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EDITORIAL

THE HIPPOCAMPUS IN AGING AND DISEASE: FROM PLASTICITY TO VULNERABILITY

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Abstract—The hippocampus has a pivotal role in learning and in the formation and consolidation of memory and is critically involved in the regulation of emotion, fear, anxiety, and stress. Studies of the hippocampus have been central to the study of memory in humans and in recent years, the regional specialization and organization of hippocampal functions have been elucidated in experimental models and in human neurological and psychiatric diseases. The hippocampus has long been considered a classic model for the study of neuroplasticity as many examples of synaptic plasticity such as long-term potentiation and -depression have been identified and demonstrated in hippocampal circuits. Neuroplasticity is the ability to adapt and reorganize the structure or function to internal or external stimuli and occurs at the cellular, population, network or behavioral level and is reflected in the cytological and network architecture as well as in intrinsic properties of hippocampal neurons and circuits. The high degree of hippocampal neuroplasticity might, however, be also negatively reflected in the pronounced vulnerability of the hippocampus to deleterious conditions such as ischemia, epilepsy, chronic stress, neurodegeneration and aging targeting hippocampal structure and function and leading to cognitive deficits. Considering this framework of plasticity and vulnerability, we here review basic principles of hippocampal anatomy and neuroplasticity on various levels as well as recent findings regarding the functional organization of the hippocampus in light of the regional vulnerability in Alzheimer's disease, ischemia, epilepsy, neuroinflammation and aging.

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Key words: hippocampus, vulnerability, neuroplasticity, subfield imaging, Alzheimer's disease, aging.

INTRODUCTION

The hippocampus is widely regarded as being in the center of a brain network supporting encoding, consolidation and retrieval of memory and, being central to the study of human memory, has been implicated in episodic and semantic long-term memory, novelty detection, sleep-dependent memory consolidation, pattern discrimination, spatial navigation and the binding of temporally and spatially distributed representations (Bartsch, 2012). Beyond these cognitive functions, the hippocampus is also involved in the regulation of emotion, fear, anxiety, and stress. The hippocampus has an intriguing cyto- and network architecture and it has been suggested that the particular circuit arrangement in different subregions of the hippocampus subserves differential mnemonic operations (Kesner and Rolls, 2015). Indeed, in recent years, a differential and complex modular organization of hippocampal anatomy and function emerged (Strange et al., 2014). Also, the concept of a regional specialization and organization of hippocampal functions has been increasingly studied in humans using high-resolution MR subfield imaging indeed showing that mnemonic operations can be attributed to subnetworks and subregions of the hippocampus (Bakker et al., 2008; Mueller et al., 2011) (Chetelat, 2008).

The hippocampus has long been considered as a classic example for the study of functional neuroplasticity as many models of synaptic plasticity such as long-term potentiation (LTP) and -depression (LTD), and spike-timing-dependent plasticity have been observed in hippocampal circuits and are thought to be fundamental to learning and memory (Bliss and Schoepfer, 2004; Pastalkova et al., 2006). Neuroplasticity is considered the ability to adapt and reorganize the structure or function to internal or external stimuli and occurs on the cellular, population, network or behavioral level (Cramer et al., 2011). Neuroplastic mechanisms are reflected in the cyto- and network architecture and are mirrored in the intrinsic properties of hippocampal neurons and circuits. Structural plasticity in hippocampal neurons and circuits includes modifications of dendritic tree size and spines, synapse number as well as the

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Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; DG, dentate gyrus; EAE, experimental autoimmune encephalomyelitis; EC, entorhinal cortex; IL-1β, interleukin-1 beta; LTD, long-term depression; LTP, long-term potentiation; MS, multiple sclerosis; MTL, medial temporal lobe; NFT, neurofibrillary tangle; ROS, reactive oxygen species; TLE, temporal lobe epilepsy.

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formation of new neurons (Leuner and Gould, 2010). Cellular neuroplasticity is not confined to physiology but also present in the context of progressive pathology, such as neurodegeneration in Alzheimer's disease (AD) in humans and is increasingly studied (Mufson et al., 2015). On a network level, neuroplasticity in hippocampal circuits drives changes in connectivity, structural modifications and behavioral outcome (Finke et al., 2013a; Ryan et al., 2015).

This high degree of hippocampal plasticity, however, is accompanied by the pronounced vulnerability of the hippocampus to deleterious conditions such as ischemia, epilepsy, neuroinflammation, chronic stress, neurodegeneration and aging suggesting that the instrinsic properties of hippocampal neurons and circuits that are critical for neuroplasticity such as glutamatergic excitability may also predispose to metabolic injuries occurring in the process of various neurological and psychiatric diseases (Bartsch et al., 2015). This view is reflected in the suggestion by Bruce McEwen that 'the plasticity of the hippocampus is the reason for its vulnerability' (McEwen, 1994).

In this special issue of *Neuroscience*: 'The hippocampus in aging and disease: from plasticity to vulnerability', we will review basic principles of hippocampal anatomy and neuroplasticity on various levels as well as recent findings regarding its functional organization with respect to regional vulnerability, which is critical for the understanding of neurocognitive diseases (Bartsch, 2012).

HIPPOCAMPAL ANATOMY

Encoding, consolidation and retrieval of mnemonic information is critically dependent on a large reciprocal network of regions that includes neocortical association regions, subcortical nuclei, the medial temporal lobe (MTL), parahippocampal areas and the hippocampal formation (Fig. 1). The hippocampus is considered the central node in this circuit. It receives input from almost all neocortical association areas via perirhinal and parahippocampal cortices and finally through the entorhinal cortex (EC) (van Strien et al., 2009). The hippocampus is a three-layered allocortical structure that is reciprocally connected to other cortical and subcortical areas (Figs. 1 and 2). The principal neurons of the hippocampus are organized in layers and receive unidirectional polymodal input from the EC, where layer II neurons project via the perforant path to granule cells in the dentate gyrus (DG) (Strange et al., 2014). The trisynaptic pathway from the DG to CA3 via mossy fibers and onward to CA1 via Schaffer collaterals is the principal feed-forward circuit involved in the processing of information through the hippocampus (Fig. 2). Additionally, layer III neurons from the EC directly project to CA1 neurons via the temporoammonic path (perforant path to CA1). CA1 pyramidal cells -the major output relay neurons – project via the subicular complex back to deep layers of the EC and to various subcortical and cortical areas (Murray et al., 2011). The regions CA1–CA3 are separated into four layers (pyramidal, stratum oriens, stratum lucidum, stratum radiatum). The structure of this feed-forward circuit with its limited redundancy may be critical for learning and memory but may also contribute to its vulnerability during insults (Lavenex and Amaral, 2000). Learning and memory processes within hippocampal circuits are regulated by synaptic plasticity mechanisms that require activation of specific molecular cascades (Aksoy-Aksel and Manahan-Vaughan, 2015). For example, the induction of LTP in the CA1 region involves postsynaptic calcium ion entry via NMDA receptors with subsequent activation of protein kinases (Aksoy-Aksel and Manahan-Vaughan, 2015).

The hippocampus receives large amounts of sensory information from neocortical structures, which is integrated in several recurrent subnetworks with distinct computational operations (van Strien et al., 2009). The DG with its three layers (molecular, granular, and polymorphic layers) consists mainly of granule cells and receives polymodal input form the EC. The axons of the DG granule cells form the mossy fiber system and project to CA3 (Amaral et al., 2007). Mossy fibers also project back onto granule cells, thus forming a recurrent network. In addition the DG receives information from the contralateral hippocampus via commissural projections (Amaral et al., 2007). Axon collaterals of CA3 pyramidal neurons synapse onto other CA3 neurons, forming a recurrent autoassociative network whereas CA3 neurons projecting back to the dentate network form a heteroassociative network (Lisman, 1999). CA1 pyramidal neurons receive information which has been pre-processed in the subnetworks of the DG and CA3, but also receives direct projections from the EC suggesting that the function of CA1 neurons includes comparing new information from the EC with stored information via CA3 in terms of mismatch, error and novelty detection (Lisman and Otmakhova, 2001).

Besides the structural layout of connectivity of these hippocampal circuits, it is believed that mnemonic information is represented and processed by spatio-temporal patterns of firing in groups of neurons, also referred to as cell assemblies involving fast oscillatory dynamics in various frequency bands (e.g. theta, sharp-wave ripples, slow oscillations and gamma oscillations) that are synchronized and temporally coordinated within and across cortical regions (Wulff et al., 2009; Battaglia et al., 2011; Buzsaki and Moser, 2013).

NEUROPLASTICITY AND THE HIPPOCAMPUS

> "*Neuroplasticity can be broadly defined as the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections; can be described at many levels, from molecular to cellular to systems to behavior; and can occur during development, in response to the environment, in support of learning, in response to disease, or in relation to therapy. Such plasticity can be viewed as adaptive when associated with a gain in function or as maladaptive when associated with negative consequences such as loss of function or increased injury, points illustrated by animal models and some human studies.*"
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> (Cramer et al., 2011).