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Nutritional status, brain network organization, and general intelligence

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ABSTRACT

The high energy demands of the brain underscore the importance of nutrition in maintaining brain health and further indicate that aspects of nutrition may optimize brain health, in turn enhancing cognitive performance. General intelligence represents a critical cognitive ability that has been well characterized by cognitive neuroscientists and psychologists alike, but the extent to which a driver of brain health, namely nutritional status, impacts the neural mechanisms that underlie general intelligence is not understood. This study therefore examined the relationship between the intrinsic connectivity networks supporting general intelligence and nutritional status, focusing on nutrients known to impact the metabolic processes that drive brain function. We measured general intelligence, favorable connective architecture of seven intrinsic connectivity networks, and seventeen plasma phospholipid monounsaturated and saturated fatty acids in a sample of 99 healthy, older adults. A mediation analysis was implemented to investigate the relationship between empirically derived patterns of fatty acids, general intelligence, and underlying intrinsic connectivity networks. The mediation analysis revealed that small world propensity within one intrinsic connectivity network supporting general intelligence, the dorsal attention network, was promoted by a pattern of monounsaturated fatty acids. These results suggest that the efficiency of functional organization within a core network underlying general intelligence is influenced by nutritional status. This report provides a novel connection between nutritional status and functional network efficiency, and further supports the promise and utility of functional connectivity metrics in studying the impact of nutrition on cognitive and brain health.

1. Introduction

The human brain has high resource demands: the adult brain represents two percent of the body weight but consumes approximately 20 percent of the body's energy (Clarke et al., 1999). This energy requirement underscores a key point: adequate nutrition is needed to support brain health (Goyal et al., 2015). Further, while energy may be derived from a variety of nutritional sources, aspects of nutrition may optimize brain health, in turn enhancing cognitive performance. Recent discoveries in nutritional epidemiology and cognitive neuroscience provide insight into the therapeutic potential of nutrition for enhanced cognitive performance and brain health across the lifespan, with the interdisciplinary field of nutritional cognitive neuroscience leading this effort (reviewed in Zamroziewicz and Barbey (2016)). Unraveling the ways in which nutritional status may influence specific aspects of brain structure and function to support cognition will have profound implications for understanding the nature of brain health and for treating neurological disease.

General intelligence represents a critical cognitive ability that has been well characterized by cognitive neuroscientists and psychologists alike, but the extent to which a vital aspect of brain health, namely nutritional status, impacts the neural mechanisms that underlie general

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intelligence is not understood. General intelligence enables adaptive reasoning and problem solving skills (Colom et al., 2010; Barbey et al., 2012, 2013a, 2013b, 2014) that are important in everyday decision making (Gottfredson, 1997) and are strongly predictive of occupational attainment, social mobility (Strenze, 2007) and job performance (Gottfredson, 1997). Thus, understanding the neural mechanisms underlying this general mental ability, and how they may be modulated by lifestyle factors, such as nutritional status, may provide significant individual and societal benefits (Colom et al., 2010).

A large body of neuroscience evidence indicates that variation in the synchronization or efficiency of communication between brain regions reliably predicts individual differences in general intelligence (reviewed in Deary et al. (2010)). Intrinsic connectivity networks, the fundamental organizational units of human brain architecture (Laird et al., 2011), display 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). Individual differences in intelligence have been related to traditional measures of resting state connectivity in neural networks involved in self-referential mental activity (i.e., default mode network), attentional control processes (i.e., dorsal attention network), and task-set maintenance (i.e., cingulo-opercular network) (Song et al., 2009; Smith et al., 2015; Yuan et al., 2012; Wang et al., 2011; Pamplona et al., 2015; Santarnecchi et al., 2015). Further, recent evidence suggests a key role for connections between prefrontal and parietal cortices that comprise the dorsal attention network (Hearne et al., 2016). Advances in neuroimaging provide a new tool that implements graph theory principles to measure and assess intrinsic connectivity networks (Watts and Strogatz, 1998). Graph theory metrics enable a precise characterization of the complex network organization of the brain (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). In particular, small world propensity presents as an accurate measure of small world architecture that is impervious to nuisance variables but sensitive to critical variables of small world organization (Muldoon et al., 2016). Importantly, nutritional status has been shown to improve brain function (Wiesmann et al., 2016; Dumas et al., 2016; Konagai et al., 2013; Boespflug et al., 2016); however, no study has investigated the influence of nutritional status on small world propensity of the intrinsic connectivity networks that support cognition.

The Mediterranean diet is a well-recognized dietary pattern thought to promote healthy brain aging (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 (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 methodology in nutritional epidemiology for the measurement of nutrient biomarker patterns (NBPs). In this approach, nutrients are measured by way of biochemical markers in the blood (i.e., nutrient biomarkers) and principal component analysis is applied to empirically derive patterns of nutrients, referred to as NBPs. This method is highly sensitive to variability within a restricted set of variables (i.e., 5–10 variables per observation; Osborne and Costello, 2004). Thus, in this study, we use NBP analysis to investigate one of the core components of the Mediterranean diet with high sensitivity and specificity: the monounsaturated fatty acid to saturated fatty acid ratio. This fatty acid ratio has been linked to cognitive function (Samieri et al., 2013; Solfrizzi et al., 1999, 2006) as well as brain function (Dumas et al., 2016). In fact, the monounsaturated fatty acid to saturated fatty acid ratio is thought to be one of the driving factors of the metabolic benefits of the Mediterranean diet on the brain (Dyson et al., 2011; Evert et al., 2013; Aranceta and Pérez-Rodrigo, 2012). However, no study has investigated how patterns of monounsaturated fatty acids and saturated fatty acids affect the intrinsic connectivity networks that underlie cognitive function.

In summary, general intelligence is an important predictor of real-world decision making and relies upon the functional integrity of underlying neural networks. The monounsaturated fatty acid to saturated fatty acid ratio, a core component of the Mediterranean diet, is known to promote cognition and brain structure, but how these fatty acids support the intrinsic connectivity networks that underlie general intelligence remains unknown. Therefore, this study applies cutting-edge methodologies from nutritional epidemiology and cognitive neuroscience to explore how nutrient profiles of monounsaturated fatty acids and saturated fatty acids impact small world propensity of intrinsic connectivity networks that support general intelligence in a sample of cognitively intact older adults.

2. Materials and methods

2.1. Participants

This cross-sectional study enrolled 122 healthy elderly adult patients through Carle Foundation Hospital, a local and readily available cohort of well-characterized elderly adults. No participants were cognitively impaired, as defined by a score of lower than 26 on the Mini-Mental State Examination (Folstein et al., 1975). Participants with a diagnosis of mild cognitive impairment, dementia, psychiatric illness within the last three years, stroke within the past twelve months, and cancer within the last three years were excluded. Participants were also excluded for 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 and no contraindication for MRI.

Of these 122 participants, 99 subjects had a complete dataset at time of data analysis, including neuropsychological testing, MRI, and blood biomarker analysis. Participants had a mean age of 69 years (range: 65–75 years) and 63 percent of participants were females. All other participant characteristics are reported in Table 1.

This work was part of a study that aimed to characterize the relationship between nutrition, cognition, and brain health in healthy older adults. This sample presents the opportunity to examine normal brain function in a population in which age-related variability in cognition and brain health may be found and in which nutrition may be used to maintain health.

2.2. Standard 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.

2.3. Neuropsychological tests

General intelligence was measured by the Wechsler Abbreviated Scale of Intelligence – second edition (WASI-II (Wechsler, 1999);). This assessment measured general intelligence by way of an estimated intelligence quotient score. Per scoring guidelines, the estimated intelligence quotient score was the product of four subtests: a block design subtest, a matrix reasoning subtest, a vocabulary subtest, and a similarities subtest. In the block design subtest, participants were asked to reproduce pictured designs using specifically designed blocks as quickly and accurately as possible. In the matrix reasoning subtest, participants were asked to complete a matrix or serial reasoning problem by selecting the missing section from five response items. In the vocabulary subtest, participants were asked to verbally define vocabulary words (i.e., What does lamp mean?) that became progressively more challenging. In the similarities subtest, participants were asked to relate pairs of concepts (i.e., How are

Table 1
Characteristics of sample.

Demographics	***n* = 99**
Age in years (M ± SD; range)	69 ± 3; 65–75
Female (%)	63
Education (%)	
Some high school	1
High school degree	11
Some college	16
College degree	71
Income (%)	
< $15,000	1
$15,000 - $25,000	3
$25,000 - $50,000	15
$50,000 - $75,000	24
$75,000 - $100,000	25
>$100,000	31
BMI (M ± SD)	26 ± 4
Depression indicated (%)	5
Plasma phospholipid nutrients	**(M ± SD, μmol/L)**
Capric acid (10:0)	0.14 ± 0.14
Lauric acid (12:0)	1.32 ± 0.87
Myristic acid (14:0)	12.60 ± 4.49
Pentadecylic acid (15:0)	6.34 ± 1.60
Palmitic acid (16:0)	723.81 ± 139.08
Stearic acid (18:0)	402.28 ± 88.05
Arachidic acid (20:0)	10.27 ± 2.08
Behenic acid (22:0)	30.85 ± 7.24
Lignoceric acid (24:0)	20.52 ± 5.40
Myristoleic acid (14:1)	1.10 ± 0.97
cis-7-Hexadecenoic acid (16:1n-9)	4.07 ± 1.09
Palmitoleic acid (16:1n-7)	15.58 ± 7.20
Oleic acid (18:1n-9)	240.22 ± 58.39
cis-Vaccenic acid (18:1n-7)	34.71 ± 7.79
Gondoic acid (20:1n-9)	3.53 ± 0.91
Erucic acid (22:1n-9)	0.43 ± 0.23
Nervonic acid (24:1n-9)	28.12 ± 7.10
Cognition	**(M ± SD)**
General intelligence	115 ± 13
Small world propensity	**(M ± SD)**
Visual network	0.542 ± 0.116
Motor network	0.515 ± 0.122
Dorsal attention network	0.584 ± 0.104
Ventral attention network	0.518 ± 0.137
Limbic network	0.554 ± 0.147
Frontoparietal network	0.664 ± 0.059
Default network	0.672 ± 0.032

Abbreviations: mean (M), standard deviation (SD), body mass index (BMI).

a cow and bear alike?) that became progressively more challenging. Per scoring guidelines, subjects' raw scores were converted to standardized scores and combined into an estimated intelligence quotient score, which provided a measure of general intelligence.

2.4. 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 (Auerbach et al., 2013) sensitive to blood oxygenation level dependent (BOLD) contrast (2.5 × 2.5 × 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).

2.5. Functional magnetic resonance imaging of small world propensity of intrinsic connectivity networks

All MRI data processing was performed using FSL tools available in FMRIB Software Library version 5.0 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). 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) segmentation (Zhang et al., 2001) was performed 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 (0.009–0.01 Hz; Van Dijk et al., 2010; Mennes et al., 2012), 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 × interquartile range (Van Dijk et al., 2010; Mennes et al., 2012; Power 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 preprocessed resting state fMRI data was 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.

The network measure of small world propensity (Muldoon et al., 2016) was investigated to quantify the extent to which functional brain networks exhibited high local clustering and short path lengths that promote efficient information flow within coupled neural systems. Small world propensity can be computed for weighted networks, thereby taking into account differential connectivity strengths that might have important implications for brain health. In this study, small world propensity measures were generated for seven intrinsic connectivity networks: default mode network, frontoparietal network, dorsal attention network, ventral attention network, limbic network, somatomotor network, and visual network. These intrinsic connectivity networks were previously identified based on the clustering of functionally coupled regions (Yeo et al., 2011).

Weighted connectivity matrices were computed for each intrinsic connectivity network across all subjects. First, Craddock's 800 brain parcel grey matter mask (http://ccraddock.github.io/cluster_roi/atlases.html; Craddock et al., 2012), was used to extract the mean time series signal from subjects' BOLD fMRI preprocessed data at each parcel/region. This parcellation level provided whole brain coverage and sufficiently high resolution for conducting network analysis on the intrinsic connectivity network nodes. Of the 800 parcellated regions, 655 regions were found to be common across all subjects. A subject-wise functional connectivity matrix reflecting pairwise Pearson correlations between the mean BOLD time series signals obtained from these 655 regions was then computed and subsequently 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 number of samples comprising the BOLD signal (Bobko, 2001). Next, a Bonferroni-corrected statistical Z-threshold was applied to identify significant positive correlations ($p < 0.05$) within each subject's functional connectivity matrix (Fox et al., 2009; Murphy et al., 2009). The p-value of 0.05 was divided by $N = 428370$ Pearson's correlations (i.e., (655 × 655) – 655)). The 655 Pearson's correlations representing self-connections

were subtracted as these were not included in the network analysis. The calculated Bonferroni corrected statistical threshold for p-value was 1.672×10^{-07}, which was equivalent to one-sided positive Z-score of 5.1705. The thresholded Z-scores were finally 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 specific intrinsic connectivity networks (mask at https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011) were obtained for each subject. Nodes within each intrinsic connectivity network were defined as the center of mass coordinate of the Craddock's parcellated units. Small world propensity was finally calculated from these weighted connectivity matrices based on the fractional deviation between a network's clustering coefficient, C_{brain}, and characteristic path length, L_{brain}, from both lattice ($C_{lattice}$, $L_{lattice}$) and random (C_{random}, L_{random}) networks having the same number of nodes and same degree distribution (Van Dijk et al., 2010; Mennes et al., 2012; MATLAB code at http://www.seas.upenn.edu/~dsb/).

2.6. Nutrient biomarker acquisition

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 cholor-oform: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 Aryen, Julkunen and Penttila (Aryen 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). The plasma lipids of interest were saturated fatty acids and monounsaturated fatty acids, listed in Table 1.

2.7. Nutrient biomarker pattern analysis of fatty acids

Nutrient biomarker pattern analysis was conducted in IBM SPSS statistical software, version 24 for Macintosh. Principal component analysis was used to identify NBPs of fatty acids from the seventeen fatty acids listed in Table 1. Of these, twelve fatty acids (capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, myristoleic acid, palmitoleic acid, *cis*-7-hexadecenoic acid, *cis*-vaccenic acid, oleic acid, gondoic acid, erucic acid) were non-normally distributed as indicated by Shapiro-Wilk test (all p-values<0.05) and therefore log-transformed to correct for skewness of variables and subsequently considered in the analysis. The appropriate rotation method was determined by examining the factor correlation matrix: varimax rotation for a correlation matrix with values less than 0.32 and direct oblimin rotation for a correlation matrix with values greater than 0.32 (Tabachnick and Fidell, 2007). Statistical validity of the factor analysis was confirmed via the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (≥0.50 (Van Dijk et al., 2010; Mennes et al., 2012; Kaiser, 1970)) and Bartlett's Test of Sphericity ($p < 0.05$ (Van Dijk et al., 2010; Mennes et al., 2012; Bartlett, 1950)). Outliers were identified as participants with factor score values greater than 3.0 and removed from all analyses (Jolliffe, 2014). The number of NBPs to be retained was determined by a combination of eigenvalues greater than 1.0, variance accounted for by each component, and scree plot inflection point. 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). Each participant received a standardized NBP score for each pattern that corresponded to a linear combination of the nutrient biomarkers.

2.8. Covariates

Covariates were included according to previous association with cognitive decline (Koen and Yonelinas, 2014; Rönnlund et al., 2005; Hurst et al., 2013; Gallucci et al., 2013; Pauls et al., 2013; Wilkins et al., 2010). The covariates included age (continuous), gender (nominal, man/woman), education (nominal, five fixed levels), income (nominal, six fixed levels), body mass index (continuous, hereafter BMI), and depression status (nominal, yes/no). Although all participants had received a diagnosis of no depression at enrollment, the SF-36 Health Survey (Ware et al., 1993) revealed five percent of participants with symptoms consistent with depression. Thus, in accordance with prior studies (Bowman et al., 2012, 2013; Witte et al., 2014), this was considered in the analysis as a covariate.

2.9. Statistical analysis

A formal mediation analysis was conducted to model the relationship between small world propensity of intrinsic connectivity networks, general intelligence, and NBPs of monounsaturated and saturated fatty acids. The analysis used a four-step framework with the ultimate goal of evaluating whether small world propensity of intrinsic connectivity networks mediated the relationship between NBPs of monounsaturated and saturated fatty acids and general intelligence. The primary requirement for mediation is a significant indirect mediation effect (Zhao et al., 2010), or the effect of the independent variable (NBPs) through the mediator (small world propensity of intrinsic connectivity networks) on the dependent variable (general intelligence) (Fig. 1).

1. In the first step, regression models were applied to identify the intrinsic connectivity networks that predict general intelligence (**path b**). Two linear regression models were fit. Model one included small world propensity of seven intrinsic connectivity networks, age, gender, and

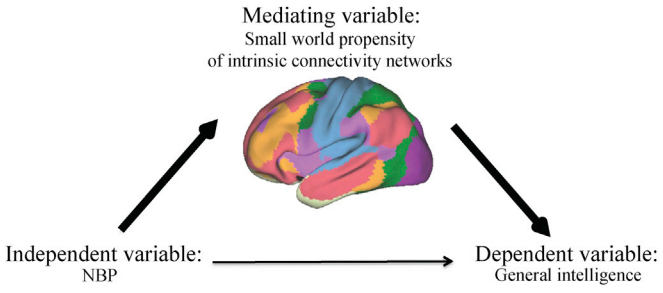

Fig. 1. Proposed mediation model: The primary requirement for mediation is a significant indirect mediation effect, defined as the effect of the independent variable (nutrient biomarker pattern, NBP) through the mediator (small world propensity of intrinsic connectivity networks) on the dependent variable (general intelligence).

education, all entered simultaneously. Model two was further adjusted for income, BMI, and depression status simultaneously. Model one aimed to avoid over-fitting and is reported in-text (Babyak, 2004), whereas model two aimed to comprehensively account for covariates that have been previously associated with cognitive decline.

2. In the second step, regression models were applied to characterize the relationship between NBPs and small world propensity of the intrinsic connectivity networks that underlie general intelligence (**path a**). Only the intrinsic connectivity networks that related to general intelligence in step one were considered. Two linear regression models were fit for each intrinsic connectivity network. Model one included each NBP, age, gender, and education, all entered simultaneously. Model two was further adjusted for income, BMI, and depression status simultaneously. As previously, model one avoided over-fitting and is reported in-text, and model two comprehensively accounted for covariates. The Supplement provides additional evidence to aid interpretation of the direction of the relationship between the NBPs and small world propensity of intrinsic networks, as the sign of the loadings and factor scores from a PCA analysis only indicate orthogonality and are not directly interpretable.

3. In the third step, regression models were applied to characterize the relationship between NBPs and general intelligence (**path c**). Two linear regression models were fit. Model one included each NBP, age, gender, and education, all entered simultaneously. Model two was further adjusted for income, BMI, and depression status simultaneously. As previously, model one avoided over-fitting and is reported in-text, and model two comprehensively accounted for covariates. Supplement provides additional evidence to aid interpretation of the direction of the relationship between the NBPs and general intelligence.

4. In the fourth step, the PROCESS macro was applied to implement the bootstrapping method to estimate mediation effects (Preacher and Hayes, 2008). PROCESS model four was used to estimate mediation effects. This analysis drew 5000 bootstrapped samples with replacement from the dataset to estimate a sampling distribution for the indirect and direct mediation effects, controlling for age, gender, education, income, BMI, and depression status. Per standard PROCESS macro procedure, bootstrap estimates of the indirect effect were calculated (http://processmacro.org). The indirect mediation effect refers to the pathway from NBPs to small world propensity of intrinsic connectivity networks to general intelligence (**path a-b**). The direct mediation effect refers to the direct pathway from NBPs to general intelligence, accounting for the effect of small world propensity of intrinsic connectivity networks (**path c'**).

Results are reported using (i) R^2 for each model, (ii) unstandardized regression coefficients (β), unstandardized regression coefficient standard error (SE β), and p of each individual regression relationship, and (iii) a 95% bias-corrected confidence interval (95% CI) for the direct and indirect effects of the mediation. Significance was accepted at $p \leq 0.05$ and a false discovery rate (FDR) correction for multiple comparisons (Benjamini and Hochberg, 1995) was applied ($q<0.05$, two-tailed). A statistically significant mediation that matches the hypothesized framework is indicated by: (i) an indirect mediation effect that does not include zero within 95% CI, and (ii) a direct mediation effect that does include zero within 95% CI (Zhao et al., 2010).

3. Results

3.1. Nutrient biomarker patterns

Principal component analysis generated four NBPs (Table 2). The factor correlation matrix contained values greater than 0.32, therefore direct oblimin rotation was implemented. Statistical validity of the factor analyses was confirmed via the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (0.780) and Bartlett's Test of Sphericity ($p < 0.001$). One outlier was removed from the dataset. Four NBPs were selected for retention because (i) after the NBP extraction with principal component analysis, 71.4 percent of the total variance was accounted for in the original set of nutrient biomarkers, and (ii) inspection of the scree plot indicated that the inflection point occurred after the fourth NBP (Fig. 2). Hereafter, NBP1 is described as SFA (i.e., it is composed of saturated fatty acids and one monounsaturated fatty acid, all derived or *de novo* synthesized from dietary sources of saturated fatty acids), NBP2 is described as SEED OIL (i.e., it is composed of saturated fatty acids and one monounsaturated fatty acid, all primarily derived from seed oils), NBP3 is described as MIXED (i.e., it is composed of saturated and monounsaturated fatty acids derived from various sources), and NBP4 is described as MUFA (i.e., it is composed of only monounsaturated fatty acids). Importantly, SEED OIL and MUFA have negative loading coefficients, therefore these two NBPs load in the opposite direction from that of the SFA and MIXED patterns.

Table 2
Nutrient biomarker pattern construction: Pattern structure and variance explained.[a].

Plasma phospholipid fatty acid	Nutrient biomarker pattern[b]			
	1	2	3	4
Palmitoleic acid (16:1n-7)	−0.815[c]			
Pentadecanoic acid (15:0)	−0.769[c]			
Myristic acid (14:0)	−0.742[c]			
Palmitic acid (16:0)	−0.535[c]	0.321		0.416
Arachidic acid (20:0)		0.914[c]		
Lignoceric acid (24:0)		0.914[c]		
Behenic acid (22:0)		0.873[c]		
Nervonic acid (24:1n-9)		0.758[c]		
Stearic acid (18:0)		0.393		0.391
Capric acid (10:0)	0.412		−0.725[c]	
Erucic acid (22:1n-9)			−0.674[c]	
Myristoleic acid (14:1)			−0.513[c]	
Lauric acid (12:0)	−0.308		−0.492	
Gondoic acid (20:1n-9)	0.326			0.928[c]
Oleic acid (18:1n-9)				0.769[c]
cis-Vaccenic acid (18:1n-7)				0.701[c]
cis-7-Hexadecenoic acid (16:1n-9)	−0.408			0.578[c]
Percent variance explained by each NBP	43.040	13.452	8.263	6.679
Cumulative percent variance explained with each extraction	43.040	56.493	64.756	71.435

Abbreviations: saturated fatty acid (SFA), monounsaturated fatty acid (MUFA).
[a] Extraction method: principal component analysis; rotation method: oblimin.
[b] NBP interpretation based on strongest loading coefficients within each pattern; only loadings with an absolute value ≥ 0.3 are shown in the table.
[c] Nutrients with absolute loadings ≥ 0.5 that are considered as dominant nutrients contributing to the particular nutrient pattern.

3.2. Mediation results

The mediation analysis indicated that small world propensity of the dorsal attention network fully mediated the relationship between the MUFA pattern and general intelligence. Each relationship within the mediation is described below in a stepwise fashion.

1. Small world propensity of the dorsal attention network (β = 32.222 SE β = 11.844, p = 0.008) and frontoparietal network (β = 42.555 SE β = 19.357, p = 0.031) predicted general intelligence (R^2 = 0.347, Table 3). Results remained significant after accounting for all covariates and because all variables of interest were included in the same model, no correction for multiple comparisons was needed (Table 3). Thus, the dorsal attention network and frontoparietal network were considered in step two.

2. Small world propensity of the dorsal attention network was positively associated with the SFA pattern (β = 0.024 SE β = 0.012, p = 0.044) and the MUFA pattern (β = 0.041 SE β = 0.012, p = 0.001), but no NBP reliably associated with small world propensity of the frontoparietal network (R^2 = 0.144, Table 4). These findings, coupled with those in Supplementary Fig. 1, suggest higher levels of fatty acids within the SFA pattern predicted lower small world propensity of the

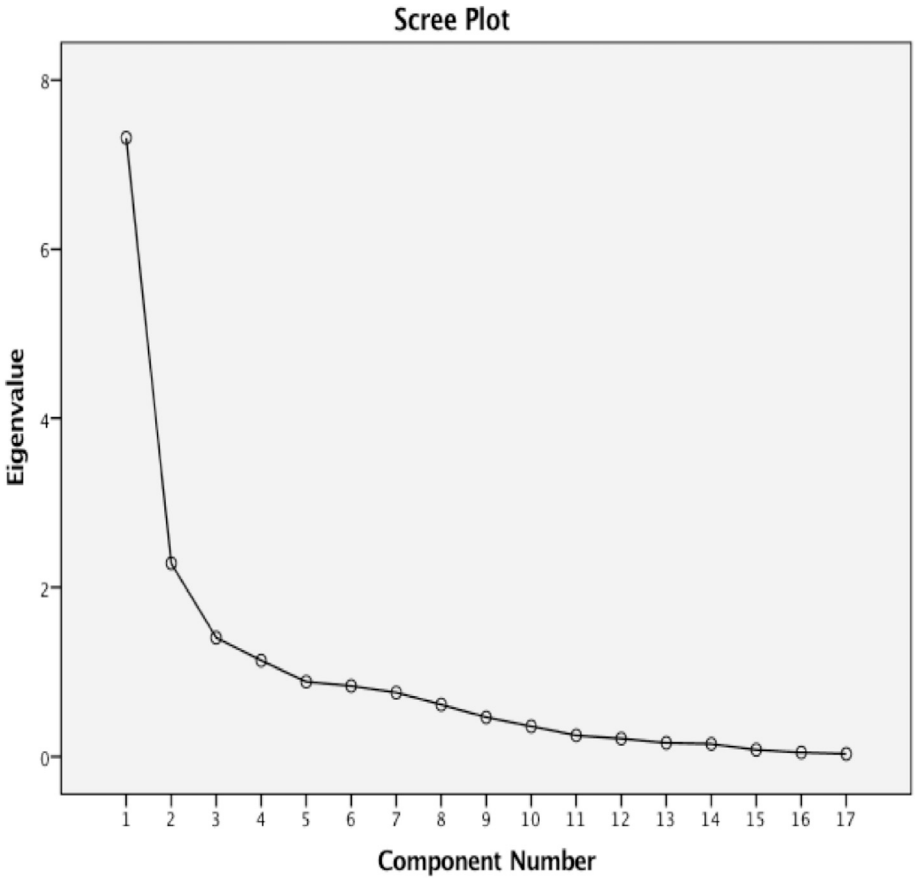

Fig. 2. Scree plot: Inspection of the scree plot indicated that the inflection point occurred after the fourth component, or nutrient biomarker pattern, was extracted.

Table 3
Linear regression models: Small world propensity of intrinsic connectivity networks associated with general intelligence.

Network small world propensity		General intelligence	
		Model 1[a]	Model 2[b]
Visual	β	12.252	9.353
	SE	9.995	10.248
Somatomotor	β	−10.242	−7.686
	SE	10.853	10.778
Dorsal attention	β	32.222*	25.451*
	SE	11.844	12.065
Ventral attention	β	−2.333	1.356
	SE	8.587	8.644
Limbic	β	−0.415	−2.277
	SE	7.966	8.065
Frontoparietal	β	42.555*	40.313*
	SE	19.357	19.125
Default	β	9.994	1.024
	SE	36.201	36.506
Model	R^2	0.347*	0.392*

*p < 0.05.
[a] Model 1: general intelligence = small world propensity of 7 networks + age + gender + education.
[b] Model 2: general intelligence = model 1 + income + body mass index + depression status.

Table 4
Linear regression models: Nutrient biomarker patterns associated with small world propensity of intrinsic connectivity networks.

NBP		Dorsal attention		Frontoparietal	
		Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
SFA	β	0.024	0.027	0.001	0.002
	SE	0.012	0.012	0.007	0.007
SEED OILS	β	−0.009	−0.013	−0.003	−0.003
	SE	0.012	0.011	0.007	0.007
MIXED	β	0.012	0.012	0.004	0.004
	SE	0.011	0.011	0.007	0.007
MUFA	β	0.041*	0.042*	0.001	0.002
	SE	0.012	0.012	0.007	0.008
Model	R^2	0.144*	0.212*	0.050	0.053

Abbreviations: nutrient biomarker pattern (NBP), nutrient biomarker pattern 1 (SFA), nutrient biomarker pattern 2 (SEED OILS), nutrient biomarker pattern 3 (MIXED), nutrient biomarker pattern 4 (MUFA).
*p < 0.05, FDR-corrected.
[a] Model 1: small world propensity of network = 4 NBPs + age + gender + education.
[b] Model 2: small world propensity of network = model 1 + income + body mass index + depression status.

dorsal attention network, whereas higher levels of fatty acids within the MUFA pattern predicted higher small world propensity of the dorsal attention network. After accounting for all covariates, results remained significant, but after correcting for multiple comparisons, only MUFA remained a significant predictor (Table 3). Thus, the dorsal attention network was considered in the context of the mediation model (Fig. 3 **path a-b**).

3. General intelligence was positively predicted by MUFA (β = 3.550 SE β = 1.373, p = 0.011), but not by any other NBP (R^2 = 0.301, Table 5). This result, along with Supplementary Fig. 2, indicate higher levels of fatty acids within the MUFA pattern predicted better general intelligence. Results remained significant after accounting for all covariates and correcting for multiple comparisons (Table 3). Thus, MUFA was considered in the context of the mediation model (Fig. 3 **path c**).

4. The indirect pathway of mediation (the pathway from MUFA to dorsal attention network small world propensity to general intelligence) was significant (95% CI [0.027, 1.931], Fig. 3 **path a-b**), but the direct

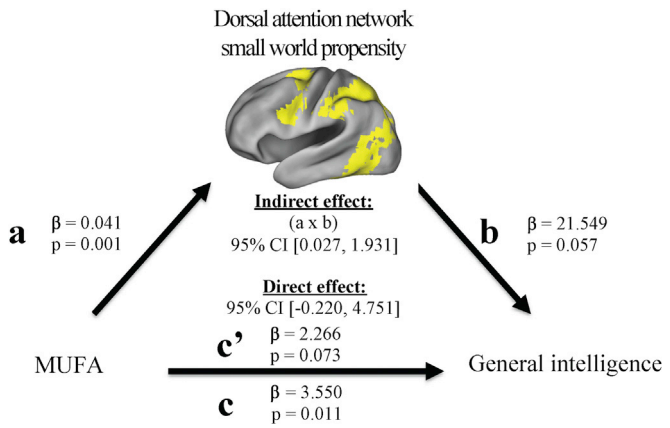

Fig. 3. Mediation model statistics: Higher levels of nutrient biomarker pattern 4 (MUFA) associated with higher small world propensity of the dorsal attention network (**path a**). Higher MUFA also associated with better general intelligence (**path c**). The indirect pathway of mediation (i.e., the effect of MUFA through dorsal attention network small world propensity on general intelligence; **path a-b**) was statistically significant. The direct pathway of mediation (i.e., the effect of MUFA on general intelligence, accounting for small world propensity of the dorsal attention network; **path c'**) was not significant. Therefore, small world propensity of the dorsal attention network fully mediated the relationship between MUFA and general intelligence.

Table 5
Linear regression models: Nutrient biomarker patterns associated with general intelligence.

NBP		General intelligence	
		Model 1[a]	Model 2[b]
SFA	β	−0.219	0.032
	SE	1.306	1.298
SEED OILS	β	−0.342	−0.651
	SE	1.299	1.273
MIXED	β	1.390	1.522
	SE	1.209	1.177
MUFA	β	3.550*	3.495*
	SE	1.373	1.351
Model	R^2	0.301*	0.365*

Abbreviations: nutrient biomarker pattern (NBP), nutrient biomarker pattern 1 (SFA), nutrient biomarker pattern 2 (SEED OILS), nutrient biomarker pattern 3 (MIXED), nutrient biomarker pattern 4 (MUFA).
*p < 0.05, FDR-corrected.
[a] Model 1: general intelligence = 4 NBPs + age + gender + education.
[b] Model 2: general intelligence = model 1 + income + body mass index + depression status.

pathway of mediation (the direct pathway from MUFA to general intelligence, accounting for the effect of small world propensity of the dorsal attention network) was not significant (95% CI [-0.220, 4.751], β = 2.266 SE β = 1.251, p = 0.073, Fig. 3 **path c'**). Therefore, the mediation indicated that small world propensity of the dorsal attention network fully mediated the relationship between MUFA and general intelligence (R^2 = 0.377, Fig. 3).

4. Discussion

This study revealed that an intrinsic connectivity network supporting general intelligence, the dorsal attention network, is influenced by monounsaturated fatty acids, and furthermore, that small world propensity of the dorsal attention network fully mediates the relationship between monounsaturated fatty acids and general intelligence. This report provides a novel link between nutritional status and functional connectivity within intrinsic connectivity networks that underlie general intelligence. The individual relationships reported within these analyses, including those between small world propensity of intrinsic connectivity networks and general intelligence (Fig. 3 **path b**), between monounsaturated fatty acids and small world propensity of intrinsic connectivity networks (Fig. 3 **path a**), and between monounsaturated fatty acids and general intelligence (Fig. 3 **path c**) are each supported by prior findings and reviewed below.

First, small world propensity of the dorsal attention network and frontoparietal network predicted general intelligence. Previous work supports the notion that functional connectivity within both the frontoparietal cortex and the dorsal attention network underlie general intelligence. In regard to cognitive function, the dorsal attention network serves externally-directed attention, whereas frontoparietal control network serves a pivotal gate-keeping role in goal-direction attention (Spreng et al., 2013). Traditionally, the frontoparietal network is thought to be responsible for intelligence (Colom et al., 2010). However, with age, regions that are typically connected to the frontoparietal cortex, including the lateral and rostral prefrontal cortex, are reassigned to the dorsal attention network (Grady et al., 2016). Importantly, tasks of general intelligence are known to recruit the lateral prefrontal cortex (Duncan et al., 2000) along with prefrontal regions that comprise the dorsal attention network (Hearne et al., 2016). Furthermore, performance on tasks of intelligence is dependent upon organization of functional brain networks (van den Heuvel et al., 2008; Song et al., 2008), and age-related disorganization in these networks has been linked to worse cognitive performance (Damoiseaux, 2017). Thus, our findings are in line with previous evidence, which suggests a role for the dorsal attention network and frontoparietal network in general intelligence in older adults. Importantly, there is significant heterogeneity in the neuropsychological tests used to measure intelligence. For instance, the work cited above employed modified tasks from standardized neuropsychological tests, such as the ETS Kit of Factor-Reference Tests (Benjamini and Hochberg, 1995) and the Cattell Culture Fair (Benjamini and Hochberg, 1995), as well as entire standardized neuropsychological tests, such as the Penn's Progressive Matrices (Hearne et al., 2016). Though the neuropsychological test of general intelligence employed in this study differed from those implemented in previous studies, our findings supported previous findings. Thus, the relationship between general intelligence and functional connectivity in these networks may be robust and not dependent upon the neuropsychological test used to measure general intelligence.

Second, small world propensity of the dorsal attention network was reliably linked to higher levels of fatty acids within the MUFA pattern. Previous evidence indicates that dietary intervention can indeed improve functional connectivity (Wiesmann et al., 2016). In fact, monounsaturated fatty acids have been shown to oppose the detrimental effects of saturated fatty acids on brain function (Dumas et al., 2016). Furthermore, dietary patterns that include high levels of monounsaturated fatty acids are known to increase metabolism in regions within the dorsal attention network (Berti et al., 2015). Therefore, our findings provide further support for the beneficial role of monounsaturated fatty acids on brain function.

Third, higher levels of fatty acids within the MUFA pattern predicted superior general intelligence. It has long been postulated that nutrition could at least in part explain secular increases in intelligence (Lynn, 1990). In older adults, fatty acid status has been linked to slower cognitive decline (Whalley et al., 2004). More specifically, high levels of monounsaturated fatty acids have been shown to improve overall cognitive status (Solfrizzi et al., 2006) as well as the trajectory of cognitive decline (Samieri et al., 2013). To our knowledge, no study has previously investigated the relationship between fatty acid status and general intelligence. Our results suggest that monounsaturated fatty acids influence an aspect of cognition that supports everyday decision making.

Lastly, small world propensity of the dorsal attention network fully mediated the relationship between the MUFA pattern and general intelligence. The mediation results are supported by the three lines of evidence outlined above, but importantly, offer a novel perspective on the relationship between nutrition, cognition, and brain health. These findings indicate that general intelligence is not only dependent on

underlying intrinsic connectivity networks, but also on nutritional status. To our knowledge, no study has previously assessed the link between nutritional status and intrinsic connectivity networks that underlie cognitive function.

The predictive power of monounsaturated fatty acids may be indicative of particular physiological mechanisms. One mechanism thought to underlie the benefits of nutrition, and particularly monounsaturated fatty acids, in the brain is the support of insulin sensitivity (Vessby et al., 2001; Sartorius et al., 2012). Type 2 Diabetes Mellitus is known to increase risk for Alzheimer's disease, but even in individuals without clinical diabetes, blood glucose levels are positively associated with accelerated cognitive decline (Crane et al., 2013). Furthermore, abnormal insulin signaling associated with metabolic dysfunction within the central nervous system has been shown to induce cognitive dysfunction (Manschot et al., 2006) as well as changes in functional connectivity (Musen et al., 2012). More specifically, the dorsal attention network has shown disruptions in functional connectivity in individuals with metabolic dysfunction (Xia et al., 2015). Importantly, insulin resistance is modifiable and Mediterranean-style diets with a high proportion of monounsaturated fatty acids have been shown to enhance insulin sensitivity (Esposito et al., 2004; Shai et al., 2008). In fact, dietary guidelines on macronutrient intake to improve glucose-insulin profiles specifically recommend increasing foods rich in monounsaturated fatty acids and reducing foods high in saturated fatty acids (Evert et al., 2013; Aranceta and Pérez-Rodrigo, 2012). Thus, our results corroborate the role of monounsaturated fatty acids in metabolic function, and further provide novel evidence for the role of monounsaturated fatty acids in supporting intrinsic connectivity networks that underlie general intelligence. Importantly, metabolic dysfunction was not measured in this study. Thus, the role of metabolic status in the observed relationships could not be assessed. Future work that incorporates biomarkers of metabolic status is needed to corroborate the proposed mechanisms of action.

The strengths of this study include the use of functional MRI and graph theory metrics to measure functional connectivity, the assessment of a critical cognitive ability that impacts everyday life, and the use of blood biomarkers to measure physiological status of monounsaturated fatty acids and saturated fatty acids. One limitation of this study is the cross-sectional design, which allowed examination of relationships during one snapshot in time. Future longitudinal work is needed to identify how changes in fatty acid patterns relate to changes in general intelligence and functional connectivity. Additionally, this study implemented a limited set of neuropsychological tests (i.e., general intelligence was measured via an abbreviated neuropsychological battery), and administration of a full neuropsychological battery is needed in future work to comprehensively measure general intelligence. Further, this study was not designed to measure relevant physiological conditions that influence brain function, such as metabolic dysfunction and hypertension, thus highlighting the need for future measurement of these factors to confirm underlying mechanisms. Finally, this work did not assess the relative contributions of diet and metabolic processes to fatty acid patterns, and future investigations of this nature are needed to characterize the relationship between diet, general intelligence, and functional connectivity.

Research at the frontline of nutritional cognitive neuroscience aims to incorporate cutting-edge measures of nutritional intake, cognitive function, and brain health to illustrate that the features of brain health which support critical cognitive abilities are influenced by nutritional status and dietary intake. In doing so, nutritional cognitive neuroscience endeavors to bridge the gap between largely disparate literature within the fields of nutritional epidemiology and cognitive neuroscience, and offer a novel perspective on brain health. Accumulating evidence suggests that certain nutrients may influence particular aspects of cognitive function by targeting specific features of brain health (Zamroziewicz and Barbey, 2016; Bowman et al., 2013; Gu et al., 2016; Zamroziewicz et al., 2015, 2016a, 2016b, 2017, 2018). The present finding contributes to this research program and provides novel evidence for the benefits of monounsaturated fatty acids on intrinsic connectivity networks that underlie general intelligence. These data support the promise and utility of functional connectivity metrics in studying the impact of nutrition on cognitive and brain health.

Competing interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.neuroimage.2017.08.043.

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