CHAPTER

2

The Mediterranean Diet and Healthy Brain Aging: Innovations From Nutritional Cognitive Neuroscience

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INTRODUCTION

An enduring aim of research in the psychological and brain sciences is to reduce the debilitating effects of cognitive aging and to establish therapeutic interventions that promote healthy brain aging. Recent research in this effort has investigated the beneficial effects of nutrition, recognizing the importance of dietary intake and nutritional status on the aging brain and their capacity to protect against age-related neurological disease. Emerging research within the field of *Nutritional Cognitive Neuroscience* demonstrates that cognitive decline depends not only upon changes in brain structure and function, but critically also upon dietary intake and nutritional status.[1] Indeed, a growing body of evidence suggests that the Mediterranean diet (MEDI) may promote healthy brain aging,[2] regardless of other lifestyle factors.[3] The MEDI is comprised of foods that are known to deliver beneficial nutrients, including olive oil that provides monounsaturated fatty acids and polyphenols, fish that delivers omega-3 polyunsaturated fatty acids and vitamin D, and fruits and vegetables that provide vitamins C and E, carotenoids, folate, and polyphenols.[4]

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Combinations of these nutrients in the diet may optimize the protective vascular, metabolic, antioxidant, and anti-inflammatory mechanisms promoted by individual nutrients.[4]

Here, we present the therapeutic potential of the MEDI from the perspective of nutritional cognitive neuroscience. We call for the study of the MEDI through use of an integrative framework that synthesizes research in nutritional epidemiology and cognitive neuroscience, incorporating (1) methods for precise characterization of adherence to the MEDI based on analysis of nutrient biomarker patterns (NBPs); (2) comprehensive cognitive and neuropsychological assessments of mental ability; and (3) modern indices of brain health derived from high-resolution magnetic resonance imaging (MRI) of brain structure and function. Further, the relationship between the MEDI and healthy brain aging cannot be fully understood without an appreciation for the underlying mechanisms that promote neuroprotective benefits of the MEDI. Thus, a discussion of the neuroprotective vascular, metabolic, antioxidant, and anti-inflammatory mechanisms of the MEDI is provided. Finally, implementation of the MEDI as a personalized nutritional intervention for healthy brain aging requires an understanding of how individual variability in genetic makeup and environmental exposure determines response to nutritional intervention. Therefore, we consider the role of genetic and environmental factors in individual responses to nutrients within the MEDI. Through this line of work, nutritional cognitive neuroscience seeks to drive innovation in the design of nutritional interventions that promote healthy brain aging.

INNOVATIONS IN NUTRITIONAL EPIDEMIOLOGY

From a nutritional epidemiology perspective, exploration of the MEDI is innovative in that it provides several conceptual and methodological advances over the investigation of single nutrients. The MEDI allows for the estimation of dietary effects, or the interactive effects of constituent nutrients within a diet. As a dietary pattern, the MEDI provides a broad picture of food and nutrient consumption. Furthermore, the cumulative effects of multiple nutrients within the MEDI may be sufficiently large to detect changes in cognition and brain health, whereas the contrasting single nutrient approach may fail to capture the potentially small effects of individual nutrients. In these ways, the MEDI may therefore be more predictive of cognition and brain health than individual foods and nutrients.[5]

Despite the innovative nature of this dietary pattern, traditional methods of measuring the MEDI largely underrepresent variability in this dietary pattern. Current MEDI scoring algorithms fall prey to the flaws of traditional dietary measurement methods of nutritional epidemiology.[6] Historically, research on nutritional epidemiology examined food intake through the implementation of self-reported dietary assessment methods, such as food frequency questionnaires, 24-h recalls, and weighted food records.[7] These methods are advantageous because they are relatively easy to implement in large samples; however, these methods are prone to measurement error (i.e., underreporting of energy expenditure, errors in recall, and misestimating of portion sizes),[8,9] limited recall in individuals with cognitive decline,[7,10] biases on the basis of age, gender, socioeconomic status, and education,[11] as well as an inability to account for individual variability in nutrient absorption.[12]

On the other hand, biochemical markers of dietary exposure provide measures of nutritional status while bypassing the measurement errors of traditional dietary assessment techniques.[13] Biochemical markers can be measured in blood, urine, or tissue, with

TABLE 2.1 MEDI Dietary Components and Respective Biochemical Markers

Dietary Component	Nutrient	Biochemical Marker
Olive oil	Monounsaturated fatty acids	Oleic acid
	Polyphenols	Hydroxytyrosol
		Tyrosol
		Cinammic acid
		Homovanillic alcohol
		p-Coumaric acid
		Oleuropein
		Elenolic acid
Fish	Omega-3 polyunsaturated fatty acids	Eicosapentaenoic acid (EPA)
		Docosahexaenoic acid (DHA)
	Vitamin D	25-hydroxy vitamin D
Fruits and vegetables	Vitamin C	Ascorbic acid
		Dehydroascorbic acid
	Vitamin E	Alpha-tocopherol
		Gamma-tocopherol
	Carotenoids	Alpha-carotene
		Beta-carotene
		Beta-cryptoxanthin
		Lutein
		Zeaxanthin
		Lycopene
	Vitamin B	Folate (vitamin B9)
	Polyphenols	Chlorogenic acid
		Caffeic acid
		Ferulic acid
		Gallic acid
		Apigenin
		Luteolin
		Quercetin
		Kaempferol
		Myricetin
		Naringenin
		Hesperetin
		Anthocyanins

concentration of a given marker reflecting intake and metabolic processing of a particular nutrient or dietary component.[7,14] Epidemiological studies have identified approximately 100 biomarkers that correlate with dietary intake.[4] Notably, the MEDI and its constituent dietary components can be characterized by a selected group of biochemical markers (Table 2.1).[4,15,16] Therefore, measurement of the MEDI using biochemical markers may provide a more sensitive assessment of nutritional status that accounts for both dietary intake and individual variability in metabolic processing of nutrients and dietary components.

In addition to the implementation of biochemical markers of MEDI adherence, study of the MEDI may benefit from the use of statistical methods that empirically derive the nutrient patterns underlying the MEDI, affording the opportunity to investigate the relative contribution of its constituents on healthy brain aging. Scientific advances in the characterization of dietary patterns and measurement of nutrient biochemical markers have led to a new methodology in nutritional epidemiology for the measurement of NBPs. In this approach, nutrients are measured by way of biochemical markers in the blood (i.e., nutrient biomarkers) to avoid the methodological limitations of traditional dietary assessment techniques.[12] Second, principal component analysis is applied to empirically derive patterns of nutrients, referred to as NBPs, that reflect a linear combination of individual nutrient biomarkers. Each participant receives a standardized NBP score for each pattern, which is subsequently applied to assess the relationship between nutrient patterns, cognitive function, and brain health. This method may shed light on whether key individual nutrients or dietary components that comprise the MEDI, or the synergistic effects of the diet as a whole, drive beneficial mechanisms in the aging brain. By deriving NBPs of nutrients that are consumed together or interact through metabolism, NBP analysis is well positioned to reveal specific and sensitive effects of the MEDI on the aging brain.

INNOVATIONS IN COGNITIVE NEUROSCIENCE

Cognitive neuroscience captures the cognitive and neurological phenomena of aging by measuring declines in cognition, brain structure, and brain function that are a product of healthy aging or neurodegenerative disease. Decline in cognition represents the functional outcome of brain aging, with decline in select cognitive functions strongly relating to impairment in daily life activities.[17] MRI enables the study of early markers of brain aging—the structural and functional brain changes that are present prior to the onset of cognitive symptoms.[18–20]

MEDI on Cognitive Outcomes

The current state of evidence suggests that the MEDI may benefit overall cognition, as well as specific facets of intelligence. A recent review reports that out of 18 empirical studies, 13 linked adherence to the MEDI with reduced rates of cognitive decline, reduced risk of conversion to Alzheimer's disease, or improved cognitive function.[21] However, notable heterogeneity still exists in this line of evidence (Table 2.2).

Theories of cognitive decline demonstrate that facets of general intelligence do not deteriorate uniformly across the lifespan, and the study of the MEDI may benefit from the

TABLE 2.2 Cognitive Outcomes Related to MEDI Adherence

DECREASED RISK	
MCI	MEDI adherence[22,23]
	Daily vegetable intake[23]
	MUFA + PUFA/SFA ratio[23]
	Moderate alcohol consumption[23]
Conversion from MCI to AD	MEDI adherence[22]
Dementia	MEDI adherence[23]
AD	MEDI adherence[6]
All-type cognitive impairment	MEDI adherence[24]
AD-related mortality	MEDI adherence[25]
POSITIVE ASSOCIATION	
Global cognition	MEDI adherence[26–32]
	MUFA/SFA ratio[26,33]
	Whole grains[30,33]
	Nuts and legumes[30]
	PUFA intake[31]
	Fish intake[34]
	Lower meat product intake[35]
	Olive oil, walnuts, wine[36]
Attention	MEDI adherence[37]
Long-term memory	MEDI adherence[38]
	MUFA/SFA ratio[33]
	Olive oil, walnuts, wine[36]
Verbal fluency	MEDI adherence[39]
Working memory	MEDI adherence[36]
NO ASSOCIATION	
Global cognition	MEDI adherence[32,34,35,39–41]
Verbal fluency	MEDI adherence[27,40]
Memory	MEDI adherence[27,33,37,40,41]
Executive function	MEDI adherence[37,41,42]
Attention	MEDI adherence[42]
Working memory	MEDI adherence[38]
Processing speed	MEDI adherence[41]
Visual-spatial ability	MEDI adherence[41]

MCI, mild cognitive impairment; AD, Alzheimer's disease; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid

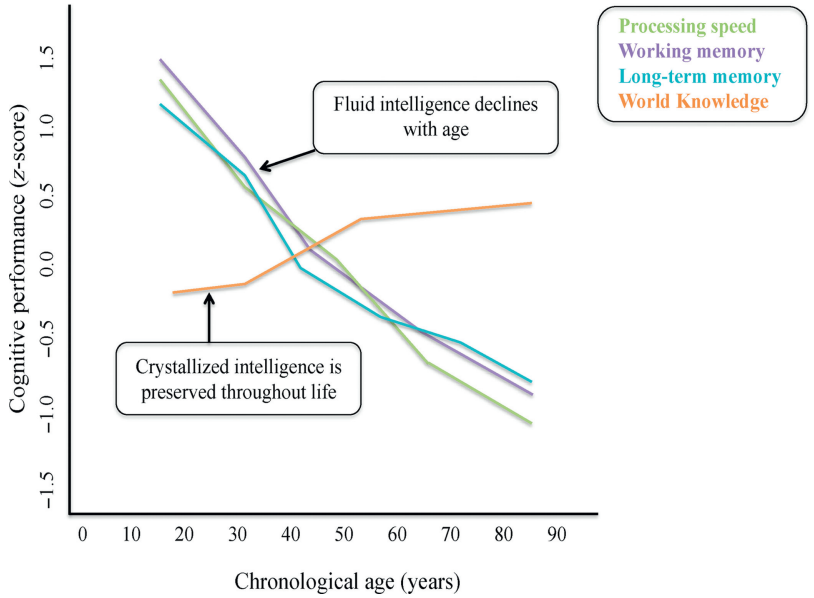

FIGURE 2.1 **Age-related changes in cognition:** Theories of cognitive decline demonstrate that facets of intelligence do not deteriorate uniformly across the lifespan, and the study of the MEDI may benefit from implementation of this theoretical approach. It is well-known that crystallized intelligence, also known as general or semantic knowledge, is well-maintained into the sixth, seventh, and even later decades of life. Conversely, fluid intelligence, or the ability to adaptively solve problems without prior knowledge or experience, shows approximately linear decreases with age. Therefore the measurement of dysfunction in facets of intelligence that show steady, age-related decline, even when measurable deficits in general cognitive function are absent, may capture the continuum of normal aging or preclinical stages of dementia in a more sensitive manner. *Adapted from Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 2009;60:173–196.*

implementation of this theoretical approach. For instance, it is well-known that crystallized intelligence, also known as general or semantic knowledge, is well-maintained into the sixth, seventh, and even later decades of life. Conversely, fluid intelligence, or the ability to adaptively solve problems without prior knowledge or experience, shows approximately linear decreases with age (Fig. 2.1).[44,45] Therefore the measurement of dysfunction in facets of intelligence that show steady, age-related decline, even when measurable deficits in general cognitive function are absent, may capture the continuum of normal aging or preclinical stages of dementia in a more sensitive manner.[46]

MEDI on Neuroimaging Outcomes

Neuroimaging evidence indicates that the MEDI benefits brain structure and function in global and region-specific ways. To our knowledge, a comprehensive review on neuroimaging outcomes related to MEDI adherence has not yet been published. As with cognitive outcomes, there is significant diversity in reports linking the MEDI to neuroimaging outcomes (Table 2.3).

Parallel to changes in cognition with age, decline in brain structure and function does not occur uniformly across the lifespan. Thus investigating how the MEDI may impact

TABLE 2.3 Neuroimaging Outcomes Related to MEDI Adherence

POSITIVE ASSOCIATION	
Total gray matter volume/integrity	MEDI adherence[47,48]
	Fish intake[48,49]
	Low meat intake[35,49]
	Moderate alcohol intake[50]
Frontal lobe	MEDI adherence[48,49,51]
	Fish intake[48]
	Vegetable intake[48]
Temporal lobe	MEDI adherence[49,51,52]
	Fish intake[48]
	Whole grain intake[48]
Parietal lobe	MEDI adherence[48,49]
	Fish intake[48]
	Legume intake[48]
	Vegetable intake[48]
Occipital lobe	MEDI adherence[48]
	Legume intake[48]
Total white matter volume	MEDI adherence[48]
White matter hyperintensity burden	MEDI adherence[53]
Structural connectivity	MEDI adherence[54]
Infarcts	MEDI adherence[53]
Lower amyloid-beta load	MEDI adherence[52]
Glucose metabolism	MEDI adherence[52]
NO ASSOCIATION	
Total gray matter volume/integrity	MEDI adherence[35,54]
White matter volume	MEDI adherence[54]
NEGATIVE ASSOCIATION	
Parietal lobe	Fruit intake[48]

different trajectories of structural and functional decline may be fruitful. For instance, gray matter atrophy varies by region, with areas such as the superior frontal, middle frontal, and superior parietal cortex showing susceptibility to early age-related atrophy (Fig. 2.2).[55] Likewise, structural connectivity, reflecting white matter tract integrity, varies by region, with superior and anterior regions showing susceptibility to age-related degeneration (Fig. 2.2).[56] Functional neuroimaging has demonstrated that age-related decline in

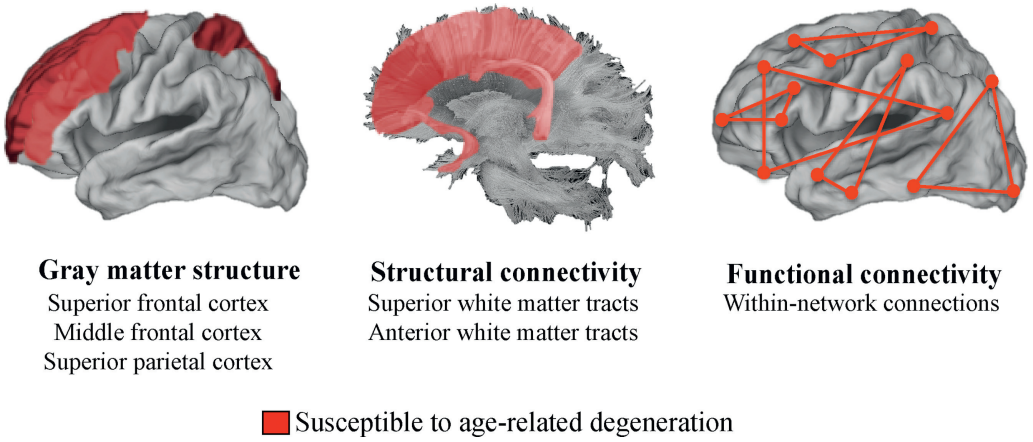

FIGURE 2.2 **Age-related changes in brain health:** Decline in brain structure and function does not occur uniformly across the lifespan. Gray matter atrophy varies by region, with areas such as the superior frontal, middle frontal, and superior parietal cortex showing susceptibility to early age-related atrophy. Structural connectivity, reflecting white matter tract integrity, varies by region, with superior and anterior regions showing susceptibility to age-related degeneration. In addition, functional connectivity between regions that work together as networks changes as a function of age and is characterized by a weakening of within-network connections.

cognitive processes begins early, even in the absence of disease.[43] Age-related changes in brain activity can be characterized by increased activity in prefrontal regions and reduced activity in posterior regions (i.e., the posterior−anterior shift theory)[57,58] as well as reduced asymmetry in prefrontal cortex activity (i.e., the HAROLD model).[59] In addition, functional connectivity between regions that work together as networks changes as a function of age. In general, a weakening of within-network connections is accompanied by a strengthening of between-network connections (Fig. 2.2).[60] While several studies have investigated the impact of the MEDI on regional gray matter atrophy (Table 2.3), there have been limited efforts to investigate the impact of the MEDI on structural connectivity (Table 2.3),[54] and, to our knowledge, no research to investigate the impact of the MEDI on functional connectivity.

Integration of Cognitive and Neuroimaging Outcomes

A growing body of evidence suggests that certain nutrients may slow or prevent aspects of age-related cognitive decline by influencing particular age-related changes in brain structure.[1,61−66] To date, no study has investigated whether the MEDI or components of the MEDI may impact specific features of cognition by targeting particular aspects of brain health. Future integration of cognitive and neuroimaging outcomes will provide several novel perspectives by (1) elucidating the specific neural structures upon which the MEDI and its constituent nutrients may act to benefit cognition and (2) accounting for differential declines in cognitive function along with underlying neural structures.

MECHANISMS OF THE MEDITERRANEAN DIET IN THE BRAIN

Long-term exposure to a healthy diet may have slow, cumulative beneficial effects on the brain.[2] In the case of the MEDI, combinations of nutrients may optimize the neuroprotective vascular, metabolic, antioxidant, and anti-inflammatory mechanisms promoted by individual nutrients, reviewed in turn in the following section.[4,26]

The MEDI promotes healthy vasculature by way of reducing total cholesterol and low-density lipoproteins (i.e., "bad cholesterol")[67] and improving endothelial function.[68] Broadly, these actions lower the risk of vascular comorbidities, dyslipidemia, hypertension, and coronary artery disease.[69] Within the brain, these actions are linked to a reduction in white matter lesions and promotion of white matter microstructure.[69] Thus, the MEDI may support white matter microstructure by way of promoting healthy vasculature.

The MEDI also plays a role in preventing metabolic dysfunction. The composition of the diet, which includes low carbohydrate (45%), moderately high total fat (35%–40%), and low saturated fat (less than 10%), may protect against metabolic syndrome, which is a constellation of interrelated metabolic dysfunctions.[69] Metabolic syndrome is known to impact brain health and has been linked to an increased risk of cognitive impairment, and more specifically, vascular dementia.[70,71] Hence, the MEDI may prevent cognitive impairment in part by promoting a healthy metabolic state.

In the aging brain, the MEDI may be especially beneficial in the reduction of oxidative stress. Aging and dementia are characterized by lipid peroxidation, nitration, free carbonyl production, and nucleic acid oxidation.[69] Complex polyphenols and other antioxidants in olive oil, wine, fruits, vegetables, vitamin C, vitamin E, and carotenoids can increase enzymes with antioxidant properties, such as paraoxonase and plasma carotenoids.[72] Antioxidants, in turn, are thought to increase concentrations of brain-derived neurotrophic factor (BDNF), which supports existing neurons in addition to promoting growth of new neurons and synapses.[73,74] Therefore, by reducing levels of oxidative stress, the MEDI may support brain structure, and subsequently, brain function.

Another mechanism through which the MEDI may promote healthy aging is the prevention of inflammation. Inflammation is associated with cognitive decline, mild cognitive impairment, and vascular dementia.[69] Adherence to the MEDI is known to reduce levels of C-reactive protein, a marker for inflammation linked to cognitive decline, Alzheimer's disease, and vascular dementia,[75,76] as well as interleukin-6, a mediatory cytokine of inflammation linked to early amyloid plaques, greater cognitive decline, and increased risk of dementia.[77–79] Thus the MEDI may also confer neuroprotective benefits by way of reducing inflammation.

Though the MEDI is known to benefit brain health through a multitude of mechanisms, future investigations are needed to clarify these benefits. First, future work should aim to identify whether the MEDI as a whole optimally promotes brain health, or whether individual dietary components or nutrients of the MEDI drive protective benefits.[69] Second, evidence on the protective mechanisms of the MEDI is not consistent. Adherence to the MEDI has also been shown to have no link to inflammatory status, as measured by C-reactive protein,[80] and metabolic status, as measured by fasting insulin and adiponectin,[80] and vascular status.[6,54] Thus future empirical work is needed to investigate whether

particular components of the MEDI offer specific protective benefits, and importantly, whether these mechanisms drive preservation or improvement of select aspects of cognition and brain health in aging.

IMPACT OF GENETIC VARIABILITY AND ENVIRONMENTAL SUSCEPTIBILITY: IMPLICATIONS FOR PERSONALIZED MEDICINE

Individual variability in response to nutrition may play a large role in contributing to the inconsistencies between studies on nutrition, cognition, and brain health.[81] In fact, inconsistencies in studies on the MEDI, which consists of a variety of neuroprotective nutrients, may at least in part be explained by individual variability in metabolism of these constituent nutrients. Individual variability can arise from a variety of factors, including genetic composition and environmental exposure, explained in turn in the following section.

In regard to genetic composition, single nucleotide polymorphisms, or changes in single nucleotides, are one example of how genetic variability may influence response to nutrition.[81] For instance, the apolipoprotein E (APOE) gene is essential for lipid transport and has been implicated in Alzheimer's disease.[82] Individuals who carry the APOE e4 allele, a risk factor for Alzheimer's disease, experience greater cognitive benefits from the MEDI than individuals who do not carry the APOE e4 allele.[24] Additionally, polymorphisms in fatty acid desaturase 2 (FADS2), a gene involved in fatty acid control,[83] may substantially influence the metabolic processing of polyunsaturated and monounsaturated fatty acids prevalent in the MEDI.[81] Thus, genetic composition, and in particular single nucleotide polymorphisms, may contribute to individual variability in metabolic response to the MEDI.

Exposure to select nutrients may also induce epigenetic effects, or changes to genetic material that induce particular phenotypes.[50] More specifically, epigenetic processes play a role in influencing non-coding RNA, which is RNA that is not translated into protein but plays a key role in transcription and gene function.[50] As transcriptionally active cells, neurons show strong expression of non-coding RNAs, and are therefore particularly susceptible to epigenetic processes.[50] One such epigenetic event is DNA methylation, which is influenced by components of the MEDI including folate, carotenoids, vitamin C, vitamin E, isoflavones, and vitamin D.[84] Another primary epigenetic process, histone modification, can also be influenced by MEDI components, including carotenoids, vitamin C, vitamin E, omega-3 polyunsaturated fatty acids, resveratrol, oleuropein, anthocyanins, and vitamin D.[84] Therefore, nutrients within the MEDI may induce epigenetic events, which in turn may prompt transcriptional alternations of neuronal structure and function.

In addition to their separable effects, genetic variability and environmental exposure may also interact to determine benefits of the MEDI in the phenomenon of telomere shortening. Telomeres represent repetitive DNA sequences at the end of eukaryotic chromosomes that prevent the loss of genomic DNA, and therefore, preserve physical integrity of the chromosome.[85] Telomere shortening, or attrition associated with each somatic cell division,[86] is a biomarker of biological aging as well as a predictor of clinical outcomes in humans.[87] Despite its strong association with age, telomere length also shows substantial variability that is independent of chronological age.[88–90] Telomere attrition is accelerated by oxidative stress and inflammation,[91,92] but may be slowed by dietary and lifestyle

choices through mechanisms of inflammation, oxidative stress, DNA integrity, and DNA methylation.[93] In fact, adherence to the MEDI has been linked to telomere length. In vitro work suggests that the MEDI protects cells from oxidative stress by preventing cellular senescence, cellular apoptosis, and reducing telomere attrition.[94] In humans, adherence to the MEDI has been associated with longer telomere length and higher telomerase activity levels.[95] Interestingly, these effects are dependent on genetic variability in the telomerase RNA component and adherence to the dietary pattern as a whole, rather than individual components of the diet.[85,96] Thus, clinical response to the MEDI may also depend on the phenomenon of telomere shortening, which presents as a combination of genetic variability and environmental exposure.

As clinical investigations of personalized and comprehensive approaches to nutritional intervention are developed, individual variability in genetic composition and environmental susceptibility cannot be overlooked. Personalized nutritional interventions will be well positioned to prevent or alleviate age-related disorders of the brain after accounting for the exogenous factor of ingestion and the endogenous factors of genetic variability and epigenetic events.[81]

NUTRITIONAL COGNITIVE NEUROSCIENCE: AN INTERDISCIPLINARY APPROACH

Increasing evidence indicates that the impact of nutrition on brain health is complex and multifactorial. Nutritional epidemiology has developed methods for sensitively deriving nutrient patterns, such as nutrient biomarker pattern analysis. Application of such methods to the study of the MEDI can improve the resolution of nutritional assessment. Cognitive neuroscience shows that brain aging is a heterogeneous process characterized by widespread changes in brain structure and brain function. The study of the MEDI will benefit from the implementation of high-resolution neuroimaging methods that account for individual variability in brain aging. Finally, recent findings indicate that particular nutrients may influence specific cognitive functions by targeting certain aspects of brain health.[1,61–66,97] This interdisciplinary approach may greatly benefit investigations that aim to elucidate the relationship between the MEDI, cognition, and brain health, along with characterizing underlying mechanisms, endogenous genetic factors, and exogenous environmental influences. Research at the frontiers of nutritional cognitive neuroscience aims to establish nutritional interventions that account for individual variability in nutritional status and brain health (Fig. 2.3). However, considerably more research is needed to unravel the complex relationships between nutrition, cognition, and brain health. Several unanswered questions remain:

- Evidence suggests that the MEDI as a dietary pattern may slow or prevent cognitive and brain aging, but also that particular nutritional components of the MEDI provide benefits to cognition and brain health. Thus, is it key individual nutrients that comprise the MEDI, or the synergistic effects of the diet as a whole, that drive beneficial mechanisms in the aging brain?

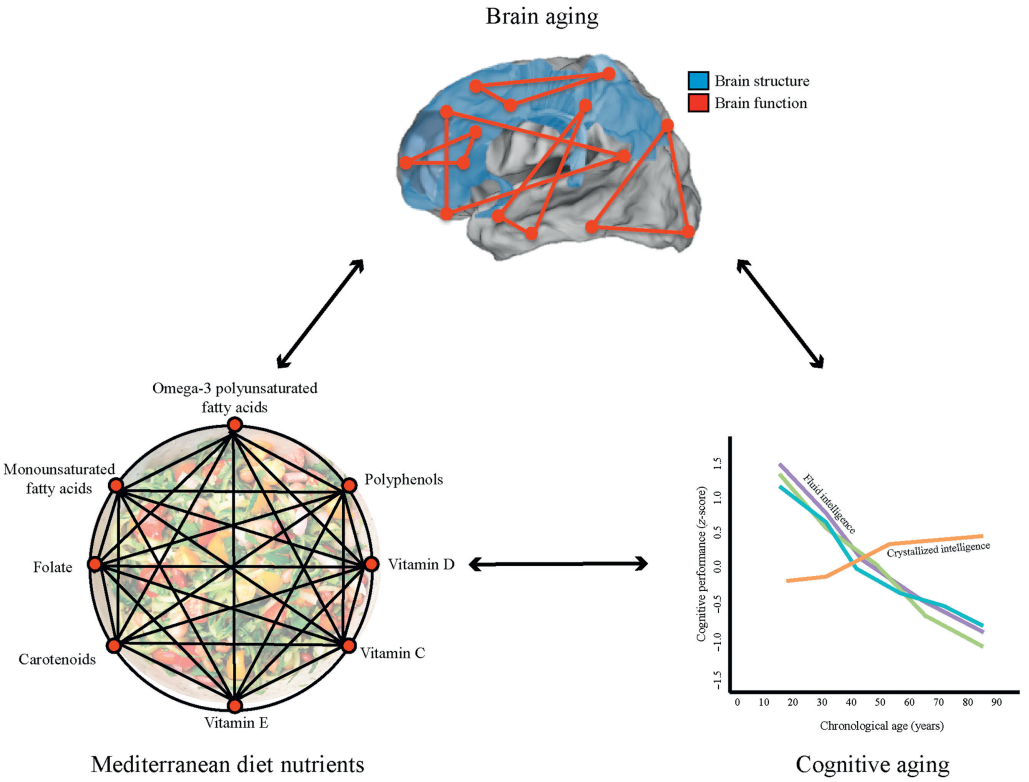

FIGURE 2.3 **The relationship between diet, cognitive aging, and brain aging is multifaceted in nature:** Nutrient patterns, such as the Mediterranean diet (MEDI), capture the interactive effects of constituent nutrients. High-resolution neuroimaging methods can characterize the widespread changes in brain structure and function associated with age. The continuum of normal aging or preclinical stages of dementia can be captured by measuring dysfunction in facets of intelligence that show steady, age-related decline. In order to understand how the MEDI can benefit cognitive and brain aging, each of these complex domains must be characterized through the use of precise methodology. Furthermore, these methods are well suited to identify whether particular nutrients may influence specific cognitive functions by targeting certain aspects of brain health.

- Theories of cognitive decline demonstrate that cognitive function does not deteriorate uniformly across the lifespan. Are cognitive benefits of the MEDI specific to particular facets of intelligence—for instance, those that show steady, age-related decline?
- Parallel to changes in cognition with age, decline in brain structure and function does not occur uniformly across the lifespan. Several studies have investigated the impact of the MEDI on regional gray matter atrophy, but there have been limited efforts to investigate the impact of the MEDI on structural and functional connectivity. Therefore, the question remains: how does the MEDI impact different aspects of brain aging?
- The MEDI is thought to benefit the aging brain through vascular, metabolic, antioxidant, and anti-inflammatory mechanisms. Is it the case that individual nutrients

within the diet promote specific neuroprotective mechanisms, or do synergistic effects of nutrient groups within the diet drive neuroprotective benefits?
- Individual variability in response to nutrition, arising from genetic composition and environmental exposure, may play a substantial role in determining how the MEDI may impact cognitive and brain aging. To what extent do genetic composition and environmental exposure determine response to nutrients within the MEDI?

CONCLUSION

A large body of evidence endorses the MEDI as a nutritional intervention for healthy brain aging, but future research from the perspective of nutritional cognitive neuroscience shows potential to clarify inconsistencies in the field. By applying cutting-edge techniques from nutritional epidemiology (nutrient biomarkers and data-driven statistical techniques) and cognitive neuroscience (sensitive and specific neuropsychological batteries and high-resolution MRI measures of brain structure and function), nutritional cognitive neuroscience will enrich our understanding of the link between the MEDI and healthy brain aging. Ultimately, this approach will enhance the precision of nutritional interventions by supporting the targeted treatment of age-related decline in cognition and brain health.

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