

# Brain aging research

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## Introduction

The last three decades produced a striking increase in investigations of the neurobiological basis of brain aging and aging-related changes in neural and cognitive function. Experimental and clinical studies of aging have become more valuable as the population, at least in industrialized countries, has become 'greyer'. The increase in adult life expectancy that occurred in the twentieth century produced the motivation and necessity to invest resources in increasing 'health span' as well as lifespan, in order to maximize quality of life and minimize the financial and social burdens associated with disability in the later years of life. Specific interest in the aging nervous system is driven by recognition that increased longevity has little appeal for most people unless it is accompanied by maintenance of cognitive abilities. Indeed, surveys of older individuals routinely show that loss of mental capacity is among their greatest fear. In recent years, neuroscientists and gerontologists, with a variety of training and experimental approaches, have applied increasingly powerful quantitative methods to investigate why neural function declines with age. New animal model systems have been developed and old ones have become better characterized and standardized. The necessary and important descriptive studies that dominated the field in earlier years are increasingly supplemented by more hypothesis-driven research, resulting in sophisticated investigations and models of the mechanisms of brain aging. This review provides a selective overview of recent and current research on brain aging. The focus throughout will be on normal brain aging and the moderate cognitive changes that often accompany it, not on aging-related neurodegenerative diseases that result in

dementia. To provide a context for studies of neurobiological changes in the aging brain, a brief overview of the types of cognitive changes that are commonly seen in aging humans is first provided. The remainder of the review focuses on animal studies that are progressively overcoming the unique challenges of aging research to reveal the neurobiological mechanisms of aging-related cognitive dysfunction, and suggest new targets for therapies to prevent or ameliorate cognitive decline.

## Cognitive changes in aging

The range of cognitive changes that occur with aging suggests that aging-related neurobiological changes are not limited to restricted neural regions, as occurs with some aging-related neurological diseases, but rather affect many and disparate areas of the brain. Nevertheless, variation among individuals in the types and extent of aging-related cognitive changes demonstrates that deficits in specific functions, mediated by different neural regions, can develop to some extent independently. The nature and range of aging-related cognitive deficits in humans has been well-described in a recent review and is discussed here only briefly.<sup>1</sup>

Basic cognitive functions, such as attention and memory, can be significantly affected by aging but, in both cases, some aspects are typically maintained while others decline. Although there is variation across studies, selective attention and the ability to sustain attention appear to be well maintained across aging.<sup>2,3</sup> Reports of aging-related deficits in visual-attention tasks and other measures of attention (such as the Stroop task) may be due to a general decline in the rate of information processing rather than specific deficits in selective attention.<sup>4</sup> Although selective attention is maintained, many older individuals have deficits in tasks that require attention-switching or attending to and processing information from multiple sources of information.<sup>5,6</sup> Such deficits

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appear to be reversible to some extent by training and even by exercise,<sup>7</sup> although it is not clear whether such improvements involve reversal of neurobiological changes that led to the deficit or development of alternative strategies.

Deficits in memory are probably the aging-related change most commonly recognized by aging individuals and most widely investigated by experimental gerontologists.<sup>8</sup> With respect to long-term memory,<sup>1</sup> aging significantly affects memory for specific events (episodic memory) whereas some other aspects of long-term memory, such as procedural memory, are well maintained. Clearly, many older individuals exhibit deficits in reorganizing and integrating information held in working memory.<sup>9–11</sup> Such dysfunction may not necessarily reflect a problem with working memory per se, but rather may be one manifestation of aging-related problems in executive control. This range of neural processes is involved in allocating attention, inhibiting irrelevant information, directing problem-solving, and essentially planning and coordinating neural activities related to cognitive functions.<sup>2,12,13</sup> These executive activities depend critically upon the proper function of the prefrontal cortex and its reciprocal connections with other cortical regions.<sup>14</sup> The prominence of aging-related changes in executive function, coupled with prominent changes in frontal cortex that are evident in imaging and postmortem analyses of the human brain, are consistent with hypotheses that executive control deficits arising from changes in the frontal lobe explain much of cognitive aging.<sup>15</sup> It is clear, however, that changes in other neural regions, such as the hippocampus, contribute as well (see below).

### **Investigating the mechanisms of aging-related cognitive decline**

The careful elucidation of aging-related cognitive deficits in humans is critical for understanding the problems faced by older adults, but human studies provide only limited ability to investigate underlying neurobiological mechanisms. Until recently, investigations of neuroanatomical and neurochemical changes associated with human cognitive decline were limited to postmortem analyses. The final state of the brain could be assessed in detail but changes occurring as cognitive deficits developed could not. With

advances in brain imaging it now is possible to assess structural changes in individual brains as they age,<sup>16–18</sup> and also to investigate aging-related changes in cerebral blood flow.<sup>19,20</sup> Moreover, developments in magnetic resonance (MR) spectroscopy and positron emission tomography now permit analysis of metabolic changes and alterations in neurotransmitters and their receptors *in vivo*.<sup>21–26</sup>

Despite such advances, experimental studies of the mechanisms of brain aging depend extensively on the use of animal models, particularly non-human primates and rodents. In the US, the importance of primate and rodent models has been recognized with extensive and critical financial support from the National Institute on Aging.<sup>27</sup> Clearly, one important consideration in the use of animal models is the extent to which they undergo aging-related cognitive changes that are similar to those that occur in humans. Rhesus monkeys have an extensive behavioral repertoire and can be trained in many tasks that assess memory and executive function in a manner analogous to human studies. Rhesus monkeys show very similar deficits in memory and executive function<sup>28,29</sup> and, as in humans, the extent of cognitive dysfunction varies among individuals.<sup>30,31</sup> Although it is more difficult to relate cognitive changes in humans to cognitive changes in rodents, learning and memory can be readily assessed using a variety of maze and other tasks.<sup>32–35</sup> Similarly, methods now have been developed for testing executive function in mice and rats and demonstrate clear aging-related decline in such frontal cortex-dependent tasks.<sup>36–38</sup> The demonstration that aging-related cognitive dysfunction is similar in humans and rodents has made it possible to claim the many experimental advantages provided by the latter, including the use of powerful molecular genetic techniques in mice.<sup>39–41</sup> Thus, it is to studies in monkeys and rodents that we owe much of the current understanding of the mechanisms of normal brain aging.

### **Structural changes in the aging brain**

Even a cursory comparison of histological sections or brain images from a young adult versus an aged individual makes it clear that the structure of the human brain changes with age, even in the absence of neurodegenerative disease. Typically, the aged

brain exhibits regionally-specific reduction in the volume of both grey and white matter.<sup>42,43</sup> Consistent with the view that functions mediated by the frontal lobes are particularly affected, the frontal cortex often appears most dramatically changed in imaging studies and those changes are most strongly correlated with cognitive deficits in individuals.<sup>44,45</sup> Although neurons clearly are lost in some regions in some species, it does not appear that normal brain aging involves extensive loss of neurons (as was once thought), not even in the frontal cortex and hippocampus, where the executive and memory functions most affected by aging are regulated. Contemporary stereological studies have established that, in contrast to Alzheimer's disease, there is not extensive and widespread loss of neurons in the normally aging brain, even in individuals with demonstrated cognitive impairment.<sup>46-51</sup>

Aging-related changes appear to involve significant changes in the neuropil and white matter, with alterations in both axons and dendrites. White matter and axonal changes include reductions in the total length of myelinated fibers and apparent loss among fibers of the smallest diameter,<sup>52-54</sup> as well as changes in myelin structure that may compromise neuronal transmission.<sup>54,55</sup> Several laboratories have reported that neurons in the aging brain undergo a reduction in dendritic length and complexity, as well as a decrease in the density of dendritic spines.<sup>49,56-60</sup> Changes in dendritic extent are not ubiquitous, however, but rather vary among and within neural regions<sup>13,61,62</sup> (Figure 1). Loss of dendritic spines may be more widespread.

Significantly, even within the dendritic arbors of individual neurons some components undergo aging-related regression while other components are maintained,<sup>63</sup> indicating that changes in dendrites are regulated very focally and may affect specific populations of inputs onto individual neurons.

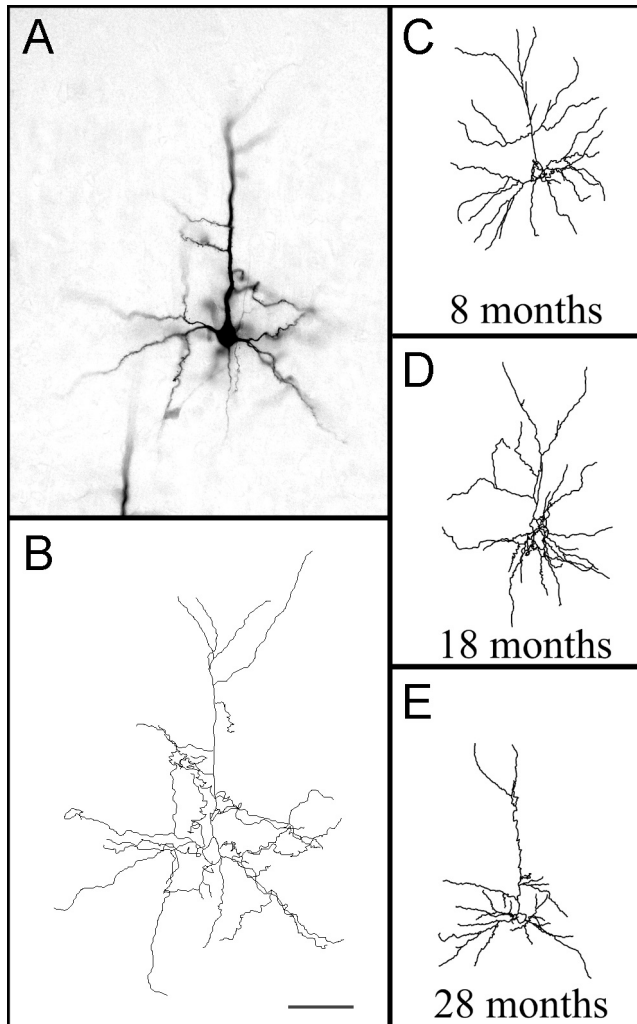
Since dendritic spines are the primary targets for excitatory synapses,<sup>64</sup> one would expect loss of dendrites and spines to be associated with a decrease in synaptic number. As for neuronal loss, however, stereological investigations have not supported early reports that there is widespread and dramatic loss of synapses in the aging brain. Stereological analyses of the hippocampus revealed loss of synapses in the dentate gyrus,<sup>65,66</sup> but the loss appears to involve only subsets of synaptic

inputs.<sup>67-69</sup> Synaptic density appears to be largely maintained across aging in other sub-regions of the hippocampus,<sup>32</sup> although synapses in CA1 may undergo a small and selective decline.<sup>70</sup> Analyses of aging-related changes in synaptic number in the cerebral cortex are mixed, even when considering only the frontal cortex, suggesting any changes in synaptic number are restricted in scope and magnitude.<sup>71-73</sup> Even in regions in which synapse number is maintained, aging-related changes in dendritic architecture could produce significant rearrangements in the pattern of synaptic inputs on to individual neurons and thereby alter neuronal function.

### Aging-related changes in synaptic function

Significant aging-related changes in synaptic transmission and plasticity occur in many neural regions in which there is no apparent loss of synapses or change in their structure, indicating that aging alters aspects of synaptic organization and function that do not have apparent structural correlates.<sup>74-77</sup> Many investigations of the synaptic changes that underlie aging-related cognitive deficits have benefited from recognition that individual rodents and non-human primates, like humans, exhibit varying degrees of aging-related cognitive dysfunction. Gallagher and colleagues have demonstrated repeatedly that individual aged rats can be classified as impaired or unimpaired on a number of cognitive tasks, including the hippocampally dependent Morris Water Maze<sup>32,33,78</sup> and measures of frontal cortical function.<sup>79</sup> Importantly, impaired individuals show deficits across multiple cognitive domains mediated by different neural regions.<sup>80</sup> Such evidence that individuals showing less successful aging are impaired on multiple tasks provides confidence that, although many structural changes are restricted to specific sub-regions of the aging brain, some mechanisms contributing to functional changes are represented more globally. Experimentally, the ability to compare cognitively impaired old rats to unimpaired rats of the same age helps investigators differentiate neurobiological changes that contribute to cognitive deficits from aging-related changes that are unrelated to function.

Regardless of whether demonstrated specifically in individuals with demonstrably impaired



**Figure 1. Neuronal labelling and analysis of dendritic extent.** A dye-injected, superficial pyramidal neuron is shown (A) with its reconstructed dendritic arbor (B). Scale bar = 40  $\mu\text{m}$ . C, D and E illustrate the dendritic arbors of representative pyramidal neurons from the cingulate cortex of rats at 8, 18 and 28 months of age and demonstrate the decrease in dendritic extent between middle- and old age. Quantitative analysis revealed a 20–25% decrease in dendritic extent for superficial pyramidal neurons, whereas neurons in deeper layers were unchanged.<sup>63</sup>

cognitive function or simply by comparing animals of different ages, recent studies have provided a wealth of information on how and why synaptic signalling changes with age. Even a cursory overview of the range of synaptic and related intra- and intercellular changes is beyond the scope of this review, but a summary of demonstrated changes in a single neurotransmitter system illustrates the growing sophistication of analyses of synaptic changes.

Glutamate and its receptors mediate the majority of excitatory neurotransmission in the CNS and are critical for neuronal signalling that underlies learning, memory, and other cognitive functions. Glutamate levels have been reported to decline in the aging cerebral cortex and hippocampus, but that change may be more related to metabolic activity than to synaptic transmission.<sup>81</sup> The most significant aging-related changes in glutamate signalling appear to arise

from many and varied changes in glutamate receptors. Glutamate signals through multiple receptors of two general classes, ionotropic receptors that form membrane-spanning ion channels and signal through ion fluxes, and metabotropic receptors that signal through intracellular second messenger systems. Each receptor type in each class comprises multiple sub-units.<sup>82,83</sup> Changes in glutamate signaling through the ionotropic N-methyl D-aspartate (NMDA) type receptor appear to underlie many changes in neural function and for detailed descriptions of aging-related changes in glutamate and NMDA signalling readers are directed to recent focused reviews.<sup>59,81,82,84–88</sup> In brief, NMDA receptors are expressed at high levels in the cerebral cortex and hippocampus and play critical roles in learning and memory and in many plasticity processes. Selective blockade of NMDA receptors impairs performance on memory tasks that are affected by aging. Several studies have demonstrated a correlation between lower densities of NMDA receptor-binding and poor memory performance. The density of NMDA receptors is reduced in some areas of the aging brain, but such changes are region-specific. In addition to the many changes in NMDA receptor function, metabotropic glutamate receptors also undergo aging-related changes in expression and ligand-binding that contribute to changes in their function.<sup>89–91</sup>

For both classes of glutamate receptors, changes in the expression and balance of specific receptor subunits and alterations in the insertion of receptors in the post-synaptic membrane alter function even in the absence of changes in overall numbers of receptors. In addition, intracellular pathways that are coupled to the receptors undergo significant aging-related changes that blunt or alter the fidelity of signalling.<sup>87,92,93</sup> Thus, even if one considers only the receptors for a single neurotransmitter, one finds abundant substrates for physiological and pathophysiological regulation that influences neural processing and cognition during aging.

### **Fundamental mechanisms of brain aging – oxidative stress and inflammation**

The breadth of aging-related neurobiological changes – including alterations in many different neuron types and changes in some structural

properties and many inter- and intracellular signalling pathways – raises the question of whether a small number of cellular and molecular regulators could underlie the variety of structural and functional changes that result in cognitive deficits. Accumulating evidence indicates that two important and related changes in the microenvironment within the brain contribute to many of the cellular and intercellular changes that occur with aging: progressive increases in oxidative stress and neuroinflammation.

Oxidative damage increases with age,<sup>94–97</sup> due to increased generation of reactive oxygen species (ROS), decreased anti-oxidant activity, and/or deficient mechanisms to prevent or repair cell and tissue damage. It is not clear whether anti-oxidant mechanisms and repair mechanisms are significantly impaired with age in all tissues,<sup>98</sup> but the levels of key antioxidant enzymes clearly decline in some regions of the brain,<sup>99–101</sup> possibly contributing to increased oxidative damage.<sup>96,102–104</sup> There is evidence for a close association between oxidative stress and aging-related functional decline in some tissues,<sup>95</sup> with oxidative stress inducing greater DNA and protein damage in older animals.<sup>105,106</sup> The increase in damaged proteins appears to be regionally specific, with the hippocampus exhibiting a twofold greater increase in oxidative damage than cortical structures.<sup>95</sup> Importantly, increased oxidative stress has been associated directly with impairments in motor and cognitive performance.<sup>95,107</sup> In addition, interventions that reduce oxidative damage (e.g. moderate caloric restriction, high antioxidant diets, or spin trapping agents) prevent or reverse some behavioral deficits observed in aged animals.<sup>96,108–110</sup>

It is reasonable to expect that increased oxidative stress would affect cellular structure and a wide variety of cellular and intercellular processes, since essentially all macromolecules in the brain – proteins, lipids and nucleic acids – are subject to oxidative damage. Moreover, recent studies have begun to reveal additional and dynamic effects of the imbalance between ROS and antioxidant defenses in the aged brain. Oxidative conditions affect a variety of redox-sensitive signalling processes, including the insulin-receptor signalling pathways. These pathways influence neurodegenerative processes and normal brain aging,<sup>111,112</sup> and may even influence lifespan.<sup>113</sup> Thus, oxidative stress in the aging brain appears to

affect multiple and complex regulatory networks within the brain.

Much of the aging-related increase in oxidative stress is likely to be an unavoidable result of metabolic processes, but ROS also are produced as part of neuroinflammatory processes that increase with age. Accumulating evidence suggests a loss of balance between pro- and anti-inflammatory signals that contributes to loss of neural function. Elevations in pro-inflammatory markers commonly are found in the CNS of healthy older people and laboratory animals.<sup>114–118</sup> Indeed, gene array studies screening for neural genes with altered expression in the aging brain found that a large percentage of the genes that showed an age-related alteration in expression were involved in the inflammatory response or in regulating oxidative stress.<sup>119,120</sup> More targeted studies demonstrated an age-dependent increase in transcription of the pro-inflammatory genes *TNF- $\alpha$* , *IL-1 $\beta$* , and *MCP-1* in the hippocampus of old versus young adult mice.<sup>121</sup> Importantly, altered regulation of inflammatory gene expression in older rodents was associated with age-related cognitive impairment; in cognitively impaired old rats expression was altered but in unimpaired old rats expression was similar to that in young adults.<sup>107</sup> The gene-expression studies are supported by evidence that basal levels of pro-inflammatory proteins are increased in the brains of old rodents compared to young.<sup>122–124</sup>

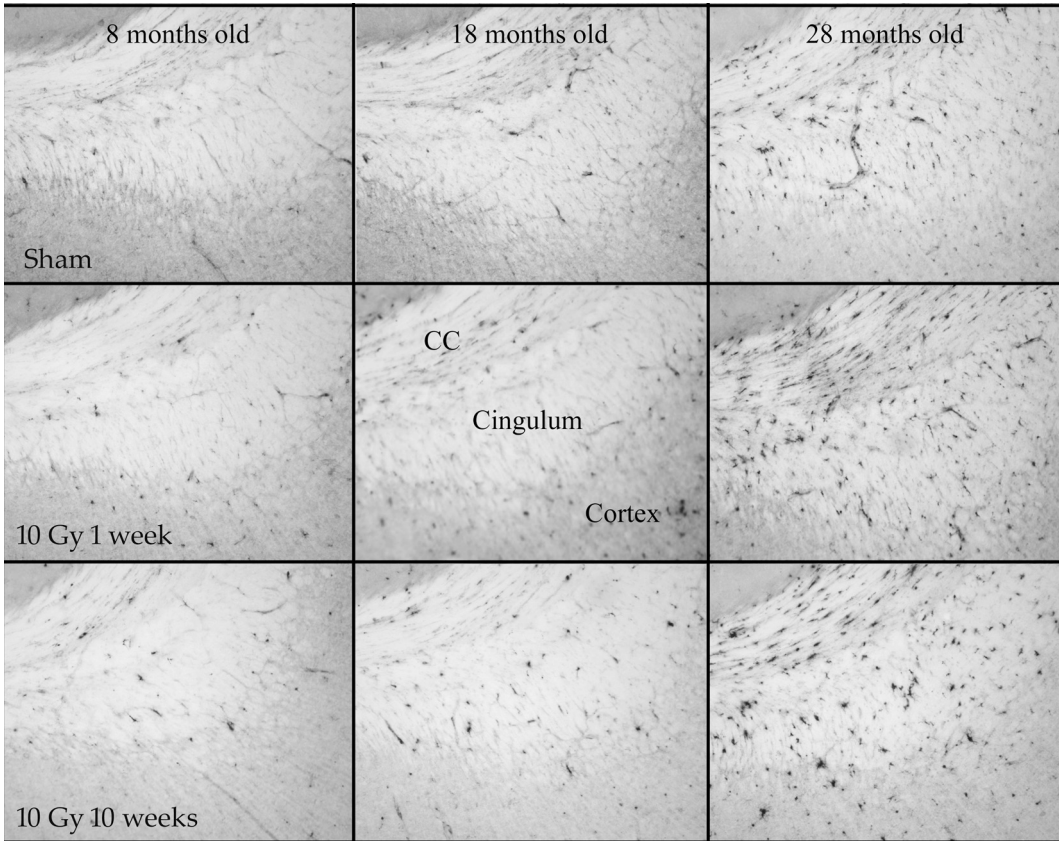
In addition to these molecular and biochemical studies, cellular effects of aging on inflammatory processes in the brain are demonstrated by changes in microglia, the cells that initiate and direct the inflammatory response in the CNS. In the absence of pro-inflammatory stimuli, microglia are characterized morphologically by the presence of long, thin, and ramified cellular processes and often are referred to as ‘resting’. Resting is a poor descriptor, however, since these microglia actively monitor their microenvironment<sup>125–127</sup> via a wide variety of cell-surface receptors.<sup>128–131</sup> Microglia respond to chemical, physical, infectious, and other factors that signal or may cause damage with morphological changes, including partial retraction and thickening of the cellular processes and rounding of the cell body, and functional changes, including migration, proliferation, and the production and secretion of pro-inflammatory proteins.<sup>132</sup> In the adult brain, the pro-inflammatory cytokines produced by activated microglia influence neurogenesis,<sup>133–135</sup> long-term

potentiation (LTP),<sup>136</sup> and cognition.<sup>137,138</sup> The importance of such changes for aging-related cognitive decline is supported by demonstrations that age-related impairments in LTP and cognition correlate with increased levels of *IL-1 $\beta$* , increased numbers of activated microglia, and decreased levels of the anti-inflammatory cytokines *IL4* and *IL10*.<sup>136,139–141</sup>

Immunohistochemical studies have demonstrated an increase in the number of activated microglia in the CNS of healthy, older rodents,<sup>142–145</sup> non-human primates,<sup>146</sup> and humans.<sup>147,148</sup> Aging apparently alters the functional state of microglia but not their number,<sup>145,149</sup> since significant functional changes occur in individual cells with little change in the size of the population. The increase in microglial activation with age is dramatic and easily demonstrated with immunomarkers that target the phagocytic nature of activated microglia or changes in cell surface receptors (Figure 2). It remains a major challenge, however, to characterize specifically the functional changes in microglia in specific regions of the aging brain. This is a critical issue in light of accumulating evidence that, depending on their functional state and the factors acting upon them, microglia may have trophic actions that support neuronal survival and function,<sup>127,150–154</sup> as well as deleterious effects on neurons and other cells. Transgenic mice with fluorescently tagged microglia offer significant promise for detailed analyses of cellular and molecular changes in activated microglia,<sup>155</sup> permitting comparisons among neural regions with greater and lesser degrees of aging-related functional changes.

### Ameliorating aging-related cognitive decline

Evidence that oxidative stress and inflammatory processes underlie many aging-related functional changes in the brain makes these processes attractive targets for therapies to prevent or reverse aging-related cognitive decline. In animal models, diets that are rich in anti-oxidants have proven effective in ameliorating some cognitive deficits in older animals (see recent reviews<sup>110,152,156–159</sup>). Anti-inflammatory treatments can decrease the number of activated microglia in the brain and also partially restore the age-dependent impairment in LTP<sup>136</sup> and spatial memory performance.<sup>137</sup> Similarly, inhibition of the enzyme responsible



**Figure 2. Aging-related increase in activated microglia and in the inflammatory response to brain irradiation.** Activated microglia can be identified using the ED1 monoclonal antibody, which recognizes a lysosomal protein (CD68) that is upregulated when microglia become activated. ED1<sup>+</sup> microglia are rare in the brain of a young control rat but increase in abundance with age (top row). A single 10 Gy dose of whole-brain irradiation produces only a modest activation of microglia in the young brain (left column) but a much greater and sustained activation in middle-aged and old rats (middle and right columns). ED1 labelling is shown in the corpus callosum (CC), cingulum and deep cerebral cortex, but similar changes are seen throughout the brain.<sup>145</sup>

for activating IL-1 $\beta$  improves age-related memory dysfunction.<sup>135</sup>

Although such animal studies indicate that antioxidant and anti-inflammatory therapies might limit aging-related cognitive deficits, evidence that oxidative damage and pro-inflammatory conditions in the human brain accumulate over many years raise the critical question of whether it would be necessary to begin therapies early in life to derive benefits. Animal studies demonstrate that supplementation with dietary antioxidants for as little as 2–4 months can reduce normal aging-related cognitive deficits in rodents.<sup>160,161</sup> As yet, however, interventional studies of antioxidant supplementation in humans have largely failed to demonstrate benefits for

cognitive function,<sup>162–164</sup> despite observational evidence of an association between nutritional intake of antioxidants and cognitive function in healthy elderly individuals.<sup>165,166</sup> Presently, there may be more translational relevance and clinical potential in studies demonstrating that antioxidant and anti-inflammatory treatments are efficacious in preventing or decreasing the effects of potentially damaging challenges, to which the aged brain is particularly vulnerable.<sup>167,168</sup>

#### Increased vulnerability to damage in the aging brain

Clinical experience and anecdotal and experimental evidence indicate that older individuals

have greater difficulty recovering from events that challenge the homeostatic mechanisms of the brain. Significantly, such challenges typically induce oxidative stress and/or inflammation, and many are common among older individuals. For example, postoperative cognitive dysfunction is more common in older than in younger adult patients, even in the absence of adverse intraoperative events.<sup>169–171</sup> As this problem has become more recognized clinically, experimental studies are beginning to investigate the underlying mechanism<sup>172,173</sup>; oxidative stress and inflammatory effects almost certainly may play an important role. Clinical and experimental studies of stroke, traumatic brain injury, axotomy, and whole-brain irradiation all support the hypothesis that aging impacts the intensity and duration of brain inflammation and microglial activation following challenges<sup>145,147,174,175</sup> (Figure 2). Functionally, old age alters the duration of radiation-induced cognitive deficits in rodents,<sup>176,177</sup> and clinical studies have identified increased age at the time of irradiation to be a risk factor for development and severity of radiation-induced cognitive side-effects.<sup>178–181</sup>

Such differences between young adult and older brains indicate that the neural effects of potentially damaging challenges may be quantitatively greater, and even mechanistically different, in middle-aged and elderly patients, presumably because older brains are in a chronic state of oxidative stress and inflammation (discussed in Schindler *et al*<sup>145</sup>). Microglia often exhibit an increased response to an acute inflammatory event when the event was preceded by a previous inflammatory stimulus; in the CNS such microglial ‘priming’ may even involve interactions between the systemic and parenchymal immune systems.<sup>182–186</sup> Microglia in the aged brain may be primed to produce an exaggerated response to any pro-inflammatory and pro-oxidative stimulus, such that a challenge that produces no significant functional effects in young individuals elicits a feed-forward and progressive oxidative stress and neuroinflammatory response that impairs neuronal function in elderly individuals. Thus, even if treatment with antioxidant and anti-inflammatory factors does not improve basal cognitive function in the aging and aged, it may provide protection from the additional cognitive deficits that often result from the inevitable neural challenges that are associated with growing older.

### Ongoing and future studies

As the survey above demonstrates, there has been tremendous progress in (1) elucidating elements of cellular structure and intercellular signalling that are compromised in the aging brain and (2) developing evidence that increased oxidative stress and neuroinflammation are critical contributors to the neurobiological changes that result in cognitive dysfunction. A primary focus now and in future studies is revealing the mechanistic pathways through which oxidative stress and inflammation alter neurotransmitter receptors, synapses, and neuronal processes.<sup>187</sup> These mechanistic links are beginning to be revealed. For example, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) interleukin 1-beta and interleukin 18 all inhibit LTP, and TNF- $\alpha$  alters expression of metabotropic glutamate receptors and potentiates glutamate excitotoxicity.<sup>188,189</sup> TNF- $\alpha$  also inhibits neurite outgrowth and thereby may limit recovery following neuronal damage.<sup>190</sup> Interferon- $\alpha$  suppresses NMDA signalling<sup>191</sup> and interleukin-6 produces subunit-specific reductions in metabotropic glutamate receptors.<sup>192</sup> Microglia can influence a variety of synaptic properties<sup>193</sup> and, under some conditions, activated microglia can even strip synapses from neurons.<sup>194</sup>

The continued revelation of the influence of oxidative stress and inflammation on the structural and functional mediators of aging-related cognitive decline should produce new targets for developing therapies to ameliorate aging-related cognitive dysfunction and more refined assays to test those therapies and promote their translation to the clinic.

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