and reshapes the synapse. *Nature Reviews Neuroscience* **20**, 133–147. doi:10.1038/s41583-019-0121-9 (Mar. 2019).
18. Ronan, J. L., Wu, W. & Crabtree, G. R. From neural development to cognition: unexpected roles for chromatin. *Nature Reviews Genetics* **14**, 347–359. doi:10.1038/nrg3413 (May 2013).
19. Holliday, R. Is there an Epigenetic Component in Long-term Memory? *Journal of Theoretical Biology* **200**, 339–341. doi:10.1006/jtbi.1999.0995 (Oct. 1999).
20. Levenson, J. M. & Sweatt, J. D. Epigenetic mechanisms in memory formation. *Nature Reviews Neuroscience* **6**, 108–118. doi:10.1038/nrn1604 (Feb. 2005).
21. Gräff, J. & Tsai, L.-H. Histone acetylation: molecular mnemonics on the chromatin. *Nature Reviews. Neuroscience* **14**, 97–111. doi:10.1038/nrn3427 (Feb. 2013).

22. Halder, R. *et al.* DNA methylation changes in plasticity genes accompany the formation and maintenance of memory. *Nature Neuroscience* **19**, 102–110. doi:10.1038/nn.4194 (Jan. 2016).
23. Gulmez Karaca, K. *et al.* Neuronal ensemble-specific DNA methylation strengthens engram stability. *Nature Communications* **11**, 639. doi:10.1038/s41467-020-14498-4 (Jan. 2020).
24. Marco, A. *et al.* Mapping the epigenomic and transcriptomic interplay during memory formation and recall in the hippocampal engram ensemble. *Nature Neuroscience* **23**, 1606–1617. doi:10.1038/s41593-020-00717-0 (Dec. 2020).
25. Rudenko, A. *et al.* Tet1 Is Critical for Neuronal Activity-Regulated Gene Expression and Memory Extinction. *Neuron* **79**, 1109–1122. doi:10.1016/j.neuron.2013.08.003 (Sept. 2013).
26. Ryan, T. J. & Frankland, P. W. Forgetting as a form of adaptive engram cell plasticity. *Nature Reviews Neuroscience* **23**, 173–186. doi:10.1038/s41583-021-00548-3 (Mar. 2022).
27. Josselyn, S. A. & Frankland, P. W. Memory Allocation: Mechanisms and Function. *Annual Review of Neuroscience* **41**, 389–413. doi:10.1146/annurev-neuro-080317-061956 (July 2018).
28. Fernandez-Albert, J. *et al.* Immediate and deferred epigenomic signatures of in vivo neuronal activation in mouse hippocampus. *Nature Neuroscience* **22**, 1718–1730. doi:10.1038/s41593-019-0476-2 (Oct. 2019).
29. Santoni, G. *et al.* Chromatin plasticity predetermines neuronal eligibility for memory trace formation. *Science* **385**, eadg9982. doi:10.1126/science.adg9982 (July 2024).
30. Rogerson, T. *et al.* Synaptic tagging during memory allocation. *Nature Reviews Neuroscience* **15**, 157–169. doi:10.1038/nrn3667 (Mar. 2014).
31. Lee, D., Lin, B.-J. & Lee, A. K. Hippocampal Place Fields Emerge upon Single-Cell Manipulation of Excitability During Behavior. *Science* **337**, 849–853. doi:10.1126/science.1221489 (Aug. 2012).
32. Yiu, A. P. *et al.* Neurons Are Recruited to a Memory Trace Based on Relative Neuronal Excitability Immediately before Training. *Neuron* **83**, 722–735. doi:10.1016/j.neuron.2014.07.017 (Aug. 2014).
33. Mocle, A. J. *et al.* Excitability mediates allocation of pre-configured ensembles to a hippocampal engram supporting contextual conditioned threat in mice. *Neuron* **112**, 1487–1497.e6. doi:10.1016/j.neuron.2024.02.007 (May 2024).
34. Han, J.-H. *et al.* Neuronal Competition and Selection During Memory Formation. *Science* **316**, 457–460. doi:10.1126/science.1139438 (Apr. 2007).

35. Park, S. *et al.* Neuronal Allocation to a Hippocampal Engram. *Neuropsychopharmacology* **41**, 2987–2993. doi:10.1038/npp.2016.73 (Dec. 2016).
36. Sano, Y. *et al.* CREB Regulates Memory Allocation in the Insular Cortex. *Current Biology* **24**, 2833–2837. doi:10.1016/j.cub.2014.10.018 (Dec. 2014).
37. Burns, A. M. *et al.* The HDAC inhibitor CI-994 acts as a molecular memory aid by facilitating synaptic and intracellular communication after learning. *Proceedings of the National Academy of Sciences* **119**, e2116797119. doi:10.1073/pnas.2116797119 (May 2022).
38. Rashid, A. J. *et al.* Competition between engrams influences fear memory formation and recall. *Science* **353**, 383–387. doi:10.1126/science.aaf0594 (July 2016).
39. Cai, D. J. *et al.* A shared neural ensemble links distinct contextual memories encoded close in time. *Nature* **534**, 115–118. doi:10.1038/nature17955 (June 2016).
40. Yokose, J. *et al.* Overlapping memory trace indispensable for linking, but not recalling, individual memories. *Science* **355**, 398–403. doi:10.1126/science.aa12690 (Jan. 2017).
41. Kastellakis, G., Silva, A. J. & Poirazi, P. Linking Memories across Time via Neuronal and Dendritic Overlaps in Model Neurons with Active Dendrites. *Cell Reports* **17**, 1491–1504. doi:10.1016/j.celrep.2016.10.015 (Nov. 2016).
42. Zovkic, I. B., Guzman-Karlsson, M. C. & Sweatt, J. D. Epigenetic regulation of memory formation and maintenance. *Learning & Memory* **20**, 61–74. doi:10.1101/lm.026575.112 (Feb. 2013).
43. Lepack, A. E. *et al.* Dopaminylation of histone H3 in ventral tegmental area regulates cocaine seeking. *Science* **368**, 197–201. doi:10.1126/science.aaw8806 (Apr. 2020).
44. Al-Kachak, A. *et al.* Histone serotonylation in dorsal raphe nucleus contributes to stress- and antidepressant-mediated gene expression and behavior. *Nature Communications* **15**, 5042. doi:10.1038/s41467-024-49336-4 (June 2024).
45. Gräff, J., Kim, D., Dobbin, M. M. & Tsai, L.-H. Epigenetic Regulation of Gene Expression in Physiological and Pathological Brain Processes. *Physiological Reviews* **91**, 603–649. doi:10.1152/physrev.00012.2010 (Apr. 2011).
46. Weaver, I. C. G. *et al.* Epigenetic programming by maternal behavior. *Nature Neuroscience* **7**, 847–854. doi:10.1038/nn1276 (Aug. 2004).
47. Lee, H.-G. *et al.* Disease-associated astrocyte epigenetic memory promotes CNS pathology. *Nature* **627**, 865–872. doi:10.1038/s41586-024-07187-5 (Mar. 2024).
48. Palacios, S. *et al.* Analog epigenetic cell memory by graded DNA methylation Apr. 2024. doi:10.1101/2024.02.13.580200.

49. Owen, J. A., Osmanović, D. & Mirny, L. Design principles of 3D epigenetic memory systems. *Science* **382**, eadg3053. doi:10.1126/science.adg3053 (Nov. 2023).
50. Odell, S. C. *et al.* Epigenomically Bistable Regions across Neuron-Specific Genes Govern Neuron Eligibility to a Coding Ensemble in the Hippocampus. *Cell Reports* **31**. doi:10.1016/j.celrep.2020.107789 (June 2020).
51. Gulmez Karaca, K., Kupke, J. & Oliveira, A. M. Molecular and cellular mechanisms of engram allocation and maintenance. *Brain Research Bulletin* **170**, 274–282. doi:10.1016/j.brainresbull.2021.02.019 (May 2021).
52. Lee, J.-H., Kim, W. B., Park, E. H. & Cho, J.-H. Neocortical synaptic engrams for remote contextual memories. *Nature Neuroscience* **26**, 259–273. doi:10.1038/s41593-022-01223-1 (Feb. 2023).
53. Tomé, D. F., Sadeh, S. & Clopath, C. Coordinated hippocampal-thalamic-cortical communication crucial for engram dynamics underneath systems consolidation. *Nature Communications* **13**, 840. doi:10.1038/s41467-022-28339-z (Feb. 2022).
54. Tonegawa, S., Morrissey, M. D. & Kitamura, T. The role of engram cells in the systems consolidation of memory. *Nature Reviews Neuroscience* **19**, 485–498. doi:10.1038/s41583-018-0031-2 (Aug. 2018).
55. Burns, A. M. & Gräff, J. Cognitive epigenetic priming: leveraging histone acetylation for memory amelioration. *Current Opinion in Neurobiology. Neurobiology of Learning and Plasticity* **67**, 75–84. doi:10.1016/j.conb.2020.08.011 (Apr. 2021).
56. Bradshaw, P. C. Acetyl-CoA Metabolism and Histone Acetylation in the Regulation of Aging and Lifespan. *Antioxidants* **10**, 572. doi:10.3390/antiox10040572 (Apr. 2021).
57. Mews, P. *et al.* Alcohol metabolism contributes to brain histone acetylation. *Nature* **574**, 717–721. doi:10.1038/s41586-019-1700-7 (Oct. 2019).
58. Gräff, J. *et al.* An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature* **483**, 222–226. doi:10.1038/nature10849 (Mar. 2012).
59. Xiong, X. *et al.* Epigenomic dissection of Alzheimer's disease pinpoints causal variants and reveals epigenome erosion. *Cell* **186**, 4422–4437.e21. doi:10.1016/j.cell.2023.08.040 (Sept. 2023).
60. De Jager, P. L. *et al.* Alzheimer's disease: early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci. *Nature Neuroscience* **17**, 1156–1163. doi:10.1038/nn.3786 (Sept. 2014).

61. Fischer, A., Sananbenesi, F., Wang, X., Dobbin, M. & Tsai, L.-H. Recovery of learning and memory is associated with chromatin remodelling. *Nature* **447**, 178–182. doi:10.1038/nature05772 (May 2007).

Conclusion

Summary

This thesis has highlighted the role of intrinsic neural properties in memory circuits under three different angles: memory allocation and linking, representational drift and epigenetics. It showed the importance of considering the intrinsic state of individual neurons when studying memory dynamics on long timescales. Experimental studies are often limited by the challenge to record neural activity over timescales of several days, which is a major limitation in memory research. Here, our computational approach provides key predictions for experimental researchers wishing to understand better how intrinsic neural properties affect memory dynamics. The first work predicts mechanisms underlying the interplay between intrinsic excitability and synaptic plasticity in memory formation. In particular, the proposed model explains the role of excitability in memory linking and allocation, consistently with past experimental works. The results of this initial work has then been extended in the second study, which shows how intrinsic excitability can be a motor for representational drift. This work not only gives a possible answer to the question of how drift happens, but also to the question of why it happens. Indeed, our model predicts how drifting ensembles can allow for time-stamping memories, and gives the conditions for this to happen. In the last part of this thesis, a new of epigenetics in a memory circuit was proposed. This work predicts the role of epigenetic priming in maintaining memories over extended timescales, in a first step towards the integration of epigenetics in computational models of memory.

Discussion about the model

In this thesis, we chose to investigate the role of neural intrinsic parameters in memory formation and maintenance using a computational approach based on realistic biological features. For example, the frequency of the stimulation could correspond to the frequency of theta waves in the hippocampus, and the firing rate are in biologically realistic ranges (Santos et al., 2018). However, it is important to keep in mind that a model cannot be considered as ground truth, and that it may not reflect the actual neuron circuitry of the brain. In fact, modelling works are crucial to understand the general mechanisms underlying the observed experimental results. The abstraction effort allows to extract general principles and bridge the gap between different corpus of the experimental literature. For example, although both related to memory, engrams and place cells are often studied distinct from each other. However, the mechanisms underlying the observed phenomena might be similar. The work developed in this thesis thus takes a step towards a possible integration of these different lines of research.

This thesis uses on a recurrent neural network, where individual memories are modeled as attractors. In this framework, the specific profile of the synaptic weights does not matter much as long as the neurons are reactivated. This was sufficient to model works from the engram literature, that uses the very robust fear conditioning paradigm for studying memories. This stereotypical behavioral task has the advantage of being robust across experiments but is very different from everyday memories. The same argument can be used for place cells, which are found during simple exploration of an environment. In reality, memories probably take the form of complex neural and synaptic representations. The level of abstraction of this model allows for generalising different behavioral paradigms and brain regions, with the hope to bridge the gap between different corpora of the experimental literature. Further works would be needed to extend these results to more complex behavioral tasks, that could require more biological details.

Following the previous point, the architecture of the network developed throughout the thesis is abstract and may not reflect the real architecture of the neural populations. Although recurrent connections and attractor dynamics have been found in brain regions like the cortex or the hippocampal CA3, the architecture of regions such as the hippocampal CA1 or the amygdala is different. In the second chapter, we tested the effect of using a sparse synaptic connectivity instead of all-to-all synapses. We found that the results were similar, suggesting that the exact architecture of the network does not significantly impact the results, at least in that case. Alternatively, a feed-forward model could also have been developed. In the first chapter for example, input synapses from the feed-forward region could have been considered plastic with the recurrent synapses kept fixed. Overall, we argue that our model provides a general understanding of the concepts, independently of the detailed architecture of the network.

In hand with the two previous discussion points, the rate-based nature of the model abstracts the actual spiking dynamics of the neurons. Other computational approaches could use spiking models to explore the problems brought in this thesis and bring complementary predictions regarding the role of intrinsic neural properties in memory dynamics (Tomé, Sadeh, and Clopath, [2022](#); Zenke, Agnes, and Gerstner, [2015](#); Kastellakis, Silva, and Poirazi, [2016](#)). In the same line, we did not consider the activity of dendrites which have previously been used to model memory linking (Kastellakis, Silva, and Poirazi, [2016](#)). Our rate-based model is less constraint to actual biological values, which limits its predictive power, but allows for a more fundamental and easier understanding of the concepts discussed in this thesis.

Future directions

Further work should include the role of neuromodulators which has not been considered here. Dopamine has been shown to play a crucial role in memory linking (Chowdhury et al., 2022). In particular, the Locus Coeruleus dopaminergic cells projecting to dCA1 are required for memory linking but not memory formation (Chowdhury et al., 2022). The mechanism underlying linking has been shown to be associated to increase in excitability, mediated by dopamine (Chowdhury et al., 2022). In that sense, the model developed in the first chapter could be adapted to include dopamine-related increase in excitability, in combination to the CREB dynamics. Considering dopamine could also explain recent results showing its role in memory reconsolidation (Gonzalez et al., 2021), although this has not been studied here. Finally, recent studies showed that dopamine and serotonin play a role in the epigenetic regulation of gene expression: histones can be dopaminylated (Lepack et al., 2020) or serotonylated (Al-Kachak et al., 2024). These recent works suggest that neuromodulators not only directly modulate neural activity but also alter the transcription of genes that could be related to learning and memory.

As discussed throughout the thesis, memory ensembles undergo continual changes (Mau, Hasselmo, and Cai, 2020), but some specificities of memory dynamics have not been considered here. Although we focused on how memories evolve across long timescales, we did not consider how memories adapt to new sensory inputs. The first chapter partially tackles this question, by modelling how old memories are linked to new ones. In this case however, the relation between the two ensembles is purely due to the temporal proximity between the memories. Conversely, memory reconsolidation suggests that old ensembles can be remodelled to adapt to new situations (Fernández, Boccia, and Pedreira, 2016). Such comparative computation could happen directly in the hippocampal CA1, which receives inputs from the Entorhinal Cortex (sensory layer) and the CA3 (memory layer) (Duncan et al., 2012). Again, excitability dynamics

in these regions could influence how new memories are integrated on previous ones. A related question is to understand the role of excitability in pattern completion and separation, which has not been explored here. In particular, a recent study (Pignatelli et al., 2019) showed that increase in excitability in the hippocampal Dentate Gyrus helps performing both pattern completion and separation. This result might be explain by a better accessibility of the engram induced by increased excitability, in turn leading to a better comparison between the memory engram and the sensory inputs. Finally, forgetting has also been associated to a silencing, but not necessarily disappearance, of memory engrams (Ryan and Frankland, 2022).

The role of neurogenesis - process through which neurons are created during adulthood (Dupret et al., 2008)- would be relevant in this thesis for two reasons. First, adult-born neurons *i.e.* newly created neurons integrating the network, are known to have a higher excitability than other neurons (Schmidt-Hieber, Jonas, and Bischofberger, 2004). Recent works suggest that this intrinsic difference between young and old neurons in the dentate gyrus helps to perform both pattern separation and completion (Tran et al., 2022; Nakashiba et al., 2012). Furthermore, neural stem cells are known to undergo epigenetic changes (Zhao et al., 2024). One can speculate that such changes are transmitted to all new neurons born via neurogenesis, therefore impacting the network as a whole even during adulthood. Future works - both computational and experimental - could therefore investigate further the intrinsic properties of new-born neurons and the implications for the neural computation.

The interaction between multiple brain regions has not been considered here. While our model can be generalised to different brain regions involved in memorisation, such as the amygdala, the hippocampus or the prefrontal cortex, it does not capture any brain-wide interactions. Recent works have shown that interactions between basolateral amygdala and insular cortex coordinate memory allocation in these regions (Lavi et al., 2023), suggesting that brain-wide communications need to be considered on top

of excitability when studying memory allocation. Other lines of work suggest that long-term memories are maintained through interactions between the hippocampus and the neocortex, in a process known as systems consolidation (Tomé, Sadeh, and Clopath, 2022; Lee et al., 2023). The work presented in this thesis could be extended to several regions, to explore how overlapping and drifting memory ensembles evolve across systems consolidation or through other brain-wide interactions.

Finally, this work provides a better understanding of the basic mechanisms underlying memory in the healthy brain. In the future, a more comprehensive computational model of memory could allow researchers to identify variations across individuals, and especially among healthy and unhealthy brains. Eventually, this could support the development of diagnosis and cure for brain diseases associated to memory, such as Alzheimer’s, dementia or Post Traumatic Stress Disorder (PTSD).

References

- Santos, Vítor Lopes-dos et al. (Nov. 2018). “Parsing Hippocampal Theta Oscillations by Nested Spectral Components during Spatial Exploration and Memory-Guided Behavior”. In: *Neuron* 100.4, 940–952.e7. DOI: [10.1016/j.neuron.2018.09.031](https://doi.org/10.1016/j.neuron.2018.09.031).
- Tomé, Douglas Feitosa, Sadra Sadeh, and Claudia Clopath (Feb. 2022). “Coordinated hippocampal-thalamic-cortical communication crucial for engram dynamics underneath systems consolidation”. In: *Nature Communications* 13.1, p. 840. DOI: [10.1038/s41467-022-28339-z](https://doi.org/10.1038/s41467-022-28339-z).
- Zenke, Friedemann, Everton J. Agnes, and Wulfram Gerstner (Nov. 2015). “Diverse synaptic plasticity mechanisms orchestrated to form and retrieve memories in spiking neural networks”. In: *Nature Communications* 6.1, p. 6922. DOI: [10.1038/ncomms7922](https://doi.org/10.1038/ncomms7922).
- Kastellakis, George, Alcino J. Silva, and Panayiota Poirazi (Nov. 2016). “Linking Memories across Time via Neuronal and Dendritic Overlaps in Model Neurons with Active

- Dendrites”. In: *Cell Reports* 17.6, pp. 1491–1504. DOI: [10.1016/j.celrep.2016.10.015](https://doi.org/10.1016/j.celrep.2016.10.015).
- Chowdhury, Ananya et al. (Aug. 2022). “A locus coeruleus-dorsal CA1 dopaminergic circuit modulates memory linking”. In: *Neuron*. DOI: [10.1016/j.neuron.2022.08.001](https://doi.org/10.1016/j.neuron.2022.08.001).
- Gonzalez, María Carolina et al. (July 2021). “Dopamine controls whether new declarative information updates reactivated memories through reconsolidation”. In: *Proceedings of the National Academy of Sciences* 118.29, e2025275118. DOI: [10.1073/pnas.2025275118](https://doi.org/10.1073/pnas.2025275118).
- Lepack, Ashley E. et al. (Apr. 2020). “Dopaminylation of histone H3 in ventral tegmental area regulates cocaine seeking”. In: *Science* 368.6487, pp. 197–201. DOI: [10.1126/science.aaw8806](https://doi.org/10.1126/science.aaw8806).
- Al-Kachak, Amni et al. (June 2024). “Histone serotonylation in dorsal raphe nucleus contributes to stress- and antidepressant-mediated gene expression and behavior”. In: *Nature Communications* 15.1, p. 5042. DOI: [10.1038/s41467-024-49336-4](https://doi.org/10.1038/s41467-024-49336-4).
- Mau, William, Michael E Hasselmo, and Denise J Cai (Dec. 2020). “The brain in motion: How ensemble fluidity drives memory-updating and flexibility”. In: *eLife* 9, e63550. DOI: [10.7554/eLife.63550](https://doi.org/10.7554/eLife.63550).
- Fernández, Rodrigo S., Mariano M. Boccia, and María E. Pedreira (Sept. 2016). “The fate of memory: Reconsolidation and the case of Prediction Error”. In: *Neuroscience & Biobehavioral Reviews* 68, pp. 423–441. DOI: [10.1016/j.neubiorev.2016.06.004](https://doi.org/10.1016/j.neubiorev.2016.06.004).
- Duncan, Katherine et al. (2012). “Evidence for area CA1 as a match/mismatch detector: A high-resolution fMRI study of the human hippocampus”. In: *Hippocampus* 22.3, pp. 389–398. DOI: [10.1002/hipo.20933](https://doi.org/10.1002/hipo.20933).
- Pignatelli, Michele et al. (Jan. 2019). “Engram Cell Excitability State Determines the Efficacy of Memory Retrieval”. In: *Neuron* 101.2, 274–284.e5. DOI: [10.1016/j.neuron.2018.11.029](https://doi.org/10.1016/j.neuron.2018.11.029).

- Ryan, Tomás J. and Paul W. Frankland (Mar. 2022). “Forgetting as a form of adaptive engram cell plasticity”. In: *Nature Reviews Neuroscience* 23.3, pp. 173–186. DOI: [10.1038/s41583-021-00548-3](https://doi.org/10.1038/s41583-021-00548-3).
- Dupret, David et al. (Apr. 2008). “Spatial Relational Memory Requires Hippocampal Adult Neurogenesis”. In: *PLOS ONE* 3.4, e1959. DOI: [10.1371/journal.pone.0001959](https://doi.org/10.1371/journal.pone.0001959).
- Schmidt-Hieber, Christoph, Peter Jonas, and Josef Bischofberger (May 2004). “Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus”. In: *Nature* 429.6988, pp. 184–187. DOI: [10.1038/nature02553](https://doi.org/10.1038/nature02553).
- Tran, Lina M. et al. (Nov. 2022). “Adult neurogenesis acts as a neural regularizer”. In: *Proceedings of the National Academy of Sciences* 119.45, e2206704119. DOI: [10.1073/pnas.2206704119](https://doi.org/10.1073/pnas.2206704119).
- Nakashiba, Toshiaki et al. (Mar. 2012). “Young Dentate Granule Cells Mediate Pattern Separation, whereas Old Granule Cells Facilitate Pattern Completion”. In: *Cell* 149.1, pp. 188–201. DOI: [10.1016/j.cell.2012.01.046](https://doi.org/10.1016/j.cell.2012.01.046).
- Zhao, Ting et al. (July 2024). “Epigenetic maintenance of adult neural stem cell quiescence in the mouse hippocampus via Setd1a”. In: *Nature Communications* 15.1, p. 5674. DOI: [10.1038/s41467-024-50010-y](https://doi.org/10.1038/s41467-024-50010-y).
- Lavi, Ayal et al. (Feb. 2023). “Local memory allocation recruits memory ensembles across brain regions”. In: *Neuron* 111.4, 470–480.e5. DOI: [10.1016/j.neuron.2022.11.018](https://doi.org/10.1016/j.neuron.2022.11.018).
- Lee, Ji-Hye et al. (Feb. 2023). “Neocortical synaptic engrams for remote contextual memories”. In: *Nature Neuroscience* 26.2, pp. 259–273. DOI: [10.1038/s41593-022-01223-1](https://doi.org/10.1038/s41593-022-01223-1).