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The Impact of Inflammation on Cognitive Function in Older Adults: Implications for Health Care Practice and Research

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Changes in cognition become more common in older age, and advanced age is the number one risk factor for cognitive decline, mild cognitive impairment, and age-related dementias such as Alzheimer's disease (Mebane-Sims, 2009). Maintenance of stable cognitive function with age is becoming particularly relevant given that the population of older adults over 65 years is growing quickly and will approach 71.5 million (or 20% of the total U.S. population) by 2030 (U.S. Census Bureau, 2004). According to Petersen (2011), only 1 in approximately 1,000 older adults exhibit no evidence of cognitive deterioration. Research demonstrates that poorer cognitive function is associated with increased risk of depression, social withdrawal, and dependence (Black & Rush, 2002; Zhu et al., 2008) and can contribute to decreased quality of life (Albert, Glied, Andrews, Stern, & Mayeux, 2002; Kelman, Thomas, Kennedy, & Cheng, 1994; Zhu) and restriction in life space, a measure of spatial mobility (Barnes, Wilson, Bienias, Mendes de Leon, & Kim, 2007; Sartori et al., 2011). While cognitive decline does not always reflect incipient dementia, even mild declines in cognitive abilities can cause frustration to individuals and incite alteration of day-to-day activities. Given that the strongest risk factor for cognitive decline is older age (Mebane-Sims, 2009), something unique about the aging process itself is likely related to increased pathology or vulnerability to declines in cognitive processing. As such, identification of risk factors that contribute to cognitive impairment and dementia in older age, particularly those risk factors that may be modifiable, is imperative.

Accumulating evidence has linked inflammation (an immune response to injury, pathogens, irritants, or oxidative stress) to cognitive decline and risk of dementia (Ader, 2009; Godbout & Johnson, 2006). Normally, inflammation is a protective response that facilitates the healing process; however, prolonged inflammation can cause tissue damage. Immune-system modulated inflammatory responses are adaptive and necessary for adequate cell and

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tissue stabilization and recovery from insults such as trauma, irritants, and pathogens (Ader; Perry, 2004). Normal aging is associated with heightened and prolonged inflammation throughout the body and – importantly for cognition – the brain. In turn, persistent increased levels of inflammation are associated with neurodegeneration, impaired neurogenesis, atherosclerotic processes, and chronic diseases (Paul et al., 2004; Raz & Rodrigue, 2006; Russo, Barlati, & Bosetti, 2010). Therefore, while increased inflammation with age may be a natural consequence of immune senescence, it can also intensify vulnerability to and risk of subsequent pathogenesis.

The importance of inflammation in brain aging is bolstered by findings that the most common forms of dementia – Alzheimer's disease and vascular dementia – are associated with a chronic and exaggerated inflammatory response that may contribute to disease advancement (Ader, Godbout, & Johnson, 2009). Evidence also suggests that some neurodegenerative diseases can be exacerbated by peripheral infection and the associated activation of immune responses (Perry, 2004). Additionally, delirium, an acute impairment in cognitive and mental status, is the most common psychiatric condition among older emergency room patients and is most frequently a consequence of peripheral infections that originate in areas of the body outside the central nervous system (Chiovenda, Vincentelli, & Alegiani, 2002). Furthermore, in clinical practice it is common to find that cognitive deficits in older adults can emerge after illness and infection, or even following a psychologically traumatic event (e.g., death of a spouse), a phenomenon labeled by some clinicians as an "unmasking" effect of a potentially underlying cognitive disorder.

The purpose of this article is to provide nurses and healthcare professionals caring for older adults with a basic understanding of inflammatory processes within the context of cognitive function and to discuss how inflammation with age may contribute to cognitive decline and increased risk of incipient cognitive disorders. Factors that can ameliorate or exacerbate inflammation (often modifiable health behaviors) will also be discussed. Finally, implications for nursing practice and research will be posited.

Aging and Cognitive Function

While changes in cognition become more common in older age, research has demonstrated that certain cognitive abilities generally remain stable even in the stages of mild to moderate dementia (e.g., reading ability) while others tend to decline (e.g., memory, executive function, processing speed) (Ellison, 2008). Interestingly, studies have shown that interventions such as exercise and certain cognitive training programs may be helpful for decreasing cognitive losses and maintaining cognitive function, which implies that the capacity for plasticity in old age does not completely extinguish (Ball et al., 2002; Colcombe & Kramer, 2003). In fact, evidence suggests that neurogenesis in the hippocampus, the same area of the brain that shows the most degeneration in early-stage Alzheimer's disease and is fundamental for new learning and memory consolidation, continues throughout older adulthood (Russo, Barlati, & Bosetti, 2010). Despite the potential for new learning and neuroplasticity, the aging brain typically manifests evidence of structural and functional changes; therefore, most older adults will experience some degree of cognitive decline over time (Petersen, 2011). Furthermore, the line between "normal" and "abnormal" cognitive decline with age may be nebulous. Schneider, Arvanitakis, Leurgans, and Bennett (2009) evaluated neuropathological substrates at autopsy of 483 older persons with diagnosed probable Alzheimer's disease, mild cognitive impairment, or no cognitive impairment. These researchers found that within the group of participants with no cognitive impairment, over 50% possessed one of three common neuropathologies: Alzheimer's disease pathology, cerebrovascular pathology, or neocortical Lewy Bodies. These results suggest that many cognitively "healthy" older adults may nevertheless have some underlying pathologies,

blurring the line between studies purporting to examine “normal” versus disease-related cognitive changes with age.

It is important to note that there is no one trajectory that all older adults will follow with respect to changes in cognition, given that much is dependent on not only baseline cognitive ability and rate of cognitive aging (influenced by environmental and genetic processes that affect neural health) but also by the interactions between the two (Whalley, Deary, Appleton, & Starr, 2004). Due to the varying degrees of cognitive impairment among older adults, interest in factors that may influence or exacerbate cognitive decline has been steadily increasing. Demographic factors such as age and education are generally accepted as significant predictors of cognitive function, yet they do not account for all or even the majority of the associated variance. Therefore, it would follow that there are numerous other variables contributing to the degree of cognitive decline in the elderly population.

Recent evidence has linked heightened levels of inflammation to increased risk of cognitive decline and dementia (Ader, 2009; Godbout & Johnson, 2006). However, research findings have been somewhat divergent regarding which inflammatory agents specifically may be most predictive of cognitive decline, or which areas of cognition may be most affected by inflammation. In part, this may be due to differences in methodological approaches, sample size and diversity, and outcome measures. Even so, findings have been generally consistent that, overall, inflammation and immune function are closely tied to cognitive function and may contribute to increased risk of cognitive decline and dementia. Therefore, it is important to understand which behavioral and health factors influence immune function and, in turn, whether markers of immune function and inflammation mediate the relationship between certain risk factors and cognitive outcomes.

Inflammation and Aging

Normally, inflammation is a protective response that facilitates the healing process. Outwardly, cardinal signs of inflammation (identified as early as the 1st century by Aulus Celsus) include: calor (warmth), dolor (pain), tumor (swelling), and rubor (redness), and each plays a critical role in healing. Within the body, biochemical signals trigger brain and endocrine activation to deliver necessary inflammatory agents such as leukocytes (white blood cells), macrophages, and cytokines to the target insult site. While leukocytes and macrophages are found throughout the blood, cytokines are special proteins secreted by cells of the nervous system that act as an immune-modulating response and can therefore increase or decrease immune system activation (Maier, Watkins & Fleshner, 1994). Inflammatory cytokines that are produced by the nervous system act on neural substrates to produce behavioral symptoms characteristic of illness: fever, lethargy, increased sleep, decreased appetite, and social withdrawal (Konsman, Parnet, & Dantzer, 2002), which are adaptive responses to enable eradication of pathogens while limiting the spread of infection (Perry, 2004).

Cytokines include the interleukins (abbreviated IL), interferons, tumor necrosis factors (TNF-α and TNF-β), and tumor growth factors. Depending on the type, cytokines can be proinflammatory (e.g., IL-6, IL-1β, TNF-α) or anti-inflammatory (e.g., IL-4, IL-10, IL-13). Thus, cytokines are able to self-regulate immune response by adjusting production as needed, and ideally a congruent balance of pro- and anti-inflammatory cytokines will exist to maintain optimal immune system function. Additionally, there are numerous other proteins that show either increased or decreased plasma concentrations as a result of inflammation, such as C-reactive protein (CRP), which is why some researchers use these factors as markers of underlying inflammatory processes (Daruna, 2004).

Among the many consequences of immune senescence is a decrease in production of anti-inflammatory proteins coupled with an exaggerated inflammatory response, thus resulting in an imbalance of modulating agents that could also lead to a heightened proinflammatory profile within the brain. Research has demonstrated that serum IL-6 levels tend to increase with advancing age, independent of any underlying comorbid disease process (Wei, Xu, Davies, & Hemmings, 1992; Wilson, Finch, & Cohen, 2002), though it is not clear whether production of IL-6 increases or whether there is instead a decrease in IL-6 inhibiting agents, such as dehydroepiandrosterone (DHEA; Wilson et al., 2002). Nevertheless, levels of IL-6 and other proinflammatory markers rise with age and instigate activation of the immune system. This prolonged, chronic exposure has the potential to inflame tissue in organs including the brain. Neuroinflammatory changes are often transient responses to acute conditions that ultimately return to a normal resting state; however, in the aging brain, immune activation may not entirely return to baseline levels, resulting in a heightened sensitivity to further activation and thus contributing to disease pathogenesis (Godbout & Johnson, 2006).

Effects of Neuroinflammation

Inflammation within the brain can have far-reaching acute and long-term effects. In addition to immediate and localized damage that occurs in response to neurotoxic inflammatory enzymes, neuroinflammation over time is associated with risk of dementia and cardiovascular pathology, including stroke (Blasko et al., 2004; Kuo et al., 2005; Paul et al., 2004). In general, neurodegeneration can be caused by inflammation due to activation of the brain's resident immune cells – microglia and cytokines – which produce a large number of proinflammatory factors (Russo et al., 2010) and are harmful to brain cells. According to Raz and Rodrigue (2006), brain tissue may be destroyed by either acute or chronic inflammation processes, both of which induce the release of neurotoxic products such as reactive oxygen species and certain damaging enzymes (Blasko et al., 2004). Limbic and associated brain structures such as the hippocampi and basal ganglia (structures that play important roles in cognitive processes like memory, attention, emotion, and perception) contain more enzymes involved in an inflammatory response than do primary motor or sensory cortices; therefore, these areas may incur increased risk of cumulative damage from subclinical inflammation (Raz & Rodrigue, 2006).

Brain inflammation has also been implicated in the pathogenesis of chronic neurodegenerative disorders (Blasko et al., 2004), and high inflammatory profiles at baseline assessment may increase risk of conversion to dementia at long-term follow-up (Schmidt et al., 2002). Furthermore, some markers of inflammation are found in amyloid plaque depositions and neurofibrillary tangles, the neuropathologic correlates of Alzheimer's disease (Kuo et al., 2005), a disorder characterized by slow and steady declines in cognitive functions, particularly in memory. Interestingly, according to Ownby (2010), average body temperatures in patients with Alzheimer's disease are increased, further implicating an inflammatory response. While human clinical trials investigating efficacy of anti-inflammatory agents in use with Alzheimer's disease have generally yielded inconclusive results, epidemiological evidence indicates that mild to moderate use of non-steroidal anti-inflammatory drugs (NSAIDs) may delay onset of (yet not prevent) Alzheimer's disease, especially in those with elevated genetic risk indicated by presence of apolipoprotein E e4 alleles (in 't Veld et al., 2001; Szekely et al., 2008).

Research has also found that acute brain insults are associated with inflammatory responses. Acute neurological events, including stroke and seizure, paradoxically trigger increased neurogenesis in specific hippocampal areas while simultaneously producing an increase in inflammation. Ekdahl, Mohapel, Elmer, and Lindvall (2001) found that after a severe

epileptic event, there is an 80% loss of newly formed neurons in the rat hippocampus, suggesting that the associated inflammatory response is detrimental to hippocampal neurogenesis. Additionally, Ekdahl, Classen, Bonde, Kokaia, and Lindvall (2003) found that administration of minocycline (an antibiotic with anti-inflammatory and neuroprotective properties) can restore impaired murine neurogenesis following seizure by inhibiting microglia activation and thus preventing an inflammatory response.

Inflammatory markers have also been implicated in incidence and prediction of stroke – a cerebrovascular event typically triggered by atherosclerotic processes that are associated with chronic inflammation. CRP in particular has emerged as an important factor in atherosclerotic processes (Paul et al., 2004) while simultaneously acting as an indicator of underlying inflammation. Rost and colleagues (2001) analyzed data from the longitudinal Framingham Study, which followed 591 men and 871 women with a mean age of approximately 70 years over a 12–14 year time period, and found that elevated serum CRP levels independently predicted risk of future stroke and transient ischemic attack (Kuo et al., 2005). Curb and colleagues (2003) utilized the Honolulu Heart Program cohort with 20 years of follow-up data and discovered that elevated CRP levels in middle age was a risk factor for future thromboembolic stroke in otherwise healthy men. Other cross-sectional and prospective studies have found similar results implicating CRP in stroke risk (e.g., Di Napoli, Papa, & Bocola, 2001; Kuo et al., 2005). In turn, atherosclerosis and stroke are risk factors for vascular dementia, a disorder of cognitive decline that often follows a stepwise deterioration pattern (Rice, 2004). Overall, it seems clear that heightened inflammation in the brain can have deleterious consequences for neuronal, cerebrovascular, and cognitive function.

Proinflammatory Proteins and Cognition

In an effort to investigate the specific effects of inflammation on cognitive function, several studies have examined inflammatory markers and their association with cognition, cognitive decline, and onset of dementia (see summary of these studies in Table 1). In a cross-sectional study, Wright and colleagues (2006) examined serum levels of CRP, cytokines IL-1, IL-2, IL-6, TNF-α, and cytokine receptors (abbreviated ‘R’) IL-2R, TNFR-1, TNFR-2 in relation to Mini-Mental State Examination (MMSE) performance in a subset of participants enrolled in the Northern Manhattan Study. Findings indicated that IL-6 was negatively associated with MMSE score even after adjusting for sociodemographic and vascular risk factors, suggesting that high levels of inflammation may have direct negative effects on cognition. As the researchers pointed out, this study was limited by its cross-sectional nature and use of MMSE as the sole outcome measure of cognitive function (due to its lack of sensitivity to detect mild changes in cognition, especially for highly educated participants) (Wright et al., 2006).

A longitudinal examination of inflammatory markers and global cognitive decline was conducted by Yaffe and colleagues (2003) in a large sample of older adults (42% African American) from the prospective Health, Aging, and Body Study. Using the Modified Mini-Mental State Examination (3MS) as a measure of cognitive function, these researchers evaluated serum levels of IL-6, CRP, and TNF-α at baseline in relation to baseline cognition and risk of cognitive decline over two years. Findings indicated that participants in the highest tertile of IL-6 or CRP serum concentrations performed significantly worse at baseline and follow-up 3MS, with a 24% increase in risk of cognitive decline over the two-year period in comparison to those participants in the lowest tertile (Yaffe et al., 2003). TNF-α did not emerge as a significant marker of cognitive function or decline in this study. Additionally, there was no interaction between race and inflammation on cognition.

While the previously mentioned studies suggest that inflammation is associated with global cognitive function, they were unable to offer insight as to which domains of cognition may be most affected by inflammation. Baune and colleagues (2008) examined circulating cytokines (serum IL-1β, IL-4R, IL-6, IL-8, IL-10, IL-12, and TNF-α) and specific neuropsychological domains of cognitive functioning – short-term memory, attention, cognitive, and motor speed – in a cross-sectional sample of 369 community-dwelling older adults enrolled in the Memory and Morbidity in Augsburg Elderly (MEMO) Study (Augsberg, Germany). These researchers found that higher levels of IL-8 were associated with poorer memory and motor function and with slower cognitive/perceptual speed performance. No significant associations were found for other cytokines or for other cognitive domains.

Ravaglia and colleagues (2003) examined predictors of performance on the Clock Drawing Test, a measure of executive function and visuospatial ability, in a cohort from the large-scale Conselice Study comprised of community-dwelling Italian participants aged 65 and older. In a cross-sectional analysis, these researchers found a significant inverse association between performance on the Clock Drawing Test and serum CRP levels despite no evidence of overt inflammatory disease or acute infection in participants, which appears consistent with CRP's role as a marker of underlying inflammation.

While results from the two studies previously discussed (Baune et al., 2008; Ravaglia et al., 2003) supported associations between proinflammatory biomarkers and different domains of cognitive function, they were limited by use of cross-sectional designs. Teunissen and colleagues (2003) utilized longitudinal data from the Maastricht Aging Study in the Netherlands to investigate the relationship between serum inflammatory protein levels and change in cognitive performance. Haptoglobin and CRP (protein markers of inflammation) levels at baseline were examined in relation to individual cognitive performance over six years. The sample included cognitively healthy persons aged 30 – 82 years. The sample was evaluated as a whole, as well as stratified to include a subset of participants aged 50 and older. Measures of cognitive function included the Word Learning Task (a measure of word list learning and recall), Letter-Digit Coding Test (a measure of processing speed), and the Stroop Test (an attentional measure of perceptual interference and response inhibition where low scores are indicative of better performance). Results yielded a significant negative correlation between serum haptoglobin levels at baseline and performance on the Stroop Test and the Delayed Recall portion of the Word Learning Test at baseline and throughout the six-year follow-up period. Additionally, among the subset of participants aged 50 and older, CRP concentration was negatively correlated with performance on Delayed Recall and Word List Total Learning from the Auditory Verbal Learning Test at baseline and through six-year follow-up (Teunissen et al., 2003). While participants differed significantly in cognitive function at baseline, there were no significant differences between persons in the course of cognitive function during follow-up, possibly due to the use of a relatively young sample that would not be expected to show much change in cognitive function; therefore, interactions between time and serum inflammation markers were not examined.

In similar research, Dik and colleagues (2005) assessed serum inflammation markers associated with risk of cognitive decline over a three-year time period in a large sample (N = 1,284) of older adults enrolled in the Longitudinal Aging Study Amsterdam. Inflammatory proteins included α_1-antichymotrypsin (ACT), CRP, IL-6, and albumin. Cognition was assessed on the following categories: general cognition (MMSE); memory (Auditory Verbal Learning Task, AVLT); fluid intelligence (Raven's Colored Progressive Matrices); and information-processing speed (Coding Task). After adjusting for age, sex, and education, ACT was associated with baseline memory performance on the AVLT and 60% increased risk of clinically relevant decline on the MMSE. ACT was not predictive of decline on other

cognitive measures. Neither CRP nor IL-6 was associated with cognitive performance or decline, which is in contrast to prior findings. The researchers suggested that low assay sensitivities for IL-6 (which was dichotomized around a selected detection limit), selective nonresponse of participants, and loss of follow-up of frail elders may have contributed to these discrepancies.

Using data from the MacArthur Study of Successful Aging, a longitudinal cohort study of 851 high-functioning older adults aged 70–79 years at baseline (1988) with follow-up assessments in 1991 and 1995, Alley, Crimmins, Karlamangla, Hu, and Seeman (2008) examined individual growth curves from baseline and follow-up performances on measures of abstraction (Wechsler Adult Intelligence Scale-Revised [WAIS-R] subtests), language (abbreviated Boston Naming Test), spatial ability (copying geometric figures), verbal recall (recall of naming items from the Boston Naming Test), spatial recognition (WAIS-R Spatial Span), and global cognitive function (summary measure derived from all subtest scores) as well as performance on the nine-item Short Portable Mental Status Questionnaire based on age, serum levels of IL-6 and CRP, and sociodemographic and health characteristics. These researchers found evidence for a cross-sectional linear relationship between inflammation and cognition, with higher levels of inflammation related to lower levels of baseline cognitive function (specifically, IL-6 with language and the global summary score, and both IL-6 and CRP with abstraction). After controlling for potential confounding variables, growth curve analysis yielded no effect of inflammation on baseline cognitive function or the rate of longitudinal cognitive change. However, when these researchers stratified inflammatory biomarkers into high-risk categories, participants in the top IL-6 tertile had 52% increased odds of decline in abstraction, 62% increased odds of decline in global cognitive function, and 88% increased odds of cognitive impairment as indicated by a decline of more than two points on the Short Portable Mental Status Questionnaire relative to those in the lowest IL-6 tertile.

In an effort to investigate predictors of maintenance of cognitive function (as opposed to decline), Yaffe, Fiocco, and colleagues (2009) studied data for 2,509 well-functioning African American and white older adults enrolled in the large-scale longitudinal Health, Aging and Body Composition (Health ABC) Study. Cognitive function was measured using the 3MS at baseline and years three, five, and eight, and cytokines IL-6, CRP, and TNF-α were used as serum markers of inflammation. These researchers found that older adults with lower levels of IL-6 and CRP were more likely to maintain their baseline levels of cognitive function over the eight-year follow-up period. Additionally, behavioral factors played an important role in maintenance of cognitive function moderate exercisers, non-smokers, infrequent drinkers of alcohol, and those who worked or volunteered regularly were more likely to maintain baseline levels of cognitive function. Notably, these contributing behavioral factors can be classified as potentially modifiable (Yaffe, Fiocco, et al., 2009).

In the above-mentioned studies, cognitive outcome measures and mean age of study groups were heterogeneous and protocols varied in terms of study design – including candidate serum proteins and stratification of assays (e.g., dichotomization versus tertiles) – and length of follow-up, making individual comparisons difficult. Furthermore, while studies may include measures of cognition in relation to inflammation, there is a paucity of research examining the interrelationships between psychological and health factors, inflammation, and cognitive function, especially with respect to changes over time. Overall, findings from existing studies generally do support an association between increased risk of cognitive decline and high inflammatory concentrations, but there is a need for further analysis of potential interrelationships between inflammation, cognitive function, and psychological and health factors.

Factors Associated with Inflammation

Given the strong associations between inflammation, cognitive function, and disease in older adults, it appears worthwhile to examine predictors of inflammation in an effort to identify those persons at heightened risk of increased inflammation as well as to identify potential areas for intervention. While heightened inflammatory profiles do appear to occur in older adults even in the absence of disease pathology (and perhaps as a natural consequence of aging), there are factors that have been found to increase inflammation levels beyond what can be attributed to senescence (Figure 1).

For example, persons with obesity, chronic obstructive pulmonary disease, diabetes, and metabolic syndrome are at an increased risk for innate and chronic inflammation (Del Zoppo & Gorelick, 2003; Plaeger et al., 2011). Lifestyle factors can also increase one's risk of inflammation, and these include smoking, poor diet, lack of physical exercise, and inadequate sleep (Ford, 2002; McDade, Hawkley & Caccioppo, 2006). Psychological distress has additionally been implicated in inflammatory response. Findings from studies indicate that depressive symptoms are associated with increases in proinflammatory cytokines (see a meta-analysis by Dowlati et al., 2010), and that the level of cytokines corresponds to the severity of depressive symptoms (Dentino et al., 1999; Levine et al., 1999). Depression, in turn, can adversely affect cognitive function by interfering with working memory, executive function, and processing speed. Additionally, depression and depressive symptoms are associated with increased risk of dementia and cognitive decline among older adults (Jorm, 2000; Saczynski et al., 2010). Further evidence for cytokines' role in depression is demonstrated by increases in depressive symptoms following cytokine therapy in otherwise psychiatrically healthy individuals (Wilson, Finch, & Cohen, 2002) and decreased levels of proinflammatory cytokines with the administration of antidepressant therapy (Basterzi et al., 2005; De Berardis et al., 2010; Frommberger et al., 1997). Additionally, some interleukins modulate central serotonergic function; deficits that, according to the monoamine hypothesis, may play a causal role in depression (Wilson et al., 2002). The monoamine hypothesis purports that imbalances in certain neurotransmitters within the monoamine family play a key role in expression of psychiatric disorders. Therefore, the role of proinflammatory cytokines in depressive symptomatology may be direct as well as indirect.

Likewise, stress can activate immune response via the hypothalamic-pituitary-adrenal (HPA) axis, a system responsible for the release of the stress hormone cortisol. High levels of cortisol are associated with memory deficits in healthy elderly persons due to effects on the hippocampi (Ownby, 2010) and chronic stress has been shown to irreversibly damage hippocampal structures in animal studies (Sapolsky, 1996). One study found that greater reactivity to stress in midlife was associated with increased risk of dementia more than 30 years later (Crowe et al., 2007). Other studies have found that high neuroticism and post-traumatic stress disorder – both markers of chronic stress – are associated with cognitive impairment in later life and dementia (Crowe et al., 2006; Wang et al., 2009; Yaffe et al., 2010). Additionally, proinflammatory cytokines IL-1 and TNF-α can stimulate the HPA axis, further contributing to stress-induced cognitive deficits (Ownby, 2010). It appears feasible that inflammation may mediate the effects of stress on cognitive function. For older adults, the transition from middle age to later years can be associated with many lifestyle changes and stressors (e.g., retirement, bereavement, disability, and economic difficulty), which could contribute to and exacerbate neuroinflammation (Guidi et al., 1998; Kiecolt-Glaser, Gouin, & Hantsoo, 2010). Additionally, many older adults take on caregiver roles for a spouse or family member, and the act of caregiving is itself associated with increased levels of stress and IL-6 production (Kiecolt-Glaser et al., 2003). According to Vitaliano and colleagues (2007), caregivers for spouses with Alzheimer's disease showed greater

functional declines, higher distress scores, cognitive decline, and increases in CRP serum levels over two years compared to non-caregivers. Additionally, caregivers of a spouse or loved-one are less likely to maintain cognitive function over time than non-caregivers (Yaffe, Weston, et al., 2009). It therefore appears that caregiver status in late life may be associated with stress, inflammation, and cognitive decline.

While there are many factors that have been shown to increase levels of inflammatory biomarkers, certain factors may reduce or protect against inflammation. From a study of 13,748 participants 20 years of age and older enrolled in the longitudinal National Health and Nutrition Examination Survey (NHANES) III, Ford (2002) found that odds ratios for elevated CRP concentration (dichotomized) were 0.98 for participants who engaged in light physical activity, 0.85 for those with moderate physical activity levels, and 0.53 for participants who engaged in vigorous physical activity over the previous month in comparison to participants who were sedentary. Similarly, Petersen and Pedersen (2005) demonstrated that exercise may reduce levels of CRP while inhibiting production of TNF-α. Ownby, Loewenstein, and Kumar (2009) suggest that reductions in CRP serum levels due to physical activity may be partially responsible for the antidepressant effects of exercise.

In addition to regular physical activity, moderate use of alcohol (5–7 drinks per week) has been linked to low levels of inflammation. Studies have reported lower levels of serum inflammatory markers among individuals who consume alcohol in moderate quantities in comparison to those who abstain or drink only on occasion (Imhof & Koenig, 2003; Imhof et al., 2001, Lu et al., 2010,). Albert, Glynn, and Ridker (2003) similarly found an association between markers of inflammation and moderate alcohol consumption, observing that this relationship remained even after controlling for cardiovascular risk factors including exercise frequency, past and current smoking, systolic blood pressure, presence of diabetes, body mass index, and HDL cholesterol in a sample of 2,833 men and women (M_{age} = 61 years). Given that moderate alcohol use is associated with decreased cardiovascular mortality (Fuchs et al., 1995; Gaziano et al., 2000; Wannamaethee & Shaper, 2002), Albert and colleagues (2003) purported that an inflammatory mechanism may mediate the effect of moderate alcohol intake on cardiovascular mortality. Interestingly, moderate alcohol use has also been linked to decreased risk of cognitive impairment, cognitive decline, and dementia (compared to heavy drinking or teetotalism) (Peters, Peters, Warner, Beckett, & Bulpitt, 2008; Stampfer, Kang, Chen, Cherry, & Grodstein, 2005), which adds further support to the potential mediating role of inflammation in vascular and cognitive health with aging.

Implications for Practice and Research

Because higher levels of inflammation are associated with a number of health conditions requiring medical treatment, nurses and other health care practitioners are likely to see patients who are at increased risk for future development of cognitive decline and impairment. Therefore, these professionals are in a position to implement early intervention strategies and monitor potential changes in cognitive function for these at-risk patients. Implementation of brief screening procedures to identify those patients with a high risk of inflammation-associated cognitive impairment could be an effective starting point for early intervention. Older patients with medical conditions that are related to increased inflammation (e.g., diabetes, obesity, chronic obstructive pulmonary disease, depression) and those who engage in lifestyle behaviors that can increase inflammatory levels (e.g., smoking, inactivity, poor diet) could be categorized as “high risk” and targeted for further intervention via patient education. Educating patients regarding increased inflammation and the subsequent risk of cognitive decline is particularly important for early intervention given that patients often have control over factors that can reduce their inflammatory levels (i.e.,

ensuring adequate control over medical conditions and practicing healthy lifestyle behaviors). By educating patients about the need to maintain or improve self-care, highlighting the importance for body and brain health, and providing concrete strategies to promote healthy behaviors, health care providers can help patients reduce their levels of inflammation and possibly decrease their risk of future cognitive impairment.

In addition to screening and education, health care providers can also monitor those patients who fall into the high risk category for subjective or objective changes in cognitive function over time. Monitoring can be implemented informally through conversation with the patient and family, as well as formally via the use of brief and validated cognitive assessment instruments like the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) or St. Louis University Mental Status Examination (SLUMS; Tariq et al., 2006). Such careful monitoring can allow for subtle cognitive changes to be identified in a timely manner, thus allowing the patient to be referred for further comprehensive evaluation and treatment.

It is also important to note that patients being treated for medical disorders may also be experiencing psychological conditions that can increase levels of inflammation, such as depression and chronic or acute stress. Nurses are in a unique position to screen and identify these patients and provide them with treatment options to alleviate psychological distress. As with cognitive function, nurses can monitor changes in the psychological functioning of patients and respond accordingly, thus increasing the likelihood of favorable outcomes.

Research will be needed to determine the effectiveness of screening, intervention, and monitoring procedures that are relevant to inflammation and the prevention of cognitive decline across acute, primary, and long-term settings. Nurse researchers can play a vital role in developing and testing such practices, targeted specifically toward high risk older adults with increased inflammatory profiles, and examining how these practices may relate to cognitive outcomes.

Conclusion

Changes in cognitive function become more common in older adulthood, and emerging evidence has implicated heightened brain inflammation as an important factor that may contribute to and exacerbate cognitive decline among older adults. Baseline levels of inflammatory biomarkers tend to increase with age, and higher levels of inflammation have been shown to negatively affect cognitive processes, including memory, speed of processing, and global cognitive function. Additionally, inflammation has been linked to incipient dementia and neurodegenerative diseases.

While to some degree rising levels of inflammation over time are likely a consequence of immune senescence, there are certain lifestyle factors and modifiable behaviors that may also play a key role in inflammatory processes. In turn, many of these factors are associated with health conditions that require medical intervention and monitoring, like diabetes, hypertension, depression, and obesity; therefore, nurses and other health care practitioners are in a position to see patients who are at increased risk for future development of inflammation-related cognitive decline and impairment. Implementation of screening measures, early intervention strategies, and careful examination of cognitive function over time are potential ways for health care practitioners to identify and monitor those high-risk patients. Future research may be aimed at determining the effectiveness of these procedures and their relation to cognitive outcomes in older adults.

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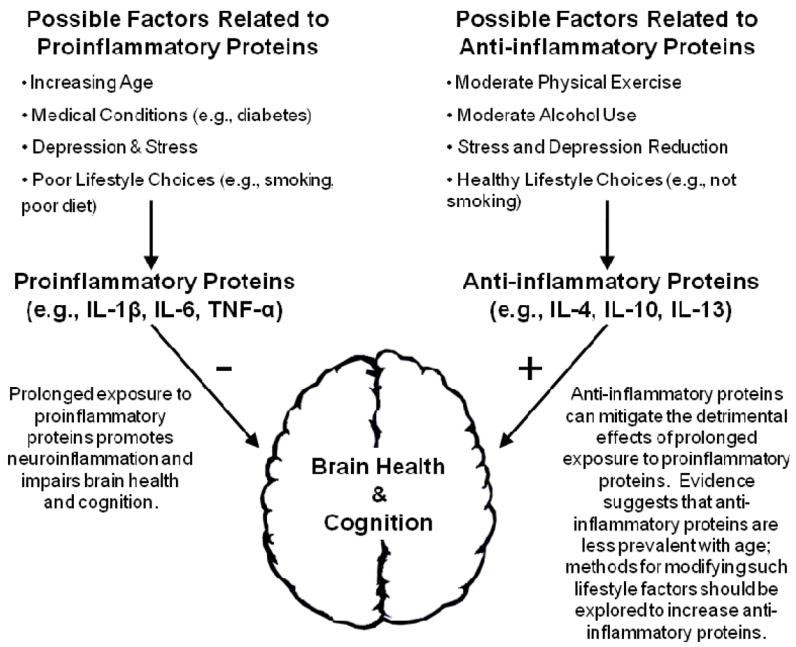

Figure 1.
Factors Related to Proinflammatory and Anti-Inflammatory Proteins.

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Table 1

Summary of Studies Examining Inflammatory Biomarkers in Relation to Cognitive Function

Study	Design	Population	Participant Age Range (Mean)	Cognitive Measures	Inflammatory Measures	Stratification of Assays	Results
Wright et al., 2006	Cross- sectional	*N* ≤ 269 Northern Manhattan Study, stroke- free cohort	40+ (67)	MMSE (log transformed)	IL-1, IL-2, IL-6, TNF-α, IL-2R TNFR-1, TNFR- 2, & CRP	Continuous and Tertiles	IL-6 negatively associated with MMSE
Baune et al., 2008	Cross- sectional	*N* = 369 MEMO Study (Germany)	65+ (73)	Memory, Attention, Cognitive Speed, Motor Function	IL-1β, sIL-4R, IL-6, IL-8, IL- 10, IL-12, & TNF-α	Continuous	IL-8 negatively associated with Memory, Speed, and Motor Function
Ravaglia et al., 2003	Cross- sectional	*N* = 744 Conselice Study (Italy)	65–93 (73)	Executive Function/Visuo-spatial (Clock Drawing Test)	CRP	Dichotomized	CRP levels negatively associated with Clock Drawing Test performance
Teunissen et al., 2003	Prospective with six-year follow-up	*N* ≤ 92 Maastricht Aging Study (Netherlands)	30–82 (57)	Learning/ Encoding, Memory, Attention, Cognitive Speed	IL-6, Haptoglobin, & CRP	Continuous	Haptoglobin negatively associated with Speed/ Attention and Memory; CRP negatively associated with Learning and Memory
Dik et al., 2005	Prospective with three-year follow-up	*N* = 1,284 Longitudinal Aging Study (Amsterdam)	62–85 (75)	Processing Speed, Memory, Fluid Intelligence, MMSE	ACT, CRP, & IL-6	Tertiles (ACT & CRP) Dichotomized (IL-6)	ACT associated with baseline Delayed Recall and Highest ACT tertile associated with increased risk of decline on MMSE
Yaffe et al., 2003	Prospective with two-year follow-up	*N = 3,031* Health ABC Study (black and white elders)	70–79 (74)	3MS	CRP, IL-6, & TNF-α	Tertiles	Highest tertiles of IL-6 and CRP associated with poorer 3MS performance at baseline and follow-up with 24% increase in risk of cognitive decline over two years, relative to lowest tertiles; No interaction with race
Yaffe, Fiocco, et al., 2009	Prospective with eight-year follow-up	*N* = 2,509 Health ABC Study (black and white elders)	70–79 (74)	3MS	CRP, IL-6, & TNF-α	Continuous, log- transformed	Lower levels of CRP & IL-6 associated with stable cog function over eight years
Alley et al., 2008	Prospective with seven-year follow-up	*N* = 851 MacArthur Study of Successful Aging, subsampled from Established Populations for	70+ (74 at baseline)	Abstraction Verbal Recall Language Spatial Ability Spatial Recog. Summary Score Mental Status	CRP IL-6	Tertiles, then dichotomized into high-risk categories in subsequent analyses	Baseline levels of CRP & IL-6 negatively associated with cognitive function (abstraction, language

Study	Design	Population	Participant Age Range (Mean)	Cognitive Measures	Inflammatory Measures	Stratification of Assays	Results
		Epidemiologic Studies of the Elderly for age 70+					& summary score); highest tertile of IL-6 had greatest risk of decline

Notes. 3MS = Modified Mini-Mental State Examination; ACT = Antichymotrypsin; CRP = C-reactive protein; IL = Interleukin; ILR = Interleukin receptor; MMSE = Mini-Mental State Examination; TNF-α = Tumor necrosis factor-alpha; TNFR = Tumor necrosis factor receptor.