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Editorial overview: Neurobiology of learning and plasticity

Scott Waddell and Per Jesper Sjöström

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Scott Waddell

University of Oxford, Centre for Neural Circuits and Behaviour, Tinsley Building, Mansfield Road, Oxford, OX1 3TA, United Kingdom
e-mail: scott.waddell@cncb.ox.ac.uk

Scott Waddell is Professor of Neurobiology at the University of Oxford, a Wellcome Principal Research Fellow in Basic Biomedical Sciences, Senior Research Fellow at Pembroke College and Vice-Director of the Centre for Neural Circuits & Behaviour. After a B.Sc. from the University of Dundee and Ph.D. in cancer biology at the University of London, he did postdoctoral research in neuroscience at Massachusetts Institute of Technology. He was group leader for a decade in the Department of Neurobiology at UMass Medical School before relocating to Oxford. Scott's lab has contributed a cellular resolution perspective of memory and motivation in *Drosophila*. They localized synaptic junctions where memory is represented and from which behavioral expression can be controlled, demonstrated systems-level consolidation, reconsolidation and extinction of memory and revealed a division of labor and an opponent operating principle within the dopaminergic system. They also generated a single-cell transcriptomic atlas of the fly midbrain.

A central tenet in neuroscience is that neuronal plasticity underpins learning and memory, as well as the refinement of neuronal circuits during development. Plasticity is therefore essential to every animal, to develop, survive in an ever-changing environment, and to reproduce. Because of its fundamental importance and broad scope, it is not possible to cover the entire topic of *Neurobiology of Learning and Plasticity* in a single issue. We therefore selected authors who could provide the reader with a broad overview of the cutting-edge in their area of learning and memory research. These articles present different viewpoints, systems of study and approaches that advance our understanding of synaptic and circuit plasticity, memory engrams, key theoretical concepts such as the credit assignment problem, and even plasticity in humans.

Hippocampal plasticity

The hippocampal formation has long been considered a prime region for the study of episodic memory. Research has largely focused on the CA1 and CA3 regions, which remain plastic into adulthood. However, studies of the CA2 regions are relatively underrepresented, perhaps because of this region's apparent resistance to plasticity. Primary sensory neocortical regions are well known for having critical periods, during which plasticity is heightened and local circuits rewire. Carstens and Dudek [1] discuss a combination of genes and extracellular matrix components that may act as brakes on plasticity in the CA2 region, suggesting possible existence of a critical period for some forms of hippocampal plasticity.

The hippocampus is also well known for its role in spatial cognition, with a subset of hippocampal neurons preferentially firing in place fields. It is currently unclear how place fields form, with some appearing to form instantaneously. Sheffield and Dombeck [2] discuss how dendritic plateau potentials may underpin instant place fields, with little or no need for plasticity. Delayed place fields, on the other hand, may be formed by local dendritic NMDA spikes triggering synaptic plasticity.

Although the hippocampal CA1 region has served as a key model for the study of learning in the brain, most studies have focused on plasticity of excitatory neurons. However, new studies reveal the importance of interneuron plasticity. For example, some inhibitory cell types can undergo anti-Hebbian plasticity, and as overviewed by Topolnik and Camiré [3], this is determined by how calcium signals are integrated in interneuron dendrites. Lamsa and Lau [4] highlight how studies of hippocampal plasticity *in-vivo* have also demonstrated the importance of interneuron plasticity during long-term memory formation.

Jesper Sjöström

Centre for Research in Neuroscience, Department of Medicine, The Research Institute of the McGill University Health Centre, Montréal, Québec, Canada
e-mail: jesper.sjostrom@mcgill.ca

Jesper Sjöström is Associate Professor in neuroscience at McGill University, where his team explores plasticity in the brain using 2-photon imaging, quadruple patching, optogenetics, and computer modelling. After an MSc in molecular biotechnology at Uppsala University in 1996, he obtained a PhD in neuroscience at Brandeis University in 2003. Following four years of postdoctoral studies at University College London, he remained as an MRC CDF awardee running his own lab. After arriving at McGill in 2011, he received the CIHR New Investigator and the FRQS *Chercheur-Boursier* awards. His research has unveiled plasticity learning rules, neocortical connectivity patterns, and unorthodox forms of NMDA receptor signaling. He is Chief Editor of Frontiers in Synaptic Neuroscience.

Turning plasticity on and off is essential for flexible learning related to e.g. reward, novelty, and attention. Palacios-Filardo and Mellor [5] propose that neuromodulators generally facilitate long-term synaptic plasticity in the hippocampus, albeit with minor differences that may reflect differential coding of uncertainty. This regulation impacts the induction of plasticity and its expression and maintenance.

Homeostasis and plasticity of intrinsic excitability

Since Hebbian learning increases connective strength among repeatedly co-active cells, it constitutes an unstable positive-feedback loop. Synaptic plasticity must therefore be coordinated across synapses, so that functionality of neuronal circuits is not compromised. This is accomplished by homeostatic plasticity, which rescales synaptic inputs in a compensatory manner. However, it is unclear how negative-feedback homeostatic plasticity precisely relates to positive-feedback Hebbian learning. Li *et al.* [6] argue that these two types of plasticity share the same mechanisms. Homeostatic plasticity may therefore act via metaplasticity to ensure optimal Hebbian learning.

Homeostatic plasticity should preserve neuronal coding, which seems to require postsynaptic multiplicative rescaling of a neuron's inputs. Presynaptic homeostatic scaling, on the other hand, not only changes synaptic gain, but could—due to alterations in short-term plasticity—also modify synaptic information transfer. Delvendahl and Müller [7] discuss how recent studies in *Drosophila* and rodents have provided detailed insight into the molecular machinery underlying presynaptic mechanisms of homeostatic plasticity.

Homeostatic plasticity can also be achieved by altering the intrinsic excitability of neurons. Although relatively overlooked compared to its synaptic counterpart, Debanne *et al.* [8] argue for the role of intrinsic plasticity in inhibitory and excitatory neurons across different brain regions. They also discuss how bidirectional intrinsic plasticity can decrease or increase excitability depending on activity and cell type.

Maintaining and controlling plasticity

Synapses must mature and stabilize or else they are lost to pruning. Interestingly, recent findings show that many synapses are tripartite, having compartments from a presynaptic and postsynaptic neuron and an accompanying process from a glial cell. Van Horn and Ruthazer [9] discuss recent developments on glial regulation of synapse maturation in the developing nervous system. Recent evidence suggests an active role for glia, particularly astrocytes, and glia-derived signals in synapse development, maintenance, and plasticity.

At the end of a critical period of development, plasticity wanes. This restricts the brain's ability to store new information, which is one reason why adults struggle to learn new languages. It would therefore be useful if plasticity could be reverted to its juvenile, more malleable state. Patton, Blundon, and Zakharenko [10] discuss recent studies relevant to the exciting possibility of re-opening the critical period in the auditory cortex.

It is known that cocaine induces persistent synaptic as well as intrinsic plasticity in dopaminergic neurons of the ventral tegmental area. However, there is currently no effective therapeutic for cocaine addiction. Francis *et al.* [11] discuss novel findings on cocaine-induced plasticity and their translational potential. For example, transcranial magnetic stimulation and transcranial direct current stimulation can via plasticity control craving and reduce relapse.

Stochasticity and credit assignment

The locus of the expression of plasticity has important computational implications. For example, changing synaptic release alters the stochastic nature of synapse function. Llera-Montero, Sacramento, and Costa [12] explore recent findings on the computational roles of plasticity at probabilistic synapses. This provides a different perspective to most theoretical studies of learning and plasticity that model changes in mean synaptic strength, largely ignoring the stochasticity of release.

The Hebbian postulate states that coincident activity in connected neurons represents information that should be associated. Sometimes, however, this may not be correct. For example, behavioral timescales may be such that the activity driving an action is long gone once the outcome of the action is known. This leads to the temporal credit assignment problem. Suvrathan [13] provides a compelling solution: learning rules are temporally tuned to specific behavioral tasks, leading to a vast diversity of plasticity mechanisms.

A different viewpoint is provided by Perrin and Venance [14] who propose that striatal learning relies on eligibility traces. These molecular learning tags are only expressed once converted by neuromodulators, such as dopamine. Eligibility traces thus enable association of activity with later reward. Perrin and Venance [14] also discuss longstanding disagreements in striatal plasticity.

In deep learning, the credit assignment problem is relatively easily solved using the error backpropagation algorithm. But real biological neuronal networks can presumably not propagate information backwards. Richards and Lillicrap [15] argue that credit information is separately integrated in distal dendrites of pyramidal cells, effectively emulating error backpropagation by forward propagation from higher cortical regions.

Common principles from studying memory systems across phyla

Studying behavioral plasticity in a variety of animals provides a comparative view of how evolution has endowed different nervous systems with the ability to code experience. The reduced numerical complexity of some simpler nervous systems provides a cellular-resolution view of how plastic neural networks can operate and may provide principles of how more complex learning systems function in higher vertebrates.

Plasticity of excitatory glutamatergic synapses in the basolateral amygdala is considered to be a key neural representation of Pavlovian fear conditioning in rodents. Ressler and Maren [16] discuss recent advances that implicate a more distributed process of memory coding in the amygdala, involving the central nucleus. Moreover, they discuss the involvement of modulatory systems and recent evidence that argues for a key role of inhibitory interneuron plasticity.

A prime model of language acquisition in humans is song learning in songbirds. Woolley [17] discusses recent cutting-edge approaches and progress in song birds which suggest that dopaminergic neuron projections to a specialized area of the striatum—Area X—drive neural plasticity required for vocal learning. These dopaminergic neurons appear to encode classic error-prediction signals that represent whether a generated song syllable is better or worse than an expected target.

López-Schier [18] discusses the challenges and opportunities of using the larval zebrafish model to study learning and memory. The article focuses on insight gained from, and the future promise of, studying habituation of the acoustic startle escape reflex. Studies have indicated the importance of both NMDA receptor-dependent plasticity and serotonergic modulation of the neural networks involving the well-described Mauthner cells.

Many studies of olfactory learning in larval and adult *Drosophila* have demonstrated the importance of dopaminergic neurons in representing the reinforcing effects of rewarding and punishing stimuli. Thum and Gerber [19] emphasize the advantages of studying molecular and cellular mechanisms of memory using genetics and the numerically more simple nervous system of the larva. They discuss how recent progress in the larvae is now greatly facilitated by a synapse-level connectome of the reinforcing dopaminergic neurons within the mushroom body output network. Moreover, a neural wiring diagram of the entire larval nervous system is forthcoming.

Grunwald-Kadow [20] covers recent work in adult *Drosophila* which demonstrates that even innate behaviors, that are often considered to be hard-wired, are plastic. Their behavioral expression, like that of learned behaviors, depends on the appropriate context and the animal's needs. This control arises via peptidergic modulation of dopaminergic neurons that innervate-specific compartments of the mushroom bodies. Since dopamine-driven plasticity of mushroom body output connections has also been shown to underlie learned behavior, these findings argue against there being a clear distinction between circuits directing innate and learned behaviors in *Drosophila*.

Although sleep is largely conserved across the animal kingdom, the reason for sleep is largely unknown. Knowledge of sleep in *Drosophila* has reached a stage where it can be induced or inhibited on demand by controlling-specific neurons. Donlea [21] discuss how these manipulations permit a detailed investigation of the relationship between sleep, plasticity and learning and memory. One

interesting idea that has emerged from these studies, and that follows a thread common to many of the reviews in the issue, is that sleep may reset the sensitivity of dopaminergic reinforcement systems.

The full extent of insect intellect is often unrecognized. Knaden [22] describes navigational learning in the desert ant, *Cataglyphis*. These ants rely on path integration and learned visual and olfactory cues to guide them home to the nest after foraging for food. The author discusses how recent advances in CRISPR/Cas gene editing and studies of the mushroom bodies and central complex in locusts, butterflies, bees and *Drosophila* provide a technical and conceptual foundation for investigating how related neural circuits in the ant guide sophisticated learned navigation.

Perry and Chittka [23] take the intellect of invertebrates even further, highlighting fascinating observations and experiments in a variety of arthropods—bees, ants, locusts, grasshoppers, dragonflies, flies and spiders—that suggest that they employ internal models of the world to guide their behavior, which the authors suggest represents a basic form of foresight. This article should forever quash the notion that invertebrate behaviors are hard-wired.

Sparse coding of sensory information has been observed in the brains of insects and mammals and is considered to be beneficial for neural networks to store large amounts of information. Rao-Ruiz *et al*. [24] describe recent technical advances that permit researchers to visualize and manipulate the sparse nature of memory engrams in the mouse. They discuss how the intrinsic excitability of neurons and local microcircuit architecture across multiple brain regions determines which neurons are allocated to a sparse memory engram.

Observational learning—that is the ability to learn from watching the behavior of others—has been documented in a large variety of animals ranging from humans to birds, rodents, fish as well as invertebrates. Carcea and Froemke [25] discuss recent progress in understanding imitation and emulation in humans and other primates, social transmission of song and tool use in birds, and threat avoidance in rodents.

Understanding memory formation in humans is an ultimate goal. Mansvelder, Verhoog, and Goriounova [26] review recent findings on the cellular mechanisms of learning in human cortical circuits. Although there are some differences between plasticity in humans and that observed in rodents, spike timing-dependent plasticity appears to be a common feature.

Conflict of interest statement

Nothing declared.

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