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EDITORIAL

Recent advances in hippocampal structure and function

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The hippocampal formation, an evolutionary old part of the mammalian temporal cortex, belongs to the most widely studied systems in modern neuroscience. While the coming and going of scientific hotspots is no entirely rational process there are some obvious scientific, clinical and methodological reasons for this widespread interest. From a basic research perspective, the hippocampus can be considered a key structure for spatial and declarative memory formation and, hence, for plasticity and adaptive functions of the central nervous system. Recent advances in the description of place-encoding cells and ensembles have elucidated the principles of spatial memory formation at an unprecedented depth, such that mnemonic functions do now belong to the best-studied examples of neuronal mechanisms underlying cognitive processes. It is probably fair to say that most of our knowledge on synaptic plasticity in mammals comes from hippocampal circuits, including the famous paradigm of long-term potentiation (LTP). More recently, the analysis of learning and the underlying neuroplastic processes has reached the level of multi-neuronal activity patterns in neuronal networks, enabling a wider, system-level perspective to these complex functions. From a medical perspective, malfunctions of the hippocampal formation are pivotal to several diseases, including epilepsy, depressive disorders, ischemic-hypoxic damage, traumatic brain injury, stress-induced pathologies and, most importantly, Alzheimer's disease. Research on these conditions, both in humans and in animal models, has not only revealed important pathophysiological mechanisms, but also fostered the understanding of basic mechanisms. Indeed, several chronic neurological conditions have been conceptualized as consequences of pathological neuronal plasticity, linking maladaptive processes with mechanisms of learning and memory formation. Finally, the clear, three-layered structure of the hippocampus allows an easy, unambiguous identification of cells and fiber tracts, at least at first glance. The recurrent networks and layer-specific synaptic connections do also facilitate the generation of large extracellular voltage gradients following synchronous input. This is the basis for stable field spontaneous or stimulation-evoked field potentials which are easy to measure, yet highly instructive for studies of synaptic plasticity and coordinated network patterns.

Understanding hippocampal functions has always been tightly linked to studies of the underlying structures. Indeed, many of the major breakthroughs during past years can be assigned to a 'functional anatomy' approach, linking neuronal activity with analysis of cell types or connectivity patterns. We therefore decided to devote a special issue of cell and tissue research to recent advances in structure and function of the hippocampus and related networks. Leading experts summarize the state-of-the-art at the level of (i) different networks and their connectivity, (ii) different cell types and their particular functions, and, (iii), specific connections and mechanisms of plasticity.

In the first series of chapters, we address different local networks, focusing on their unique architecture and connectivity with other regions. It is clear that the precise properties of such sub-networks account for their functional specialization and determine their role in the systemic functions of the hippocampal formation as a whole. This is illustrated by

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Robert et al. (2018) who provide an overview of CA2, a recently "re-discovered" hippocampal subfield, which plays a key role at the interface between CA3 and CA1, and appears to serve highly specific functions in the generation of patterned network activity and social memory. Similarly, Simonnet and Fricker (2018) describe the components, connectivity and specific place- or position-encoding function of the presubiculum. This more complex cortical area has also been highly understudied, but it is now clear that its unique neuronal architecture may be important for understanding the encoding of head direction in space-exploring animals. Böhm et al. (2018) widen this view to the more classical subicular network, which forms the major interface between the hippocampus proper and neocortical networks. Again, recent advances on cellular diversity as well as internal and external connectivity give rise to interesting functional hypotheses on diverse, parallel streams of information between the hippocampus and its target areas. Müller and Remy (2017) complete these reviews on specific sub-networks by elucidating interactions between the septum and the hippocampus, which are key to state-specific changes in excitability and network patterns. Again, recent technical advances have allowed important insight into the role of different cell types in these interactions. The network level-related chapters of this special issue end with a review by Rolls (2017) who summarizes the contribution of different networks to different memory-related cognitive functions. Taking a theoretical neuroscientist's perspective, he illustrates how different network architectures support different cognitive operations. Thereby, his review provides a comprehensive and timely account of structure-function relationships in cortical networks.

The second series of chapters puts the focus on the specific structure and function of different cell types. Understanding cellular heterogeneity and cell type-specific circuit integration is a critical level between molecular-cellular and systemic neurosciences. Although dating back to the days of Cajal, this tradition of functional anatomy is very lively and raises increasing interest. We begin with a chapter by Preston-Ferrer and Burgalossi (2017) who address the important question of cell type identification in behaving animals in vivo. How can measurements of single neurons - discharge patterns or even subthreshold behavior - in behaving animals be related to cell types? Recent methodological advances allow unprecedented insight into mechanisms of cell-network-integration. While Preston-Ferrer and Burgalossi focus on principal neurons in the dentate gyrus, Booker and Vida (2018) explain the heterogeneity and differential connectivity of inhibitory interneurons – a major leitmotiv in functional neuroanatomy as well as cellular- and network-level neurophysiology during past decades. Not at least, understanding interneuron structure and function is a prerequisite to make sense of the dominant patterns of network oscillations, another research focus during the past two decades. The review by Scharfman (2017) addresses a peculiar cell type at the interface between the dentate gyrus and CA3: hilar mossy cells. Understanding the important function of these highly active excitatory interneurons requires a highly interdisciplinary approach including high-resolution anatomy, and cellular electrophysiology in vitro and in vivo, as well as modern cell-type specific molecular tools. The final article of this series gives credit to the important and growing field of research on glia cells. Seifert and Steinhäuser (2017) provide an overview of macroglia, i.e., the subtypes, properties and functions of non-neuronal cells except microglia.

The third and final group of articles makes use of many of the ideas and results presented before by reviewing special types of connections, neurogenesis and modulation. We do not provide a review on classical plasticity of chemical synapses, i.e., LTP, long-term depression (LTD) and related issues, which are well covered by available literature. We rather highlight four topics with major impact on understanding structure and function of the hippocampal formation. First, Traub et al. (2018) review the role of gap junctions as electrical inter-neuronal connections. Such electrical synapses play an established role for synchronization of interneurons. Their presence and synchronizing role for principal neurons remains controversial, especially with respect to the hypothesized inter-axonal localization. Evidence for such connections and functional consequences are systematically reviewed. Toda and Gage (2017) review another non-canonical mechanism: adult neurogenesis. The generation and circuit integration of new neurons in the hippocampus is now well established and has major impacts on activity-dependent plasticity, although its significance in humans is still a matter of different opinions. This field of neuroscience raises great interest, not at least due to its potential role for life-long learning and plasticity. Edelmann and Lessmann (2018) address the important neuromodulatory function of dopamine, another important mechanism for state-dependence of function and plasticity of hippocampal networks. While its importance is undisputed, the details of dopamine release and downstream effects are far from completely understood. Finally, von Bohlen und Halbach and von Bohlen und Halbach (2018) provide an overview of the action of an important neuromodulatory protein – BDNF. Again, the importance of this molecule for hippocampal structure and function is clearly established, but many details remain to be clarified. With these two reviews on neuromodulators we conclude the section on non-conventional mechanisms of connectivity and plasticity.

Together, the series of reviews, written by leading researchers in the respective fields, shall help to provide overviews and updates on the most recent developments in structure and function of the hippocampus and related systems. The choice of topics highlights new topics, methods and concepts. We hope it will be helpful to old and new members of the growing 'hippocampus scence'.

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