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Multiscale Mechanisms of Memory: From Synapses to Systems

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Abstract. Learning and memory arise from biochemical events taking place in nanometre-sized synaptic compartments and scale up to coordinated activity patterns that span the whole brain. Classical models of memory focused on N-methyl-d-aspartate-receptor (NMDAR)–dependent long-term potentiation (LTP) and long-term depression (LTD), treating these synaptic mechanisms as the molecular currency of information storage. However, new discoveries over the past two decades have compelled adoption of a broader, multiscale view of memory. This perspective integrates glial modulation, dynamic neuronal ensembles (engrams), oscillatory brain states, and advanced neurotechnologies. This review synthesises advances across five nested scales—molecules, synapses, circuits, networks, and technologies—highlighting how mechanisms at each level both constrain and enable those above and below. Throughout, we contrast past dogma with new evidence, identify unresolved gaps, and discuss translational opportunities for disorders such as Alzheimer's disease and post-traumatic stress disorder. By unifying molecular insight with systems-level interrogation and AI-assisted neural decoding, we outline a roadmap toward a predictive, multiscale science of memory.

Keywords: Engram, Plasticity, Integration, Neuroscientific Techniques, Memory Therapy

1. Introduction

Few capacities are as fundamental to human experience as the ability to learn from the past and adapt to new circumstances. From recalling a childhood melody to mastering a foreign language, memory endows organisms with a temporal bridge that links prior events to future behaviour. Historically, the quest to understand memory has oscillated between two extremes: reductionist efforts to locate a single cellular locus of storage, and holistic frameworks that emphasise network-wide dynamics [1]. Contemporary neuroscience views these poles as complementary. Molecular events occurring within a single synapse can imprint long-lasting changes, yet the behavioural expression of a memory inevitably recruits distributed circuits that interact across multiple timescales. Notably, earlier single-level theories left critical explanatory gaps: synapse-focused models could not fully explain how transient molecular changes yield stable, network-wide memories, while purely circuit-level theories lacked mechanisms to link activity to enduring synaptic change [2]. The advent of high-resolution imaging, optogenetic control, and spatial multi-omics has now rendered the once-invisible mechanisms of memory observable and

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manipulable, enabling researchers to probe memory processes across scales. Accordingly, a multiscale framework—one that respects the unique causal rules at each biological tier while revealing their interdependence—has become imperative for both fundamental understanding and therapeutic innovation. This article surveys recent progress across such scales, drawing explicit links from biochemical cascades to systems-level consolidation, and concludes by exploring how these insights can be translated into therapeutic interventions.

2. Molecular and synaptic mechanisms

Historically, synaptic plasticity has occupied centre stage in memory research. Hebb's cell assembly hypothesis, combined with the discovery of LTP in the hippocampus, established an intuitive correspondence between synaptic strength and experience-dependent change [3]. Yet the molecular landscape within a potentiated synapse is far richer than a simple binary switch [4]. Below, we examine three key themes that redefine how synapses encode information.

2.1. Canonical LTP/LTD revisited

Traditional models portrayed LTP as a neuron-autonomous process in which high-frequency stimulation opened postsynaptic NMDARs, allowing Ca^{2+} influx that activated Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). The activated CaMKII then phosphorylated AMPA receptor (AMPAR) subunits, promoting their insertion into the postsynaptic density and thereby strengthening transmission. Conversely, low-frequency stimulation favoured protein phosphatase 1 (PP1) activity, driving AMPAR endocytosis and resulting in LTD [5]. Recent phospho-proteomic studies revealed that >1,000 distinct phosphorylation events occurred within sixty seconds of potentiation, suggesting that synapses occupy a high-dimensional biochemical state space rather than a binary "on/off" configuration [6]. Single-particle tracking further showed that AMPARs diffused laterally and clustered into nanodomains that reshaped within minutes, indicating a fluid architecture capable of representing graded information [7]. Such findings motivated a new theoretical framework: instead of a binary switch, synaptic strength could be encoded as a high-dimensional vector of molecular states. This view vastly increases the potential information storage per synapse (beyond a single bit) while maintaining energetic stability [8].

2.2. The tripartite synapse and astrocytic regulation

Once relegated to a supportive role, astrocytes are now recognised as active participants in plasticity. Calcium waves in astrocytic end-feet trigger the release of gliotransmitters such as d-serine and ATP, which modulate NMDAR co-agonism and extracellular glutamate clearance [9]. Chemogenetic silencing of astrocytic Ca^{2+} signalling abolished late-phase LTP in hippocampal CA1 and disrupted remote contextual fear memories [10]. Meanwhile, spatial transcriptomic analyses uncovered coordinated neuron–astrocyte gene programs that bloomed around four hours post-learning [11]. These results suggested that astrocytes gate the induction threshold for plasticity and might even bias memory allocation through local metabolic states. Given this influence, an intriguing possibility is that distinct "astro-engrams" might also exist—stable astrocytic traces that contribute to memory encoding. This prospect remains an open question, ripe for investigation with single-cell multi-omic and optogenetic tools.

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2.3. Metaplasticity and synaptic tag-and-capture

Classically, synaptic plasticity is defined as the ability of synapses to change their strength (the structural and functional flexibility of connections). However, this capacity for change can itself be modified by experience—a phenomenon termed metaplasticity, literally the plasticity of plasticity. Metaplasticity accounts for phenomena such as learning-induced lowering of LTP thresholds and the conversion of short-term into long-term memories [12]. The synaptic tag-and-capture hypothesis posits that weak stimulation leaves a molecular "tag" that later "captures" plasticity-related proteins (PRPs) synthesised after strong events, thereby consolidating the earlier experience [13]. Live-cell super-resolution imaging visualized these tags as phase-separated CaMKII condensates (liquid-like clusters of CaMKII molecules) that persisted for about forty minutes, precisely aligning with behavioural tagging windows observed in vivo [14]. This direct visualization provided empirical confirmation of the synaptic tag-and-capture mechanism, explicitly linking a transient molecular mark to the timescale of memory consolidation. The emerging view is that synapses encode not only the strength of past inputs but also a predictive signal about future plastic potential, integrating experiences across minutes to hours.

3. Engram identification, linking, and plasticity

While synapses provide the molecular substrate of storage, memories manifest behaviourally via the concerted activity of discrete neuronal ensembles known as engrams. Modern genetic and optical tools have made it possible to label, observe, and manipulate these ensembles with unprecedented precision.

3.1. Principles of engram labelling

Targeted Recombination in Active Populations 2 (TRAP2) couples the Fos promoter to tamoxifen-inducible Cre-ERT2, enabling permanent genetic tagging of neurons active within a defined temporal window [15]. Optogenetic reactivation of TRAP2-tagged prelimbic cortex cells reinstated fear memories days to weeks later, demonstrating that reactivating those cells was sufficient for recall. In parallel, complementary TetTag systems (tetracycline-dependent tagging) and c-Fos immunolabelling broadened the toolkit, albeit with coarser temporal resolution. The term "engram" thus refers to a sparsely distributed yet functionally coherent ensemble whose activity is necessary and sufficient for recall [16].

3.2. Engram stability versus drift

Longitudinal two-photon calcium imaging revealed a striking phenomenon: 30–60% of engram neurons were replaced over weeks, a process named "drift." Despite this cellular turnover, behavioural performance remained stable, implying that memories were stored redundantly across overlapping ensembles. In support of this idea, computational models suggested that activity-dependent synaptic rewiring allowed the ensemble's functional identity to persist even as its cellular composition changed [17]. Drift may therefore serve an adaptive role, facilitating the integration of new information while preserving core content.

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3.3. Linking memories across time

Experiences separated by mere hours often become linked: reactivating one cues recall of the other. At the cellular level, back-propagating action potentials elevate cyclic AMP response-element binding protein (CREB) activity, heightening intrinsic excitability for several hours and biasing subsequent engram allocation to the same neurons. Disrupting this excitability window prevented linkage, underscoring a metaplastic rule that bridges minutes to hours. For example, when researchers optogenetically silenced neurons to suppress their heightened excitability right after an initial learning event, the expected linking of that memory with a subsequent event failed to occur. This finding confirms that the timing of excitability is critical for linking memories. Linking thus provides a mechanistic account for how the brain weaves episodic events into coherent narratives [18].

4. Systems-level integration and network oscillations

The behavioural expression of memory recruits distributed networks that coordinate via oscillatory dynamics. Interactions between hippocampus, thalamus, and cortex during sleep exemplify how systems-level mechanisms consolidate and transform memories over time.

4.1. Hippocampal–cortical dialogue

The standard model of systems consolidation envisioned a unidirectional transfer from hippocampus to cortex. Recent magnetoencephalography (MEG) studies revealed bidirectional influences: cortical up-states could pre-position hippocampal networks, while hippocampal sharp-wave ripples (SWRs) aligned phase-specifically with thalamo-cortical spindles. Closed-loop auditory stimulation timed to endogenous spindles augmented hippocampal–prefrontal synchrony and improved overnight recall in humans. Notably, stimulation had to fall within ±50 ms of the SWR peak to be effective, underscoring the millisecond-scale precision required at the systems level [19].

4.2. Beyond the hippocampus: distributed hubs

Beyond the hippocampus, several other brain regions have emerged as important memory hubs. For example, chemogenetic silencing revealed that retrosplenial cortex and nucleus reuniens could sustain remote spatial memories even when the hippocampus was lesioned. Whole-brain functional MRI during recall suggested a dynamic core–periphery organisation: core regions such as the medial temporal lobe and midline prefrontal cortex flexibly recruited task-specific peripheral areas [20]. This distributed architecture may enable both resilience to local damage and rapid context-dependent retrieval.

4.3. Oscillations as a scaffold for plasticity

Nested oscillations provide temporal reference frames for coding and plasticity. Theta–gamma coupling is thought to multiplex item and context information, whereas beta rhythms coordinate top-down predictions. Optogenetic stimulation of entorhinal inputs at specific theta phases selectively strengthened or weakened cue–place associations, providing causal evidence that oscillatory phase can gate the direction of synaptic plasticity. Despite these advances, understanding how molecular rules such as spike-timing-dependent plasticity (STDP) integrate with macroscopic rhythms remains a central challenge for multiscale modelling [21].

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5. Cutting-edge technologies and spatial multi-omics

The past decade has witnessed a rapid proliferation of technologies that illuminate and manipulate memory with cell-type and sub-second precision. Here we survey key advances and their implications.

5.1. Optogenetics and chemogenetics

Channelrhodopsin-2 affords millisecond-precision activation, while anion-conducting opsins enable inhibition. Red-shifted variants and up-conversion nanoparticles now allow deep-brain stimulation without fibre implants. These innovations achieve deep stimulation without implants by using longer-wavelength light (which penetrates tissue more effectively) and nanoparticles that convert external light into localized high-frequency illumination. Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) provide hours-long modulation suitable for behavioural tagging [22]. Emerging GPCR-based magnetogenetics (in which magnetic fields remotely activate engineered G-protein-coupled receptors) promises truly wireless control, though heating and immune responses remain concerns [23]. Collectively, these tools allow precise experimental manipulation of memory circuits. For instance, researchers can now reactivate specific engram cells using optogenetics to induce the recall of a particular memory, or silence those cells via chemogenetics to test whether that memory is blocked. Such causal interventions directly link defined neural activity patterns to memory outcomes.

5.2. High-resolution imaging of engram dynamics

Two-photon and microendoscopic calcium imaging permit chronic recordings in freely behaving animals, capturing thousands of neurons across weeks. Light-field microscopy extends field-of-view to >20,000 neurons at the cost of axial resolution. Hybrid techniques combining voltage-sensitive dyes with deep-learning-based deconvolution aim to restore temporal fidelity, opening windows on sub-millisecond ensemble dynamics [24].

5.3. AI-based neural decoding

Self-supervised convolutional transformers trained on terabytes of EEG (electroencephalography) and fMRI (functional MRI) data learned latent manifolds that predicted single-trial memory strength. Such models enabled closed-loop neuro-prosthetics that delivered stimulation precisely when endogenous dynamics forecast memory decay, paving the way for personalised cognitive augmentation. In practical terms, this approach could allow devices to monitor brain activity and intervene when a memory is predicted to falter. For example, an AI system might trigger a targeted burst of brain stimulation at the moment neural patterns indicate an emerging memory lapse, potentially boosting memory retention in individuals with cognitive impairment [25].

5.4. Spatially resolved single-cell multi-omics

MERFISH (Multiplexed Error-Robust Fluorescence in situ Hybridization) combined with Visium spatial transcriptomics maps RNA, chromatin accessibility, and protein localisation in situ. Applying this pipeline to the mouse hippocampus identified astrocyte–neuron gene modules that peaked four to six hours after learning, aligning with the synaptic tag-and-capture window. Such atlases

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pinpointed potential therapeutic targets—for example, astrocytic SERCA pumps that modulate calcium homeostasis during consolidation.

6. Translational applications

Multiscale insights are now informing a variety of interventions for memory disorders. Broadly, these advances can be grouped into neuromodulation therapies, molecular diagnostics, and targeted engram interventions.

6.1. Neuromodulation therapies

In early Alzheimer's disease, multi-session repetitive transcranial magnetic stimulation (rTMS, 10 Hz over dorsolateral prefrontal cortex) modestly improved cognitive scores. Invasive deep-brain stimulation (DBS) of the fornix slowed hippocampal atrophy in small trials, hinting at a potential disease-modifying effect. Similarly, closed-loop ripple-locked stimulation in rodents reduced post-traumatic stress disorder–like symptoms and was entering human pilot studies. These stimulation-based approaches demonstrate that externally modulating brain networks can yield memory benefits, though the results so far have been modest or preliminary [26]. Non-invasive methods like rTMS are safe but produce relatively small improvements, whereas invasive techniques like DBS may achieve stronger effects at the cost of neurosurgery [26]. Notably, emerging closed-loop paradigms aim to boost efficacy by timing stimulation to endogenous brain activity (for example, delivering pulses timed to hippocampal ripples), an approach that showed promise in rodent models of PTSD.

6.2. Omics-based biomarkers for diagnosis

Peripheral blood multi-omics analyses identified inflammatory signatures (e.g. elevated interferon-γ) that predicted non-response to therapy, enabling patient stratification. In practice, such molecular biomarkers could be used to personalise treatment—for example, flagging patients unlikely to respond to standard interventions so that alternative strategies can be pursued [27]. This approach illustrates how high-dimensional genomic and proteomic data can guide clinical decision-making in memory disorders, moving the field toward more tailored therapeutic strategies.

6.3. Engram-targeted gene therapies

Looking forward, one radical proposal is to combine activity-dependent tagging techniques like TRAP2 with viral CRISPR interference to selectively depotentiate pathological engrams. If successful, this approach could erase specific traumatic memories (for example, in post-traumatic stress disorder), but it would require rigorous ethical oversight [28]. The prospect of editing or erasing memory traces at the cellular level represents a fundamentally new therapeutic direction. While still speculative, such gene-editing strategies highlight the potential to directly target the physical substrates of memory—an extremely powerful capability for conditions like PTSD or addiction, albeit one fraught with ethical and safety considerations.

7. Conclusion

Memory research is entering a predictive era. By integrating biochemical state spaces, dynamic engrams, oscillatory dialogues, and AI-assisted decoding, neuroscience approaches a unified theory

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of how experiences sculpt the brain. Notably, multiscale strategies have begun to yield tangible benefits. For example, closed-loop stimulation guided by brain oscillations has been shown to enhance memory recall in humans and reduce pathological fear responses in rodents, illustrating the translational potential of this framework. Yet major questions remain: How do astrocytic metabolic states influence engram allocation? By what rules do ensemble drift reconcile flexibility with stability? And can closed-loop stimulation be deployed safely at scale? Answering these questions will require tight interdisciplinary collaboration and vigilant ethical oversight. The prospect of alleviating memory disorders makes the endeavour not only intellectually compelling but profoundly humanitarian.

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