Editorial overview: Neurobiology of learning and plasticity

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Plasticity is a critical feature of the brain and describes the changes thought to underlie memory formation and forgetting, as well as learning and encoding new experiences. Understanding the underlying mechanisms of plasticity remains a long-standing question in neuroscience. Previously, studies have described distinct forms of plasticity from molecular to circuit changes, but there were limited examinations of how these different aspects of plasticity interact to underpin learning or memory formation and the resulting effects on behavior. Recent methodological advances have facilitated studies that focus on linking plasticity across spatial scales: connecting changes in genetics, molecules, synapses, cells, and networks to memory formation and behavior.

This volume of *Current Opinion in Neurobiology* presents the latest thinking from a diverse group of investigators at the very forefront of the study of plasticity and memory. The common theme of these reviews is behavior. That is, each examines particular aspects of plasticity and memory at different spatial scales of analysis using the latest tools, but does so in the context of behavior. In addition to exploring the relationship between changes in the brain and the resulting behavior, experiments in behaving subjects have allowed for the examination of interactions between brain regions and the role of context and behavioral state in plasticity. Work in behaving animals additionally helps facilitate translation between models, including zebrafish, fruit fly, rodent and human plasticity studies.

Recent studies have sought to examine the role of epigenetic changes, such as DNA methylation or histone modification, in memory formation. Here, Zovkic describes the latest findings on the critical role of histone isoforms and chromatin remodelling factors in epigenetic regulation of memory formation in rodents. Burns and Graff focus on the contribution of histone acetylation in memory formation. They describe a theory of “cognitive epigenetic priming” and explore its role in neurodegenerative disease.

Suratkal, Yen and Nishiyama review recent tools that allow researchers to gain greater insights into the molecular mechanisms of synaptic plasticity, specifically the reorganization of actin cytoskeleton and subsynaptic structures. At another level of investigation, Chater and Goda examine spatial interactions on the dendrites, highlighting signaling molecules and dendritic non-linearities that underlie plastic interactions between neighboring synapses and the implications for synaptic plasticity rules. Tsutsumi and Hayashi-Takagi show how novel optical tools can be used examine causal interactions between synaptic and cellular plasticity associated with behavioral learning in animal models. Optical tools are also highlighted by Lu and Zuo. They focus on techniques for investigating the synaptic and cellular assemblies underlying learning and memory and discuss the outstanding questions in the field such as how stable memory exists in the face of ongoing plasticity. Finally, Raman and O’Leary explore how the connectivity of the network influences its capacity for plasticity and how these connectivity patterns can enhance learning.

Sparsely distributed ensembles of neurons, termed engrams, are proposed to be responsible for representing particular experiences and to be composed of neurons active at the time of an experience. This ensemble of cells' coordinated activity is argued to be both necessary and sufficient to induce recall of a particular memory. In the past decade or so, an expanding body of work has investigated the biological properties of these ensembles. Here, Ryan, Ortega de San Luis, Pezzoli and Sen discuss the latest methods to understand the molecular, cellular and network underpinnings of engrams, and how data arising from these new approaches suggest that memories may be encoded through changes in connectivity between neurons in an engram. Sweis, Mau, Rabinowitz and Cai contribute a provocative review in which they explore the cellular composition of an engram in rodents and propose that the fluidity of membership and diversity of cells (including inhibitory cells) involved contribute to memory flexibility.

Much work has been devoted to understanding the role of excitatory neurons in plasticity, engrams and memory. However, the important contribution of other cells types is becoming increasingly appreciated. Spiegel reviews new data describing experience-dependent changes to specific GABAergic interneuron subtypes and molecular regulators of these plastic changes in the developing and adult cortex. The role of cell-autonomous and non-autonomous secreted factors in driving interneuron plasticity is highlighted. Herstel and Wierenga propose a novel framework for inhibitory regulation of excitatory plasticity in mice, where inhibition is changing its influence depending on context and activity levels. Hartung and Letzkus propose a novel role for specific inhibitory subtypes in layer 1 of cortex, with two distinct subtypes, Marinotti cells and layer 1 interneurons, being implicated in learning-related plasticity and associative learning, respectively.

Moving beyond a "neurocentric" view of plasticity and memory, Wahis, Hennes, Arckens and Holt propose a critical role for astrocytes in regulating and enhancing plasticity in cortical circuits. Kol and Goshen review new studies proposing key roles for astrocytes and oligodendrocytes in different stages of memory (formation, consolidation, remote memory) in mice. These authors highlight the key role of new tools in showing the importance of glia in memory across time.

Across many species, learning is known to change the activity of neurons across multiple brain regions. Gründemann reviews recent work on the encoding of fear learning and proposes that fear memories are distributed between the thalamus and amygdala in rodents. Gilissen and Arckens propose a novel role of the posterior parietal cortex in cross-modal plasticity through the contextual plasticity associated with this brain area in rodents. Rundstrom and Creanza explore the time courses of plasticity in songbirds, from rapid to long-term, as well as the genetic and neuronal underpinnings of the plasticity underlying song-learning. Lovett-Barron discusses insights from brain-wide imaging of optically-transparent larval zebrafish. This review examines both technical and conceptual aspects of paradigms to assess associative and non-associative learning in larval zebrafish to more thoroughly understand brain-wide learning-dependent neuronal activity.

Traditionally, the neuroscience of plasticity and memory has focused on memory acquisition. More recently, experiments are also being conducted on the neurobiological processes underlying memory after it has been formed. Here, Felsenberg discusses memory formation, and how learned memories are modified in light of additional evidence and experience in the adult fruit fly. This review not only examines how network changes can strengthen or weaken memories, but also highlights the ability of fruit flies to perform complex learning tasks akin to vertebrate animals. Animals and humans can learn new information throughout their lifetime, while preserving old information. Barron proposes that GABA-mediated neural inhibition in the cortex protects existing memories while new memories are forming, comparing new data in humans to previous work in experimental animals. Andermane, Joensen and Horner explore how episodic memories are forgotten in humans. Episodic events are thought to be represented hierarchically across brain regions. This review combines experimental approaches with statistical modelling to propose that forgetting may occur via different mechanisms depending on the hierarchical level (items, events and episodic narratives). Cordi and Rasch discuss recent studies questioning the effect of sleep on declarative memory in humans and call for new studies to help disambiguate these inconsistencies.

Dopamine (DA) has been heavily implicated in reinforcement learning. DA is often thought to provide a teaching signal or reward prediction error (defined as the difference between the expected and received reward) to mediate learning. Here, Starkweather and Uchida integrate theoretical and recent experimental rodent work on DA and its role in reward learning, particularly in reinforcement learning models where DA serves as a temporal difference error signal. Moreover, the authors propose that in uncertain environments DA neurons compute errors signals using belief states. Lerner, Holloway and Seiler discuss how recent data has updated the reward prediction error hypothesis. They highlight the importance of sensory prediction errors, distributional encoding and belief states, and how results arising from molecular subtyping of ventral tegmental area (VTA) DA neurons may be incorporated into reward prediction error theories. Flossmann and Rochefort discuss how navigation-related signals may play a role in gain control and sensorimotor predictive coding. They focus on how activity in the visual cortex of rodents is modulated by locomotion and associated signals, such as self-motion, distance travelled, spatial context and head movements.

Finally, the functional significance of cortical reorganization is discussed in two reviews. First, Muret and Makin examine homeostatic plasticity in the somatosensory cortex in the human brain and its role in cortical reorganization after loss of a hand. The authors argue that because plasticity and stability must be carefully balanced in neural systems, despite remapping, amputated representations may persist, providing a new perspective on synaptic and cellular mechanisms underlying sensory remapping. Second, Röder and Kekunnaya link non-human primate studies with studies of humans who have a transient phase of congenital blindness. Human studies confirm sensitive periods and limitations of recovery to transient blindness.

Together, the reviews in this volume synthesize our current knowledge on plasticity and memory and highlight recent advances in our understanding of the relationship between plasticity and behavioral changes across a range of experimental species. By outlining the most important remaining gaps in our understanding, these reviews also emphasize the next key steps for the field given the recent technological advances and important future directions for exploration.