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Integrating Nutrient Biomarkers, Cognitive Function, and Structural MRI Data to Build Multivariate Phenotypes of Healthy Aging

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A B S T R A C T

Background: Research in the emerging field of nutritional cognitive neuroscience demonstrates that many aspects of nutrition—from entire diets to specific nutrients—affect cognitive performance and brain health.
Objectives: Although previous research has primarily examined the bivariate relationship between nutrition and cognition or nutrition and brain health, this study sought to investigate the joint relationship between these essential and interactive elements of human health.
Methods: We applied a state-of-the-art data fusion method, coupled matrix tensor factorization, to characterize the joint association between measures of nutrition (52 nutrient biomarkers), cognition (Wechsler Abbreviated Test of Intelligence and Wechsler Memory Scale), and brain health (high-resolution MRI measures of structural brain volume) within a cross-sectional sample of 111 healthy older adults, with an average age of 69.1 y, 62% being female, and an average body mass index of 26.0 kg/m^2.
Results: Data fusion uncovered latent factors that capture the joint association between specific nutrient profiles, cognitive measures, and cortical volumes, demonstrating the respects in which these health domains are coupled. A hierarchical cluster analysis further revealed systematic differences between a subset of variables contributing to the underlying latent factors, providing evidence for multivariate phenotypes that represent high and low levels of performance across multiple health domains. The primary features that distinguish between each phenotype were as follows: *1*) nutrient biomarkers for monounsaturated and polyunsaturated fatty acids; *2*) cognitive measures of immediate, auditory, and delayed memory; and *3*) brain volumes within frontal, temporal, and parietal cortexes.
Conclusions: By incorporating innovations in nutritional epidemiology (nutrient biomarker analysis), cognitive neuroscience (high-resolution structural brain imaging), and statistics (data fusion), this study provides an interdisciplinary synthesis of methods that elucidate how nutrition, cognition, and brain health are integrated through lifestyle choices that affect healthy aging.

Keywords: nutritional cognitive neuroscience, nutrient biomarker analysis, data fusion, healthy aging, phenotypes

Introduction

One of the greatest scientific challenges of our time is to reduce the incidence of age-related neurologic disease and the burden of associated cognitive impairments on health decisions, social function, and quality of life [1]. A central aim of this effort is to examine modifiable risk factors and lifestyle choices, such as diet and nutrition, which may have beneficial effects on brain health and serve to guide public policy recommendations regarding dietary choices that promote healthy brain aging. Despite the importance of this goal and promising evidence in favor of specific nutrients for the promotion of brain health, clinical trials examining nutritional supplementation have been predominately unsuccessful [2–9].

Accumulating evidence suggests that this disconnect may be explained by a focus on single nutrients and a failure to consider the interactive action and metabolism of nutrient combinations [10,11]. Historically, research in nutritional epidemiology has investigated the beneficial effects of specific nutrients on human health, aging, and disease. However, this single nutrient approach is known to have several limitations [12]: *1*) the failure

Abbreviations used: CMTF, coupled matrix tensor factorization; NVC_{Hi}, nutrition, volume, cognition high group; NVC_{Lo}, nutrition, volume, cognition low group.

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to capture the interactive or synergistic effects among nutrients found in dietary patterns; *2*) the high level of intercorrelation among nutrients (such as potassium and magnesium), which may limit the ability to examine nutrients in isolation; *3*) the small effect sizes of single nutrients relative to the cumulative effects of multiple nutrients in a dietary pattern; and *4*) the association of single nutrients with specific dietary patterns, which may significantly influence health outcomes. These considerations have led to an increasing emphasis in nutritional epidemiology on characterizing dietary patterns and broadening the scope of standard single nutrient approaches. Therefore, this study sought to assess dietary intake based on a wide range of nutrient biomarkers measured in blood plasma, such as carotenoids, vitamins, saturated and trans-fatty acids, and monounsaturated and polyunsaturated fatty acids.

To investigate the role of nutrition on cognitive performance and brain health, this study administered well-validated neuropsychologic tests of general intelligence and memory [13], in addition to high-resolution MRI measures of structural brain volume [14]. Although previous research has primarily examined bivariate associations between nutrition and cognitive performance or nutrition and brain health [15], this study sought to investigate the joint relationship between all 3 health domains, enabling new insights into how nutrition, cognition, and brain health are integrated through lifestyle decisions that affect healthy aging. This novel approach is motivated by research in the emerging field of nutritional cognitive neuroscience, which seeks to understand nutrition's effect on cognitive performance and brain health across the lifespan [16].

Research in this burgeoning field demonstrates that nutrition has pervasive effects on both cognition and brain health [10,11,17], setting the stage for new methods to uncover multivariate phenotypes of healthy brain aging derived from the joint analysis of nutrient biomarkers, cognitive performance, and MRI measures of brain health. Motivated by these considerations, this study sought to build multivariate phenotypes of healthy aging through the application of a state-of-the-art data fusion method, coupled matrix tensor factorization (CMTF [18]), within a large sample of neurologically healthy older adults (n = 111). By incorporating innovations in nutritional epidemiology (nutrient biomarker analysis), cognitive neuroscience (high-resolution structural brain imaging), and statistics (data fusion), this study enables an interdisciplinary synthesis of methods that elucidate how nutrition, cognition, and brain health are integrated through lifestyle choices that affect healthy aging.

Methods

Study participants

In total, 111 healthy older adults were recruited from the Carle Foundation Hospital as study participants. Participant demographics are reported in Table 1. This cross-sectional study enrolled healthy elderly adults from the Illinois Brain Aging Study cohort, a sample of community-dwelling Caucasian men and women aged 65–75 y. The mean age of participants was 69 y and 63% were women. Participants were neurologically healthy and did not have evidence of cognitive impairment, as determined by a score of <26 on the mini-mental state examination. Participants with mild cognitive impairment, dementia, a psychiatric illness within the past 3 y, a stroke within the past 12 mo, cancer in the past 3 y, an inability to complete study activities, previous involvement in cognitive training or dietary intervention studies, or contraindications for MRI examination were excluded. All participants were right-handed with normal, or corrected to normal, vision.

TABLE 1
Participant demographics[1]

Demographic	Values
Age (y)	69.1 ± 3.18
Body mass index (kg/m^2)	25.9 ± 3.62
Females	62
Education	
Some high school	1
High school degree	10
Some college	17
College degree	72
Income ($)	
<15,000	1
15,001–25,000	4
25,001–$50,000	19
50,001–$75,000	22
75,001–$100,000	23
>100,000	31

Values are given as mean ± SD or percentages.
[1] Sample size is 111. Averages and percentages are computed from the total sample size.

Protocol approval and participant consent

This study was approved by the University of Illinois Institutional Review Board and the Carle Hospital Institutional Review Board, and in accordance with the stated guidelines, all participants read and signed informed consent documents.

Nutrient biomarkers

Complete blood-based biomarker data were available for 52 dietary nutrients, which included carotenoids, vitamins, saturated and trans-fatty acids, monounsaturated and polyunsaturated fatty acids. Plasma lipid concentrations were measured with gas chromatography using flame ionization and peaks of interest identified by comparison with authentic fatty acid standards (the methods are detailed in [19], under the Plasma Phospholipid Polyunsaturated Fatty Acid Acquisition section). Ethylenediaminetetraacetic acid–treated plasma carotenoid and vitamin concentrations were analyzed using high-performance liquid chromatography with a photodiode array detector using ultraviolet detection [20]. Table 2 lists all 52 nutrients along with their sample means and standard deviations.

Cognitive assessment

Two well-validated cognitive batteries were administered to assess cognitive performance: the Wechsler Abbreviated Scale of Intelligence and the Wechsler Memory Scale. Descriptive statistics for these tests are reported in Table 3. Moreover, a description of the types of items included in these test batteries is presented in Supplemental Methods 1.

Structural MRI

Structural MRI data were acquired using a Siemens Magnetom 3 Tesla Trio scanner with a 32-channel head coil in the MRI

TABLE 2
Average plasma concentration for 52 nutrient biomarkers of 111 participants

Nutrient class	Nutrient biomarker	Mean ± SD
Monounsaturated fatty acids (μmol/L)	*cis*-7 Hexadecenoic acid (16:1n-9)	4.08 ± 1.05
	Palmitoleic acid (16:1n-7)	16.2 ± 7.35
	Oleic acid (18:1n-9)	247 ± 62.7
	cis-Vaccenic acid (18:1n-7)	36.1 ± 8.73
	Eicosenoic acid (20:1n-9)	3.65 ± 1.02
	Euricic acid (22:1n-9)	0.436 ± 0.269
	Nervonic acid (24:1n-9)	28.0 ± 6.91
Polyunsaturated fatty acids (μmol/L)	Linoleic acid (18:2n-6)	623 ± 162
	γ-Linolenic acid (18:3n-6)	2.80 ± 1.61
	Dihomolinoleic acid (20:2n-6)	9.32 ± 2.68
	Dihomo-γ-linolenic (20:3n-6)	73.1 ± 26.1
	Arachidonic acid (20:4n-6)	311 ± 78.5
	Docosadienoic acid (22:2n-6)	0.298 ± 0.118
	Adrenic acid (22:4n-6)	10.9 ± 3.67
	Docosapentanoic acid (22:5n-6)	6.56 ± 2.65
	α-Linolenic acid (18:3n-3)	5.47 ± 2.68
	Stearidonic acid (18:4n-3)	2.41 ± 0.881
	Sciadonic acid (20:3n-3)	1.32 ± 0.564
	Eicosapentaenoic acid (20:5n-3)	25.5 ± 17.0
	Docosapentaenoic acid (22:5n-3)	23.5 ± 7.10
	Docosahexaenoic acid (22:6n-3)	81.8 ± 33.2
Saturated fatty acids (μmol/L)	Capric acid (10:0)	0.128 ± 0.132
	Lauric acid (12:0)	1.33 ± 0.957
	Myristic acid (14:0)	12.8 ± 4.73
	Pentadecyclic acid (15:0)	6.45 ± 1.71
	Palmitic acid (16:0)	770 ± 181
	Stearic acid (18:0)	414 ± 89.4
	Arachidic acid (20:0)	10.3 ± 2.16
	Behenic acid (22:0)	30.7 ± 7.34
	Lignoceric acid (24:0)	20.3 ± 5.48
Trans-fatty acids (μmol/L)	*trans*-Palmiteloleic acid (16:1n-9)	0.492 ± 0.377
	trans-Palmitoleate acid (16:1n-7)	4.34 ± 1.80
	trans-Vaccenic acid (18:1n-7)	5.07 ± 2.44
	trans-Eladidic acid (18:1n-9)	4.38 ± 2.27
	Petroselaidic acid (18:1n-12)	0.214 ± 0.366
	Linoelaidic (18:2T)	1.07 ± 0.739
	Conjugated linoleic acid (18:2)	0.360 ± 0.220
Carotenoids (nmol/L)	α-Carotene	193 ± 174
	cis-13-β-Carotene	50.2 ± 26.4
	trans-β-Carotene	780 ± 625
	Cryptoxanthin	181 ± 141
	trans-Lutein	379 ± 244
	cis-Lutein	60.1 ± 40.5
	Zeaxanthin	86.3 ± 68.9
	Lycopene-9-*cis*	215 ± 106
	Lycopene-13-*cis*	423 ± 219
	trans-Lycopene	843 ± 413
Vitamins (nmol/L)	A1 (Retinol)	2870 ± 902
	K1 (Phylloquinone)	3.14 ± 3.86
	E (α-tocopherol)	44,400 ± 18,500
	E (γ-tocopherol)	5140 ± 2800

TABLE 3
Average cognitive test scores for WASI and WMS of 111 participants

Test	Score ± SD
Verbal comprehension (WASI)	115 ± 15
Perceptual reasoning (WASI)	113 ± 13
Full scale IQ (WASI)	116 ± 13
Auditory memory index (WMS)	49 ± 9
Visual memory index (WMS)	24 ± 4
Immediate memory index (WMS)	37 ± 5
Delayed memory index (WMS)	36 ± 6

Laboratory of the Beckman Institute Biomedical Imaging Center at the University of Illinois. A high-resolution multiecho T1-weighted magnetization-prepared gradient-echo structural image was acquired for each participant (0.9-mm isotropic; repetition time: 1900 ms; inversion time: 900 ms; time to echo: 2.32 milliseconds, with generalized autocalibrating partially parallel acquisitions and an acceleration factor of 2). A volumetric analysis involved cortical reconstruction with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). Volumes were estimated for the 68 gray matter regions defined by the FreeSurfer Desikan-Killiany atlas [21]. Each gray matter volume was also adjusted for the total intracranial volume size to consider differences in head size. Table 4 identifies the 68 gray matter regions and corresponding sample volumetric means and standard deviations.

Statistical methods

Data fusion: integrating nutritional, cognitive, and structural MRI data

The common factor structure explaining variability in nutrient biomarkers, cognitive performance, and structural brain volume was determined using the CMTF data fusion method [17]. CMTF was applied to derive the component factor matrices for each mode [22]. The obtained factor matrices capture common sources of variation within the coupled data set and are representative of the observed data in a low dimensional space. Supplemental Methods 2 provides further detail regarding the data fusion analysis.

Hierarchical clustering of fused data to identify population subgroups

Hierarchical clustering of the CMTF results enabled the discovery of statistical regularities among participants based on the joint modeling of nutrition, cognition, and structural brain volume. A dissimilarity matrix based on Euclidean distance was generated from the observed data for the subset of variables contributing to the underlying latent factors obtained from

TABLE 4
Average gray matter volumes (mm^3) in the left and right hemispheres of 111 participants

Region of interest (ROI)	Left hemisphere ± SD	Right hemisphere ± SD
Bank superior temporal	2240 ± 452	2170 ± 393
Caudal anterior cingulate	1770 ± 431	2000 ± 450
Caudal middle frontal	5800 ± 1010	5410 ± 975
Cuneus	2670 ± 410	2820 ± 483
Entorhinal	1790 ± 380	1710 ± 359
Frontal pole	801 ± 177	1080 ± 232
Fusiform	9240 ± 1410	8950 ± 140
Inferior parietal	11,300 ± 1690	13,400 ± 1680
Inferior temporal	10,100 ± 1660	9710 ± 1560
Insula	6410 ± 687	6540 ± 764
Isthmus cingulate	2460 ± 424	2290 ± 455
Lateral occipital	10,900 ± 1540	10,800 ± 1430
Lateral orbitofrontal	6810 ± 798	6740 ± 775
Lingual	6110 ± 990	6160 ± 837
Medial orbitofrontal	4690 ± 679	4750 ± 642
Middle temporal	9470 ± 1470	10,800 ± 1470
Paracentral	3150 ± 521	3590 ± 527
Parahippocampal	2060 ± 336	1920 ± 269
Pars opercularis	4260 ± 649	3620 ± 567
Pars orbitalis	2050 ± 269	2430 ± 335
Pars triangularis	3250 ± 468	3790 ± 674
Pericalcarine	1920 ± 360	2140 ± 378
Postcentral	9310 ± 1160	8850 ± 1140
Posterior cingulate	2840 ± 455	2850 ± 423
Precentral	12,400 ± 1380	12,100 ± 1330
Precuneus	8740 ± 1090	9100 ± 1100
Rostral anterior cingulate	2600 ± 480	2100 ± 418
Rostral middle frontal	14,200 ± 1830	14,600 ± 2010
Superior frontal	20,000 ± 2110	19,300 ± 2180
Superior parietal	12,300 ± 1360	12,500 ± 1600
Superior temporal	10,800 ± 1560	10,700 ± 1420
Supramarginal	10,700 ± 1500	9430 ± 1440
Temporal pole	2430 ± 382	2220 ± 334
Transverse temporal	1080 ± 213	827 ± 167

CMTF. Agglomerative hierarchical clustering, with complete linkage, was applied to the dissimilarity matrix to identify population subgroups.

Cohen's d effect sizes for phenotypes

Cohen's d effect sizes of mean differences were computed from the 2 groups determined by hierarchical clustering. The Cohen's d statistic is computed by taking the difference between the means of each group and expressing it in standard deviation units, with larger values reflecting a larger difference between the 2 groups. The Cohen's d effect sizes of 0.2 are small; 0.5 moderate; and >0.8 large. Cohen's d effect sizes were computed for nutrient levels and cognitive test scores, and volumetric measures was conducted using the Cohen's d measure [23]. Then, nutrients, cognitive tests, and structural brain volumes that exhibited large effect size differences between clustered groups were identified as distinct phenotypes.

Results

Data fusion

The fusion of nutritional, cognitive, and structural MRI data using CMTF revealed underlying latent factors capturing common patterns of variability for the 3 data domains. The CMTF model fit was 91.2% with respect to the first component of the derived latent factors and improved only slightly to 92.6% and 93.5% for the second and third components, respectively. Therefore, we selected the first latent component that accounted for the largest variance within the fused data set to estimate nutrient biomarkers, cognitive test scores, and volumetric measures. a Column-wise correlation was then performed between the estimated and observed measures within each data domain in order to identify the subset of nutrient biomarkers, cognitive tests, and structural brain volumes, which contributed largely to the first latent component (variable names in Tables 5–7).

Hierarchical clustering

Having identified the subset of nutrient biomarkers, cognitive tests, and structural brain volumes (see step 7 in Supplemental Methods 2), we then investigated whether these variables differentiated the sample population into distinct subgroups using hierarchical clustering. Two subgroups were identified (Figure 1). One group demonstrated larger average nutrient levels, cognitive scores, and brain volumes (labeled NVC_{Hi} for nutrition, volume, cognition high group), whereas the other was

TABLE 5
Cohen's d effect sizes between groups for nutrients, ordered from the largest to the smallest

Nutrient	Nutrient category	Cohen d
cis-7 Hexadecenoic acid	Monounsaturated fatty acid	1.29
Stearic acid	Saturated fatty acid	1.07
Oleic acid	Monounsaturated fatty acid	1.04
Dihomo-γ-linolenic	Polyunsaturated fatty acid	0.97
cis-Vaccenic acid	Monounsaturated fatty acid	0.96
Eicosenoic acid	Monounsaturated fatty acid	0.90
Palmitic acid	Saturated fatty acid	0.88
Dihomolinoleic acid	Polyunsaturated fatty acid	0.85
γ-Linolenic acid	Polyunsaturated fatty acid	0.84
Stearidonic acid	Polyunsaturated fatty acid	0.74
Linoleic acid	Polyunsaturated fatty acid	0.74
Myristic acid	Saturated fatty acid	0.70
Conjugated linoleic acid	Trans-fatty acids	0.70
Palmitoleic acid	Monounsaturated fatty acid	0.69
Docosapentaenoic acid	Polyunsaturated fatty acid	0.68
Pentadecyclic acid	Saturated fatty acid	0.66
Arachidonic acid	Polyunsaturated fatty acid	0.61
trans-Palmitoleate acid	Trans-fatty acids	0.60
Behenic acid	Saturated fatty acid	0.57
Methyl linoelaidate	Trans-fatty acids	0.54
trans-Vaccenic acid	Trans-fatty acids	0.53
Lignoceric acid	Saturated fatty acid	0.51
E (α-tocopherol)	Vitamin	0.46
cis-Lutein	Carotenoid	0.45
Eicosapentaenoic acid	Polyunsaturated fatty acid	0.41
Docosadienoic acid	Polyunsaturated fatty acid	0.40
Arachidic acid	Saturated fatty acid	0.40
α-Linolenic acid	Polyunsaturated fatty acid	0.40
Docosahexaenoic acid	Polyunsaturated fatty acid	0.33
Sciadonic acid	Polyunsaturated fatty acid	0.31
trans-Lutein	Carotenoid	0.28
trans-Lycopene	Carotenoid	0.26
Lycopene-9-*cis*	Carotenoid	0.24
Zeaxanthin	Carotenoid	0.21
Nervonic acid	Monounsaturated fatty acid	0.16

TABLE 6
Cohen's d effect sizes between groups for brain volumes, ordered from the largest to the smallest

Region of interest (ROI)	Lobe	Cohen d
Left precuneus	Parietal	1.03
Right precuneus	Parietal	0.98
Left paracentral	Frontal/Parietal	0.97
Right superior temporal	Temporal	0.96
Left superior parietal	Parietal	0.90
Left rostral middle frontal	Frontal	0.89
Right caudal anterior cingulate	Frontal	0.88
Right insula	Insular	0.87
Left caudal anterior cingulate	Frontal	0.85
Left superior temporal	Temporal	0.83
Left medial orbitofrontal	Frontal	0.75
Right posterior cingulate	Parietal	0.74
Left caudal anterior cingulate	Frontal	0.73
Right pars opercularis	Frontal	0.72
Right supramarginal	Parietal	0.72
Left pars opercularis	Frontal	0.71
Right superior parietal	Parietal	0.70
Right inferior temporal	Temporal	0.70
Left lateral orbitofrontal	Frontal	0.70
Right middle temporal	Temporal	0.69
Left inferior temporal	Temporal	0.68
Left supramarginal	Parietal	0.66
Right paracentral	Frontal/Parietal	0.63
Right isthmus cingulate	Parietal	0.62
Left insula	Insular	0.62
Left precentral	Frontal	0.61
Left transverse temporal	Frontal	0.56
Right rostral middle frontal	Frontal	0.56
Right caudal middle frontal	Frontal	0.56
Left entorhinal	Temporal	0.56
Left parahippocampal	Temporal	0.56
Left caudal middle frontal	Frontal	0.55
Right precentral	Frontal	0.55
Left pars orbitalis	Frontal	0.54
Right cuneus	Parietal	0.54
Right superior frontal	Frontal	0.53
Left lateral occipital	Occipital	0.52
Left inferior parietal	Parietal	0.52
Right lateral orbitofrontal	Frontal	0.50
Left frontal pole	Frontal	0.48
Right pars orbitalis	Frontal	0.46
Left superior frontal	Frontal	0.41
Right medial orbitofrontal	Frontal	0.40
Right temporal pole	Temporal	0.35
Right frontal pole	Frontal	0.32
Left posterior cingulate	Parietal	0.30
Right inferior parietal	Parietal	0.29
Left temporal pole	Temporal	0.24
Right parahippocampal	Temporal	0.24

TABLE 7
Cohen's d effect sizes between groups for cognitive scores, ordered from the largest to the smallest

Cognitive test	Domain	Cohen d
Immediate memory index	Immediate memory	0.92
Auditory memory index	Auditory memory	0.85
Delayed memory index	Delayed memory	0.83
Perceptual reasoning	Fluid intelligence	0.65
Full scale IQ	General intelligence	0.63
Visual memory index	Visual memory	0.61

lower on an average for the corresponding measures (labeled NVC_{Lo} for nutrition, volume, cognition low group). Effect size differences between the group means for nutrient levels, cognitive test scores, and volumetric measures were computed using Cohen's d (Tables 5–7).

Large effect size differences (Cohen's $d > 0.8$) were observed for several nutrients. These nutrients fell into 3 categories, namely, monounsaturated fatty acids (eicoenoic acid, *cis*-vaccenic acid, oleic acid, and *cis*-7 hexadecenoic acid), polyunsaturated fatty acids (γ-linolenic acid, dihomolinoleic acid, and dihomo-γ-linolenic acid), and saturated fatty acids (palmitic and stearic acids). The nutrient demonstrating the largest difference between the 2 groups was *cis*-7 hexadecenoic acid.

Regarding cognitive test scores, large effect size difference was found for several measures of the Wechsler Memory Scale, including the immediate, auditory, and delayed tests of memory (Table 7). The analysis of structural MRI measures revealed large effect size differences for 10 volumetric measures computed for regions within the frontal (left rostral anterior cingulate, right caudal anterior cingulate, and left rostral middle frontal), temporal (left and right superior temporal gyri), parietal (left paracentral and left and right precuneus), and insular (right insula) cortexes (Table 6). The largest difference in volumetric measure between the 2 groups was found in the left precuneus. Figure 2 displays a surface brain map illustrating the effect size differences in volumetric measures across the different cortical regions, with large differences colored in red.

Discussion

Accumulating evidence in the emerging field of nutritional cognitive neuroscience demonstrates that many aspects of nutrition—from entire diets to specific nutrients—affect cognitive performance and brain health [16]. Although prior research has primarily focused on the bivariate relationship between nutrition and cognition or nutrition and brain health [15], this study sought to investigate the joint relationship between these essential and interactive elements of human health.

We used a state-of-the-art data fusion method, CMTF, which has been previously used and validated on multimodal data sets [15]. In this study, we characterized the joint association between measures of nutrition (52 nutrient biomarkers), cognition (Wechsler Abbreviated Test of Intelligence and Wechsler Memory Scale), and brain health (high-resolution MRI measures of structural brain volume) within a sample of 111 healthy older adults. Data fusion uncovered latent factors that capture the joint association between specific nutrient profiles, cognitive measures, and cortical volumes, demonstrating the respects in which these data domains are coupled. A hierarchical cluster analysis further revealed systematic differences between the subset of variables contributing largely to the first latent constuct derived from CMTF, providing evidence for multivariate phenotypes that represent high and low levels of performance across multiple health domains. The primary features that distinguish between each phenotype were as follows: *1*) nutrient biomarkers for monounsaturated and polyunsaturated fatty acids; *2*) cognitive measures of immediate, auditory, and delayed memory; and *3*) brain volumes within frontal, temporal, and parietal cortexes. We review each phenotypic pattern in detail further.

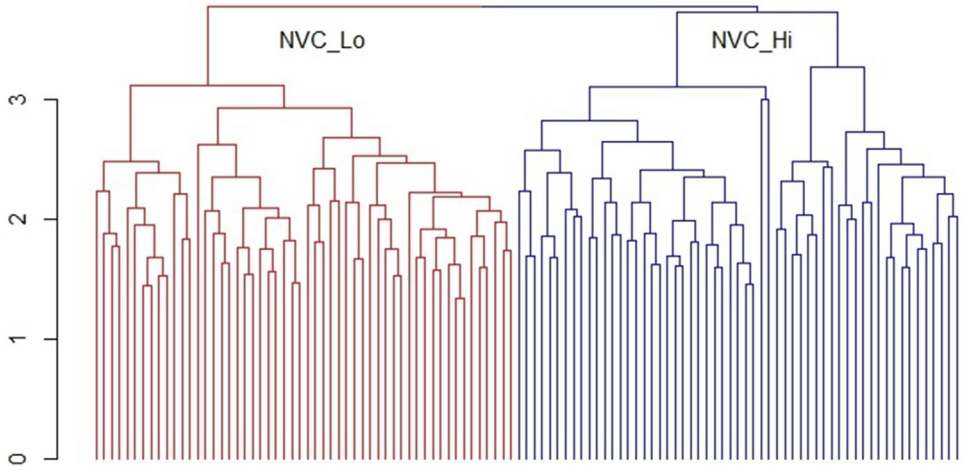

FIGURE 1. Hierarchical clustering reveals 2 subgroups: NVC_{Lo} stands for nutrient, volume, cognition, low group (red, left side of dendrogram) and NVC_{Hi} stands for nutrient, volume, cognition high group (blue, right side of dendrogram).

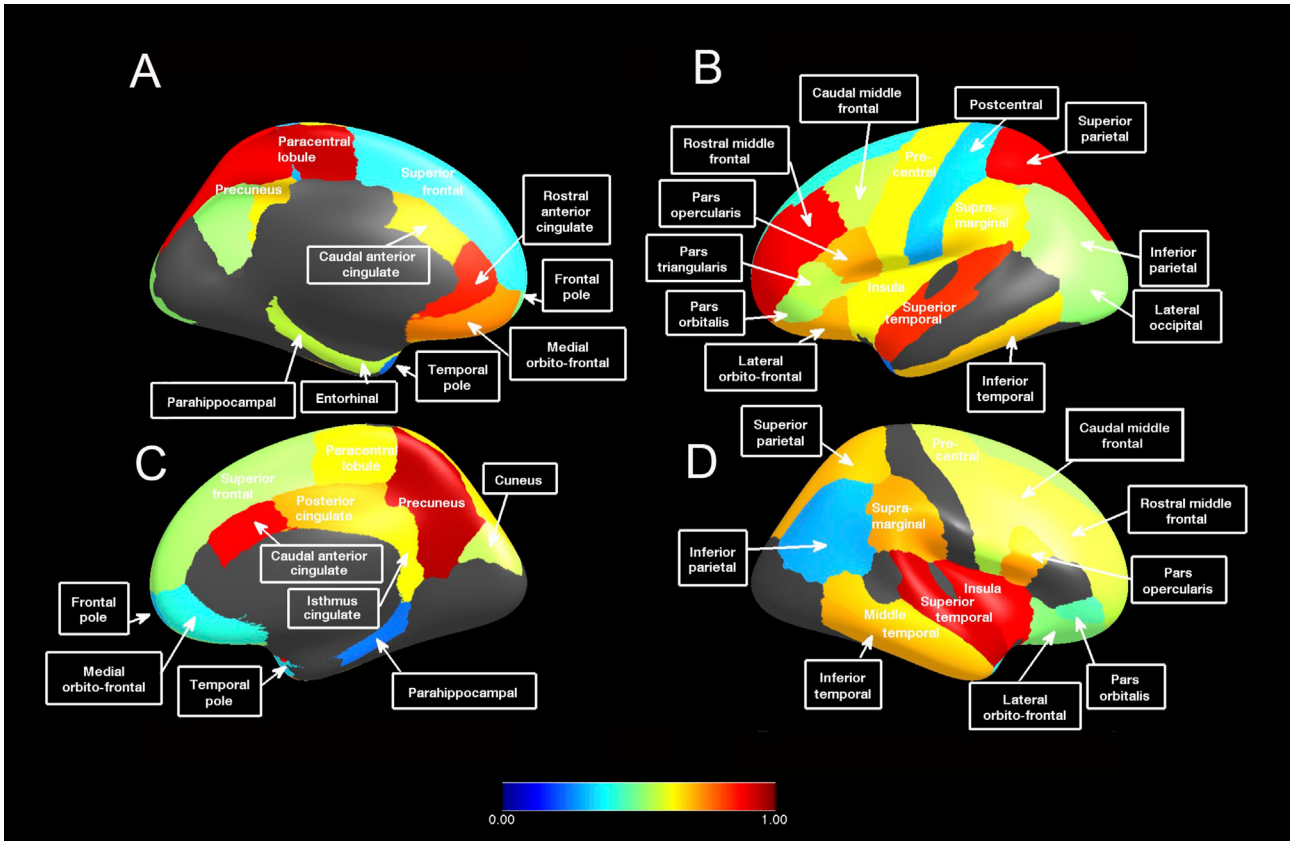

FIGURE 2. A cortical surface map showing Cohen's d effect size differences in structural brain volumetric measures between the 2 groups, NVC_{Lo} and NVC_{Hi}. (A) The left hemisphere medial view; (B) the left hemisphere lateral view; (C) the right hemisphere medial view; and (D) the right hemisphere lateral view. The color map shows the effect size ranging from 0 (blue) to 1 (red). NVC_{Hi}, nutrition, volume, cognition high group; NVC_{Lo}, nutrition, volume, cognition low group; RH, right hemisphere.

Phenotypic patterns revealed from the nutrient biomarker analysis

Multiple nutrients from the monounsaturated and polyunsaturated fatty acid categories displayed large effects size differences between each phenotype. Among the monounsaturated fatty acids, *cis*-7 hexadecenoic acid, oleic acid, *cis*-vaccenic acid, and eicosenoic acid concentrations were higher in the NVC_{Hi} group than those in the NVC_{Lo} group. These nutrients belong to the ω-9 (n-9; *cis*-7 hexadecenoic acid, oleic acid, and eicosenoic acid) and the ω-7 (*cis*-vaccenic acid) monounsaturated fatty acid class. ω-9 Fatty acids have been shown to exert neuroprotective properties and reduce age-related

cognitive decline [24,25]. Previous research in animals indicated that ω-9 fatty acids can inhibit development of Aβ peptides and amyloid plaques implicated in Alzheimer disease [26]. On the contrary, ω-7 fatty acids confer beneficial effect on brain function through regulation of brain glucose metabolism [27,28].

The NVC_{Hi} group also demonstrated higher concentrations of several polyunsaturated fatty acids than the NVC_{Lo} group (γ-linolenic acid, dihomolinoleic acid, and dihomo-γ-linolenic). These nutrients belong to the ω-6 polyunsaturated fatty acid category, which play an important role in neurotransmission and synaptogenesis [29]. Recent studies have linked ω-6 fatty acids to memory function in older adults [30] and the ratio of ω-6:ω-3 fatty acids with working memory and executive functions (e.g., planning and problem-solving skills in young children [31]).

Two saturated fatty acids (palmitic and stearic acids) were also found to be higher in concentration in the NVC_{Hi} group than those in the NVC_{Lo} group. Although saturated fatty acids have been generally linked to poor brain health and cognitive functions [32–34], recent studies have shown that these nutrients in appropriate quantities are beneficial for brain health. For example, Martin et al. [35] observed that membrane structures associated with cell signaling in the human prefrontal cortex comprised largely palmitic and stearic acids. In addition, stearic acid is involved in the biosynthesis of oleic acid, which is known to promote axonogenesis in the striatum during brain development [36].

Phenotypic patterns revealed from cognitive assessments

Multiple cognitive measures demonstrated large effect size differences between each phenotype, such as performance on the immediate, auditory, and delayed tests of memory from the Wechsler Memory Scale. The NVC_{Hi} group showed higher scores on all 3 tests of memory. Previous studies have indicated that memory function is significantly affected by age-related cognitive decline [37,38]. In particular, working memory and episodic memory functions can decline owing to normal aging [39,40]. The large effect size differences between the NVC_{Lo} and NVC_{Hi} groups on the tests of memory motivates further research to examine their role as predictors of intervention efficacy in studies designed to enhance nutrition, cognition, and brain health.

Phenotypic patterns revealed from structural brain imaging

Multiple brain areas demonstrated large effect size differences between each phenotype, such as regions in frontal, temporal, parietal, and insular cortexes. These regions are known to play central roles in executive function (frontal cortex), memory (frontal and temporal cortexes), attention (frontal and parietal cortexes), and emotion (insular cortex). In particular, frontal lobe regions, such as the left rostral and caudal anterior cingulate cortex, showed higher volumetric measures in the NVC_{Hi} group than those in the NVC_{Lo} group (Figure 1). The anterior cingulate cortex has been implicated in executive control processes such as conflict detection, performance monitoring, and response selection [41,42]. Moreover, this region is known to support mechanisms of attention and reward-based learning [43,44]. The NVC_{Hi} group also demonstrated a higher volumetric measure in the rostral middle frontal gyrus than the NVC_{Lo} group. This region is part of the dorsolateral prefrontal cortex and is critical for executive function, such as cognitive control and working memory [45,46].

Temporal lobe structures, such as left and right superior temporal gyri, were larger in volume for the NVC_{Hi} group than that in the NVC_{Lo} group. The left superior temporal gyrus is involved in language processing and auditory short-term memory, whereas the right superior temporal gyrus in known to contribute to spatial attention [47–49].

In the case of the parietal lobe, the left superior parietal lobule, the left and right precuneus, and the left paracentral lobule were larger in volume for the NVC_{Hi} group than those in the NVC_{Lo} group. The superior parietal lobule is known to play an important role in visuospatial and attentional processing [50]. This region has been also linked to manipulating information in working memory [51]. On the contrary, the precuneus is known to support memory (e.g., episodic memory retrieval) and attention (e.g., orientation and shifting), in addition to core visual processes [52,53]. The paracentral lobule is known to support somatosensory function but is also implicated in attention [54]. Regarding the insular cortex, the NVC_{Hi} group recorded a larger volumetric measure in this region than the NVC_{Lo} group. The insula is a cortical center of visceral information processing and interoception and plays a crucial role in emotional experience and subjective feelings [55].

Importantly, several of the brain regions identified in this work are known to exhibit significant age-related cortical atrophy. Gray matter loss with age has been observed in regions such as the anterior cingulate cortex and the rostral middle frontal gyrus [56,57]. Additional studies have reported age-related decline in volumes within the superior temporal gyrus, inferior parietal lobule, and precuneus [58,59]. Hence, in this study, the brain regions demonstrating large differences in cortical volume between phenotypes included areas that demonstrate significant age-related cortical atrophy—providing evidence to support the relevance of this work to the study of healthy cognitive and brain aging.

We focused on plasma nutrients because of the need to understand MRI measures of brain health. Blood-based nutritional biomarkers were selected for the analysis in this study because it is necessary for nutrients to pass through the blood–brain barrier [60]. Moreover, several fatty acids and vitamins included in this analysis are known to cross the blood–brain barrier and affect brain and cognitive function [61]. Studies have shown a close correspondence between nutrients measured from diet history questionnaires and blood biomarkers [62]. Nonetheless, future research should examine the role of the fatty acids and vitamins selected in our study in the context of diet and nutritional recommendations. To this end, Tables 5–7 provide Cohen's d effect size estimates, which can be used for sample size calculations in future nutritional cognitive neuroscience studies.

Limitations

Although this study represents one of the largest and most comprehensive investigations of nutrient biomarkers, cognitive function, and structural brain volumes in older adults, it is important to present our findings in the light of several

limitations. First, the novel application of data fusion methods in this study (CMTF) should be further tested and validated within the field of nutritional cognitive neuroscience. Further research to examine the generalizability of our findings should be conducted, applying similar methods in the context of more comprehensive nutrient biomarker assays and in more diverse populations. Second, the nutrient biomarkers in this study were selected from previous research providing evidence of their favorable effects on brain and cognition [16]. However, the selection of nutrients is not comprehensive and, therefore, may omit important elements that contribute to healthy brain aging. Third, these findings do not permit inferences about the causal role of nutrient biomarkers on cognitive performance and brain health. Future studies should investigate intervention effects on the nutrient phenotypes from this study for the promotion of cognitive performance and brain health. Fourth, our sample population represents relatively high performing, well-educated, neurologically healthy older adults. Therefore, these characteristics may limit the generalizability of findings to different, more diverse study populations. Thus, it is important for future research to further test and validate the novel methods used in this study, applying a broader range of nutrient biomarkers, cognitive measures, and neuroscience methods within more diverse populations. Finally, some of the nutrient biomarkers measured in Table 2 showed lower serum concentrations. Future research will need to determine the significance of these biomarkers for brain and cognitive functioning.

In conclusion, this study identified novel multivariate phenotypes that are associated with healthy cognitive aging, contributing to the burgeoning literature in nutritional epidemiology and network neuroscience that aims to advance the development of novel nutritional therapies for the targeted treatment and clinical management of cognitive and neurological impairments in the aging brain. Our findings demonstrate that multivariate phenotypes comprised nutrient biomarkers, cognitive performance measures, and structural brain volumes account for a significant proportion of variance in healthy aging and motivate an interdisciplinary approach that applies methods from nutritional epidemiology (nutrient biomarker analysis), cognitive neuroscience (high-resolution structural brain imaging), and statistics (data fusion) to characterize the effect of nutrition on human health, aging, and disease.

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The authors' responsibilities were as follows—AKB, TT, CEZ: designed the research (project conception, development of overall research plan, and study oversight); TT, CEZ: conducted the research (hands-on conduct of the experiments and data collection; TT, CEZ: analyzed the data and performed the statistical analysis; AKB, TT, CEZ: wrote the paper; TT: had primary responsibility for the final content; and all authors: read and approved the final version of the manuscript.

Data Availability

The data described in this article will be made available on request pending application and approval.

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Author disclosures

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2023.03.016.

References

[1] A. Börsch-Supan, M. Brandt, H. Litwin, G. Weber, Active ageing and solidarity between generations in Europe: First results from SHARE after the economic crisis, Walter de Gruyter, Berlin, Germany, 2013.
[2] P.S. Aisen, L.S. Schneider, M. Sano, R. Diaz-Arrastia, C.H. van Dyck, M.F. Weiner, et al., High-dose B vitamin supplementation and cognitive decline in Alzheimer disease—a randomized controlled trial, JAMA 300 (2008) 1774–1783.
[3] A.H. Ford, L. Flicker, H. Alfonso, J. Thomas, R. Clarnette, R. Martins, et al., Vitamins B-12, B-6, and folic acid for cognition in older men, Neurology 75 (2010) 1540–1547.
[4] E.R. Greenberg, J.A. Baron, T.D. Tosteson, D.H. Freeman Jr., G.J. Beck, J.H. Bond, et al., A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group, N. Engl. J. Med. 331 (1994) 141–147.
[5] O.P. Heinonen, J.K. Huttunen, D. Albanes, J. Haapakoski, J. Palmgren, P. Pietinen, et al., Effect of vitamin-E and beta-carotene on the incidence of lung-cancer and other cancers in male smokers, N. Engl. J. Med. 330 (1994) 1029–1035.
[6] C.H. Hennekens, J.E. Buring, J.E. Manson, M. Stampfer, B. Rosner, N.R. Cook, et al., Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease, N. Engl. J. Med. 334 (1996) 1145–1149.
[7] J.H. Kang, N. Cook, J. Manson, J.E. Buring, F. Grodstein, A randomized trial of vitamin E supplementation and cognitive function in women, Arch. Intern. Med. 166 (2006) 2462–2468.
[8] R.C. Petersen, R.G. Thomas, L.J. Thal, Vitamin E and donepezil for the treatment of mild cognitive impairment—reply, N. Engl. J. Med. 353 (2005) 951–952.
[9] J.F. Quinn, R. Raman, R.G. Thomas, K. Yurko-Mauro, E.B. Nelson, C. Van Dyck, et al., Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease a randomized trial, JAMA 304 (2010) 1903–1911.
[10] M.K. Zamroziewicz, M.T. Talukdar, C.E. Zwilling, A.K. Barbey, Nutritional status, brain network organization, and general intelligence, Neuroimage 161 (2017) 241–250.
[11] C.E. Zwilling, T. Talukdar, M.K. Zamroziewicz, A.K. Barbey, Nutrient biomarker patterns, cognitive function, and fMRI measures of network efficiency in the aging brain, Neuroimage 188 (2019) 239–251.
[12] F.B. Hu, Dietary pattern analysis: a new direction in nutritional epidemiology, Curr. Opin. Lipidol. 13 (2002) 3–9.
[13] A.K. Barbey, S. Karama, R. Haier, The Cambridge handbook of intelligence and cognitive neuroscience, Cambridge University Press, Cambridge, United Kingdom, 2021.
[14] P.D. Watson, E.J. Paul, G.E. Cooke, N. Ward, J.M. Monti, K.M. Horecka, et al., Underlying sources of cognitive-anatomical variation in multimodal neuroimaging and cognitive testing, Neuroimage 129 (2016) 439–449.

[15] R. Power, A. Prado-Cabrero, R. Mulcahy, A. Howard, J.M. Nolan, The role of nutrition for the aging population: implications for cognition and Alzheimer's disease, Ann. Rev. Food Sci. Technol. 10 (2019) 6179, 6139.
[16] M.K. Zamroziewicz, A.K. Barbey, Nutritional cognitive neuroscience: innovations for healthy brain aging, Front. Neurosci. 10 (2016) 240.
[17] T. Talukdar, M. Zamroziewicz, C. Zwilling, A.K. Barbey, Nutrient biomarkers shape individual differences in functional brain connectivity, Hum. Brain Mapp 40 (2019) 1887–1897.
[18] E. Acar, R. Bro, A.K. Smilde, Data fusion in metabolomics using coupled matrix and tensor factorizations, Proc. IEEE 103 (2015) 1602–1620.
[19] M.K. Zamroziewicz, E.J. Paul, C.E. Zwilling, A.K. Barbey, Predictors of memory in healthy aging: polyunsaturated fatty acid balance and fornix white matter integrity, Aging Dis 9 (2018) 1.
[20] Z. Xu, L.R. Howard, Analysis of antioxidant-rich phytochemicals, Wiley-Blackwell, West Sussex, United Kingdom/Ames, Iowa, 2012, p. 1, online resource (xi, 391 pages).
[21] R.S. Desikan, F. Segonne, B. Fischl, B.T. Quinn, B.C. Dickerson, D. Blacker, et al., An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest, Neuroimage 31 (2006) 968–980.
[22] R.A. Harshman, Foundations of the PARAFAC procedure: models and conditions for an "explanatory" multimodal factor analysis, University of California, Los Angeles, CA, 1970.
[23] J. Cohen, Statistical power analysis fort he behavioral sciencies, Baskı, Hillsdale NJ, 1988.
[24] E.H. Martinez-Lapiscina, P. Clavero, E. Toledo, B. San Julian, A. Sanchez-Tainta, D. Corella, et al., Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial, J. Nutr. Health Aging 17 (2013) 544–552.
[25] A. Pelletier, C. Barul, C. Feart, C. Helmer, C. Bernard, O. Periot, B. Dilharreguy, et al., Mediterranean diet and preserved brain structural connectivity in older subjects, Alzheimers Dement 11 (2015) 1023–1031.
[26] Z. Amtul, D. Westaway, D.F. Cechetto, R.F. Rozmahel, Oleic acid ameliorates amyloidosis in cellular and mouse models of Alzheimer's disease, Brain Pathol 21 (2011) 321–329.
[27] A.L. Berger, Insulin resistance and reduced brain glucose metabolism in the aetiology of Alzheimer's disease, J. Insulin Resist. 1 (2016) 1–7.
[28] P.K. Crane, R. Walker, E.B. Larson, Glucose levels and risk of dementia, N. Engl. J. Med. 369 (2013) 1863–1864.
[29] F. Darios, B. Davletov, Omega-3 and omega-6 fatty acids stimulate cell membrane expansion by acting on syntaxin 3, Nature 440 (2006) 813–817.
[30] M.K. Zamroziewicz, E.J. Paul, C.E. Zwilling, A.K. Barbey, Predictors of memory in healthy aging: polyunsaturated fatty acid balance and fornix white matter integrity, Aging Dis 8 (2017) 372–383.
[31] K.W. Sheppard, C.L. Cheatham, Omega-6 to omega-3 fatty acid ratio and higher-order cognitive functions in 7- to 9-y-olds: a cross-sectional study, Am. J. Clin. Nutr. 98 (2013) 659–667.
[32] P.K. Elias, M.F. Elias, R.B. D'Agostino, L.M. Sullivan, P.A. Wolf, Serum cholesterol and cognitive performance in the Framingham Heart Study, Psychosom. Med. 67 (2005) 24–30.
[33] C.E. Greenwood, G. Winocur, High-fat diets, insulin resistance and declining cognitive function, Neurobiol. Aging 26 (Suppl 1) (2005) 42–45.
[34] S. Kalmijn, M.P.J. van Boxtel, M. Ocke, W.M.M. Verschuren, D. Kromhout, L.J. Launer, Dietary intake of fatty acids and fish in relation to cognitive performance at middle age, Neurology 62 (2004) 275–280.
[35] V. Martin, N. Fabelo, G. Santpere, B. Puig, R. Marin, I. Ferrer, et al., Lipid alterations in lipid rafts from Alzheimer's disease human brain cortex, J. Alzheimers Dis. 19 (2010) 489–502.
[36] E. Polo-Hernandez, F. De Castro, A.G. Garcia-Garcia, A. Tabernero, J.M. Medina, Oleic acid synthesized in the periventricular zone promotes axonogenesis in the striatum during brain development, J. Neurochem. 114 (2010) 1756–1766.
[37] R.L. Buckner, Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate, Neuron 44 (2004) 195–208.
[38] D.L. Schacter, A.W. Kaszniak, J.F. Kihlstrom, M. Valdiserri, The relation between source memory and aging, Psychol. Aging 6 (1991) 559–568.
[39] O.R. Burack, M.E. Lachman, The effects of list-making on recall in young and elderly adults, J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 51 (1996) P226–P233.
[40] S.A. Small, Y. Stern, M. Tang, R. Mayeux, Selective decline in memory function among healthy elderly, Neurology 52 (1999) 1392–1396.
[41] W.H. Alexander, J.W. Brown, Computational models of performance monitoring and cognitive control, Top. Cogn. Sci. 2 (2010) 658–677.
[42] M.M. Botvinick, T.S. Braver, D.M. Barch, C.S. Carter, J.D. Cohen, Conflict monitoring and cognitive control, Psychol. Rev. 108 (2020) 624.
[43] P.W. Frankland, B. Bontempi, The organization of recent and remote memories, Nat. Rev. Neurosci. 6 (2005) 119–130.
[44] B.Y. Hayden, S.R. Heilbronner, J.M. Pearson, M.L. Platt, Surprise signals in anterior cingulate cortex: neuronal encoding of unsigned reward prediction errors driving adjustment in behavior, J. Neurosci. 31 (2011) 4178–4187.
[45] A.K. Barbey, R. Colom, J. Grafman, Dorsolateral prefrontal contributions to human intelligence, Neuropsychologia 51 (2013) 1361–1369.
[46] E.K. Miller, J.D. Cohen, An integrative theory of prefrontal cortex function, Ann. Rev. Neurosci. 24 (2001) 167–202.
[47] E.D. Bigler, S. Mortensen, E.S. Neeley, S. Ozonoff, L. Krasny, M. Johnson, et al., Superior temporal gyrus, language function, and autism, Dev. Neuropsychol. 31 (2007) 217–238.
[48] P.P. Shah-Basak, P. Chen, K. Caulfield, J. Medina, R.H. Hamilton, The role of the right superior temporal gyrus in stimulus-centered spatial processing, Neuropsychologia 113 (2018) 6–13.
[49] M. Vander Ghinst, M. Bourguignon, M. Op de Beeck, V. Wens, B. Marty, S. Hassid, et al., Left superior temporal gyrus is coupled to attended speech in a cocktail-party auditory scene, J. Neurosci. 36 (2016) 1596–1606.
[50] M. Corbetta, G.L. Shulman, F.M. Miezin, S.E. Petersen, Superior parietal cortex activation during spatial attention shifts and visual feature conjunction, Science 270 (1995) 802–805.
[51] M. Koenigs, A.K. Barbey, B.R. Postle, J. Grafman, Superior parietal cortex is critical for the manipulation of information in working memory, J. Neurosci. 29 (2009) 14980–14986.
[52] P.C. Fletcher, C.D. Frith, S.C. Baker, T. Shallice, R.S. Frackowiak, R.J. Dolan, The mind's eye—precuneus activation in memory-related imagery, Neuroimage 2 (1995) 195–200.
[53] B.N. Lundstrom, K.M. Petersson, J. Andersson, M. Johansson, P. Fransson, M. Ingvar, Isolating the retrieval of imagined pictures during episodic memory: activation of the left precuneus and left prefrontal cortex, Neuroimage 20 (2003) 1934–1943.
[54] M.-H. Grosbras, A.R. Laird, T. Paus, Cortical regions involved in eye movements, shifts of attention, and gaze perception, Hum. Brain Mapp. 25 (2005) 140–154.
[55] T. Tayah, M. Savard, R. Desbiens, D.K. Nguyen, Ictal bradycardia and asystole in an adult with a focal left insular lesion, Clin. Neurol. Neurosurg. 115 (2013) 1885–1887.
[56] M.N. Rajah, R. Languay, C.L. Grady, Age-related changes in right middle frontal gyrus volume correlate with altered episodic retrieval activity, J. Neurosci. 31 (2011) 17941–17954.
[57] E.R. Sowell, B.S. Peterson, P.M. Thompson, S.E. Welcome, A.L. Henkenius, A.W. Toga, Mapping cortical change across the human life span, Nat. Neurosci. 6 (2003) 309–315.
[58] H.I.L. Jacobs, M.P.J. Van Boxtel, H.B.M. Uylings, E.H.B.M. Gronenschild, F.R. Verhey, J. Jolles, Atrophy of the parietal lobe in preclinical dementia, Brain Cogn 75 (2011) 154–163.
[59] T. Ohnishi, H. Matsuda, T. Tabira, T. Asada, M. Uno, Changes in brain morphology in Alzheimer disease and normal aging: is Alzheimer disease an exaggerated aging process? AJNR Am. J. Neuroradiol. 22 (2001) 1680–1685.
[60] P. Campos-Bedolla, F.R. Walter, S. Veszelka, M.A. Deli, Role of the blood-brain barrier in the nutrition of the central nervous system, Arch. Med. Res. 45 (2014) 610–638.
[61] S. Yehuda, D.I. Mosotfsky (Eds.), Handbook of essential fatty acids biology: biochemistry, physiology, and behavioral neurobiology, Humana Press, NY, 1997.
[62] G.E. Fraser, K. Jaceldo-Siegl, S.M. Henning, J. Fan, S.F. Knutsen, E.H. Haddad, et al., Biomarkers of dietary intake are correlated with corresponding measures from repeated dietary recalls and food-frequency questionnaires in the Adventist Health Study-2, J. Nutr. 146 (2016) 586–594.