Putative mechanisms of cognitive decline with implications for clinical research and practice

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Abstract

Multiple intrinsic and extrinsic mechanisms contribute to vulnerability of cognitive decline and nurses play a significant role in assisting individuals and families to use strategies for healthy cognitive aging. The objective of this narrative review is to provide a synthesis of the intrinsic and extrinsic mechanisms of cognitive decline and conditions that are associated with cognitive decline. Well-established intrinsic mechanisms of cognitive decline include aging, apolipoprotein E (APOE) $\epsilon 4$ carrier status, *SORL1* mutations, neuroinflammation, mitochondrial dysfunction, amyloid deposition, and demyelination. Extrinsic risk factors include obesity, diabetes, hypertension, elevated lipid panel, metabolic syndrome, depression, traumatic brain injury, substance use, heart failure, and stroke. The various definitions of cognitive decline as well as the intrinsic and extrinsic factors that impact cognition as humans age should be incorporated in future clinical research studies. Nurses may use this information to help patients make lifestyle choices regarding cognitive health.

Keywords

cognition; cognitive decline; cognitive impairment; dementia

1 | INTRODUCTION

Cognitive function is a critical component of healthy aging and a major concern for the growing number of older adults who will make up 20% of the population by the year 2030.¹ Healthy aging entails the maintenance of neurocognitive function, although minor deficiencies in visuospatial function, conceptual reasoning, memory, and processing speed are expected as adults enter the later years of life.² However, cognitive decline that impairs the ability to perform activities of daily living most likely represent the effect of comorbid

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CONFLICT OF INTEREST

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disease.³ This is of particular importance, since older adults are living longer but have a higher prevalence of comorbidities that can place them at risk of cognitive decline with potential progression to mild cognitive impairment (MCI) and dementia.

While the number, type, and severity of comorbidities are factors to consider in the risk of cognitive decline, there are also risk factors along the life span that may increase vulnerability to accelerated brain aging. Both intrinsic (i.e., genomic) and extrinsic (i.e., comorbidities, lifestyle, environment) mechanisms impact vulnerability to cognitive decline, and may one day be quantified to inform individual health promotion/disease prevention decisions regarding cognitive health and generate new strategies to retain cognitive function into the extremes of old age. In this review, the different definitions of cognitive decline and relevant comorbidities and exposures that may impact the trajectory of cognitive decline over the life span are examined. Emerging areas of research are discussed that will likely facilitate new insights and the translation of current knowledge into clinical practice.

2 | DEFINING COGNITIVE DECLINE

Cognition is measured through testing mental status, verbal and nonverbal learning, memory, attention, executive function, language, visuospatial abilities, intelligence, and functional assessments. In primary clinical settings, it is often difficult to recognize changes in cognition, although routine use of the mini mental status examination (MMSE) for older adults may help to identify changes over time. However, it has been noted that changes in the MMSE likely represent the onset of neurodegenerative processes that are at a stage of limited amenability.¹

In order to identify the early trajectory of cognitive decline, when secondary interventions may be implemented before neuronal damage becomes irreversible, the diagnostic category of MCI was developed (Table 1). MCI is an intermediate stage between normal cognition and dementia in which there is objective evidence of impairment in one or more cognitive domains in the absence of functional decline or dementia.⁴ MCI represents a high-risk group because dementia develops at a rate of 10–15% per year as compared to the general population of 1–2%. The incidence of MCI is higher in males compared to females and twice as high in subjects with <12 years of education compared to participants with >12 years of education. Interventions developed for individuals with MCI have not been successful in decreasing the rate of conversion to dementia, most likely because extensive neuronal loss has already occurred by the time MCI is recognized.⁴

These findings prompted efforts to operationalize a pre-MCI stage, which focuses on subjective cognitive complaints, defined as self- or informant-reported cognitive disturbances occurring in the absence of an objective impairment in cognitive performance.⁵ However, in clinical studies self- and informant-based subjective decline correlate with greater psychological distress and only slightly lower cognitive performance.⁶ Longitudinal studies, in contrast to cross-sectional analyses, have reported a strong association between subjective memory complaints and the development of cognitive decline or dementia over a period of 1–7 years.⁷ However, psychological distress is strongly associated with subjective memory complaints, vascular risk factors are only weakly associated with self-reported

cognitive decline.⁶ Overall subjective cognitive complaints have been suggested as a risk factor of cognitive decline, and led to development of early and late MCI definitions (Table 1). Yet, the complexity of applying these definitions in clinical practice has hindered early recognition and prompt intervention in clinical practice settings.⁴

More recently, the concept of cognitive frailty, a state of reduced neurophysiological reserve that may represent a precursor of neurodegenerative processes, has been defined as the presence of physical frailty and cognitive impairment with exclusion of concurrent Alzheimer's disease dementia or other dementias.⁴ This concept represents a growing urgency to identify a preclinical or asymptomatic stage of cognitive decline that may only be quantified by established risk factors and/or biomarker evidence. The use of risk factors (similar to the Framingham score for cardiovascular disease risk) and biomarkers (such as the HbA1c used to detect and monitor diabetes mellitus) have been suggested as a strategy to improve the ability to implement prevention strategies before irreversible cellular and tissue damage occur. Ideally, nurses could then use cognitive risk factor scores to develop an individualized preventative plan to help patients maintain cognitive health over the life span.

3 | PROTECTIVE AND RISK FACTORS

Strategies to preserve cognitive function are rarely discussed beyond maintaining baseline weight and blood pressure.⁸ However, cardiometabolic risk factors of cognitive decline are commonly cited in the literature, including vascular risk factors (hypertension, elevated lipid panel, metabolic syndrome), comorbid conditions such as obesity and diabetes, and genetic risk factors, mainly the *APOE* genotype.^{9,10} Adiposity, diabetes, heart failure (HF), and stroke are risk factors for nonamnesic MCI, whereas HF and stroke are risk factors of functional decline.¹¹ In contrast to younger populations, systolic blood pressure (SBP), and pulse pressure (PP), readings among the oldest old (over age 85) are positively associated with resiliency to physical and cognitive decline, particularly in individuals with pre-existing physical disability. In the oldest old, SBP and PP are associated with lower annual increases in disability and MMSE scores.¹²

In addition to cardiometabolic factors, keeping the brain active through engaging in new activities, regular sleep cycles, and cardiovascular exercise help to maintain cognition.¹³ Leisure activities, whether they are mental, physical, and/or social, protect cognitive function in older adults.¹⁴ Lifestyle behaviors, such as sleep, can also influence cognitive decline—difficulty initiating sleep and early morning awakening has been associated with amnesic MCI and difficulties in maintaining sleep with nonamnesic MCI.¹⁵ Cognitively normal older adults who report higher levels of physical activity may have slightly better cognitive performance, but the potential cognitive benefits of higher levels of physical activity over time may be most evident in individuals at genetic risk for Alzheimer's disease (*APOE* $\epsilon 4$ carriers).¹⁶ In addition, interactions among depressive symptoms, *APOE* $\epsilon 4$ allele, and cognitive decline were demonstrated in a prospective population-based sample of individuals 65 years and above interviewed at 3-year intervals. Cognitive function decreased more rapidly in individuals with depression who had one or more copies of the *APOE* $\epsilon 4$ allele compared to those with no depressive symptoms. For each additional symptom of

depression, cognitive decline increased among those with no copies and more than doubled the rate of decline among those with one or more copies of the *APOE ε4* allele.¹⁷

4 | MECHANISMS OF COGNITIVE DECLINE

Gray matter atrophy has been consistently regarded as the etiology of cognitive decline. However, in early stage Alzheimer's patients with decreased scores on the MMSE, atrophy of the white matter has also been described, particularly of the corpus callosum—the largest white matter fiber bundle of the brain.¹⁸ However, how these changes occur remains elusive. At this point in time, the mechanisms underlying cognitive decline appear to be a cascade that links neuroinflammation, mitochondrial dysfunction, amyloid deposition, and demyelination. Cumulative “brain insults” over time may hasten the cascade and accelerate cognitive decline.

Neuroinflammatory activation through high-mobility group box 1 (HMGB1) protein, a ubiquitous nucleosomal protein, ensues via activation and trafficking of circulating bone marrow derived macrophages to the brain. Postoperative neuroinflammation and cognitive decline including delirium and postoperative cognitive dysfunction can be prevented by abrogating the effects of HMGB1.¹⁹ In addition, oxidative stress and mitochondrial dysfunction can lead to neuronal loss. Mitochondria are the major intracellular source of reactive oxygen species (ROS). Under normal physiological conditions, ROS act as cell signaling molecules and modulate expression of several redox-sensitive genes. However, accumulation of ROS can cause oxidative damage to phospholipid, protein, and DNA, leading to alterations of membrane properties, inactivation of enzymes and receptors, genomic instability, and alterations in gene expression. While there is a major focus of research in this area, it remains unclear whether increased oxidative stress of the aging brain results from increased production of ROS, accumulation of prooxidant factors such as transition metals, a fall in antioxidant enzymes, or a combination of all these factors.²⁰

While these pathways may explain the mechanisms of neuronal loss that contribute to cognitive decline, there is also the component of neuronal reserve to consider; that is, the amount of neuronal reserve may be more important than neuronal loss in dictating the rate of cognitive decline. It has been suggested that the density of noradrenergic neurons in the locus coeruleus is a structural component of neural reserve. More specifically, the locus coeruleus neuronal density, brainstem tangles, and brainstem Lewy bodies have independent associations with the rate of cognitive decline. Higher density of noradrenergic neurons in the locus coeruleus is associated with reduced cognitive decline even after accounting for common neurodegenerative lesions in these nuclei and elsewhere in the brain.²¹

Brainstem tangles and plaques are commonly cited as a direct mechanism of cognitive decline. However, A-beta amyloid deposition measured by cerebrospinal fluid A- β 42, or Pittsburgh compound B positron emission tomography imaging, demonstrated that A-beta amyloid deposition initiates the pathological cascade, but is not the direct cause of cognitive impairment, whereas hippocampal atrophy indicates how far one is along the neurodegenerative path.²² A-beta normally functions as an antimicrobial peptide in the innate immune system in response to clinically relevant pathogenic microorganisms. A-beta

monomers, dimers, and higher order oligomeric forms may be an early and toxic form of amyloid deposition.

APOE $\epsilon 4$ carriers have a higher total amyloid load in Alzheimer's disease (AD), and in MCI display a higher amyloid burden; in presymptomatic APOE $\epsilon 4$ carriers, there is reduced cerebral glucose metabolism, increased cerebral amyloid deposition, and enhanced cortical atrophy and accelerated memory decline.²³ In contrast, the *DHCR24* gene appears to play a protective role and has been shown to confer resistance to A-beta and oxidative stress induced apoptosis by inhibiting caspase-3 activation.²⁴ The *SORL1* gene is a neuronal receptor that binds ApoE and plays a crucial regulatory role in the processing of the amyloid precursor protein (APP); a mutation of this gene has been associated with increased vulnerability to AD.²⁴

Demyelination starts in the structures affected by neurofibrillary pathology and its presence correlates with the clinical picture of cognitive decline, indicating a mechanism of MCI-to-AD progression.²⁵ Demyelination of the medial temporal lobe and posterior structures, including white matter and gray matter, in single- and multiple-domain MCI has been demonstrated.²⁶ The spread of demyelination to prefrontal white matter and insula gray matter was seen in executive multidomain MCI. As these cellular and structural events progress, changes in brain function occur that manifest as cognitive decline.^{25,27}

Comorbid conditions and various exposures throughout the life span contribute to the intrinsic and extrinsic mechanisms of cognitive decline described above. Studies that involve participants with some of the more well-known exposures and comorbidities that accelerate cognitive decline may provide valuable insights on how cumulative brain insults may be quantified as well as to test predictive models. Ultimately, the objective, mechanistic assessments could be used by nurses to guide the development of more targeted interventions as well as to evaluate the effect of the intervention on the mechanisms of cognitive decline.

5 | TRAUMATIC BRAIN INJURY

Each year, an estimated 1.7 million American sustain traumatic brain injury (TBI) and there are current 5.3 million American living with TBI. The pathophysiology of TBI has been described as a disease process in contrast to an event and may include short- and long-term sensorimotor, psychological and cognitive impairments. TBI is the best known established epigenetic risk factor for later development of neurodegenerative diseases and dementia.²⁸ People sustaining TBI are more than four times more likely to develop dementia at a later stage than people without TBI. Genetic background of *B-APP*, *apolipoprotein E* (ApoE), *presenilin* (PS), and *neprilysin* (NEP) genes are associated with exacerbation of neurodegenerative processes after TBI.²⁹

Alzheimer's dementia is characterized by the presence of extracellular amyloid beta (AB) senile plaques and intracellular neurofibrillary tangles (NFTs). Senile plaques are formed of aggregated AB, whereas NFTs are composed of paired helical filaments (PHFs) made of pathologically phosphorylated tau microtubule-associated proteins (MAPs). There are many

pathological features common to both acute brain injury and AD, including AB disposition, tau phosphorylation, neuritic degeneration, apoptosis, synapse loss, astrogliosis/microgliosis, and neuroinflammation. In particular, neuroinflammation appears to play key role in mediating the secondary neuronal injury cascade and serves as a common denominator between TBI and AD. Genetic background of both *ApoE* and *Neprilysin* genes are associated with aggravated load of AB plaque after TBI. In contrast to AD, in TBI, AB plaques were observed to diminish within months following injury and with survival of more than a year, plaques reemerge with a greater cerebral load than observed initially after injury.²⁸ *APOE e4+* genotypes in the young and middle-aged groups predicted lower baseline cognitive performance in the context of TBI.²⁹ Baseline cognitive performance was better for young females than males, but this pattern reversed in middle and old age. The findings suggest TBI history is associated with long-term cognitive impairment and decline across the adult life span.

6 | SUBSTANCE USE

The brain regions and neural processes that underlie substance use and addiction overlap extensively with those that support cognitive and executive functioning, defined as changes in fluency, working memory, reasoning, response inhibition, cognitive flexibility, and decision making. Neurobiological adaptations in fronto-cortico-striatal circuitry and neurotoxicity from continued substance abuse results in cognitive deficits that result in maintenance of drug use, relapse, as well causing decline in areas of executive functioning. The unique pharmacological profile of each class of abused drugs produces distinct patterns of cognitive impairment that varies with the specific drug, the environment and genetic factors.

Studies evaluating the influence of moderated *alcohol exposure* have shown that there may be some benefit to cognition in men and women. In men, there were no differences in cognitive decline among alcohol abstainers, quitters, and light or moderate alcohol drinkers (<20 g/day) over 10 years.³⁰ However, alcohol consumption >36 g/day was associated with faster decline in all cognitive domains compared with consumption between 0.1 and 19.9 g/day over 10 years. In women, 10-year abstainers showed faster decline in the global cognitive score and executive function compared with those drinking 0.1–9.9 g/day of alcohol. A second study showed that among women, a higher total consumption of alcoholic beverages was linearly associated with a smaller decline in global cognitive function with the smallest decline in the highest quantile corresponding to two to three glasses of alcoholic beverages per day. Women who drank about two to three glasses of alcoholic beverages per day showed less than half the decline in global cognitive function compared with those who drank no to very little alcohol. Individuals who drank 1.5 glasses of red wine per day showed a smaller decline in global cognitive function compared with those with the lowest consumption of red wine.³¹

In contrast with moderated alcohol use, excessive alcohol exposure can lead to accelerated brain atrophy. Parahippocampal/hippocampal atrophy was specific to alcoholics with cognitive decline and atrophy of the thalamus and enlargement of the third ventricle was more severe in the cognitive decline group compared to the cognitively normal group. The

parahippocampal and hippocampal cortices may play a crucial role in the retention of short-term memory in alcoholics.³² In alcohol-dependent patients, trail making A, a test related to basic executive function, showed a correlation with insulin-like growth factor 1 (IGF-1).³³

Cocaine-dependent users display cognitive impairment in several areas of functioning that persists even after abstinence.³⁴ Specifically, attention, learning, memory, inhibitory control, and cognitive flexibility are often impaired in cocaine abusers.³⁵ Deficits in cognitive function are associated with marked white matter impairment in the prefrontal cortex (PFC) and altered serotonergic and dopaminergic function in the brain.³⁶ There was a consistent finding of poorer performance of the cocaine sample relative to cocaine and alcohol abusers on measures of complex psychomotor and simple motor functioning. Pure cocaine abusers, but not abusers of both cocaine and alcohol, also performed more poorly than normal on a measure of global neuropsychological functioning. Vascular complications associated with cocaine use have been suggested as a possible mechanism of cognitive impairment with elevated cocaethylene levels and increased platelet aggregation found in cocaine abusers.³⁷

Chronic *amphetamine* users show deficits in a range of cognitive skills, including verbal fluency, pattern recognition, planning, and the ability to shift attention from one frame of reference to another.³⁸ The decision-making deficits observed in these individuals are similar to those with prefronto-cortical damage.³⁹ Prolonged but not recreational *methamphetamine* use (METH) induces cognitive deficits in neuropsychological tasks, motor function, and memory, which are only partially ameliorated following extended abstinence.⁴⁰ At a neurobiological level, chronic METH use leads to reduction of dopamine transporters and dopaminergic metabolism in the thalamus and accumbens. However, only some of these neurochemical adaptations are normalized following protracted abstinence and may explain persistent neuropsychological deficits in these subjects. Similarly, abusers of 3,4-methylenedioxymethamphetamine (*MDMA*, ecstasy) continued to score relatively poorly in tests of immediate and delayed word recall after extended abstinence.⁴¹

Opiate (heroin, morphine, methadone, prescription pain killers) dependence is also well known to impair cognitive function.⁴² Heroin dependence is associated with deficits in memory, attention, and impulse control.³⁸ Chronic pain patients and those in methadone maintenance also display comparable deficits in neuropsychological testing.⁴³ These deficits appear to be related in changes in functioning of the PFC.³⁸

Acute *marijuana* exposure results in reversible deficits in attention, memory, and decision making.⁴⁴ Accumulating evidence suggests that long-term, heavy cannabis use may cause enduring neuropsychological impairment that persists beyond the period of acute intoxication.⁴⁵ Studies of long-term, heavy cannabis users consistently show that these individuals perform worse on neuropsychological tests,⁴⁵ and some^{46,47} studies suggest that impairment may remain even after extended periods of abstinence. The magnitude and persistence of impairment may depend on factors such as the quantity, frequency, duration, and age of onset of cannabis use, as more severe and enduring impairment is evident among individuals with more frequent and prolonged heavy use and a younger age of onset.⁴⁸ Postulated mechanisms for cognitive decline include neurobiological adaptations to

cannabinoid receptors in the CNS; structural differences in the hippocampus and other brain regions involved in cognitive functioning.⁴⁹

Prolonged *cigarette smoking* and smoking history are associated with cognitive decline, deficits in impulse control, and decision making.⁵⁰ In one study, smokers' cognitive speed declined nearly twice as much as nonsmokers' over 5 years. In addition, declines in smokers' cognitive flexibility and global cognition were significantly faster than that of nonsmokers.⁵¹ Recent quitters' scores in these areas were similar to smokers, and ex-smokers performed at levels intermediate between smokers and nonsmokers. In another study, smokers' performance deteriorated more over 10 years than nonsmokers' on tests of verbal memory and attention.⁵² Recent studies have suggested that neurotoxic effects from heavy cigarette smoking has an increased risk of dementia in current smokers, including Alzheimer's disease, vascular dementia, and can lead to greater declines in mental state testing compared to those who have never smoked cigarettes.⁵³ In addition to excessive alcohol and substance use exposures, comorbidities may contribute to cognitive decline. Diseases such as HF or exposure to chemotherapeutic agents may also increase the risk of cognitive decline.

7 | HEART FAILURE

The prevalence of cognitive decline is high among patients with HF compared with healthy age and gender-matched controls.⁵⁴ HF with preserved and reduced ejection fraction is associated with defects in several domains of cognition. Another study suggests that cognitive difficulties in memory, reasoning, and processing speed may occur prior to HF diagnosis, while those with HF may experience steeper declines in reasoning over time as measured by the word series test.⁵⁵ A potential mechanism of HF-related cognitive decline involves the effect of increased angiotensin II in causing accelerated apoptosis of adult hippocampal cells.⁵⁶ Increased levels of angiotensin II leads to an increase in mitochondrial ROS and mitochondrial morphological changes as well as activation of AMP-activated protein kinase (AMPK) and consequently peroxisome proliferator-activated receptor gamma coactivator 1-alpha expression resulting in cell apoptosis. Future research in this area should focus on identifying the mechanisms of cognitive decline in patients with HF and test therapies for improving cognition in this patient population.

8 | CHEMOTHERAPEUTIC EXPOSURE

Cognitive decline has been reported by cancer survivors, particularly those who have received chemotherapy, and has been referred to as "chemobrain" or "chemofog." It is clear that many factors may contribute to cognitive disturbances in individuals with cancer, including stress, anxiety, depression, hormonal fluctuations, fatigue, and treatments. Data from animal and imaging studies, along with evidence of a dose-response relationship between chemotherapy and cognitive disturbance, have a strong indication that systemic chemotherapy can be neurotoxic and its effects can lead to cognitive changes. Some longitudinal studies that extended beyond the end of treatment have suggested that in most cases chemotherapy-related cognitive impairment (CRCI) ceases over time, however, there have also been cross-sectional and longitudinal studies indicating that there may be a small

subgroup of patients that experience chronic cognitive decline that continues after treatment.⁵⁷ Short- and long-term memory, speed of processing, attention and concentration, language, and executive functioning were domains reported by breast cancer survivors 1 year post treatment.⁵⁸

Heflin et al.⁵⁹ found that among 486 monozygotic geriatric twin pairs discordant for cancer, long-term cancer survivors were twice as likely to be diagnosed with dementia as their unaffected sibling. However, studies in unrelated patients exposed to chemotherapy have resulted in conflicting results.⁶⁰ While there is no definitive evidence that chemotherapy increases the risk of developing dementia later in life, it is imperative to provide cognitive screening for patients undergoing chemotherapy and other forms of cancer treatment. Future studies should aim to provide new knowledge on mechanisms of neurotoxicity with chemotherapy and evaluate regimens to prevent or ameliorate cognitive deficits during and after cancer treatment.⁵⁹

9 | HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

Individuals with human immunodeficiency virus (HIV) often experience deficits in the domains of memory and executive functions during and after combined retroviral therapy (cART) that is referred to as HIV-associated neurocognitive disorders (HANDs). The manifestation of HAND can decrease adherence to pharmacotherapy, lower cognitive reserve, and increase the incidence of psychiatric comorbidities.⁶¹ Longitudinal studies that have examined dysregulated sphingolipid and sterol metabolism in the central nervous system suggest that a progressive disorder of lipid metabolism that is similar to disorders of lipid storage may contribute to the pathogenesis of HAND.⁶¹ Other studies have noted significant neuroinflammation in patients receiving cART, which may lead to neurocognitive decline. HMGB1 is a nonhistone chromosomal protein that acts as a potent proinflammatory cytokine when secreted from immune cells and activates microglial cells to cause neuroinflammation. A study conducted by Gougeon et al.⁶² found that cerebral spinal fluid HMGB1 levels were positively correlated with HIV-1 DNA in aviremic HAND patients, indicating a positive impact of HMGB1 on HIV reservoirs. Furthermore, circulating anti-HMGB1 IgG antibody levels could discriminate patients with no HAND from patients with no HAND and a single cognitive deficit, allowing for early identification of neurocognitive impairment. It was concluded that central nervous system inflammation is correlated with increased levels of HMGB1 and anti-HMGB1 IgG in the cerebral spinal fluid among patients with HIV receiving cART. Moreover, anti-HMGB1 IgG was identified as a very early biomarker of neurological impairment in patients without HAND, leading to the possibility of identifying patients who are at high risk for developing neurological disorders.⁶²

10 | FIBROMYALGIA

Patients with fibromyalgia syndrome (FMS) commonly report cognitive disturbances, known as “fibrofog.” The prevalence and cooccurrence of cognitive dysfunction and severity were assessed in 57 patients with FMS and 57 patients with rheumatic disease without FMS.⁶³ Information relating to memory decline, confusion, and speech difficulty was extracted

from questions embedded in a health questionnaire and a blind retrospective chart review. Pain, morning stiffness, fatigue, and sleep difficulty were established on a 0 to 100 mm visual analog scale and variable of confusion, fatigue, tension, depression, anger, and vigor were assessed using the Profile of Mood States. Patients with FMS complained more often of memory decline, confusion, and speech difficulty. Memory decline were coupled more often in patients with FMS and patients with this combination also reported more pain, stiffness, fatigue, and disturbed sleep than patients with FMS with memory problems alone. Cognitive decline was also associated with younger age in FMS with 65.2% of those less than 50 years of age complaining of cognitive change compared to 29.4% of non-FMS patients of similar age. Patients with rheumatic disease differ substantially in cognitive vulnerability with FMS patients at considerably higher risk. However, measures of episodic memory and processing speed, markers of preclinical Alzheimer's disease, are in the normal range for fibromyalgia patients with cognitive complains for more than 7 years.⁶⁴ Nevertheless, this impact of cognitive symptoms for patients with FMS can be devastating and warrant further study to identify potential therapeutic strategies.⁶³

11 | IMPLICATIONS FOR NURSING PRACTICE

Nurses play a significant role in health promotion and disease prevention by providing education, support, and enhancing self-management skills of individuals and families. To promote cognitive health, nurses can encourage a healthy diet, active lifestyle, and adequate sleep as well as help individuals reduce harmful exposures that can contribute to cognitive decline. Individuals and families may have risk factors that are static, such as a cognitive risk allele or single nucleotide polymorphism, or risk factors that are dynamic, such as environmental risk factors that change over time.^{65,66} Recognizing that chronic conditions, such as HF, HIV, and fibromyalgia, may add vulnerability to accelerated cognitive decline, nurses can institute screening measures and interventions to optimize cognition and physical functioning for specific populations.

12 | IMPLICATIONS FOR NURSING RESEARCH

Nursing research focused on identifying the mechanisms of cognitive decline and designing interventions to reduce intrinsic and extrinsic risk factors and/or integrate protective strategies to help preserve cognitive over time will contribute to population health. A deeper understanding of the mechanisms of cognitive decline and the quantification of exposures over time could lead to more precise preventative or treatment interventions. Knowledge regarding how chronic conditions increase vulnerability to cognitive decline could lead to innovative disease-management strategies that incorporate cognitive health interventions early on in the course of the disease. Innovations in tracking cognitive health using biomarkers and/or technology may lead to better identification of those at risk and help facilitate timely interventions that focus on delaying decline and preserving cognition and function for as long as possible.

13 | CONCLUSIONS

Recent advances in the study of cognitive decline as an aspect of aging or associated with chronic comorbidities highlight the complex nature of studying cognition across populations. The various definitions of cognitive decline as well as the intrinsic and extrinsic factors that impact cognition over the life span should be considered in future clinical research studies (Figure 1). As more information is gleaned from studies that identify specific mechanisms associated with cognitive decline, there may be more direct methods of quantifying vulnerability over the life span that could lead to more informed decision making by individuals regarding their treatments and lifestyle choices. Conditions in which cognitive deficits are perceived by individuals but for which no direct mechanism can be identified may still benefit from adhering to cognition-preserving strategies. Nurses working with patients who are at risk of cognitive decline or report cognitive disturbances can use this information to discuss lifestyle choices that impact cognition and various strategies for improving cognitive and physical functioning over the life span.

Biography

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REFERENCES

1. Centers for Disease Control and Prevention. Healthy aging. 2017 <https://www.cdc.gov/aging/index.html> Accessed April 2017.
2. Royall DR, Palmer RF, Chiodo LK, Polk MJ. Towards an agingspecific cognitive phenotype: the Freedom House study. *Exp Aging Res.* 2014;40(3):245–265. [PubMed: 24785590]
3. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. *Psychol Aging.* 2016;31(2):166–175. [PubMed: 26796792]
4. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging.* 2013;17(9):726–734. [PubMed: 24154642]

5. Abdulrab K, Heun R. Subjective memory impairment. A review of its definitions indicates the need for a comprehensive set of standised and validated criteria. *Eur Psychiatry*. 2008;23(5):321–330. [PubMed: 18434102]
6. Paradise MB, Glozier NS, Naismith SL, Davenport TA, Hickie IB. Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: a cross-sectional study. *BMC Psychiatry*. 2011;11:108. [PubMed: 21722382]
7. Caselli RJ, Chen K, Locke DEC, et al. Subjective cognitive decline: self and informant comparisons. *Alzheimers Dement*. 2014;10:93–98. [PubMed: 23562429]
8. Craft S, Foster TC, Landfield PW, Maier SF, Resnick SM, Yaffe K. Session III: mechanisms of age-related cognitive change and targets for intervention—inflammatory, oxidative and metabolic processes. *J Gerontol*. 2012;67(7):754–759.
9. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(9):2672–2713. [PubMed: 21778438]
10. Knopman DS, Mosley TH, Catellier DJ, Coker LH, The Atherosclerosis Risk in Communities Study Brain MRI Study. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI study. *Alzheimers Dement*. 2009;5:207–214. [PubMed: 19362884]
11. Ganguli M, Fu B, Snitz BE, Hughes TF, Chang CH. Mild cognitive impairment: incidence and vascular risk factors in a population-based cohort. *Neurology*. 2013;80:2112–2120. [PubMed: 23658380]
12. Sabayan B, Oleksik AM, Maier AB, et al. High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-Plus Study. *J Am Geriatr. Soc*. 2012;60:2014–2019. [PubMed: 23126669]
13. Wang H, Jin Y, Hendrie HC, et al. Late life leisure activities and risk of cognitive decline. *J Gerontol Med Sci*. 2013;68(2):205–213.
14. Wei X, Ji L. Effect of handball training on cognitive ability in elderly with mild cognitive impairment. *Neurosci Lett*. 2014;566:98–101. [PubMed: 24582900]
15. Dlugaj M, Weinreich G, Weimar C, et al. Sleep-disordered breathing, sleep quality, and mild cognitive impairment in the general population. *J Alzheimers Dis*. 2014;41:479–497. [PubMed: 24643134]
16. Pizzie R, Hindman H, Roe CM, et al. Physical activity and cognitive trajectories in cognitively normal adults: the adult children study. *Alzheimer Dis Assoc Disord*. 2014;28:50–57.
17. Rajan KB, Wilson RS, Skarupski KA, Mendes de Leon CG, Evans DA. Gene-behavior interaction of depressive symptoms and the Apolipoprotein E ϵ 4 allele on cognitive decline. *Psychosom Med*. 2014;76:101–108. [PubMed: 24434953]
18. Zhu M, Wang X, Gao W, et al. Corpus callosum atrophy and cognitive decline in early Alzheimer's disease: longitudinal MRI study. *Dement Geriatr Cogn Dis*. 2014;37:214–222.
19. Vacas S, Degos V, Tracey KJ, Maze M. High-mobility group box 1 protein initiates postoperative cognitive decline by engaging bone marrow-derived macrophages. *Anesthesiology*. 2014;120(5):1160–1167. [PubMed: 24162463]
20. Chakrabarti S, Munshi S, Banerjee K, Thakurta IG, Sinha M, Bagh MB. Mitochondrial dysfunction during brain aging: role of oxidative stress and modulation by antioxidant supplementation. *Ag Dis*. 2011;3:242–256.
21. Wilson RS, Nag S, Boyle PA, et al. Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. *Neurology*. 2013;80:1202–1208. [PubMed: 23486878]
22. Jack CR, Jr., Wiste HJ, Vemuri P, et al. Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain*. 2010;133:3336–3348. [PubMed: 20935035]
23. Pham E, Crews L, Ubhi K, et al. Progressive accumulation of amyloid-beta oligomers in Alzheimer's disease and in amyloid precursor protein transgenic mice is accompanied by selective alterations in synaptic scaffold proteins. *FEBS J*. 2010;277:3051–3067. [PubMed: 20573181]
24. Mufson EJ, Binder L, Counts SE, et al. Mild cognitive impairment: pathology and mechanisms. *Acta Neuropathol*. 2012;123(1):13–30. [PubMed: 22101321]

25. Seo EH, Lee DY, Lee J, et al. Whole-brain functional networks in cognitively normal, mild cognitive impairment, and Alzheimer's disease. *PLoS One*. 2013;8(1):e53922. [PubMed: 23335980]
26. Carmeli C, Donati A, Antille V, et al. Demyelination in mild cognitive impairment suggests progression path to Alzheimer's disease. *PLoS One*. 2013;8(8):e72759. [PubMed: 24023644]
27. Zhang Y, Schuff N, Camacho M, et al. MRI markers for mild cognitive impairment: comparisons between white matter integrity and gray matter volume measurements. *PLoS One*. 2013;8(6):e66367. [PubMed: 23762488]
28. Chauhan NB. Chronic neurodegenerative consequences of traumatic brain injury. *Restor Neurol Neurosci*. 2014;32:337–365. [PubMed: 24398724]
29. Eramudugolla R, Bielak AAM, Bunce D, Eastale S, Cherbuin N, Anstey KJ. Long-term cognitive correlates of traumatic brain injury across adulthood and interactions with APOE genotype, sex and age cohorts. *J Int Neuropsychol Soc*. 2014;20:444–454. [PubMed: 24670469]
30. Sabia S, Elbaz A, Britton A, et al. Alcohol consumption and cognitive decline in early old age. *Neurology*. 2013;82:332–339.
31. Nooyens ACJ, Bas Bueno-de-Mesquita H, van Gelder BM, van Boxtel MPJ, Verschuren WMM. Consumption of alcoholic beverages and cognitive decline at middle age: the Doetinchem cohort study. *Br J Nutr*. 2014;111:715–723. [PubMed: 23967806]
32. Matsui T, Yokoyama A, Matsushita S, Higuchi S. Involvement of limbic-diencephalic circuits in alcoholics with cognitive decline: an MRI study by voxel-based morphometric analysis (VBM). *Alcohol Alcohol*. 2014;49(S1):i25 10.1093/alcalc/agu054.25.
33. Han C, Bae H, Kim DJ, Bae JY, Oh SI. The relationship between insulin-like growth factor-1 and cognitive function in alcohol-dependent patients. *Neurosci Lett*. 2014;583(7):205–209. [PubMed: 25283991]
34. Bolla K, Ernst M, Kiehl K, et al. Prefrontal cortical dysfunction in abstinent cocaine abusers. *J Neuropsychiatry Clin Neurosci*. 2004;16(4):456–464. [PubMed: 15616172]
35. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. *Am J Psychiatry*. 2001;158(11):1783–1793. [PubMed: 11691682]
36. Cunningham KA, Anastasio NC. Serotonin at the nexus of impulsivity and cue reactivity in cocaine addiction. *Neuropharmacology*. 2014;76:460–478. [PubMed: 23850573]
37. Robinson JE, Heaton RK, O'Malley SS. Neuropsychological functioning in cocaine abusers with and without alcohol dependence. *J Int Neuropsychol Soc*. 1999;5:10–19. [PubMed: 9989019]
38. Ornstein TJ, Iddon JL, Baldacchino AM, et al. Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. *Neuropsychopharmacology*. 2000;23(2):113–126. [PubMed: 10882838]
39. Rogers RD, Everitt BJ, Baldacchino A, et al. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology*. 1999;20(4):322–339. [PubMed: 10088133]
40. Hart CL, Marvin CB, Silver R, Smith EE. Is cognitive functioning impaired in methamphetamine users? A critical review. *Neuropsychopharmacology*. 2012;37(3):586–608. [PubMed: 22089317]
41. Thomasius R, Zapletalova P, Petersen K, et al. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. *J Psychopharmacol*. 2006;20(2):211–225. [PubMed: 16510479]
42. Soyka M, Limmer C, Lehnert R, et al. A comparison of cognitive function in patients under maintenance treatment with heroin, methadone, or buprenorphine and healthy controls: an open pilot study. *Am J Drug Alcohol Abuse*. 2011;37(6):497–508. [PubMed: 21851203]
43. Mintzer MZ, Stitzer ML. Cognitive impairment in methadone maintenance patients. *Drug Alcohol Depend*. 2002;67(1):41–51. [PubMed: 12062778]
44. Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. *J Int Neuropsychol Soc*. 2007;13(5):807–820. [PubMed: 17697412]
45. Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. *Curr Drug Abuse Rev*. 2008;1(1):81–98. [PubMed: 19630708]

46. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. *Neurol.* 2002;59(9):1337–1343.
47. Pope HG, Jr., Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association. *Drug Alcohol Depend.* 2003;69(3):303–310. [PubMed: 12633916]
48. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci USA.* 2012;109(40):E2657–E2664. [PubMed: 22927402]
49. Hirvonen J, Goodwin RS, Li CT, et al. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Mol Psychiatry.* 2012;17(6):642–649. [PubMed: 21747398]
50. Bloom EL, Matsko SV, Cimino CR. The relationship between cigarette smoking and impulsivity: a review of personality, behavioral, and neurobiological assessment. *Addict Res Theory.* 2014;22(5):386–397.
51. Nooyens AC, van Gelder BM, Verschuren WM. Smoking and cognitive decline among middle-aged men and women: the Doetinchem cohort study. *Am J Public Health.* 2008;98(12):2244–2250. [PubMed: 18923116]
52. Richards M, Jarvis MJ, Thompson N, Wadsworth ME. Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. *Am J Public Health.* 2003;93(6):994–998. [PubMed: 12773367]
53. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol.* 2007;166(4):367–378. [PubMed: 17573335]
54. Alagiakrishnan K, Mah D, Ahmed A, Ezekowitz J. Cognitive decline in heart failure. *Heart Fail Rev.* 2016;21(6):661–673. [PubMed: 27299309]
55. Alwerdt J, Edwards JD, Athilingam P, O'Connor ML, Valdes EG. Longitudinal differences in cognitive functioning among older adults with and without heart failure. *J Aging Health.* 2013;25:1358. [PubMed: 24084526]
56. Kim MS, Lee GH, Kim YM, et al. Angiotensin II causes apoptosis of adult hippocampal neural stem cells and memory impairment through the action on AMPK-PGC1 α signaling in heart failure. *Stem Cells Transl Med.* 2017 10.1002/sctm.16-0382 (Epub ahead of print.).
57. O'Farrell E, MacKenzie J, Collins B. Clearing the air: a review of our current understanding of chemo fog. *Curr Oncol Rep.* 2013;15:260–269. [PubMed: 23483375]
58. Von Ah D, Habermann B, Carpenter JS, Schneider BL. Impact of perceived cognitive impairment in breast cancer survivors. *Eur J Oncol Nurs.* 2013;17:236–241. [PubMed: 22901546]
59. Heflin LH, Meyerowitz BE, Hall P, et al. Cancer as a risk factor for longterm cognitive deficits and dementia. *J Natl Cancer Inst.* 2005;97:854–856. [PubMed: 15928306]
60. Walker CH, Drew BA, Antoon JW, Kalueff AV, Beckman BS. Neurocognitive effects of chemotherapy and endocrine therapies in the treatment of breast cancer: recent perspectives. *Cancer Invest.* 2012;30:135–148. [PubMed: 22250588]
61. Bandaru VVR, Mielke MM, Sacktor N, McArthur JC, Grant I, Letendre S, Chang L, Wojna V, Pardo C, Calabresi P, Munsaka S, Haughey NJ. A lipid storage-like disorder contributes to cognitive decline in HIV-infected subjects. *Neurol.* 2013;81(17):1492–1499.
62. Gougeon ML, Poirier-Beaudouin B, Durant J, et al. HMGB1/anti-HMGB1 antibodies define a molecular signature of early stages of HIV-associated neurocognitive disorders (HAND). *Heliyon.* 2017;3(2):e00245. [PubMed: 28224137]
63. Kravitz HM, Katz RS. Fibrofog and fibromyalgia: a narrative review and implications for clinical practice. *Rheumatol Int.* 2015;35(7):1115–1125. [PubMed: 25583051]
64. Walitt B, Ceko M, Khatiwada M, et al. Characterizing “fibrofog”: subjective appraisal, objective performance, and task-related brain activity during a working memory task. *Neuroimage Clin.* 2016;11:173–180. [PubMed: 26955513]
65. Jak AJ, Bangen KJ, Wierenga CE, Delano-Wood L, Corey-Bloom J, Bondi MW. Contributions of neuropsychology and neuroimaging to understanding clinical subtypes of mild cognitive impairment. *Int Rev Neurobiol.* 2009;84:81–103. [PubMed: 19501714]

66. Sachdev PS, Lipnicki DM, Crawford J, et al. Factors predicting reversion from mild cognitive impairment to normal cognitive functioning: a population-based study. *PLoS One*. 2013;8(3):e59649. [PubMed: 23544083]

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FIGURE 1.
Intrinsic and extrinsic mechanisms of cognitive decline

TABLE 1

Definitions of cognitive decline/impairment used in the literature

Term	Abbreviation	Definition
Mild cognitive impairment	MCI	Objective evidence of impairment in one or more cognitive domains; preservation of independence in functional abilities; not demented
Early (pre-)MCI	EMCI	Concern on memory impairment and objective memory performance between 1.0 and 1.5 SD below the normative mean in a standardized test
Late MCI	LMCI	Concern on memory impairment and objective memory performance between 1.5 and below the normative mean in a standardized test
Amnestic MCI	aMCI	Memory deficits; early stage of Alzheimer's disease
Amnestic MCI-single domain	aMCI-s	Memory deficit is the only domain of cognition affected
Nonamnestic MCI-single domain	naMCI-s	A single domain of cognition is affected excluding memory
Multidomain amnestic MCI	aMCI-m	Multiple domains of cognition are affected including memory
Multidomain Nonamnestic MCI	naMCI-m	Multiple domains of cognition are affected excluding memory
ExecutiveMCI	eMCI	Impairment of executive functions, including attention; high risk of progressing to Alzheimer's disease
Cognitive frailty	CF	Presence of physical frailty and cognitive impairment with exclusion of concurrent Alzheimer's disease dementia or other dementias