A Theoretical Memory Molecule Model of Long-Term Memory Storage and Retrieval

Author: Dr Derek Stefaniw

Abstract

The study of memory is one of the most intensively studied areas of neuroscience. Many models of memory have been proposed. However, few of the previous models of long-term memory have proposed very detailed mechanisms of memory creation, storage and retrieval. Furthermore, very few models propose a role for astrocytes in long-term memory. To bridge these gaps in knowledge, the author has proposed a comprehensive theoretical memory molecule model of long-term memory whereby all types of memory are stored in a similar manner in memory molecules located in discrete memory modules. Each memory molecule can store one elementary unit of memory in binary form based on the conformation of the memory molecule. A novel memory read/write mechanism has been proposed to store and retrieve memories. The model emphasises the essential role of astrocytes in long-term potentiation; creating, supporting, and activating neural circuitry; and facilitating long-term memory. The model can provide possible explanations for the results of several memory studies, and the causes of some neurological conditions such as Alzheimer's Disease.

Keywords: astrocytes, long-term memory, memory stores, memory molecules, prions

1. Introduction

Short-term memory and working memory stores pass some recently stored memories to the hippocampal and other neocortical memory stores, especially if the memories are memorable or learning rehearsal occurs, to become long-term memories (Lisman et al., 2017). This process is termed memory consolidation (Dudai et al., 2015). Over time, the stored memories are transferred to dendritic spines in a various cortical memory stores for permanent storage (Squire et al., 2015). Many models of long-term memory have been proposed, but few of the models propose detailed mechanisms of memory creation, storage and retrieval. In addition, few models have proposed a role for astrocytes in long-term memory. The model proposed in this article is a comprehensive theoretical memory molecule model of long-term memory in which astrocytes have a critical role in facilitating long-term potentiation; creating, supporting and activating neural circuitry; and facilitating long-term memory.

A brief review of some models of memory is presented in the next section to enable a comparison of the proposed model of memory with previous models.

2. A review of some models of memory

Models of memory can be classified as either association/connectionist (A/C) or computational/representational (C/R) conceptions (Langille & Gallistel, 2020).

2.1 Computational/representational models of memory

Some C/R models of memory posit that memories are stored in discrete molecules that can store information residing alone or in molecular structures located in neuronal plasma membranes or intracellularly. Memories are created by biochemical or biophysical operations on information-storing models (Gershman, 2024). Other C/R models of memory posit that each long-term memory is encoded in the epigenome of neurones.

Model 1 (C/R)

Lisman (1985) proposed that a bistable kinase chemical switch could store one elementary unit of memory indefinitely despite protein turnover. His initial model posits that a kinase molecule (K_1) can exist in an inactive state or an active state. Neuronal stimulation activates a different kinase (K_2) which in turn activates kinase K_1 by phosphorylation. He rejected this model because he argued that maintenance of the on state was too power hungry and too sensitive to perturbations of cellular concentrations. His second model posits that a less power hungry and more stable bistable kinase chemical switch can be formed by phosphorylation of an autocatalytic phosphatase to produce an autocatalytic

kinase. He proposed that activated kinase reacts with other biological molecules to modify the properties of a neurone such that the activity of the neurone in its neural circuitry is altered.

Lisman's model has several strengths. His models are based on powerful mathematical modelling, memory storage which is stable indefinitely despite rapid molecular turnover, and switches which are localised so they act independently of switches located in other dendritic spines. In addition, the models are simple with many potential applications in neurobiology. However, Lisman's model has several weaknesses. He did not name a possible kinase central to his models. His description for the mechanism of action of activated kinase is not detailed. He did not identify possible substrates acted on by activated kinase, the cellular properties modified by such actions, and the possible behavioural characteristics of the neurone/neuronal network.

Lisman did not emphasise the importance of his ideas. Chemical bistable on-off switches may be involved in myriads of biological systems. For example, bistable chemical switches could isolate memories stored in subcellular domains, such as spines, until memory retrieval takes place to prevent memory corruption and false signalling. Bistable switches in neurones can readily permit assembly and disassembly of neurones in unique neural circuitry. Furthermore, clusters of switches could potentially store memory stably in binary form. Switches may lie at the heart of mental cognition.

Model 2 (C/R)

Other researchers have advanced Lisman's ideas. For example, Nicoll and Schulman (2023) argued that the bistable autophosphorylated kinase posited in Lisman's second model includes calmodulin-dependent protein kinase II (CaMKII). In this model, long-term potentiation (LTP) increases the rate of calcium ion entry through synaptic MMDA receptors. The increased levels of intracellular calcium ions induces autophosphorylation of CaMKII to produce the activated form of CaMKII. Activated CaMKII migrates to the postsynaptic density (PSD) where it binds to GluN2B. The complex induces the PSD to rearrange structurally. CaMKII-GluN2B undergoes aggregation to form a stable macromolecular complex. Nicoll posited that the complex is capable of storing memories.

A strength of Nicoll's model is that he addresses some of the weaknesses of Lisman's model. Another strength is that it identifies the name and location of the memory molecules. The main weakness of Nicoll's model is that it fails to propose how a memory is encoded, stored, and retrieved from aggregated CaMKII.

Some C/R models of memory, such as C/R models 3 and 4, posit that each long-term memory is encoded in the epigenome of a neurone.

Model 3 (C/R)

Bernstein (2022) proposed a model of long-term memory in which each memory is physically encoded in the epigenome of a neurone by methylation and demethylation of cytosines present in the DNA of a neural cell body. Gene expression is altered which facilitates the storage and retrieval of long-term memories.

The strengths of this model are that memories are stored on a very stable platform, and storage is potentially very large.

A weakness is that it fails to propose how gene expression facilitates memory retrieval.

Model 4 (C/R)

An earlier model of this type proposed that methylation or absence of methylation of cytosines present in the DNA of neurones encodes memories in binary form (Holliday, 1999). A strength of this model is that it proposes an easily understood model of encoding a memory. Another strength is that this storage system is capable a great number of memories – just 30 methylation sites are capable of storing 2^{30} (more than one billion) units of memory. A weakness is that it does not propose a read-write mechanism nor does it explain the role of dendritic spines in long-term memory.

2.2 Association/connectionist models of memory

Some A/C models of memory, such as A/C models 5 to 7, posit that memory storage occurs in neuronal synapses.

Model 5 (A/C)

Rogerson and colleagues (2014) posited that clusters of synapses are the sites of memory creation, and retrieval, as well as computation.

Model 6 (A/C)

Pfeiffer and colleagues (2020) posited that groups of ion channels facilitate short-term memory storage via changes in the potential of synaptic plasma membranes.

Model 7 (A/C)

Abraham and colleagues (2019) posited that memories are stored in neural circuitries as weighted synapses. The weighting of each synapse in the circuitry is set via synaptic plasticity when a memory is stored. In some models, the synaptic weightings are posited to change to accommodate new learning; other models posit that the synaptic weightings are retained throughout the lifetime of the memory.

Other A/C models of memory, such as A/C model 8, focus on neural circuitries and/or neuronal activity.

Model 8 (A/C)

Sun and colleagues (2020) posited that memories are stored in neural ensembles termed 'engrams' or memory traces.

2.3 Synthesis models of memory

Some researchers have attempted to incorporate specific C/R and A/C models into unified models of memory, such as models 9 to 11.

Model 9 (Synthesis)

The MMM model of memory (Zeltser et al., 2022) posits that each elementary unit of memory, termed a 'memory item' in this model, is stored in discrete memory molecules situated in the plasma membrane of a neurone - a C/R concept.

Simultaneously, unique oscillatory waveforms, which vary in amplitude and frequency, encode memories. The waveforms are located in unique neural circuitries – an A/C concept.

Model 10 (Synthesis)

Gershman (2023) posited that memories are formed via biochemical or biophysical operations on memory molecules – a C/R concept. Further, he posited that neuronal synapses store the parameters of an approximate probability distributive distribution of a generative memory model - an A/C concept. Simultaneously, information storing molecules located in neuronal cell bodies store the parameters of the generative model of memory – a C/R concept.

Model 11 (Synthesis)

Fitch (2023) posited that memory storage occurs in synapses and dendritic connectivity - A/C concepts. In addition, he posited that memories are stored in dendritic intracellular structures and neuronal epigenomes via methylation and demethylation of cytosine molecules - C/R concepts.

2.4 Astrocyte models of memory

Some researchers have emphasised the role of astrocytes in consolidation of long-term memories.

Model 12 (Astrocyte)

Kol and colleagues (2020) reported that hippocampal-cortical communication during learning promoted memory formation. Further support for the role of astrocyte in memory formation was provided by Sharma and colleagues (2023) who reported that learning-induced dephosphorylation of eIF2α in hippocampal astrocytes promoted hippocampal consolidation of long-term memory. Further, they reported that their results showed that increased mRNA translation alone in hippocampal astrocytes facilitates persistent synaptic plasticity and long-term memory. A strength of this model is that it emphasises the important role of astrocytes in neuronal transmission and long-term memory formation. A weakness is that Sharma and colleagues did not propose a mechanism of astrocytic support of memory. The model proposed in this article furnishes a detailed mechanism of astrocytic support of long-term memory.

3. Critiques of some models of memory

3.1 A critique of memory storage in the form of complex waveforms.

Some researchers have produced critiques of some models of memory. Zeltser and colleagues (2022) pointed out that it is known that memories can survive intact for many decades, but predicted that synaptic noise would corrupt memories stored in the form of neuronal activity to prevent stable long-term storage. Hence, they suggested that this form of memory storage is not feasible.

Keenan and colleagues (2016) provided a critique of neuronal activity models of memory storage. It has been shown that cooling a human brain can silence neuronal activity, as they noted during surgical operations involving brain

cooling. Hence, if memories are stored as neuronal activity, memories should be erased by brain cooling. However, brain cooling does not result in memory erasure. Keenan and colleagues suggested that these findings show that memory storage occurs independently of neuronal activity.

It is suggested that their conclusion that storage of memory in the form of complex waveforms in neural circuits is not possible may not be correct. It is likely that the relative amplitudes and the absolute frequencies of the component waves in a complex waveform will not change during brain cooling, but the magnitude of neuronal activity will decrease to an imperceptible level. However, it is unlikely that the neuronal activity will be completely extinguished during brain cooling so that, it can be conjectured, neuronal activity and memory will return on brain warming.

However, it is suggested that memory storage in the form of neuronal activity, is unlikely to occur in the brain based on energy considerations. The energy costs of continuous neuronal activity coupled with the necessity to prevent the brain overheating is predicted to be very high. It is likely that other mechanisms of memory storage, with a lower power consumption, such as memory molecules, will have evolved instead.

3.2 A critique of connectivity models of memory storage

It has been argued that long-term memories cannot be stored in connectivity because long-term memories are much more fluid than predicted by connectivity models and reconditioning takes place when memories are retrieved (Nader & Hardt, 2009).

3.3 A critique of models based on memory storage in DNA

Lisman (1985) argued against memory storage in DNA because he believed that it is difficult to conceive of a mechanism involving DNA which could regulate or be regulated by activities localised in subcellular domains such as dendritic spines.

4. A Theoretical Memory Molecule Model of Long-Term Memory Storage and Retrieval

Memories stored in the hippocampus are transferred over time to other regions of the brain for long-term storage.

Each facet of a memory is stored in an individual dendritic spine with a unique position identifier and unique neural pathways between the different storage sites of the facets of a memory. It is suggested that the unique position identifiers are stored in the hippocampus.

Related episodic memories are stored in clusters of dendritic spines.

Transfer of a facet of a memory stored in the hippocampus is initiated when the hippocampus sends a tetanus (a train of high frequency action potentials) along a neural pathway (neural circuit 1) to a dendritic spine storing a facet of a different memory (not a facet of the memory to be stored).

Metabotropic receptors in astrocytes neighbouring neural circuit 1 sense the synaptic activity in neural circuit 1. It is suggested that calcium ion signalling from each astrocytic receptor is processed and integrated by the nuclei of some of neighbouring astrocytes to couple astrocytes that follow the line of neural circuit 1 to form a unique astrocytic circuit (astrocytic circuit 1).

Also, the cell bodies in astrocytic circuit 1 use calcium ion signalling to coordinate the activation of synapses in silent (inactive) neighbouring neurones to create a unique neural circuit (neural circuit 2). Retrograde action potentials are generated in the neural circuit 2 to check its continuity as it is built. Neural circuit 2 connects the hippocampus to a dendritic spine. Then, the dendritic spine is tagged to receive a facet of memory from the hippocampus.

Next, the hippocampus sends a tetanus along neural circuit 2 to initiate long-term potentiation in the circuit to permit the transfer of a facet of a memory. In addition, nutrients in the blood vessels attached to the astrocytes in astrocytic circuit 1 are transferred to the synaptic clefts of the neurones in neural circuit 2 to facilitate synaptic plasticity of the neurones.

Calcium ion signalling to astrocytic nuclei increases mRNA production in the nuclei. mRNA granules are transferred by myosin motors to the tagged dendritic spine and the synaptic cleft of each tripartite synapse in neural circuit 2. Translation produces proteins required to produce receptors, memory molecules, actin filaments, neurotransmitters and other molecules needed to facilitate synaptic plasticity in neurones and astrocytes.

Next, rigid actin filaments and sheets of polymeric prions or protein molecules with similar properties interact in the body or PSD of the tagged dendritic spine to form memory modules (Figure 1). Each module contains many parallel sheets of polymeric prion molecules or prion-like molecules. Each prion or prion-like molecule is termed a memory molecule in this model. It is proposed that cross-links bind rigid actin filaments lengthwise to each polymeric sheet to form a stable platform for memory storage. The short-term memory stores contain the fewest number of memory modules, whilst long-term memory stores contain the most modules. It is proposed that the modules are parallel packed in memory stores to maximise storage capacity.

Prions and related proteins are intrinsically disordered proteins which change conformation constantly unless constrained when bound to other proteins (Du, 2011). It is proposed that all of the memory molecules in a newly created memory module have the same conformation, termed conformation 0 in this model, and each memory molecule can store one elementary unit of memory (termed a unit of memory in this model).

It is proposed that binary coding is used to store memories in all types of memory including short-term and long-term memory. Each unit of a memory corresponds to the output of a single receptor or group of receptors in a sense organ which initially forms the memory or facet of a memory after being processed. It is proposed that during storage of a memory or facet of a memory, a myosin molecule jumps stepwise along a memory module actin filament. The myosin molecule carries a cargo protein which possesses a current/voltage sensing domain. The carriage of a cargo protein with a current/voltage sensing domain has not been reported or suggested previously. After each jump, the cargo protein lies over a memory molecule for a short time (Figure 2). If a current flows in the actin filament at that point, as a result of an action potential generated by a sense receptor or a memory transferring memory store, the cargo protein conformation changes which induces a change in the conformation of the memory molecule. It is believed that this is the first report or suggestion that actin filaments can carry action potentials within neurones or cells. The new memory molecule conformation is termed conformation 1 in this model. If no current is detected, the conformation of the memory molecule remains in conformation 0. The memory is transferred elementary unit of memory by elementary unit of memory until the transfer is complete.

It is suggested that each facet of a memory is locked in a spine unless retrieved. It is suggested that locking occurs when GABA is released by astrocytes to inactivate the neural circuits connected to the dendritic spine. It is suggested that locking decreases the risk of memory corruption and false retrieval.

The model can be readily modified to provide a mechanism for memory retrieval. The process is almost the converse of memory storage in a memory store. However, the myosin cargo protein in this case is a protein that generates a current flow along an actin filament towards the synapse if the memory protein is in conformation 1; no current flow is generated if the conformation of the memory protein is 0. The memory is retrieved elementary unit of memory by elementary unit of memory.

5. Discussion

The proposed model is based on memory molecules where each molecule can store an elementary unit of memory. However, unlike other models, each unit of memory is encoded in binary form based on the of the conformation the memory molecule.

Some researchers have noted that memory molecules/structures may be unstable because of rapid protein turnover (Lisman, 1985). The memory modules in the proposed model are stabilized by cross-linking between memory molecule in polymeric sheets and rigid actin filaments (Figure 1). Hence, memories can potentially be stored indefinitely.

A strength of the model is that it proposes a simple read/write mechanism which permits memories to be readily encoded, erased or updated.

Few models of memory recognise the role of astrocytes in LTP and LTM. This model emphasises the possible role of astrocytes in these processes.

The model can provide possible explanations for long-term memory degradation over time (perturbations in a dendritic neurone can cause random conformational changes in the memory molecules in the memory modules), cognitive decline in Alzheimer's Disease (the normal memory molecules in memory modules are replaced by faulty prion molecules which cannot interact with the myosin cargo proteins to store or retrieve memories and/or tau proteins that stabilise the actin filaments in memory modules misfold and aggregate so that stabilisation fails leading to memory

module disassembly), and the association between the number of dendritic spines and cognitive decline (it is proposed that each dendritic spine holds exactly one long-term memory or facet in memory modules, so a decrease in the number of dendritic spines reduces the number of stored memories available for efficient cognitive function).

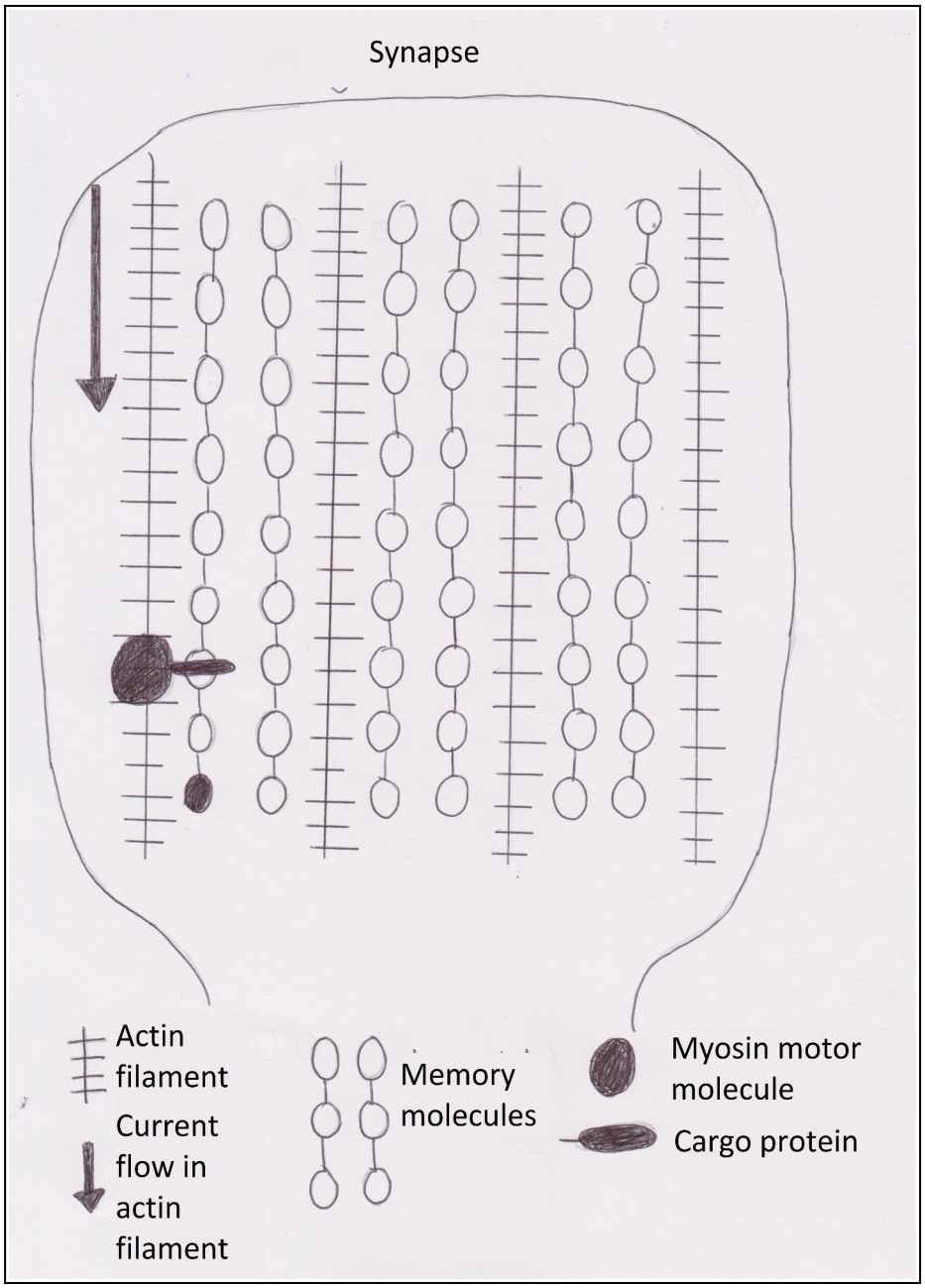

Figure 1. Copying a memory to a memory module.

During storage of a memory, a myosin molecule moves stepwise along a memory module actin filament. The myosin molecule carries a cargo protein which possesses a current sensing domain. After each jump, the cargo protein lies over a memory molecule. If a current flows in the actin filament at that point, as a result of an action potential generated by a sense receptor or the memory store transferring the memory, the cargo protein conformation changes which induces a change in the conformation of the memory molecule. The new conformation of the memory molecule is termed conformation 1 in this model. If no current is detected, the conformation of the memory molecule remains in conformation 0. The memory is transferred one elementary unit of memory by elementary unit of memory until the transfer is complete.

6. Conclusions

Several models of memory have been proposed but most fail to explain in detail how individual long-term memories are created, stored and retrieved. This model attempts to address this gap in knowledge by proposing several novel concepts in memory including a novel read/write mechanism of memory storage and retrieval. In addition, in this model, unlike most other models, astrocytes play a prominent role in long-term potentiation and neural circuitry. The strength of this model has been demonstrated by its provision of plausible explanations for the results of several memory studies. However, further research needs to be carried out to identify the prions and cargo proteins which are essential components of the model, and further test the validity of the model.

References

Abraham, W. C., Jones, O. D., & Glanzman, D. L. (2019). Is plasticity of synapses the mechanism of long-term memory storage?. *NPJ science of learning*, *4*, 9.

Bernstein C. (2022). DNA methylation and establishing memory. *Epigenetics insights, 15,* 25168657211072499.

Du Z. The complexity and implications of yeast prion domains. *Prion*. 2011 Oct-Dec;5(4):311-6.

Dudai, Y., Karni, A., & Born, J. (2015). The consolidation and transformation of memory. *Neuron*, *88*(1), 20–32.

Fitch W. T. (2023). Cellular computation and cognition. *Frontiers in computational neuroscience*, *17*, 1107876.

Gershman SJ. (2023). The molecular memory code and synaptic plasticity: A synthesis. *Biosystems*. Feb;224:104825.

Holliday R. Is there an epigenetic component in long-term memory? *J Theor Biol*. 1999;200:339-341.

Iqbal, J., Huang, G. D., Xue, Y. X., Yang, M., & Jia, X. J. (2023). The neural circuits and molecular mechanisms underlying fear dysregulation in posttraumatic stress disorder. *Frontiers in neuroscience*, *17*, 1281401.

Keenan, J. E., Wang, H., Ganapathi, A. M., Englum, B. R., Kale, E., Mathew, J. P., Husain, A. M., & Hughes, G. C. (2016). Electroencephalography during hemiarch replacement with moderate hypothermic circulatory arrest. *The Annals of thoracic surgery*, *101*(2), 631–637.

Kol, A., Adamsky, A., Groysman, M., Kreisel, T., London, M., & Goshen, I. (2020). Astrocytes contribute to remote memory formation by modulating hippocampal-cortical communication during learning. *Nature neuroscience*, *23*(10), 1229–1239.

Langille, J. J., & Gallistel, C. R. (2020). Locating the engram: Should we look for plastic synapses or information-storing molecules?. *Neurobiology of learning and memory*, *169*, 107164.

Lisman J. E. (1985). A mechanism for memory storage insensitive to molecular turnover: a bistable autophosphorylating kinase. *Proceedings of the National Academy of Sciences of the United States of America*, *82*(9), 3055–3057.

Lisman J, Buzsáki G, Eichenbaum H, Nadel L, Ranganath C, Redish AD. Viewpoints: how the hippocampus contributes to memory, navigation and cognition. *Nat Neurosci.* 2017 Oct 26;20(11):1434-1447.

McNeill, J., Rudyk, C., Hildebrand, M. E., & Salmaso, N. (2021). Ion Channels and Electrophysiological Properties of astrocytes: Implications for emergent stimulation technologies. *Frontiers in cellular neuroscience*, *15*, 644126.

Nader, K., & Hardt, O. (2009). A single standard for memory: the case for reconsolidation. *Nature reviews. Neuroscience*, *10*(3), 224–234.

Nicoll, R. A., & Schulman, H. (2023). Synaptic memory and CaMKII. *Physiological reviews*, *103*(4), 2877–2925.

Pfeiffer, P., Egorov, A. V., Lorenz, F., Schleimer, J. H., Draguhn, A., & Schreiber, S. (2020). Clusters of cooperative ion channels enable a membrane-potential-based mechanism for short-term memory. *eLife*, *9*, e49974.

Rogerson, T., Cai, D. J., Frank, A., Sano, Y., Shobe, J., Lopez-Aranda, M. F., & Silva, A. J. (2014). Synaptic tagging during memory allocation. *Nature reviews. Neuroscience*, *15*(3), 157–169.

Sharma, V., Oliveira, M. M., Sood, R., Khlaifia, A., Lou, D., Hooshmandi, M., Hung, T. Y., Mahmood, N., Reeves, M., Ho-Tieng, D., Cohen, N., Cheng, P. C., Rahim, M. M. A., Prager-Khoutorsky, M., Kaufman, R. J., Rosenblum, K., Lacaille, J. C., Khoutorsky, A., Klann, E., & Sonenberg, N. (2023). mRNA translation in astrocytes controls hippocampal long-term synaptic plasticity and memory. *Proceedings of the National Academy of Sciences of the United States of America*, *120*(49).

Squire, L. R., Genzel, L., Wixted, J. T., & Morris, R. G. (2015). Memory consolidation. *Cold Spring Harbor perspectives in biology*, *7*(8).

Sun, X., Bernstein, M. J., Meng, M., Rao, S., Sørensen, A. T., Yao, L., Zhang, X., Anikeeva, P. O., & Lin, Y. (2020). Functionally distinct neuronal ensembles within the memory engram. *Cell*, *181*(2), 410–423.

Zeltser, G., Sukhanov, I. M., & Nevorotin, A. J. (2022). MMM - The molecular model of memory. *Journal of theoretical biology*, *549*, 111219.