HHS Public Access

Author manuscript

Neuroscience. Author manuscript; available in PMC 2016 November 19.

Published in final edited form as:

Neuroscience. 2015 November 19; 309: 17–28. doi:10.1016/j.neuroscience.2015.08.001.

Distinguishing adaptive plasticity from vulnerability in the aging hippocampus

Daniel T. Gray[1,2] and **Carol A. Barnes**[1,2,3]

[1]Evelyn F. McKnight Brain Institute, University of Arizona, Tucson, AZ

[2]ARL Division of Neural Systems, Memory and Aging, University of Arizona, Tucson, AZ

[3]Department of Psychology, Neurology, and Neuroscience, University of Arizona, Tucson, AZ

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.

Keywords

dentate gyrus; CA1; CA3; medial entorhinal cortex; plasticity

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

Correspondence to: Carol A. Barnes, Evelyn F. McKnight Brain Institute, University of Arizona, Life Sciences North, Rm 362, Tucson, AZ 85724-5115, carol@nsma.arizona.edu.

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 century has 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. Figure 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 distally in CA1 project to the proximal subiculum. The output of the subiculum distributes widely to other cortical areas, including the deep layers of the entorhinal cortex, to which CA1 also directly projects. Age-related changes have been

noted at many steps in this circuit, some of which will be discussed below. Using this circuit we provide five examples that illustrate how seemingly independent age-related changes may interact to provide adaptive compensatory responses to changing neuronal environments. Because the data to demonstrate the direction of causation between putative primary and secondary brain changes do not currently exist, each example below will be proposed as a hypothesis.

Hypothesis 1: Global changes in cholinergic drive and gap junctional connectivity may balance network excitability

Conceptually, a neuronal process vulnerable to the effects of aging may negatively affect function in numerous brain regions. There is, in fact, evidence for generalized vulnerability within the hippocampal circuit. Two such examples serve as excellent illustrations of the concept of adaptive changes in response to age-related vulnerabilities, and highlight the difficulty in disentangling the two. First, compared to young rats, the effective cholinergic drive onto hippocampal principal neurons is about half as powerful in the dentate gyrus, CA3 and CA1 regions of behaviorally-impaired aged rats (Shen and Barnes, 1996). Two candidate mechanisms for these decreases are the conformational changes in muscarinic receptors noted with age (Lippa et al., 1985; Chouinard et al., 1995) and decreased functional output from two subcortical sources of cholinergic input to the hippocampus, the medial septum and the diagonal band complex (Schliebs and Arendt, 2011). Acetylcholine renders hippocampal neurons more excitable by reducing specific potassium conductances (Ben-Ari et al., 1981; Krnjevic et al., 1981; Nakajima et al., 1986), thus decreased cholinergic drive would be expected to result in less excitable neurons. Perhaps paradoxically, however, there are no decreases observed in firing rates of single units in behaving animals. The second example of an age-related change that occurs across the hippocampus is an increase in gap junctional connections between principal neurons. Specifically, gap junction connectivity increases in aged rats by 15%, 18% and 15% between granule cells of the dentate gyrus and both CA3 and CA1 pyramidal cells, respectively (Barnes et al., 1987). This increased electrotonic coupling might be expected to increase neuronal excitability across all subregions of the hippocampus, and would functionally operate in direct opposition to the decreased cholinergic drive onto the same populations of neurons.

While it is unclear how the two general hippocampal changes described above interact to balance the overall excitability of these circuits, a number of possibilities can be considered. For example, it is conceivable that decreased cholinergic drive onto hippocampal neurons plays a role in inducing increased gap junctional protein expression. It is also possible that other homeostatic processes participate in combatting the reduced neuronal excitability resulting in an electrophysiologically ‘balanced’ network. Taking this view, cholinergic function would be the ‘vulnerable trait’ during aging, and the increase in gap junction expression an adaptive response to this change. Alternatively, increased neuronal excitability from electrotonic coupling could induce conformational change in muscarinic receptors. An equally likely third alternative can also be proposed - the two processes may be independent of one another, and by coincidence work in opposition to preserve single unit firing rates in the circuit. The current understanding of how these (and other) age-

related changes co-vary is lacking, and these are the fundamental questions and data necessary for a fuller appreciation of how widespread and consistent changes within a circuit can result in apparently adaptive solutions for brain function. This is not to imply that these adjustments do not alter output signals from the hippocampus - they almost certainly do. Regardless, the more important point remains: age-related alterations in the hippocampus, such as the two described above, must be considered as a balance between dynamic processes and not as isolated changes.

Hypothesis 2: Synaptic strengthening of medial entorhinal cortical input to the dentate gyrus may balance the effects of synapse loss

In the dentate gyrus there are fewer axospinous synapses from projection neurons of the medial entorhinal cortex (MEC) on to granule cells in aged rats (Geinisman et al., 1992, 1995). The inputs from MEC contact the middle third of the granule cell molecular layer. Cells are not lost with age in MEC (Gazzaley et al., 1997; Merrill et al., 2000, 2001), and therefore cannot account for this synapse loss. Rather, electrophysiological data suggest that reduced synapse number is due to axon collateral pruning, as aged animals exhibit reduced perforant path presynaptic fiber potential amplitudes (Barnes and McNaughton, 1980). In line with these findings, MRI volumetric measurements, diffusion tensor imaging and tractography suggests that aged humans also have significant decreases in parahippocampal white matter, which includes the axons of the perforant path (Rogalski et al., 2012; Stoub et al., 2012).

Alongside the reduction of axon collaterals from the entorhinal cortex, the amplitude of the field excitatory postsynaptic potential (fEPSP) of aged rat granule cells is also reduced (Barnes, 1979; Barnes and McNaughton, 1980). The resulting reduction in the depolarization of aged granule cells from a major cortical input could profoundly affect the ability of the circuit to accurately carry out network computations. How do the granule cells reach action potential discharge threshold with such a significant loss of synapses? Another observed age-related change in this circuit may provide at least a partial answer to this question. It is possible to measure the amplitude of the intracellularly-recorded depolarization caused by stimulation of a single axon collateral (unitary EPSP), thereby enabling an estimate of the strength of individual synapses. When such an experiment was conducted in young and aged rats, each perforant path - granule cell synapse was found to be more powerful on average in the older animals (Barnes and McNaughton, 1980). Thus, it is possible that more potent synapses help counterbalance the effects of synaptic loss in this region. This may well be an example of biological compensation at the level of a single synapse.

Although the observations discussed above suggest system adaptation for maintenance of a certain level of granule cell output, when behavior-induced activity markers are used to monitor cell spiking over wide areas of the hippocampus, there are fewer active granule cells in aged compared to young or middle-aged animals (Chawla and Barnes, 2007). This suggests that the compensatory increase in synapse strength is not sufficient to completely restore network activity during natural conditions. Nevertheless, an important question to consider is how the network would behave in the absence of such synaptic strengthening. In

fact, in the same aged rats that show reduced numbers of active granule cells, the numbers of CA1 and CA3 pyramidal cells active during exploratory behavior does not change. It is tempting to speculate that without synaptic strengthening, the system might fall below some critical threshold for functional circuit throughput. This hypothesis predicts that aged animals with higher cognitive ability may have more synapses, more potent synapses, or both, than those showing lower performance levels. This experiment remains to be conducted.

Hypothesis 3: Compensation for decreased excitatory input to CA3 may arise through decreased inhibition

Mossy fiber axons arising from granule cells in the dentate gyrus constitute a major excitatory projection into CA3. Other excitatory inputs include those from perforant path axons from layer II of the entorhinal cortex, bilateral projections from the contralateral CA3 region and associational connections originating within CA3 itself (Witter, 2007). Unfortunately, data demonstrating age-related changes in the synaptic contacts from each of these pathways is sparse. Synaptophysin expression has been shown to decrease in the stratum lacunosum moleculare, the main input target of the medial entorhinal cortex (Smith et al., 2000), suggesting that CA3 pyramidal neurons receive less excitatory input from this cortical projection. It is not known if mossy fiber synaptic contacts or associational connections similarly decline with age in CA3; however, as described in the previous section, the data are consistent with the likelihood that CA3 receives weaker excitatory input from two prominent sources - granule cells and layer II entorhinal cortical cells.

In spite of reduced input from at least two major excitatory sources, single unit firing rates have been observed to increase in the CA3 region of both aged rodents (Wilson et al., 2005) and aged macaques (Thome et al., 2015). Aged humans with memory deficits also show an increased BOLD signal in CA3 and dentate gyrus regions of the hippocampus (Yassa et al., 2011). The neural hyperexcitability of this region in the face of deprived input from the dentate gyrus indicates that changes occur locally in CA3 that cause neurons to become more responsive. One possibility is that neuromodulatory systems could change the gain on the network and render the neurons more excitable. Because, for example, excitatory cholinergic modulation significantly decreases in CA3 with age (Shen and Barnes, 1996), this seems unlikely. Another possibility is that mossy fiber or perforant path synapses onto the dendrites of CA3 neurons could strengthen with age as is observed with perforant path synapses in the dentate gyrus (Barnes and McNaughton, 1980), thus reducing the input threshold for neuronal activation. Unfortunately, no quantification of the synaptic strength of mossy fiber or perforant path synapses onto CA3 pyramidal cells exists to date, therefore this hypothesis can neither be supported nor disproven.

Although the mechanisms that contribute to increased excitability in CA3 of old animals is not known, it is known that there are decreases in hippocampal neurons that express glutamic acid decarboxylase (GAD). This enzyme converts glutamic acid to the inhibitory neurotransmitter GABA, and neurons expressing GAD have been reported to decrease both in aged rodents (Shetty and Turner, 1998; Shi et al., 2004; Spiegel et al., 2013), and more recently in aged macaques (Spiegel et al., 2014; Thome et al., 2015). There remains,

however, considerable disagreement between studies as to the exact regional, laminar, and cell-type specificity of these changes, which are outside the scope of this review. Nevertheless, there are reports that the number of cells that express GABA in CA3 declines with aging. An important question to consider when interpreting these results is whether GABAergic interneurons are being lost due to cell death or a phenotypic switch from a GAD-expressing state to a non-GAD-expressing state. Cell death would likely reflect an age-related vulnerability, whereas a switch in phenotype could result in negative or positive changes depending on the neuronal environment in which they occur. For example, in CA3, where excitatory inputs from the dentate gyrus and MEC are reduced with age, having fewer inhibitory cells could function adaptively to increase functional throughput to the output regions of the hippocampal circuit.

Stanley and Shetty (2004) used neuron-specific nuclear antigen (NeuN) immunohistochemistry alongside GAD immunohistochemistry in CA1 and CA3 to demonstrate that there are no declines in total interneuron number with age. There is a decrease in interneurons that express GAD, however, supporting the idea that GAD-expressing interneurons switch phenotypes to non-GAD expressing states in aged animals. Switches in the chemical phenotype of neurons are not unprecedented in the nervous system, and have been extensively documented in sensory systems such as the auditory system of both rodents (Ouda et al., 2008; Burianova et al., 2009) and macaques (Gray et al., 2013; Engle et al., 2014). The mechanisms driving these phenotypic changes are not known, and the functional consequences of having altered numbers of GABAergic neurons remains largely speculative as well. In the hippocampus, however, one reasonable deduction is that a decreased inhibitory drive from these populations of inhibitory cells could help increase the excitability of CA3 neurons in the face of a sparser dentate gyrus input (Figure 3). Indeed, a tight correlation exists between the density of somatostatin-expressing GABAergic interneurons in the stratum oriens of CA3 and baseline firing rates of pyramidal cells in aged macaque monkeys (Thome et al., 2015). Interneuron density from this same study showed a positive relationship with behavioral performance on a hippocampus-dependent task (Figure 3C), suggesting that these phenotypic changes may be adaptive rather than detrimental to the functioning of the hippocampal system.

Hypothesis 4: Silent synapses and longer after-hyperpolarizing potentials in CA1 functionally buffer the hyperexcitability of Schaffer collateral input

Regardless of the exact mechanisms that induce hyperexcitability of CA3 pyramidal cells, this increase in activity might be expected to result in hyperexcitability in CA1 as well. In awake, behaving animals, however, CA1 single unit firing rates are similar in young and aged rats (Schimanski et al., 2013). Again, this observation suggests that changes may occur to combat the effects of increased CA3 drive in order to preserve normal network activity. One mechanism that could act to decrease CA3's drive onto CA1 would be to reduce synaptic contacts from Schaffer collateral axons onto CA1 pyramidal neurons (such synaptic loss is observed from perforant path synapses onto granule cells and CA3 pyramidal cells). The number of Schaffer collateral synapses onto CA1 pyramidal cells, however, is unchanged with age (Geinisman et al., 2004), making this mechanism unlikely.

While there is no outright synaptic loss in CA1, a subset of Schaffer collateral synaptic contacts does show a reduced postsynaptic density (PSD) size in old rats, while the remaining PSDs are unchanged compared to young (Nicholson et al., 2004). The observed age-related anatomical change could result in weaker synaptic input. This prediction would be consistent with the observations that while there is no change in the presynaptic fiber potential amplitude (no axon pruning), there is a reduction in the amplitude of the extracellularly recorded fEPSP of aged CA1 neurons (Landfield et al., 1986; Barnes et al., 1992; Deupree et al., 1993). If the smaller PSDs result in a reduction of synaptic strength, then this would suggest that the distribution of unitary EPSP amplitudes should be bimodal in old rats – with one group of unitary response sizes similar to the synaptic strength observed in young animals, and another shifted to a reduced amplitude (Figure 4). Interestingly, however, the distribution of unitary EPSP amplitudes in CA1 does not differ between young and old rats (Barnes et al., 1992), ruling this possibility out. This suggests that the subset of synaptic contacts with reduced PSD sizes in old rats is 'functionally silent' rather than active with reduced strength. By this logic, it is the 'silent synapses' that are responsible for the reduced fEPSP amplitudes in old rats. So for CA1, and the Schaffer collateral synapse, there is no synapse loss, and no axon pruning, as there is in the dentate gyrus. Instead, it appears that one mechanism engaged to combat the effects of increased excitatory drive from CA3 may be a reduced number of functional synapses.

Another mechanism that may participate in stabilizing firing rates in CA1 neurons is the observed larger afterhyperpolarizing potentials (AHPs) in these cells in aged rats (Landfield and Pitler, 1984). The larger hyperpolarization after an action potential in older cells predicts slower repolarization to firing threshold, and thus with all else being equal, larger AHPs should slow firing rates. Because of the hyperexcitability of the CA3 input to this region in old rats, however, this larger AHP could act as a temporal buffer for CA1 cells, and could assist in firing rate normalization. On the other hand, it is possible that the change driving this circuit adjustment in aging is the AHP increase in CA1, which sits at the major output stage of the hippocampus. By this logic, perhaps old CA1 pyramidal cells would rarely fire if CA3 cells did *not* increase their firing rates. This would mean that it is the increased firing rates in CA3 that is the primary adaptive change.

Hypothesis 5: Reduced granule cell neurogenesis may trigger adaptive plasticity by engaging 'retired' granule cells

The dentate gyrus is an unusual region in the mammalian brain, as it is an active area of neural stem cell proliferation in adults (Eriksson et al., 1998; Kornack and Rakic, 1999). Neurons born in the subgranular zone, at the border of the dentate gyrus and hilus, migrate to and integrate into the granule cell layer (Gage, 2000; Ramirez-Amaya et al., 2006; Tashiro et al., 2007) and have been proposed to enhance the function of the hippocampal network (Schinder and Gage, 2004; Piatti et al., 2013). With age, the rate of neurogenesis in the subgranular zone decreases in both rodents and non-human primates by up to 80 percent (Galvan and Jin, 2007). The general view has been that the introduction of new neurons into the dentate gyrus should improve memory function, and reduced neurogenesis should impair memory function. In terms of aging, neurogenesis shows a decline in middle age, but is dramatically reduced in rats that are over 25 months (Kuhn et al., 1996; Bizon and

Gallagher, 2003). These ‘new neurons’ in old rats, however, retain their ability to participate in functioning hippocampal circuits, and the cells born at old ages, actually show probabilities of becoming active at similar levels to those of younger rats (Marrone et al., 2012).

A number of issues should be considered concerning the idea that reduced neurogenesis during aging contributes to memory decline. First, the reduction of granule cell proliferation begins in middle age, before significant age-related changes in hippocampal-dependent memory are typically detected. Second, even if new neurons normally do play a role in hippocampal memory encoding (Aimone et al., 2006; Frankland, 2013; Piatti et al., 2013), data exist that suggest that neurogenesis may not be *necessary* for intact spatial learning (Jaholkowski et al., 2009; Arruda-Carvalho et al., 2011; Martinez-Canabal et al., 2013; Urbach et al., 2013). In fact, experiments in aged rats suggest that those old rats with *lower* levels of neurogenesis paradoxically show *better* spatial learning capacity (Bizon et al., 2004; Bizon and Gallagher, 2005). The observations that blocking adult neurogenesis does not always result in a negative cognitive phenotype in adult mice (Urbach et al., 2013), and that reduced neurogenesis in aged rats is associated with better cognition, suggests a different framework for understanding the role of adult-born granule cells. It has been suggested that a small population of recently-generated granule cells normally participate in the encoding of most experiences, while the majority of granule cells are effectively silent, and typically do not participate in creation of new representations (Alme et al., 2010). It is possible that mature granule cells that would not normally participate in active circuits have the capacity to become re-engaged, in order to compensate for disrupted neurogenesis (Frankland, 2013). If “retired, or older granule cells” can be *revived* to compensate for cases in which neurogenesis is suppressed in young mice (Urbach et al., 2013), then perhaps reduced neurogenesis in aging may induce granule cells to come out of retirement in older rats as well. Such a mechanism could partly compensate for the reduction of newly born cells in aging, and is at least consistent with the Bizon et al. (2004) observation that better cognition is observed in old animals with reduced neurogenesis. More direct tests of these ideas will be needed to resolve such a hypothesis. The outcome of such studies, however, could have important implications for guiding therapeutic goals that target increased neurogenesis in aging.

Summary of adaptive plasticity/vulnerability examples

These five examples serve to illustrate the importance of appreciating the multiple points of change that control circuit function in the aged brain. In order to understand where therapeutics should be targeted, it is imperative to understand whether there is a ‘primary change’, and perhaps target that, rather than those that represent adaptive changes in response to this primary event. Because of the potentially beneficial outcomes of circuit rearrangements during the aging process, it is likely that interventions would have to occur quite early, before profound network rearrangements occur. Additionally, it should be anticipated that the most effective treatments to apply will change in an age-dependent manner – so it will be necessary to determine the “biological age” of the individual, which could be defined as the state of adaptive change along some continuum of function. Variations in cognitive abilities of aged animals may stem from differences in the plasticity

of neural networks, and where those differences place the animal along this continuum. To begin gaining traction on this problem, future studies on hippocampal aging must focus on the interaction of changes by studying how different systems co-vary in high and low functioning aged animals.

Similarities and differences in aging across different brain regions

It appears that throughout evolution, there has been a tradeoff made in the metabolic resources dedicated to reproduction and repair mechanisms. Because of the importance of species continuation, this balance has favored investing resources into fertility rather than into better repair processes that could result in extreme longevity, beyond reproductive age (Kirkwood and Austad, 2000). As a consequence, cellular components eventually accumulate insults from oxidative damage or other stressors over time. While it is tempting to seek a global theory of brain aging, the data make it clear that vulnerability to insufficient repair is expressed uniquely in different brain regions. For example, the prefrontal cortex is a region responsible for executive functions that include working memory, task flexibility and planning. While aged humans and other animals show deficits in these cognitive processes (Greenwood, 2000; Gazzaley and D'Esposito, 2007), it appears that the physiological changes responsible for these age-related differences are quite distinct from those that are altered in the hippocampal circuit we have just discussed. Wang et al. (2011) demonstrated that delay cell activity in the lateral frontal cortex of aged macaque monkeys is significantly decreased compared to young monkeys. This reduction in robust firing properties of old frontal cortical neurons is strikingly distinct from the hyperexcitability found in hippocampal CA3 cells of aged rodents and macaques (Wilson et al., 2005; Thome et al., 2015). Another example of region-selective, age-related change comes from the observations of reduced numbers of neurons expressing calcium binding proteins in the aged hippocampus (Lolova and Davidoff, 1992; Potier et al., 1994), which differs from many auditory nuclei where increases in the number of these cell-types have been reported with age (Gray et al., 2013; Engle et al., 2014). These observations make it clear that it will be difficult for principles of brain aging to be generalized from one region to the next without rigorous investigation.

Closing remarks

In this review we use the hippocampal circuit to illustrate the range of vulnerability and plasticity that exists in the normally aging brain. The inherent ability of neural networks to dynamically change in the face of perturbations generated by internal and external inputs, effectively defines biological adaptation. Because some normative age-related changes may reflect dynamic adjustments to optimize circuit function, the conceptual dialogue about biological aging needs to be broadened to take into account these complexities. Thus, incorporating an appreciation of brain aging in the context of such local adaptation has the potential to greatly improve our understanding of aging throughout the brain, as well as to shed light upon the biological basis for our species' great accomplishments in improving our cognitive lifespans over the past century.

Acknowledgements

We would like to thank Bevin Dunn for her assistance with the figures. This work was supported by the McKnight Brain Research Foundation and NIH grant AG003376.

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Highlights

1. An adaptive view of brain aging is proposed through a review and discussion age-related changes in the hippocampus.
2. Age-related changes in cholinergic systems, synaptic strength, inhibition and neurogenesis are all key discussion points.
3. The importance of appreciating the impressive variation in cognitive abilities in aged populations is highlighted.

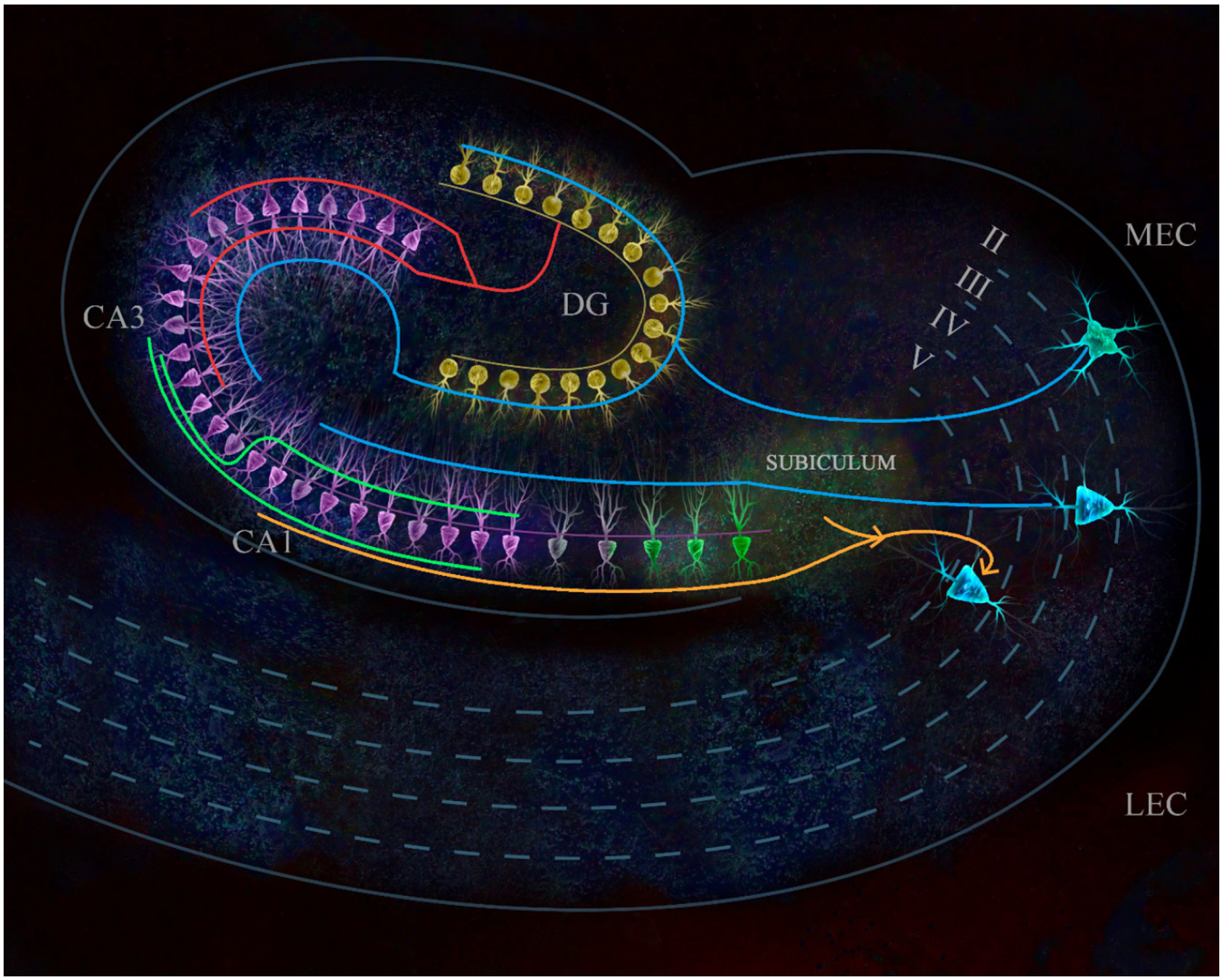

Figure 1.

Schematic representation in horizontal section of components of the medial temporal lobe circuit discussed in the present manuscript. Stellate cell (turquoise) axons from layer II medial entorhinal cortex (MEC) combine with layer III projection neuron (blue) axons to form the perforant path (depicted as blue lines entering the hippocampus). Layer II cells make synaptic contacts with the dendrites of granule cells (yellow) in the middle molecular layer of the dentate gyrus (DG) and in the stratum lacunosum moleculare (distal apical dendrites) of CA3 pyramidal cells (purple). Layer III projection neurons make synaptic contacts with dendrites of neurons in the stratum lacunosum moleculare of the subiculum (green) and CA1 (purple). Depicted in red are the mossy fiber axons of granule cells in the dentate gyrus that terminate in the stratum oriens and stratum radiatum of CA3. Green lines represent CA3 Schaffer collateral axons that project to the stratum radiatum and stratum oriens of the CA1 region. Finally, orange lines represent output axons from CA1 pyramidal neurons that combine with output from the subiculum to terminate in layer V of the medial entorhinal cortex.

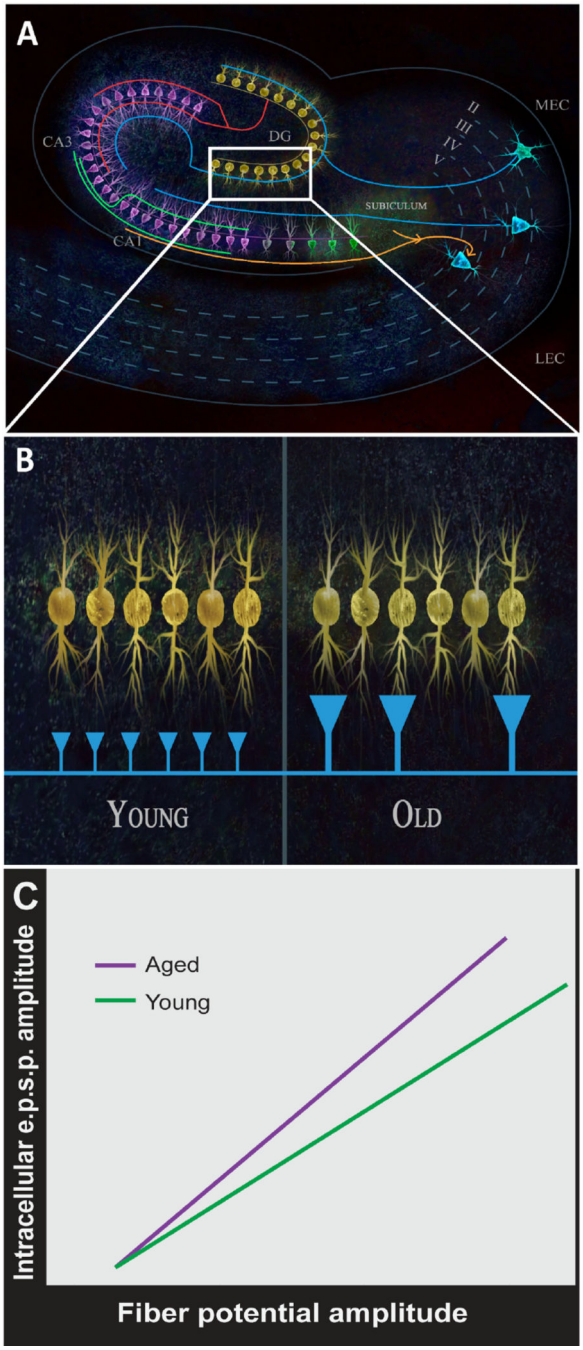

Figure 2.

Granule cells lose synaptic contacts with age, but individual synapses become more potent. **A)** Dentate gyrus granule cells (as outlined by white box) receive input from perforant path axons (blue) from layer II stellate cells in the medial entorhinal cortex. **B)** Quantification of synapse numbers (blue) in the middle molecular layer of the dentate gyrus reveals significant decreases with age. **C)** While fewer in number, the remaining synapses in old rats produce larger intracellularly-recorded EPSPs with respect to the extracellularly recorded presynaptic fiber potential (Barnes and McNaughton, 1980).

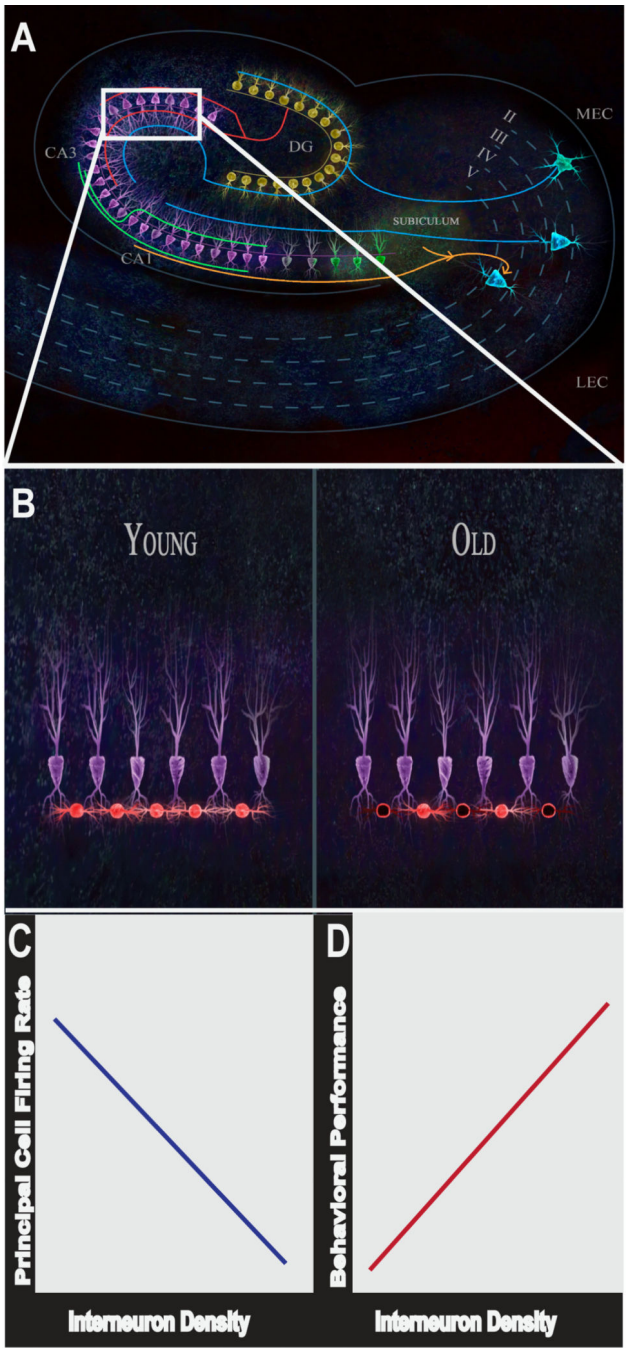

Figure 3.

Age-related phenotypic switches of hippocampal GABAergic neurons. **A)** CA3 pyramidal neurons (as outlined by white box) receive synaptic contacts from a number of inhibitory interneuron subtypes found in the stratum oriens. **B)** Using glutamic acid decarboxylase (GAD) immunohistochemistry in conjunction with NeuN immunohistochemistry, the number of neurons that express GAD has been found to decline with age. The number of cells that express NeuN, a general neuronal marker, does not (Stanley and Shetty, 2004). These results indicate that GABAergic neurons switch phenotypes to become non-

GABAergic neurons rather than die with age. Similar reductions have recently been demonstrated in the hippocampus of aged macaque monkeys. In CA3, the number of somatostatin-expressing interneurons correlates both with **C)** firing rates of principal neurons, and **D)** performance on a hippocampus-dependent task (Thome et al., 2015).

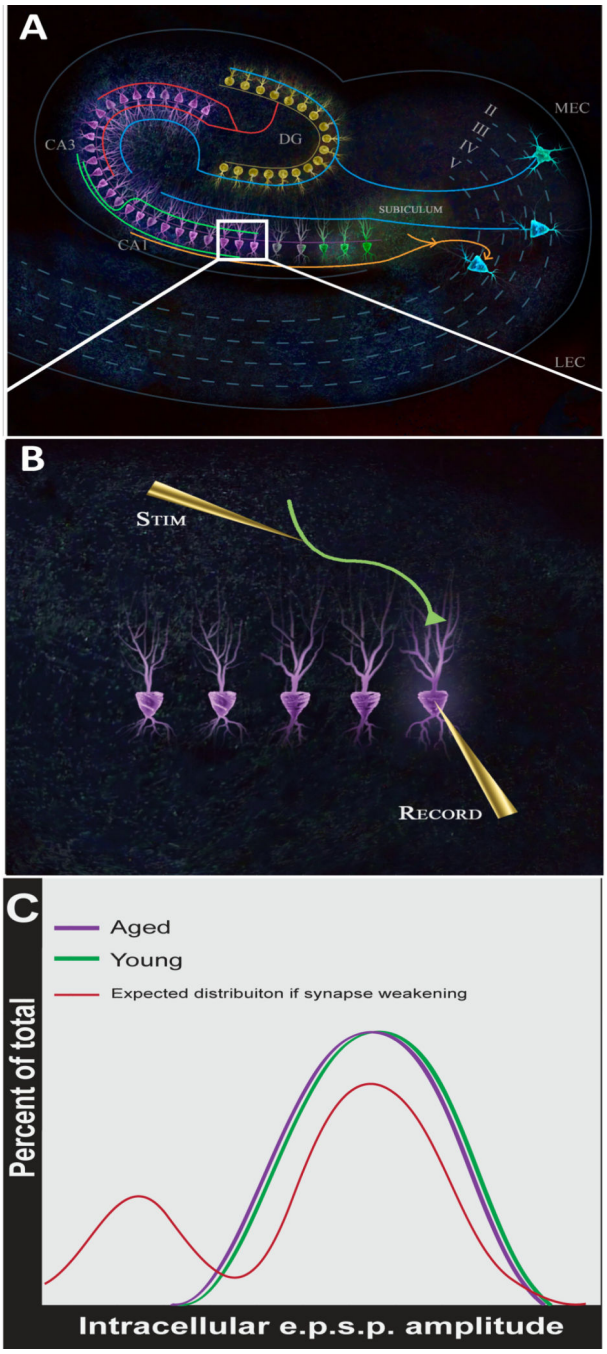

Figure 4.

Electrophysiological evidence for silent synapses in aged CA1. **A)** CA1 pyramidal cells (as outlined in white box) receive excitatory synaptic input from Schaffer collateral axons in the stratum radiatum and stratum oriens. **B)** Schematic of the experimental procedure used to record unitary EPSPs in CA1 pyramidal cells. The depolarization elicited in single CA1 pyramidal cells by stimulation of a single axon collateral from CA3 (green), allows one to measure the amplitude of the intracellularly-recorded 'unitary EPSP.' **C)** If a subset of unitary responses was to weaken with age, one would predict a bimodal distribution as is

schematically drawn in red. The distributions of unitary EPSP amplitudes of young and old animals (green and purple, respectively) were identical, however, suggesting that the strength of this population of synapses does not change with age. Because there is no synapse loss and the fEPSP amplitude is reduced with age, this suggests that a subset of Schaffer collateral CA1 synapses becomes functionally inactive. Consistent with the idea of "silent synapses" in this region is the anatomical observation of a reduction in postsynaptic density size in a subset of these synaptic contacts.