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Microglia and modifiable life factors: Potential contributions to cognitive resilience in aging

Michael R. Duggan, **Vinay Parikh***

Department of Psychology and Neuroscience Program, Temple University, Philadelphia, PA 19122

Abstract

Given the increasing prevalence of age-related cognitive decline, it is relevant to consider the factors and mechanisms that might facilitate an individual's resiliency to such deficits. Growing evidence suggests a preeminent role of microglia, the prime mediator of innate immunity within the central nervous system. Human and animal investigations suggest aberrant microglial functioning and neuroinflammation are not only characteristic of the aged brain, but also might contribute to age-related dementia and Alzheimer's Disease. Conversely, accumulating data suggest that modifiable lifestyle factors (MLFs), such as healthy diet, exercise and cognitive engagement, can reliably afford cognitive benefits by potentially suppressing inflammation in the aging brain. The present review highlights recent advances in our understanding of the role for microglia in maintaining brain homeostasis and cognitive functioning in aging. Moreover, we propose an integrated, mechanistic model that postulates an individual's resiliency to cognitive decline afforded by MLFs might be mediated by the mitigation of aberrant microglia activation in aging, and subsequent suppression of neuroinflammation.

Keywords

cognitive aging; microglia; neuroinflammation; diet; exercise; cognitive enrichment

1. Introduction

Across the globe, there is an unprecedented shift in aging demographics; by 2050, the elderly (i.e. > 65 years old) will exceed 21% of the population (an increase from 10% in 2010), and, for the first time in human history, will surpass the population of youth (i.e. 10–24 years old) [1]. Despite the subsequently increased prevalence of cognitive impairments

*Corresponding author: Vinay Parikh, Department of Psychology and Neuroscience Program, Temple University, Philadelphia, PA 19122. Phone: 215-204-1572, vinay.parikh@temple.edu.

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Declaration of competing interest

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and dementia, including Alzheimer's disease (AD), currently available pharmacotherapies provide only symptomatic relief, and do not halt or reverse the progression of these age-related conditions [2, 3].

Although decline in several cognitive domains is frequently documented in aging, including information processing, attention, memory and executive functions, the extent of age-related functional changes can vary greatly between individuals [4–7]. Some older individuals retain intact cognitive functioning, or display only minimal decline, while others show significant cognitive impairments and can eventually develop AD as well as other forms of dementia [8]. However, the neurobiological underpinnings of this individual variation in cognitive aging remain unclear. Given the contemporary shift in aging demographics, as well as the lack of effective therapies to treat age-related cognitive deficits, there is considerable interest in elucidating the protective mechanisms that afford *resilience* to cognitive decline in old age. Here, we operationalize resilience as a higher level of cognitive functioning than otherwise expected in the face of age-related injury and/or neuropathology [9].

Accumulating evidence suggests modifiable life factors (MLFs; i.e. diet, physical activity, cognitive engagement) can facilitate variation in cognitive decline and render some individuals more resilient to such age-related detriments [10–12]. As advanced age itself remains the most prominent risk factor for dementia, while MLFs have been shown to induce substantial cognitive benefits, recent investigations have focused on the specific mechanisms by which these factors might modulate neurobiological functioning in aging [13–15].

There is a general consensus that neuroinflammation increases with advancing age, and poses risk for developing neurodegenerative conditions in the elderly [16–18]. Age-related neuroinflammation, if uncontrolled, results in an exaggerated production of pro-inflammatory cytokines, as well as other cytotoxic mediators, that can exert detrimental effects on neurons and contribute to cognitive dysfunction [19–21]. Hence, the abnormal activation of inflammatory mechanisms induced by a chronically dysregulated immune state may contribute to age-related variation in cognitive capacities. As the primary mediators of the brain's immune responses, microglia cells play a critical role in maintaining an array of homeostatic processes in the central nervous system (CNS) [22, 23]. Recent evidence indicates that during the course of aging, these cells become dysregulated and contribute to a chronic state of neuroinflammation [24, 25]. Provided that MLFs can exert beneficial effects on cognition, while aberrant immune-inflammatory responses can render elderly individuals vulnerable to cognitive deterioration, an individual's resiliency to cognitive decline afforded by MLFs might be mediated by the mitigation of aberrant microglia activation in aging.

In this review, we summarize the physiological contributions of microglia in maintaining CNS homeostasis in aging, as well as the cellular mechanisms underlying microglia reactivity and subsequent neuroinflammation that might increase an individual's susceptibility to age-related dementia and AD (see Glossary in Box 1 for key definitions on immune system and inflammation). Next, we review evidence from human and animal studies which highlight the impact of MLFs on cognitive aging. Here, aging generally refers to durations relative to probable life expectancies (i.e. ≥ 65 years in humans, ≥ 20 months in

rats, ≥ 18 months in mice). Specifically, we focus on diet, physical activity, and cognitive enrichment as MLFs that can augment cognitive capacities in aging by potentially modulating the brain's innate immune responses and microglia-driven inflammatory processes. Moreover, we provide a hypothetical mechanistic model which postulates that the benefits of MLFs on cognitive capacities in aging might converge upon microglia functioning. Finally, in stipulating some of the prominent limitations of this framework, we encourage future directions for interdisciplinary research that would inform the proposed model and advance our neurobiological understanding of individual variation in age-related cognitive decline.

2. Microglia and cognitive aging

2.1. Description and functions of microglia

First characterized by Robertson and Nissl over a century ago, microglia are non-neuronal cells that range between 0.5%–16% of all brain cells in mammals, including humans, (i.e. depending upon the neuroanatomical region), and play a fundamental role in various neurobiological processes, such as neurodevelopment, neurogenesis, synaptic pruning and the modulation of synaptic transmission [26–30]. As resident macrophages (i.e. immune cells involved in phagocytic function) of the brain, these cells are unique in their function as the primary mediator of the brain's innate immune response, and therefore play an important role in the regulation of CNS homeostasis [23, 31, 32]. Microglia express membrane proteins called pattern recognition receptors (PRRs; e.g. toll-like receptors or TLRs, scavenger receptors or SRs) that monitor the CNS environment for pathogens, tissue/cellular injury, or other indications of neuronal dysfunction [33, 34]. The recognition/detection process alerts microglia to danger and involves the interaction of PPRs with specific biomolecules, such as pathogen-associated molecule patterns (PAMPs) or damage-associated molecular patterns (DAMPs), which share conserved molecular structures. PAMPs are foreign molecules expressed by various microbes that trigger an inflammatory response during infection. One of the best characterized PAMPs is lipopolysaccharide (an endotoxin), located in the outer membrane of gram-negative bacteria [35]. On the other hand, DAMPs are endogenous molecules that can be released either by damaged cells or by cells undergoing apoptosis, such as reactive oxygen species (ROS), purine metabolites (urate crystals), calcium-binding proteins and lipotoxic ceramides, which activate innate immune responses to produce non-infectious (sterile) inflammation [31, 32, 36].

In a normal healthy brain, microglia generally maintain a homeostatic phenotype that is visually characterized by diffuse, ramified and dynamically moving protrusions, which constantly scan the surrounding microenvironment [37–40]. Following the detection of pathogens or endogenous danger signals, microglia migrate to the site of injury/infection, and initiate an immune response through a number of complementary processes (Figure 1). For example, they digest and degrade microbes as well as dead cells via phagocytosis [41]. Microglia also release a wide range of soluble proteins that include inflammatory mediators (e.g. cytokines and chemokines), trophic factors such as brain-derived neurotrophic factor (BDNF), and other immunomodulators which help the clearance of cellular debris that is critical for cellular repair and cellular regeneration [42, 43]. While their classification

remains actively debated, these immune mediators can be broadly categorized as pro-inflammatory, (e.g. tumor necrosis factor alpha [TNF-α], interleukin [IL]-6, IL-1, interferon [IFN]-γ) and anti-inflammatory (e.g. transforming growth factor β, IL-4, IL-10, IFN-β) [33, 44]. Recent evidence indicates that following acute brain injury or infection, activated microglia can change their phenotype and become either pro-inflammatory or anti-inflammatory/neuroprotective, depending upon the severity and duration of the injury [45–48]. Although the balance between pro-inflammatory and neuroprotective microglia phenotype is critical for CNS repair and maintaining homeostasis, little is known about how the interaction between these two phenotypes governs neuroinflammation.

2.2. Microglia in normal and pathological aging

A mild state of chronic inflammation in the absence of overt infection (referred to as sterile inflammation, or *inflammaging*) is a pervasive feature of normal aging. Nevertheless, higher levels of inflammaging are a significant risk factor for age-related pathologies [49, 50]. Numerous studies in rodents and humans have shown that during aging, an increasing proportion of microglia across different brain regions, including the hippocampus and cortex, transition to a *dystrophic* (senescent) phenotype [51–53]. The morphology of dystrophic microglia is distinct from the ramified appearance of the homeostatic phenotype or the reactive/hyperactive morphology of activated microglia, and is usually characterized by deramification (i.e. loss of branching), cytoplasmic deterioration, atrophy, thinning, twisting and fragmentation of protrusions [54]. This age-related shift in microglia morphology is associated with increased production of pro-inflammatory mediators, such as TNF-α, IL-1β, and IL-6, and reduced levels of anti-inflammatory cytokines, such as IL-10 [55–58].

In a non-elderly CNS, when there is an injury or infection, reactive microglia respond with an optimal balance of secreted pro-inflammatory and anti-inflammatory mediators to exert neuroprotective effects. However, microglia become highly dysregulated in aging and the balance shifts to a predominantly pro-inflammatory response. This can have deleterious consequences on the surrounding environment, resulting in neuronal dysfunction and contributing to neurodegeneration. For instance, a cross-sectional aging study in mice reported reduced volume coverage by microglial processes – as if they have retracted - in older animals as compared to young animals, which correlated with increased expression of pro-inflammatory cytokines [58]. Moreover, brain tissues from a transgenic AD mouse model showed a similar microglia phenotype and inflammatory changes in relatively young mice, suggesting that in AD there is an accelerated transition to a microglial phenotype associated with aging. Microglia senescence (or dystrophy) has also been associated with reduced phagocytosis of amyloid-β (Aβ), resulting in its accumulation, and eventual cytotoxic plaque formation in AD [59–62]. Furthermore, microglia express higher densities of antigen binding receptors with age (e.g. TLRs, SRs and mitogen histocompatibility complex class II); in turn, the activation of these receptors can trigger signal transduction cascades that result in the sustained production and release of pro-inflammatory cytokines and exert detrimental effects on neuronal functioning [63, 64]. Collectively, these studies support the hypothesis that senescent/dystrophic microglia could impact phagocytic clearance mechanisms for the efficient removal cytotoxic proteins that accumulate with age,

and exacerbate chronic neuroinflammation. Although the causal factors underlying age-associated microglial malfunctioning remain debated, several age-dependent variables are likely to contribute. These include the reduced ability of microglia to proliferate due to telomere attrition, abnormal accumulation of lysosomal inclusions and proteinaceous aggregates, elevated mutations in mitochondrial DNA, increased iron load, accumulation of lipid droplets, as well as ROS overproduction and oxidative stress [52, 65].

While the role of microglia is considered to be generally neuroprotective, there are indications that in neurodegenerative disorders, the uncontrolled activation of these cells and an excessive pro-inflammatory response could exert direct neurotoxic effects by phagocytosing not only damaged cellular debris but also intact neurons [66–69]. This raises an important question concerning functional differences between dystrophic microglia and the reactive/hyperactive form of microglia. Post-mortem brains from AD subjects containing high amyloid loads demonstrated a significantly higher degree of microglial dystrophy than is found in nondemented, amyloid-free aged-matched control subjects [70]. Dystrophic rather than activated microglia were found to be colocalized with neural structures positive for neurofibrillary plaques and tangles in the post-mortem brains of AD subjects [54]. Moreover, the phenotype of microglia in aging can differ from those found in AD, as indicated by varying arborization areas and stages of activation, as well other morphological characteristics (e.g. cytoplasmic fragmentation; cytorrhexis) [71–73]. These observations support the idea that microglia senescence rather than microglia activation may contribute to the pathogenesis of AD. However, as noted above, an activated pro-inflammatory state of microglia has been observed in the brains of both aged humans and rodents, even in the absence of overt neuropathology. Moreover, in a phenomenon that has been described as microglial priming, the reactivity of microglia to immunological challenges, including pathogenic infections or increased accumulation of cytotoxic proteins, generally increases with age in humans and animals [74, 75]. Such primed microglia might themselves mediate an exaggerated neuroinflammatory response and disrupt cellular homeostasis in aging [76, 77]. Therefore, it remains unclear whether age-related hyperactive and primed microglia represent penultimate phases of dystrophic microglia, or if these are distinct phenotypes entirely. Further investigations are necessary to discern the functional differences between hyperactive, primed and senescent/dystrophic microglia, and whether the neuroinflammatory changes mediated by these phenotypes differ between normal aging and age-related neurological conditions. Regardless of these phenotypic differences, the consensus amongst current literature indicates that aged microglia, in general, are chronically overactive, disrupted in morphology as well as function, and predominantly release pro-inflammatory mediators that together exert detrimental effects on neuronal systems.

2.3. Microglia, neuroinflammation, and age-related cognitive decline

The postulation for the potential role of microglia in contributing to age-related cognitive decline is due to several justifications, including observations from studies that illustrate disrupted microglia in the brains of cognitively impaired older adults and people with AD (Table 1 summarizes some of the human investigations). Evidence from postmortem human studies demonstrate significantly increased expression of microglial pro-inflammatory proteins and immune dysregulation across numerous brain regions of older adults with

cognitive impairments, including those with mild cognitive impairment (MCI) or AD, as compared to non-demented healthy older adults and/or young adults [72, 78–81]. In humans, there currently exists only one direct way to measure microglia activation and associated neuroinflammation *in vivo*: Positron Emission Tomography (PET) imaging using radiolabeled ligands that bind to the 18 kDa translocator protein (TSPO) present on the mitochondria of activated microglia and macrophages. Several studies have reported increased TSPO binding in the brains of elderly subjects with cognitive impairments. For instance, a notable imaging study employed the PET ligand [^{11}C]*(R)*-PK11195 to compare microglia activation between healthy young/elderly individuals and those subjects diagnosed with MCI/AD based on assessment of mini-mental state examination (MMSE) and clinical dementia rating (CDR) scale [82]. While the study reported no significant age-related changes in TSPO binding in any brain region except the thalamus in healthy controls, an exaggerated microglial activation response was noted in MCI/AD subjects amongst those brain regions that are implicated in attentional and mnemonic function, including the inferior and middle temporal gyri (right: control 0.13±0.03, MCI/AD 0.23±0.05, $p = 0.0001$; left: control 0.13±0.04, MCI/AD 0.26±0.08, $p = 0.001$), left parahippocampal gyrus (control 0.09±0.03, MCI/AD 0.18±0.07, $p = 0.003$) and inferior parietal lobule (right: control 0.12±0.05, MCI/AD 0.23±0.10, $p = 0.01$; left: control 0.08±0.04, MCI/AD 0.23±0.12, $p = 0.005$). Such findings have been replicated by other investigators, where increased microglial TSPO-binding and associated neuroinflammatory changes correlated with impaired performance across a range of neuropsychological tests in older adults with dementia and AD [83–86]. Another PET imaging study reported higher binding in specific brain regions of MCI subjects that developed dementia 5 years after imaging (i.e. compared to healthy, age-matched control participants), indicating that elevated microglial activation may precede the onset of dementia and predict the progression of cognitive decline in AD [87]. Along with genetic and histopathological data specifically implicating dysfunctional microglia in late-onset AD, such neuroimaging results suggest the chronic activation of microglia over time, as well as the corresponding progressive shift towards a more dystrophic phenotype, coincide with later stages of neuropathology [88–90]. While TSPO radioligands have been extensively used to examine microglia activation in age-related neurodegenerative disorders, issues regarding sensitivity and specificity should be considered. For instance, some of these ligands are also known to bind to reactive astrocytes (another type of glial cells in the CNS); likewise, these ligands do not have the ability to discriminate between different phenotypes of microglia (e.g. hyperactive vs dystrophic) [91].

Genomic investigations, including genome wide association studies (GWAS) that examined rare coding variants of genes expressed on microglia, have provided further insights into the role of these immune cells in pathological aging. Several studies have reported a significant association between people diagnosed with AD and a missense mutation (rs75932628-T) in the gene encoding for the triggering receptor expressed on myeloid cells 2 (TREM2), a receptor expressed by microglia that is known to facilitate phagocytosis [71, 92–94]. Interestingly, older adults who carried this mutation but were not diagnosed with AD also exhibited impaired cognitive functioning (a mean increase of 0.87 units on Cognitive Performance Scale, $p = 0.003$) as compared to non-carriers [94]. Given the protective role of TREM2 in inflammation, these studies supported the notion that reduced anti-inflammatory

response and reduced phagocytosis in aging may interfere with the ability of the brain to clear age-related aberrant/toxic products (such as Aβ) and increase the risk for AD. Complementary to such findings, a separate group of researchers identified differential gene expression of multiple facets of microglial functioning and inflammation, including those associated with TREM2, across multiple brain regions in postmortem tissues of people with late-onset AD [95]. Furthermore, genomic variation in multiple microglia receptors that are known to initiate innate immune responses, including cluster of differentiation 33 (CD33), complement receptor 1 (CR1) and membrane spanning four-domain subfamily A members 4A and 6A, have been associated with late-onset AD, further illustrating the association between disrupted microglia function and pathological age-related cognitive decline [96–103]. Along with investigations that have examined the functional impact of microglia-associated genes, several magnetic resonance imaging (MRI) studies reported individuals who carry allelic polymorphisms of the pro-inflammatory cytokine IL-1β, had higher white matter hypersensitivity, hippocampal shrinkage, disrupted activation of brain networks, and impaired performance on cognitive switching tasks [104–108].

Animal studies suggesting an association between microglia and cognition in aging/AD have primarily employed procedures where the mitigation of microglia activation preserved brain homeostasis and cognition (Table 2). For instance, in transgenic AD mouse models (e.g. APP23, APP/PS1 mice), ablation of genes associated with inflammatory signaling, such as TNF-α receptor or IL12/23 receptor, reduces Aβ load and suppresses microglial activation [109, 110]. Moreover, these manipulations preserved hippocampus-dependent memory capacities across multiple behavioral paradigms, including the hole-board memory test, object recognition task, contextual fear conditioning and the Barnes maze. Likewise, pretreatment with Biacalin (a flavonoid with anti-inflammatory and neuroprotective properties) or overexpression of IL-4 (an anti-inflammatory cytokine) mitigates reactive microglia-induced neuroinflammation and rescues cognitive detriments in transgenic AD mouse models [111, 112]. Similar conclusions were drawn in a study that employed a rat model of AD, where treatment with the anti-inflammatory cytokine IFN-β suppressed microglia activation induced by intra-hippocampal Aβ injections and reversed memory impairments [113, 114].

The association between the detrimental effects of neuroinflammation and cognitive deficits has not only been limited to rodent AD models, but has also been extended to normal aged rodents. For instance, a study conducted by Barrientos and colleagues demonstrated that elevations in pro-inflammatory cytokines in the hippocampus and ensuing memory impairments in a fear conditioning task induced by laparotomy in aged rats were reversed by IL-1β antagonist [115]. Similarly, in aged mice displaying significant impairments on a spatial memory task, the elimination of dystrophic microglia, and subsequent repopulation of homeostatic microglia was capable of restoring hippocampal integrity, synaptic plasticity and improving cognitive function [116].

It is noteworthy that rodent models of AD have multiple translatable limitations, such as the non-physiological development of pathological features and inaccurate representation of functional changes in late-onset AD [117, 118]. Likewise, normally aged rodents do not fully recapitulate the cognitive heterogeneity and neurodegeneration observed in humans

[119]. Therefore, direct extrapolation of the reviewed findings on microglia in rodent brains requires extreme caution.

2.4. Limitations and further considerations

Although considerable evidence points towards a robust association between aberrant microglia functioning and age-related cognitive deficits, some human and animal studies have reported conflicting results. For instance, several PET-imaging studies failed to find differences in microglial activation between MCI and non-demented subjects [120, 121]. Further, some post-mortem gene expression studies reported higher expression of immunity-related transcripts in the brains of cognitively-intact elderly subjects [120, 121]. Similarly, transgenic mice lacking a functional subset of microglia receptors known to trigger inflammation (i.e. TLR-2) maintain impaired cognitive functions across multiple behavioral paradigms, while partial restoration of the same receptor rescued such cognitive capacities [122]. In addition, a recent GWAS study in humans reported a positive association between higher polygenic scores for IL-1β and hippocampal volume, which is counterintuitive given the detrimental effects of pro-inflammatory cytokines on neuronal systems [123]; however, it should be noted that such an association may be dependent on age, given that such results were determined from two independent samples (young and older participants). Despite these reports, current evidence remains somewhat inconclusive to sufficiently discriminate between the degree of microglia activation that is necessary to combat the age-dependent accumulation of cytotoxic substrates, and the persistent aberration in microglia functioning as well as subsequent neuroinflammation that is associated with neurodegeneration and cognitive decline.

Along with such considerations, potential alternative mechanisms leading to chronic inflammation in CNS must be considered. Indeed, circulating monocytes are capable of infiltrating the CNS and consequently contributing to a state of chronic inflammation that may exacerbate neuronal damage [124–126]. In addition, the activation of peripheral immune mechanisms can generate inflammatory mediators (e.g. cytokines) that are capable of directly communicating with resident microglia in the brain, thereby lowering the ensuing threshold for their activation and driving subsequent inflammation [127, 128]. Such hypotheses are particularly plausible provided that the blood brain barrier is known to become compromised with age, while peripheral inflammation is known to positively correlate with age [129, 130]. It should also be noted that other cell types within the CNS (e.g. astrocytes, oligodendrocytes, mast cells) as well as neurons themselves can release and respond to pro-inflammatory mediators [131–133]. Although the contribution of peripheral and non-microglia mechanisms in neuroinflammation cannot be dismissed, the primary factor contributing to age-related cognitive decline and AD could still be resident microglia. This view is supported by genomic investigations that reported positive associations between cognitive decline and a number of genes implicated microglia functioning (e.g. CD33, TREM2, CR1), rather than genomic markers of peripheral immunity or other cell-specific immune processes [94, 97, 99]. Therefore, it must be acknowledged that a dysregulated immune response emanating from the periphery and/or non-microglia cells (e.g. astrocytes) may either exacerbate microglia-induced inflammation or contribute to neuroinflammation via mechanisms independent of microglia.

3. Modifiable Life Factors

3.1. Diet and cognition

Growing evidence indicates that a healthy diet is crucial for maintaining overall brain health and cognitive functioning in elderly subjects, while unhealthy dietary habits are associated with deleterious effects of cognition [134–136]. Recent longitudinal and observational cohort studies have focused on the beneficial cognitive effects of the Mediterranean diet (MeDi), which is characterized by the consumption of fruits, vegetables, whole grains, olive oil, fish and nuts. Elderly individuals of Hellenic origin that adherently followed MeDi (self-reported measures) exhibited improved performance across a range of cognitive measures, including visuospatial perception, executive functioning and working memory, as well as lower rates of dementia, in comparison to elderly subjects with lower adherence to this diet [137, 138]. Given the robust association between cardiovascular disorders and cognitive decline, researchers have also found that aged individuals who followed the DASH (Dietary Approach to Stop Hypertension) diet (i.e. consuming MeDi but with a higher intake of dairy products and lower intake of saturated fats) maintain slower rates of global cognitive decline [139, 140]. Similarly, elderly subjects who followed the MIND (Mediterranean-DASH diet Intervention for Neurodegeneration Delay) diet, which is a modified version of MeDi that includes high intake of green leafy vegetables and berries, subsequently displayed significantly enhanced cognitive capacities and reduced risk of cognitive impairments [141, 142]. Conversely, an unhealthy diet (e.g. saturated fats, red meat, refined sugars) is a risk factor for cognitive decline [143–145]. In addition, the intake of specific micronutrients common in healthy diets, such as polyphenols and polyunsaturated fatty acids (PUFAs), are suggested to benefit cognitive capacities in aged subjects [146–153]. A graphic outlining different types of diets that are associated with improved cognitive functions among the elderly in prospective cohort studies is illustrated in Figure 2.

Similar to human studies, animal investigations have amassed a growing body of evidence indicating the benefits of healthy nutrition on cognition in aging. Aged rodents exposed to constituents commonly found in healthy dietary regimens, particularly those that contain high levels of polyphenolic flavonoids (e.g. blueberries) or natural polyphenols such as curcumin, display enhanced performance across a number of behavioral tasks, including object recognition and spatial working memory tests [154–164]. In addition to polyphenols, other organic compounds that are found in healthy diets, such as PUFAs, have also been shown to afford benefits to age-induced cognitive detriments [165]. For instance, aged mice supplemented with omega-3s over the course of two months subsequently exhibit improved associative learning, object recognition and spatial memory [166–168]. The most conclusive evidence yet for the resiliency to cognitive decline afforded by specific micronutrients comes from an investigation that applied a series of multi-nutritional diets in aged animals over the course of 4 months; here, subjects were assigned to one of eight dietary conditions, each with specified concentrations of nutrients commonly found in the dietary regimens used in human studies. The condition with the highest quantity of such nutrients (i.e. citicoline, Vitamins B9 and E, PUFAs, and polyphenol), not only improved associative learning performance compared to other treatment groups, but resulted in performance equivalent to their younger control counterparts [169].

The implementation of modified nutritional programs and micronutrient supplementations are increasingly recognized as potential non-pharmacological strategy to prevent or delay the progression of cognitive decline in the elderly [170, 171]. Indeed, growing bodies of data indicate nutritional interventions can result in cognitive benefits for the elderly [180–196]. The cognitive effects of some of these intervention studies are summarized in Table 3. However, it should be noted that several dietary intervention studies reported either no significant improvement or limited cognitive benefit [172–177]. These inconsistencies may be due to substantial methodological variation across studies designs (e.g. intervention type, dosages, treatment time), cultural differences and eating habits, and other sources of variation between populations that ultimately render it difficult to determine the precise dietary treatments necessary to induce cognitive benefits. For instance, some data suggest positive effects are induced after extended modifications (i.e. > 6 months), while others argue that acute exposure (i.e. < 6 months) is sufficient [178, 179]. In addition, many investigations fail to adequately control for pre-existing metabolic conditions, baseline nutritional intake, and non-intervention eating habits during the course of study. Furthermore, the role of contemporary patterns in food consumption, such as non-GMO, organic, and other alternative eating practices (e.g. vegetarian, vegan) and diets (e.g. Atkins, Paleo, Keto) have not been properly accounted for in some of these investigations. Future investigations are encouraged to adopt more reliable and valid study designs in order to determine the effectiveness of nutritional interventions on cognition in aging and age-related cognitive disorders.

3.2. Diet and age-related cognitive decline: contributions of microglia

Evidence from studies in rodents suggests that increased cognitive decline linked to unhealthy nutrition might be mediated by dysregulated microglia. Investigations utilizing both adult and aged rodents have demonstrated that exposure to diets with a high proportion of saturated fats and cholesterol subsequently causes increased neuroinflammation and microglial activation throughout the CNS, which is accompanied by decreased performance across a multitude of memory tasks [197–203]. Indeed, the depletion of microglia in rodent models inhibits neuronal stress responses, the recruitment of immune cells from the periphery and neuroinflammation otherwise induced by high-fat diets [204, 205]. Similarly, mouse models of hypercholesterolemia demonstrate significantly impaired spatial and working memory capacities, in conjunction with enhanced neuroinflammation, Aβ accumulation and microglia activation [203, 206, 207].

Consistent with such findings, a growing body of evidence suggests the resiliency to cognitive decline afforded by healthy dietary regimens might be exerted through those mechanisms that suppress aberrant microglial functioning (Figure 3). In aged rodents that exhibit impairments across various measures of cognitive performance, polyphenol supplementation (naturally found in chocolate, red wine, and turmeric, as well as other foods) not only improved performance in these subjects, but also ameliorated microgliosis and reduced the levels of pro-inflammatory cytokines in the brain [161, 208–210]. Similar results were also obtained in transgenic AD mice that otherwise maintained elevated neuroinflammatory profiles and illustrated profound deficits in hippocampal dependent paradigms [112, 161, 208–210].

In addition to polyphenols, the dietary application of PUFAs (found in oily fish and many nuts/seeds) has been shown to mitigate cognitive decline, potentially through the inhibition of those mechanisms that perpetuate the prolonged activation of microglia. In aged (18 month old) mice, the application of a 4-month multinutrient diet with high concentrations of PUFAs subsequently mitigated neuroinflammation in the hippocampus and preserved performance in an associative learning task, in comparison to aged animals given a control diet with less micronutrients [169]. Note that mice typically live about 22–24 months, so this intervention was approximately $1/6^{th}$ of their life; an equivalent intervention in humans would be about 13 years, based on a life expectancy of 80 years. Importantly, even limited PUFA supplementation (i.e. 2 months) in aged rodents resulted in a similarly attenuated neuroinflammatory state compared to aged-matched controls (e.g. decreased microglia activation, pro-inflammatory cytokine expression), and beneficial effects on measures of spatial memory [211, 212]. Along with observations employing age induced cognitive decline and neuroinflammation, investigations employing transgenic models have illustrated that exposure to increased PUFAs can afford resiliency across multiple cognitive domains, in conjunction with blunted neuroinflammation, including decreased levels of nuclear factor κB (NFκB; a transcription factor that enhances the expression of various pro-inflammatory genes) [213, 214].

The benefits afforded by healthy dietary interventions might also be mediated through those processes that accelerate microglia senescence, such as oxidative stress. Specifically, polyphenols are potent inhibitors of ROS [215, 216]. Indeed, resveratrol treatment has been shown to preserve memory function by reducing ROS and protecting hippocampal neurons in a rat model of AD [217]. Consistent with the effects of polyphenols, PUFAs have been shown to improve cognitive capacities in AD rat models through the reduction in ROS concentrations across multiple brain regions, including those implicated in attentional and memory processes [218, 219].

Although evidence is lacking from human studies to link the beneficial effects of healthy diets directly to the suppression of microglia activation, certain nutritional interventions have been found to exert generalized effects on inflammation. For instance, amongst a cohort of older adults who adhered to 3-month MeDi supplemented with either olive oils or nuts, reduced plasma levels of pro-inflammatory cytokines were observed as compared to the control diet (e.g. TNF-α: MeDi+olive oil, 95% CI −2.7, −1.1, $p = 0.006$; IFN-γ: MeDi+nuts, 95% CI −10.0, −0.6, $p = 0.03$) at 5 years follow up [220, 221]. Likewise, reduced circulating inflammatory biomarkers and oxidative stress have been reported in middle-aged and older adults who maintained fish oil and omega-3s supplementation [222, 223]. Indeed, it has been suggested that systemic inflammation is itself a moderator between the effects of diet and cognition [224]. In light of these findings, as well as the direct association between systemic inflammation and neuroinflammation, it is possible that healthy dietary supplements may have the potential to exert cognitive benefits by attenuating systemic inflammation, which can subsequently suppress aberrant microglia-mediated neuroinflammation in aging. However, further research is needed to demonstrate the validity of such a hypothesis.

3.3. Exercise and cognitive aging

Increasing frequency and intensity of physical activity has been shown to predict proportional decreases in the probability and degree of age-related cognitive impairments. For example, aged individuals that engaged in high levels of physical activity for several years had reduced risks for AD and other types of dementia, as compared to age-matched control participants that adopted a sedentary lifestyle with no exercise [225–229]. Along with combating cognitive decline in aging, evidence also suggests that physical activity interventions can in fact boost cognitive performance amongst the elderly (Table 4). For instance, healthy aged subjects enrolled in a 3 month aerobic training regimen (3 times/ week, 60 min/day) demonstrated significantly improved executive functions compared to age matched control subjects [230]. Similarly, exercising on a treadmill, stationary bicycle or elliptical trainer over 6 months (4 days/week, 60 minutes/day) resulted in improved performance across a variety of executive and memory functions in aged individuals diagnosed with MCI [231]. Likewise, several other studies that implemented aerobic training programs reported similar results [232–235]. Along with aerobic fitness, data also suggest that regimens of resistance training (i.e. anaerobic exercises, such as strength training) can enhance executive functioning in normal elderly individuals, and stabilize cognitive capacities in people with MCI [236–242].

Similar to patterns observed in human studies, forced or voluntary physical activity (e.g. running on a treadmill) initiated in rodents either in adulthood or in middle age and maintained until old age can reverse age-related impairments across various measures of cognitive performance [243–246]. Moreover, rodents exposed to physical activity of mild intensity and limited duration during old age alone also exhibit improved hippocampus-dependent memory capacities in comparison to sedentary aged animals [247–252]. Likewise, in transgenic animal models of AD, treadmill exercise has been shown to alleviate decline in spatial learning and memory [247–250]. Interestingly, in parallel to results obtained from human studies, preclinical investigations are also beginning to demonstrate the cognitive benefits afforded by anaerobic exercise [253, 254].

Although the implementation of exercise regimens is increasingly recognized as a therapeutic option to combat cognitive decline in aging, it is noteworthy that some investigations do not illustrate significant improvements in cognitive capacities following increased physical activity [255–258]. Substantial variation in the methodology and study design (e.g. control conditions, intervention type, duration) across experimental settings warrants consideration in interpreting such findings. For instance, some investigations indeed suggest slowed cognitive decline in response to increased aerobic activity, but these results can be masked by adherence to exercise interventions or baseline cognitive predispositions (e.g. MCI vs amnesic MCI) [259–262]. In addition, the presently available data are lacking consistency in exercise type (i.e. aerobic vs. restraint), modality (e.g. walking vs. running), as well as the nature of control conditions (e.g. sedentary vs. stretching). Furthermore, given the subjective nature of physical activity, studies have largely failed to implement concurrent objective assessments of physical expenditure, such as a heart rate monitor or VO2 max. Future investigations should implement amended procedures

in order to further demonstrate a reliable and valid association between elevated physical activity and the inhibition of cognitive decline.

3.4. Can exercise protect against age-related cognitive decline via microglial-inflammatory mechanisms?

The increased risk for age-related cognitive impairments associated with inadequate levels of physical activity could be a consequence of aberrant microglia activation and an unimpeded CNS inflammatory state. For instance, sedentary rats have elevated levels of pro-inflammatory cytokines (i.e. IL1-β, IL1–6) across multiple regions of the brain, including the hippocampus, in comparison to physical active counterparts [263, 264]. Conversely, engagement in aerobic exercise in aged rodents has been associated with reduced activation of microglia and increased levels of anti-inflammatory cytokines (e.g. IL-10) [265, 266]. Likewise, human studies have consistently shown that physical activity exerts a positive modulatory effect on peripheral inflammation (e.g. as measured by peripheral blood draw) by reducing pro-inflammatory cytokines and increasing anti-inflammatory cytokines [267–269]. In addition, functional magnetic resonance imaging (fMRI) studies conducted in older adults that received 4–12 months of aerobic exercise interventions illustrated increased functional connectivity in brain regions that are critical for executive and mnemonic functions [270, 271]. It remains unknown whether the effects of aerobic exercise observed in these studies are directly linked to reduced neuroinflammation and improved microglia function or if they are due to changes in brain perfusion (e.g. due to increased extension of capillary beds).

The purported relationship between the benefits of exercise on cognitive aging and microglia is derived from investigations which demonstrate that physical activity might counteract those mechanisms associated with chronic microglial activation and neuroinflammation in aging. For instance, age-related decline in aversive memory using the passive avoidance task, and increased hippocampal levels of inflammatory mediators, such as TNF-α, IL1-β and NFκB, have been observed in sedentary rats; however such age-related differences were absent in rats that underwent forced exercise [248]. Furthermore, this study reported a significant association between the levels of inflammatory cytokines and performance. Complementary to such findings, voluntary running in aged subjects was also shown to attenuate peripheral infection-induced neuroinflammatory responses and microglial sensitization, as well as impairments in contextual fear memory [252]. Likewise, compared to sedentary controls, 3-weeks of running in transgenic AD mice not only improved performance in the radial arm maze, but also reduced the levels of neurotoxic cytokines and enhanced Aβ clearance in the brain [272, 273]. In elderly humans, being sedentary and having higher levels of the pro-inflammatory cytokine IL-12p40 has been associated with lower volumes of the prefrontal cortex and hippocampus, as well as accelerated decline in MMSE, in comparison to those subjects who were physically active and those who had lower cytokine levels [274]. Another clinical study reported increased levels of soluble TREM2 (important for normal microglia function) in the cerebrospinal fluid (CSF) of AD subjects who received moderate to high intensity aerobic exercise interventions for 16-weeks as compared to non-exercise controls [275]. Together, these studies suggest that physical activity has the capacity to render some individuals more resilient to the detrimental effects

of age and age-related neuropathology, which could presumably be linked to reduced inflammation and preserved microglial function.

Although the precise molecular mechanisms by which exercise enables homeostatic microglia to exert neuroprotection and benefit cognitive capacities in aging remain unclear, data demonstrating its reliable modulation of oxidative stress and trophic factors, such as BDNF, warrant due consideration. For instance, in aged rodents and transgenic AD mouse models, exercise has been shown to alleviate ROS generation and increase the activity of antioxidant enzymes in the brain, which was in turn associated with enhanced memory performance [244, 276]. As microglia reactivity can be exacerbated by ROS in aging, it is plausible that by reducing oxidative stress, physical activity may mitigate the perpetuation of prolonged microglial activation and subsequent elevation in pro-inflammatory cytokines. In regard to trophic factors, ample evidence from rodent models demonstrate that physical activity increases the expression of BDNF, which is known for its enhancement of neurogenesis, synaptic plasticity, and learning and memory [277–282]. Likewise, human studies report elevated levels of blood serum BDNF following physical activity, and this increase correlates with improved cognitive performance, including measures of visuospatial attention and working memory in both young and older adults [283–285]. As microglia derived BDNF is critical for maintaining homeostatic neuronal functioning (e.g. learning-induced spine formation), while decreased BDNF secretion by activated microglia can accompany aging, these studies support the view that the beneficial effects of exercise on cognition could be associated with BDNF [286, 287]. Further studies are warranted to validate the effects of physical activity on the dynamic interaction between BDNF and aberrant microglia reactivity, and to test the hypothesis that the beneficial effects of exercise on cognition in aging could be linked to BDNF-mediated reduction in microglial activation/inflammation as well as enhanced neuronal plasticity.

3.5. Cognitive engagement and age-related cognitive decline

Engagement in cognitively stimulating activities, including lifestyle enrichment, is increasingly considered a reliable strategy to protect against cognitive decline in the elderly [346–360]. This view is based on a construct termed “cognitive reserve”, which posits that lifetime cognitive engagement and other environmental activities can enable the brain to compensate for age-related alterations in neural functioning, either by utilizing pre-existing neural networks more efficiently or engaging alternative networks that can offset deficiencies in existing networks [288, 289]. Thus, individuals with higher cognitive reserve are suggested to cope more efficiently with compromised neuronal functioning in aging, as opposed to individuals with low levels of reserve. In regard to its precise definition, it is notable that researchers have made a distinction between the concepts of cognitive reserve, compensation and maintenance [290, 291]. Specifically, reserve involves increases in neural resources to protect cognitive functions prior to the onset of age-related cognitive decline, while maintenance refers to the enhancement of alternative neural networks during aging itself, and compensation relates to changes in neural resources that occur during short-term increases in cognitive demands. Together, these concepts are applied to enhance the understanding of individual differences in cognitive resilience during aging and to develop approaches that prevent age-related dementia [292].

Epidemiological studies demonstrate that high levels of education, cognitively-demanding occupations, and social engagement correlate with lower incidence of dementia and AD in the elderly [293–295]. Furthermore, evidence from population-based studies have illustrated that elevated levels of routine cognitive activities (i.e. more active tasks, such as reading, playing chess, vs. more passive tasks, such as listening to the radio, watching television) can render individuals more resilient to cognitive decline [296–300]. Increased engagement in these activities has not only been associated with reduced risk of AD, but also elevated performance on a variety of cognitive measures, including global cognition, working memory and perceptual speed in the elderly subjects. Notably, the benefits of cognitively stimulating activities persist even after controlling for level of education as well as known measures of neuropathology [301–305].

Along with such observations, accumulating evidence also suggests that cognitive training given as a behavioral intervention can afford resiliency to age-related cognitive detriments. For instance, limited cognitive training (i.e. 60–75min/10 trainings/6 weeks) via domain-specific tasks subsequently preserves functional capacities across a number of cognitive measures (e.g. executive processing, immediate recall), both in extended (i.e. 2 years) as well as long term (i.e. 10 years) follow up assessments in older adults [306, 307]. Similar benefits were found when measures were assessed more proximal to the intervention (i.e. 2–4 months), regardless if the intervention was communal based (e.g. guided group activities) or employed individual training (e.g. structured neuropsychological training) [308–310]. Moreover, not only do healthy aged individuals and those subjected to age-related detriments benefit from such interventions, but the degree of benefit appears to be proportional to the degree of cognitive training [311, 312]. In addition, some evidence suggests that individuals with the lowest indices of cognitive activity display the greatest resiliency to cognitive detriments following such training regimens [310, 313]. Interestingly, in regard to the increasing implementation of computerized training procedures, not only does evidence indicate that such programs offer similar resiliency to cognitive decline, but they are more cost effective, domain specific and easily accessible compared to traditional behavioral therapies [314–317].

In addition to human investigations, environmental enrichment (EE) and similar modifiable paradigms have allowed researchers to model and assess the effects of cognitive interventions in animal models. Compared to a standard housing environment (i.e. food and water only), EE induces cognitive stimulation through the introduction of novel objects, increases in social interactions or physical contact with conspecifics, as well as more domain specific modifications including cognitive tasks themselves (e.g. maze exploration) [318, 319]. As such, exposure to EE for limited periods (i.e. 3 hours/day for 2 weeks), moderate (i.e. 6 weeks), extended periods (i.e. 10 weeks) or throughout life is capable of preserving memory capacities in aged animals, such that performance in various behavioral tasks is significantly improved in comparison to age matched controls [320–325]. Moreover, rats exposed to enriching environments throughout life not only displayed improved spatial learning performance at all ages, but also had reduced age-related deficits in attention, as compared to those animals that were exposed to standard/impoverished environments [326]. The benefits of cognitive engagement in rodents are not solely limited to normal age-related differences in cognition, but also extended to models of age-related pathologies. For

instance, previous work from our laboratory indicated that the disruption of nerve growth factor receptor signaling implicated in AD produced robust impairments in attentional capacities in aged rats; however, such disruption in attentional functions was not observed in aging rats that remained cognitively engaged throughout life [327–329]. Similarly, transgenic AD mice maintained for extended periods of time (i.e. > 4 months) in a cognitively stimulating environment, (i.e. initiated during adolescence, adulthood or in old age), subsequently display significantly improved performance across multiple cognitive domains once in old age, including working memory and spatial recall [330–332]. In interpreting these findings from rodents, it should be noted that baseline conditions in standard housing environments contain minimal levels of stimulation; given that humans inherently maintain more enriched environments during normal daily functioning, the effects of enrichment in rodents may be exacerbated when compared to clinical samples.

Although many studies have demonstrated that elevated cognitive activity protects against age-related cognitive decline, some studies do not report this effect [333–337]. Similar to studies of diet and exercise, variation in methodologies, experimental design, study duration, and control procedures present interpretational challenges that warrant further consideration. For example, while some intervention therapies indeed report improved performance in certain cognitive domains (e.g. working memory), such benefits may not transfer to other cognitive processes (e.g. attention) or may be dependent on a specific cognitive task, despite assessment of the same cognitive domain [338–342]. In addition, some results suggest the positive effects of cognitive stimulation may be dependent on the context in which the stimulation is applied; specifically, although individualized cognitive training sessions with a care provider can result in improved capacities, robotic or self-guided application methods may prove to be more efficacious [343, 344]. Furthermore, it has been suggested that the beneficial effects of cognitive engagement might be temporary and mitigated over time [345]. Therefore, it is possible that continued cognitive enrichment outside of intervention techniques may be necessary to stabilize cognitive benefits across the lifespan.

3.6. Cognitive enrichment, neuroinflammation and microglia

The evidence that engagement in cognitively stimulating activities might exert beneficial effects in aging and AD by mitigating aberrant microglial functioning and neuroinflammation has come primarily from animal studies. In transgenic AD mouse models which otherwise display profound CNS inflammation (i.e. increased pro-inflammatory cytokines) and dystrophic microglia (i.e. ameboid morphology, decreased branching), EE resulted in significantly blunted inflammatory signaling and the preservation of healthy microglia phenotypes [351]. Likewise, in a transcriptomic study conducted in rats, we recently reported that the elevated expression of transcripts associated with innate immune pathways and neuroinflammation in the prefrontal cortex of aged rats was ameliorated by cognitive engagement [352]. Moreover, we reported age-related decrements in attentional capacities associated with increased transcription of genes linked to exosomes; such extracellular vesicles can be released by different brain cells, including microglia, and play a key role in regulating intercellular communication as well as neuroinflammation [353]. Other investigations employing EE in rat models have reported significant reductions

amongst a variety of pro-inflammatory mediators, including IL-1β and TNF-α, as well as elevations in neurotropic factors such as BDNF [354, 355].

Several studies have indicated that the beneficial effects of EE on cognition and neuroinflammation could be linked to reduction in oxidative stress. For instance, EE reduced ROS and elevated antioxidant defense mechanisms in those brain regions implicated in higher-order cognitive processes, such as the hippocampus and cortex, in normal rats [356, 357]. Likewise, in both aged-impaired rats and transgenic AD mice that otherwise display cognitive impairments, exposure to EE for several weeks downregulated pro-inflammatory and pro-oxidative mediators, reduced the expression of pro-apoptotic markers, and enhanced the levels of antioxidant enzymes while reversing memory deficits [356–359]. As discussed earlier, ROS overproduction in aging and age-related cognitive disorders could perpetuate tonic microglia activation and neuroinflammation. Therefore, it is possible that EE could improve cognitive capacities in pathological aging by attenuating microglia dystrophy via reducing oxidative stress.

While the beneficial effects of cognitive stimulation and EE on cognitive aging is apparent, and the existing evidence from rodent studies provides some support for the involvement of microglia and neuroinflammation as a possible mechanism, no human studies have directly tested such a hypothesis. This raises the question of whether microglial neuroinflammatory mechanisms could be translated to humans and explain the resiliency in aging that is afforded by cognitive enrichment. In light of this gap in knowledge, it is worth noting a number of fMRI studies have reported that healthy older adults or people with MCI/AD with higher education levels (a proxy for cognitive reserve) maintain higher functional connectivity, more efficient recruitment of brain networks, and/or higher activation of compensatory networks, in comparison to those with lower education [360–363]. Moreover, MCI/AD diagnosed individuals with higher cognitive reserve were able to cope with a greater neuropathological burden as compared to patients with lower cognitive reserve [364]. Together, these studies support the view that environmental/cognitive enrichment facilitates neural systems/circuits plasticity, and has the potential to slow age-related cognitive decline as well as the progression of cognitive deterioration in AD. Whether the enhancement of neural network efficiency/plasticity associated with cognitive enrichment is directly linked to reduction in microglia dystrophy, enhanced phagocytic capacity, and reduced neuroinflammation requires further elucidation.

4. Proposed model: Microglia function as a critical determinant of individual variation in cognitive aging

Based on the above discussion, we propose a hypothetical mechanistic model that embodies the state of microglia as a primary determinant of individual variation in cognitive aging, with MLFs as a possible moderator of this relationship (Figure 4). Stable dynamics between the homeostatic and reactive state of microglia is associated with elevated anti-inflammatory response, balanced release of pro-inflammatory cytokines, efficient phagocytosis, and enhanced release of trophic factors to support neuroplasticity. Together, these processes ensure removal of cellular debris and cytotoxic substrates from the extracellular space,

promote CNS homeostasis and therefore preserve neural circuits that support higher cognitive functions. With advancing age, the morphology and functionality of microglia progressively switches from a stable functional state to an aberrant dystrophic/senescent state. Although aging alone is associated with dystrophic microglia and their aberrant functioning to some extent, environmental (e.g. sedentary lifestyles) and genetic risk factors, infection and associated systemic inflammation, as well as neuropathology, can further exacerbate microglia malfunctioning. Such a transition to a dystrophic phenotype can result in persistent neuroinflammation, decreased release of anti-inflammatory cytokines, heightened oxidative stress and impaired phagocytic function. In turn, this may lead to a deleterious microenvironment with the accumulation of cytotoxic substrates and compromised neuronal functioning that contributes to cognitive decline. By controlling systemic inflammation, oxidative stress (i.e. lowering ROS, boosting antioxidant defense mechanisms), and elevating the levels of neurotrophins (such as BDNF), modifiable life factors (healthy diet, physical exercise, and cognitive enrichment) inhibit the transition of stable (homeostatic/reactive) microglia to dystrophic microglia, and induce resiliency to cognitive decline in aging. As indicated earlier, our model does not negate the involvement of other glial cells (i.e. astrocytes and oligodendrocytes) which may also play an important role in maintaining CNS homeostasis via interactions with microglia.

Although we acknowledge that there is a clear dichotomy between normal and pathological cognitive aging, and that there could be heterogeneity in cognitive performance within each state, our model considers cognitive variation in the elderly as a continuum between the two dimensions. On one side of the spectrum there could be elderly individuals who perform at par with middle aged subjects and/or young adults (e.g. Super Agers) or those who carry Aβ burden but show no signs of dementia [365–368]. These individuals are categorized as *cognitive resilient* based on our model. Conversely, on the other side of the spectrum are other individuals who develop MCI, AD and other forms of age-related dementia. Considering aging as a natural process capable of inducing some microglia senescence/dystrophy and related inflammaging, we hypothesize that normal age-related cognitive variation lies between these two extremes, and is dependent upon the transition of microglia from a stable to dystrophic state. Future clinical studies are warranted to test specific hypotheses concerning the causal relationship between microglia senescence and age-related cognitive decline, as well as the moderation of this relationship by MLFs.

5. Conclusions and future directions

Although there are clear generalities and common principles observed in cognitive aging, what is perhaps most compelling about age-related cognitive change is its variability. Given that advancing age remains the most prominent risk factor for cognitive decline, mechanisms that account for such variability and predict resilience to cognitive detriments in aging are becoming increasingly relevant. Moreover, with the percentage of elderly individuals continuing to increase globally and the scarcity of effective pharmacotherapies that limit the progression of MCI/AD as well as other forms of age-related dementia, it is critically important to develop interventions that target such mechanisms to attenuate cognitive decline. This review highlights many of the studies in both animals and humans that help to bridge the gap in our understanding of the contributions from microglia in regulating

neuroinflammation and maintaining neurocognitive processes in aging. Moreover, we present a hypothetical mechanistic model that postulates microglia senescence/dystrophy as a primary predictor of an individual's risk for age-related cognitive impairments; here, an individual's cognitive resiliency afforded by MLFs might be mediated by mitigating the age-related transition of stable (homeostatic/reactive) microglia phenotype to a dystrophic/aberrant phenotype, and consequent suppression of neuroinflammation.

While the conceptual framework for the proposed model predominantly relies on investigations from animal research, correlational evidence from human PET-imaging studies and investigations of post-mortem brain tissues also supports the association between microglia dysfunction and cognitive decline. A major challenge with human studies is the lack of biomarkers that could provide a valid index of senescent/dystrophic microglia. As noted earlier, although PET ligands that bind to TSPO provide important information concerning microglia activation in the brains of clinical subjects, this marker cannot discern between different microglia phenotypes (i.e. hyperactivated, primed, dystrophic). Furthermore, these ligands are not always specific to microglia and can bind to other cells under certain conditions, such as macrophages and astrocytes. The practicality of PET imaging must also be considered, given that many research centers do not maintain a PET scanner, and the cost of PET scanning can be prohibitive (e.g. in Philadelphia it costs around $3000/subject). Unfortunately, the most readily available technique used to measure inflammatory biomarkers utilizes blood, but this cannot specifically predict microglia senescence, nor can it discriminate between inflammation emanating from microglia and other immune cells (e.g. macrophages). Indeed, the measurement of peripheral biomarkers represents a relatively crude approach as it does not provide reliable information concerning the neural origin of an inflammatory response. One technique that should not be overlooked is the measurement of biomarkers in CSF (e.g. from lumbar puncture), which has the potential to reflect neuroinflammatory changes in the brain. This technique is cheaper than PET imaging and provides stronger evidence than that gleaned from a peripheral blood draw. Further research is needed to develop more specific PET ligands, MRI pulse sequences/contrast agents, and peripheral biomarkers to examine microglia function in cognitive aging and the potential effect of MLFs on this relationship. Given the recent advancements in molecular approaches, such as next-generation RNA sequencing that has allowed researchers to identify gene clusters specific to microglia [369], we also encourage more investigations to determine whether alterations in microglia-specific genes are linked to cognitive variation in aging.

Recent evidence suggests that systemic inflammatory and metabolic changes that begin during young age predict poor outcome in older adults [370]; moreover, such alterations have been linked to impaired microglia function [371, 372]. Similarly, it has been suggested that environmental factors which perturb the physiological functions of microglia during early development may have long term detrimental consequences on behavior [373]. Indeed, environmental factors can substantially influence microglia gene expression, which may contribute to their differential responses during aging [374]. For instance, studies in rodents indicate a balanced diet or aerobic exercise can mitigate the upregulated expression of proinflammatory processes that are otherwise observed in response to advancing age [201, 375]. Therefore, human studies examining the relationship between microglia function and

cognitive aging should consider a life span perspective that takes into account the dynamic interplay between environmental factors and physiological functions which could impact microglia senescence/dystrophy in aging.

Although research in both animals and human subjects has provided valid evidence that MLFs can exert beneficial effects in aging and MCI/AD, there remains no direct clinical evidence demonstrating that MLFs can afford resiliency by boosting microglia function and minimizing neuroinflammation. Additionally, the benefits of MLFs likely involve non-microglia mechanisms that should be considered. For instance, GSK3β is a potent regulator of pathological peptides linked to AD (e.g. phosphorylated Tau), and data from rodent models suggest variation in MLFs (i.e. balanced diet, aerobic exercise) may inhibit the accumulation of such peptides by modulating GSK3β [376–380]. Further clinical research is needed to expand our understanding of the causal relationship between microglia functioning as well as non-microglia mechanisms induced by MLFs and behavioral outcomes in human samples. For instance, future studies should determine the optimal timing and degree of each MLF that is necessary to achieve the greatest reduction in microglia-mediated neuroinflammation and subsequent cognitive resiliency among at-risk patients using a longitudinal study design. Provided that the cognitive benefits of MLFs can vary between individuals, such studies should also address individual differences in responding to MLFs, and how corresponding variation in microglia functioning might further optimize conditions. For example, variation in microglia gene expression may determine the efficacy of a particular intervention, as suggested by existing data where individual genetic predispositions can determine the efficacy of multi-domain interventions [381]. Given the current lack of therapies that decelerate or prevent the progression of cognitive decline associated with age-related neurodegenerative disorders, MLFs could be considered as non-pharmacological interventions that improve cognitive resiliency amongst elderly subjects who possess a higher risk of developing dementia, as exemplified by the recently established Alzheimer’s Prevention Clinic [382–384].

Finally, additional research efforts are needed to delineate the biological mechanisms that decelerate microglia senescence or normalize microglia function, which could be exploited as therapeutic targets for developing neuroprotective and cognition–enhancing medications. Studies from animal models have remained critically important for providing us with a vivid understanding of the neurobiological functions of microglia in aging and AD. By better comprehending how this knowledge translates to humans, we can gain insights into the neurobiological underpinnings of cognitive variation in aging and develop more efficacious therapies. To facilitate this translation, we encourage more dynamic collaborations and crosstalk among neuroscientists, psychologists, immunologists, and clinicians.

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Abbreviations:

Aβ	amyloid β
AD	Alzheimer's Disease
BDNF	brain-derived neurotrophic factor
CD	Cluster of Differentiation
CDR	Clinical Dementia Rating
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CR1	Complement Receptor 1
DAMPs	Damage Associated Molecular Patterns
DASH	Dietary Approach to Stop Hypertension
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
EE	Environmental Enrichment
fMRI	Functional Magnetic Resonance Imaging
GWAS	Genome Wide Association Studies
IFN	Interferon
IL	Interleukin
MMSE	Mini-Mental State Exam
MCI	Mild Cognitive Impairment
MeDi	Mediterranean Diet
MRI	Magnetic Resonance Imaging
MLFs	Modifiable life factors
NFκB	Nuclear Factor nuclear factor κB
PAMPs	Pathogen Associated Molecular Patterns
PET	Positron Emission Tomography
PRRs	Pattern Recognition Receptors
PUFAs	Polyunsaturated fatty acids
ROS	Reactive Oxygen Species
SRs	Scavenger Receptors

TLRs	Toll-like receptors
TNF-α	tumor necrosis factor α
TREM2	triggering receptor expressed on myeloid cells 2
TSPO	translocator protein

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Box 1:

Glossary

Adaptive immunity (acquired immunity)

Latent immune responses that are specific to the pathogens presented. Adaptive immune cells include T and B lymphocytes, which provide long-lasting protection against pathogens.

Anti-inflammatory cytokines

Immunoregulatory molecules that counterbalance or suppress inflammation. These include IL-4, IL-6, IL-10, IL-11, IL-13, IFN-β and transforming growth factor β.

Cytokines

Signaling molecules that are primary messengers of immunity-related processes.

Dystrophic (senescent) microglia

Physiologically maladaptive microglial phenotype typically observed in the aging brain and characterized by an exaggerated pro-inflammatory response and reduced release of anti-inflammatory mediators.

Inflamm-aging (sterile inflammation)

Low-grade chronic inflammation that occurs in the absence of overt infection in aging.

Innate immunity

A first line of defense mechanism that is generic to all types of pathogens or tissue injuries. Innate immunity is characterized by a rapid inflammatory response that involves recognition of conserved molecular patterns on pathogens or damaged molecules by the immune cells.

Microglia

Primary mediators of immune responses within the CNS. These non-neuronal cells are distinct from other glial cells (e.g. astrocytes, oligodendrocytes) and maintain a variety of innate immune responses, including phagocytosis as well as cytokine production.

Neuroinflammation

A complex response to brain injury involving the activation of glial cells (primarily microglia) and release of inflammatory mediators such as cytokines and chemokines (a class of cytokines).

Pattern recognition receptors (PRRs)

Proteins present on the membranes of immune cells (e.g. microglia) that are capable of recognizing molecules frequently found in pathogens (also called Pathogen-Associated Molecular Patterns or PAMPs), or molecules that are released by damaged cells (also called Damage-Associated Molecular Patterns or DAMPs)

Phagocytosis

A process by which a cell ingests or engulfs other cells or particles.

Pro-inflammatory cytokine

A cytokine that is released from immune cells and promotes inflammation. Examples of proinflammatory cytokines include IL-1, IL-12, IL-18, IFN-γ, TNF-α etc.

Homeostatic microglia

Physiologically favorable microglial phenotype characterized by balanced pro-inflammatory and anti-inflammatory processes as well as functional benefits for neuronal viability.

Reactive oxygen species (ROS)

Unstable damage-causing oxygen-containing molecules that easily react with DNA, RNA and proteins in cells.

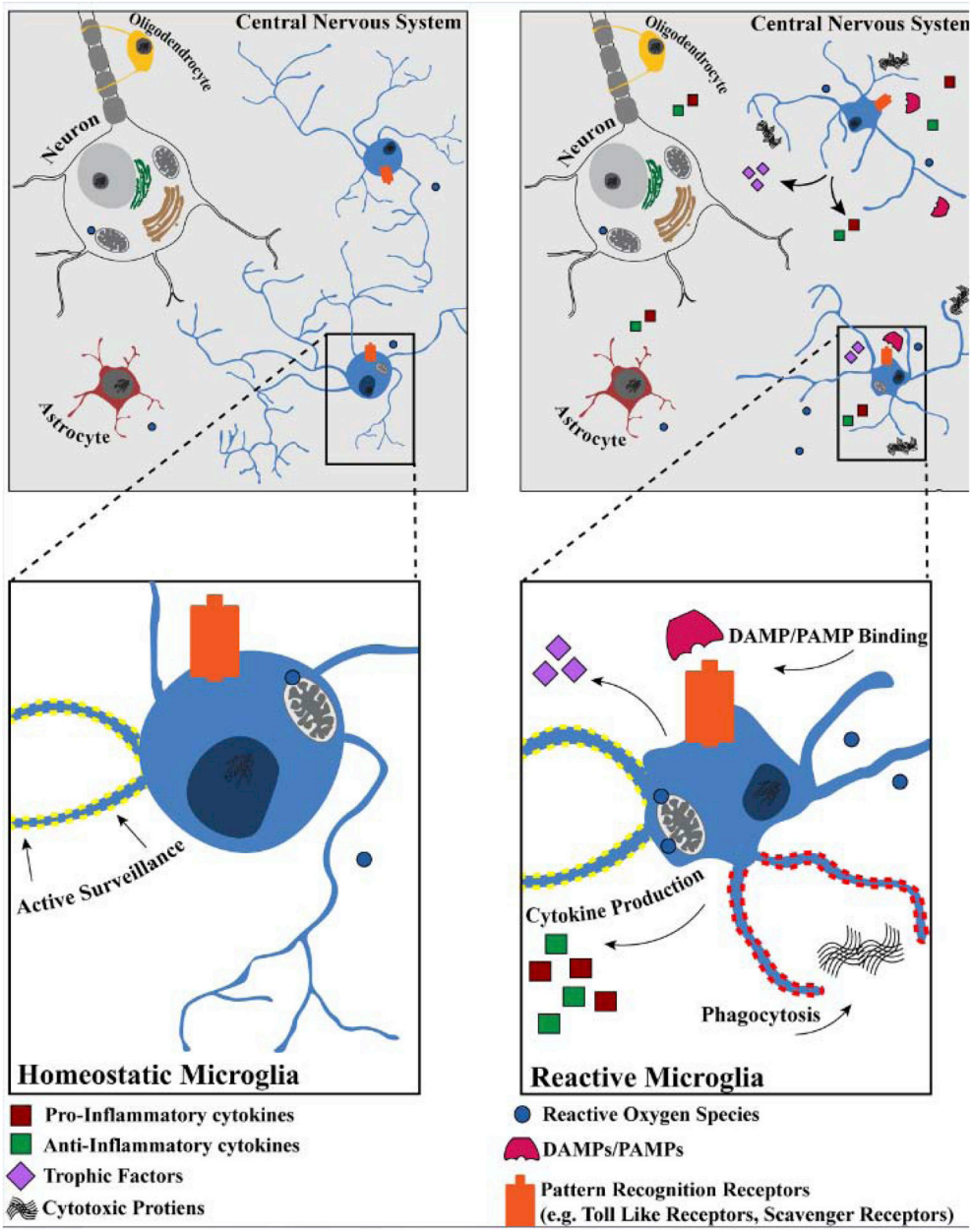

Figure 1:

Illustration depicting the functions of microglia in normal CNS. Under normal physiological conditions, microglia actively surveil their surrounding microenvironment in a homeostatic state. These cells maintain various pattern recognition receptors (e.g. toll-like receptors, scavenger receptors) that are capable of detecting aberrant molecular patterns in their microenvironment, such as those from malformed polypeptides, pathogens or other cellular debris. Following the detection of cytotoxic factors, microglia become reactive (ameboid) to remove and degrade these aberrant materials that might otherwise compromise the CNS microenvironment, while exhibiting a balanced production of both inflammatory and anti-inflammatory messengers, such as cytokines, as well as trophic factors.

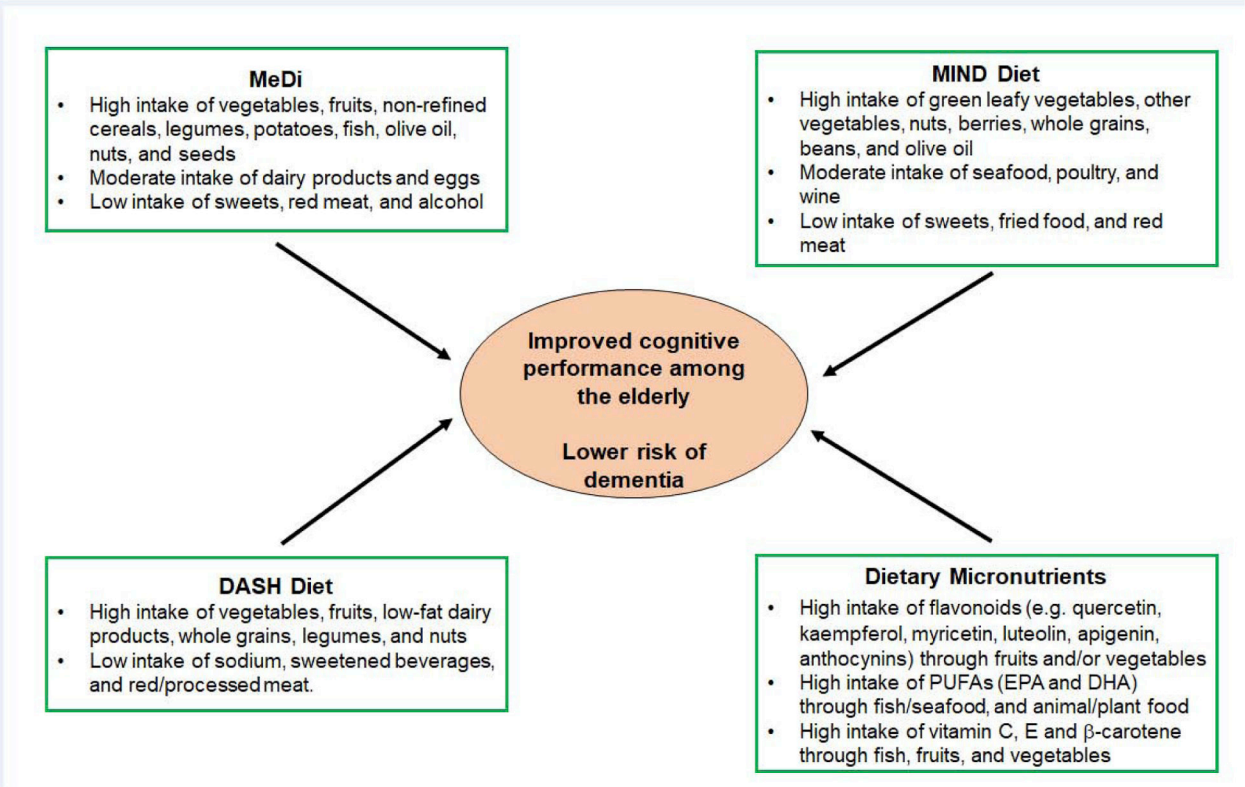

Figure 2:

Schematic depicting the composition of different diets and micronutrients used in prospective cohort studies to examine the impact of nutritional patterns on cognitive health in the elderly.

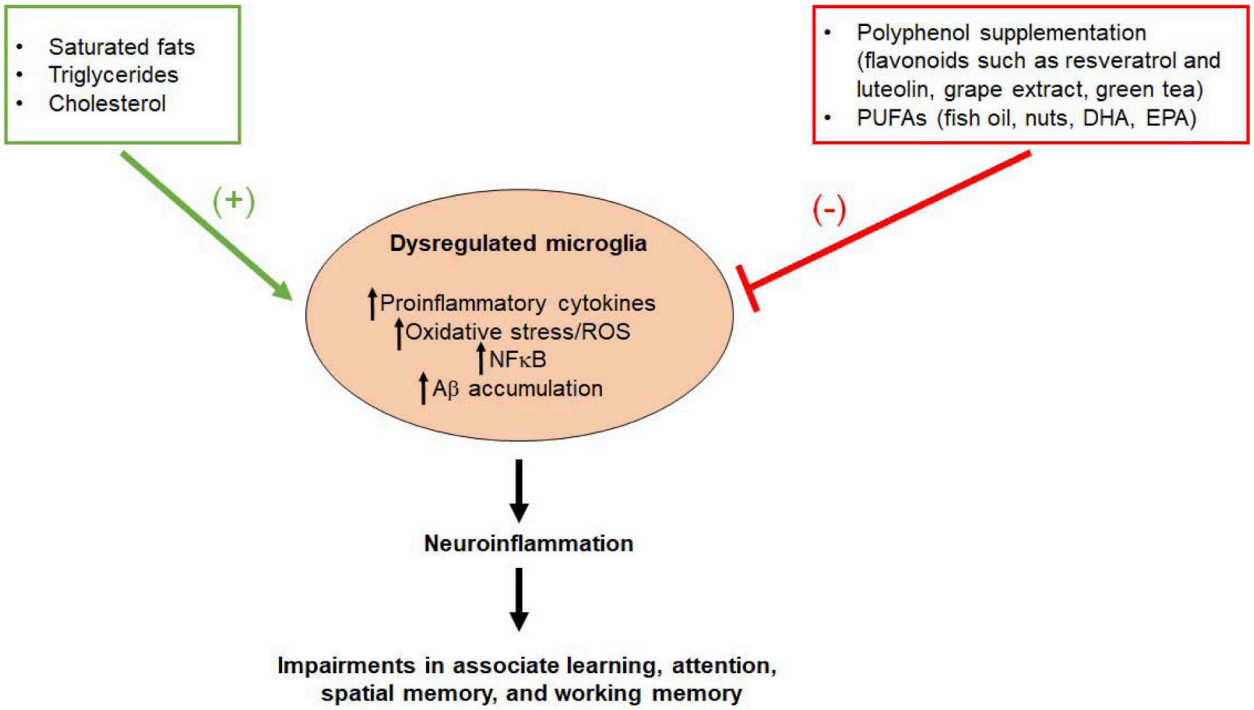

Figure 3:

Schematic summarizing the effects of dietary supplements on microglia and cognitive functioning in rodent models of aging and AD. Exposure to high-fat/high-cholesterol diets produces abnormal activation of microglia and consequent increase in neuroinflammation, thereby impairing attention and memory. Conversely, supplementation with polyphenols/PUFAs blunt this effect, and preserve cognition by suppressing proinflammatory processes as well as oxidative stress.

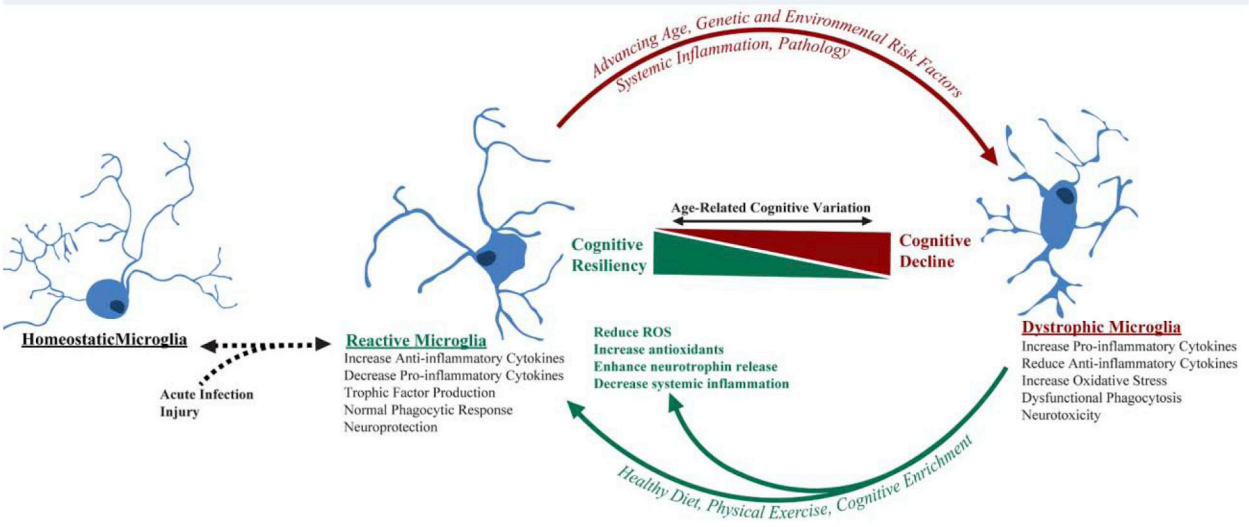

Figure 4:

Proposed model depicting microglia as a critical determinant of cognitive variation in aging. Normal dynamics between the homeostatic and the reactive state of microglia regulate CNS homeostasis by supporting neurogenesis, synaptic plasticity, reducing inflammation, and fulfilling normal phagocytic role (i.e. removing cellular debris and neurotoxic substrates in response to acute infection or injury that otherwise cause neuronal damage). Together, these processes are critical to maintain the neuronal activity which supports higher cognitive functions. Advancing age produces microglia senescence/dystrophy to some extent and this process could be exacerbated by genetic and environmental factors, systemic inflammation and pathological conditions. Dystrophic microglia result in chronic abnormalities that increase oxidative stress as well as pro-inflammatory cytokines, and compromised ability for optimal phagocytic function. This facilitates sustained neuroinflammation and neurotoxicity, thereby jeopardizing efficient recruitment of neural networks that support cognitive functions, and resulting in increased risk for age-related dementia as well as AD. By controlling oxidative stress (i.e. lowering ROS, boosting antioxidant defense mechanisms), elevating the levels of neurotrophins (such as BDNF), and reducing systemic inflammation, modifiable life factors (healthy diet, physical exercise, and cognitive enrichment) inhibit the transition of stable (homeostatic/reactive) microglia to dystrophic microglia, and induce resiliency to cognitive decline in aging.

Table 1.

Summary of human studies linking microglia activation and neuroinflammation to cognitive decline in aging and Alzheimer's Disease (AD).

Reference	Sample description (age)	Primary behavioral/ clinical assessment measure	Assessment of microglia activity, regions of interest and measurement technique
[79]	AD and NC (not specified): post-mortem	AD subjects were characterized with clinically evaluation; test battery not specified	Medial hippocampus, frontal cortex; HLA-DR IHC
[81]	AD and NC (Mean age: 88 years): post-mortem	Clinically evaluated; test battery not specified	Superior temporal cortex; CD68 IHC
[80]	AD and NC (73–103 years): post-mortem	CDR	Entorhinal cortex, hippocampus; HLA-DR IHC
[78]	AD, NC and dementia with non-AD, and unknown dementia (77–93 years) : post-mortem	MMSE	Cerebral cortex; HLA-DR, CD68, CD64 and MSR-A IHC
[82]	AD /MCI and NC (32–80 years)	MMSE, CDR	Entorhinal, temperoparietal, and cingulate cortex, and thalamus; [^{11}C]PK11195-PET
[83]	MCI/AD (53–81 years)	MMSE, ACE-R, RAVLT	Hippocampus, medial and inferior temporal cortex; [^{11}C]PK11195-PET
[84]	MCI and NC (65–73 years)	RAVLT and WAIS	Frontal, temporal, and parietal cortex; [^{11}C]PK11195-PET
[87]	AD /MCI and NC (52–79 years)	MMSE, CDR, ADAS-cog	Prefrontal cortex (dorsolateral and medial) cortex, cingulate cortex, lateral temporal cortex, parietal cortex, occipital cortex, posterior cingulate cortex, striatum, thalamus and cerebellum [^{11}C]DAA1106-PET
[85]	AD /MCI and NC (52–79 years)	NINDS-ADRDA, DSM-IV	frontal cortex, temporal cortex, parietal cortex, occipital cortex, hippocampus, amygdala and cerebellum; [^{11}C]PK11195-PET
[86]	AD /MCI and NC (62–73 years)	NINDS-ADRDA, MMSE, CDR	prefrontal cortex, temporal and parietal lobes, striatum; [^{11}C]PBR28-PET

Abbreviations: ACE-R, Addenbrooke's Cognitive Examination-Revised; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CD, Cluster of Differentiation; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; HLA-DR, Human Leukocyte Antigen – D Region, IHC, Immunohistochemistry; MMSE, Mini-Mental State Exam; MSR-A, Macrophage Scavenger Receptor A; MCI: Mild Cognitive Impairment; NINDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association test; NC=normal control; PET, Positron Emission Tomography; RAVLT, Rey Auditory Verbal Learning Test; WAIS, Wechsler Adult Intelligence Scale.

Table 2.

Summary of animal studies that linked microglia activation and neuroinflammation to cognitive decline in aging and Alzheimer's disease.

References	Subjects description (age)	Behavioral task	Microglia markers, regions of interest, and measurement technique
[110]	APP23 and APP23/TNRF1$^{-/-}$ transgenic mice (24 months)	Novel object recognition, hole-board memory task	Entorhinal cortex, hippocampus; CD11b, CD45 IHC
[112]	APP/PS1 transgenic mice with Baicalin pretreatment (14 months)	Passive avoidance, Morris water maze	Hippocampus; IBA1 immunoreactivity; IL1-β, IL-18, NLRP3 and TLR4 WB
[109]	APPPS1 and APPPS1 × Il12rb$^{-/-}$ transgenic mice (8 months)	Novel object recognition, contextual fear conditioning, Barnes maze	CD11b, CD11c, CD45 and TNFα flow cytometry; IL23, IL12, TNFα qPCR
[115]	F344xBNF1 rats with laparotomy and systemic IL-1R antagonist injection (22 months)	Contextual fear Conditioning	Hippocampus; IL1-β ELISA IL1-β, IL-6 and TNFα qPCR
[116]	C57BL/6 mice with CSF1R inhibitor treatment (3 months and 22 months)	Morris water maze	Hippocampus; IBA1, CD68, TMEM119, P2RY12 IHC
[111]	APP+PS1 bigenic mice with AAV-mediated IL-4 expression (8 months)	Radial arm water maze	Hippocampus; IL-4 ELISA IBA1 IHC
[114]	Wistar rats with intrahippocampal injection of Aβ and IFNβi treatment (3 months)	Novel object recognition	Hippocampus; IBA1 IHC IL1-β and IL-6 WB

Abbreviations: CD: cluster of differentiation; ELISA: enzyme-linked immunosorbent assay; FACS, fluorescence activated cell sorting; IBA-1, ionized calcium binding adaptor molecule 1; IHC, immunohistochemistry; IL, interleukin; NLRP3, NOD like receptor protein 3; P2RY12, purinergic receptor P2Y; qPCR, quantitative polymerase chain reaction; TLR4, toll-like receptor 4; TMEM119, transmembrane protein 119; TNFα, tumor necrosis factor α; WB, Western blotting

Table 3:

Human studies summarizing the effects of nutritional interventions on cognition in the elderly subjects.

References	Subject description, sample size, sex, age	Intervention type, dosage, frequency	Primary cognitive assessment (*p* value and/or effect size for treatments)
[195]	N = 183 (120 F, 63 M); non-demented elderly with subjective memory complaints Mean age: 76 years	Placebo PUFA supplementation (DHA: 800mg/day + EPA: 225 mg/day) 3 years	Controlled Oral Word Association Test (95% CI 0.6 to 4.0, $p = 0.009$ vs placebo)
[186]	N=9 (4 F, 8M); elderly subjects with prospective memory lapses Mean age: 76.2 years	Blueberry juice (6–9 ml/kg/day) 3 months	Response time-recall ($p = 0.027$, $\eta^2 = 0.12$) Paired Associate Learning test ($p = 0.009$, $d = 1.78$) CVLT free recall ($p = 0.040$, $d = 1.18$) All comparisons vs pre-intervention baseline
[183]	N = 522 (289 F, 233 M); elderly subjects with higher cardiovascular risk Mean age: 74.6 years	Low-fat control diet MeDi + olive Oil (1L/week) MeDi + mixed nuts (walnuts, hazelnuts, almonds; 30g/day) 6.5 years	MMSE ($p = 0.005$, 95% CI +0.18 to +1.05; MeDi + olive oil vs control) MMSE ($p = 0.015$, 95% CI +0.11 to +1.03; MeDi + mixed nuts vs control) CDT ($p = 0.001$, 95% CI +0.20 to +0.82; MeDi + olive oil vs control) CDT ($p = 0.048$, 95% CI +0.003 to +0.67; MeDi + mixed nuts vs control)
[184]	N = 212 (106 F, 106 M); mild AD subjects Mean age: 73.7 years	Control drink Souvenaid Multi-nutrient (125mL/day) 3 months	Delayed verbal recall: WMS-r ($p = .021$, $d = 0.20$ Souvenoid vs control drink)
[180]	N = 334 (170 F, 164 M); elderly subjects with higher cardiovascular risk Mean age: 66.8 years	Control diet MeDi + olive oil (1L/week) MeDi + Mixed nuts (walnuts, hazelnuts, almonds; 30g/day) 4.1 years	Memory: RAVLT, WMS-paired associates (95% CI −0.04 to 0.24, $p = 0.04$ MeDi + mixed nuts vs control diet) Frontal cognition: WAIS, Color Trail Task (95% CI 0.02 to 0.43, $p = 0.004$ MeDi + olive oil vs control diet) Global cognition: all measures, including MMSE (95% CI −0.12 to 0.20; $p = 0.008$ MeDi + olive oil vs control diet)
[196]	N = 485 (282 F, 203 M); normal elderly subjects Mean age: 70 years	Placebo DHA (900mg/day) 6 months	Paired Associate Learning test (95% CI −3.1 to −0.14, $p = 0.032$ vs placebo) Verbal Recognition Memory test ($p = 0.015$ vs placebo)

Abbreviations: CVLT, California Verbal Learning Test; DHA, Docosahexaenoic acid; MeDi, Mediterranean diet; MMSE, Mini-Mental State Exam; PUFA, Polyunsaturated Fatty Acids; RAVLT, Rey Auditory Verbal Learning Test; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale

Table 4.

Human studies summarizing the effects of aerobic and resistance training (RT) on cognition in the elderly subjects.

References	Subject description, sample size, sex, age	Intervention type, dosage, frequency	Primary cognitive assessment (*p* value and/or effect size for treatments)
[230]	N = 24 (13 F, 11 M); sedentary elderly subjects Mean age: 70.7 years	Stretching control Aerobic training: walking, gradual running, circuit training (40–60% of heart rate reserve) 60 min/3days/week; 12 weeks	WCST ($p < .05$, $d = 0.66$ vs control)
[231]	N = 33 (17 F, 16 M); MCI subjects Mean age: 70 years	Stretching control (<50% of heart rate reserve) High intensity aerobic exercise: walking, stationary bicycle, elliptical (75–85% of heart rate reserve) 45–60 min/4days/week; 6 months	Symbol-digit modalities ($p = 0.05$ vs control, $f_{women} = 0.67$, $p = 0.04$; $f_{men} = 0.29$, $p = 0.33$) Verbal fluency ($p = .04$ vs control, $f_{women} = 0.88$, $p = 0.01$; $f_{men} = 0.28$, $p = 0.39$) Stroop test (($p = 0.02$ vs control, $f_{women} = 0.76$, $p = 0.02$; $f_{men} = 0.05$, $p = 0.86$) Trails B ($p = 0.04$ vs control, $f_{women} = 0.56$, $p = 0.09$; $f_{men} = 0.70$, $p = 0.05$)
[239]	N = 155 (all F); elderly subjects from community dwelling Mean age: 69.6 years	BAT (stretching control) RT (high intensity mini squats, mini lunges and lung walk) 60 min/1–2days/week; 1 year	Stroop test (2 years follow-up: $\beta = 0.48$, $p = 0.002$ 1xRT vs BAT; $\beta = 0.31$, $p = 0.005$ 2xRT vs BAt) DSST (2 years follow-up: $\beta = 0.29$, $p = 0.146$ 1xRT vs BAT; $\beta = 0.45$, $p = 0.002$ 2xRT vs BAt)
[240]	N = 62; sedentary elderly subjects Mean age: 68.2 years	Control: warm-up and stretching without overload EMODERATE (RT with loads 50% of 1RM) EHIGH (RT with loads 80% of 1RM) 60 min/3 days/week; 24 weeks	DST (Forward: $p < 0.001$ both EMODERATE and EHIGH vs control; Backward: $p > 0.17$ for both training conditions vs control) Corsi's block tapping task (similarities score: $p < 0.02$ EMODERATE vs control; $p < 0.08$ EHIGH vs control) Rey-Osterrieth complex figure (immediate recall: $p < 0.02$ both EMODERATE and EHIGH vs control)
[237]	N = 32 (21 F, 11M) inactive elderly subjects Mean age: 62 years	Control RT (upper and lower body resistance exercise) MCT (treadmill 70–75% hear rate for 47 min) HIIT (4 × 4-min treadmill at 90–95% heart rate) 3days/week; 16 weeks	Stroop neutral; reaction time ($p < 0.05$ vs pre-test for HIIT $d = 1.11$, RT $d = 1.00$) Stroop-incongruent; reaction time ($p < .05$ vs pre-test for MCT $d = 1.28$, RT $d = 1.12$, control $d = 0.94$) Stroop-interference; reaction time ($p < .05$ vs pre-test for MCT $d = 1.31$, RT $d = 1.07$, control $d = 0.95$)
[232]	N = 31 (23 F, 8M); patients with age-related dementia Mean age: 81.9 years	Control (no physical activity) Aerobic training: walking, stationary bicycle, dancing 60 min/3days/week; 15 weeks	Rapid evaluation of cognitive functions test ($p < 0.01$ vs control)
[241]	N = 77 (all F); elderly subjects from community dwelling with MCI and subjective memory complaints Mean age: 75.1 years	BAT (control) RT 2days/week; 6 months	Stroop test ($p = 0.04$ RT vs BAT) Associative memory task ($p = 0.03$ RT vs BAT).
[233]	N = 140 (56 F, 84 M); subjects with AD from community dwelling care Mean age: 77.9 years	Control (usual community care) Exercise: strength, balance and aerobic training (nordic walking) 60 min/2days/week; 1 year	CDT ($p = .030$, $d = .31$ vs control) Verbal Fluency and MMSE (no group differences)

Abbreviations: AD, Alzheimer's disease; BAT, balancing and toning; CDT, Clock drawing test; DST, Digit span test; DSST, Digit Symbol Substitution Test; EHIGH, Experimental high; EMODERATE, Experimental moderate; HIIT, High intensity aerobic interval training; MCI, Mild Cognitive Impairment; MCT, Moderate continuous aerobic training; MMSE, Mini-Mental State Exam; RM, Repetition Maximum; WCST, Wisconsin Card Sorting *Test*