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REVIEW

DISTINGUISHING ADAPTIVE PLASTICITY FROM VULNERABILITY IN THE AGING HIPPOCAMPUS

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Abstract—Hippocampal circuits are among the best described networks in the mammalian brain, particularly with regard to the alterations that arise during normal aging. Decades of research indicate multiple points of vulnerability in aging neural circuits, and it has been proposed that each of these changes make a contribution to observed age-related cognitive deficits. Another view has been relatively overlooked – namely that some of these changes arise in adaptive response to protect network function in aged animals. This possibility leads to a rather different view on the biological variation of function in the brain of older individuals. Using the hippocampus as a model neural circuit we discuss how, in normally aged animals, some age-related changes may arise through processes of neural plasticity that serve to enhance network function rather than to hinder it. Conceptually disentangling the initial age-related vulnerabilities from changes that result in adaptive responses will be a major challenge for the future research on brain aging. We suggest that a reformulation of how normal aging could be understood from an adaptive perspective will lead to a deeper understanding of the secrets behind successful brain aging and our recent cultural successes in facilitating these processes.

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Key words: dentate gyrus, CA1, CA3, medial entorhinal cortex, plasticity.

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INTRODUCTION

A reformulation of how normal aging might be understood within a framework of continual adaptive change, rather than accelerating vulnerability, is timely. For example, the December 2014 Nobel Week Dialogue Series was devoted to discussions of ''The Age to Come'' – or predictions for the evolving biology and demographics of future generations and what social impact these changes will bring. Although not directly stated, a number of speakers acknowledged a shift in Zeitgeist across gerontological disciplines from a focus on the vulnerabilities that arise during aging, to an appreciation of the cultural achievement that longer lives and health spans reflect. Two examples from eminent psychologists capture the tone of the discussions. This includes the suggestion made by Ursula Staudinger that instead of referring to the current demographic trend as ''Aging Societies'', it would be more appropriate to frame the lifespan gains in terms of ''Societies of Longer Lives''. Laura Carstensen suggested an even bolder framework for appreciating our survival gains as a species, emphasizing the fact that this group of largely healthy older individuals is perhaps the only natural resource in the world that is not shrinking.

The biological benefits of increased access to nutrition, education and medical care over the past

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Abbreviations: AHPs, afterhyperpolarizing potentials; fEPSP, field excitatory postsynaptic potential; GAD, glutamic acid decarboxylase; MEC, medial entorhinal cortex; PSD, postsynaptic density.

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century have resulted in the current generation of individuals over 65 years of age having significant brain and cognitive health advantages. While the maximum lifespan attainable is probably not changing, this cultural evolution has allowed substantial extension of average productive lifespans. Indeed, elderly individuals remain active in the work force longer today than in previous generations (Helman et al., 2010). Despite these improvements, a substantial number of individuals still face the difficulties that can arise with age-related cognitive impairments. A major goal of brain aging research is to understand the basic biological processes that enable high-functioning aged individuals to sustain cognitive health, and what differs between these individuals and those who experience more serious cognitive impairments. Decades of work, both in humans and other animal subjects, have proven fruitful in understanding this basic biology.

In all species examined, brain functions critical for cognition change across the lifespan. Age-related functional alterations have been identified at the level of molecules, cells, circuits, and behavior; yet no well-accepted comprehensive theory of brain aging exists. The ability to understand the life course of brain aging is complicated by the great variability in behavioral performance that is apparent even throughout development and young adulthood. During aging, this variation continues to manifest itself in individuals through the range of subtle cognitive change to dementia. Our understanding of why some individuals appear more vulnerable to age-related cognitive decline than others is far from complete (Plassman et al., 2007; Luo and Craik, 2008), and the answer to this question likely lies in the interaction between the basic biology of the aging brain and the ever-changing environment that the brain interacts with.

A process fundamental to brain function is the ability of neurons to alter their molecular expression profile, connectivity and physiological response properties based upon their interactions with both internal physiological processes and the external world. Age-related declines in neural plasticity mechanisms have been described previously in some detail (Burke and Barnes, 2006), and are believed to be a major driving force behind the cognitive changes associated with aging. It has almost become 'dogma' to consider such age-related changes as vulnerabilities that compromise function. While age-related vulnerabilities certainly exist and do lead to dysfunction, there are other processes at play in normally aged brains that engage mechanisms of plasticity that can serve to buffer the negative outcome of these changes. An 'adaptive view' of brain aging is not meant to replace the reality that some processes become vulnerable with age, but rather to emphasize that neural networks are dynamic, and many age-related alterations in the brain likely make use of these plastic mechanisms to adjust functionality. This framework is meant to emphasize that it may be difficult to distinguish the 'primary pathology' from a change that is adaptive. The conceptual disentanglement of positive and negative age-related alterations is crucial, however, when interpreting brain and cognitive aging data, and thus remains a major challenge for future aging research. Such a task is complex as different networks of neurons may have unique vulnerabilities that engage different adaptive solutions. Unfortunately, few regions of the brain have been investigated with enough depth to achieve this level of understanding.

The hippocampus, situated in the medial temporal lobe, is among the best studied regions of the brain, particularly with respect to normal aging (Gallagher and Rapp, 1997; Rosenzweig and Barnes, 2003; Kelly et al., 2006; Morrison and Baxter, 2012). This brain structure is crucial for the formation of episodic memories (Burgess et al., 2002; Gilboa et al., 2006; Moscovitch et al., 2006; Bird and Burgess, 2008), and damage to the hippocampus results in memory defects that show some similarities to those experienced during normal aging. Unlike in pathological conditions such as Alzheimer's disease, the number of principal neurons in the hippocampus and the adjacent entorhinal cortex is preserved in aged rodents (Rapp and Gallagher, 1996; Rasmussen et al., 1996; Merrill et al., 2001; Rapp et al., 2002), monkeys (Gazzaley et al., 1997; Merrill et al., 2000; Keuker et al., 2003) and humans (West et al., 1994; Morrison and Hof, 1997), suggesting that age-related memory deficits arise from numerous subcellular changes. In this special issue, a variety of experimental data are presented and discussed with the goal of conceptually disentangling vulnerable processes from potentially adaptive ones at play in the hippocampus. While the present contribution will not be a comprehensive review of hippocampal aging, its intent is to provide a novel perspective on the current interpretation of some of its age-related changes.

ADAPTIVE CHANGES IN THE HIPPOCAMPUS OF AGED ANIMALS

To illustrate how some age-related changes may function in adaptive ways in response to changing neuronal environments, we will emphasize how age-related changes interact and combine to produce a variety of functional outcomes, both adaptive and non-adaptive. Fig. 1 provides a schematic of the relevant components of the circuit we will examine (Amaral and Lavenex, 2007). Briefly, projection neurons from the superficial layers of the entorhinal cortex constitute the perforant path axons, which terminate on granule cells of the dentate gyrus and pyramidal neurons in CA3 and CA1. We will focus on the layer II medial entorhinal cortical cell input to the dentate gyrus and CA3 for the purpose of this discussion. The axons of these cells form en passant synapses on the middle third of the granule cell dendritic tree, and the outer branches of CA3 pyramidal cells. The axons of granule cells in the dentate gyrus form mossy fiber synapses that innervate above, below and within the pyramidal cell layer of CA3. Together, the CA3 pyramidal cell axons form the Schaffer collateral fiber pathway that innervate apical dendrites of CA1 pyramidal cells in the stratum radiatum and their basal dendrites in the statum oriens. CA1 pyramidal cell axons project topographically within the subiculum. Cells residing more proximally in CA1 innervate distal subiculum and cells residing

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