Published in final edited form as:
Nat Rev Neurosci. ; 13(4): 240–250. doi:10.1038/nrn3200.

The Aging Cortical Synapse: Hallmarks and Implications for Cognitive Decline

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Abstract

Normal aging is associated with impairments in cognitive function, including memory, and with specific and relatively subtle synaptic alterations in the hippocampus and prefrontal cortex. The authors describe these structural changes reported in monkeys and rodents, how they might affect age-associated cognitive decline and potential strategies to limit their impact.

Preface

Normal aging is associated with impairments in cognitive function, including memory. These impairments are linked, not to a loss of neurons in the forebrain, but to specific and relatively subtle synaptic alterations in the hippocampus and prefrontal cortex. Here we review studies that have shed light on the cellular and synaptic changes observed in these brain structures during aging that can be directly related to cognitive decline in young and aged animals. We also discuss the influence of the hormonal status on these age-related alterations and recent progress in the development of therapeutic strategies to limit the impact of aging on memory and cognition in humans.

Introduction

Humans, like other mammals, are vulnerable to age-related cognitive decline in the absence of Alzheimer's disease (AD) or other forms of neurodegenerative disease (Box 1). The cognitive processes mediated by the hippocampus (e.g., declarative memory) and the dorsolateral prefrontal cortex (dlPFC) (e.g., working memory) are those that are most vulnerable to aging. Studies in humans and animal models suggest that age-related cognitive decline is more likely to be associated with alterations in synaptic connectivity than with neuronal loss. This article will review the cellular and synaptic changes observed in the hippocampus and the PFC during aging that can be directly related to cognitive performance and decline, highlighting important differences in the nature of synaptic aging between these regions. The hormonal status also influences these age-related alterations, suggesting that neural and cognitive aging must be viewed from a broad physiological perspective rather

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than as processes that are isolated from other organ systems. Finally, although the synaptic alterations that underlie age-related cognitive decline differ from the extensive neuron loss that leads to dementia in AD, they may render neurons more vulnerable to degeneration induced by disease processes, reinforcing the importance of early intervention to maintain synaptic health.

Box 1

"Successful aging" and individual differences

Even in the absence of pathological conditions such as AD, some elderly individuals are cognitively-impaired relative to adults, whereas others show cognitive abilities well within the range of healthy adult performance. This phenomenon can be observed in mice, rats, rhesus monkeys, and humans: see Figure on spatial memory (rats), object recognition memory (rhesus monkeys), and delayed recall (humans) performance in adult and elderly individuals (adapted from [154]). Elderly individuals that experience a reduction in cognitive ability that is not a consequence of neurodegenerative disease can be said to be suffering from age-related cognitive impairment (ARCI), which is distinct from amnestic mild cognitive impairment (MCI) — associated with markers of brain atrophy and often a prelude to AD. A major goal of research in the neurobiology of cognitive aging has been to define the extent to which age-related biological changes represent correlates of impaired or maintained cognitive ability, rather than being associated simply with advanced chronological age (like gray hair or wrinkled skin). For example, within a group of individuals of similar chronological age, a loss of a particular neuromodulator in cognitively-impaired individuals relative to cognitively-intact may represent a target for intervention. Conversely, a neurobiological change seen in cognitively-intact elderly individuals relative to cognitively-impaired (or young) individuals may indicate an adaptive change associated with preserved cognition in old age. The discovery of the basis for this change could also lead to novel interventions.

The notion that cognitive ability and chronological age are not necessarily directly coupled within individuals has led to the concept of "mindspan"[155], similar to "lifespan" and "healthspan", which defines the period of time during which intact cognitive ability is maintained. The goal of research on the neurobiology of cognitive aging is to discover the means by which mindspan can be maximized, maintaining the quality of life that is associated with intact cognitive ability.

Synaptic Aging in the Prefrontal Cortex

Studies of nonhuman primates (NHPs), rhesus monkeys in particular, have shown that the dlPFC is required for cognitive tasks reliant on working memory (WM), and related tasks such as executive function and implementation of goal-directed behavior. This important role in cognition has been demonstrated most clearly in area 46 of the rhesus monkey brain[1–4]. Importantly, WM as mediated by area 46 is not dependent on current sensory perception of the outside world, nor is it directly mediating motor responses, but it is required to integrate these neural representations to guide goal-directed behavior. WM has been referred to as "the ability to keep events in mind"[2], and as such it is constantly updated and does not represent long-term memory of events or places. The cognitive domain of dlPFC has been defined as the capacity to "acquire and implement the 'rules of the game' needed to achieve a given goal in a given situation" which is further complicated by the ongoing requirement to modify such rules[3]. There is also an element of timing to the cognitive domain mediated by area 46 as the process must be organized and executed in an appropriate sequence if the goal is to be achieved[4]. These are perhaps the most complex cognitive tasks performed by the cerebral cortex, and it is no surprise that dlPFC is greatly

expanded in humans and NHPs compared to other mammals. Such complex tasks require complex circuitries that have been shown to be highly vulnerable to aging[5–10]. In both humans and NHPs, these cognitive functions are among the first to be affected by aging, suggesting that in primates the dlPFC may be more vulnerable to aging than the hippocampus[5–10]. Such functions — particularly establishing ever-changing rules to guide goal-directed behavior — may require an extraordinary level of synaptic plasticity, perhaps more than any other brain region. Such short-term memory frameworks have been proposed to be mediated by recurrent activity of modules of interconnected pyramidal neurons in layer 3 of area 46 modulated by both GABAergic and dopaminergic inputs[2], a concept that has recently been further elucidated in the context of neuroplasticity[11]. The requirement for extensive synaptic plasticity might explain why the cognitive functions mediated by area 46 in monkeys are so vulnerable to aging.

Efforts to reveal the neurobiological underpinnings of age-related cognitive decline in area 46 of rhesus monkeys have focused on the synapse for several reasons. First, there does not appear to be any significant neuron loss in dlPFC[12], although age-related neuron loss has been reported in the frontal eye fields[13]. There is an age-related decrease in volume of dlPFC that is not apparent in other regions of PFC[14,15]. EM studies have shown that there is substantial synapse loss in area 46, particularly in layers 1 (30–60%) and 3 (30–35%) ([16,17]), suggesting that a potential loss of neuropil rather than actual neuron loss may be responsible for apparent shrinkage of area 46. However, not all synapses are equally vulnerable; glutamatergic axospinous synapses account for the vast majority of lost synapses[16,17]. Furthermore, the extent of axospinous synapse loss in layer 3 correlates with the degree of cognitive impairment[16,17], although this is not the case for layer 5[16], suggesting that the extensive corticocortical convergence that occurs in layer 3 is more affected by aging than the downstream projections that emanate from layer 5. This conclusion is supported by the demonstration of the loss of spines in neurons known to furnish corticocortical projections between the temporal and prefrontal cortex[18]. In addition, an age-related disconnection of dlPFC from other cortical regions is supported by extensive loss of myelinated fibers and myelin defects in area 46 and related white matter tracts[19–21]. Regression analyses demonstrated that these myelin defects correlate with impaired cognitive performance[19,21]. A key role for age-related alterations in layer 3 in cognitive aging is also supported by electrophysiological analyses that implicate increased excitability of layer 2/3, but not layer 5, pyramidal neurons in age-related cognitive impairments[22–24]. The interactions between structural and functional changes in layer 3 of dlPFC, for example whether spine loss and excitability changes counteract or exacerbate each other, have not been elucidated.

The focus on axospinous synapses and layer 3 led to the analysis of the spines of layer 3 pyramidal neurons in area 46. Spines have been divided into three major categories[25,26]: mushroom, thin, and stubby. The role of stubby spines remains elusive. By contrast, mushroom spines, which have relatively large spine heads, a high concentration of AMPA receptors, and a high degree of structural stability, have been shown to mediate strong synaptic currents. Thin spines, which emerge from the dendrite over a short time frame and can either stabilize or retract, are associated with a high degree of plasticity compared to mushroom spines[27–31]. It has been hypothesized that the large, stable mushroom spines mediate long term memories while small, thin spines are more closely associated with learning new information[28,31,32]. Thin spines predominantly have small, nonperforated synapses of which only ~60% have detectable AMPA receptor immunoreactivity[27,33–35] and may represent the location of immature ‘silent synapses’ that bear NMDA but not AMPA receptors (but see [36,37]). To determine whether a given spine class was more vulnerable to ageing, the dendritic arbor, spine density, spine size and morphology were analysed in rodent and NHP pyramidal neurons filled with Lucifer yellow[38–42] (Figure 1). This approach revealed that 33% of spines on layer 3 pyramidal neurons in area 46 are lost with

aging, which is remarkably close to the 32% loss demonstrated with EM counts of axospinous synapses. Perhaps more importantly, virtually all spine loss is accounted for by the loss of thin spines, in that nearly half (46%) of the thin spines are lost with aging, whereas there is no loss of mushroom or stubby spines with age[17]. If a significant proportion of the thin spines contain silent synapses then there may also be an age-related loss of this class of highly plastic synapses. In addition, while axospinous synapse density as determined by EM counts correlates with the capacity to learn delayed nonmatching-to-sample (DNMS), the relationship is stronger when behavior is correlated with thin spine density[17]. Furthermore, the mean size of the spine head in thin spines correlates with the capacity to learn DNMS for a given monkey, with a Pearson's correlation (r) value of 0.97, the strongest correlation ever reported between a morphologic measurement and cognitive performance. Neither the density nor size of mushroom spines correlate with performance (Figure 2). These data suggest that one of the strongest contributors to age-related cognitive decline in area 46 is the loss of the most plastic thin spines, which reflects a decreased capacity for both plasticity and dynamic shifts in the glutamatergic inputs to layer 3 pyramidal neurons in area 46. It is possible that the thin spines and their capacity for dynamic plasticity play a critically important role in the 'synaptic strategy' employed by area 46 to meet the demands of WM and accomplish tasks that require a high degree of cognitive flexibility, such as executive function, learning and planning. As discussed below, there is likely to be a class of thin spines that is highly stable as well. Interestingly, the relative stability of the mushroom spines, which mediate more stable circuits, may be related to the maintenance of expertise with aging[17], which has been demonstrated in human studies[43,44].

Other electrophysiological and pharmacological studies of area 46 in aged rhesus monkeys have also highlighted the possible interaction between channels bound to dendrites and spines, including thin spines, as a key factor in the maintenance of youthful cognitive performance. Neurons that fire preferentially during the delay period in a delayed response (DR) task (thought to be the essential electrophysiological component of WM[2]) display a loss of persistent firing across the delay by middle age that is further exacerbated in aged monkeys[45]. (Figure 3) Neurons that preferentially fire during the cue phase of the DR task (i.e. respond to the sensory input), displayed no such decrease with age. It has previously been shown that in young monkeys the capacity for persistent firing during the delay phase is dependent on key signaling events in spines. For example, signals that inhibit cAMP levels within the spine, such as α2A-adrenoreceptor (α2A AR) activation, enhance firing during the delay phase[46]. This is mediated by decreasing cAMP-mediated activation of potassium channels in dendrites, such as the hyperpolarization-activated cyclic nucleotide-gated channel (HCN), which enhances persistent firing during the delay. Conversely, pharmacological manipulations that increase cAMP-HCN activity decrease persistent firing across the delay in DR[11,46,47]. EM studies have shown that all the essential protein machinery for such signaling cascades is present in thin spines of neurons in layer 3 of area 46 [11], suggesting that the thin spines play a crucial role in mediating WM. Presumably, the thin spines that are critically involved in WM represent a stable class of thin spines that maintain their morphologic characteristics over time. Given the dramatic loss of these spines with age[17] one would predict that these signaling cascades would be profoundly affected by age. Indeed, the age-related decrease in firing during the delay phase described above was reversed by inhibiting cAMP signaling or by directly blocking HCN channels[45]. Together, these data have led to a potential drug target for protection against age-related decline in WM. Guanfacine, an α2A AR agonist, has been shown to enhance WM in rhesus monkeys[48], presumably through activation of α2A AR on thin spines[11], although this is unlikely to be the only site of action. As the unique molecular attributes of both stable and dynamic thin spines (and their synapses) are characterized, additional therapeutic strategies for protection against age-related decline in prefrontal functions should emerge.

The data from rat PFC are far less extensive than from the NHP model, perhaps because the anatomical homology between rodent and primate prefrontal cortex is controversial[49,50]. However, studies of the infralimbic (IL) and prelimbic (PL) areas within rat medial PFC (mPFC), the most likely functional homologue of dlPFC in NHP and human, largely support the results from rhesus monkey. First, aged rats show impairments in the same attentional set-shifting task that has been shown to be reliant on mPFC in young rats[51]. They are also impaired on delayed alternation in a T maze[52], a test of WM similar to the spatial delayed response task in monkeys. As in the NHP studies described above, dysregulation of cAMP has been implicated in age-related cognitive decline mediated by mPFC[52,53]. In addition, rat pyramidal neurons in layer 3 of PL display age-related spine loss that is evident by middle age, and as with rhesus monkeys, the small, thin spines are most vulnerable to aging[42]. Neuron numbers in the PL/IL of aged rats are the same as those in young rats[54]. These studies indicate that the same spine class and related signaling mechanisms that lead to age-related cognitive decline linked to dlPFC in monkeys may be responsible for loss of cognitive functions mediated by the mPFC in rats. Future studies of synaptic aging in the rat PFC should use behavioral assessments that are sensitive to PFC function, such as attentional set-shifting, as a behavioral correlate to identify age-related changes that are related to impairment of cognitive abilities that depend on the PFC.

Recent studies on stress and aging in rat mPFC have suggested that the effects of stress and aging may converge in this brain region. Interestingly, attentional set shifting is also impaired following chronic stress[55] in rats, and the same chronic stress paradigm leads to dendritic shrinkage and loss of spines in young rats[56–58]. The synaptic effects of stress are both structurally[59] and functionally[60] reversible, which indicates that there is a high level of behaviorally induced synaptic plasticity during both damage and recovery. Recent studies that examined the interactive effects of stress and aging on dendritic arbors and spines of neurons in the PL area showed that although layer 3 neurons recover their full dendritic arbor during a rest period following chronic stress in young rats, this capacity for recovery is compromised in middle-aged rats and completely lacking in aged rats[41]. Interestingly, although chronic stress reduces spine density on the same neurons that exhibit dendritic retraction in young rats, there is no effect on spine density in middle aged or aged rats[42]. In fact, the middle-aged and aged rats displayed extensive spine loss (35%), and the small thin spines were particularly vulnerable, suggesting that the remaining spines are resistant to experience-dependent plasticity. Although the experience that failed to induce plasticity in this paradigm was stress, it is possible that the age-related loss of plasticity in these neurons reflects a general inability to adapt that would negatively impact cognitive tasks that require a high degree of synaptic flexibility.

Synaptic Aging in the Hippocampus

The hippocampus is the focal point of a network of cortical areas (the medial temporal lobe, MTL) that are associated with declarative or explicit memory function. Generally, this refers to memory in the everyday sense of the word, for facts and events, that (in humans) can be consciously accessed and verbalized. The MTL is critical for memories of personal experience and events, but many forms of enduring behavioral change as a consequence of experience can occur in the absence of the MTL. Many different behavioral tests have been devised to measure the functional integrity of the MTL in animals. Tests of stimulus recognition are impaired by damage to the MTL, particularly the entorhinal and perirhinal cortex[61,62], with the hippocampus potentially playing an indirect role[63]. Spatial navigation tasks are commonly used in rats as measures of the functional integrity of the hippocampus[64,65].

Some investigators have identified the hippocampus more specifically with episodic memory, that is, memory for events occurring at specific places and times. Human episodic memory is defined in terms of mental states and linguistic ability (e.g.[66]), which has created challenges in terms of developing animal models. A number of creative behavioral tasks have been developed to address this problem, some of which have been applied to the study of cognitive impairment in aged rats (e.g.[67]). For the purposes of this review, we will consider cellular and synaptic changes in the context of general impairments in hippocampal-dependent memory abilities, usually in tests of spatial learning. This provides a basis for defining functional impairment (or preservation) of the hippocampus. The advent of more specific tests that may serve as behavioral probes of particular cortical regions (e.g.[68,69]) and hippocampal subregions promise a finer-grained analysis of the relationship between neurobiological and behavioral changes in aging.

Analyses of the functional neurobiology of aging in the dlPFC have focused on the domain of spatial working memory and the neurophysiological and neuroanatomical correlates related to WM-dependent tasks. This represents an ideal model system for investigating the synaptic strategy of the prefrontal cortex, which is associated with extensive and rapid plasticity to allow for rapid updating of information that is relevant to immediate behavior. This contrasts with the hippocampus and the MTL, which are associated with the formation of long-term memories of facts and events, dictating a different synaptic strategy with different neuroanatomical and neurophysiological correlates. Because more kinds of behavioral tasks have been employed to probe hippocampal and MTL function in aging, a greater number of different anatomical and physiological correlates have been explored. The synaptic basis of memory processes in the hippocampus and the MTL is less clearly defined relative to that of working memory in the primate PFC.

A number of recent studies in rats and monkeys, using modern quantitative neuroanatomical methods that include unbiased stereological estimation, have demonstrated that aging is not associated with neurodegeneration in MTL structures. Aged rats have no loss of principal hippocampal neurons relative to young rats[70], or neurons in cortical areas of the MTL[71,72]. Aging in monkeys is not associated with loss of hippocampal volume[73] or with loss of neurons in entorhinal cortex[74,75], though both of these changes are associated with pathological memory decline (and progression to Alzheimer's disease) in elderly humans[76–78]. Hippocampal synapse number seems to be preserved in aged rodents in some regions, and decreased in other regions. For example, stereological quantification of spinophilin-immunoreactive spines[79] and electron micrographic analyses of synapses have revealed that there is no age-related synapse loss in hippocampal area CA1[80]. Loss of CA1 synapses is characteristic of AD and, to a lesser extent, mild cognitive impairment in humans[81]. Collectively, these data highlight the differences between normal aging, characterized by structural preservation in the MTL, and AD, which is associated with neuronal and synaptic loss in the MTL and in the hippocampus in particular.

Against this background of substantial structural preservation in CA1, subtle and region-specific alterations in synapses have been identified that are associated with impairment in hippocampal-dependent memory in aging. For example, a reduction in the size of postsynaptic densities of perforated synapses in hippocampal CA1 has been reported in aged rats with spatial learning impairment[82] in the absence of synapse loss. A decrease in synaptophysin immunoreactivity in the lacunosum-moleculare layer of hippocampal CA3 was noted in aged, spatial-learning impaired rats[83]. Additionally, levels of synaptophysin staining in the outer and middle portions of the dentate gyrus molecular layer, in the absence of an age-related decrease, correlated with spatial learning ability in aged rats. A recent electron microscopic analysis confirmed that there is an age-related loss of synapses in the lacunosum-moleculare layer[84], which is particularly interesting because this is the layer in

CA3 that receives input from the entorhinal cortex. EM studies of dentate gyrus have revealed an age-related loss of both perforated and nonperforated synapses in the portion of the molecular layer that receives input from the entorhinal cortex as well as other portions of the molecular layer[85], however it is the loss of perforated synapses in the sublayer of the dentate gyrus that receives input from the entorhinal cortex that correlates with memory impairments[86] in aged rats, further emphasizing the importance of entorhinal/hippocampal connections to cognitive aging[87]. In contrast, in aged monkeys the density of perforated synapses in the dentate gyrus is preserved relative to young monkeys, although this is modulated by ovarian status in aged female monkeys[88]. Instead, a reduction in synaptic contacts per axonal bouton was associated with cognitive impairment[89], suggestive of a failure of complex synaptic inputs to the dentate gyrus in aged monkeys rather than a reduction of synaptic strength in the dentate gyrus of aged rats (Figure 4). In addition, there is an age-related *increase* in nonsynaptic boutons in the portion of the molecular layer that receives input from the entorhinal cortex in aged monkeys[89], suggesting that there is a decreased capacity to sustain this critically important circuit that negatively impacts cognition. The potential for age-related synaptic changes in monkey CA1 that are associated with cognitive performance requires further analysis. There have been reports of age-related decreases in NMDA receptors and AMPA receptors in hippocampus (reviewed in[90]). Although these studies lack the resolution to equate precise levels and subunit profiles of these receptors in axospinous synapses to age-related memory impairment, we hypothesize that altered glutamate receptor profiles in intact complex axospinous synapses might also contribute to age-related decline in tasks mediated by hippocampus.

Gene expression profiling studies have highlighted changes in hippocampal CA3 in aged rats with preserved spatial learning ability, including a downregulation of genes associated with synaptic transmission and plasticity[91]. Interestingly, age-related changes in place-cell firing properties, associated with spatial coding in the hippocampus, also predominate in CA3 [92]. These examples indicate that small changes in specific classes of hippocampal synapses may translate into substantial functional impairment, and that these alterations can be found in all subfields of the hippocampus. As in the PFC, stress and aging both affect hippocampal structure and function, as recently reviewed elsewhere[93–95].

The role of neurogenesis in the dentate gyrus of adult animals has also been examined with respect to cognitive status in aging. Because neurogenesis in the dentate gyrus declines dramatically with age, this represents another possible cause of age-related impairment in hippocampal-dependent memory. However, the current data are not consistent with respect to a causal link between decreased neurogenesis and age-related cognitive decline. Despite a significant age-related reduction in neurogenesis in the dentate gyrus, the level of birth of new neurons was uncorrelated with spatial learning ability[96–98]. Survival of new neurons correlated with better spatial learning in one study[98] and worse spatial learning in another[99]. An age-related decline in hippocampal neurogenesis has also been documented in primates[100–102], although the relationship of this decline to cognitive impairment is unclear[101]. Thus, even though the functional role of hippocampal neurogenesis in memory is still not fully understood, the degree to which a decrease in the capacity for generation of new neurons plays a primary role in age-related impairments in hippocampal-dependent memory remains elusive and requires further investigation.

Although we do not focus on age-related neurophysiological changes in this article, we note that many baseline neurophysiological properties of hippocampal neurons are preserved in aging (see review by [103]). A notable exception is age-related changes in calcium regulation in aged hippocampal neurons, which have an increased Ca^{2+} influx through L-type calcium channels. This increased Ca^{2+} influx in response to an action potential activates a calcium-sensitive potassium current that prolongs hyperpolarization in aged hippocampal neurons

(see [104 and 105] for more extensive discussion), and these neurons show a reduced firing rate in response to a tonic current injection. This is an interesting contrast with layer 3 pyramidal cells in dlPFC, which also show an increased afterhyperpolarization, but show increased firing rate after injection with a depolarizing current[24].

Differences between synaptic aging in hippocampus and PFC

We have discussed how the hippocampus and PFC employ different synaptic strategies related to their different roles in cognitive function. Synaptic aging and cognitive impairment in PFC is associated primarily with an extensive loss of axospinous synapses, and this loss is highly selective in that nearly 50% of the thin dendritic spines are lost, with other spines classes unaffected by aging. Given that thin spines (potentially the location of silent synapses) are highly plastic and dynamic, compared with the mushroom spines that are stable across time[27–31], the cognitive tasks mediated by PFC that decline with age are likely to be associated with dynamic spine turnover and plasticity that may be particularly important for temporary coding of information. By contrast, memory encoding (and successful subsequent retrieval) in the hippocampus is associated with synaptic stability, and the conversion of simple axospinous synapses into complex synapses such as perforated synapses and multisynaptic boutons. Indeed, an increase in the number of perforated synapses has been associated with the induction and maintenance of long-term potentiation (LTP)[106,107], and multisynaptic boutons are increased in CA1 following associative learning[108], LTP induction[109], or estrogen treatment[110]. There are specific classes of synapses that are vulnerable to aging in the hippocampus. Unlike the PFC, it is the large, complex synapses that appear to be most vulnerable. In this regard, the reduction in length of perforated synapses in hippocampal CA1 (in rats), the loss of perforated synapses in dentate gyrus (of rats), and the reduction in multisynaptic axonal boutons (in aged monkey dentate gyrus) — phenomena all associated with impaired hippocampal and MTL-dependent memory — are likely to reflect a disruption of synaptic complexity and the capacity for encoding and retrieving complex information over time periods that exceed the span of working memory. Notably, in the hippocampus, thin spines, ~40% of which do not have detectable AMPA receptor immunoreactivity and thus may bear silent synapses [33,34], are not lost in aging. Thus, aging in prefrontal cortex may be characterized by a loss of silent synapses, whereas aging in hippocampus may be characterized predominantly by a loss of established, previously-potentiated synapses.

Thus, just as the hippocampus and PFC have very different synaptic strategies to perform quite different cognitive tasks, they have very different synaptic vulnerabilities to aging. These differences suggest that different molecular mechanisms may be responsible for synaptic aging in each region, which has important therapeutic implications. A failure to form thin spines implies that actin dynamics may be compromised in pyramidal cells within PFC. Thus, proteins that regulate actin dynamics such as LIM kinase and cofilin[111–113] are potential targets for intervention in PFC. However, in hippocampus, perforated synapses are the main class of synapse affected by aging, suggesting that regulation of the expansion of the PSD in existing synapses and related trafficking of AMPA receptors[82,114] may be the key cellular process that should be targeted to protect against synaptic aging in this brain region. Much more work is needed to define the cellular and molecular processes in each case, but the synaptic patterns described above strongly suggest that the molecular mechanisms of synaptic aging will display regional heterogeneity and specificity, as do the structural differences.

Reversing synaptic ageing: a role for estrogen

The average age of both menopause and life expectancy for American women in 1900 was slightly over fifty years old. Although the average age of menopause remains the same, life expectancy has risen to the early eighties, such that women can now expect to live one-third of their lives after the menopausal transition, making a compelling case for determining the beneficial effects of the popular combined hormone treatment regimen (HT; estrogens and a progestin) on synaptic health and cognition.

The Women's Health Initiative Memory Study (WHIMS) concluded that HT did not improve cognitive function[115], and "increased the risk for probable dementia in postmenopausal women aged 65 or older"[116]. However, multiple observational studies have demonstrated a protective effect of HT with respect to onset of AD[117–124]. This is also perplexing given other data linking ovarian hormones to cognition in women (reviewed in [125]). One explanation for this mismatch is that there is a "critical period" for hormone therapy (HT) to have beneficial effects on cognitive function, such that benefits are seen when HT is initiated soon after menopause but not when treatment is delayed[118,126–130], a notion that finds some support in studies in rats [122]. Whereas women enrolled in the WHIMS were beyond the critical period, and thus did not benefit from HT, women in observational studies reporting beneficial neurocognitive effects of HT began treatment soon after the onset of menopause, and so received the maximal benefit[130].

Studies in animal models have attempted to explore the relationship between estrogen and cognitive ageing further. Estradiol treatment induces spines in the CA1 of young ovariectomized (OVX) female rats but fails to do so in aged OVX females[131], which is consistent with the lack of estradiol-induced memory enhancement in aged female rats[132]. Quantitative electron microscopic immunogold analyses of key signaling molecules in axospinous synapses within CA1 have revealed multiple age-related changes in the molecular phenotype of these synapses that may explain the blunted synaptic response to estradiol. First, synaptic ERα is decreased with aging by 50% in CA1 and estradiol no longer affects the synaptic levels of ERα[133]. Synaptic pLIMK, which is likely involved in regulating spine formation in CA1[134] and is responsive to estradiol[135], is also decreased in CA1 of aged females and no longer increased by estradiol as it is in young rats[136]. The rat model of estrogen and aging has been very useful for dissecting the age-related molecular alterations of CA1 synapses that lead to compromised estradiol-induced plasticity, but it has been less valuable for determining direct links to cognitive performance compared with the NHP model. Recent reports that estradiol increases spines in mPFC of female rats[137,138] suggest that rat studies targeting mPFC and related cognitive tasks may be feasible and promising.

Similar studies comparing young and aged OVX monkeys with and without estradiol have attracted interest as they tend to include a cognitive assessment of the subjects. Estradiol also appears to increase spine density in CA1 of young OVX female rhesus monkeys[139,140], and interestingly, this effect may be retained in aged monkeys[139], although this has not been confirmed with electron microscopic analyses of synapse density. In addition, estradiol treatment improves performance on a cognitive task (DNMS) linked to the integrity of the medial temporal lobe[115]. The aged vehicle-treated monkeys displayed only a modest decline in performance on DNMS when compared to estradiol-treated monkeys, but a dramatic decline on DR performance was seen compared to both young treatment groups and the aged estradiol-treated group. The effect on DR pointed to dlPFC as a potential target of estradiol, which is consistent with some of the clinical reports on women[141]. With respect to spine density and size the age and treatment effects were striking; age decreased the number of thin spines in layer 3 of area 46, whereas estradiol induced their formation such that aged

untreated monkeys experience a “double hit” of age and depletion of gonadal estradiol that results in aged vehicle-treated monkeys having one third as many thin spines (head diameter <0.4 μm) as young estradiol-treated monkeys. As with the studies of gonadally-intact aged NHPs described above, the thin spine class emerges as the key to both age-related cognitive decline and estradiol-induced protection against such decline (Figure 5). Importantly, these findings indicate that the loss of thin spines and related cognitive decline is not inevitable, and both can be prevented or reversed with intervention. Like guanfacine, the findings with estradiol illustrate the power of studies of synaptic aging to point towards potential therapeutic mechanisms. Although the utility of hormones themselves as therapeutic agents may be problematic, alternative strategies – based either on more selective estrogen receptor modulators or drugs designed to promote the formation and stability of thin spines directly – may have greater clinical utility.

Future Directions

The relative vulnerability of thin spines in the PFC of aged rhesus monkey compared with the stability of mushroom spines needs to be examined at the molecular level. These spine classes probably differ in their glutamate receptor profile[28], however, such differences will likely be subtle and unlikely to definitively differentiate spine classes. Future studies should aim to shed light on the synaptic proteins that are relatively specific to each class of spine, and mechanistically linked to the structural plasticity of thin spines or to the GluR trafficking and complexity of mushroom spines. Such studies will not only reveal targets that have spine class specificity, which will likely be required for optimal interventions, but they will also be important if protecting hippocampal synapses in the face of aging requires different approaches than those that are successful in protecting pyramidal neurons in PFC from losing their thin spines. Future efforts must be guided by both the recognition that different spine classes have differential vulnerability to aging, and that there is regional selectivity to the differential vulnerability of axospinous synapses.

One of the most important areas for future investigation is to determine the degree to which synaptic alterations leave a neuron vulnerable to neurodegeneration, and the conditions that promote such vulnerability. This is particularly important with respect to AD. Though more work needs to be done at the synaptic level in brains from elderly humans without AD, there is a high degree of synapse loss early in AD[142,143] and it may precede significant tangle formation and neuron loss. There are data that link synapse loss to degeneration in animal models (reviewed in [144]). Mouse models of AD with high levels of circulating Aβ and plaques do not have significant neuron loss, though they do have spine loss[145], and soluble Aβ causes synaptic pathology[146,147]. Specific effects of Aβ oligomers on hippocampal synaptic plasticity have been identified, which correlate with behavioral impairment (reviewed in [148]). Thus, the effects of Aβ in AD may actually be primarily synaptic and occur much earlier than neuron death attributed to neurofibrillary tangle formation. These effects of Aβ may interact with the synaptic changes that occur with normal aging, which may increase the neurons’ vulnerability to the disruptive effects of Aβ oligomers on synaptic plasticity and neuronal health. If so, maintaining synaptic health in the face of aging may be important to prevent AD (see also [149]).

HT for women has traditionally consisted of replacing estradiol, decreased through surgical or natural menopause, with a mixture of estrogenic compounds alone or in combination with P or other progestins. However, as we learn more about the molecular pathways activated by estradiol, we may be able to target key pathways and synapses from the broader context of preventing age-related cognitive decline in both postmenopausal women and men as they age. Although the studies in rats provide insights into age-related alterations in important signaling molecules that may influence therapeutic strategies, the NHP model will be

particularly powerful for delineating the synaptic molecular profiles that correlate with cognitive performance. One obvious target for such analyses is synaptic ERα. ERα is present in axospinous synapses in area 46, but unlike the case for rat CA1, it does not decline with age, nor is it altered by OVX or estradiol[150]. However, the abundance of synaptic ERα does correlate with performance on DR, but only in the young VEH group. This suggests that in the absence of gonadal estradiol, young monkeys have the capacity to activate synaptic ERα in area 46 through alternative mechanisms, such as locally synthesized estradiol that can modulate synaptic plasticity, as has been described in pyramidal cells in rat CA1[151,152], or perhaps alternatively by ERα agonists that are of adrenal origin[153]. Importantly, this suggests that synaptic ERα in area 46 may be linked to the cognitive resilience demonstrated by young female monkeys in the absence of gonadal estradiol. If so, it appears that such an alternate mechanism is attenuated with age. Future studies should be aimed at delineating these mechanisms and promoting their resilience with age.

The data on the effects of stress and sex steroids on the aging brain and cognition, particularly in the PFC, make it clear that the brain can not be viewed in isolation with respect to the neurobiological basis of cognitive decline. Given the impact of menopause on women's health, as well as the requirements to maintain optimal executive function in the face of stressful conditions, future work should target the nature of these interactions with an eye toward interventions that might be behavioral as well as pharmaceutical. We are at the very early stages of understanding these (and other) endocrine influences on PFC and related cognitive functions in the context of aging, but clearly this needs to be a major focus going forward.

Acknowledgments

We thank Drs. Yuko Hara, Graham Ellis-Davies, and Erik Bloss for helpful comments on the manuscript. We also thank Dr. Yuko Hara, Dr. Dani Dumitriu, and Bill Janssen for assistance with the figures. Reconstruction and visualization of Figure 1 was done by our colleagues from theVisualMD. The authors' research is supported by NIH grants P01-AG016765, R37-AG06647, and R01-AG010606.

Glossary

axospinous synapses	Synapses between the axon from one neuron and the dendritic spine of another neuron
delayed nonmatching-to-sample (DNMS)	A test of recognition memory, commonly used in monkeys. A monkey's memory for a sample object is tested by offering a choice between the sample and a novel object, and the monkey is rewarded for choosing the novel object (nonmatching). Performance in this task is dependent on an intact medial temporal lobe
delayed response (DR) task	A test of spatiotemporal working memory, commonly used in monkeys. A monkey is cued to remember a location in space for a brief interval and then is rewarded for selecting that location at the end of the interval. Performance in this task is dependent on an intact prefrontal cortex
attentional set-shifting task	A test of executive function in which discrimination problems among stimuli with multiple independently-variable relevant characteristics (dimensions), such as shape and color, are presented in succession. Attentional shifting is engaged when the relevant dimension for solving the discrimination problems changes

spinophilin	A protein that is highly enriched in dendritic spines and that is often used as an immunohistochemical marker of dendritic spines
perforated synapses	Large synapses implicated in memory-related plasticity. Perforated synapses are characterized by a discontinuity in the postsynaptic density, resulting in a hole, a slit, or a complete segmentation of the postsynaptic density plate
synaptophysin	A synaptic vesicle protein that is highly enriched in synapses and that is often used as an immunohistochemical marker of synapses
lacunosum-moleculare layer	The most superficial layer of the CA1–3 fields of the hippocampus. In CA3, it contains synapses from the perforant path (the projection from the entorhinal cortex to the hippocampus)
multisynaptic bouton	An axonal bouton that forms synaptic contacts with more than one dendritic spine or shaft. Multisynaptic boutons are implicated in hippocampus-dependent learning

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Biographies

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Online 'at-a-glance' summary

- Individual differences are a hallmark of cognitive and synaptic aging. Neurobiological differences between individuals of the same chronological age may underlie the preservation of cognitive abilities in advanced age, versus cognitive impairment.
- In general, age-related cognitive impairments that occur in the absence of neurodegenerative diseases are not associated with loss of cortical neurons. Instead, they seem to be associated with subtle synaptic alterations.
- The prefrontal cortex controls higher-order, complex behaviors. A hallmark of cognitive aging is impaired prefrontal function, including impairments in spatial working memory.
- One synaptic correlate of age-related impairments in working memory that has been identified in monkeys is a loss of thin spines in layer 3 of the dorsolateral prefrontal cortex.
- The medial temporal lobe, including the hippocampus, is responsible for memories of everyday events. Mild impairments in medial temporal lobe function are also observed in cognitive aging.
- A variety of synaptic alterations in hippocampal function have been described that correlate with age-related memory impairments. These have been observed in all subfields of the hippocampus, and differ between subfields.
- A notable synaptic alteration in the aged monkey hippocampus is the loss of multisynaptic boutons in the dentate gyrus, which correlates with cognitive impairments.
- Cyclical estradiol treatment of aged, surgically-menopausal monkeys increases the density of thin dendritic spines in prefrontal cortex and improves working memory. This illustrates the potential of synaptic and cognitive changes in aging to be reversible.
- Loss of synapses may predispose neurons to degeneration in disease states. Thus a better understanding of mechanisms that promote stability of synapses in aging should lead not only to amelioration of age-related cognitive impairments, but may also impact vulnerability to neurodegenerative diseases.

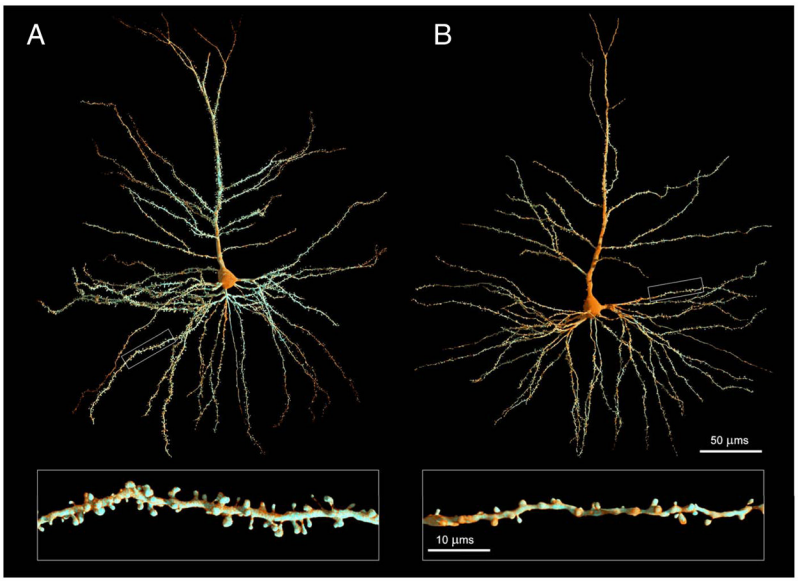

Figure 1. Cortical neuron spines in young and aged non-human primates

Representative examples of Lucifer Yellow-filled prefrontal cortical neurons from young (A) and aged (B) non-human primates. Z-stack tiles of the two neurons were imaged using a Zeiss 510 confocal laser-scanning microscope (CLSM) and rendered into the complete neuronal reconstructions by tiling the entire set of z-stacks. The rectangle identifying a basal dendritic segment in each neuron is shown at higher magnification below each neuron. Note that while the overall dendritic arborization does not diminish with age, the robust spine density present in the young animal is significantly reduced with age, particularly the thin spines (C). Scale bar (low magnification) = 50 μm, scale bar (high magnification) = 10 μm. Image courtesy of theVisualMD.

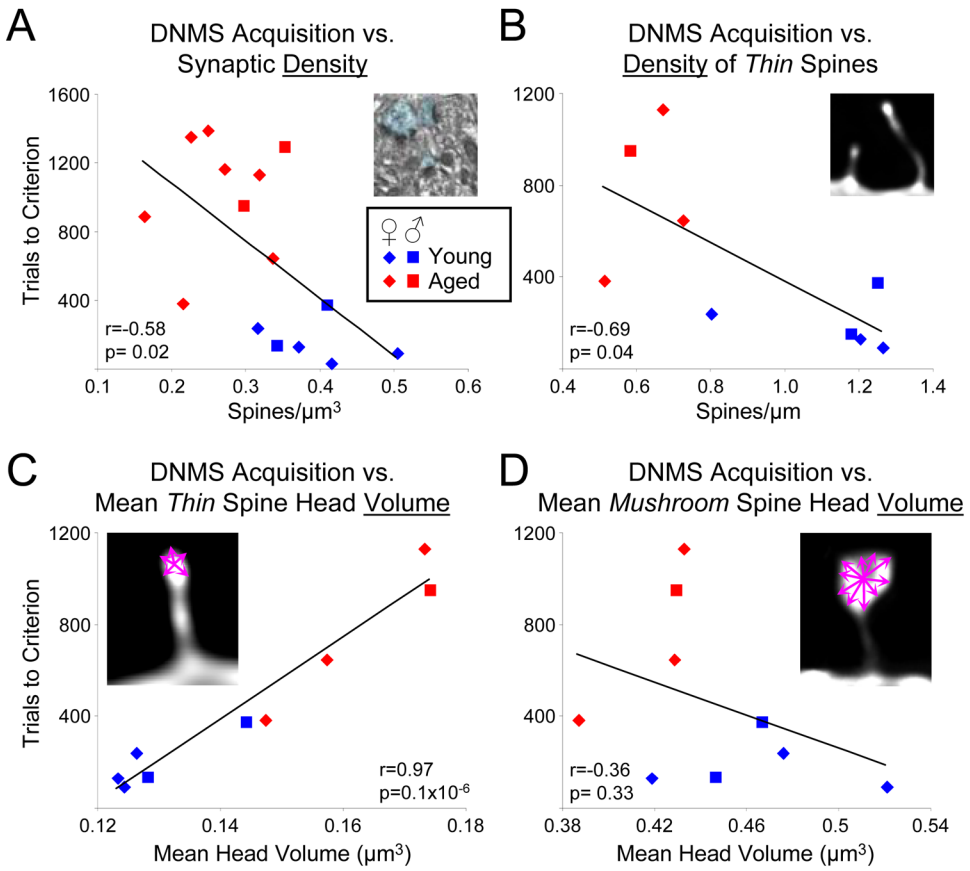

Figure 2. DNMS acquisition correlates with synaptic indices

A) The scatter plot of DNMS acquisition (trials required to reach 90% accuracy with a 10 second delay) versus EM synaptic density shows a moderate though significant inverse correlation, meaning that higher synaptic density is predictive of faster learning. **B)** This inverse correlation is somewhat strengthened when the density of only thin spines is used on the subset of animals for which spine density analysis was performed ($r=-0.58$ in A and $r=-0.69$ in B; $p<0.05$ for both). **C)** DNMS acquisition correlates most strongly with the mean volume of thin spines, where smaller volumes are predictive of faster learning. **D)** In contrast, no correlation is seen between learning of the DNMS task and mean mushroom head volume. R = Pearson correlation coefficient. (Taken from Figure 8, ref. [16,17])

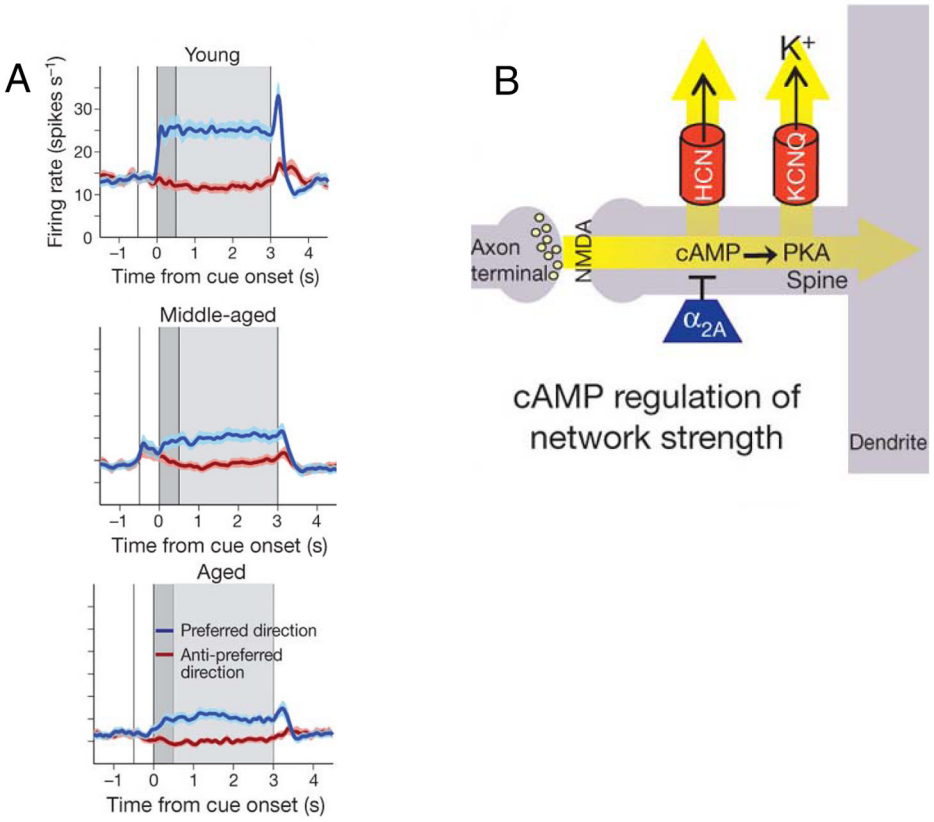

Figure 3. Age-related changes in the response properties of neurons within area 46 of rhesus monkey during a DR task

A) The average firing rate of delay neurons in area 46 recorded in young, middle-aged, and aged monkeys. Blue indicates the firing rate for the preferred direction, and red for the anti-preferred direction. Dark grey background coincides with the time during which the cue is visible and the light grey background designates the delay period. Note that the activity during the delay is decreased in both middle-aged and aged monkeys. B) A schematic of the spines thought to play a key role in WM where the strength of the synapse is modulated by c-AMP-PKA signaling that regulates the activity of HCN and KCNQ channels. This signaling pathway in select synapses is disrupted by aging, and this is thought to occur primarily in thin spines. (A and C taken from Figure 1, ref. [45]).

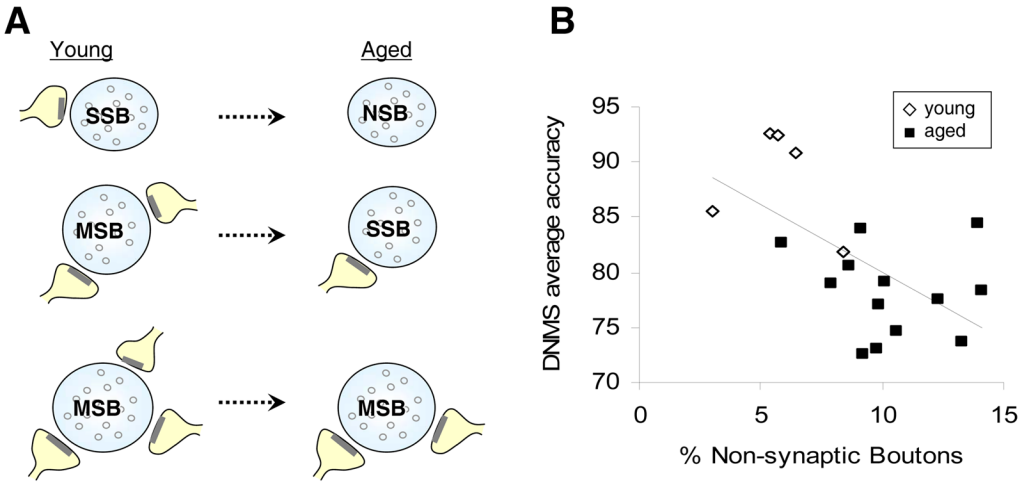

Figure 4. Age-related changes in the synaptic characteristics of monkey dentate gyrus axonal boutons

A) Schematic diagrams illustrating the synaptic subtypes in the dentate gyrus that are vulnerable to the effects of aging. Aged monkeys have increased nonsynaptic boutons (NSB), decreased multisynaptic boutons (MSB), and decreased number of synaptic contact per MSB. SSB, single-synaptic bouton. B) A significant inverse correlation is observed between the percentage of NSBs in the monkey dentate gyrus and DNMS average accuracy. Pearson correlation; n=18, r=−0.600, p=0.008.

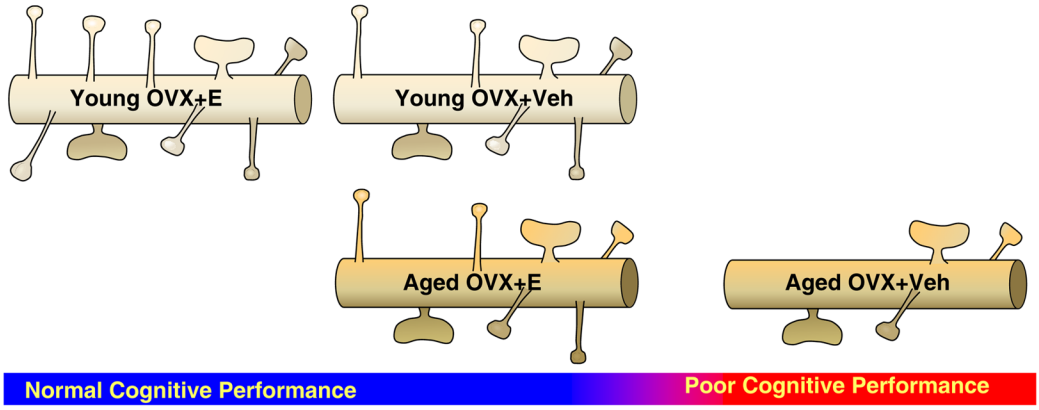

Figure 5. A schematic representation of the effects of age and estradiol treatment on small spines and cognitive performance in monkeys

The "double hit" of aging and lack of estradiol leads to a dramatic decrease in small spines that leads to cognitive decline. The intermediate spine levels observed in the young ovariectomized (OVX) monkeys treated with vehicle (Veh) and aged OVX monkeys treated with estradiol, along with their sustained performance on the delayed response task, suggests that in the aged OVX+Veh monkeys the number of small spines may fall below the threshold needed to sustain cognitive performance.

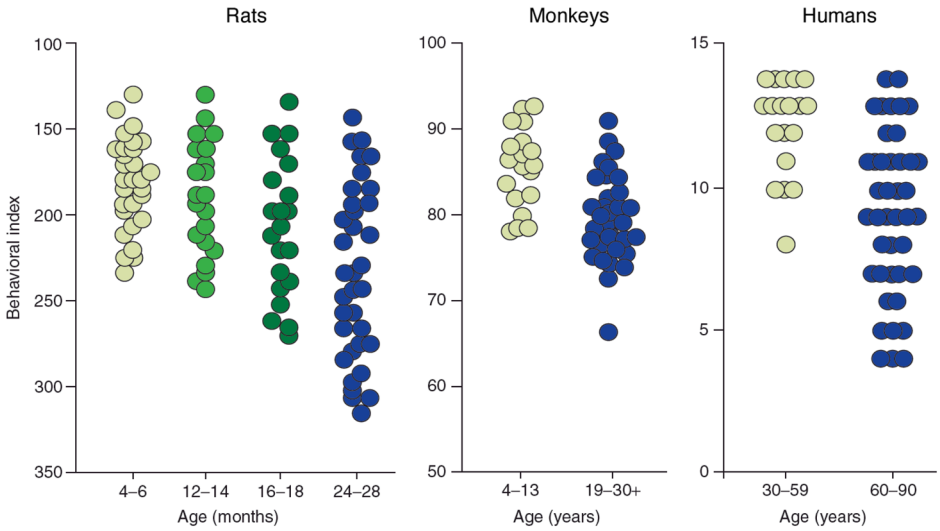

Figure.