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Impact of Aging Brain Circuits on Cognition

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Abstract

Brain networks that engage the hippocampus and prefrontal cortex are central for enabling effective interactions with our environment. Some of the cognitive processes that these structures mediate, such as encoding and retrieving episodic experience, wayfinding, working memory and attention are known to be altered across the lifespan. As illustrated by examples given below, there is remarkable consistency across species in the pattern of age-related neural and cognitive change observed in healthy humans and other animals. These include changes in cognitive operations that are known to be dependent on the hippocampus, as well as those requiring intact prefrontal cortical circuits. Certain cognitive constructs that reflect the function of these areas lend themselves to investigation across species allowing brain mechanisms at different levels of analysis to be studied in greater depth.

Keywords

prefrontal cortex; hippocampus; synapse; spatial learning; working memory

Overview

Over the past several decades it has become clear that multiple cognitive trajectories can be experienced during the aging process, both in humans and in other animals. A fundamental dichotomy in the human case is whether individuals are on a path towards dementia, or on a path towards reasonably intact cognitive function over their lifespan. Epidemiological studies have resulted in varied estimates of what proportion of us will fall into one or the other category. While some of the apparently contradictory findings are attributable to issues of sampling bias, at least one group has used a design that has overcome this limitation. Plassman *et al.* (2007) examined the prevalence of dementia in a representative sample taken from all regions of the United States in people over 70 years of age. The proportion of those 71 and older who could be categorized as being demented was 14%, while 86% were not. This suggests to some (e.g., Wagster *et al.*, 2012; Small *et al.*, 2011; Roberson *et al.*, 2012) that it is critical to understand normal cognitive aging processes in their own right, not only as a backdrop to understanding diseases that can co-occur in aging. The data reviewed here will be taken from studies that examine this non-dementia aging trajectory, focusing on the more moderate cognitive changes that occur across the 86% of us over 71 years. Within this category, there are clear individual differences, as the impact of the aging process is far from uniform.

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Two primary brain circuits will be reviewed here – the hippocampus and frontal cortex. Both are known to be important for cognitive operations in humans and other animals and both show functional changes with age. Because no brain region operates independently, when the data are available, interactions among structures with age will also be discussed. This overview is not intended to be comprehensive. Rather, selected experiments in human subjects and animal models are highlighted that illustrate the types of neurobiological change that alter these neural circuits and contribute to cognitive aging across species.

Age-related cognitive changes that depend on hippocampal circuits

The hippocampus is critically involved in the formation and utilization of 'cognitive maps'. Tolman's classic paper entitled "Cognitive maps in rats and man" (1948) outlined the kind of choices animals make in navigating mazes or finding ones way home. He described two learning strategies used to navigate: one that involves learning the configuration of landmarks in the environment (place), and the other involves learning a particular route (response). O'Keefe and Nadel (1978) argued that in addition to place and response strategies, cue strategies consisting of the approach or avoidance of some salient cue can be used. They also proposed that the hippocampus is critically involved in place learning and the formation and flexible utilization of cognitive maps that are independent of habitual routes or salient cues. Although spatial cognition is a broad psychological construct that can engage multiple brain circuits, the hippocampus appears to be necessary for wayfinding (place learning), while striatal systems are critical for route learning. Moreover, this general concept of regional specialization appears to hold across mammalian species. An example from the human literature is the finding that when humans navigate a virtual environment using a place strategy, the hippocampus is activated as assessed by neuroimaging, whereas when the participants use a response strategy to navigate, the caudate nucleus is activated (Iaria *et al.*, 2003).

What happens to hippocampus-dependent behavior during aging? If rats are given the opportunity to learn a T-maze problem that can be solved equally effectively by using a place, response or cue strategy, each animal adopts a favored strategy to solve the problem. Probe trials can be used to test for spontaneous strategy use. When young and old rats are compared, there are no differences between age groups in number of trials to learn the task, but the predominant strategy chosen by young rats was 'place', whereas old rats chose 'response' (Barnes *et al.*,1980). These data indicate a shift away from hippocampus-dependent behaviors by old rats, if other solutions are equally effective. While this observation is consistent with hippocampal dysfunction, the experiment did not test spatial learning directly. When old rats are forced to use a place strategy for optimal task performance, direct evidence is found for spatial learning and memory deficits. Examples include deficits on the Barnes maze (e.g., Barnes, 1979) and Morris watermaze (e.g., Gage *et al.*, 1984) spatial learning and memory tasks (for review, Foster *et al.*, 2012). Rapp *et al.* (1997) has also shown spatial strategy changes in aged rhesus macaques.

Advanced age also impacts navigational abilities in humans (e.g., Uttl & Graf, 1993; Burns, 1999; Driscoll *et al.*, 2005; Moffat *et al.*, 2006; Iaria *et al.*, 2009; Jansen *et al.*, 2010). For example, Head and Isom (2010) examined young and older adult performance on two different types of navigational tasks – one that required wayfinding, and the other that required route learning. The virtual maze environment was identical in the two tasks. For the wayfinding task the participants were allowed to freely explore the entire environment, and then at test, were asked to find their way to a particular landmark using the shortest route. For the route learning condition, the participants learned a specific route through the virtual environment marked by arrows, and then at test, the arrows were removed. For the behavior, older participants ranging in age from 56-88, as compared to a young group (18-22 years),

showed significantly impaired performance in acquiring a specific route through the environment, although the difference was relatively small. There were large age differences, however, observed between age groups in wayfinding. Additionally, structural MRI scans were performed on the older subjects, and volumes of the hippocampus, caudate and prefrontal cortex were obtained. There were no significant associations between prefrontal cortex volume and navigation performance, but there were associations with the other two structures examined. The volume of the hippocampus (but not caudate, Figure 1 part C) was associated with wayfinding accuracy - those older individuals with the largest hippocampi showed the shortest distances to find the landmark (Figure 1 part A). The volume of the caudate (not hippocampus, Figure 1 part B), on the other hand was associated with accuracy in the route learning task – the older individuals with the largest caudate volume also exhibited the most accurate routes (Figure 1, part D). While this study did not explicitly examine whether the difficulty that older adults have in the use of cognitive maps is in their formation or their use, data from Iaria *et al.* (2009) suggest that older adults take longer to form effective maps and also use them less accurately once acquired.

While there are many more demonstrations that behaviors dependent on the hippocampus are altered in aging, those described above illustrate one consistent cognitive change that is observed across species boundaries – namely impaired wayfinding. This consistent observation provides an opportunity to examine these behaviors in relation to the neurobiological changes that may be responsible for this cognitive outcome.

Age-related anatomical changes in the hippocampus

One possible contribution to age-related declines on hippocampus-dependent tests was mentioned in the previous section – change in volume. While noninvasive imaging methods have great power to assess brains in the absence of potential histological artifacts, the reasons for the volume changes cannot be specified at the resolution of these methods, and additional cell, synapse counts and morphological analyses are required. Nonetheless, various MRI techniques can be used across species to help dissect changes due to aging versus those of prodromal disease. Because the full pathological syndrome known as Alzheimer's disease (AD) only occurs spontaneously in humans, animal models that age, but do not exhibit AD, are helpful guides for understanding and separating what is normal from what is pathological. Not surprisingly, in the human cognitive aging literature, there are reports of hippocampal atrophy across age (e.g., O'Brien *et al.*, 1997; Tisserand *et al.*, 2000; Raz *et al.*, 2004; Raz *et al.*, 2010), along with reports of stability of overall hippocampal volume during aging (e.g., Van Petten, 2004; Sullivan *et al.*, 2005). Studies examining aging in the nonhuman primate and rodent using structural MRI methods suggest that hippocampal volume in these animals is preserved across age (Shamy *et al.*, 2006; Alexander *et al.*, 2011); while frontal cortical gray matter volumes do show changes with age in both species (Alexander *et al.*, 2008; Shamy *et al.*, 2011; Alexander *et al.*, 2011).

Using a high resolution variant of fMRI developed to evaluate resting state metabolism within hippocampal substructures, Small and his colleagues (Small *et al.*, 2002; Small *et al.*, 2004; Moreno *et al.*, 2007) have shown reduced metabolism in the dentate gyrus of aged mice, monkeys and humans. In animal models, this correlated with memory impairment. Thus, examining activity within hippocampal subregions provides a sensitive method to detect functional changes, even if volume does not differ. Furthermore, it has also been shown that taking individual health into account helps to explain subregion volume differences across age. Shing *et al.* (2011) report that reduced CA3 and dentate gyrus volume in older adults correlates with memory decline, while reduced volume of the CA1 region correlates with hypertension. Additionally, there is evidence in human samples for age-related signal degradation of white matter in the region of the perforant pathway (Yassa

et al., 2010), the main input to the hippocampus from the entorhinal cortex, reduced white matter volume in this region (Stoub *et al.*, 2012), and dendritic diffusion defects in the dentate gyrus-CA3 region (Yassa *et al.*, 2011). Interestingly, data obtained from electrically-evoked field potential recordings in the dentate gyrus of aged rats (Barnes & McNaughton, 1980; Foster *et al.*, 1991) predicted entorhinal axon collateral pruning. The observation that led to this suggestion was the fact that there was no change in the stimulus current necessary to elicit responses from these axons (i.e., no threshold change), but the maximum amplitude of the compound action potential response was reduced in old compared to young rats. Assuming no layer II entorhinal cortical cell loss with aging (confirmed in rats, Merrill *et al.*, 2001: Rapp *et al.*, 2002; and in monkeys, Gazzaley *et al.*, 1997), the reduced maximal amplitude in old rats suggested that there were fewer entorhinal axon collateral fibers running in the perforant pathway. This hypothesis fits rather well with the MRI observation of age-related reductions in perforant path white matter volume in normal aged humans reported by Stoub *et al.* (2012), but direct counts of entorhinal axon collaterals has yet to be made in aged rats.

With the advent of stereological methods, one feature of the aging hippocampus that can be ruled out as significantly contributing to volume or metabolic changes is cell number. That is, cell numbers are preserved in normal aging in the principal cell types of the hippocampus (granule cells, CA1 and CA3 pyramidal cells) in humans (e.g., West *et al.*, 1993), nonhuman primates (e.g., Keuker *et al.*, 2003) and rodents (Rapp & Gallagher, 1996; Rassmussen *et al.*, 1996). A lack of dendritic deterioration has also been reported for hippocampal cells in rodents and humans (e.g., Flood *et al.*, 1987; Turner & Deupree, 1991; Flood, 1993), and alterations in dendritic spines are region-specific, and will be discussed in terms of synapse number below. In rodents, there is loss of axospinous synapses from the layer II medial entorhinal cortex projection to granule cells (Geinisman *et al.*, 1992) and reduced synaptophysin staining in the dendritic region of CA3 pyramidal cells (Smith *et al.*, 2000) during aging. The synaptic input to CA1 pyramidal cells from CA3, however, does not show synapse reduction (Geinisman *et al.*, 2004). However, a subset of the synaptic contacts in this region exhibit reduced postsynaptic density size (Nicholson *et al.*, 2004), and electrophysiological evidence suggests that this group of synapses may reflect nonfunctional, ‘silent’ synapses (Barnes *et al.*, 1997; Burke & Barnes, 2010).

Clearly, anatomical changes do occur within the hippocampus in normal aging, although they are rather subtle compared with those known to occur in pathological conditions that arise during aging, such as Alzheimer’s disease (e.g., Ballard *et al.*, 2011). The impact that these neurological changes have on plasticity and circuit function is discussed below.

Age-related physiological changes in the hippocampus

Hippocampal cell function in aging animals is strikingly well preserved. In rats it is possible to study the detailed biophysics of individual hippocampal principal cells using *in vitro* recording methods. Most biophysical properties in these aging cells do not change (for reviews, Burke & Barnes, 2006; Hoang *et al.*, 2012), with a small number of exceptions, including a larger after-hyperpolarizing potential in CA1 pyramidal cells of old rats (e.g., Landfield & Pitler, 1984). This change may be due to an increased number of L-type calcium channels in old CA1 cells (e.g., Thibault & Landfield, 1996). This increase in channel numbers is hypothesized to lead to age-related disruption of neuronal calcium homeostasis, suggesting an interesting potential therapeutic target (for review, Kumar *et al.*, 2009). There are two additional electrophysiological changes that are observed in all 3 subregions of the hippocampus. These include reduced amplitude of the stimulation-induced cholinergic slow EPSP (Shen & Barnes, 1996), and an increase in gap junction-mediated electrotonic coupling between aged CA1 and CA3 pyramidal cells, as well as granule cells

(Barnes *et al.*, 1987). The former age-related change suggests reduced effectiveness of a modulatory input, and the latter increased electrical communication between cells. The alterations described above are consistent with both increased excitability (increased calcium conductance, increased electrotonic coupling) and decreased excitability (reduced cholinergic modulation) of old cells. Taken together the data suggest a complex set of mechanisms at play that may tend to keep overall cell function stable in the aged brain.

Two examples can be offered that may reflect cellular adaptation in aged hippocampal circuits. The first involves the fact that the synapses that arise from the medial entorhinal cortex and make contact within the middle third of the granule cell dendritic tree, are reduced in number by about one third in old rats (e.g., Geinisman *et al.*, 1992). The remaining synapses in that dendritic region, however, are more powerful – the depolarization caused by activation of a single synapse is larger in the old rats (Barnes & McNaughton, 1980). Fewer but stronger synapses could be interpreted as an adaptive response, keeping overall depolarization levels of the granule cells within some optimal range. Another example involves the fact that there have been consistent reports of increased AHP amplitudes of old CA1 pyramidal cells measured *in vitro* (e.g., Landfield & Pitler, 1984; Disterhoft *et al.*, 1996). The inference made from these intracellular recording studies is that this increased hyperpolarization after an action potential should slow the repolarization that enables another action potential to be generated, and thus predicts reduced behavior-induced firing rates for old CA1 pyramidal cells. A slowing of CA1 cell firing rates, however, is not observed in the intact, freely-behaving aged rat (e.g., Markus *et al.*, 1994; Shen *et al.*, 1997; Schimanski *et al.*, 2013), suggesting that an adaptation has occurred that keeps output rates constant in these aged cells.

There are a number of examples of changes in the function of plasticity mechanisms that occur within the hippocampus. Because experimentally induced changes in synaptic communication are thought to underlie the acquisition, storage, consolidation and reconsolidation of memory (e.g., Bliss *et al.*, 2007), the processes of long-term potentiation (LTP) and depression (LTD) are prime targets for studying the physiology of altered cognitive functions observed during aging. The first demonstration that LTP and behavioral performance may be related was provided by an experiment conducted in awake, freely-behaving young and old rats, in which LTP was induced at the perforant path-granule cell synapse. In this study, individual differences in the durability of LTP were significantly correlated with spatial memory accuracy, and this behavior/plasticity relationship was observed in each age group independently (Barnes, 1979). The same relationship between LTP durability and spatial behavior on the circular platform task was also observed at synapses in CA1 in young and old mice (Bach et al., 1999). Differences in induction of LTP have also been noted (e.g., Deupree *et al.*, 1993; Moore *et al.*, 1993; Barnes *et al.*, 2000), and Foster and his colleagues have shown that LTD and LTP reversal are easier to induce in older, spatial memory-impaired rats (e.g., Norris *et al.*, 1996). Additionally, a behaviorally-induced form of plasticity dependent on NMDA receptor mechanisms (Ekstrom *et al.*, 2001) is altered in aged rats (Shen *et al.*, 1997). This behavior involves an expansion and backwards shift of place-specific firing of hippocampal cells that can be observed when rats engage in repeated route following behaviors. Mehta *et al.* (1997) have called this phenomenon place field expansion plasticity. Although the description of hippocampal cell firing characteristics is elaborated below, it is important to note here that along with age-related deficits in plasticity measured in response to artificial electrical stimulation, behaviorally-driven LTP-like plasticity mechanisms are also observed to change with age. Moreover, this place field expansion plasticity is reminiscent of Hebb's (1949) theoretical idea of phase sequences in cell assemblies, which he postulated could provide a means to encode sequences or episodes of experience. Together, these data suggest clear changes in synaptic plasticity mechanisms in the normally aging brain, as well as potential mechanisms

through which therapeutic targets can be developed (e.g., Bach *et al.*, 1999; Burke *et al.*, 2005; Foster, 2006; Huang & Kandel, 2006; Rose *et al.*, 2007; Bodhinathan *et al.*, 2010).

There have been a number of experiments that have investigated the potential causes for these types of age-related plasticity deficits in aging. One approach has been to examine the role of immediate early genes (IEGs) in these processes. *Arc* (Lyford *et al.*, 1995) has been useful in this regard because when Arc protein is knocked down in hippocampus of young rats, LTP decays significantly faster compared to the case when normal levels of Arc are present, and spatial memory consolidation is also disrupted (Guzowski *et al.*, 2000; Plath *et al.*, 2006). Penner *et al.* (2011) examined *Arc* mRNA activity in hippocampal cells of young and aged rats induced by spatial behaviors. The expression of *Arc* within cells provides an activity marker for those neurons that participate in a recent behavioral event (Guzowski *et al.*, 1999). They used methods that allowed behavior-induced *Arc*-positive cells to be counted, and *Arc* mRNA to be quantified by rtPCR within the same animal and cell type. For example, in CA1, the same numbers of pyramidal cells across age groups express *Arc* following exploratory behavior, but old pyramidal cells transcribe less *Arc* (Penner *et al.*, 2011). Epigenetic mechanisms such as DNA methylation are known to affect RNA expression, and can influence cell function by altering the amount of RNA transcribed from a gene. Interestingly, Penner *et al.* (2011) also observed a very distinct pattern of methylation change with age in the Arc gene in CA1 cells. Thus, it appears that aging is accompanied by significant changes in epigenetic regulation of at least this important plasticity gene. These data, taken together with more recent observations suggesting that there is reduced coordination of epigenetic regulation dynamics of plasticity genes in aging (Castellanos *et al.*, 2012), strongly suggest that epigenetic mechanisms are fundamental to both age-related changes in circuit modifiability and cognition. Deeper understanding of how transcription is regulated by chromatin modification dynamics is going to be central in choosing targets for therapeutic optimization of cognition during aging.

When the activity of ensembles of hippocampal cells are examined in behaving young and old rats, interesting changes are observed in cell population dynamics between spatial experiences. O'Keefe and Dostrovksy (1971) first described the activity patterns of individual hippocampal cells as place-specific, and named these cells "place cells". As discussed earlier, this was a prime impetus behind the development of the idea that the hippocampus had an important role in cognitive mapping, and in spatial strategies that drive behavioral performance. All three principal hippocampal cell types show place-related firing, although only CA1 and CA3 pyramidal cells have been recorded and compared across age groups. While there is stability of CA1 and CA3 spatial firing patterns within a given recording session for young and old rats (i.e., the distribution of cell firing in the first half of the behavior session, is highly correlated with the distribution of place-specific firing in the second half of the session), between session dynamics are different between age groups, and across cell types. For CA1, the cell firing pattern, or "map", is stable in young rats across two daily sessions in an identical environment. For old rats, however, the cell firing pattern can completely change from one session to the next, and occurs on about a third of the recording days for any individual old rat. In other words, the hippocampus "remaps", as though the first and second session are recorded in different environments (Barnes *et al.*, 1997). For CA3, on the other hand, when environments are changed between sessions, young rats remap appropriately between the first and second sessions. For old rats, however, the hippocampus appears to sometimes retrieve the same map for the two distinct environments. In this case, the hippocampus fails to remap (Wilson *et al.*, 2005). It is likely that these altered dynamics of hippocampal representation of space contribute to the spatial behavioral differences noted between age groups.

In the context of changing circuit dynamics with age, it is important to highlight conditions under which the hippocampus is activated differentially in young and older adults in fMRI experiments. One, among a number of examples of this, is a study by Maguire and Frith (2003) who used fMRI imaging methods that assessed hippocampal and medial prefrontal cortical network activation in young and older adults. While in the scanner, the participants retrieved details of specific episodic memories for autobiographical events. These past experiences were obtained from each individual before being scanned, and the details of the autobiographic memories during test retrieval were matched for detail across age groups. Activation comparisons were between retrieval of autobiographical events and general semantic knowledge. There was no difference between age groups in prefrontal cortical activation during retrieval, but there were differences between groups in hippocampal activation. As in previous studies of autobiographical retrieval, there was significant activation of the left hippocampus in young participants. For the old participants, however, there was significant activation of both left and right hippocampi, suggesting that the older adults recruited additional circuits when recalling episodes from specific times and contexts. This result may suggest a neural compensatory process for recall of detailed episodes, or different strategies used for recall in the older adults. Regardless, it is likely that this difference in regional activation is initiated because of functional changes within the circuits responsible for these behaviors.

Age-related cognitive changes that depend on frontal cortical circuits

One of the most replicated results in the cognitive aging literature is that cognitive processes that rely on frontal cortical areas are particularly vulnerable to the effects of aging. In particular, maintaining a representation through working memory is reliably affected (e.g., Alexander *et al.*, 2012; Störmer *et al.*, 2012). Older adults show a decline in performance on tasks that require updating items in working memory (e.g., Hartman *et al.*, 2001), in accuracy during trials with larger memory loads (e.g., Cappell *et al.*, 2010) and in responding after a delay (e.g., Lyons-Warren *et al.*, 2004). Similarly, aged nonhuman primates and rats also show deficits in tasks that require working memory (for review Bizon *et al.*, 2012). That is, when a delay is incorporated into the design of the task, aged animals are particularly disadvantaged (e.g., Bartus *et al.*, 1978; Rapp & Amaral, 1989; Muir *et al.*, 1999; Grottick & Higgins, 2002; Ramos *et al.*, 2003; Smith *et al.*, 2004; Bizon *et al.*, 2009). Two widely used working memory tasks implemented in monkey experiments include the delayed response task (DR), which relies on the dorsolateral prefrontal cortex (PFC; Goldman & Rosvold, 1970; Passingham, 1985; Funahashi *et al.*, 1993) and the delayed nonmatching-to-sample task (DNMS), which relies on the ventromedial PFC (Arnsten & Goldman-Rakic, 1990, Figure 2C). In the DR task, a monkey is required to remember a spatial location on a screen over a brief delay period, after which it must make a saccade towards that location in order to receive a juice reward. Aged monkeys are slower to acquire the task and are impaired when longer delays are imposed (e.g., Bartus *et al.*, 1978; Rapp & Amaral, 1989; Bachevalier *et al.*, 1991). In the DNMS task, a monkey is first exposed to one object that it displaces to receive a reward. After a delay period, the monkey is exposed to two objects and the task requires that the novel object is displaced for the 'nonmatch' requirement of the task. Reward is obtained when the displaced object was the one that was not previously presented. As with the DR task, aged monkeys are slower to learn the task and perform more poorly as delay intervals are increased (Shamy *et al.*, 2011).

Behavioral flexibility is another frontal-dependent cognitive process that is compromised with aging. This has been studied using a variety of tasks, notably extradimentional set shifting and reversal tasks in humans (Ridderinkhof *et al.*, 2002; Marschner *et al.*, 2005; Weiler *et al.*, 2008), monkeys (Bartus *et al.*, 1979; Lai *et al.*, 1995; Voytko, 1999; Moore *et al.*, 2003) and rats (Stephens *et al.*, 1985; Barense *et al.*, 2002; Schoenbaum *et al.*, 2002;

Nicolle & Baxter, 2003; Mizoguchi *et al.*, 2010). Interestingly, lesions of area 9 in marmoset monkeys affected extradimentional set-shifting performance, whereas lesions of the orbital PFC affected reversal performance (Dias *et al.*, 1996). These data suggest that these tasks rely on different brain structures within the PFC. Extradimentional set-shifting (EDS) refers to the problem of switching attention between cues that are in different perceptual dimensions in order to perform the task correctly. An example of this is to train a rat to use light cues to determine which arm to select in a maze, and then shift the relevant cue to an auditory stimulus. When the EDS occurs, the rat must shift its strategy and follow the sound cue in order to select the correct baited arm (e.g., Insel *et al.*, 2012). In contrast, reversal learning refers to adapting a behavior to the changing contingencies required to reach a goal. For example, a rat can initially learn to press a lever in a 'light-on' condition to receive reward. After a reversal, the rat must adapt its behavior to press during the 'light-off' condition (e.g., Nomura *et al.*, 2004).

In parallel to the age-related cognitive deficits discussed above, aging is also associated with changes in attentional processes (Gazzaley & D'Esposito, 2007; Prakash *et al.*, 2009; Hedden *et al.*, 2012). This is accompanied by a greater susceptibility to distraction or interference during the delay period of a working memory task in humans (Bowles & Salthouse, 2003; Campbell *et al.*, 2012) and monkeys (Bartus & Dean, 1979; Prendergast *et al.*, 1998). Additionally, fMRI studies in older adults have reported that there is increased activity in brain regions mediating distraction (Milham *et al.*, 2002; Stevens *et al.*, 2008), and in cases where task-irrelevant stimuli are presented (Gazzaley *et al.*, 2005).

Age-related anatomical changes in frontal cortical circuits

One of the most consistent finding in the literature on aging brain is a decline in the volume of the prefrontal cortex (PFC) of humans, monkeys and rodents. This decline is one of the earliest changes detected, and for almost fifty years, it was thought that the decrease in frontal lobe volume was the result of cell loss (Haug, 1986; Peters, 2002). The early reports of cell loss, however, turned out to be an error resulting from differential shrinkage of young and aged tissue during processing (Haug *et al.*, 1981; Terry *et al.*, 1987; Haug & Eggers, 1991). It is now believed that cell numbers in the frontal cortex are preserved through aging in humans (Haug *et al.*, 1981, 1984; Freeman *et al.*, 2008). Similar conclusions have been drawn for frontal areas in non-human primates (Peters *et al.*, 1996; Peters *et al.*, 1998a; Smith *et al.*, 2004), with the exception of prefrontal area 8A, a region of the dorsolateral PFC, which was shown to have a significant decline of Nissl-stained neurons (Smith *et al.*, 2004). In rodents the cell counting results are conflicting. One group reports decreases in neuron numbers in the dorsal PFC areas but preservation in the ventral PFC areas (Stranahan *et al.*, 2012), and another found the opposite, with cell loss in the ventral PFC and preservation in dorsal PFC (Yates *et al.*, 2008). Because the same rat strain was utilized, Stranahan and colleagues (2012) suggest that different delineation of brain structures during counting could explain the disparate findings. Nonetheless, the current view is that the cell numbers in the PFC are reasonably well preserved during aging, although there may be focal points of cell loss in non-human primates and rodents.

In line with the overall reduction in frontal lobe volume mentioned above, age-related decreases in gray matter volumes and cortical thickness have been reported in humans (Haug & Eggers, 1991; Raz *et al.*, 1997, 2005; Good *et al.*, 2001; Tisserand *et al.*, 2002; Salat *et al.*, 2009; Bergfield *et al.*, 2010; Giorgio *et al.*, 2010; Thambisetty *et al.*, 2010; Burzynska *et al.*, 2012; Kalpouzos *et al.*, 2012), nonhuman primates (Alexander *et al.*, 2008; Shamy *et al.*, 2011; Figure 2B) and rats (Alexander *et al.*, 2011). However, an earlier stereological study performed using Nissl stained slices of monkeys reported a general preservation of area 46 (O'Donnell *et al.*, 1999), which is in contrast with the findings from

MRI studies presented above. These differences may be the result of the research method employed or maybe caused by inter-individual variability of age effects on this part of the brain. Nonetheless, the changes in volume of the dorsolateral PFC in nonhuman primates was also shown to correlate with accuracy on a recognition memory task (Shamy *et al.*, 2011). Specifically, aged monkeys with larger PFC volumes identified more correct nonmatch objects on the DNMS task than did monkeys with smaller PFC volumes (Shamy *et al.*, 2011; Figure 2D). This correlation held even when the analysis was restricted to PFC gray matter or white matter volumes separately.

Rather than cell loss, the gray matter volume decrease in the PFC is in part caused by age-related changes in neuron morphology, particularly the loss of synapses and the regression of apical dendrites (reviewed in Peters *et al.*, 1996; Markham & Juraska, 2002; Dickstein *et al.*, 2007; Luebke *et al.*, 2010; Pannese, 2011; Morrison & Baxter, 2012). Decreases in spine numbers, density and changes in spine morphology have been reported in humans (Jacobs *et al.*, 1997), non-human primates (Page *et al.*, 2002; Duan *et al.*, 2003; Peters *et al.*, 2008; Dumitriu *et al.*, 2010) and rats (Bloss *et al.*, 2011, 2013). This change in spines represents the most consistent age-related alteration of cellular morphology reported in the frontal cortical literature, and is illustrated in Figure 3. With respect to the dendritic arbor, significant regression only occurs at the level of the apical dendrites in the PFC of aged humans (de Brabander *et al.*, 1998), monkeys (Cupp & Uemura, 1980; Duan *et al.*, 2003; Kabaso *et al.*, 2009) and male rodents (Grill & Riddle, 2002; Markham & Juraska, 2002). The regression of terminal dendrites and synaptic loss that occur during aging likely affects dendritic excitability and plasticity processes in the PFC, thus contributing to the age-related decline in learning and working memory. In support of this, there is a decline in spine numbers and reduced thin spine volumes in area 46 in monkeys. This reduction was shown to correlate with acquisition and performance on a DNMS task (Peters *et al.*, 1998b; Dumitriu *et al.*, 2010). Additionally, a recent study was able to show that there is a correlation between the age-related overactivation of PKC, the length of basal dendrites and working memory performance in aged rats (Brennan *et al.*, 2009), suggesting that altered PKC activity may be at the basis of some of the anatomical and functional deficits found in aged animals.

Despite cortical volume and cellular changes reported in the frontal cortex of older adults, many fMRI studies report areas of overactivation, greater bilateralization or recruitment of additional structures in PFC areas of older adults during performance certain cognitive tasks (e.g., Spreng *et al.*, 2010; Morcom & Friston, 2012; Spaniol & Grady, 2012). This is a phenomenon thought to reflect compensatory mechanisms and in support this hypothesis, greater activation of frontal areas was shown to be associated with better performance (Grady *et al.*, 2005). Thus, it is plausible that plastic mechanisms in the PFC compensate for changes occurring in the PFC and other parts of the brain in older adults, thereby contributing to preservation of cognitive function. In support of this idea, under some circumstances accurate retrieval of autobiographical events in older adults also show a similar pattern (as outlined previously). That is, during retrieval, the hippocampi of older adults show bilateral activation, whereas young adults show hippocampal activation lateralized to the left hemisphere (Maguire & Frith 2003).

In contrast to gray matter volumes that decrease linearly with age, white matter volume change across the lifespan follows a parabolic shape, with the largest volumes in the mid-fifties and an accelerated decline after 65 years of age (Allen *et al.*, 2005; Gunning-Dixon *et al.*, 2009; Bennett *et al.*, 2010; Giorgio *et al.*, 2010; Malykhin *et al.*, 2011). Decreases in white matter volume have also been reported in aged nonhuman primates (Peters & Sethares, 2002; Luebke *et al.*, 2010; Shamy *et al.*, 2011). A number of studies using diffusion tensor imaging have also revealed that the integrity of white matter is altered

during aging in humans and nonhuman primates, particularly in the frontal lobe (Gunning-Dixon *et al.*, 2009; Madden *et al.*, 2009; Bennett *et al.*, 2010; Giorgio *et al.*, 2010; Luebke *et al.*, 2010; Samanez-Larkin *et al.*, 2012). In addition, aging is associated with an increased incidence of white matter hyperintensities (WMH) around the ventricles and in the deep white matter (Gunning-Dixon *et al.*, 2009). Greater numbers of WMH and reduced white matter integrity were both found to correlate with poorer cognitive performance in older adults, particularly processing speed and attention (Gunning-Dixon & Raz, 2000; Madden *et al.*, 2009; Penke *et al.*, 2010; Hedden *et al.*, 2012). Reductions in white matter integrity could affect the connectivity between distributed brain networks, and contribute to some of the age-related changes observed in cognition (see Madden *et al.*, 2009). In support of this, a correlation between white matter integrity in the genu of the corpus callosum, intrinsic functional connectivity, and choice reaction time was reported for older but not younger adults (Chen *et al.*, 2009).

Age-related physiological changes in frontal cortical circuits

Age-related changes in gamma oscillations in humans and rodents

Older adults are more prone to have deficits in attentional control than are younger adults (Prakash *et al.*, 2009; Hedden *et al.*, 2012). They show a selective impairment in visual attention tasks in which the goal is to determine whether a target object is present among distractor objects that share features with it - a task condition called conjunctive search (Plude & Doussard-Roosevelt, 1989). Solving such a task requires subjects to intentionally focus their attention toward the various objects - a form of attention referred to as top-down (Talsma *et al.*, 2010; Awh *et al.*, 2012). A recent aging study found that under conjunctive search conditions, there were differences between age groups in the power of gamma in the PFC-posterior parietal network. Older adults fail to show an increase in low-gamma power (22-34 Hz) in the easier task condition (Phillips & Takeda, 2010), while younger adults show increases in low-gamma power at all difficulty levels of this task (Phillips & Takeda, 2009). This result adds further support to the inferences made in the imaging literature (e.g., Madden *et al.*, 2007; Gazzaley, 2011) that altered PFC-posterior parietal network activation in older adults may be responsible for a less efficient top-down attentional control of visual search.

Gamma rhythms have also been reported to be altered in aged rats. In aged rodents, behavioral slowing during decisions made in an extra-dimensional set-shifting task was found to correlate with slower gamma oscillations (30-100 Hz) in the anterior dorsal cingulate cortex, an area within the medial PFC (Insel *et al.*, 2012). Specifically, the mean peak frequency of gamma oscillations, while performing this set-shifting task, was 56.4 Hz in young rats and 53.5 Hz in aged rats (Insel *et al.*, 2012), and this difference was statistically reliable. Because gamma frequencies are thought to be mediated by network interactions between glutamatergic and GABAergic cells (Tiesinga *et al.*, 2001; Börgers *et al.*, 2005; Wang, 2010), the changes in gamma frequency suggest that the interaction between these cell types may be compromised in aged animals. In support of this, Insel and colleagues found that, during the performance of the task, putative excitatory and inhibitory neurons of the medial PFC fired preferentially at different phases of the gamma cycle in young and aged rats. When cross correlation analysis was applied to simultaneously recorded excitatory-inhibitory cell pairs, the interval between the excitatory drive onto inhibitory cells was lengthened in the older rats (Insel *et al.*, 2012). While arguments for direct causation cannot be made, these studies suggest that GABAergic transmission is altered in the PFC of aged rodents and that this may contribute to altered gamma synchrony among medial PFC networks.

Decreased persistent firing neurons during delayed response tasks, role for cAMP

Converging evidence links age-related working memory impairments to dysfunction of adrenergic systems in primates. Indeed, age-related disinhibition of cyclic adenosine monophosphate (cAMP) signaling was shown to lead to decreases in persistent firing of area 46 neurons that are active through a delay period during working memory tasks (Ramos *et al.*, 2003; Arnsten *et al.*, 2010; Wang *et al.*, 2011). These delay-firing neurons show a sustained activation that lasts for the duration of the cue delay period of a delayed response task (Goldman-Rakic, 1995). This increased activation is modulated by spatial location on a screen, and is greatest for the neurons' preferred direction. In aged monkeys, there is an age-related loss in response modulation of these neurons to their preferred spatial location during working memory tasks, to a point where delay neurons show very little increase in firing rate during the cue delay period (Wang *et al.*, 2011). The decrease in activity of delay neurons in aged monkeys could be rescued using local drug administration that either inhibited cAMP or the downstream potassium channels that cAMP is known to activate (HCN, KCNQ) (Wang *et al.*, 2011). The same results could be obtained using local infusion of guanfacine, an α_{2A} adrenergic agonist that inhibit cAMP signaling (Wang *et al.*, 2011). Guanfacine and clonidine are both α_{2A} adrenergic agonist known to enhance working memory performance in aged rats (Arnsten *et al.*, 1988; Arnsten & Goldman-Rakic, 1990; Ramos *et al.*, 2003). Because α_{2A} adrenergic agonists have no effects on a visual pattern discrimination task, (Arnsten & Goldman-Rakic, 1985), the effects of guanfacine on working memory performance is likely through its action on the activity of PFC neurons. These findings support the notion that age-related working memory deficits are mediated, at least in part, by physiological changes occurring in the dorsolateral PFC.

As with nonhuman primates, the activity of the PFC during the delay period of working memory tasks is altered in older adults. Indeed, a fMRI study revealed age differences in the pattern of activation of the lateral PFC that were dependent on the trial phase, with lower activation during task delays, and greater activation at the time of the probe in older adults (Paxton *et al.*, 2008). These results suggest that aging may also affect delay neurons, not only in monkeys, but perhaps in human as well.

Decreased sensitivity of orbitofrontal cortex (OFC) neurons to delays

The activity of OFC neurons has been characterized in young and aged rats, while performing two different tasks, a delay discounting task and a reversal task (Schoenbaum *et al.*, 2006; Roesch *et al.*, 2012). In a delay discounting task, rats have the choice between a small immediate reward and a large reward delivered after a delay. In this task, aged rats were found to prefer the large reward, regardless of the length of the delay, whereas young rats were more prone to switch their behavior towards the small immediate reward as the delay increased (Simon *et al.*, 2010). Using a delay discounting task, Roesch and colleagues (2012) addressed whether there are age-related differences in the activity of OFC neurons in response to varying the length of delays. They found a higher prevalence of neurons responsive to long delay rewards in aged rats. While about 50% of reward-responsive neurons were active during short delays in aged rats, about 75% of the neurons fired preferentially to short delays in young rats (Roesch *et al.*, 2012). There was no age difference in the proportions of cells responding to large over small rewards (Roesch *et al.*, 2012). Thus, aging appears to selectively affect OFC delay neurons. It is possible that age-related changes in plastic processes in OFC biased the older neurons from adapting their activity in a manner similar to that of the younger animals. This lack of adaptation of OFC cells may be responsible for the lack of willingness of older animals to change their behavior towards receiving a large reward, in spite of the long delay associated with doing so.

Aged rats are known for their behavioral impairments on reversal tasks (Schoenbaum *et al.*, 2002; Mizoguchi *et al.*, 2010). Whereas older rats are able to acquire discrimination problems at high levels of performance, some are impaired when contingencies are reversed. Because the OFC is critical for reversal performance, Schoenbaum and colleagues (2006) recorded neurons from this brain region in young and aged rats while they performed a go, no-go task with reversals. In this task, rats learned to associate pairs of odors predicting either reward or punishment. Following presentation of a "go" odor, rats learned to go to the food port to receive a reward. Following a "no-go" odor, rats learned to avoid going to the food port where an aversive quinine solution was delivered. They found that age-impaired rats had fewer neurons that were cue selective, and most of these cells lost their cue-selective firing after reversal (Schoenbaum *et al.*, 2006). In contrast, young and aged-unimpaired rats had a larger number of cells that were more sensitive to one of the odor cues, and a significant proportion of these cells reversed their activity in response to the new odor after reversal (Schoenbaum *et al.*, 2006). These results suggest that a loss in flexible responding of OFC neurons to changing contingencies might underlie the behavioral deficits found in some aged rats during reversal performance.

Increased excitability of cells in area 46

The electrical properties of pyramidal cells of area 46 of young and aged monkeys have been examined using *in vitro* preparations. The general findings suggest an increased excitability of pyramidal cells located in layer 2/3, but not in layer 5 (Luebke *et al.*, 2004; Chang *et al.*, 2005; Luebke & Chang, 2007; Dickstein *et al.*, 2012; Luebke & Amatrudo, 2012). Specifically, the authors report an age-related decrease in spontaneous excitatory post-synaptic currents and increases in spontaneous inhibitory post-synaptic currents (Luebke *et al.*, 2004). Additionally, the authors report an increased input resistance and firing frequency of layer 3 pyramidal neurons (Chang *et al.*, 2005). Layer 3 mainly contains pyramidal neurons that project to other cortical areas (Page *et al.*, 2002; Yeterian *et al.*, 2012), thus increased excitability suggests increased output from these cells. Because aged monkeys with the highest and lowest firing rates displayed the poorest performance levels in working memory tasks, a balance in the activity of area 46 might be necessary for optimal performance (Chang *et al.*, 2005). The exact impact that this age-related increase in excitability has on wider PFC networks in non-human primates remains to be explored.

Summary

Overall, the patterns of age-related change in brain function and cognitive domains are remarkably conserved across mammals, as has been reviewed here. The depth of analytic approaches that can be used in animals other than humans has made it possible to understand the neurobiological processes that are vulnerable across the lifespan in greater detail. Equally striking in this comparison of temporal and frontal lobe systems is the apparent selectivity and differential vulnerability of these brain structures to the changes that do occur with age. While the reasons for these differences are the target of active investigation, there is no clear explanation for why frontal lobe systems appear to 'age at a different rate' (faster, earlier signs of change) than do temporal lobe systems. Clearly the brain region specificity of neural changes with aging needs to be taken into account in the development of strategies targeted at optimization of cognitive function across the lifespan.

Another important point to emphasize is that while it has been suggested that cognitive decline is not apparent until after 60 years of age (e.g., Hedden & Gabrieli, 2004), there are also data suggesting that changes in cognition can occur much earlier (e.g., Finch, 2009; Salthouse, 2009). In fact, one longitudinal study has reported that the decline in some domains can be detected across large populations of those in their forties (Singh-Manoux *et al.*, 2011). This suggests that it will be important to develop interventions that optimize

neural circuit function, in regions such as the hippocampus and prefrontal cortex, beginning at least in mid-age and probably earlier. As discussed here, progress in understanding the biology of lifespan development and how neural change drives cognitive change has led to a number of key insights that can now be directed towards the development of tools that can help maintain cognitive health across the lifespan.

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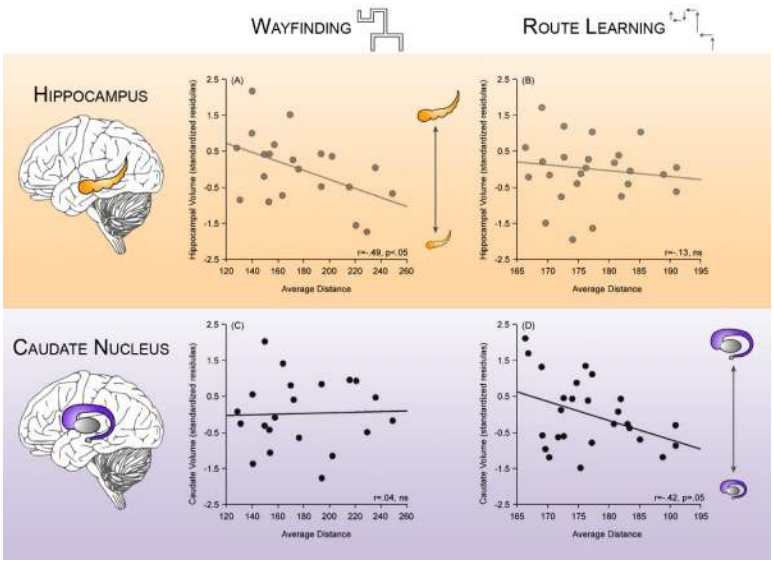

Figure 1.

Older participants (56-88 years) were trained to use either a wayfinding strategy or a route strategy to learn to navigate through a virtual environment. Correlations are shown between MRI-derived volumes of hippocampus and caudate nucleus in these individuals and performance levels on these two types of spatial navigation tasks. **A)** Participants with larger hippocampal volumes traveled shorter virtual distances to find a landmark when using a wayfinding strategy. **B)** There was no correlation between hippocampal volume and performance levels when using a route learning strategy. **C)** There was no significant relationship found between caudate nucleus volumes and wayfinding performance. **D)** Participants with larger caudate nucleus volumes, on the other hand, showed more accurate performance when they used a route learning strategy. Adapted with permissions from (Head and Isom, 2010).

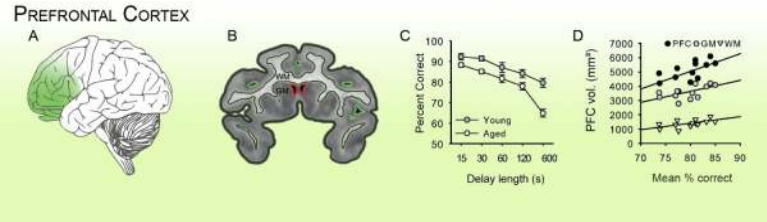

Figure 2.

Prefrontal cortical (PFC) volume correlates with performance on a DNMS task, in aged rhesus macaques. **A.** Illustration of a human brain with the frontal lobe highlighted in green. **B.** Example coronal section of the PFC, illustrating the areas taken for ROIs for gray matter (dark grey) and white matter (light grey) volumes. The red marks the delineation of the ventricles. **C.** Aged monkeys (grey circles) were less accurate than were young monkeys (white circles) on a DNMS task, particularly at longer delays. **D.** The gray matter (grey circles), white matter (white triangles) and total PFC volumes (black circles) correlated with task accuracy in aged animals. Adapted with permissions from (Shamy *et al.*, 2011).

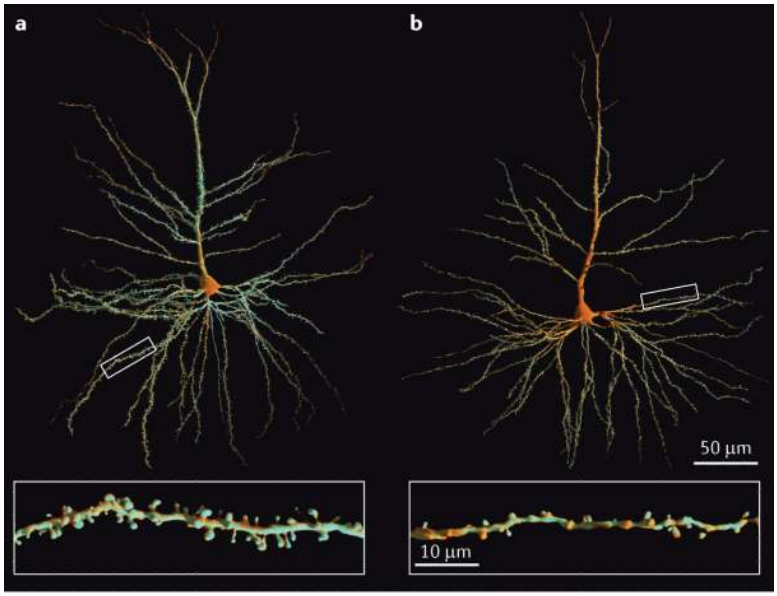

Figure 3.

The spine density of prefrontal cortical (PFC) neurons is greatly reduced in aged monkeys. Illustration of a Lucifer yellow-filled PFC neurons from a young (left) and an aged (right) monkey. In the cells presented here, there are no age differences in the extent of dendritic arborization; however a marked decreased in spine density is observed. The rectangles show a higher magnification of a portion of a basal dendrite from each neuron. Reproduced with permissions from (Morrison & Baxter, 2012).