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Editorial overview: Introduction to neurobiology of learning and plasticity

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Understanding the neural basis of learning and memory is one of the fundamental quests in neuroscience. Since the proposal of Hebb and the discovery of long-term potentiation (LTP) by Bliss and Lomo, synaptic plasticity has emerged as the main cellular mechanism of learning. Decades of research has revealed a plethora of synaptic plasticity rules and their molecular underpinnings. While plasticity is universally observed across brain regions, the rules and mechanisms vary depending on specific sets of synapses as well as the context and the prior history of neuronal activity. New tools and techniques are being used to determine whether and how these mechanisms relate to various forms of learning and plasticity *in vivo*. Invertebrate model organisms have helped illuminate molecular mechanisms in intact organisms. Altered synaptic plasticity has also been implicated in several neurological disorders and the precise mechanisms are being elucidated. The classic synaptic plasticity rules have also been expanded to include non-neuronal cells such as glia. In this current issue on Neurobiology of Learning and Plasticity, we highlight select recent developments and ideas, which address these new areas of investigation.

Learning and memory

Hebbian synaptic plasticity, such as LTP and long-term depression (LTD), can explain unsupervised learning well, but is inadequate for supervised learning like Pavlovian learning. This is because the instructive reward signal for reinforcing plasticity is often delayed in time—the distal reward problem. Two papers in this issue address this timing dilemma. Shouval and Kirkwood discuss synaptic eligibility traces (eTraces), while Murai and Goto introduce the concept of behavioral time scale plasticity (BTSP). eTraces and BTSP bridge the reward time gap via different mechanisms: eTraces are "silent" traces produced at the synapses receiving coincident activity that convert to LTP or LTD upon delayed neuromodulator signals, while in BTSP, the instructive signal occurs via plateau potentials. Shouval and Kirkwood propose that having separate LTP and LTD eTraces allow learning of reward timing by sustaining neural firing until the predicted reward. Murai and Goto discuss how plateau potentials in the distal dendrites, which receive inputs from the entorhinal cortex, are critical for CA1 place field formation.

Memory consolidation often occurs offline after learning and during sleep. Murai and Goto summarize how CA1 sharp-wave ripples that occur during wakefulness after learning or non-REM sleep facilitates memory consolidation. Episodic memories are initially stored in the hippocampus and

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later transferred to various brain regions for long-term storage, a process now being studied using novel optical tools. Menarchek and Bridi discuss how sleep promotes plasticity by latent plasticity mechanisms triggered during prior wakefulness. Upregulation of activity-dependent immediate early genes during sleep may protect potentiated synapses while depressing others to improve memory. The authors propose that experience during the awake period "tags" synapses and plasticity-related molecules elevated during sleep "capture" them to remodel synapses.

de Snoo and Frankland review new insights into the mechanisms of forgetting. Opto-tagging of engrams and reactivating them after amnesia suggests a failure of accessing engrams. Both internal factors, such as emotional valence, and external factors, including social context, affect the accessibility of memory without necessarily altering the memory engram. The mechanisms likely differ for long-term forgetting, which may occur through degradation of the engrams via adult neurogenesis in the hippocampus and microglia-mediated remodeling.

Sensory learning and plasticity

Barth et al. provide an overview on the role of sensory learning-related plasticity in reinforcement learning paradigms. The authors highlight that sensory neocortices offer some advantages over higher-order areas to connect synaptic plasticity mechanisms to learning, because of the well-defined nature of their cellular architecture and local connectivity, and the reproducibility of neuronal responses to well-controlled sensory stimuli.

Gavornik and Bear argue that visual evoked potentials (VEPs), which are local field potentials derived from the synaptic population activity surrounding the electrode, are a powerful tool for studying cortical plasticity because VEPs can detect subthreshold activity. The authors review classical experiments using VEPs to elucidate the mechanisms of ocular dominance plasticity and recent studies examining visual recognition memory and predictive coding.

Since Hubel and Wiesel, it has been recognized that sensory cortices exhibit a clear critical period for experience-dependent plasticity. Radulescu et al. extend this further by providing an overview of how specific forms of plasticity exhibit age-related changes in the sensory cortex. By understanding the mechanisms of age-related changes, the authors suggest that plasticity may be rejuvenated to promote healthy aging.

Altered synaptic plasticity in disease

Larsen et al. highlight how a central protein in synaptic plasticity, calcium/calmodulin-dependent protein kinase II (CaMKII), becomes maladaptive in disease. Under physiological conditions, CaMKII supports LTP by binding to the GluN2B subunit of N-methyl-D-aspartate (NMDA) receptors and autophosphorylation, which allows it to remain autonomously active and translocate to excitatory synapses. Soluble amyloid-β (Aβ), a key factor in Alzheimer's disease, disrupts CaMKII's synaptic localization by blocking its GluN2B binding, preventing LTP. Similar mechanisms contribute to LTP deficits in cerebral ischemia and CaMKII inhibition protects against both acute neuronal damage and long-term synaptic impairments. Thus, pathological LTP impairment may involve "active" misregulation of CaMKII, rather than loss-of-function, offering alternative therapeutic strategies.

Exposure to drugs of abuse can prime neurons for future plasticity through altering excitability and epigenetic states. Brida and Day describe how diverse transcriptional responses arise from drugs of abuse, highlighting the role of specific epigenetic regulators contributing to enhancer activation and long-term changes in gene accessibility. Recent findings show that cocaine-activated ensembles evolve depending on exposure history, which suggests that addiction may be driven by selective, cell-type-specific transcriptional and epigenetic adaptations within sparse neural populations.

Insights from invertebrate model organisms

Frankel and Kurshan outline a series of molecular events mediating synapse formation and plasticity in *C. Elegans*. Synapse identity is set by neuron-type-specific and pan-neuronal transcriptional programs, while cell adhesion molecules orchestrate synapse stabilization by defining neurite positioning or protecting synapses from elimination. Presynaptic assembly is initiated by the phase separation of scaffold proteins and voltage-gated calcium channels. After these "hard-wired" events, neuronal activity induces synaptic remodeling during development or learning, via activity-dependent transcription factors that regulate synaptic genes.

He and Dickman review the suite of molecular mechanisms underlying homeostatic synaptic plasticity at the Drosophila neuromuscular junction and how they contribute to synapse heterogeneity. Super-resolution microscopy has revealed differences in active zone nanoarchitecture underlying functional differences in specific synapses across neurons. Even with similar core protein expression, distinct transcriptional signatures and post-transcriptional regulation result in synapse-specific specializations. This baseline diversity is dynamically reshaped by homeostatic plasticity, which preserves neural circuit stability in response to challenges like injury or receptor dysfunction.

Noncanonical forms of synaptic plasticity

Welle and Smith outline how inhibitory synapses adapt through multiple forms of plasticity. Postsynaptic forms of inhibitory synaptic plasticity (iLTP/iLTD) result from changes in network activity. Central to these processes is the trafficking and nanoscale positioning of $GABA_A$ receptors ($GABA_ARs$). Like excitatory synapses, subsynaptic nanostructures containing $GABA_ARs$ and associated proteins are aligned with presynaptic release sites to form highly efficient ""nanocolumns." Disruption of these nanocolumns weakens inhibitory transmission, highlighting their functional relevance. Mechanistically, *de novo* protein synthesis driven by activity-dependent suppression of specific microRNAs is necessary for maintaining iLTP by upregulating $GABA_ARs$.

Sheu and Delong review new work implicating axociliary synapses in a novel form of serotonergic signaling. Unlike classical synapses, serotonergic axons form direct synaptic contacts with the primary cilia of hippocampal pyramidal neurons, which trigger a unique signaling cascade leading to chromatin remodeling and transcriptional reprogramming within the nucleus. The authors propose that this cilium-to-nucleus signaling pathway represents a new mode of neuromodulation in mature neurons.

RNA processing and noncoding RNAs (ncRNAs) are emerging as players in synaptic plasticity and memory formation. Walsh and Bredy argue that ncRNAs are not merely regulatory add-ons but are key coordinators of plasticity by localizing to subcellular compartments. At the nucleus, ncRNAs control gene expression, splicing, and chromatin modification, while at synapses, they may modulate local translation, receptor trafficking, and spine morphology. Specific RNA modifications, which allow ncRNAs to respond to environmental signals, may also underlie experience-dependent plasticity by fine-tuning gene expression.

Role of glia

Once thought to be inert, glia have now been shown to have surprising roles in plasticity and memory. Vita et al. outline how glial phagocytosis, which selectively engulfs synapses, refines circuits. Microglia prune retinal inputs during early postnatal development via the complement cascade, while astrocytes and OPCs take over during later experience-dependent plasticity. Microglial cytokine signaling mediates activity-dependent synapse disassembly in both developing and adult brains. Glia also remodels the extracellular matrix (ECM), including perineuronal nets, to regulate plasticity; microglia promote remodeling by clearing ECM components, while astrocytes stabilize circuits by suppressing ECM-degrading enzymes.

New techniques, summarized by Asher and Goshen, have uncovered novel roles for astrocytes in memory formation. Use of chemogenetic and optogenetic tools, which enable cell-type-specific and temporal control of astrocytic signaling pathways, reveals that Gq activation in hippocampal astrocytes enhances recent memory recall, while Gi activation impairs remote memory by disrupting hippocampal—cortical communication. Intriguingly, astrocytes may themselves form astrocytic engrams, as shown by tagging and manipulating astrocyte ensembles involved in learning.

Conclusions

The new ideas and studies reviewed in this issue open more questions for the future. When and how do different mechanisms of plasticity engage to mediate learning? How do neuronal and glial mechanisms

interact? How are these mechanisms dysregulated in disease? New techniques and tools are unraveling the precise mechanisms of plasticity that naturally occur during learning and memory, which add complexity to the known plasticity rules.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.