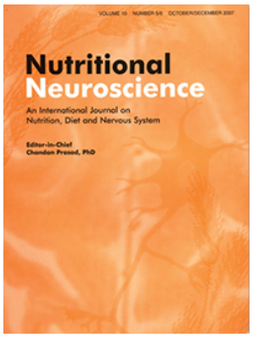

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Determinants of fluid intelligence in healthy aging: Omega-3 polyunsaturated fatty acid status and frontoparietal cortex structure

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Introduction: Accumulating evidence indicates that cognitive decline depends not only upon changes in brain health, but critically, also upon nutritional status. Decline in fluid intelligence, one of the most debilitating aspects of cognitive aging, has been linked to omega-3 polyunsaturated fatty acid (PUFA) status; however, it is not known whether this phenomenon results from specific omega-3 PUFAs acting on particular aspects of brain health. Therefore, this study aims to explore whether particular patterns of omega-3 PUFAs influence fluid intelligence by supporting specific neural structures.

Methods: We measured six plasma phospholipid omega-3 PUFAs, fluid intelligence, and regional gray matter volume in the frontal and parietal cortices in 100 cognitively intact older adults (65–75 years old). A four-step mediation analysis was implemented using principal component analysis and multivariate linear regressions, adjusted for age, gender, education, and body mass index.

Results: The mediation analysis revealed that one pattern of omega-3 PUFAs, consisting of alpha-linolenic acid, stearidonic acid, and eicosatrienoic acid, was linked to fluid intelligence, and that total gray matter volume of the left frontoparietal cortex (FPC) fully mediated the relationship between this omega-3 PUFA pattern and fluid intelligence.

Discussion: These data demonstrate that fluid intelligence may be optimally supported by specific omega-3 PUFAs through preservation of FPC gray matter structure in cognitively intact older adults. This report provides novel evidence for the benefits of particular omega-3 PUFA patterns on fluid intelligence and underlying gray matter structure.

Keywords: Nutrient biomarkers, Nutrient biomarker patterns, Cognitive performance, Cognitive aging, Cortical integrity, Brain aging, Nutritional cognitive neuroscience

Introduction

Nutrition has increasingly been recognized for its ability to help prevent and protect against disease, and at the frontiers of this effort is research within the emerging interdisciplinary field of *Nutritional Cognitive Neuroscience*. This line of work demonstrates that cognitive decline depends not only upon changes in brain structure and brain function, but critically, also upon dietary intake and nutritional status.[1] As the United States experiences rapid growth in the proportion of older adults, the search for effective strategies to promote healthy brain aging provides a catalyst for research to investigate the beneficial effects of nutrition on the aging brain.

In the absence of neurodegenerative disease, decline in fluid intelligence presents as one of the most debilitating aspects of cognitive aging.[2] Fluid intelligence refers to the intellectual abilities required for adaptive problem solving in novel situations, and reflects the capacity to creatively and flexibly grapple with the world in ways that do not rely on prior knowledge.[3] A fundamental issue in the study of cognitive aging has historically been whether fluid intelligence can be maintained in late adulthood.[4] Indeed, recent

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evidence indicates that age-related decline in fluid intelligence is mediated by nervous system health, highlighting the potential for intervention by neuroprotective nutrients.[5]

Increasing evidence suggests that omega-3 (n-3) polyunsaturated fatty acids (PUFAs) benefit the aging brain.[6] PUFAs are known to contribute to structural integrity of neuronal membranes, control inflammation and oxidation, and promote energy metabolism.[7] Omega-3 PUFAs have been linked to the preservation of cognitive functions vulnerable to age-related decline, including fluid intelligence.[8] However, it is not known which brain structures n-3 PUFAs may act upon to support fluid intelligence, and whether particular patterns of n-3 PUFAs preferentially provide support.

Fluid intelligence engages a distributed brain circuit within the frontal and parietal cortex.[9,10] Specifically, fluid intelligence is linked to structural integrity and neural activity within the lateral prefrontal and posterior parietal cortices, regions cumulatively referred to as the frontoparietal cortex (FPC).[11,12] Importantly, n-3 PUFAs slow age-related structural decline in the FPC,[13,14] and in this way, could prevent age-related decline in fluid intelligence. Thus, the FPC plays a critical role in fluid intelligence and is amenable to n-3 PUFAs, making it a target region of interest for investigating the impact of n-3 PUFAs on the cognitive and neural mechanisms of fluid intelligence.

In summary, one of the most debilitating aspects of cognitive aging, decline in fluid intelligence and degeneration of the underlying FPC, may be ameliorated by n-3 PUFA intake. However, it is not known whether particular patterns of n-3 PUFAs influence core brain regions to support fluid intelligence. Therefore, this study aims to (i) identify nutritional biomarkers of fluid intelligence by empirically deriving patterns of n-3 PUFAs and (ii) distinguish the neural structures that mediate the beneficial effect of n-3 PUFAs on fluid intelligence.

Materials and methods

Study participants

This cross-sectional study enrolled 122 healthy elderly adult patients from 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.[15] Participants with a diagnosis of mild cognitive impairment, dementia, psychiatric illness within the last 3 years, stroke within the past 12 months, and cancer within the last 3 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, 22 participants did not have a complete dataset, which included neuropsychological testing, MRI, and blood biomarker analysis. Therefore, 100 participants were considered in the current analysis.

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.

Biomarker acquisition and analysis

Plasma lipids were extracted by the method of Folch *et al.*[16] 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 minutes, 4°C). Then 1.5 ml of 0.88% KCl was added to the supernatant, shaken vigorously and the layers were allowed to settle for 5 minutes. 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 were allowed to settle for 15 minutes. 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 *et al.*[17] Then the phospholipid fraction was methylated by adding 2 ml of 14% BF3-MeOH and incubating at 95°C for 1 hour.[18] 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, USA) 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 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 programed at 80°C, held for 16 minutes and then increased to 180°C at a rate of 5°C/minute. After 10 minutes, the temperature was increased to 192°C at a rate of 0.5°C/minute, and held for 4 minutes. The final temperature was 250°C reached at a rate of 405°C/minute and held for 15 minutes. Peaks of interest were identified by

comparison with authentic fatty acid standards (Nu-Chek Prep, Inc., Waterville, MN, USA) and expressed as absolute concentration (μmol/l). The plasma phospholipid lipids of interest were n-3 PUFAs, including α-linolenic acid (ALA, 18:3n-3), stearidonic acid (SDA, 18:4n-3), eicosatrienoic acid (20:3n-3, ETE), eicosapentaenoic acid (EPA, 20:5n-3), docosapentaenoic acid (DPA, 22:5n-3), and docosahexaenoic acid (DHA, 22:6n-3).

Nutrient biomarker pattern analysis of PUFAs

Nutrient biomarker pattern (NBP) analysis was conducted in the IBM SPSS statistical software, version 24 for Macintosh. Principal component analysis was used to identify NBPs from the six n-3 PUFAs of interest. Of these, five n-3 PUFAs (ALA, ETE, EPA, DPA, and DHA) 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 was chosen for a correlation matrix with values less than 0.32 and direct oblimin rotation was chosen for a correlation matrix with values greater than 0.32.[19] Statistical validity of the factor analysis was confirmed via the Kaiser–Meyer–Olkin measure of sampling adequacy (≥ 0.50)[20] and Bartlett's test of sphericity ($P < 0.05$).[21] 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 an 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.

Neuropsychological tests

Fluid intelligence was measured by the Wechsler Abbreviated Scale of Intelligence – second edition (WASI-II).[22] This assessment measured fluid intelligence by way of a perceptual reasoning index, which was the product of two subtests: a block design subtest and a matrix reasoning 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. Subjects' raw scores were converted to normalized scaled scores and subsequently combined into a perceptual reasoning index, which provided a measure of nonverbal reasoning and fluid intelligence.

Volumetric brain MRI

Volumetric analysis was performed on data from a 3D high-resolution T1-weighted scan using MPRAGE acquisition (0.9 mm isotropic voxel; TR: 1900 ms, TI: 900 ms, TE: 2.32 ms, with GRAPPA and an acceleration factor of 2). Cortical reconstruction was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications.[23–35] All cortical reconstructions were manually checked for accuracy, as recommended by the software developers. The volumetric analyses focused on gray matter volume in the FPC, given the role of this cortical region in fluid intelligence[11,12] and its sensitivity to n-3 PUFAs.[13,14] As provided by Freesurfer parcellation, the FPC consisted of the following regions of interest: superior frontal cortex, rostral middle frontal cortex, caudal middle frontal cortex, pars opercularis, pars triangularis, pars orbitalis, superior parietal cortex, supramarginal cortex, and precuneus.[36,37] The volumetric analyses took into consideration total gray matter volume of the FPC as well as gray matter volume of individual regions within the FPC.

Covariates

Covariates were included according to the previous association with cognitive decline.[38–43] The covariates included age (continuous), gender (nominal, man/woman), education (nominal, five fixed levels), and body mass index (continuous). Volumetric analyses of the total FPC additionally accounted for intracranial volume (continuous), and volumetric analyses of individual regions within the FPC additionally accounted for total FPC volume (continuous) in an effort to isolate the contribution of each individual region.

Statistical analysis

A formal mediation framework was applied to: (i) identify predictive nutritional biomarkers of fluid intelligence, as derived by NBP analysis, and (ii) distinguish the neural structures that mediate the beneficial effect of n-3 PUFA patterns on fluid intelligence. First, regression models characterized the three relationships within the mediation framework: (i) the relationship between NBPs and fluid intelligence, (ii) the relationship between gray matter volume within the FPC and fluid intelligence, and (iii) the relationship between NBPs and gray matter volume within the FPC. Second, taking into account results of the regression analyses, a mediation model assessed whether gray matter volume within the FPC

mediated the relationship between NBPs and fluid intelligence (Fig. 1). Statistics were performed as follows:

(1) In the first step, one linear regression model was used to characterize the relationship between NBPs and fluid intelligence (Fig. 3 path a). This analysis accounted for covariates listed in *Covariates*. The results of this regression model indicated independent variables for consideration in the mediation model.

(2) In the second step, linear regression models were applied to characterize the relationship between each gray matter volume within the FPC, including total FPC volume and volume of individual regions within the FPC, and fluid intelligence (Fig. 3 path c). This analysis accounted for covariates listed in *Covariates* and applied a false discovery rate (FDR) correction for multiple comparisons ($q < 0.05$, one-tailed).[44] The results of these regression models indicated mediatory variables for consideration in the mediation model.

(3) In the third step, linear regression models were used to characterize the relationship between NBPs and each gray matter volume within the FPC, including total FPC volume and volume of individual regions within the FPC (Fig. 3 path b). This analysis accounted for covariates listed in *Covariates* and applied an FDR correction for multiple comparisons ($q < 0.05$, one-tailed).[44] The results of these regression models further specified mediatory variables for consideration in the mediation model.

(4) In the fourth step, the PROCESS macro designed for SPSS was applied to implement the bootstrapping method to estimate mediation effects.[45] This analysis drew 1000 bootstrapped samples with replacement from the dataset to estimate a sampling distribution for indirect and direct mediation effects, controlling for covariates listed in *Covariates*. The indirect mediation effect refers to the pathway from NBPs to gray matter volume within the FPC to fluid intelligence (Fig. 3 paths b–c). The direct mediation effect refers to the direct pathway from NBPs to fluid intelligence, accounting for the effect of gray matter volume within the FPC (Fig. 3 path a′). As shown in Fig. 1, the primary requirement for mediation is a significant indirect mediation effect, or the effect of the independent variable (NBPs) through the mediator (gray matter volume within the FPC) on the dependent variable (fluid intelligence).[46] To further validate the proposed mediation model, an alternative mediation model, incorporating FPC as the independent variable, NBPs as the mediating variable, and fluid intelligence as the dependent variable, was also tested.

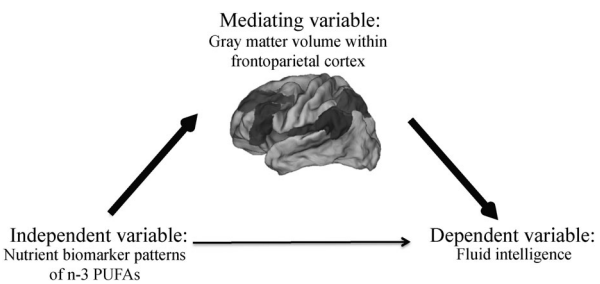

Figure 1 ***Proposed mediation model*. the primary requirement for mediation is a significant indirect mediation effect, defined as the effect of the independent variable (NBPs) through the mediator (gray matter volume within the FPC) on the dependent variable (fluid intelligence).**

Results are reported using (i) R^2 and P 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 $P \leq 0.05$. 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.[46]

Results

Participant characteristics

Participants ($n = 100$) had a mean age of 69 years and 62% of participants were females ($n = 62$). All other participant characteristics are reported in Table 1.

Nutrient biomarker patterns

Principal component analysis generated two 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 (0.728) and Bartlett's test of sphericity ($P < 0.001$). Two NBPs were selected for retention because (i) after the second NBP extraction with principal component analysis, 71.8% 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 second NBP (Fig. 2). Hereafter, the first NBP is described as product n-3 PUFAs (i.e. it is composed of downstream n-3 PUFAs, including EPA, DPA n-3, and DHA), and the second NBP is described as precursor n-3 PUFAs (i.e. it is composed of three n-3 PUFAs that serve as precursors to EPA and DHA).

Nutrient biomarker patterns, fluid intelligence, and gray matter volume with the FPC

The mediation analyses indicated that fluid intelligence was linked to precursor n-3 PUFAs as well as total gray matter volume within the FPC, and furthermore, that total gray matter volume of the left FPC fully mediated the relationship between precursor n-3

Table 1 Characteristics of sample

Demographics	$n = 100$
Age in years (M ± SD)	69 ± 3
Female (%)	62
Education (%)	
Some high school	1
High school degree	11
Some college	18
College degree	70
Income (%)	
<$15 000	1
$15 000–$25 000	4
$25 000–$50 000	15
$50 000–$75 000	23
$75 000–$100 000	26
>$100 000	31
Body mass index (M ± SD)	26 ± 4
Depression indicated (%)	6
Plasma phospholipid nutrients	(M ± SD, μmol/l)
ALA (18:3n-3)	5.2 ± 2.7
SDA (18:4n-3)	2.4 ± 0.9
ETE (20:3n-3)	1.2 ± 0.5
EPA (20:5n-3)	25.0 ± 17.8
DPA (22:5n-3)	23.0 ± 7.1
DHA (22:6n-3)	79.6 ± 33.4
Psychometrics	(M ± SD)
Fluid intelligence score	112 ± 14
Volumetric MRI (gray matter volume)	(M ± SD, mm^3)
Intracranial volume	1447671.9 ± 149653.5
FPC (R, L)	80184.6 ± 7766, 80627.4 ± 7765.7
Superior frontal cortex (R, L)	19403.7 ± 2220.8, 19995.9 ± 2111.2
Rostral middle frontal cortex (R, L)	14689.5 ± 2047.5, 14219.0 ± 1840.3
Caudal middle frontal cortex (R,L)	5455.2 ± 983.8, 5807.3 ± 992.2
Pars opercularis cortex (R, L)	3599.5 ± 549.6, 4275.3 ± 634.9
Pars triangularis cortex (R, L)	3774.7 ± 628.5, 3265.1 ± 480.4
Pars orbitalis cortex (R, L)	2430.2 ± 347.5, 2040.5 ± 270.5
Superior parietal cortex (R, L)	12389.2 ± 1538.2, 12243.7 ± 1320.2
Precuneus cortex (R, L)	9060.8 ± 1067.2, 8718.7 ± 1082.4
Supramarginal cortex (R, L)	9381.8 ± 1383.2, 10062.0 ± 1519.4

Mean (M), standard deviation (SD), right hemisphere (R), left hemisphere (L).

Table 2 NBP construction: pattern structure and variance explained[a]

Plasma phospholipid fatty acid	NBP[b]	
	1	2
ALA (18:3n-3)	0.190	0.742*
SDA (18:4n-3)	0.065	0.715*
ETE (20:3n-3)	−0.131	0.827*
EPA (20:5n-3)	0.960*	−0.053
DPA (22:5n-3)	0.805*	0.143
DHA (22:6n-3)	0.902*	−0.028
Percent variance explained by each NBP	52.781	18.989
Cumulative percent variance explained with each extraction	52.781	71.770

Nutrient biomarker pattern, NBP.
[a]Extraction method: principal component analysis; rotation method: oblimin.
[b]NBP interpretation based on strongest loading coefficients within each pattern.
*Nutrients with absolute loadings ≥0.5 that are considered as dominant nutrients contributing to the particular nutrient pattern.

PUFAs and fluid intelligence. Each relationship within the mediation is described below in a stepwise fashion:

(1) Better fluid intelligence was predicted by higher precursor n-3 PUFAs ($R^2_{model} = 0.133$, $P_{model} = 0.035$; $\beta = 3.236$, SE $\beta = 1.544$, $P_{variable} = 0.039$), but not higher product n-3 PUFAs (Table 3). Therefore, precursor n-3 PUFAs were considered as a candidate independent variable in the mediation model (Fig. 3 path a).

(2) Better fluid intelligence was predicted by larger volume of the left FPC ($R^2_{model} = 0.181$, $P_{model} = 0.004$; $\beta = 0.001$, SE $\beta < 0.001$, $P_{variable} = 0.009$) and smaller volume of the right supramarginal cortex ($R^2_{model} = 0.220$, $P_{model} = 0.001$; $\beta = -0.004$, SE $\beta = 0.001$, $P_{variable} = 0.006$), but no other region of the FPC (Table 4). Therefore, left FPC and right supramarginal cortex were considered as candidate mediators in the mediation model (Fig. 3 path c).

(3) Higher precursor n-3 PUFAs also predicted larger volume of the left FPC ($R^2_{model} = 0.641$, $P_{model} < 0.001$; $\beta = 1494.073$, SE $\beta = 557.356$, $P_{variable} = 0.009$), but no other region of the FPC (Table 5). Therefore, only left FPC was retained as a candidate mediator in the mediation model (Fig. 3 path b).

(4) The mediation model investigating the mediatory effect of the left FPC on the relationship between precursor n-3 PUFAs and fluid intelligence indicated a full mediation ($R^2_{model} = 0.30$, $P_{model} = 0.001$). The indirect pathway of mediation was significant (95% CI [0.178–2.741], Fig. 3 path b–c; $\beta = 0.007$, SE $\beta = 0.0003$, $P_{variable} = 0.007$, Fig. 3 path c). However, the direct pathway of mediation was not significant (95% CI [−1.573–4.023], $\beta = 1.225$, SE $\beta = 1.408$, $P_{variable} = 0.387$, Fig. 3 path a′). Therefore, the mediation indicated that gray matter volume of the left FPC fully mediated the relationship between precursor n-3 PUFAs and fluid intelligence (Fig. 3). Examination of an alternative mediation model, which incorporated FPC as the independent variable, NBPs as the mediating variable, and fluid intelligence as the dependent variable, yielded an insignificant indirect effect (95% CI [−0.0001–0.0003]) and significant direct effect (95% [0.0002–0.0013]). The alternative mediation model did not present a statistically sound mediation approach and therefore confirmed the validity of the primary proposed mediation model.

Discussion

This study revealed fluid intelligence is predicted by specific n-3 PUFA patterns and FPC structure, and that FPC structure mediates the relationship between n-3 PUFA status and fluid intelligence. This report identifies a novel nutritional biomarker for fluid

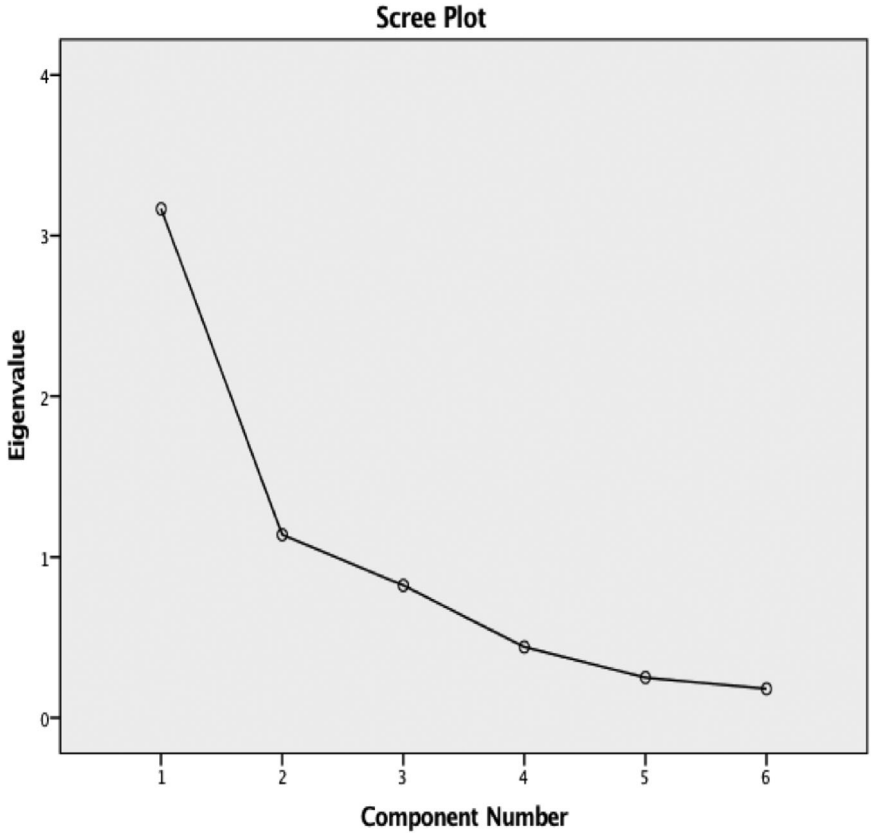

Figure 2 ***Scree plot*. inspection of the scree plot indicated that the inflection point occurred after the second component, or NBP, was extracted using a direct oblimin rotation.**

intelligence as well as a novel mediatory relationship between n-3 PUFAs, FPC structure, and fluid intelligence. The individual relationships reported within the mediation, including those between n-3 PUFAs and fluid intelligence (Fig. 3 path a), between FPC and fluid intelligence (Fig. 3 path c), and between n-3 PUFAs and FPC (Fig. 3 path b), are each supported by previous work reviewed in turn below.

First, precursor n-3 PUFAs positively associated with fluid intelligence. Red blood cell phospholipid total n-3 PUFAs have been previously linked to intelligence in older adults.[47] More specifically, serum concentration of EPA, DPA n-3, and DHA has been linked to better performance on tests of frontal function in older adults[8,48]; however, to our knowledge, no study has examined the effects of ALA or its immediate downstream products, including SDA and ETE, on intelligence or tests of frontal function in older adults. Importantly, ALA in serum,[49] red blood cell phospholipids,[50] and plasma[51] has been linked to risk for dementia. Decline in fluid intelligence is a key feature of the cognitive changes that precede dementia,[2] thus ALA and its immediate downstream products, including SDA and ETE, could serve as predictive biomarkers for fluid intelligence.

Table 3 Linear regression models: n-3 PUFA patterns associated with fluid intelligence

NBP		Fluid intelligence Model 1[a]
NBP1	β	−0.645
	SE	1.604
NBP2	β	3.236*
	SE	1.544
Model	R^2	0.133*

Nutrient biomarker pattern, NBP.
[a]Model: fluid intelligence = NBP1 + NBP2 + age + gender + education + body mass index.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Second, structural integrity of the FPC was linked to fluid intelligence. More specifically, gray matter volume of the left FPC positively predicted fluid intelligence. Evidence indicates that fluid intelligence relies on the structure and function of regions within the FPC.[9,10,12] The unilateral effect is supported by prior work, which suggests that regions within the left hemisphere may be selectively susceptible to degeneration.[52] Conversely, gray matter volume of the right supramarginal cortex negatively predicted fluid intelligence. Although the supramarginal cortex is considered part of the FPC,[36,37] neural activity in this region decreases during tests of intelligence.[53] In line with prior evidence, our results suggest that while the supramarginal cortex may contribute to the FPC as a whole, its individual contributions to intelligence are not congruent to that of the entire FPC.

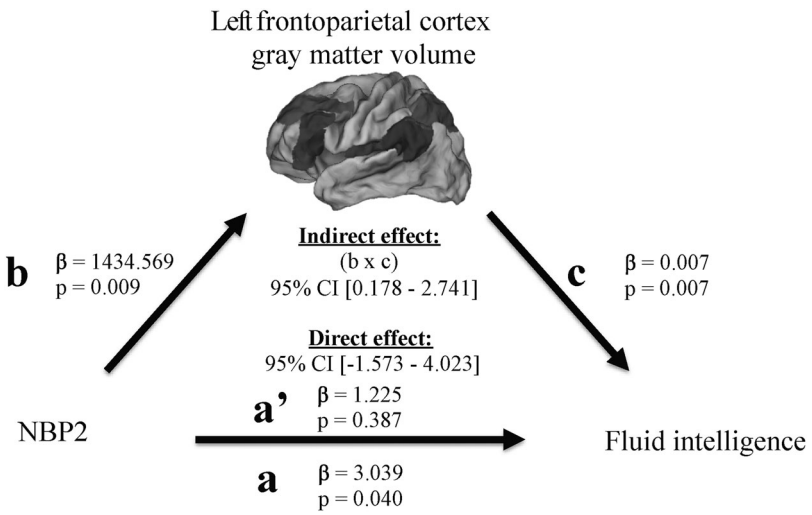

Figure 3 ***Mediation model statistics*. a mediation model was used to characterize the relationship between NBP2, left FPC gray matter volume, and fluid intelligence. NBP2 positively associated with fluid intelligence (path a). NBP2 positively associated with total gray matter volume of the left FPC (path b). The indirect pathway of mediation (i.e. the effect of NBP2 through total gray matter volume of the left FPC on fluid intelligence; paths b–c) was statistically significant. The direct pathway of mediation (i.e. the effect of NBP2 on fluid intelligence, accounting for total gray matter volume of the left FPC; path a′) was not significant. Therefore, total gray matter volume of left FPC fully mediated the relationship between NBP2 and fluid intelligence.**

Third, precursor n-3 PUFAs positively predicted structural integrity of the left FPC. Higher red blood cell levels of DHA,[8] combined EPA and DHA,[54] and ALA[55] have been linked to greater total brain volume and markers of reduced brain atrophy. In addition, supplementation of EPA and DHA increases gray matter volume in the frontal and parietal cortices of the left hemisphere in healthy, older adults.[14] However, to our knowledge, no study has examined the effects of ALA or its immediate downstream products, including SDA and ETE, on FPC gray matter structure.

Table 4 Linear regression models: gray matter regions associated with fluid intelligence

		Fluid intelligence		
Region	Hemisphere	β	β SE	Model R^2
FPC	Left[a]	0.001$^{**\#}$	<0.001$^{**\#}$	0.181**
	Right[a]	0.001	<0.001	0.153*
Superior frontal	Left[b]	−0.001	0.001	0.179**
	Right[c]	0.001	0.001	0.165**
Rostral middle frontal	Left[b]	<0.001	0.001	0.178**
	Right[c]	<0.001	0.001	0.153*
Caudal middle frontal	Left[b]	0.001	0.002	0.179**
	Right[c]	<0.001	0.002	0.153*
Pars opercularis	Left[b]	0.002	0.002	0.184**
	Right[c]	0.003	0.003	0.159*
Pars triangularis	Left[b]	0.003	0.003	0.187**
	Right[c]	0.001	0.003	0.154*
Pars orbitalis	Left[b]	−0.007	0.006	0.190**
	Right[c]	0.004	0.005	0.160*
Superior parietal	Left[b]	<0.001	0.002	0.178**
	Right[c]	0.001	0.001	0.154*
Precuneus	Left[b]	−0.001	0.002	0.180**
	Right[c]	0.001	0.002	0.156*
Supramarginal	Left[b]	<0.001	0.002	0.178**
	Right[c]	−0.004$^{**\#}$	0.001$^{**\#}$	0.220**

Frontoparietal cortex, FPC.
[a]Model: fluid intelligence = regional gray matter volume + age + gender + education + body mass index + intracranial volume.
[b]Model: gray matter volume = regional gray matter volume + age + gender + education + body mass index + left FPC volume.
[c]Model: gray matter volume = regional gray matter volume + age + gender + education + body mass index + right FPC volume.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, $^{\#}P < 0.05$, FDR-corrected.

Lastly, gray matter volume of the left FPC fully mediated the relationship between precursor n-3 PUFAs and fluid intelligence. Thus, precursor n-3 PUFAs may influence fluid intelligence by promoting structural integrity of the left FPC. Each of the three relationships within the mediation is supported by prior findings, described above, but the mediation analysis provides a novel link between particular n-3 PUFAs, a cognitive function that is particularly vulnerable to age-related decline, and an underlying neuroanatomical network. These findings contribute to accumulating evidence, suggesting that certain nutrients may slow or prevent aspects of age-related cognitive decline by influencing particular aspects of brain structure.[1,56–61]

The predictive power of one NBP, the precursor n-3 PUFA pattern, has noteworthy implications for the neuroprotective potential of n-3 PUFAs on fluid intelligence. The precursor n-3 PUFA pattern is reflective of either metabolic processing of n-3 PUFAs or dietary intake of n-3 PUFA-rich oils, nuts, and seeds.[62,63] Metabolic processing of n-3 PUFAs within the precursor n-3 PUFA pattern may be neuroprotective because ALA, SDA, and ETE are converted to EPA, and to a smaller extent, DHA. Although DHA is the most abundant long-chain n-3 PUFA in the

Table 5 Linear regression models: n-3 PUFA patterns associated with gray matter structure of the frontoparietal cortex

Region	Hemisphere	NBP1		NBP2		Model R^2
		β	β SE	β	β SE	
FPC	Left[a]	−389.183	580.267	1494.073$^{**\#}$	557.356$^{**\#}$	0.641***
	Right[a]	−508.141	560.816	1424.340*	538.816*	0.673***
Superior frontal	Left[b]	−44.492	129.989	−213.372	128.783	0.754***
	Right[c]	−238.769	131.753	34.029	130.181	0.772***
Rostral middle frontal	Left[b]	107.278	125.255	12.413	124.093	0.700***
	Right[c]	82.595	153.719	−15.483	151.885	0.634***
Caudal middle frontal	Left[b]	−165.806	95.989	53.767	95.098	0.393***
	Right[c]	9.079	96.967	1.954	95.810	0.370***
Pars opercularis	Left[b]	23.717	67.597	59.900	66.970	0.265***
	Right[c]	83.108	53.686	15.063	53.046	0.381***
Pars triangularis	Left[b]	90.942	47.264	9.672	46.826	0.372***
	Right[c]	79.649	64.295	−37.704	63.528	0.321***
Pars orbitalis	Left[b]	15.187	28.148	−21.612	27.887	0.298***
	Right[c]	46.995	35.625	−27.554	35.200	0.318***
Superior parietal	Left[b]	102.797	92.112	56.757	91.257	0.684***
	Right[c]	42.707	122.006	−10.367	120.550	0.592***
Precuneus	Left[b]	−172.987	73.955	−91.045	73.269	0.697***
	Right[c]	−118.534	80.577	−6.624	79.616	0.630***
Supramarginal	Left[b]	43.363	103.833	133.520	102.870	0.697***
	Right[c]	13.211	121.662	46.687	120.211	0.498***

Nutrient biomarker pattern, NBP; frontoparietal cortex, FPC.
[a]Model: gray matter volume = NBP1 + NBP2 + age + gender + education + body mass index + intracranial volume.
[b]Model: gray matter volume = NBP1 + NBP2 + age + gender + education + body mass index + left FPC volume.
[c]Model: gray matter volume = NBP1 + NBP2 + age + gender + education + body mass index + right FPC volume.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, $^{\#}P < 0.05$, FDR-corrected.

brain,[64] but both EPA and DHA have physiological effects that can improve brain health. These include reducing inflammation, reducing oxidative stress, reducing platelet aggregation, improving blood pressure, and improving arterial compliance.[65] Alternatively, dietary consumption of precursor n-3 PUFAs may support neuronal health through the unique neuroprotective benefits of ALA and its immediate downstream products. Previous work has shown that phospholipid ALA may prevent brain atrophy[55] by providing glucose to the brain through efficient ketogenesis,[66] increasing serotonin and dopaminergic neurotransmission in the frontal cortex,[67] and increasing plasma levels of brain-derived neurotrophic factor, thereby indirectly promoting neurogenesis and neuronal survival.[68] Importantly, few studies have investigated the neuroprotective potential of n-3 PUFAs within the precursor n-3 PUFA pattern, and even fewer have derived empirical patterns of plasma phospholipid n-3 PUFAs. The methodology employed in the current study allowed for an unprecedented comprehensive assessment of nutritional status of n-3 PUFAs, and provided support for novel nutritional biomarkers of fluid intelligence and underlying cortical structure. Future mechanistic studies are needed to investigate whether precursor n-3 PUFAs are neuroprotective by way of conversion to EPA and DHA or whether these precursors possess unique neuroprotective benefits, as well as the endogenous and exogenous factors that contribute to the neuroprotective effects. Future longitudinal studies are also warranted to investigate the time scale on which precursor n-3 PUFAs influence fluid intelligence and underlying cortical structure. While measurement of n-3 PUFAs in plasma phospholipids reveals that short-term intake of these nutrients influences cognition and brain health, measurement of n-3 PUFAs in adipose tissue will indicate the neuroprotective effects of long-term n-3 PUFA intake.[69]

The strengths of this study include: (i) the use of blood biomarkers to measure physiological status of n-3 PUFAs, (ii) the use of NBP analysis to empirically derive patterns of n-3 PUFAs, (iii) the use of structural MRI to measure cortical integrity with high spatial resolution, and (iv) the assessment of a particular cognitive function that is known to be sensitive to age-related decline, rather than a global measure of cognitive function that presents with little variability in healthy aging adults. The limitations of this study include: (i) relatively small sample size ($n = 100$), (ii) cross-sectional design, (iii) limited neuropsychological testing (i.e. only fluid intelligence), (iv) limited neuroimaging domains (i.e. only structural neuroimaging), (v) inability to explore mechanisms that support the relationship between precursor n-3 PUFAs and FPC structure, (vi) inability to explore contributions of diet and metabolic processes to n-3 PUFA patterns, and (vii) isolation of a specific dietary component. Thus, directions for future research include: (i) replication of results in a larger sample, (ii) implementation of a longitudinal study to examine how changes in

n-3 PUFAs relate to changes in fluid intelligence and integrity of the FPC, (iii) examination of other facets of cognitive function, (iv) investigation of other neuroimaging domains, such as white matter microstructure and functional activity, (v) examination of the mechanisms that support the relationship between precursor n-3 PUFAs and FPC structure, (vi) investigation of the relative contributions of diet and metabolic processes to n-3 PUFA patterns, (vii) examination of potential synergistic interactions between n-3 PUFAs and other known neuroprotective dietary components, such as antioxidant vitamins (i.e. carotenoids, vitamin E), that may reduce oxidation of ingested fatty acids and therefore optimize neuroprotective effects.

Research at the frontline of *Nutritional Cognitive Neuroscience* suggests that certain nutrients may slow or prevent aspects of age-related cognitive decline by influencing particular age-related changes in brain structure.[1,56–61] The present finding contributes to this research program, and provides a novel link between nutritional and neuroanatomical biomarkers for fluid intelligence in healthy, older adults. Ultimately, this line of work can inform clinical studies of personalized and comprehensive approaches to nutritional intervention for healthy brain aging.

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