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Senescent Synapses and Hippocampal Circuit Dynamics

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Abstract

Excitatory synaptic transmission is altered during aging in hippocampal granule cells, and in CA3 and CA1 pyramidal cells. These functional changes contribute to age-associated impairments in experimentally-induced plasticity in each of these primary hippocampal subregions. In CA1, plasticity that is evoked by stimulation shares common mechanisms with the synaptic modification observed following natural behavior. Aging results in deficits in both artificially- and behaviorally-induced plasticity, which may in part reflect age-related changes in Ca²⁺ homeostasis. Other observations, however, suggest that increased intracellular Ca²⁺ levels are beneficial under some circumstances. This review focuses on age-associated changes in synaptic function, how these alterations may contribute to cognitive decline, and the extent to which altered hippocampal circuit properties are detrimental or reflect compensatory processes.

Keywords

aging; place fields; plasticity; calcium; rat

Shifting demographics: the aging brain

Humans around the world are living to older ages. In the year 2000, the net balance of the world's elderly population grew by more than 795,000 people each month [1]. In the United States, for example, declining birthrates and an increased average life expectancy will lead to nearly equivalent numbers of individuals above the ages of 65 and below the ages of 15 by the year 2025 (US Census Bureau projections). The demographic fact that there are more elderly individuals today than in recorded history, places understanding the aging process among the great challenges for scientific inquiry today.

Although aging affects the entire body, its impact on the brain and cognition is easy to appreciate, as we all have personal anecdotes of 'forgetfulness' that increase across the lifespan. In fact, the famous Canadian psychologist D.O. Hebb, best known for his neurophysiological postulate of cell assembly formation and learning, wrote a personal

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account of the malfunction of memory that he faced. When Hebb reached his 70s he noted, “I have long believed that the best way to remember to take something with me is to put it on the doorstep, so I see it when I leave; now this works better if the object is big enough to trip me” [2].

One brain region that is clearly critical for normal episodic memory (i.e., the ability to recall when and where an event occurred) is the hippocampus [3]. This medial temporal lobe structure has been shown to undergo functional changes over the lifespan [for review, see 4,5]. Importantly, during normal aging, the numbers of primary hippocampal glutamatergic neurons counted stereologically in humans [6,7], monkeys [8] or rats [9] do not decline (including dentate gyrus, CA3 and CA1 principal cells) [for review, see 10]. If cell numbers are not affected, why do older adults have memory deficits? One likely answer to this question resides in the subtle changes known to occur at the synapse that result in altered mechanisms of plasticity [for review, see 4,11]. This review focuses on how age-related changes in hippocampal excitatory synapses drive region-selective changes in functional connectivity and plasticity. Both experimentally- and behaviorally-induced plasticity will be reviewed for each region, although most of the available data on this topic are from CA1. The possible contribution of Ca^{2+} dysregulation to age-related impairments will also be discussed due to its critical role in synaptic modification and because data suggest that this pathway is a promising therapeutic target. Finally, to understand “successful aging”, it is critical to differentiate those neurobiological alterations that are disadvantageous from those that confer advantage. Thus the strength of the arguments for compensation [12–14] versus deterioration [15,16] are also critically evaluated here.

Summary of age-related changes at excitatory hippocampal synapses

Anatomy

While a comprehensive evaluation of hippocampal circuitry across the lifespan has not yet been completed, three excitatory synaptic connections have been examined in some detail. These include synapses from the entorhinal cortex to the dentate gyrus granule and CA3 pyramidal cells (perforant path projection), and the synapses from the CA3 pyramidal cells to CA1 (Schaffer collateral projection). As very little is known regarding the functional integrity of other prominent hippocampal synapses during aging (e.g., dentate gyrus mossy fiber to CA3 synapse, the commissural projections of CA3, or the direct perforant path projection to interneurons), the synapses mentioned above will be the focus of this review.

The afferent projections to the dendrites of granule cells within the dentate gyrus are anatomically distinct. The inner molecular layer receives input primarily from the GABAergic inhibitory interneurons, mossy cells of the polymorphic layer, and subcortical modulatory inputs [for review, see 17]. Although data indicate that interneurons are affected during normal aging (see Text Box 1) [e.g., 18,19], little is known regarding physiological functioning of the synapses in the polymorphic layer in old age. In contrast, the middle and outer molecular layers receive afferent projections from the medial and lateral entorhinal cortices, respectively [for review, see 17]. In aged rats, electron microscopy (EM) shows that the total number of axospinous synaptic contacts per granule cell is significantly diminished in both the middle molecular layer and inner molecular layer relative to young adults (the outer molecular layer has not been examined by serial section EM analysis) [20]. Consistent with the data for the middle molecular layer, when the presynaptic marker synaptophysin is labeled in young and aged rats, old spatially-impaired animals show reduced levels of this protein in the middle as well as the outer molecular layers [21]. This indicates reduced synaptic contacts from axons originating in layer II of both the medial and lateral entorhinal cortices.

Another age-related change that could affect synaptic function within the dentate gyrus is a reduction in neurogenesis in old animals. It is now well documented that the dentate gyrus of the adult brain acquires new neurons throughout the lifespan [for review, see 22,23]. The rate of neurogenesis, however, declines in older rats [e.g., 24]. This has led to the hypothesis that a decreased ability for the aged brain to acquire new neurons could be a contributing factor in age-associated cognitive dysfunction. Although a reasonable hypothesis, the available data do not support this idea. While aged rats show a reduction in neurogenesis, the old rats with the lowest neurogenesis rates in the dentate gyrus actually have better spatial memory than the old rats with the greatest number of new neurons [25,26]. These data indicate that in old animals more neurogenesis does not correlate with better cognitive outcomes, and suggest that altered neurogenesis over the lifespan may not be a viable explanation for age-associated cognitive decline.

Although the impact of advanced age on synaptic connections within the CA3 subregion has not been well characterized in old learning-impaired rats, there is evidence for reduced layer II entorhinal synaptic input to CA3. Specifically, as in the dentate gyrus, labeling for the presynaptic vesicle marker synaptophysin is reduced in the dendritic region receiving direct entorhinal input (the stratum lacunosum-moleculare), but not in the region that receives input from intrinsic hippocampal projections (stratum lucidum) [21].

In contrast to the dentate gyrus and CA3 [21], there is no loss of synaptic contacts in CA1 with advanced age [for review, see 11]. This is true for both the Schaffer collateral–CA1 synapse [27] and the layer III entorhinal cortex–CA1 synapse [21]. When the postsynaptic density (PSD) areas of the Schaffer collateral axospinous synapses are compared between young and aged learning-impaired rats, however, the impaired animals have a larger proportion of perforated synapses with significantly smaller PSD areas [28]. These findings support the notion that some proportion of hippocampal perforated synapses become non-functional or silent in old animals (discussed more fully below).

Electrophysiology

Electrophysiological data support the anatomical observation that there is a reduction in synapse number in the dentate gyrus. In the aged rat, the field excitatory postsynaptic potential (EPSP) elicited by stimulation of entorhinal cortical afferents is reduced [12,29–31]. This reduction in EPSP amplitude is accompanied by a decrease in the perforant path presynaptic fiber potential amplitude [12,30]. Because there is no loss of entorhinal cells in rats [32,33] or primates [34] with age, this observation is consistent with there being a reduction of perforant path axon collaterals from layer II entorhinal cortex. Interestingly, the ratio of the presynaptic fiber-potential amplitude to either the extracellularly- or intracellularly-recorded EPSP amplitude is larger in aged rats [12]. Additionally, the ‘unitary’ intracellular EPSP amplitude elicited by minimal stimulation protocols is also greater in the older animals [30], suggesting that the surviving synapses are stronger [for review, see 4]. This increase in unitary EPSP size in the dentate gyrus is probably mediated by an increase in AMPA receptor currents, as they are enhanced in old relative to young animals for a given fiber potential amplitude [31]. In contrast, NMDA receptor-mediated currents are decreased in old compared to young rats [31], consistent with data obtained from non-human primates showing a decrease in NMDA receptors in the dentate gyrus [35].

In contrast to the perforant path projection to the granule cells, there is no age-related change in the amplitude of the Schaffer collateral pre-synaptic fiber potential [36], indicating that there is no pruning of CA3 axons [for review, see 4,11]. While the numbers of Schaffer collateral synaptic contacts does not change in aged, memory-impaired rats (see above), the amplitude of the Schaffer collateral-induced field EPSP recorded in CA1 is reduced compared to that of young rats [37–39]. As discussed above, a subset of perforated

synapses in CA1 of old rats have reduced PSD sizes [28]. If this group of synapses were functionally silent, then this could explain the smaller field EPSPs recorded. Electrophysiological data directly support this idea. The size of the unitary EPSP measured at the CA3–CA1 synapse is unchanged in aged versus young rats, suggesting that the strength of individual synaptic connections is not weakened, but remains the same [36]. This is consistent with fewer overall synapses being active in CA1 of old rats. Unfortunately, there are no comparable biophysical studies that have been conducted on CA3 pyramidal cells.

The effects of age on the functional plasticity of these synaptic connections can be assessed by measuring age-associated alterations in long-term potentiation (LTP) and long-term depression (LTD) (see Figure 1A and B). Importantly, some of the age-related deficits in plasticity correlate with memory impairments in old animals [29] (See Figure 1C). Aged rats have deficits in both LTP induction and maintenance and an increased probability of both LTD and LTP reversal [for review, see 4, 11]. These deficits, however, are complex, protocol-dependent and region-specific. Figure 2 summarizes the known age-associated alterations in experimentally-induced plasticity. Briefly, when robust stimulus protocols are used to induce LTP, no age-related induction deficits are detected in the dentate gyrus [29], CA3 [40] or CA1 [41]. Even under these conditions, however, aged rats have deficits in the maintenance of LTP in both the dentate gyrus [29] and CA3 [40]. When weaker stimulation protocols are used to induce LTP, aged rats do show induction deficits in both the dentate gyrus [42, 43] and in CA1 [for review, see 4, 11]. Finally, although the maximal capacity for LTD is unaffected by aging at the Schaffer collateral–CA1 synapse [16, 44], aged rats are more susceptible to LTD induction and LTP reversal at this synapse [45]. Importantly, these observed changes in experimentally-induced plasticity with advanced age likely share a common etiology with the age-related deficits in behaviorally-driven plasticity that will be discussed in the next section.

Behaviorally-induced hippocampal plasticity in aged CA1 neurons

It is widely agreed that modifiable neuronal ensembles support cognition. The findings that experimentally-induced LTP and LTD are affected during normal aging (described in the previous section; Figure 2) suggest that age-associated memory impairments may be due to changes in how hippocampal networks adapt in response to behavioral experience. One way to investigate this is to measure the dynamic properties of hippocampal neurons in awake-behaving animals.

Neuronal recordings from the hippocampus of adult rats reveal that when a rat explores an environment, pyramidal [46] and granule [47–49] cells show patterned neural activity that is highly correlated with a rat's position in space [the 'place field' of the cell; 50]. Importantly, analogous spatial selectivity has also been observed in the firing patterns of monkey [51,52] and human [53] hippocampal neurons (Text Box 2).

The initial expression of hippocampal place fields does not require NMDA receptor-dependent plasticity [54]. In fact, in both young and old rats, the same proportions of CA1 neurons are active during an episode of environmental exploration [55], and these cells express the same number of place fields in a single environment [56]. Plasticity-dependent properties of place fields, however, are disrupted during aging [56], and when the NMDA receptor is blocked in young rats [57]. For young rats, a form of behaviorally-driven plasticity can be observed in the place field firing characteristics of CA1 pyramidal cells [Figure 3A;58,59]. This experience-dependent place field expansion plasticity is attenuated in aged rats [Figure 3B;56], and does not occur when young rats are administered the

NMDA receptor antagonist CPP [57]. Thus, it is likely that this age-associated reduction in behaviorally-induced plasticity is a result of defective LTP-like processes.

It has recently been found that removal of the CA3 input to CA1 does not affect the expression and specificity of CA1 place fields [60]. Thus, it is possible that place-specific firing in CA1 is initially set up by neurons in layer III of the medial entorhinal cortex [61]. After repeated traversal of a route (e.g., running multiple laps around a track), a spike-timing dependent plasticity mechanism could strengthen synaptic contacts of a CA3 cell that had a place field adjacent to a CA1 neuron's field [59,62]. The result is a backward, asymmetric shift of the CA1 field and an increase in its size (Figure 3A). Because CA1 place field expansion resets between episodes of track running [59], it is possible that this reset process is controlled by activity at the entorhinal cortex layer III–CA1 synapse during the rest or sleep episode after behavior. This idea is supported by the recent observation that the entorhinal cortex layer III–CA1 synapse can erase LTP induced at the Schaffer collateral–CA1 synapse [63]. In this view, the same entorhinal input that first establishes CA1 place-specific firing may be responsible for resetting the synaptic weights during rest or sleep after that episode of behavior.

If behaviorally-induced place field expansion plasticity results from an increase in synaptic efficacy at the CA3 to CA1 Schaffer collateral synapse, then age-related deficits in LTP and the increased ease of LTD induction at this synapse could explain why aged rats show reduced experience-dependent place field expansion plasticity under normal conditions. Interestingly, it has been shown that memantine (approved for treatment of cognitive disorders associated with Alzheimer's disease) can, at least partially, reinstate experience-dependent place field expansion plasticity in aged rats [64] to levels reminiscent of that observed in young rats (Figure 3C). The efficacy of memantine at reinstating experience-dependent place field expansion plasticity may be attributed to its binding affinity for the NMDA receptor and its ability to reduce entry of Ca^{2+} into the neuron [65], the role of which will be discussed in the next section.

The role of Ca^{2+} dysregulation in age-associated impairments in artificially- and behaviorally-induced hippocampal plasticity

A number of hypotheses have been advanced to explain why changes in excitatory synaptic function occur during aging (Text Box 3). Among these is the idea that Ca^{2+} dysregulation in aged CA1 neurons disrupts the circuit dynamics of aged pyramidal cells. Alterations in the homeostatic control of intracellular Ca^{2+} levels in old rats have been linked to changes in gene expression [for review, see 66], and can account for many of the observed age-related plasticity deficits at the CA3–CA1 Schaffer collateral synapse *in vitro*, and the decrease in behaviorally-induced plasticity in CA1 of awake-behaving old rats described in the previous sections. Moreover, therapeutic treatments that can alter intracellular Ca^{2+} levels in active neurons can improve both plasticity [64,67,68], and cognition in aged animals [69–71].

Aged CA1 pyramidal cells have increased Ca^{2+} conductances due to a higher density of L-type Ca^{2+} channels [15]. This may lead to disrupted Ca^{2+} homeostasis that ultimately contributes to age-related plasticity deficits [for review, see 72]. Moreover, it has been hypothesized that post-synaptic intracellular levels of Ca^{2+} are involved in setting the synaptic modification curve, which determines the probability that a synapse will be depressed or potentiated for a given pattern of input [73]. If Ca^{2+} homeostasis is disrupted in aged animals [15,72], then it is likely that the probability for a given synapse to be potentiated or depressed will also be altered. Figure 4 shows hypothetical synaptic modification curves for a young rat (green) and an aged rat (purple). Even though the threshold for LTP is unchanged in CA1 for aged rats, the old animals have an increased

probability for LTD accompanied by a decreased probability for LTP when weak stimulation is administered. In line with this idea is the finding that the inhibition of Ca^{2+} -induced Ca^{2+} release from intracellular stores reduces LTD induction in aged CA1 neurons [68].

If the disruption of experience-dependent CA1 place field expansion in aged rats is related to altered Ca^{2+} homeostasis, then it is possible that reducing the amount of Ca^{2+} entering a neuron through the activated NMDA receptor may reinstate this behaviorally-induced plasticity phenomenon. Memantine has low to moderate affinity for the NMDA receptor channel, strong voltage-dependent channel blocking characteristics (similar to Mg^{2+}), and fast channel unblocking kinetics [74]. Therefore, it is possible that memantine restores place field expansion in old rats through the mechanism just described. Moreover, if the mechanism for memantine's efficacy is to reduce Ca^{2+} levels, then this predicts that blocking L-type Ca^{2+} channels should also reinstate this expansion plasticity. Although, the involvement of L-type Ca^{2+} channels in experience-dependent place field expansion plasticity has not been tested empirically, it is known that the L-type Ca^{2+} channel blocker MEM 1003 diminishes deficits in trace eye-blink conditioning in aged rabbits, a behavior known to be hippocampal-dependent [71]. While these data suggest that L-type Ca^{2+} channels may play a role in age-associated cognitive decline, recently it has been suggested that increased L-type Ca^{2+} channels [14] and an increased probability of LTD [13] in the aged hippocampus could potentially play a compensatory role. These conflicting possibilities will be discussed further in the next section.

Is there compensation in the aged hippocampus?

For the purpose of this discussion, a “compensatory change” will be considered to involve an age-related functional change within the hippocampus that results in better behavioral performance in a given old rat. While several neural changes have been proposed to fulfill this definition, upon careful inspection, none can unequivocally do so. Among these, three will be considered in some detail below: 1) the increase in AMPA receptor-mediated currents in dentate gyrus granule cells [31]; 2) the increased probability of LTD induction [13]; and 3) the increase in voltage gated L-type Ca^{2+} channel-dependent LTP [14].

As discussed in a previous section, aged rats show axon collateral pruning of perforant path fibers and reduced synapse numbers. This change is accompanied by an increase in AMPA receptor-mediated currents in dentate gyrus granule cells [31], and increased EPSP amplitudes from a given synaptic input [12]. It is possible that with aging additional AMPA receptors are inserted into the post-synaptic membranes of granule cells in order to balance levels of excitability in the face of reduced synaptic numbers. While such a mechanism could plausibly maintain stable hippocampal output, there is no direct evidence that this process results in better behavioral performance over the lifespan within a given animal. In fact, it has been shown that environmental enrichment, which does improve hippocampal-dependent behavior in aged rats, fails to affect the amplitude of the AMPA receptor-mediated field EPSP [31]. Thus, this observation of age-related increase in AMPA receptor-mediated currents reflects a fixed developmental process. It remains to be determined, however, whether age-related behavioral deficits would be even more profound without this mechanism for maintaining adequate excitatory input onto granule cells.

Aged rats have also been shown to exhibit increased NMDA-receptor-dependent LTD induction at the Schaffer collateral–CA1 synapse [16,45]. Recently, a seemingly contradictory pattern of age-associated change in LTD has been reported. In this experiment both spatial learning-impaired and learning-unimpaired aged rats were shown to have reduced NMDA receptor-dependent LTD, while only the unimpaired aged rats exhibited

enhanced NMDA receptor-independent LTD [13]. The interpretation offered for this pattern of data is that “shifting” to an NMDA receptor-independent mechanism for LTD confers a more “successful” cognitive profile [13]. Although, these data are consistent with the hypothesis that an NMDA receptor-independent form of LTD may be a compensatory, an elevated $\text{Ca}^{2+}/\text{Mg}^{2+}$ ratio (2.5/1.5) was used in the *in vitro* experimental preparation. When this ratio is above 1, LTD induction is increased even in young rats that normally do not show LTD [16,45]. Moreover, when a ratio of 1 is used, which is similar to the normal physiological levels in humans [75], old rats readily show enhanced NMDA receptor-dependent LTD induction that is associated with spatial memory impairments [16]. This still leaves open the question of whether or not NMDA receptor-independent LTD could result in compensation for other forms of LTD that are already enhanced with advanced age. One way to test this would be to manipulate the $\text{Ca}^{2+}/\text{Mg}^{2+}$ ratios systematically, allowing direct measurements of NMDA receptor-independent LTD in young and old rats. It will also be important to evaluate the extent to which this form of LTD occurs *in vivo*.

The NMDA receptor-independent LTP process at the Schaffer collateral-CA1 synapse relies on voltage-gated L-type Ca^{2+} channels, and has also been suggested to reflect a compensatory process in old memory-intact rats. Specifically, more L-type Ca^{2+} channels may enable other forms of LTP to occur when NMDA receptor-dependent LTP is disrupted by the aging process [14]. In line with the idea that the increase in voltage-gated Ca^{2+} channel-dependent LTP is compensatory, aged rats that are better spatial learners also show more robust induction of this form of LTP *in vitro*. Before these data can be regarded as an example of compensation, however, they need to be reconciled with previous observations suggesting that *increases* in L-type Ca^{2+} channels are associated with cognitive dysfunction [76]. In fact, blocking L-type Ca^{2+} channels in old animals improves synaptic plasticity [67], and cognition [69,71]. At present, these data cannot be reconciled without further examination of NMDA-receptor independent LTP in young and old rats. One possibility is that this form of LTP requires activation of both L-type Ca^{2+} channels and some other unidentified factor that is intact in young and aged-unimpaired rats but disrupted in the old rats with behavioral deficits.

Conclusions

Whether or not age-related compensatory changes within the hippocampus promote better behavioral outcomes in old animals remains an open question. What is clear, however, is that variability in memory performance increases over the lifespan [77], and the potential neurobiological mechanisms that contribute to better cognitive outcomes in the elderly need to be determined. Although some of the observed age-associated impairments in memory can be correlated with functional changes in excitatory hippocampal synapses and alterations in plasticity, the subtle and distinct ways in which advanced age impacts the hippocampus is still not fully understood. This topic is complicated by the fact that individual hippocampal subregions each show a different profile of synaptic change over the lifespan and changes in one hippocampal subregion can affect the circuit dynamics of downstream structures. In order to fully understand hippocampal age-related alterations, it is going to be important to examine different subregions simultaneously. Although a few studies have utilized this approach and have shown dissociations between CA1, CA3 and the dentate gyrus [e.g., 21,55,78] additional research needs to be conducted with methods that allow for the concurrent examination of these structures. Furthermore, there are glaring holes in our knowledge of all the synaptic components that participate in the input and output pathways that comprise the entire hippocampal network. Among these are the CA3 commissural projection, the granule cell-mossy fiber synapse, the mossy cell projection to the granule cells, and the synapses onto and from inhibitory interneurons. Although it is unknown what each of these connections might contribute to the functional phenotype of the

hippocampus, from the extant literature, we can be sure that any age-related changes will be complex and diverse. Why haven't these experiments been done? A partial answer is that these studies are technically demanding, timing consuming, and methods will need to be developed to study these synapses *in vivo*, in order to validate initial *in vitro* investigations.

While a comprehensive account of age-related synaptic changes has not been completed, there have been successful transitions from identifying changes *in vitro* and then studying the results of these alterations *in vivo*. For example, ensemble recording of single cells in CA1 of awake-behaving young and old animals have revealed that changes in experimentally-induced plasticity may be linked to age-associated deficits in synaptic modification that occur during behavior [56], and have suggested that reducing the entry of calcium in aged neurons may improve both plasticity [64] and cognition [69,71,79] in old animals. Because, a close examination of age-related changes in CA1 pyramidal neurons has lead to the identification of modulating intracellular Ca^{2+} levels as a promising therapeutic target, it is conceivable that acquiring a better understanding of functional changes in other hippocampal cell types will lead to the development of additional agents that can improve cognitive outcomes in the elderly.

Text Box 1: Interneurons in the aging brain

During aging there is a reduction in the number of hippocampal cells that are positively-labeled for GAD67, the enzyme that catalyzes the decarboxylation of glutamate to GABA. Importantly, this reduction is not accompanied by an overall decrease in interneuron number [18], suggesting that there is no degeneration of interneurons with age, rather many interneurons are hypofunctional or lose their phenotype in old animals. When the expression levels of different mRNA markers for specific interneuron subtypes are measured it appears that cells expressing somatostatin and neuropeptide Y are the most affected, while those interneurons expressing parvalbumin mRNA, which includes basket cells, are not significantly reduced in old compared to young rats [19]. It appears from these data that the interneurons with synapses further from the soma are more vulnerable to aging. The observation that basket cells and other interneurons that synapse near the cell body are relatively unaffected in old age could explain why feedforward and feedback inhibition is not altered in old animals [29], and prominent hippocampal EEG patterns also appear to be intact over the life span [56,86]. The interneurons that are affected, however, could alter the delicate balance between inhibition and excitation accounting for the observation of reduced seizure threshold in old animals [87].

Text Box 2: Hippocampal activity patterns across species

Although place-specific firing characteristics are most clearly observable in the rat, evidence has accumulated suggesting that monkeys [52] and humans [53] may also show cellular firing correlates that are selective to specific spatial contexts. Although the spatial firing properties of primate hippocampal neurons lack the precise tuning observed in place fields recorded from the dorsal hippocampus of the rat [88] (homologous to the posterior hippocampus in primates [for review, see 17]), methodological limitations of the recording environments have made direct comparisons across species difficult.

In rats it is known that self-motion is critical for place-specific cellular activity to be expressed. In fact, when a rat is trained to accept restraint and is passively moved through the place where a neuron fired in an unrestrained condition, the cell is rendered silent [89]. Moreover, when a rat is trained to press a lever to ride on a car through space, the active place fields are significantly larger compared to when the animal is self-locomoting through the same space [90]. When hippocampal cell recordings are obtained from humans or monkeys, the subject is typically navigating through a virtual

environment [51,53], or is restrained while driving a car through space [51]. These conditions are analogous to the situation in which a rat drives a car because the self-motion cues are restricted resulting in large place fields. "View cells" have also been reported in the moving primate, suggesting that the place to which the monkey directs its gaze may modulate the firing properties of hippocampal cells [91].

Although there are currently no data available from freely moving primates that could enable a direct comparison of hippocampal recordings across species, recent chronic recordings from isolated hippocampal neurons have shown that the firing properties and EEG patterns of hippocampal neurons are remarkably similar between rodents and monkeys [92]. As in the rat [93], the monkey hippocampus has 'complex spike cells,' with spike trains consisting of long periods of silence interspersed with bursts of activity during behavior at low rates (0.3 Hz) [92]. Moreover, during quiet rest or sleep periods, the monkey hippocampal EEG shows "sharp wave/ripple" events [92]. These events also occur in rats during periods of inactivity or rest [94]. Thus, theories and models of hippocampal memory function developed on the basis of rat data may be applicable to primates.

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Figure 1. Long-term potentiation (LTP) and long-term depression (LTD)

A) A schematic of the extracellular excitatory post-synaptic potential (EPSP) recorded in the dendritic region in response to stimulation of presynaptic fibers before (broken lines) and after (solid lines) plasticity is induced. In both **A** and **B** the X axis is time and the Y axis EPSP amplitude in mV, the blue component of the trace indicates the 1 ms of stable recording before stimulation, the red is the stimulus artifact, and the black in the evoked response. Long-term potentiation (LTP) reflects an increase in synaptic strength that is measured experimentally as a change in the amplitude of the EPSP following patterned electrical stimulation. The hypothesis is that the brain normally stores information as a pattern of synaptic weights, and that artificially-induced LTP reflects a mechanism that the brain could deploy to modify synapses. If synaptic connections were only strengthened, however, the network would readily approach saturation and the acquisition of new information would be prevented. **B)** Long-term depression (LTD) and LTP reversal are mechanisms for selectively decreasing synaptic weights, presumably preventing such saturation [for review, see 4]. LTD can be measured as a decrease in EPSP amplitude. In the hippocampus most forms of LTP and LTD require Ca^{2+} to enter through the NMDA receptor. Depending on intracellular Ca^{2+} concentrations a cascade of events will occur that will either induce LTP or LTD [73]. **C)** Changes with age in the maintenance of LTP correlate with spatial memory (green lines – young rats; purple lines – aged rats) [29]. Rats prefer small dark spaces to open bright ones, and thus, over days, learn to find the place where escape is possible below the platform surface (Barnes maze; left panel). When spatial memory accuracy and LTP durability are examined in the same rats, there is a significant correlation, within each age group, such that those rats that show inaccurate spatial behavior for that group, also show faster LTP decay rates (right panel, dentate gyrus) [29].

Figure 2. Summary of age-related alterations in LTP and LTD between young and aged animals
 The Y-axes reflect the change in the extracellular EPSP (mV) following LTP or LTD induction and the X-axes time following induction of LTP or LTD (green lines - young rats; purple lines - aged rats). **A)** LTP induction at perforant path–CA3 synapse is intact in aged rats when robust (supra-threshold) stimulation protocols are used, but LTP maintenance over days is impaired [40]. **B)** LTP induction is also intact at the perforant path–granule cell synapse when robust stimulation parameters are used. Similar to what is observed in CA3, LTP decays more rapidly over days in the dentate gyrus of old rats [left panel; 29]. When weak (peri-threshold) stimulation protocols are used, however, aged rats also show LTP induction deficits at the perforant path dentate gyrus synapse [right panel; 42,43]. This induction impairment could, in part, result from the higher threshold in LTP induction at this synapse [80]. **C)** At the Schaffer–CA1 synapse both LTP induction and decay over hours is similar across age groups when robust stimulation protocols are used [top left panel; 41]. As shown above for the dentate gyrus, however, when weak stimulation parameters are used, LTP induction deficits are unmasked in old rats [top right panel; 81,82]. This LTP induction deficit is not due to a threshold change at Schaffer collateral synapses in old rats [83]. For CA1, aged rats have also been shown to be more susceptible to the induction of LTD following low-frequency stimulation (LFS) [bottom left panel; 45]. Moreover, LTP can be reversed with same stimulation protocol that induces LTD. While LTP is not completely reversed by this LFS in young rats, old rats are also more prone to this reversal of LTP [bottom right panel; 45].

Figure 3. Experience-dependent place field expansion plasticity in young and old rats

(A) In young rats CA1 place fields expand asymmetrically during repeated route following, which results in an increase in place field size and a shift in the distribution of place field spiking in the direction opposite to the rat's trajectory [58,59]. Specifically, when a rat first traverses a cell's place field on a fixed path, the firing rate distribution of the place field is Gaussian such that as the rat enters the place field the neuron shows increased spiking that reaches a maxima at the center of the field and then decreases as the rat exits (Lap 1; white). After repeated traversals, the field expands in the direction opposite to that of the rat's path (Laps >5; grey). This experience-dependent place field expansion plasticity is consistent with neural network models dating back to Hebb's (1949) concept of the 'phase sequence' of

cell assemblies, which have suggested that an associative, temporally-asymmetric synaptic plasticity mechanism could serve to encode sequences or episodes of experience [84,85]. **(B)** A plot of place field size by traversals through a place field (laps) during track running (green circles – young rats; purple circles - old rats). Young rats show significant place field expansion plasticity while old rats fail to show this form of experience-dependent plasticity as robustly (filled circles; data from [56]). **(C)** Old rats given memantine (10 mg/kg; red circles) show improved place field expansion plasticity compared to old saline controls (purple circles; data from [64]).

Figure 4. Hypothetical synaptic modification curves for young (green) and aged (purple) CA1 neurons

The X-axis shows different stimulation parameters used to induce LTP or LTD, and the Y-axis is magnitude and sign of synaptic modification. (1) In old CA1 neurons altered Ca^{2+} homeostasis causes a change in the synaptic modification curve, such that there is a greater probability of LTD following 900 pulses of 1 Hz stimulation (LFS) [45]. (2) This age difference can be eliminated by increasing the ratio of Ca^{2+} to Mg^{2+} in the recording medium [44]. (3) Additionally, with weak stimulation parameters (i.e., theta burst stimulation of 4, 100 Hz pulses), there is a lower probability of LTP induction in aged compared to young CA1 neurons [81,82]. (4) When more robust stimulation is used (i.e., fifteen 20 ms bursts at 400 Hz) the amount of synaptic modification is equivalent between age groups [41].