Cognitive dysfunction with aging and the role of inflammation

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***Abstract*:** As the average lifespan continues to climb because of advances in medical care, there is a greater need to understand the factors that contribute to quality of life in the elderly. The capacity to live independently is highly significant in this regard, but is compromised by cognitive dysfunction. Aging is associated with decreases in cognitive function, including impairments in episodic memory and executive functioning. The prefrontal cortex appears to be particularly vulnerable to the effects of advancing age. Although the mechanism of age-related cognitive decline is not yet known, age-related inflammatory changes are likely to play a role. New insights from preclinical and clinical research may give rise to novel therapeutics which may have efficacy in slowing or preventing cognitive decline with advancing age.

***Keywords*:** aging, cognitive dysfunction, elderly, inflammation, quality of life

Introduction

The world's population is rapidly aging and age-related disease constitutes a growing proportion of healthcare burden. The segment of the population that is 85 or older is growing faster than any other age group and is projected to account for 4.3% of the US population by 2050 [Merck Institute of Aging & Health *et al.* 2007]. These changes in the population have led to a growing realization that measures must be taken to ensure a high quality of life in addition to increased longevity. Foremost among factors that determine quality of life is the ability to live independently [Bowling, 2005], and cognitive functioning is particularly important in this regard [Desai *et al.* 2010]. The biological basis of age-related cognitive decline is not currently known with certainty, in part because aging in humans is associated with numerous age-related disease conditions that complicate the attribution of causality. For this reason, insights gained from animal models are important because causality can be established with greater certainty. A growing body of preclinical and clinical literature suggests that age-related inflammatory changes may contribute to cognitive changes.

Our goal here is to review evidence that aging is associated with relatively selective deficits in cognition that contribute to disability in the elderly, and that neuroinflammation is an important factor contributing to age-related cognitive decline. We base these conclusions on research findings drawn from the clinical literature as well as research performed using animal models. Although our focus is on cognitive decline associated with normal aging, we discuss evidence that the effects of inflammation on cognition are further exaggerated in pathological disease states such as in neurodegenerative diseases. Finally, we review some possibilities for intervening to reduce age-related neuroinflammation in the hope of slowing or preventing age-related cognitive decline. Because of the importance cognition plays in one's ability to live independently, reducing the impact of inflammation on cognition during aging is likely to significantly impact on the quality of life of older persons.

Normal aging is associated with declines in memory and executive function

In normal human aging, certain facets of cognition seem to be affected more than others. Here we review evidence that aging primarily affects episodic memory and executive functioning while leaving other aspects of cognition relatively intact. We discuss the role of inflammation in these age-related changes in cognition in subsequent sections below.

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Memory is not a unitary construct and distinct components of memory are affected by aging differently [Nilsson, 2003]. Explicit memory includes episodic memory, which involves the conscious recall of events and experiences, and semantic memory, which involves the conscious recall of facts and information [Tulving, 1987]. Episodic memory is affected by aging much more than semantic memory. The Betula study, a 10-year longitudinal project examining memory and health in 1000 people between the ages of 35 and 80 years, showed a striking decrease in episodic memory performance as people age [Nilsson *et al.* 1997], which is consistent with results from other studies [Birren *et al.* 2006]. These changes are likely because of age-related dysfunction of the hippocampus and the cortex, since explicit memory is largely encoded in the hippocampus, though other brain regions, such as various neocortical areas, are also thought to be involved [Grady *et al.* 2003].

Difficulties with free recall and temporal ordering in elderly people have been shown to be associated with deficits in encoding and retrieval of information [Daum *et al.* 1996]. The frontal lobes play an important role in the encoding of information [Fletcher *et al.* 1998; Dolan and Fletcher, 1997]. Functional magnetic resonance imaging studies have correlated poor episodic memory performance in older people with reductions in left frontal lobe activation during the initial encoding of a memory [Stebbins *et al.* 2002]. Therefore, older people may benefit from the use of encoding strategies and cues, which result in increases in left frontal lobe activation and improved memory performance [Logan *et al.* 2002]. The frontal lobe is also involved in the filtration of irrelevant information that would otherwise interfere with the encoding of pertinent information [Lustig *et al.* 2001]. Episodic memory capacity in particular relies on successful inhibition of irrelevant and interfering information [Craik and Salthouse, 2007]. In addition, free recall of information seems to depend on prefrontal function, although cued recall and recognition do not [Mesulam, 2000; Jetter *et al.* 1986]. It is possible that the age-related sensitivity of episodic memory in comparison to semantic memory is due in part to the greater demand on prefrontal functioning during the encoding of transitory events such as autobiographical events (episodic memory) compared with the encoding of public, noncontextual facts (semantic memory).

Semantic memory is not as significantly affected by aging. In the Betula study, there were no observable differences in tests of vocabulary between 35-year-old people and 50-year-old people. In addition, after controlling for level of education, there were no age-related declines in general knowledge among people younger than 75 years [Nilsson *et al.* 1997]. Similarly, the Berlin Aging Study, a 6-year longitudinal project exploring the intellectual abilities of elderly people, showed that while factors such as perceptual speed, episodic memory, and fluency declined with age, other factors such as knowledge (measured by vocabulary) remained relatively stable and intact [Singer *et al.* 2003].

Some studies have, in fact, demonstrated improvements in semantic memory with age, despite losses in episodic memory performance. One study tested individuals of various ages on knowledge of events occurring from the 1930s to the 1990s, and showed that general knowledge about such historical facts (which required semantic memory) was found to be positively correlated with age [Schacter Daniel, 1987]. Another study revealed that older people had a better recall of facts (semantic details), despite having a poorer recall of thoughts and feelings (episodic details), relative to younger people [St Jacques and Levine, 2007]. Thus, semantic memory remains relatively spared by normal aging and performance may, in fact, increase with age.

Implicit memory, much like semantic memory, also remains relatively stable with age [Ackerman and Rolfhus, 1999]. However, unlike the semantic and episodic components of explicit memory, implicit memory involves information that is utilized without conscious awareness. An important type of implicit memory is procedural memory which involves unconscious, experience-dependent learning of how to perform specific tasks, such as riding a bike. In animal models it has been shown that, after adjusting for differences in baseline and gross motor abilities, there are no significant implicit memory changes associated with advancing age [Churchill *et al.* 2003].

Implicit memory is mediated by regions of the brain such as the basal ganglia and cerebellum [Hikosaka *et al.* 2002]. People with damage to the striatum (such as patients with advanced Parkinson's disease) exhibit evidence of impaired

learning of novel movements and difficulties acquiring visuomotor skills [Laforce and Doyon, 2002]. People with bilateral striatal damage also have difficulties acquiring new stimulus–response motor associations [Laforce and Doyon, 2001]. These regions are, however, relatively spared by normal aging.

Executive function is also affected by aging. Executive function can be defined as the set of capacities involved in planning, mental flexibility, inhibiting inappropriate actions, attending to relevant sensory information, and ignoring irrelevant sensory information [Stuss and Benson, 1986]. Executive dysfunction is an important component of many neurodegenerative diseases such as Alzheimer's disease (AD) [Swanberg *et al.* 2004], Parkinson's disease [Zgaljardic *et al.* 2006], frontotemporal dementia [Kertesz, 2006], and other neuropsychiatric conditions (e.g. schizophrenia [Green, 2006]). Within executive function, attention, or the ability to focus on relevant sensory input and ignore irrelevant sensory input, is of particular interest to this discussion.

Attention, like other components of executive function, is dependent on the prefrontal cortex (PFC), which plays many important roles in cognition and has numerous subregions with specialized functions [Fuster, 1997]. A recent comprehensive review of the literature on attention argues for a fundamental role of working memory, top-down sensitivity control, competitive selection, and automatic bottom-up filtering for salient stimuli, with important roles for PFC and posterior parietal cortex in the former three processes [Knudsen, 2007]. It has been argued that the decline of attention with aging is related to inadequate inhibitory processes rather than deficiencies in activation [Hasher and Zacks, 1988]. As such, memory-impaired adults are more likely to experience difficulty ignoring task-irrelevant inputs and suppressing knowledge that is no longer applicable. In tests of selective attention, patients with prefrontal lesions are less able to ignore irrelevant information than healthy controls [Chao and Knight, 1997]. In addition, it appears that older adults are more vulnerable to distractors than younger adults. This idea is supported by brain-imaging studies that show that older people exhibit more cortical activation compared with younger people when presented with task-irrelevant information, while cortical activity is similar in both age groups when task-relevant information is presented [Gazzaley *et al.* 2005]. In contrast, sustained attention, which is the ability to maintain attention over a period of time, is relatively stable with age [Berardi *et al.* 2001]. When measuring sustained attention using a high-speed digit discrimination task, researchers found no age-related differences in sustained attention capacity among young, middle-aged, and elderly people [Berardi *et al.* 2001].

Given the evidence for decreased PFC function with advancing age, it is not surprising that neuroimaging and neuroanatomical studies have identified structural changes in the PFC with advancing age in a number of mammalian species. For example, aging is correlated with a thinning of layer I of area 46 in monkeys [Peters *et al.* 1998]. A recent study examined the effects of aging on layer III pyramidal neurons in the dorsolateral PFC of rhesus monkeys [Dumitriu *et al.* 2010]. The authors determined that aging was associated with a loss of dendritic spines, especially small and thin spines, and a reduction in axospinous synapses. Synapse density and spine morphology were found to correlate with acquisition and performance on the delayed nonmatching-to-sample test. Similarly, another study [Erraji-Benchekroun *et al.* 2005] demonstrated a disorganization of 'microcolumns' in area 46 of the PFC of monkeys which was highly correlated with declines in spatial working memory and recognition memory. In addition to these changes in gray matter, aging is also associated with alterations in frontal white matter. For example, diffusion tensor imaging has demonstrated a selective disruption of frontal cortical circuitry with aging in humans [Pfefferbaum *et al.* 2005].

It is possible that the declines in episodic memory and attention are not due solely to age-related area-specific deficiencies within the brain, but that global reductions in brain efficiency also contribute. This view suggests that aging people experience cognitive decline because of 'global brain aging' in addition to area-specific degradation [Rabbitt and Lowe, 2000]. This concept of 'global brain aging' informs the processing speed theory of cognitive aging, which suggests that there is an age-related decrease in the speed and efficiency of processing throughout the brain. More specifically, cognitive performance is reduced because the required cognitive operations cannot be executed in the necessary amount

of time and because of a reduced ability to process multiple concepts simultaneously [Salthouse, 1996]. Thus, aging may lead to a global reduction in processing efficiency, which may also contribute to the observed age-related declines in both episodic memory and attention that are described above.

Overall, normal aging is associated with relatively selective declines in episodic memory and in executive function, while both semantic and implicit memories are relatively spared. Because episodic memory requires frontal lobe activity for encoding and retrieval, frontal lobe dysfunction appears to play a particularly important role in cognitive decline with normal aging. It is important to note that age-related cognitive decline has important implications for elderly people because cognition is strongly predictive of disability [McGuire *et al.* 2006; Dodge *et al.* 2005] and decline in executive functioning seems especially important in this regard [Johnson *et al.* 2007; Royall *et al.* 2005; Cahn-Weiner *et al.* 2002].

Age-related cognitive decline is due in part to age-related increases in inflammation

The notion that neuroinflammation leads to a decline in cognitive function is supported by the association between markers of inflammation and several pathological conditions, such as AD, Parkinson's disease, and mild cognitive impairment (MCI). Postmortem examinations of people with late-stage AD, for example, have revealed that beta-amyloid plaques, one of the defining characteristics of AD, are frequently colocalized with a variety of inflammatory factors, including proinflammatory cytokines, acute phase proteins, complement factors, and activated microglia [Eikelenboom *et al.* 2006; Eikelenboom and van Gool, 2004]. Neuroinflammation within the diseased brain does not appear to be widespread, however, because it is restricted to regions of the brain that are particularly affected by AD [McGeer and McGeer, 2002]. Additionally, as discussed in more detail below, there is some evidence that the risk of AD is reduced in people who have a history of nonsteroidal anti-inflammatory drug (NSAID) use [Wyss-Coray, 2006; Tuppo and Arias, 2005; Lukiw and Bazan, 2000]. Likewise, polymorphisms in several inflammatory factors appear to serve as risk factors for the development of AD [Eikelenboom *et al.* 2002; Lukiw and Bazan, 2000].

While it is not yet known whether neuroinflammatory events precede disease states or are a direct consequence of the damage that occurs with ensuing pathology, beta-amyloid plaques appear to act in a proinflammatory fashion [Halliday *et al.* 2000; Tuppo and Arias, 2005]. It is not surprising then, that several groups agree that it is likely that neuroinflammatory events initiate or even aid in the progression of AD [Heneka and O'Banion, 2007; Bales *et al.* 2000]. Indeed, as discussed in more detail below, inflammatory factors have been identified as a potential target in the treatment of AD [Heneka and O'Banion, 2007; McGeer and McGeer, 2003, 2002; Moore and O'Banion, 2002; Rogers *et al.* 1996]. Nevertheless, it is difficult to establish whether the cognitive decline observed in cases of pathology (e.g. patients with AD) is caused by inflammatory events or other aspects of the progressing disease. To address this issue, nonpathological neuroinflammation must also be explored.

To date, a link between nonpathological neuroinflammation and cognitive impairment has been established in a variety of species, including pigeons [Holden *et al.* 2008], rodents [Barrientos *et al.* 2009, 2006; Wan *et al.* 2007; Gemma *et al.* 2005; Heyser *et al.* 1997], and humans [Hilsabeck *et al.* 2010; van den Kommer *et al.* 2010; Magaki *et al.* 2007; Dik *et al.* 2005]. Inflammation, especially within the central nervous system (CNS), leads to impairments in a variety of cognitive domains, including learning [Hein *et al.* 2010; Terrando *et al.* 2010; Barrientos *et al.* 2009, 2006], memory [Frank *et al.* 2010; Hirshler *et al.* 2010; Abraham and Johnson, 2009; Wang *et al.* 2009] and attention [Holden *et al.* 2008]. For example, mutant mice overexpressing the proinflammatory cytokine interleukin (IL)-1 [Moore *et al.* 2009], and rats given chronic ventricular administration of lipopolysaccharide (LPS) [Rosi *et al.* 2006], a potent activator of innate immunity, are significantly impaired in spatial working memory tasks. Microarray analyses of cortical tissue obtained from mice given a single intracerebroventricular injection of LPS revealed that, in addition to enrichment for inflammation-related genes, neuroinflammation leads to a significant reduction in genes known to be involved in learning and memory [Bonow *et al.* 2009]. That being said, neuroinflammation may lead to cognitive and behavioral changes via multiple mechanisms including regulation of gene expression

[Bonow *et al.* 2009; Godbout *et al.* 2005], alterations in neuronal function [Motoki *et al.* 2009; van Gassen *et al.* 2005], reduced neurogenesis [Bachstetter *et al.* 2009; Koo and Duman, 2008; Aalami *et al.* 2003; Monje *et al.* 2003; Vallieres *et al.* 2002] and impaired long-term potentiation [Min *et al.* 2009; Lewitus *et al.* 2007; Griffin *et al.* 2006; Lynch *et al.* 2004; Hauss-Wegrzyniak *et al.* 2002; Kelly *et al.* 2001, 2003; Murray and Lynch, 1998].

Peripheral inflammation is also capable of producing cognitive dysfunction [Buchanan *et al.* 2008; Tonelli and Postolache, 2005; Reichenberg *et al.* 2001] and markers of inflammation, such as peripheral cytokines, have been associated with lower cognitive performance [Hilsabeck *et al.* 2010; Rothenburg *et al.* 2010; Gimeno *et al.* 2008; Rafnsson *et al.* 2007]. Like central administration, systemic LPS has been found to produce deficits in working memory in rodents [Murray *et al.* 2010; Zhang *et al.* 2009]. In humans, a connection between peripheral inflammation and cognitive dysfunction has been demonstrated repeatedly in people experiencing acute infection [Elison *et al.* 2008; Wratten, 2008; Logan *et al.* 2002; Reichenberg *et al.* 2001] and recent surgical procedures [Xie *et al.* 2009; Beloosesky *et al.* 2007; Gao *et al.* 2005]. In addition, immune-related impairments in cognitive performance have served as a major hypothesis for the development of a variety of neurodegenerative diseases and dementias [e.g. Cerejeira *et al.* 2010; McNaull *et al.* 2010; Morales *et al.* 2010; Murray *et al.* 2010; de Rooij *et al.* 2007; Vaccarino *et al.* 2007].

The effects of peripheral immune activation, however, still occur in direct association with increases in inflammation within the CNS [Buchanan *et al.* 2008]. While it is plausible that inflammatory agents or molecules penetrate the CNS to produce direct effects on behavior and cognition, the brain was initially believed to be immunologically privileged, protected from such occurrences by the blood–brain barrier. However, during situations involving the breakdown of the blood–brain barrier [Cunningham *et al.* 2009; Serres *et al.* 2009; McColl *et al.* 2008], sepsis [Semmler *et al.* 2008; Wratten, 2008; Reichenberg *et al.* 2001], or chronic repeated stress [Munhoz *et al.* 2008, 2006], peripheral inflammation leads to increases in proinflammatory cytokine expression within the brain parenchyma and, potentially, cognitive decline [Popescu *et al.* 2009]. Regardless, whether by direct signaling of inflammatory molecules within the CNS, or by alternative means, peripheral inflammation has been shown to be a potent regulator of neurocognition [Cerejeira *et al.* 2010; Richwine *et al.* 2009; Myers *et al.* 2008; Meyers *et al.* 2005].

As discussed in the previous section, normal aging is associated with relatively selective declines in episodic memory and executive functioning, with a relative sparing of semantic and implicit memory. If inflammation is responsible for these cognitive changes one would expect that inflammation would be associated with declines in episodic memory and executive functioning more than semantic and implicit memory. Although information is limited, some studies have provided some insight into this question. Marsland and colleagues [Marsland *et al.* 2006] examined serum IL-6 in a cohort of healthy people aged 30–54 years in relation to cognition. IL-6 levels were inversely related to performance on tests of auditory memory and attention/working memory and executive function but not with word list recall, verbal paired associates, mental control, faces, family pictures, or digit span tests. Schram and colleagues examined the association between serum C-reactive protein (CRP), IL-6, and alpha1-antichymotrypsin and cognition based on data from two large studies [Schram *et al.* 2007]. The authors found that CRP and IL-6 were associated with worse global cognition [Mini Mental Status Exam scores (MMSE)] and executive function in one study, and that IL-6 levels were associated with steeper declines in performance on a picture memory test in the other study. Hoth and colleagues studied the association between peripheral inflammation and cognition in patients with cardiac disease [Hoth *et al.* 2008]. CRP levels were found to be associated with declines in attention-executive-psychomotor performance but not language, episodic memory, or visuospatial performance. Associations between genetic variation in IL-1 beta-converting enzyme (ICE) and IL-1beta levels and cognition were recently demonstrated [Trompet *et al.* 2008]. ICE variants that predicted lower serum IL-1beta levels were associated with better executive functioning, but associations with episodic memory were not significant. Serum levels of CRP have been found to be associated with reduced fractional anisotropy in the frontal lobes, corona radiata, and the corpus callosum by diffusion tensor magnetic

resonance imaging, as well as with decreased executive functioning [Wersching *et al.* 2010]. Not all studies have found an association between inflammation and executive function. For example, Noble and colleagues studied associations between CRP levels and cross-sectional cognitive performance [Noble *et al.* 2010]. People with the highest CRP levels had higher rates of episodic memory impairment and visuospatial impairment but not executive or language impairment.

Although the results of such studies are not entirely consistent, possibly because of differences in assessment methods and differences in the subject populations studied, there is strong evidence for a role of inflammation in decreased executive functioning as well as episodic memory. Selective effects of inflammation on particular cognitive domains could be due to at least two mechanisms which are not mutually exclusive. First, it is possible that neuroinflammation may not uniformly affect the brain. This view is supported by evidence that inflammatory cytokines are not expressed uniformly in the mammalian brain. For example, Lemke and colleagues examined IL-6 expression in the rat brain using antibody-based as well as *in situ* hybridization methods and found that IL-6 mRNA and protein are enriched in the hippocampus and cortex, with much stronger expression in neurons than astrocytes or microglia [Lemke *et al.* 1998]. The IL-6 receptor in the mouse is most highly expressed in the olfactory bulb, retrohippocampal region, and hippocampus, with lower expression in the cortex, striatum, and other regions. IL-1beta is expressed at low levels in the mouse brain with highest levels in the thalamus, hypothalamus, striatum, and brainstem with somewhat lower levels in the cortex, and even lower levels in the hippocampus. Tumor necrosis factor (TNF)-alpha is expressed most strongly in the olfactory bulbs, ventral striatum, and pallidum, with more intermediate expression in the hippocampus and cortex (http://mouse.brain-map.org). Therefore, it is possible that the distribution of inflammatory cytokine expression is partially responsible for the differential effects of inflammation on certain cognitive domains, but other factors must also play a role. For example, it is also possible that certain brain regions are more vulnerable to the effects of inflammation than other brain regions, and this possibility will require further research to assess.

It is interesting to note that one recent study [Grigoleit *et al.* 2010] tested the effects of LPS administration on healthy humans. The authors tested 12 healthy men before and after the intravenous administration of 0.4 ng/kg LPS. Although the injections caused transient (<4 h) fever, elevated neutrophils, and elevated IL-6, IL-10, and TNF-alpha levels, no changes in episodic memory performance or performance on the Stroop Color Word task were noted. Therefore, it is likely that chronically elevated cytokine levels are required to affect cognition.

Age-related increases in inflammation linking deficits in cognition and physical function

Whereas inflammation has been linked to cognitive dysfunction in older people, it also has been found to be associated with physical function in this population. Because of the link between cytokines and several disabling conditions, including cerebrovascular disease [Vila *et al.* 2000; Kostulas *et al.* 1998] and coronary heart disease [Tracy *et al.* 1997; Biasucci *et al.* 1996], it has been hypothesized that inflammation is a pathophysiological mechanism leading to decline in physical function among older people. Increasing serum levels of IL-6 have been found to be associated, cross sectionally, with disability in basic activities of daily living (ADLs) [Cohen *et al.* 1997]. Similarly, an analysis of four studies of older people with differing comorbidities found that increasing serum levels of both IL-6 and CRP, but not TNF-alpha, were negatively associated with performance-based mobility function, such as longer time to complete a 4 m walk and lower grip strength [Brinkley *et al.* 2009]. These associations were largely independent of factors such as age, race, and body composition, and were generally consistent among various chronic diseases such as chronic obstructive pulmonary disease and congestive heart failure [Brinkley *et al.* 2009]. Increased IL-6 has also been found to be associated with incident self-reported ADL disability [Ferrucci *et al.* 1999] and mobility disability in longitudinal studies of older people [Brinkley *et al.* 2009; Penninx *et al.* 2004; Ferrucci *et al.* 1999], with the study by Penninx and colleagues also indicating that participants with increased serum levels of CRP and TNF-alpha were more likely to report mobility disability at the 4-year follow-up assessment [Brinkley *et al.* 2009; Penninx *et al.* 2004; Ferrucci *et al.* 1999]. Participants having high

levels of all three of these markers showed a particularly high incidence of self-reported mobility disability, with associations persisting even after people with cardiovascular disease were excluded, thereby indicating that the relationship between inflammation and subsequent mobility function is independent of cardiovascular disease [Penninx *et al.* 2004]. Inconsistencies across studies in the assessment of multiple inflammatory markers, evaluation of physical function (e.g. self report *versus* performance based), as well as differing follow-up periods, pose challenges in summarizing the findings of these studies. However, these inconsistencies also indicate opportunities for future research.

In addition to being associated with impairments in cognition and physical function, inflammation also may play a role in contributing to increased depressive symptoms in older people. Because depression is also associated with cognitive impairment and disability, the effects of inflammation on depressive symptoms may mediate some of the effects of inflammation on cognition and disability. Cross-sectional [Bremmer, *et al.* 2008; Penninx *et al.* 2003; Dentino *et al.* 1999] and longitudinal studies [Stewart *et al.* 2009] indicate that increased serum levels of IL-6 are associated with depression in older people. Studies evaluating the relationship between CRP and depression, however, report inconsistent relationships; two report a positive association [Stewart *et al.* 2009; Penninx *et al.* 2003] and two report no association [Bremmer *et al.* 2008; Ladwig *et al.* 2005]. Like the studies evaluating the association between inflammation and physical function, the methodological discrepancies across these studies, such as differences in study design and whether or not the investigators are evaluating depressive symptoms or major depression, hinder researchers' ability to draw conclusions about the association between inflammatory markers and depression, in general.

Importantly, however, because impairments in cognition, physical function, and mood are common in older people, are risk factors for each other [Yogev-Seligmann *et al.* 2008; Johnson *et al.* 2007; Yanagita *et al.* 2006; Wilson *et al.* 2004; Sheridan *et al.* 2003; Lockwood *et al.* 2002; Penninx *et al.* 2000], and have repeatedly been shown to have profound deleterious effects on everyday functioning [Inzitari *et al.* 2006; Studenski *et al.* 2006; Raji *et al.* 2004; Stuck *et al.* 1999], it has been postulated that inflammation may be the underlying mechanism largely responsible for the widely reported associations between deficits in cognition, physical function, and mood in older people.

It is however impossible to definitively establish causality from the epidemiologic studies. As noted above, inflammation is associated with many disease states which may affect physical functioning independently of inflammation. True experimental designs are for the most part impractical and unethical in humans, with the study of Grigoleit and colleagues reviewed above, as one notable exception [Grigoleit *et al.* 2010]. Therefore, animal models are essential for determining whether inflammation can in fact cause cognitive impairment and disability. As reviewed in the previous section, it is clear from preclinical research that inflammatory insults are sufficient to cause cognitive and behavioral impairment. Although the precise contribution of inflammation to age-related disability remains unclear, when the existing body of clinical and preclinical data is considered together it is evident that inflammation is likely to be an important contributor to disability in the elderly.

Aging and inflammation: mechanism

Normal aging is thought to include some aspects of inflammation. The aging brain, for example, is said to be in a state of transition from relative immunocompetence and surveillance, to one of primed immune activation [Dilger and Johnson, 2008; Sparkman and Johnson, 2008]. Microarray analysis has found that inflammatory genes account for the vast majority of those that are upregulated in the aging brain [Godbout *et al.* 2005; Prolla, 2002]. Additionally, changes are observed in the activation of a variety of immune-related cells. Microglia, for example, the major immune cells of the CNS, switch from a state of relative quiescence to one of activation in which they exhibit an increase in their expression of many inflammatory markers [Deng *et al.* 2010; Njie *et al.* 2010; von Bernhardi *et al.* 2010; Miller and Streit, 2007; Conde and Streit, 2006]. Microglia, particularly when activated, are the primary source of proinflammatory cytokines within the brain [e.g. ILs, interferons (IFNs), and chemokines]. While increases in proinflammatory cytokines are often observed during times of infection, these same factors are found to be upregulated as a function of

increasing age, in the absence of any overt signs or symptoms of illness [Campuzano *et al.* 2009; Dilger and Johnson, 2008; Sparkman and Johnson, 2008]. IL-1, IL-6 and IFN-alpha for example, have all been found to be greater in the brains of old-aged mice and rats compared with adults [Campuzano *et al.* 2009; Sparkman and Johnson, 2008]. Additionally, primed and activated microglia residing in the aging brain often show an exaggerated response to infection and stress [Dilger and Johnson, 2008; Henry *et al.* 2008; Rosczyk *et al.* 2008; Godbout *et al.* 2005; Kelly *et al.* 2003].

Peripheral markers of inflammation are also elevated in elderly people. Normally low under nonpathological conditions, serum levels of proinflammatory cytokines, such as the ILs and IFN-gamma, have been found to be elevated in aging humans [Zhu *et al.* 2009; Pietschmann *et al.* 2003] and animals [Campuzano *et al.* 2009; Sparkman and Johnson, 2008]. In addition, evidence of peripheral inflammation serves as a risk factor for the development of age-related neurodegenerative disease [Tan and Seshadri, 2010; Tan *et al.* 2007; McRae *et al.* 1993] and may play a primary role in the etiology or progression of age-associated pathologies [McNaull *et al.* 2010; Morales *et al.* 2010; Tan *et al.* 2010; Holmes *et al.* 2009; Pompl *et al.* 2003]. In general, elderly people are far more sensitive to mild inflammatory insults, such as those associated with surgical procedures [Aalami *et al.* 2003]. Indeed, increasing age is the primary risk factor for the development of postoperative cognitive dysfunction, memory deficits that persist from days to months following even mild surgical procedures [Ramaiah and Lam, 2009; Rasmussen, 2006]. Given the evidence of greater basal inflammation and the morphological changes observed in neuroimmune cells, it is not surprising that aging people are increasingly sensitive to insults or perturbations and often experience cognitive and behavioral consequences to infection and stress that are larger, more robust and more prolonged than in adults.

Considering the already established links between aging and cognitive decline, aging and inflammation, and inflammation and cognitive dysfunction, it is not surprising that increasing age has been shown to exacerbate the effects of neuroinflammation on cognition and, likewise, inflammation may worsen the effects of aging on cognitive decline. As mentioned previously, aging organisms are more sensitive to the consequences of mild insults, inflammation and perturbations [Ramaiah and Lam, 2009; Aalami *et al.* 2003; Kelly *et al.* 2003]. The inflammatory response to chronic mild repeated stress, for example, is exaggerated in old-aged mice compared with adult mice [Buchanan *et al.* 2008]. Elderly people are at an increased risk for the development of postoperative cognitive dysfunction, which is likely mediated through inflammation-related events [Xie *et al.* 2009]. Likewise, LPS administration augments the cognitive deficits observed in diseased animals [Cunningham *et al.* 2009], and may speed the progression of age-related degenerative disorders [Vaccarino *et al.* 2007].

Inflammation as a therapeutic target

As reviewed above, neuroinflammation clearly does occur with advancing age in the brain. Because there is evidence that inflammation may cause cognitive decline, a number of efforts have focused on reducing inflammation in an effort to prevent or treat cognitive decline associated with normal aging as well as neurodegenerative disease. Here we review the major classes of pharmaceuticals that have been studied with respect to neuroinflammation, with a focus on AD and MCI. Because the literature on these drugs is very large, we focus here on the proposed mechanism of action of these agents as well as a selected review of the clinical findings obtained to date.

Because of the long availability of NSAIDs, inhibitors of cyclooxegenase 1 and 2 (COX1 and 2), this class of compounds has been extensively studied. At a cellular level, membrane phospholipids are converted to arachidonic acid by phospholipase A_2. Arachidonic acid is then converted to the prostaglandins (PG) PGG_2 and PGH_2 by cyclooxygenases and PGH_2 is then converted to a variety of prostaglandins and thromboxane A_2. In humans, the cyclooxygenases are coded by the genes PTGS1 (COX1) and PTGS2 (COX2). Both enzymes are expressed in the brain, although there are regional and cell-type specific differences in expression that have been reported. In autopsy specimens, COX1 was found to be highly expressed in microglia and weakly expressed in neurons, whereas COX2 was undetectable in control brains but highly expressed in neurons and

microglia after an acute ischemic event [Hoth *et al.* 2008]. COX3 is a splice variant of COX1 and is expressed particularly in endothelium, such as the major arteries and microvasculature of the rat brain [Noble *et al.* 2010]. The expression of COX1 in the mouse brain is particularly high in the medulla, cortex, pallidum, cerebellum, and hippocampus, whereas COX2 is highest in the hippocampus followed by the cerebellum, olfactory bulbs, retrohippocampal region, and cortex (http://mouse.brain-map.org). PGE_2 is a particularly important product of COX and exerts its effects by interaction with a family of PGE receptors (PTGER1–PTGER4) which are coupled to Gq, Gs, Gi/Go, and Gs class G proteins, respectively [Grigoleit *et al.* 2010]. COX inhibitors reduce PGE_2 levels, and because PGE_2 is capable of increasing IL-1beta levels, the levels of this important inflammatory mediator are reduced by COX inhibitors. NSAIDS have certain effects that are independent of their ability to inhibit COX. For example, NSAIDS can reduce the levels of reactive oxygen species (ROS), inhibit NF-kappaB, and activate peroxisome proliferator activated receptor (PPAR) gamma [Grigoleit *et al.* 2010].

COX inhibitors have been found to have efficacy in relation to normal aging in preclinical models. In the rat, celecoxib administered at 12 months of age was found to reduce age-related increases in IL-1beta, TNF-alpha and PGE_2 in the hippocampus, and to reduce circulating corticosterone levels at 16 and 22 months of age [Trompet *et al.* 2008]. Interestingly, the authors found that when the drug was started at 18 months of age, after the inflammatory changes had already developed, no differences in inflammatory cytokine levels were noted at 22 months, suggesting that the drug must be given prior to the onset of neuroinflammation. Drug treatment also improved Morris water maze performance at 16, but not 22 months of age. Another group [Schram *et al.* 2007] administered the COX2 inhibitors nimesulide and rofecoxib and the nonselective COX inhibitor, naproxen, for 15 days to aged (16-month-old) mice and found that the drugs improved passive avoidance performance in aged but not young (3-month-old) mice. Another group [Marsland *et al.* 2006] studied the effects of 2 months of oral sulindac in aged (18-month-old) rats. The drug was found to reduce age-related alterations in performance on the radial arm maze and contextual fear conditioning relative to young (6-month-old) rats and also reduced age-related increases in hippocampal IL-1beta levels.

NSAIDs have been tested in humans in relation to AD and the results have been controversial [Trepanier and Milgram, 2010; Marsland *et al.* 2006]. On the one hand, positive evidence for the efficacy of NSAIDS has been demonstrated in some studies. For example, the Rotterdam study [Trompet *et al.* 2008] involved a cohort of 6989 people who were free of dementia at baseline. People were screened 2–3 years later and again 6–8 years later. AD risk was analyzed in relation to NSAID use, which was estimated from pharmacy records, and the level of NSAID use was inversely related to the risk of developing AD. Similarly, the Baltimore Longitudinal Study of Aging examined AD risk in relation to the use of aspirin and other NSAIDs over a 15-year period in a cohort of 1686 people [Schram *et al.* 2007]. Longer duration of NSAID use, but not aspirin or acetaminophen use, was associated with a lower risk of developing AD. Not all observational studies have been positive, however. For example, one group examined 2736 dementia-free people for up to 12 years and determined that people using NSAIDs most heavily had the highest incidence of AD [Breitner *et al.* 2009]. Additionally, studies using randomized controlled trials have been largely negative. As recently reviewed [Imbimbo, 2009], celecoxib and naproxen given over 2 years to patients aged 70 and over with AD risk factors failed to prevent the development of AD and, in fact, increased the incidence of AD (although this was not statistically significant) [Lyketsos *et al.* 2007]. Results have also been mixed when NSAIDs were studied for MCI. Trials of rofecoxib [Thal *et al.* 2005], triflusal [Gomez-Isla *et al.* 2008], and celecoxib [Small *et al.* 2008] in patients with MCI were inconsistent. The first study was negative, the second study showed a trend toward improved cognition and significantly reduced risk of developing AD, and the later study showed some benefit with regard to executive functioning and language/semantic memory.

Estrogens are another class of agents that have received considerable attention. At a cellular level, estrogens signal through nuclear receptor superfamily receptors coded by the genes ESR1 (ERalpha) and ESR2 (ERbeta). Both genes are subject to extensive alternative splicing. The two

receptors have similar affinities for the endogenous estrogen 17beta-estadiol. ERalpha and ERbeta have somewhat distinct distributions in mammalian brain [Hughes *et al.* 2009]. In the nonhuman primate brain ERalpha immunostaining is present in several amygdaloid and hypothalamic nuclei, lateral septum, nucleus of the stria terminals, subfornical organ, and periaqueductal gray, with sparse staining in the cholinergic basal forebrain [Blurton-Jones *et al.* 1999]. ERalpha expression has been observed in pyramidal neurons as well as nonpyramidal neurons of the PFC of humans, monkey, and rat [Montague *et al.* 2008]. A recent quantitative electron microscopy study determined that ERalpha is present within excitatory synapses, and presynaptic expression was correlated with performance on a PFC-dependent task [Wang *et al.* 2010]. ERbeta distribution in nonhuman primate brain has been examined by *in situ* hybridization which revealed high expression levels in the preoptic area, paraventricular nucleus, and ventromedial nucleus of the hypothalamus, the substantia nigra, caudal linear raphe nuclei, dorsal raphe, and pontine nuclei of the midbrain, the dentate gyrus, CA1, CA2, CA3, CA4, and the prosubiculum/subiculum areas of the hippocampus. Expression in the suprachiasmatic region, supraoptic nucleus, arcuate nucleus, and amygdala was less intense [Gundlah *et al.* 2000]. Estrogen receptors signal by a 'classical' route that involves dimerization of the receptor and recruitment of SRC and N-CoR, and by a nonclassical route that involves direct interaction with activator protein-1 (AP1), NFkappaB, and specificity protein-1 (SP-1), as well as extracellular signal-regulated kinase (ERK), AKT, and protein kinase A activation [Hughes *et al.* 2009]. Estrogens, particularly ERbeta agonists, have been found to have anti-inflammatory effects and reduce expression of IL-1beta and TNF-alpha. ERalpha agonists reduce IL-1beta expression [Hughes *et al.* 2009].

A protective effect of estrogen use with respect to risk for AD is supported by a number of observational studies. For example, Baldereschi and colleagues studied 2816 women aged 65–84 years and found a higher frequency of estrogen use among nonpatients than among patients with AD [Baldereschi *et al.* 1998]. The results of randomized trials, however, have been less positive. One randomized, placebo-controlled, cross-over study tested 12 weeks of estrogen *versus* placebo in 43 men with MCI and noted a benefit only for the men randomized to placebo followed by estrogen [Sherwin *et al.* 2009]. The Women's Health Initiative Memory Study determined the effects of estrogen plus progestin on the incidence of dementia and MCI in 4532 postmenopausal women without dementia who were aged 65 and older. The authors noted increased risk in the patients receiving estrogen and progestin [Shumaker *et al.* 2003]. Estrogens have also been tested in several randomized controlled trials for AD. In one study, 120 women with AD were randomized to 1 year of estrogen or placebo and no group differences were noted [Mulnard *et al.* 2000]. Similarly, Henderson and colleagues randomized 42 women with AD to estrogen *versus* placebo for 16 weeks and no differences were detected [Henderson *et al.* 2000].

Endocannabinoids are lipids which interact with cannabinoid receptors including CB1 (coded by the gene CNR1) and CB2 (coded by the gene CNR2) which couple to Gi/Go class G proteins. Whereas CB1 receptors are widely expressed in brain, CB2 receptors are expressed on immune cells, including T cells, macrophages, B cells, and microglial cells [Wolf *et al.* 2008]. The anti-inflammatory effects of cannabinoids are mediated mainly by activation of CB2 receptors. Activation of CB2 receptors inhibits the expression of proinflammatory cytokines such as TNF-alpha, IL-1beta, IL-6, and IL-8, and increases the expression of anti-inflammatory cytokines [Wolf *et al.* 2008]. Although this class of drugs has received attention in preclinical studies, we are not aware of any randomized controlled trials in humans in relation to MCI or AD.

Drugs that act as PPAR agonists have found clinical application mainly in the area of diabetes but have been tested experimentally for efficacy in neuroinflammation. The PPARs are nuclear hormone receptors and are coded by the genes PPARA, PPARB, and PPARG in humans. These receptors regulate gene expression by forming heterodimers with retinoid X receptors (coded by RXRA, RXRB, and RXRG) and interact with PPRE sequences on target genes [Shie *et al.* 2009]. All of the PPARs are expressed in neurons and astrocytes, and PPARG is the main isoform expressed in microglia. PPARG agonists are capable of inhibiting activated microglia and astrocytes [Storer *et al.* 2005]. The most potent endogenous ligand is 15d-PGJ2, a derivative of the prostaglandin, PGD_2. Most of the experimental work on this system has relied on thiazolidinediones (TZDs; also known as glitazones) [Shie

et al. 2009]. In addition, a class of compounds known as heterocyclic thiadiazolidinones (TDZDs) is under development and may have much better CNS permeability than the TZDs and are GSK3beta inhibitors in addition to being PPARG agonists [Shie *et al.* 2009]. In addition to these compounds, NSAIDS have some ability to activate PPARG. Some data support the use of PPARgamma agonists in AD. For example, Watson and colleagues randomized 30 people with mild AD or amnestic syndrome to 6 months of rosiglitazone or placebo. People receiving rosiglitazone showed improved delayed recall compared with people receiving placebo [Watson *et al.* 2005].

The activation of microglial cells contributes to increased oxidative stress. A number of studies have examined the ability of drugs with antioxidant properties to interfere with this process. One such drug is resveratrol, a naturally occurring compound found in red wine that is readily available as a dietary supplement. This drug has been found to be neuroprotective in a variety of preclinical studies and has the ability to inhibit microglial activation [Zhang *et al.* 2010]. The mechanism is thought to involve effects on reduction of ROS, decreased mitogen-activated protein kinase signaling, and activation of the Sirt1 pathway, and the drug is capable of reducing inflammatory cytokine release as well [Zhang *et al.* 2010].

N-Acetylcysteine (NAC) has seen widespread use in preclinical and clinical studies. It is believed that the thiol group has antioxidant effects and acts as a free radical scavenger. In addition to its US Food and Drug Administration (FDA) approved use in acetaminophen overdose and renal protection, it has proven effective in a wide range of neuropsychiatric conditions [Dean *et al.* 2010]. Thus far, NAC has not been subjected to any randomized trials for MCI to our knowledge. It has been tested for AD [Adair *et al.* 2001] in a small study involving 43 people with probable AD. Although no differences were noted at 24 weeks on the primary outcome measures, a trend toward improvement on MMSE scores and figure recall and significant improvements on letter fluency were noted. Similarly, omega-3 fatty acids have received some attention. Omega-3 fatty acids such as eicosapentaenoic acid and docosahexaenoic acid are found in oily fish. Omega-3 fatty acids have been studied as potential treatments for AD with no clear positive effects but further research is needed [Cederholm and Palmblad, 2010].

A large number of pharmaceuticals have been developed to specifically combat neuroinflammation associated with conditions such as multiple sclerosis (MS). Although these drugs have for the most part not been tested for normal aging, AD, or MCI, the pharmacology is of potential importance for these conditions.

IFNs include type I IFNs (IFN-alpha, IFN-beta, and IFN-omega) and type II IFNs (IFN-gamma). IFNs play an important role in host response to viral infection and enhance major histocompatibility complex I (MHC I) and MHC II expression and immunoproteasome activity [Codarri *et al.* 2010]. Thus far, only the type I IFNs have found clinical application, with IFNalpha used in hepatitis. IFNbeta-1a (Avonex [Biogen Idec, Weston, MA, USA], Rebif [EMD Serono, Inc., Rockland, MA, USA], and CinnoVex [CinnaGen company, Tehran, Iran]) and IFNbeta-1b (Betaseron [Bayer HealthCare Pharmaceuticals, Leverkusen, North Rhine-Westphalia, Germany], Extavia [Novartis, Basel, Switzerland]) are FDA approved for use in MS.

Glucocorticoids such as dexamethasone and methylprednisolone have proven efficacy in MS. Despite powerful anti-inflammatory effects, these drugs are limited by numerous adverse neuropsychiatric effects. Preclinical studies (e.g. Li and colleagues [Li *et al.* 2010]) show that glucocorticoids worsen outcomes in animal models of AD. Prednisone has been tested in one randomized trial for AD [Aisen *et al.* 2000] which involved a high dose over 4 weeks followed by a lower dose over 1 year. No differences in cognition were noted between the treatment groups, but prednisone worsened behavioral decline.

Glatiramer acetate (Copaxone) [TEVA Neuroscience, Inc, Kansas City, Missouri, USA] has proven efficacy in relapsing–remitting MS. Although the drug is thought to mimic the myelin basic protein component of myelin, it has been found to have numerous other anti-inflammatory effects. There is some support for the use of this agent in AD based on preclinical models. For example, vaccination of doubly transgenic APP/PS1 mice with amyloid beta-peptide (Abeta) and glatiramer acetate reduced plaque formation and cognitive decline [Butovsky *et al.* 2006]. A similar report based on Abeta vaccination given along with glatiramer acetate showed clearing of Abeta fibrils.

Many pharmaceutical companies are developing pharmaceuticals known as biologics, which include recombinant antibodies and proteins that may have more highly targeted actions than small molecules. Natalizumab (Tysabri [Biogen Idec, Weston, MA, USA]) is a humanized monoclonal antibody against the cellular adhesion molecule alpha4-integrin. The drug is believed to work by inhibiting the migration of leukocytes into the CNS. Its use is limited primarily by the infrequent occurrence of progressive multifocal leukoencephalopathy [Clifford *et al.* 2010; Warnke *et al.* 2010] and has not been tested in AD or MCI. Another important biologic is etanercept, a recombinant molecule consisting of a soluble TNF receptor 2 fused to the Fc portion of IgG1. Although the drug is FDA approved for arthritis and ankylosing spondylitis, some preliminary findings, based on open-label administration, suggest possible efficacy in AD [Tobinick and Gross, 2008a, 2008b; Tobinick, 2007].

In addition to pharmaceuticals, certain lifestyle factors are known to have important roles in inflammation and cognition, and may help to inform future drug development. One of the most replicated findings in the aging field is that caloric restriction slows the rate of aging through, at least in part, a reduction of inflammation in both the periphery and CNS. The results of a landmark 20-year study of caloric restriction in Rhesus macaques were recently published [Colman *et al.* 2009] featuring 46 males and 30 females randomized to 30% caloric restriction or control. Of the animals that died of age-related causes, 37% of control animals died compared with only 13% of the caloric restriction animals. Improved maintenance of muscle mass, glucose homeostasis, a 50% decline in cancer, and a 50% drop in cardiovascular disease was noted. Within the CNS, caloric restriction led to decreased atrophy of subcortical regions, mid-cingulate cortex, lateral temporal cortex, and right dorsolateral frontal lobe. A recent meta-analysis of caloric restriction and aging in mice [Swindell, 2009] found evidence for an upregulation of numerous immune-related genes such as complement components and CD antigens with aging and a reversal of these changes by caloric restriction. The mechanism of caloric restriction is an area of intense investigation. One important hypothesis involves the mammalian target of rapamycin (mTOR) pathway, which plays an important role in nutrient sensing [Kapahi *et al.* 2010]. Interestingly, mTOR appears to play an important role in microglial activation in response to cytokines as well as in microglial survival [Dello Russo *et al.* 2009], suggesting that mTOR inhibitors may have therapeutic value. It is likely that research on the mechanism of caloric restriction will continue to suggest novel therapeutic targets for age-related cognitive decline.

Conclusions

Whereas aging is associated with declines in executive functioning as well as episodic memory, semantic memory is only affected much later in life, and implicit memory appears to be relatively spared. Since prefrontal functioning is likely to be more important for episodic memory than semantic memory and directly mediates executive functioning, it is not surprising that these differences in sensitivity to aging are consistent with a particular sensitivity of prefrontal cortex to aging.

Age-related declines in cognition, especially in executive functioning, significantly affect a person's ability to live independently, along with their overall quality of life. As the population ages, maintaining a high quality of life is a very important objective. The etiology of age-related cognitive decline is not entirely clear, but a model where age-related increases in inflammation lead to decrements in cognition is consistent with the literature, although other mechanisms also likely play a role. Such a model would suggest that aging effects on cognition are not inevitable and are potentially modifiable by reductions in inflammatory signaling. There is some evidence that pharmaceuticals directed against neuroinflammation can affect cognitive changes associated with normal aging as well as neurodegenerative diseases but much more research is needed to develop more effective drugs for this application. In the future, drugs which target CNS inflammation may prove effective in preventing or slowing age-related cognitive decline and promise to increase the quality of life in this growing segment of the population.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this manuscript.

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