Editorial

1 INTRODUCTION

Current thinking about how the brain learns from experience and encodes memories focuses on changes in synaptic strength (synaptic plasticity), while neuronal morphology and the pattern of synaptic connections are usually considered fixed. However, the adult brain is not as hard-wired as traditionally thought. By extending or withdrawing axons and dendrites, or changing the number of axonal boutons and dendritic spines (the pre- and postsynaptic parts of synapses), neurons can establish new synaptic connections or break existing ones (structural plasticity).[1] Structural changes and rewiring of connections accompany memory formation[2] and are triggered by adult neurogenesis,[3] brain and peripheral lesions,[4–6] and neurodegeneration.[7] Structural plasticity is known since the late 1960s, but its guiding principles and relevance for brain function and pathology remain poorly understood.

Exploring structural plasticity can be greatly assisted by mathematical and computational modeling.[8] In general, building models forces one to be precise and self-consistent, potentially exposing inconsistencies, hidden assumptions and missing pieces of experimental data.[9] Importantly, models enable one to deduce the implications of cellular and molecular processes for higher-level system dynamics. Models can test the plausibility of hypotheses, generate new hypotheses and make testable predictions, thereby guiding further experimental research. Moreover, models can help explain and integrate existing experimental data.[10]

Despite the evidence for structural plasticity in the brain, most traditional neural network models have fixed neuronal morphologies and a static connectivity pattern, with plasticity merely arising from changes in the strength of existing synapses (synaptic plasticity). In this volume, we for the first time bring together modeling studies that investigate the implications of structural plasticity for brain function and pathology. The book opens with a section on the experimental background of structural plasticity, followed by sections on models of homeostatic structural plasticity, models exploring the implications of structural plasticity for connectivity and learning and memory, models of neurogenesis-related structural plasticity, and models of structural plasticity in neurological disorders.

2 EXPERIMENTAL BACKGROUND

Chapter 1, Structural Plasticity and Cortical Connectivity, reviews the current state of knowledge of structural plasticity in the adult brain. Structural plasticity occurs at multiple levels, ranging from changes in axonal boutons and dendritic spines to large-scale rearrangements of axonal and dendritic trees. The chapter describes structural plasticity following enriched experience and sensory deprivation or stimulation, outlines the implications of structural plasticity for cognition and cortical connectivity, and discusses the activity-dependent and -independent processes that control structural plasticity.

In the hippocampus and the olfactory bulb, new neurons are continuously generated and integrated into pre-existing networks throughout life. Chapter 2, Structural Plasticity Induced by Adult Neurogenesis, reviews the morphological and electrophysiological evidence for neurogenesis-induced synaptic rewiring, highlighting the progress that has been made in understanding the advantages that adult-generated cells confer to brain plasticity and function.

After stroke, neurons that survive must rebuild and establish new synaptic connections. Chapter 3, Structural Neural Plasticity During Stroke Recovery, provides an up-to-date perspective on structural plasticity in the stroke-affected brain, reviewing experimental data indicating that axonal sprouting, dendritic spine formation and synaptogenesis surge in the weeks following stroke, causing rewiring of connections and partial recovery of lost functions.

As shown in Chapter 2, Structural Plasticity Induced by Adult Neurogenesis, neurogenesis-induced rewiring occurs in a manner that maintains a homeostatic balance of electrical activity. Likewise, Chapter 3, Structural Neural Plasticity During Stroke Recovery, discusses the possibility that structural changes following stroke may represent a homeostatic response to restore normal levels of activity. Chapter 4, Is Lesion-Induced Synaptic Rewiring Driven by Activity Homeostasis?, further elaborates on the role of activity homeostasis in synaptic rewiring, arguing that after loss of input, neurons strive to bring their activity back to a desired level by making new synaptic connections or breaking existing ones. The chapter reviews in vitro and in vivo experiments, including stroke and sensory deprivation studies, that suggest that activity homeostasis may drive the spine dynamics and axonal and dendritic remodeling that underlie the restructuring of synaptic connectivity following lesions.

3 HOMEOSTATIC STRUCTURAL PLASTICITY

Chapter 5, Network Formation Through Activity-Dependent Neurite Outgrowth: A Review of a Simple Model of Homeostatic Structural Plasticity, reviews one of the first models of (homeostatic) structural plasticity, showing how a wide range of phenomena can emerge from activity-dependent neurite outgrowth. In the model, each neuron grows out when its electrical activity is below a homeostatic set-point and retracts when it is above the set-point. As a result, the neurons self-organize, via a transient phase of high connectivity, into a synaptically connected network. At equilibrium the network has critical connectivity and characteristic differences in cell size, as well as the ability to self-repair following cell loss (stroke) and to reorganize after insertion of new cells (neurogenesis).

Chapter 6, Clustered Arrangement of Inhibitory Neurons Can Lead to Oscillatory Dynamics in a Model of Activity-Dependent Structural Plasticity, uses the same model to demonstrate that not only the ratio of inhibitory to excitatory cells but also the spatial arrangement of cells determines network activity and structure, with spatial clustering of inhibitory cells leading to complex oscillations in activity and connectivity.

Chapter 7, A Detailed Model of Homeostatic Structural Plasticity Based on Dendritic Spine and Axonal Bouton Dynamics, presents a detailed model of homeostatic structural plasticity based on dendritic spine and axonal bouton dynamics. In the model, spine and bouton numbers are governed by bell-shaped growth curves, with an optimal neuronal activity level for the creation of new spines and boutons, a homeostatic set-point above which, and a minimum level below which, spines and boutons are deleted. The model serves as proof-of-concept that brain repair after lesions can be brought about by homeostatic structural plasticity, producing functional and structural changes like those observed experimentally after lesions, such as spine turnover, axonal spouting, activity restoration, remapping of inputs, and alterations in network topology.

Chapter 8, Critical Periods Emerge From Homeostatic Structural Plasticity in a Full-Scale Model of the Developing Cortical Column, describes how the model of structural plasticity (MSP) introduced in the previous chapter is implemented in NEST, a well-known simulator for large-scale spiking neural networks. Using NEST simulations the authors show that critical periods emerge from homeostatic structural plasticity in a full-scale model of the developing cortical column. The timing of these periods was found to be set by the developing inhibition. Furthermore, the chapter presents a new algorithm for optimally parallelizing MSP that makes use of the Barnes-Hut algorithm from particle physics.

Chapter 9, Lesion-Induced Dendritic Remodeling as a New Mechanism of Homeostatic Structural Plasticity in the Adult Brain, proposes that in addition to the activity-dependent spine and bouton dynamics explored in the previous two chapters, another form of homeostatic structural plasticity based on remodeling of dendritic morphology may be operating after lesions. Using realistic compartmental models of healthy and denervated cells, the authors show that denervation-induced dendritic retraction boosts neuronal excitability, precisely compensating the denervation-associated loss of synapses. This dendritic plasticity is hypothesized to act in synergy with structural plasticity of the axon initial segment.

The next two sections explore further forms of structural plasticity, the interactions between structural plasticity and synaptic plasticity, and the implications of structural plasticity for connectivity and learning and memory.

4 STRUCTURAL PLASTICITY AND CONNECTIVITY

Chapter 10, The Role of Structural Plasticity in Producing Nonrandom Neural Connectivity, studies the impact of reconfiguration of neural connections on circuit topology and connection strength distribution. Using a model in which connections are randomly formed but maintained by Hebbian-like synaptic plasticity, the author shows that structural plasticity yields unimodal synaptic strength distributions and highly interconnected clusters of neurons that are responsive to the same stimulus, just as in cortical networks.

Using an established model of a self-organizing neural network with structural plasticity, Chapter 11, Structural Plasticity and the Generation of Bidirectional Connectivity, shows that any inhomogeneity in connection probability will lead to the observed overabundance of bidirectional connections in cortical microcircuits as compared with random networks. The authors discuss various factors influencing this overrepresentation, including spike timing-dependent synaptic plasticity of excitatory and inhibitory synapses.

Chapter 12, Spike Timing-Dependent Structural Plasticity of Multicontact Synaptic Connections, summarizes models of spike timing-dependent synaptic and structural plasticity, showing how cooperative synapse formation and the observed multisynapse connections in cortex can arise from the dependence of dendritic spine dynamics on pre- and postsynaptic spiking. In addition, the chapter demonstrates how cooperation between spines leads to stable synaptic connections with highly reliable synaptic transmission.

Chapter 13, Selection of Synaptic Connections by Wiring Plasticity for Robust Learning by Synaptic Weight Plasticity, shows that structural plasticity can generate functionally efficient connectivity structures. Using a simple model of an inference task, the authors found that a Hebbian form of structural plasticity selectively eliminates noninformative connections and so can enhance learning by synaptic plasticity. Furthermore, the generated connectivity was shown to be noise resilient, a property especially beneficial in rapidly changing environments.

5 STRUCTURAL PLASTICITY AND LEARNING AND MEMORY

Chapter 14, Within a Spine's Reach, reviews computational and experimental studies that address how dendritic spine dynamics can change synaptic connectivity and the dendritic distribution of synapses. The authors consider how spine dynamics might be harnessed to fine-tune information processing and storage, and discuss the importance of microscale connectivity for neurorealistic simulation and neuromorphic computing.

Chapter 15, Impact of Structural Plasticity on Memory Capacity, focuses on computational models that simulate learning using structural plasticity, showing that activity-dependent reallocation of synapses (rewiring) and dendritic remodeling enhance learning and storage capacity by exploiting nonlinear dendritic mechanisms. The authors also discuss efforts towards hardware implementation of models of structural plasticity.

Chapter 16, Long-Term Information Storage by the Interaction of Synaptic and Structural Plasticity, concentrates on multisynapse connections and the interactions between synaptic and structural plasticity. The chapter shows how synaptic connectivity can be controlled by external stimulation and how multisynapse connections enable long-term memory storage despite the continuous turnover of synapses observed in cortical networks.

Chapter 17, Impact of Structural Plasticity on Memory Formation and Decline, further discusses possible functions of structural plasticity for memory formation, showing that structural plasticity increases storage efficiency and stability of memories in Willshaw- and Hopfield-type network models. Moreover, the author demonstrates that models with structural plasticity can explain cognitive phenomena such as retrograde amnesia better than models based solely on synaptic plasticity.

6 NEUROGENESIS-RELATED STRUCTURAL PLASTICITY

Chapter 18, Adult Neurogenesis and Synaptic Rewiring in the Hippocampal Dentate Gyrus, describes a combined experimental and computational study on synaptic rewiring induced by the integration of adult-generated cells into the hippocampal circuitry. The chapter shows that higher rates of cell proliferation lead surprisingly to less synaptic rewiring. This experimental finding is explained by the model of homeostatic structural plasticity introduced in Chapter 7, A Detailed Model of Homeostatic Structural Plasticity Based on Dendritic Spine and Axonal Bouton Dynamics, which is here extended to incorporate neurogenesis and apoptosis.

Chapter 19, Modifications in Network Structure and Excitability May Drive Differential Activity-Dependent Integration of Granule Cells into Dentate Gyrus Circuits During Normal and Pathological Adult Neurogenesis, presents a computational model showing that both intrinsic cellular excitability and network connectivity, through their effect on network-wide activity patterns, critically influence the integration of new-born cells into established circuits. The model also reveals under what conditions aberrant structural integration of new cells may occur in chronic pathologies such as epilepsy.

Chapter 20, Computational Perspectives on Adult Neurogenesis, reviews a variety of computational models, ranging from simple abstract neural network models to complex biology-based models, that have been built to understand the functional role of adult neurogenesis. Proposed functions of neurogenesis include improving pattern separation, encoding temporal context, and learning novel information. The authors also introduce a neural modeling language called Neurons to Algorithms, suitable for modeling neurogenesis and structural plasticity in general.

Chapter 21, Restricted Boltzmann Machine Models of Hippocampal Coding and Neurogenesis, challenges the widely held assumption that neurogenesis increases pattern separation. The authors

propose that the hippocampus forms a probabilistic, generative model of its input. Using Restricted Boltzmann Machine models, they show that networks with neurogenesis are more robust against interference but produce less pattern separation. Furthermore, they show that models with neurogenesis can learn representations of locations and sequential events.

7 STRUCTURAL PLASTICITY AND PATHOLOGY

In stroke, both the primary lesion site and adjacent and remote brain areas experience cell death and loss of connections. Chapter 22, Modeling the Impact of Lesions in the Brain, reviews computational models that explore the impact of such structural changes on brain topology and dynamics. In addition, the authors discuss how the brain may adapt to structural damage, and how their models can be applied to other brain disorders with aberrant connectivity, such as epilepsy, schizophrenia and Parkinson's disease.

Epilepsy can develop after a brain-damaging insult, such as stroke, through a number of molecular and cellular changes (epileptogenesis). Chapter 23, Network Models of Epilepsy-Related Pathological Structural and Functional Alterations in the Dentate Gyrus, reviews computational models that address the impact on brain dynamics of structural alterations in the adult hippocampus during epileptogenesis, such as hilar cell loss and mossy fiber sprouting. The models examine the relationship between pathological network reorganization and the emergence of hypersynchronous network activity.

Neuromotor recovery after stroke is the result of a complex interplay between activity-dependent reorganization of brain areas close to the lesion, the recruitment of new neural pathways, and the development of novel motor strategies. Chapter 24, Computational Models of Stroke Recovery, reviews various computational models of stroke recovery, relating them to mechanisms of synaptic and structural plasticity and discussing their implications for stroke treatment.

A treatment procedure that is increasingly used to alleviate the symptoms of degenerative brain disorders, such as Parkinson's disease, is deep brain stimulation (DBS). Chapter 25, Neural Plasticity in Human Brain Connectivity: The Effects of Deep Brain Stimulation, explores the changes in functional and structural connectivity induced by DBS and shows how these changes can be characterized and quantified by advanced graph theoretical measures and dynamic mean field models. The authors argue that DBS might have a restorative effect on damaged fiber tracts, opening up new avenues for the treatment of stroke.

8 OUTLOOK

The majority of plasticity studies in the past focused on synaptic plasticity rather than structural plasticity. With the advance of new imaging techniques, interest in structural plasticity has recently resurged. Many findings have revealed that the adult brain is capable of altering its wiring diagrams, but the driving forces underlying structural plasticity and its role in brain function remain unclear. This book reviews the current state of knowledge of structural plasticity and shows how unraveling the workings of structural plasticity may benefit from computational approaches. We hope that the book will inspire further research, both computational and experimental, and will help computational and experimental neuroscientists in their quest to understand the full adaptive potential of the adult brain.

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