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Nutrient biomarker patterns, cognitive function, and fMRI measures of network efficiency in the aging brain

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A B S T R A C T

A central aim of research in the psychological and brain sciences is to establish therapeutic interventions to promote healthy brain aging. Accumulating evidence indicates that diet and the many bioactive substances present in food are reasonable interventions to examine for dementia prevention. However, interdisciplinary research that applies methods from nutritional epidemiology and network neuroscience to investigate the role of nutrition in shaping functional brain network efficiency remains to be conducted. The present study therefore sought to combine methods across disciplines, applying nutrient biomarker pattern (NBP) analysis to capture the effects of plasma nutrients in combination and to examine their collective influence on measures of functional brain network efficiency (small-world propensity). We examined the contribution of NBPs to multiple indices of cognition and brain health in non-demented elders ($n = 116$), investigating performance on measures of general intelligence, executive function, and memory, and resting-state fMRI measures of brain network efficiency within seven intrinsic connectivity networks. Statistical moderation investigated whether NBPs influenced network efficiency and cognitive outcomes. The results revealed five NBPs that were associated with enhanced cognitive performance, including biomarker patterns high in plasma: (1) ω-3 and ω-6 polyunsaturated fatty acids (PUFAs), (2) lycopene, (3) ω-3 PUFAs, (4) carotenoids, and (5) vitamins B (riboflavin, folate, B12) and D. Furthermore, three NBPs were associated with enhanced functional brain network efficiency, including biomarker patterns high in plasma: (1) ω-6 PUFAs, (2) ω-3 PUFAs, and (3) carotene. Finally, ω-3 PUFAs moderated the fronto-parietal network and general intelligence, while ω-6 PUFAs and lycopene moderated the dorsal attention network and executive function. In sum, NBPs account for a significant proportion of variance in measures of cognitive performance and functional brain network efficiency. The results motivate a multidisciplinary approach that applies methods from nutritional epidemiology (NBP analysis) and cognitive neuroscience (functional brain network efficiency) to characterize the impact of nutrition on human health, aging, and disease.

1. Introduction

A rapidly changing demographic landscape will result in a doubling of the population 65 years and older in the US by the year 2050 (Ortman et al., 2014). A successful strategy to promote healthy brain aging is therefore of great interest to public health efforts and the US economy. Accumulating evidence from Nutritional Cognitive Neuroscience (Zamroziewicz and Barbey, 2016) indicates that diet and the many bioactive substances present in food are reasonable interventions to examine for dementia prevention. However, despite an abundance of evidence in favor of a single or a few nutrients for the promotion of cognitive health (Morris et al., 2002, 2005; Rinaldi et al., 2003; Seshadri et al., 2002; Scarmeas et al., 2006; Barberger-Gateau et al., 2007; Schaefer et al., 2006) and brain aging (Zamroziewicz and Barbey, 2016; Zamroziewicz et al., 2015a, 2016a, 2016b, 2017a, 2017b, 2017c; Talukdar et al., in press), clinical trials using nutritional supplementation have been predominately unsuccessful (Petersen et al., 2005; Aisen et al., 2008; Quinn et al., 2010; Ford et al., 2010; Kang et al., 2006; Heinonen et al., 1994;

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Greenberg et al., 1994; Hennekens et al., 1996). The disconnect may be explained by a focus on single nutrients and a failure to take into account the interactive action and metabolism of nutrient combinations (Bowman et al., 2011, 2012; Tangney et al., 2011). Thus, a better understanding of the distinct nutrient combinations that contribute to cognitive and neuroimaging phenotypes would permit more refined clinical trial designs that drive innovation in novel therapeutic nutrition.

The present study therefore employed principal component analysis to capture the effects of plasma nutrient biomarkers in combination (Bowman et al., 2012; Zamroziewicz et al., 2017b). This approach enables an investigation of the interactive features of nutrients and their collective influence on cognitive aging and functional brain network efficiency. We examined the contribution of nutrient biomarker patterns to multiple indices of cognition and brain health in non-demented elders, investigating performance on measures of general intelligence, executive function, and memory, and resting-state fMRI measures of brain network efficiency within seven intrinsic connectivity networks. Finally, we tested whether an increased level of nutrient biomarkers resulted in more efficiently organized brain networks and better cognitive outcomes of intelligence and executive function.

2. Methods

2.1. Population

This cross-sectional study enrolled 116 healthy elderly adults from the Illinois Brain Aging Study cohort, a sample of community-dwelling Caucasian men and women aged 65–75 years. Participants were neurologically healthy, with no evidence of cognitive impairment, as defined by a score of lower than 26 on the Mini-Mental State Examination (Folstein et al., 1975). Exclusion criteria include: diagnosis of mild cognitive impairment, dementia, psychiatric illness within the last three years, stroke within the past twelve months, cancer within the last three years, current chemotherapy or radiation, an inability to complete study activities, prior involvement in cognitive training or dietary intervention studies, and contraindications for magnetic resonance imaging (MRI). All participants were right handed with normal, or corrected to normal, vision.

The enrolled subjects had a complete dataset at time of data analysis, including cognitive testing, resting-state fMRI, and blood biomarker analysis. Participants had a mean age of 69 years and 63 percent of participants were female. Participant demographics are reported in Table 1.

2.2. Standard protocol approval and patient consent

In accordance with the University of Illinois and Carle Foundation Hospital Institutional Review Boards, informed consent was obtained from all participants in this study.

Table 1
Participant demographics ($n = 116$).

Age in years (average)	69 (±3.2)
Female	63%
Body Mass Index (average)	26.0 (±3.6)
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%

2.3. Nutrient biomarker acquisition and analysis

Fasting plasma was collected from each participant between 7:00 AM and 12:00 noon Central Time. Thirty-two nutrient biomarkers of the Mediterranean Diet (Zamroziewicz and Barbey, 2017) were examined (Table 2), comprising three general classes of nutrients: fatty acids, carotenoids and vitamins. Ethylenediaminetetraacetic acid (EDTA) plasma carotenoids and tocopherols were analyzed by high performance liquid chromatography with a photodiode array detector (HPLC-PDA) using UV detection (Xu and Howard, 2188). Plasma lipids were measured with gas chromatography using flame ionization and peaks of interest were identified by comparison to authentic fatty acid standards (Folch et al., 1957). Vitamins B9 and B12 were measured by a chemiluminescent immunometric assay (Babson, 1991). EDTA plasma 25-hydroxy Vitamin D was measured after extraction by radioimmunoassay (Hart et al., 2006). Appendix e−1 presents the nutrient biomarker analysis in greater detail.

2.4. Nutrient biomarker pattern analysis

The nutrient biomarker pattern analysis was conducted within the *psych* package of R statistical computing software (Rizzo, 2008) (Version 3.4.2). Each nutrient biomarker was first checked for normality by visually inspecting the histogram of values for all participants. If the biomarker was not normally distributed, it was log transformed. Then, all nutrient biomarkers were scaled between 0 and 1, as principal component analysis requires all variables to have the same scale.

A principal component analysis (PCA), with varimax rotation, was used to identify nutrient biomarker patterns (NBP's) from the 32 Mediterranean Diet nutrients listed in Table 2.

The number of NBPs to be retained was determined by the number of eigenvalues greater than, or equal to, 1.0. Interpretation of each factor was based on identifying biomarkers with an absolute loading value of greater than 0.50 on the NBP (i.e., identifying the dominant biomarkers contributing to each particular NBP) (Bowman et al., 2012).

2.5. Covariates

Covariates were determined according to previous association with age-related cognitive decline (Koen and Yonelinas, 2014; Ronnlund et al., 2005; Hurst et al., 2013; Gallucci et al., 2013; Pauls et al., 2013; Wilkins et al., 2010) and included: age (continuous), gender (categorial, male/female), education (categorical, five fixed levels), income (categorical, six fixed levels) and Body Mass Index (continuous, hereafter BMI).

2.6. MRI data acquisition

All data were collected on a Siemens Magnetom 3T Trio scanner using a 32-channel head coil in the MRI Laboratory of the Beckman Institute Biomedical Imaging Center at the University of Illinois.

A high-resolution multi-echo T1-weighted magnetization prepared gradient-echo structural image was acquired for each participant (0.9 mm isotropic, TR: 1900 ms, TI: 900 ms, TE = 2.32 ms, with GRAPPA and an acceleration factor of 2). The functional neuroimaging data were acquired using an accelerated gradient-echo echoplanar imaging (EPI) sequence sensitive to blood oxygenation level dependent (BOLD) contrast ($2.5 \times 2.5 \times 3.0$ mm voxel size, 38 slices with 10% slice gap, TR = 2000 ms, TE = 25 ms, FOV = 230 mm, 90-degree flip angle, 7 min acquisition time). During the resting-state fMRI scan, participants were shown a white crosshair on a black background viewed on a LCD monitor through a head coil-mounted mirror. Participants were instructed to lie still, focus on the visually presented crosshair, and to keep their eyes open (Van Dijk et al., 2010).

Table 2
Study sample serum concentration mean ± standard deviation for 32 Mediterranean Diet nutrients. Units are in μmol/L.

Carotenoids	Vitamins	Fatty Acids
α-Carotene 200 ± 170	A1 (Retinol) 2885 ± 854	Alpha Linolenic Acid (C18.3n.3) 6 ± 3
β-carotene-13-cis 49 ± 26	B2 (Riboflavin) 3.5 ± 3	Stearidonic Acid (C18.4n.3) 2.4 ± 0.9
trans-β-carotene 809 ± 616	B2 (FMN/FAD) 15 ± 6	Sciadonic Acid (C20.3n.3) 1.4 ± 0.6
Cryptoxanthin 172 ± 136	B6 (Plp) 157 ± 161	Eicosapentaenoic Acid (EPA, C20.5n.3) 26 ± 17
trans-Lutein 392 ± 253	B9 (Folate) 21 ± 13	Docosapentaenoic Acid (DPA, C22.5n.3) 23 ± 7
Lycopene-9-cis 229 ± 109	B12 (Cobalamin) 670 ± 600	Docosahexaenoic Acid (DHA, C22.6n.3) 80 ± 33
Lycopene-13-cis 453 ± 236	D 38 ± 13	Linoleic Acid (C18.2n.6) 606 ± 162
trans-Lycopene 883 ± 421	E (α-Tocopherol) 44314 ± 17606	Dihomolinoleic Acid (C20.2n.6) 10 ± 3
Zeaxanthin 85 ± 67	E (γ-Tocopherol) 4891 ± 3302	Dihomo-γ-Linolenic (C20.3n.6) 72 ± 26
		Arachidonic Acid (C20.4n.6) 301 ± 79
		Docosadienoic Acid (C22.2n.6) 0.3 ± 0.1
		Adrenic Acid (C22.4n.6) 11 ± 4
		Docosapentanoic Acid (22.5n.6) 6 ± 3
		MUFA:SFA Ratio 0.3 ± 0.0

2.7. MRI data preprocessing

All MRI data processing was performed using FSL tools available in FMRIB Software Library version 5.0. The high-resolution T1 Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) was brain extracted using the Brain Extraction Tool (BET) (Smith, 2002). FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001) was applied to delineate gray matter, white matter, and cerebral spinal fluid (CSF) voxels. The resting-state fMRI data were pre-processed using the FSL FMRI Preprocessing and Model-Based Analysis (FEAT) analysis tool (Jenkinson et al., 2012; Satterthwaite et al., 2012). Pre-processing entailed: slice timing correction, motion correction, spatial smoothing (3 mm full width at half maximum kernel), nuisance signal regression (described below), standard fMRI temporal bandpass filtering (0.009–0.1 Hz; 47,52), linear registration of functional images to structural images, and non-linear registration of structural images to the MNI152 brain template (2 mm isotropic voxel resolution).

Nuisance variables were modeled via General Linear Modeling (GLM) analyses to remove spurious correlations, noise introduced by head motion, and variables of no interest. These included head motion correction parameters (using the extended 12 motion parameters estimated in FEAT preprocessing), modeling of individual volume motion outliers estimated using DVARS (outliers flagged using the boxplot cutoff 1.5 x interquartile range (Jenkinson et al., 2012)), and averaging of mean white matter and cerebrospinal fluid signals across all voxels identified from the segmentation of the high resolution MPRAGE. The fully pre-processed resting-state fMRI data comprised the residual obtained from fitting these nuisance variables in the GLM framework. The residuals were transformed into normalized MNI152 space and re-sampled to 4 mm isotropic voxels in order to reduce computational complexity in post data processing for network analysis.

2.8. Functional brain network efficiency

The efficiency of brain network function was examined by investigating the small-world organization (Muldoon et al., 2016a) of 7 well-established intrinsic connectivity networks, or ICNs, of the brain (Yeo et al., 2011a) (Fig. 1). A small-word organization represents the optimal balance of local and global network efficiency, providing a parsimonious neural architecture that supports high local clustering (local efficiency) and short average path length (global efficiency). The procedure for computing small-world propensity is presented below.

First, the mean fMRI BOLD time series was extracted from subjects' grey matter voxels using the Craddock parcellated brain atlas as a mask (Craddock et al., 2012). This parcellation of 800 regions provided whole brain coverage and sufficiently high spatial resolution for conducting network analysis (Craddock et al., 2012). A subject-wise functional connectivity matrix reflecting pairwise Pearson correlations between the mean BOLD time series signals obtained from nodes defined by the Craddock atlas was then computed and Fisher's Z-transformed to achieve normality. These were standardized to Z-scores through multiplication with their standard deviation approximated as $\sigma = 1/\sqrt{n-3}$, where n is the number of time points corresponding to the BOLD signal (Ree, 2002). A Bonferroni-corrected statistical Z-threshold was applied to identify significant positive correlations ($p < 0.05$) within each subject's whole brain functional connectivity matrix derived from the Craddock's 800 parcellation atlas (Fox et al., 2009; Murphy et al., 2009). The thresholded Z-scores were rescaled to represent connection weights ranging from 0 to 1. Based on these positive connection weights, weighted connectivity matrices representing functional connectivity between nodes representative of seven ICNs were obtained for each subject (Yeo et al., 2011b). These ICN maps—visual, somatosensory, limbic, default mode, dorsal attention, ventral attention and fronto-parietal (see Fig. 1)—are at https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011.

We then examined small-world propensity within the rescaled connectivity matrices derived for each of the seven ICNs. Small world propensity Φ is calculated as the fractional deviation between a network's clustering coefficient, C_{obs}, and characteristic path length, L_{obs}, from both lattice (C_{latt}, L_{latt}) and random (C_{rand}, L_{rand}) networks constructed with the same number of nodes and the same degree distribution (Muldoon et al., 2016b):

$$\phi = 1 - \sqrt{\frac{\Delta_C^2 + \Delta_L^2}{2}} \quad (1)$$

where,

$$\Delta_C = \frac{C_{latt} - C_{obs}}{C_{latt} - C_{rand}} \quad (2)$$

and

$$\Delta_L = \frac{L_{obs} - L_{rand}}{L_{latt} - L_{rand}} \quad (3)$$

The ratios Δ_C and Δ_L represent the fractional deviation of the metric (C_{obs} or L_{obs}) from its respective null model (a lattice or random network).

2.9. Cognitive measures

Neuropsychological tests investigating general intelligence, executive function, and memory were administered. The Wechsler Abbreviated Scale of Intelligence (WASI) (McCrimmon and Smith, 2013) was administered to investigate general intelligence, the Delis-Kaplan Executive Function System (DKEFS) (Baron, 2004) was administered to assess executive function, and the Wechsler Memory Scale (WMS) (Lichtenberger et al., 2001) was administered to test memory.

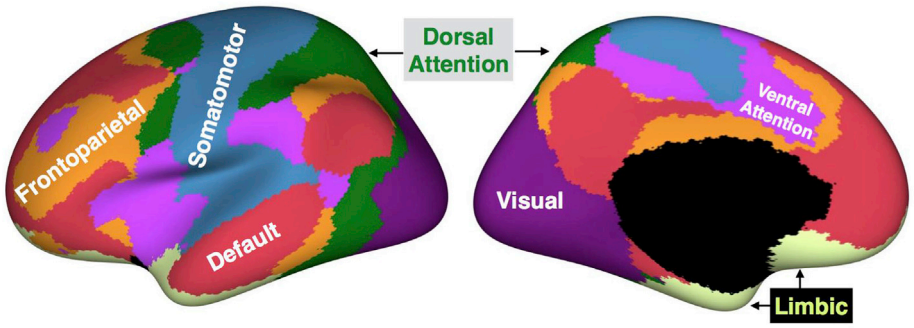

Fig. 1. Seven brain networks for which small-world propensity was computed (Yeo et al., 2011a).

2.10. Statistical analysis

Dominant nutrients within each NBP (i.e. factor scores greater than 0.50) were averaged together to create a composite score for each component. These composite nutrient scores were then used as predictor variables in separate multivariate regression models to predict: (i) the small-world propensity for the 7 brain networks and (ii) cognitive performance on the administered tests of general intelligence, executive function, and memory. Composite nutrient scores were used in place of factor scores in these regression models to isolate the effect of the dominant nutrients within each pattern. Regression models were also used to predict cognitive performance from the small-world propensity measure for the 7 ICNs. Statistical moderation was employed to investigate whether the relationship between brain network efficiency and cognitive performance is moderated by nutrition. The false discovery rate (FDR), which controls for falsely rejected null hypotheses, was employed to control for multiple comparisons in all analyses.

3. Results

3.1. Nutrient biomarker pattern construction and interpretation

The first 10 components demonstrated eigenvalues greater than, or equal to, 1.0 (see Fig. 2). The 10 NBP's, ordered from most variance explained to least, are: (1) ω-3/ω-6 mixture, (2) lycopene, (3) ω-6, (4) ω-3, (5) carotenoid, (6) carotene, (7) vitamin B and D, (8) ratio of monounsaturated fatty acids (MUFA) to saturated fatty acids (SFA), (9) vitamin A and B, and (10) vitamin B6. The factor loadings for each NBP are presented in Table 3.

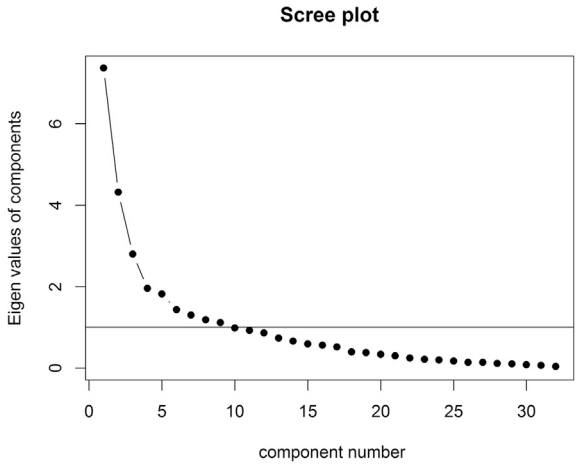

Fig. 2. Scree plot from the principal component analysis. The horizontal line represents an eigenvalue of 1.0. Ten components demonstrated eigenvalues of one or greater.

3.2. Nutrient biomarker patterns and functional brain network efficiency

The beta coefficients and p-values from regressing the small-world propensity measure of each ICN onto the NBP composite scores are presented in Table 4. We observed a significant relationship for 5 of the 10 NBP's: (1) ω-6, (2) ω-3, (3) carotene, (4) vitamin BD, and (5) the MUFA:SFA ratio. The ω-6 pattern was positively associated with the somatomotor ($\beta = 0.04$) and ventral attention ($\beta = 0.04$) networks, indicating that higher concentrations of ω-6 nutrients in the diet are associated with higher small-world propensity in these two ICNs. The ω-3 pattern was also positively associated with the visual network ($\beta = 0.04$). The carotene pattern demonstrated a positive association with the limbic network ($\beta = 0.05$). In contrast to these positive associations, the vitamin BD pattern was negatively associated with the fronto-parietal ($\beta = -0.02$) and default ($\beta = -0.02$) networks, indicating that lower concentration of these vitamins are associated with higher small-world propensity. In addition, the MUFA:SFA ratio pattern was negatively associated with ventral attention ($\beta = -0.05$), indicating that a smaller MUFA:SFA ratio is associated with larger small-world propensity. After FDR correction, all significant results remained significant. The table of eta-squared effect sizes is in Appendix e−2.

3.3. Nutrient biomarker patterns and cognitive function

The beta coefficients and p-values from regressing the 3 cognitive measures onto the NBP composite scores are presented in Table 5. We observed a significant relationship for 6 of the 10 NBP's: (1) ω-3/ω-6 mixture, (2) lycopene, (3) ω-3, (4) carotenoids, (5) vitamin BD and (6) the MUFA:SFA ratio. The ω-3/ω-6 mixture was positively associated with two measures of memory: WMS auditory ($\beta = 13.9$) and WMS delayed ($\beta = 10.0$). Lycopene was positively associated with three measures of memory: WMS auditory ($\beta = 10.9$), WMS immediate ($\beta = 5.8$) and WMS delayed ($\beta = 9.3$). The ω-3 pattern was positively associated with three measures of executive function: DKEFS switch ($\beta = 2.7$), DKEFS switch minus search ($\beta = 3.3$) and DKEFS switch minus an aggregate score for numbers and letters ($\beta = 3.5$). The carotenoid component was positively associated with two measures of intelligence: WASI verbal index ($\beta = 24.0$) and WASI full-scale IQ ($\beta = 16.7$). Two patterns were associated with the same measure of executive function, DKEFS switch minus search: the vitamin BD pattern demonstrated a positive association ($\beta = 3.9$) while the MUFA:SFA ratio has a negative association ($\beta = -2.5$). The negative association between the MUFA:SFA ratio and executive function indicates that a smaller ratio is associated with a larger DKEFS score. After FDR correction, all significant results remain significant. The table of eta-squared effect sizes is in Appendix e−2.

3.4. Functional brain connectivity and cognitive function

The beta coefficients and p-values from regressing the 3 cognitive measures onto the small-world propensity measure of each ICN are presented in Table 6. A significant relationship exists for two ICNs, the

Table 3
Factor loadings of 32 Mediterranean Diet nutrients on 10 components.

	ω3/ω6 mix	Lycopene	ω6	ω3	Carotenoid	Carotene	BD	MUFA :SFA	AB	B6
Linoleic Acid (C18.2n.6)	0.82									
Dihomolinoleic Acid (C20.2n.6)	0.80									
Alpha Linolenic Acid (C18.3n.3)	0.78									
Stearidonic Acid (C18.4n.3)	0.63									
Sciadonic Acid (C20.3n.3)	0.57									
Docosadienoic Acid (C22.2n.6)	0.39									
Lycopene-9-cis		0.93								
trans-Lycopene		0.92								
Lycopene-13-cis		0.90								
Docosapentanoic (22.5n.6)			0.87							
Adrenic Acid (C22.4n.6)			0.85							
Arachidonic Acid (C20.4n.6)			0.76							
Dihomo-γ-Linolenic (C20.3n.6)			0.55							
Eicosapentaenoic Acid (EPA)				0.86						
Docosahexaenoic Acid (DHA)				0.76						
Docosapentaenoic Acid (DPA)				0.72						
Zeaxanthin					0.86					
trans-Lutein					0.71					
Cryptoxanthin					0.64					
Vitamin E (α-Tocopherol)					0.48					
trans-β-carotene						0.76				
α-Carotene						0.75				
β-carotene-13-cis						0.61				
Vitamin B12 (Cobalamin)							0.76			
Vitamin D							0.69			
Vitamin B2 (Riboflavin)							0.59			
Vitamin B9 (Folate)							0.57			
MUFA:SFA Ratio								0.77		
Vitamin E (γ-Tocopherol)								−0.58		
Vitamin B2 (FMN/FAD)									0.80	
Vitamin A1 (Retinol)									0.48	
Vitamin B6 (Plp)										0.79
Cumulative Variance	0.11	0.22	0.32	0.40	0.48	0.56	0.63	0.68	0.72	0.76
Proportion Explained	0.15	0.14	0.13	0.12	0.11	0.11	0.09	0.06	0.05	0.05
Cumulative Proportion	0.15	0.29	0.42	0.53	0.64	0.74	0.83	0.90	0.95	1.00

EPA = C20.5n.3; DHA = C22.6n.3; DPA = C22.5n.3; MUFA:SFA = ratio of monounsaturated to saturated fatty acids.

Table 4
Beta coefficients and p-values from regressing small world propensity measures onto nutrition components.

	ω3/ω6 mix	Lycopene	ω6	ω3	Carotenoid	Carotene	BD	MUFA:SFA	AB	B6
Visual	0.00	0.02	0.02	0.04	0.01	0.02	0.01	−0.01	−0.01	−0.01
	0.92	*0.25*	*0.13*	*0.00**	*0.41*	*0.36*	*0.41*	*0.38*	*0.57*	*0.61*
Motor	0.01	0.02	0.04	0.02	0.00	0.02	0.02	0.00	0.00	0.00
	0.48	*0.29*	*0.01**	*0.33*	*0.95*	*0.28*	*0.21*	*0.84*	*0.92*	*0.91*
Dorsal	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.00	−0.01	0.01
	0.99	*0.66*	*0.89*	*0.71*	*0.84*	*0.44*	*0.80*	*0.87*	*0.37*	*0.65*
Ventral	0.00	0.03	0.04	0.00	0.03	0.03	−0.01	−0.05	0.00	0.01
	0.96	*0.06*	*0.04**	*0.95*	*0.12*	*0.26*	*0.41*	*0.01**	*0.78*	*0.75*
Limbic	−0.01	0.02	0.01	0.03	0.00	0.05	0.02	0.00	−0.02	0.03
	0.81	*0.38*	*0.64*	*0.19*	*0.87*	*0.05**	*0.20*	*0.98*	*0.27*	*0.12*
Frontal	−0.01	0.01	−0.01	0.01	−0.02	−0.01	−0.02	0.01	0.01	−0.01
	0.57	*0.51*	*0.41*	*0.35*	*0.08*	*0.26*	*0.04**	*0.31*	*0.47*	*0.40*
Default	−0.01	0.00	−0.01	0.01	−0.01	−0.01	−0.02	0.01	0.01	−0.01
	0.22	*0.64*	*0.09*	*0.47*	*0.25*	*0.53*	*0.03**	*0.09*	*0.28*	*0.22*

The first row for each ICN is the unstandardized beta coefficient and the p-value for each unstandardized beta coefficient is italicized. An asterisk * on the p-value denotes $p < 0.05$.

fronto-parietal and dorsal attention. The fronto-parietal network is positively associated with the WASI measure of general intelligence (β = 32.7) and WASI perceptual reasoning (β = 32.0). The dorsal attention network is positively associated with all three measures of intelligence: WASI verbal index (β = 43.5), WASI perceptual reasoning (β = 27.0), and WASI full-scale IQ (β = 40.6). The dorsal attention network is also positively associated with two measures of executive functioning, DKEFS switch (β = 6.4) and DKEFS switch minus search (β = 4.6). After FDR correction, all significant results remained significant. The table of eta-squared effect sizes is in Appendix e−2.

3.5. Nutrient biomarker patterns moderating functional brain network efficiency and cognitive function

The final analysis tested for NBP's that moderate the significant relationships in Table 6 between functional brain connectivity—specifically the fronto-parietal and dorsal attention networks—and cognitive measures of intelligence and executive function. Only NBP's that demonstrated a positive association with ICNs from Table 3 were tested for moderation and, of that subset, three moderation results were significant. The ω-3 NBP moderates the fronto-parietal network in

Table 5
Beta coefficients and p-values from regressing cognitive measures onto nutrition components.

	ω3/ω6 mix	Lycopene	ω6	ω3	Carotenoid	Carotene	BD	MUFA:SFA	AB	B6
DKEFS (Switch)	1.26	1.22	−0.05	−1.27	−1.67	0.12	−2.42	2.17	−0.05	0.53
	0.45	*0.31*	*0.97*	*0.30*	*0.24*	*0.92*	*0.18*	*0.27*	*0.97*	*0.68*
DKEFS (Switch-Search)	3.29	1.09	−0.27	2.74	3.34	2.12	2.69	−2.82	−1.23	0.37
	0.08	*0.42*	*0.86*	*0.05**	*0.04**	*0.15*	*0.22*	*0.21*	*0.52*	*0.80*
DKEFS (Switch-NumsLetters)	1.01	0.19	0.82	0.13	−1.36	−0.89	−0.39	−0.03	−2.01	0.15
	0.43	*0.83*	*0.42*	*0.89*	*0.21*	*0.36*	*0.80*	*0.99*	*0.12*	*0.88*
DKEFS (Switch-Speed)	1.83	−0.68	−1.00	−0.78	0.66	1.13	1.11	−3.83	−2.14	−0.27
	0.22	*0.53*	*0.40*	*0.47*	*0.61*	*0.33*	*0.52*	*0.03**	*0.16*	*0.82*
WMS (Auditory Memory)	1.71	−0.08	−0.16	3.26	4.21	1.65	3.93	−4.35	−1.18	−0.03
	0.35	*0.95*	*0.91*	*0.01**	*0.01**	*0.26*	*0.05*	*0.05**	*0.52*	*0.98*
WMS (Verbal Memory)	1.46	1.77	0.73	3.52	2.68	0.99	1.58	1.01	0.90	0.64
	0.39	*0.15*	*0.59*	*0.00**	*0.06*	*0.46*	*0.40*	*0.62*	*0.58*	*0.62*
WMS (Immediate Memory)	2.29	0.90	−1.09	2.61	4.70	3.00	3.08	−2.79	0.78	0.22
	0.25	*0.53*	*0.49*	*0.07*	*0.01**	*0.05*	*0.19*	*0.24*	*0.70*	*0.89*
WMS (Delayed Memory)	1.14	0.37	−0.39	1.02	1.64	0.85	1.24	−0.70	0.66	0.01
	0.15	*0.52*	*0.53*	*0.07*	*0.01**	*0.17*	*0.19*	*0.46*	*0.41*	*0.98*
WASI (Verbal)	14.1	10.9	3.73	7.65	13.4	9.42	8.58	1.78	−0.84	−0.57
	*0.03**	*0.02**	*0.47*	*0.10*	*0.01**	*0.06*	*0.22*	*0.82*	*0.90*	*0.91*
WASI (Perceptual Reasoning)	2.84	4.24	−3.07	−0.98	1.87	2.65	3.07	−4.27	−3.47	2.13
	0.40	*0.08*	*0.25*	*0.69*	*0.51*	*0.31*	*0.40*	*0.28*	*0.31*	*0.43*
WASI (Full-scale IQ 4)	6.48	5.83	−1.12	3.82	7.89	5.46	5.44	−4.54	−0.88	1.21
	0.13	*0.05*	*0.74*	*0.22*	*0.03**	*0.10*	*0.24*	*0.37*	*0.84*	*0.72*

The first row for each cognitive measure is the unstandardized beta coefficient and the p-value for each unstandardized beta coefficient is italicized. An asterisk * on the p-value denotes $p < 0.05$.

Table 6
Beta coefficients and p-values from regressing cognitive measures onto small world propensity measures.

	Visual	Motor	Dorsal	Ventral	Limbic	Frontal	Default
DKEFS (Switch)	0.60	1.77	6.36	−2.43	1.71	1.07	−2.52
	0.77	*0.35*	*0.00**	*0.15*	*0.29*	*0.73*	*0.52*
DKEFS (Switch-Search)	1.56	2.06	4.58	−2.26	0.86	1.98	−3.14
	0.43	*0.26*	*0.04**	*0.17*	*0.58*	*0.51*	*0.41*
DKEFS (Switch-NumsLetters)	−0.04	1.91	3.80	−1.01	1.79	0.09	1.02
	0.98	*0.26*	*0.06*	*0.51*	*0.21*	*0.97*	*0.77*
DKEFS (Switch-Speed)	1.70	1.61	2.60	−1.84	1.46	0.20	1.77
	0.43	*0.42*	*0.28*	*0.31*	*0.39*	*0.95*	*0.67*
WMS (Auditory Memory)	1.56	−7.72	−2.69	1.04	1.49	−0.91	−6.50
	0.81	*0.21*	*0.72*	*0.85*	*0.78*	*0.93*	*0.61*
WMS (Verbal Memory)	0.63	−3.43	6.64	0.58	1.33	7.68	2.95
	0.86	*0.31*	*0.10*	*0.85*	*0.64*	*0.16*	*0.67*
WMS (Immediate Memory)	1.77	−6.18	3.97	0.50	0.17	4.93	−2.93
	0.69	*0.13*	*0.43*	*0.89*	*0.96*	*0.46*	*0.73*
WMS (Delayed Memory)	0.42	−4.97	−0.03	1.12	2.65	1.84	−0.61
	0.93	*0.26*	*1.00*	*0.78*	*0.48*	*0.79*	*0.95*
WASI (Verbal)	14.9	−10.8	43.5	−3.20	−5.89	23.7	−37.4
	0.23	*0.35*	*0.00**	*0.76*	*0.55*	*0.21*	*0.12*
WASI (Perceptual Reasoning)	16.6	12.5	27.0	8.29	1.60	32.0	−10.9
	0.13	*0.22*	*0.03**	*0.37*	*0.85*	*0.05**	*0.61*
WASI (Full-scale IQ 4)	17.0	2.18	40.6	2.92	−2.31	32.7	−26.4
	0.11	*0.83*	*0.00**	*0.74*	*0.78*	*0.04**	*0.20*

The first row for each cognitive measure is the unstandardized beta coefficients and the p-value for each unstandardized beta coefficient is italicized. An asterisk * on the p-value denotes $p < 0.05$.

Table 7
Moderation analysis results.

	Descriptive Regression Model						Predictive Regression Model		
	Nutrient		ICN		Interaction				
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	Beta	Beta
Model 1	ω3		frontal		ω3*frontal		ω3 = 0	ω3 = 0.5	ω3 = 1
	−24.7	0.046*	38.0	.078	38.2	0.040*	38.2	57.3	76.4
Model 2	ω6		dorsal		ω3*dorsal		ω6 = 0	ω6 = 0.5	ω6 = 1
	−5.4	0.018*	7.0	0.029*	8.1	0.028*	7.0	11.1	15.1
Model 3	Lycopene		dorsal		Lycopene*dorsal		Lyco = 0	Lyco = .5	Lyco = 1
	−5.7	0.034*	6.9	0.034*	9.6	0.034*	6.9	11.7	16.6

An asterisk * on the p-value denotes $p < 0.05$.

predicting WASI full scale intelligence. The beta coefficients (and associated p-values) from the regression model for the ω-3 NBP term, the fronto-parietal network term, and their interaction term are listed as Model 1 in Table 7. A significant interaction term—a β of 38.2 with a *p*-value of 0.040 in this case—determines moderation. One way to illustrate the moderation effect is by predicting the outcome of WASI full scale intelligence from the fronto-parietal network, while conditioning on a chosen value of ω-3. The right-hand side of Table 7, under the Predictive Regression Model heading, provides the predicted value of WASI full scale for three illustrative values of ω-3: 0, 0.5 and 1.0. The predicted WASI full scale scores are the beta coefficients. These betas for Model 1 are further illustrated in Fig. 3, which represent the slope of the line at the chosen value of ω-3. More generally, one can select any value within the range of ω-3 in Fig. 3 and use the regression line to determine the predicted WASI full scale intelligence score.

Two additional moderation results were observed. The ω-6 NBP moderates the dorsal attention network in predicting DKEFS switch measure of executive function ($\beta = 8.1$, $p = 0.028$). This result is illustrated in Fig. 4. And the lycopene NBP moderates the dorsal attention network in predicting DKEFS switch measure of executive function ($\beta = 9.6$, $p = 0.033$). This result is illustrated in Fig. 5.

4. Discussion

This cross-sectional study reports distinct nutrient biomarker patterns that are associated with measures of cognitive health and functional brain network efficiency in a sample of dementia-free elders. The findings advance prior research applying nutrient biomarker pattern analysis (Bowman et al., 2012) by demonstrating novel associations with the functional efficiency of core intrinsic connectivity networks in the aging brain (Zamroziewicz et al., 2017b).

Historically, research in nutritional epidemiology has investigated the beneficial effects of specific nutrients on human health, aging, and disease. This single nutrient approach, however, is known to have several limitations (Hu, 2002), including: (1) failure to capture the interactive or synergistic effects among nutrients found in dietary patterns; (2) the high

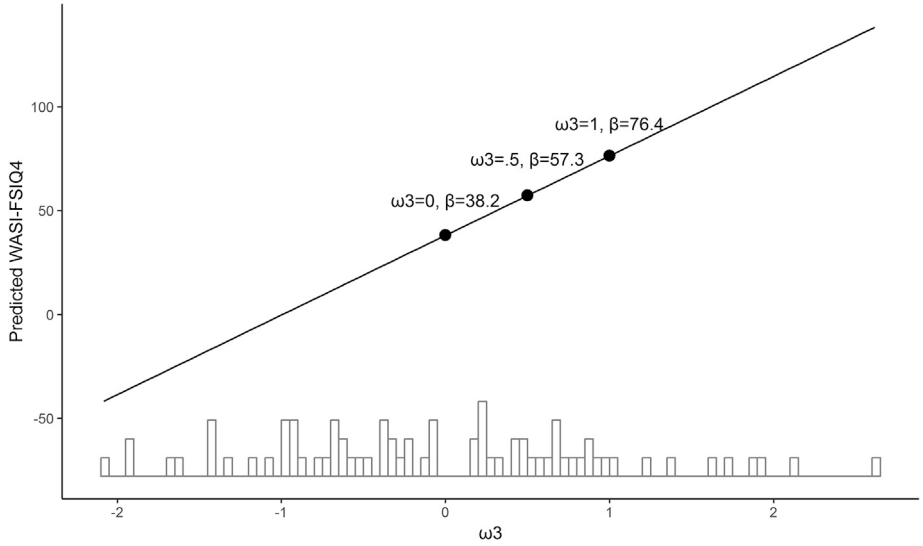

Fig. 3. Conditional coefficients plot illustrating the linear predictive relationship between WASI-FSIQ4 and fronto-parietal network efficiency, for a given level of ω-3. The three dots on the line represent ω-3 values of 0, 0.5 and 1.0 and the associated conditional predicted value for the WASI-FSIQ4. The histogram along the x-axis represents the distribution of ω-3 in the sample.

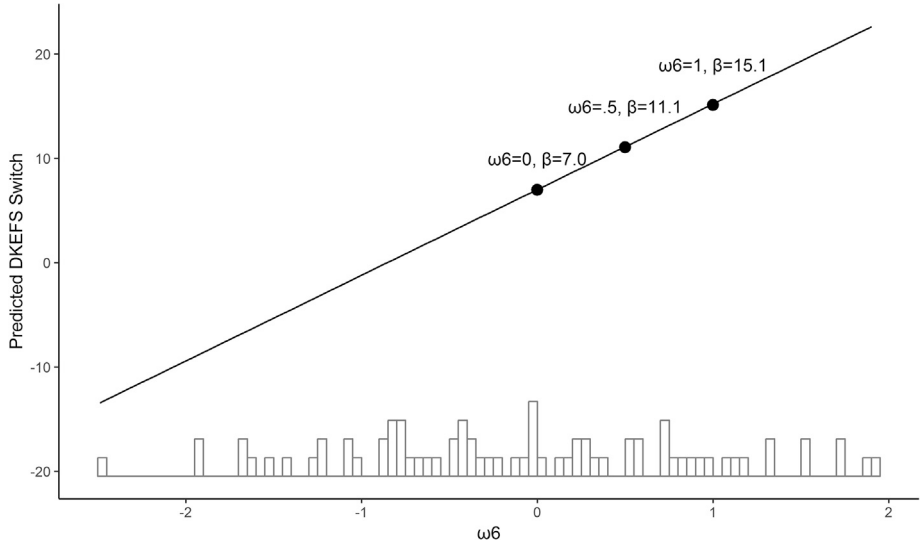

Fig. 4. Conditional coefficients plot illustrating the linear predictive relationship between DKEFS Switch score and dorsal attention network efficiency, for a given level of ω-6. The three dots on the line represent ω-6 values of 0, 0.5 and 1.0 and the associated conditional predicted value for the DKEFS. The histogram along the x-axis represents the distribution of ω-6 in the sample.

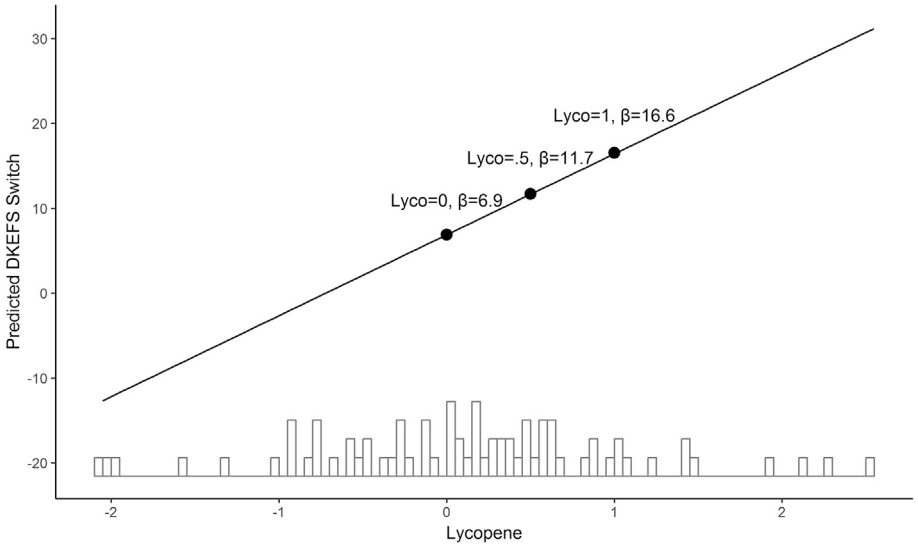

Fig. 5. Conditional coefficients plot illustrating the linear predictive relationship between DKEFS Switch score and dorsal attention network efficiency, for a given level of lycopene. The three dots on the line represent lycopene values of 0, 0.5 and 1.0 and the associated conditional predicted value for the DKEFS. The histogram along the x-axis represents the distribution of lycopene in the sample.

level of intercorrelation among nutrients (such as potassium and magnesium), which may limit the ability to study 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.

Considerable research in this effort supports the Mediterranean diet, a well-established dietary pattern known to promote healthy brain aging (Zamroziewicz and Barbey, 2017; Feart et al., 2015). Indeed, adherence to Mediterranean-style diets has been shown to support cognitive performance (Hardman et al., 2016) as well as brain structure and function in late life (Staubo et al., 2017; Matthews et al., 2014). Scientific advances in the characterization of dietary patterns and measurement of nutrient biomarkers have led to a new method in nutritional epidemiology for the measurement of NBPs (Bowman et al., 2012; Zamroziewicz et al., 2017b). This approach has set the stage for major advances in understanding the functional significance of nutrition on brain health, enabling an investigation of the interactive features of nutrients and their collective influence on fMRI indices of functional brain network efficiency. The present study therefore investigated the beneficial effects of multivariate nutrient profiles on indices of cognitive performance and brain health, derived from cognitive measures of general intelligence, executive function, and memory, and resting-state functional connectivity assessed by fMRI.

The results identify five NBPs that are associated with enhanced cognitive performance, including biomarker patterns that are high in plasma: (1) ω-3 and ω-6 polyunsaturated fatty acids (PUFAs), (2) lycopene, (3) ω-3 PUFAs, (4) carotenoids, and (5) vitamins B (riboflavin, folate, cobalamin) and D. Previous research has shown that a balance of ω-3 and ω-6 PUFAs may be physiologically favorable because it allows for proportional production of long-chain PUFAs for integration into plasma membranes or conversion into prostanoids, therefore promoting brain structure and function (Zamroziewicz et al., 2017d). Evidence indicates that lycopene may also have favorable effects on cognitive performance in healthy adults (Polidori et al., 2009), possibly due to its role as an antioxidant (Stahl and Sies, 2005). ω-3 PUFAs have been previously linked to global cognition (Baierle et al., 2014a; Eriksdotter et al., 2015; Nishihira et al., 2016), executive function (Baierle et al., 2014b; Bowman et al., 2013; Zamroziewicz et al., 2015b), general intelligence (Tan et al., 2012), and memory (Baierle et al., 2014b; Yuan et al., 2016). Prior work demonstrates that intake of green leafy and cruciferous vegetables – both major dietary sources of carotenoids – is positively associated with cognitive function (Kang et al., 2005; Morris et al., 2006). Finally, higher plasma levels of vitamin B have been linked to superior cognitive performance (Riggs et al., 1996) while lower vitamin D levels have been associated with poorer cognitive function and a higher risk for Alzheimer's disease (Balion et al., 2012).

Accumulating neuroscience evidence demonstrates that variation in the synchronization or efficiency of communication between brain regions reliably predicts individual differences in cognitive ability (Gottfredson, 1997). Intrinsic connectivity networks, the fundamental organizational units of human brain architecture (Laird et al., 2011), exhibit consistent spatial patterns of functional connectivity at rest that reflect information processing capabilities (Lowe et al., 1998; Raichle et al., 2001; Beckmann et al., 2005; Damoiseaux et al., 2006). Recent advances in neuroimaging provide new tools for characterizing the topology and dynamics of ICNs (Watts and Strogatz, 1998; Bullmore and Sporns, 2009), with efficient information flow across functional brain networks representing a small-world organization defined by a high level of local clustering and a short path length between brain regions (Sporns and Zwi, 2004; van den Heuvel et al., 2008). Research in network neuroscience has consistently observed that the topology of human brain networks indeed exemplifies a small-world architecture, which has been demonstrated across multiple neuroimaging modalities, including structural (He et al., 2007), functional (Eguiluz et al., 2005; Achard et al., 2006; Achard and Bullmore, 2007), and diffusion tensor magnetic resonance imaging (MRI) (Hagmann et al., 2007). Emerging neuroscience evidence further indicates that general intelligence is directly linked to characteristics of a small-world topology (Barbey, 2018), demonstrating that individual differences in intelligence are associated with network measures of global efficiency (van den Heuvel et al., 2009; Cole et al., 2012). Alterations in the topology of a small-world network have also been linked to multiple disease states (Stam et al., 2007; Stam, 2014), pharmacological interventions (Achard and Bullmore, 2007), and age-related cognitive decline (Zuo et al., 2017), establishing their importance for understanding human health and disease (Bassett and Bullmore, 2009).

The present study therefore employed modern methods from network neuroscience to characterize the small-world organization of seven ICNs of the brain (Fig. 1), investigating whether specific NBPs reliably predict the functional efficiency of network organization within each ICN. The results identify three NBPs that are associated with more favorable

functional efficiency in the aging brain, including biomarker patterns high in plasma: (1) ω-6 PUFAs, (2) ω-3 PUFAs, and (3) carotene. Increasing evidence suggests that ω-6 and ω-3 PUFAs benefit the aging brain (Parletta et al., 2013). PUFAs are known to contribute to structural integrity of neuronal membranes, control inflammation and oxidation, and promote energy metabolism (Cunnane et al., 2009). One of the mechanisms for the beneficial effects of PUFAs on brain network efficiency is the myelination of white matter (Fields, 2005), which is critical for information transmission and synaptic response across long fiber tracks underlying small-world networks. Lipids in myelin are known to contain much higher proportions of long chain fatty acids than lipids in gray matter (Sherman and Brophy, 2005), suggesting that long chain fatty acids may be critical for healthy lipid composition in myelin and therefore may support information transfer in small-world brain networks. Carotenoids accumulate in neural tissue and are thought to provide a variety of neuroprotective benefits (Nolan et al., 2018; Johnson et al., 2013a; Johnson, 2002). Carotene may act as an antioxidant by quenching free radicals in brain tissue, therefore contributing to favorable functional efficiency (Sies and Stahl, 1995).

A large body of neuroscience evidence indicates that the functional organization of the human brain reflects intrinsic connectivity networks and that their efficiency of information processing (e.g., as measured by small-world organization) is associated with cognitive performance. The current study provides evidence that the small-world organization of the fronto-parietal and dorsal attention networks are associated with multiple measures of intelligence (e.g., the full-scale WASI and WASI perceptual reasoning). These findings corroborate existing studies demonstrating linkages between the fronto-parietal network and intelligence (Barbey et al., 2012) and the dorsal attention network with intelligence and executive function (Reineberg et al., 2018).

Finally, the moderation results of the current study provide evidence that the positive association between brain network efficiency and cognitive performance is moderated by specific nutrient biomarkers. In particular, the current study demonstrated that higher levels of ω-3 PUFAs moderate the association between fronto-parietal network efficiency and general intelligence. This result is consistent with a randomized control trial where an ω-3 supplement improved brain structure, function and cognitive outcomes (Witte et al., 2014). The observed benefits of ω-3 PUFAs are believed to result from their role in supporting cell plasma membrane structures and metabolic cascades in the brain. Docosahexaenoic acid (DHA), one type of ω-3 PUFA, comprises one-third of total phospholipid composition of plasma membranes in the brain and can enhance membrane integrity. Healthier neural membranes promote increased neuronal activation and better synaptic function (Gómez-Pinilla, 2008). ω-3 PUFAs also sit at the head of certain metabolic cascades that ultimately result in the formation of proteins that support neuron survival, growth and differentiation, like brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF1). Both BDNF and IGF1 support pre- and post-synaptic signaling systems that enhance synaptic transmission, neuroplasticity and cognitive function (Witte et al., 2014).

A second moderation result demonstrated that higher levels of ω-6 PUFAs moderate the association between the efficiency of the dorsal attention network and performance on tests of executive function (i.e., the D-KEFS). As in the case of ω-3 PUFAs, ω-6 PUFAs are known to support multiple facets of brain health, including the maintenance of cell structure and functions underlying neuronal excitability, neurotransmitters and neuromodulators, and signal transduction (Giles et al., 2014). Accumulating evidence indicates that ω-6s confer beneficial effects on cognitive performance when their ratio with respect to ω-3 PUFAs approaches one (Simopoulos, 2011). The ratio of ω-6 to ω-3 NBPs observed in the present study is 0.93, approximating the ideal ratio needed to confer benefits to cognitive performance and brain health (Andruchow et al., 2017; Haag, 2003; Sheppard and Cheatham, 2017).

The final moderation result demonstrates that higher levels of lycopene moderates the association between the efficiency of the dorsal attention network and performance on tests of executive functions (i.e., the D-KEFS). The existing literature on lycopene's effect on the brain and cognition in humans suggest lycopene may serve a protective role in brain aging and cognitive decline (Min and Min, 2014; Johnson et al., 2013b). One study found that higher serum levels of lycopene were associated with lower incidences of Alzheimer's mortality and the other study found higher serum levels of lycopene was related to less severe dementia (Min and Min, 2014; Johnson et al., 2013b). Animal models support the hypothesis that lycopene works in a protective manner. One recent study showed that a lycopene supplement in mice reduced age-related memory loss and cognitive decline, reversed age-related neuronal degradation and loss of synaptic function in the brain, reduced amyloid-beta brain plaques and reduced neuroinflammation (Zhao et al., 2018). Other animal studies have shown similar benefits of lycopene, by reducing oxidation and inflammation and promoting the release of inhibitory neurotransmitters like GABA and 5-HT, which confer protective effects on the brain (Yang et al., 2018; Prakash and Kumar, 2014).

Although the current study represents one of the largest and most comprehensive investigations of the role of NBPs on functional brain network efficiency, it is important to present our findings in the light of several limitations. First, the novel application of principal component analysis in the present study employs statistical conventions, such as an eigenvalue criterion of 1.0 for the selection of NBPs, that should be further tested and validated within the context of nutritional cognitive neuroscience. Moreover, the components are formed from common structure in the data and may not reflect a common mechanism of action in the body. Second, the NBPs in the current study were selected from the Mediterranean Diet based on prior research indicating that vitamins and nutrients from this diet have favorable effects on brain and cognition (Lichtenberger et al., 2001). However, the selection of nutrients is not comprehensive of the Mediterranean Diet and therefore may omit important nutrients that contribute to healthy brain aging. Third, the present findings are based on an observational study and therefore do not permit inferences about the causal role of NBPs on cognitive performance and functional brain network efficiency. Finally, our sample population represents relatively high performing, well-educated, Caucasian and neurologically healthy older adults. As a consequence, 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 employed in the current study, applying a broader range of nutrient biomarkers, cognitive measures, network neuroscience methods, networks (such as the cingulo-opercular (Andrews-Hanna et al., 2010) and graph theory metrics, within more diverse populations. Future studies should also investigate clinical markers of health status, such as diabetes and obesity, given that nutrition may impact individuals with certain types of disease differently than healthy individuals.

In conclusion, the present study identified distinct NBPs that are associated with enhanced cognitive performance and functional brain network efficiency, contributing to the burgeoning literature in nutritional epidemiology and cognitive 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.

Author contributions

Dr. Zwilling conducted the study analysis, contributed to the interpretation of findings, and drafted the manuscript. Dr. Talukdar assisted in the neuroimaging analysis, interpretation of findings, and drafting of the manuscript. Dr. Zamroziewicz assisted in the interpretation of the nutritional cognitive neuroscience findings and drafting of the manuscript. Dr. Barbey conceptualized the study as part of a larger grant, led study procedures, and contributed to the interpretation of findings and drafting of the manuscript.

Disclosure

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Appendix e−1. Nutrient biomarker analysis. The analysis procedure for the 32 nutrient biomarkers examined in the current study are presented below.

Fatty acids. Plasma lipids were extracted by the method of Folch, Lees and Sloane-Stanley (Folch et al., 1957). Briefly, the internal standard (25 μg each of PC17:0) was added to 200 μL of serum, followed by 6 mL of choloroform:methanol:BHT (2:1:100 v/v/w). The protein precipitate was removed by centrifugation (2500 g, 5 min, 4 °C). Then 1.5 mL of 0.88% KCl was added to the supernantent, shaken vigorously and the layers were allowed to settle for 5 min. The upper layer was discarded and 1 mL of distilled water:methanol (1:1 v/v) was added, the tube was shaken again and the layers allowed to settle for 15 min. The lower layer was transferred into a clean tube and evaporated to dryness under nitrogen. The phospholipid subfraction was separated by solid-phase extraction using aminopropyl columns as described by Agren, Julkunen and Penttila (Agren et al., 1992). Then the phospholipid fraction was methylated by adding 2 mL of 14% BF3-MeOH and incubating at 95 °C for 1 h (Morrison and Smith, 1964). The supernatant containing the fatty acid methyl esters (FAMEs) was dried down under nitrogen, resuspended in 100 μL of hexane, transferred into amber GC vials and stored at −20 °C until the time of analysis. The phospholipid FAMEs were analyzed by a CLARUS 650 gas chromatograph (Perkin Elmer, Boston MA) equipped with a 100 m × 0.25 mm i.d (film thickness 0.25 μm) capillary column (SP-2560, Supelco). Injector and flame ionization detector temperatures were 250 °C and 260 °C, respectively. Helium was used as the carrier gas (2.5 mL/min) and the split ratio was 14:1. The oven temperature was programmed at 80 °C, held for 16 min and then increased to 180 °C at a rate of 5 °C/minute. After 10 min, the temperature was increased to 192 °C at a rate of 0.5 °C/minute, held for 4 min. The final temperature was 250 °C reached at a rate of 405 °C/minute and held for 15 min. Peaks of interest were identified by comparison with authentic fatty acid standards (Nu-Chek Prep, Inc. MN) and expressed as absolute concentration (μmol/L).

Carotenoids. Serum was prepared for extraction using 100 μL of sample and 0.5 mL 0.9% saline. Echinenone, in ethanol, was added as an internal standard (DSM Nutritional Products). The mixture was extracted by using 2 mL $CHCL_3$:CH_3OH (2:1, vol/vol). The mixture was vortexed and then centrifuged at 800g for 15 min at 4 °C. The $CHCl_3$ layer was removed and evaporated to dryness under nitrogen. A second extraction was performed on the mixture using 3 mL hexane. The mixture was vortexed and centrifuged as above. The hexane layer was combined with the first extraction and evaporated to dryness under nitrogen. The residue was re-dissolved in 100 μL of ethanol, vortexed, and sonicated for 30 s. A 20 μL aliquot was used for HPLC analysis.

Carotenoids, retinoids, and tocopherols were measured using a reversed-phase, gradient HPLC system. The system consisted of a Waters Alliance 2695 Separation Module LC pump, auto-sampler, Waters 2996 Photo-Array Detector (Millipore, Milford, MA) and a semi-bore C30 column (3 μm, 150 × 4.6 mm, YMC, Wilmington, NC). The chromatographic separations were performed on a Waters Alliance 2695 (Millipore, Milford, MA) system using a UV detector and Waters Empower Pro software. The flow rate was 0.4 mL/min and the gradient elution used two mixtures of methanol, tert-butyl methyl ether, and water (mixture A: 83/15/2; v/v/v), mixture B: 8/90/2, v/v/v). The gradient procedure was: 0–1 min 100% A, 1–8 min linear gradient to 70% A, 8–13 min 70% A, 13–22 min linear gradient to 45% A, 22–24 min 45% A, 24–34 min linear gradient to 5% A, 34–38 min 5% A, 38–40 min linear gradient to 100% A, and 40–50 min 100% A.

The method yields adequate separation of lutein (all-*trans*, *cis*), zeaxanthin, cryptoxanthin, α-carotene, 13-*cis*-β-carotene, all *trans*-β-carotene, and 9-*cis*-β-carotene, as well as four geometrical isomers of lycopene (15-*cis*, 13-*cis*, 9-*cis*, and all-*trans*). Carotenoids were quantified at 445 and 455 nm, retinoids at 340 nm, and tocopherols at 292 nm. Quantification was determined from peak areas in the HPLC chromatograms calibrated against known amounts of standards. Concentrations were corrected for extraction and handling losses by monitoring the recovery of the echinenone internal standard. The lower detection with this method is 0.2 pmol for each carotenoid, 2.0 for retinol and 2.7 pmol for α- and γ-tocopherol.

Vitamins. Vitamin B12 was measured with a preliminary heat denaturation step followed by a chemiluminescent, competitive immunometric assay, (IMMULITE Vitamin B12, Catalog Number: LKVB1, Siemens Healthcare Diagnostics, Los Angeles, CA 90045). The intra- and inter-assay CVs are 7.5% and 9.0% accordingly (Babson, 1991). 25-Hydroxy Vitamin D was measured after extraction by an equilibrium ^{125}I radioimmunoassay procedure (25(OH)Vitamin D, Catalog: 68100E. DiaSorin Inc, Stillwater, MN 55082) using a Packard Cobra II Gamma Counter according to the technical document. The intra- and inter-assay CVs are 9.0% and 11.0% accordingly (Hart et al., 2006).

Appendix e−2. Tables of standardized effect sizes, η^2.

Table e-2.1
η^2 effect sizes from regressing cognitive measures onto NBPs.

	ω3/ ω6 mix	Lycopene	ω6	ω3	Carotenoid	Carotene	BD	MUFA:SFA	AB	B6
DKEFS (Switch)	0.0101	0.0103	0.0000	0.0206	0.0240	0.0016	0.0241	0.0000	0.0034	0.0134
DKEFS (Switch-Search)	0.0129	0.0022	0.0058	0.0349	0.0403	0.0209	0.0206	0.0051	0.0022	0.0077
DKEFS (Switch-NumsLetters)	0.0153	0.0000	0.0019	0.0024	0.0284	0.0220	0.0009	0.0037	0.0324	0.0083
DKEFS (Switch-Speed)	0.0069	0.0031	0.0315	0.0126	0.0000	0.0006	0.0056	0.0074	0.0124	0.0124

(*continued on next column*)

Table e-2.1 (*continued*)

	ω3/ ω6 mix	Lycopene	ω6	ω3	Carotenoid	Carotene	BD	MUFA:SFA	AB	B6
WMS (Auditory Memory)	0.0275	0.0007	0.0043	0.0677	0.0809	0.0074	0.0515	0.0047	0.0002	0.0000
WMS (Verbal Memory)	0.0442	0.0115	0.0057	0.1049	0.0568	0.0214	0.0098	0.0000	0.0024	0.0000
WMS (Immediate Memory)	0.0351	0.0022	0.0018	0.0423	0.0888	0.0541	0.0234	0.0113	0.0057	0.0004
WMS (Delayed Memory)	0.0256	0.0002	0.0018	0.0223	0.0392	0.0182	0.0234	0.0001	0.0067	0.0027
WASI (Verbal)	0.0008	0.0275	0.0035	0.0112	0.0308	0.0319	0.0202	0.0191	0.0000	0.0035
WASI (Perceptual Reasoning)	0.0009	0.0551	0.0554	0.0015	0.0078	0.0338	0.0097	0.0326	0.0440	0.0002
WASI (Full-scale IQ 4)	0.0097	0.0218	0.0360	0.0054	0.0281	0.0263	0.0189	0.0010	0.0036	0.0007

Table e-2.2
η^2 effect sizes from regressing cognitive measures onto small world propensity measures.

	Visual	Motor	Dorsal	Ventral	Limbic	Frontal	Default
DKEFS (Switch)	0.0062	0.0007	0.0039	0.0005	0.0039	0.0024	0.0014
DKEFS (Switch-Search)	0.0008	0.0076	0.0674	0.0178	0.0100	0.0011	0.0036
DKEFS (Switch-NumsLetters)	0.0057	0.0001	0.0515	0.0024	0.0005	0.0015	0.0228
DKEFS (Switch-Speed)	0.0014	0.0001	0.0177	0.0099	0.0000	0.0015	0.0116
WMS (Auditory Memory)	0.0055	0.0109	0.0369	0.0162	0.0027	0.0039	0.0059
WMS (Verbal Memory)	0.0000	0.0111	0.0300	0.0038	0.0135	0.0000	0.0007
WMS (Immediate Memory)	0.0056	0.0058	0.0102	0.0092	0.0065	0.0000	0.0016
WMS (Delayed Memory)	0.0003	0.0022	0.0054	0.0157	0.0007	0.0065	0.0090
WASI (Verbal)	0.0005	0.0137	0.0011	0.0003	0.0007	0.0001	0.0022
WASI (Perceptual Reasoning)	0.0003	0.0091	0.0233	0.0003	0.0019	0.0176	0.0016
WASI (Full-scale IQ 4)	0.0014	0.0195	0.0055	0.0002	0.0000	0.0048	0.0010

Table e-2.3
η^2 effect sizes from regressing cognitive measures onto NBPs.

	ω3/ ω6 mix	Lycopene	ω6	ω3	Carotenoid	Carotene	BD	MUFA:SFA	AB	B6
Visual	0.0001	0.0144	0.0262	0.1094	0.0074	0.0092	0.0074	0.0084	0.0035	0.0029
Motor	0.0068	0.0152	0.0892	0.0129	0.0001	0.0155	0.0216	0.0005	0.0001	0.0002
Dorsal	0.0000	0.0032	0.0003	0.0022	0.0007	0.0099	0.0011	0.0004	0.0131	0.0034
Ventral	0.0000	0.0461	0.0575	0.0001	0.0316	0.0166	0.0086	0.0831	0.0010	0.0013
Limbic	0.0007	0.0102	0.0029	0.0223	0.0003	0.0525	0.0216	0.0000	0.0157	0.0317
Frontal	0.0041	0.0054	0.0086	0.0111	0.0391	0.0160	0.0578	0.0133	0.0067	0.0089
Default	0.0198	0.0028	0.0386	0.0069	0.0172	0.0051	0.0671	0.0372	0.0151	0.0194

Appendix e—3. Network level correlation.

Table e-3.1
Correlations between 2 mm and 4 mm resolution for the 7 ICNs.

Network	Correlation
Visual	0.93
Motor	0.89
Dorsal	0.78
Ventral	0.59
Limbic	0.66
Frontal	0.60
Default	0.90

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