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Omega-3 fatty acids and neurocognitive ability in young people at ultra-high risk for psychosis

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ABSTRACT

*Background:*Neurocognitive impairments are core early features of psychosis and are observed in those at ultra-high risk (UHR) for psychosis. The aim of the present study was to explore whether neurocognition is associated withpolyunsaturated fatty acids (PUFAs), as has been observed in other clinical populations.
Method: Erythrocyte levels of total omega-3-andomega-6 PUFAsthe omega-3/omega-6 ratio, were measured in 265 UHR individuals. Six domains of neurocognitionas well a composite score, were assessed using the Brief Assessment of Cognition in Schizophrenia. Pearson's correlations were used to assess the relationship between PUFAs and neurocognition. All analyses were controlled for tobacco smoking.
Results: Verbal Fluency correlated positively with eicosapentaenoic acid (p=.024) and alpha-linolenic acid (p=.01), and negatively with docosahexanoic acid (p=.007) and Working Memory positively correlated with omega-3/omega-6 ratio (p=.007).
Conclusions: The current results provide support for a relationship between Verbal Fluency and omega-3 PUFAs in UHR. Further investigation is required to elucidate whether these biomarkers are useful as risk markers or in understanding the biological underpinning of neurocognitive impairment in this population.

Key words: ultra-high risk, neurocognition, poly-unsaturated fatty acids, omega-3

Word count: Abstract = 172; Body = 2,990

1. Introduction

Neurocognitive impairments are prominent early in the course of psychotic disorders (Kahn & Keefe, 2013). Research consistently finds that schizophrenia is associated with impairments in memory, attention, processing speed, language, visuospatial ability, and executive function (Bortolato, Miskowiak, Köhler, Vieta, & Carvalho, 2015; Dickinson, Ragland, Gold, & Gur, 2008). Poor performance in a number of these domains is evident relative to controls at the first-episode of psychosis (FEP; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009) and in populations at ultra-high risk for psychosis (UHR), althoughto a lesser extent(Hauser et al., 2017; Simon et al., 2012). UHR individuals who transition to psychosis are characterised by mild to moderately poorer verbal fluency(Fusar-Poli et al., 2012), working memory(De Herdt et al., 2013; Hauser et al., 2017), processing speed(Hauser et al., 2017)and verbal memory (Fusar-Poli et al., 2012; Hauser et al., 2017) at baselinethan those who do not transition.Even amongst those who do not transition to psychosis, neurocognitive performance is predictive of poorer functional outcomes(Lin et al., 2011; Sawada et al., 2017). While neurocognitive impairments are important inclusions to risk profiles for the development of psychosis (Bolt et al., 2018; Cannon et al., 2016; Schmidt et al., 2018), there is little understanding of its underlying biological mechanisms, which impedes research into the development of tailored preventative interventions. Recent research in this area has begun to investigate a number of biological correlates of neurocognitive impairment, in particular polyunsaturated fatty acids (PUFAs;Kim et al., 2014; Satogami, Takahashi, Yamada, Ukai, & Shinosaki, 2017).

Omega-3 (n3) PUFAs, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and their precursor alpha-linolenic acid (ALA), are essential fatty acidsobtained through diet (Bazinet & Layé, 2014)andhave neuroprotective effects (Simopoulos, 2011). Modern western diets tend to be higher in omega-6 (n6) PUFAs and lower n3-PUFAs(Simopoulos, 2011)and this has been linked to a number of health risks (Simopoulos, 2011), including mental health risks(Berger et al., 2017). Inflammatory

processes have been posited as a possible mediator of the relationship between neurocognition and PUFAs, as n3-PUFAs have anti-inflammatory properties whilemost n6-PUFAs have pro-inflammatory properties (Calder, 2015).In addition, PUFAsare a component the myelin sheaths surrounding white matter tracts, as such white matter integrity has also been proposed as a potential mechanism for the relationship between PUFAs and neurocognition (Gu et al., 2016), as well as PUFAs and psychosis(Vijayakumar et al. 2016).

In UHR individuals, levels of EPA and ALA are lower compared to healthy controls(Rice et al., 2015) and negative symptoms have been found to be inversely associated with total n3-PUFA levels and positively associated with n6/n3-PUFA ratios(Kim et al., 2016). Furthermore, supplementation with EPA and DHA over a period of 3 months has been found to reduce symptom severity and the likelihood of transition to psychosis (Amminger et al., 2010; 2015), although these results were not replicated in a larger trial (McGorry et al., 2017). While these studies did not investigate the relationship between PUFAs and neurocognition,higher levels of serum EPA and DHA have been associated with higher scores on a composite measure of neurocognitive functioning in patients with schizophrenia(Satogami et al., 2017). In ageing populations, diets high in n3-PUFAs or high erythrocyte levels of n3-PUFAs have been found to have beneficial effects on neurocognition (Masana et al., 2017), while higher n6/3-PUFA ratios have been associated with poorer neurocognition(Conquer et al., 2000; Roberts et al., 2010).In addition to overall measures of neurocognition, a range of neurocognitive domains have been investigated in aging populations (Masana et al., 2017), however domain-specific findings have been inconsistent and this had not been investigated in those experiencing or at risk of psychosis.

At present, there is evidence to suggest that neurocognitive functioning is linked to PUFAs, but this has not been investigated in UHR populations. Furthermore, it is unclear whether these associations are specific to certain domains of neurocognition. Hence, the aims of the present study are to investigate if, in UHR,an association exists

between specific domains of neurocognition andPUFA-markers. The association with the following neurocognitive domains will be explored: verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, executive functioning,and global cognition (Keefe et al., 2004). Based on previous research, it was predicted that higher levels of EPA, DHA, ALA, n3-PUFA totaland n3/n6-PUFA ratios will be associated with superior neurocognitive functioning, and highertotal n6-PUFAlevels and n6/n3-PUFA ratios will be associated with poorer neurocognitive functioning.

2. Methods

This study conducted secondary analysis of baseline data from the North American, Europe, Australia Prodrome (NEURAPRO-E) Study, a multi-site randomized controlled trial of n3-PUFA supplementation for the prevention of psychosis in UHR(McGorry et al., 2016; Australian and New Zealand Clinical Trial Registry number 12608000475347). Ethics approval was obtained from the relevant ethical review bodies for each site.

2.1. Setting and Participants

Participants were recruited from clinics in Melbourne, Sydney, Vienna, Singapore, Basel, Hong Kong, Copenhagen, Zurich, Jenna and Amsterdam. Help-seeking individuals aged 13-40 years, who met the UHR criteria definedby Yung et al (2005) were eligible to participate in the study. The Comprehensive Assessment of At Risk Mental State (CAARMS; Yung et al., 2005)was used to determine whether participants met at least one of three UHR categories: vulnerability based on trait and state risk factors, attenuated positive psychotic symptoms, and brief limited intermittent psychotic symptoms. In addition to the exclusion criteria relevant to the larger study(see Markulev et al., 2015), participants were excluded from the current study if they did not complete baseline neurocognitive assessments.

2.2. Measures

2.2.1. Participant Characteristics. Demographic information collected at baseline included age, gender, race, highest level of education, type of work, subjective health (measured on a six point scale from excellent to very poor) and body mass index (BMI). Estimated IQ was measured using the Wechsler Adult Intelligence Scale-3rd Edition-Short Form (WAIS-III-SF; Weschler, 1987). Smoking status was determined using the World Health Organisation Alcohol, Smoking and Substance Involvement Screening Test (WHO ASSIST Working Group, 2002). Levels of positive, negative and depressive symptoms were measured using the Brief Psychiatric Rating Scale-Psychotic subscale (BPRS-P; Overall & Gorham, 1962), Scale for the Assessment of Negative Symptoms (SANS) and Montgomery Asberg Depression Rating Scale (MADRS), respectively. The Social and Occupational Functioning Scale was used to measure general psychosocial functioning (SOFAS; Smith et al., 2011).

2.2.2. Neurocognitive Assessment. The Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) was used to measure neurocognition. In addition to a composite score, the neurocognitive domains measured by the BACS are Verbal Memory, Working Memory, Motor Speed, Verbal Fluency, Attention and Processing Speed, and Executive Functioning. All scores were converted to z-sores standardized for both age and gender (Keefe et al., 2008).

2.2.3. Fatty acid analysis. Fasting blood samples of approximately 20mL were collected from participants. Samples underwent preliminary processing, including extraction of erythrocytes and stored at -80 degrees Celsius until analysed(Smesny et al., 2014).Erythrocyte markers are a relatively stable longer-term marker of fatty acid profiles(Brenna et al. 2018).The phospholipid fraction used was phosphatidylethanolamine (PE), located on the inner side of the cell membrane. This fraction is most relevant to the presumed pathology underlying phospholipid

alterations in psychotic illness including increased peroxidation (i.e., oxidative stress; Kim et al., 2016). Gas chromatography was used to determine proportions of fatty acid measures of interest (mol% of total fatty acid levels) in the PE fraction. These were EPA, DHA, ALA, n3-PUFA (total), n6-PUFA (total) and the n6/3-PUFA ratio. Samples that could not be tracked to a unique client ID or time point were excluded from the analysis. All data were screened for implausible values that may indicate problems with the sample, such as degradation.

2.3. Statistical Analysis

All analyses were completed using IBM SPSS Statistics 23. Values for neurocognitive variablesthat were four standard deviations above/below the mean were checked against the original research file and corrected if needed. Independent-samples t-tests for continuous data and chi-squared tests for categorical data were used to compare those who did and did not complete neurocognitive assessments on key demographic variables to investigate any systematic differences between this sample and the original. This methodology was also used to examine any systematic differences in those excluded from analysis due to missing biological data.

Pearson's product-moment correlations were calculated between each of the six neurocognitive domains, and the composite score, and each of the six PUFA biomarkers. Significant relationships identified in this analysis were then included in a partial correlation analysis controlling for common variance between these variables due to tobacco smoking (Yes/No); these factors have been associated with both neurocognition and PUFA markers (Murff et al., 2016; Vermeulen et al., 2018). Significant relationships involving n3/n6-PUFA ratio were repeated controlling for MADRS scores, given the relationship between this variable and depression (Berger et al., 2017). Visual inspection of scatterplots was used to determine whether a linear relationship existed between these variables. The Pearson correlation analysis had 80%

power to detect a small effect size (Cohen, 1992). For all analyses alpha was set at the 0.05 level. An a priori decision was made to not make a bonferroni adjustment to avoid increasing the risk of a Type II error (Armstrong, 2014; Perneger, 1998).

3. Results

3.1. Participant characteristics, neurocognition and biomarker levels

For the NEURAPRO-E study, 977 individuals were screened, 673 were excluded and 304 entered the study(McGorry et al., 2016). A further 17 were excluded from the present study as they did not complete the baseline neurocognitive assessment. No statistically significant differences were found on any demographic or symptomatic variables between participants who did or did not have neurocognitive data at baseline. Table 1 shows the key characteristics of the total sample (*N*=287).Table 2 shows the neurocognitive and PUFA marker characteristics of the sample.

3.2. Association between PUFAs and Neurocognition

Pearson correlations were calculated between neurocognitive scores and PUFA variables (Table 3). Verbal Fluency was positively correlated with EPA and ALA but negatively with DHA. Working Memory was positively correlated with n6/3-PUFA ratio, but negatively correlated with total n3-PUFA level. The BACS composite score was negatively correlated with DHA. Analyses involving Executive Functioning and EPA were repeated using Spearman's Rho correlations due to evidence of skew for these variables, however this did not alter the findings. All statistically significant relationships were examined with adjustment for tobacco smoking. The partial correlation between Working Memory and n3-PUFA was no longer significant ($r(260)=-.119$, $p=.055$). The partial correlations between Verbal Fluency, EPA ($r(260)=.139$, $p=.024$) and ALA ($r(258)=.160$, $p=.01$), and Working Memory and n6/3-PUFA ratio

(r(260)=.145, p=.019) remained small and positive, while the partial correlation between Verbal Fluency and DHA (r(260)=-.166, p=.007) remained small and negative. The Composite Score, which is partially derived from the Verbal Fluency score, was negatively correlated with DHA, therefore a partial correlation analysis was run between the Composite Score and DHA controlling for Verbal Fluency. The relationship between the Composite Score and DHA was no longer significant, r(261)=.01, p=.878.

An ancillary analysis was conducted examining the correlation between Verbal Fluency and the ratio of EPA to DHAdue to the unexpected direction of the relationship between Verbal Fluency and DHA and its incongruence with the direction of relationship with EPA as EPA is converted to DHA in the cell membrane. A significant small, positive correlation (r(265)=.213, p<.001) was found,which remained significant after controlling for smoking (r(260)=.197, p=.001). In addition, the partial correlation between Working Memory and n6/n3-PUFA remained significant when controlling for MADRS scores and was small and positive, r(259)=.144, p=.02.

4. Discussion

The present study sought to examineifneurocognitionwas associated with PUFA - biomarkers in the UHR population. The study found that Verbal Fluency was significantly correlated with the three individual n3-PUFA markers examined; positively with EPA and ALA, but negatively with DHA. Working Memory was found to be positively associated with n6/n3 ratio. All significant correlation were small. When controlling for smoking status, Verbal Memory, Motor Speed, Attention and Processing Speed, Executive Function and the Composite score were not significantly associated with the PUFA markers investigated.To the authors' knowledge, this is the first study to identify a relationship between performance in specific neurocognitive domains and PUFA markers in an UHRsample. The study was exploratory in nature and caution must be taken interpreting the findings, particularly given the small effect sizes.Nevertheless, the consistency of the significant relationships for the n3-PUFAs within the domain of Verbal Fluency suggests findings for this domain may be replicable.

Verbal Fluency is one of multiple domains found to be impaired in UHR populations compared to healthy controls(Hauser et al., 2017) and poorer performance in this domain was also observed in those who transition to psychosis compared to those who do not (Becker et al., 2010; Hauser et al., 2017). While there has been limited research specifically investigating Verbal Fluency and PUFAs in populations with an at risk mental state of psychosis, the present research is partially consistent with research byD'Ascoli et al., (2016)who found Verbal Fluency was positively associated with serum EPA and DHA in a healthy aging population (D'Ascoli et al., 2016).While the positive association between Verbal Fluency and EPA is consistent with this research, and the neurocognition literature more broadly (Satogami et al., 2017), the negative association with DHA is inconsistent.Similarly, the positive relationship between Working Memory and n6/n3-PUFA ratio was also unexpected. While these findings are surprising, there has been limited research in the UHR population specifically and it is possible that these relationships may be unique to this population. For example, there is evidence in UHR

populations of a relationship between PUFA markers and the activity of enzymes implicated in phospholipid metabolism being inversely associated in those who transition to psychosis compared to those who do not(Smesny et al., 2014).The unexpected finding for Verbal Fluency and DHA may have beeninfluenced bymethodological differences, as previous studies have often used absolute serum levels(Satogami et al., 2017), whereas the present study used percentage of cell membrane, which is a relative measure.Therefore, the present methodology may be more sensitive to the relationship between the PUFAs composing the cell membrane.

Given the unexpected direction of findings for DHA,and that EPA is converted to DHA in the cell membrane, a supplementary analysis was conducted to examine the relationship between the EPA and DHA ratio. This analysis found that a higher ratio of EPA compared to DHA was positively associated with Verbal Fluency. This suggests that the relative levels of EPA and DHA are important to consider when investigating neurocognition in this population, as it is possible that EPA hasa preferential role in Verbal Fluency compared to DHA. This would be consistent with a recent meta-review of nutritional supplements for mental disorders, which found high-EPA formulas were the most effective form of n3-PUFA supplementation for improving a range of symptoms, including cognitive dysfunction (Firth et al., 2019). However, these findings were primarily found in populations with depressive disorders and Attention-Deficit/Hyperactivity Disorder.It is also possible that EPA and DHA have distinct mechanisms and may independently impact brain functioning and / or neuroplasticity (Calder, 2015). While it is possible that EPA has a direct relationship with Verbal Fluency, it is also possible that an independent factor may impact activity in the beta-oxidation pathway between EPA and DHA, making the ratio incidentally associated

Previous research seeking to understand the biological underpinnings of deficits in this domain, found that poorer Verbal Fluency was associated with elevated blood-based inflammatory biomarkers and reduced Broca's area volume in those with schizophrenia (Fillman et al., 2016). Verbal Fluency performance has also been

associated with volume and activity in Broca's area in UHR (Iwashiro et al., 2016; Meijer et al., 2011). Fillman et al., (2016) suggested that inflammation may play a role in neurotoxicity that leads to reduced brain volumes and associated deficits in functioning, however the causal mechanism has not been investigated.Given the anti-inflammatory properties of n-3PUFAs, future research should consider investigating whether the relationship between Verbal Fluency and n-3PUFAs is mediated by inflammatory mechanisms.White matter integrity could also be considered as an avenue for further research forunderstanding the potential relationship between PUFAs and neurocognition in psychosis (Gu et al., 2016; Vijayakumar et al. 2016).

We need to acknowledge several limitations of the current study. First, it is exploratory in nature and we did not use bonferonni correction. Second, it should be noted that peripheral biomarkers were measured in the current study and while these peripheral measures correspond with central measure (Harris et al., 2012), they are a proxy in terms of understanding the neurobiology of neurocognitive deficits(Simopoulos, 2006). Third, this study did not include a healthy control group, as such it cannot be determined whether this potential relationship between PUFAs and neurocognition is unique to the UHR population. While a strength of this study was the large simple size, facilitated by the multi-site nature of this study, the number of study sitesmay have contributed to heterogeneity of the sample and possible site effects. Strengths of this study included controlling for smoking status and the use of erythrocyte membrane levels of PUFAs (a stable measure less likely to be influenced by recently consumed PUFAs (Brenna et al., 2018; Katan et al., 1997)).

Despite reduced neurocognitive functioning being predictive of poorer prognosis in the UHR population, there is limited understanding of the underlying pathophysiology or how to intervene to improve outcomes. This research suggests that PUFA biomarkers may be useful for identifying clinical profiles characterised by poorer neurocognitive functioning, particularly in Verbal Fluency. This finding may guide further research investigating the biological mechanisms of neurocognitive functioning

in UHR with the possibility of informing tailored pro-cognitive interventions and aiding in a preventative care approach to psychosis.Future research may consider investigating whether supplementation with n3-PUFAs is associated with improvements in neurocognitive functioning in this population, particularly for those with low levels of n3-PUFAs.This study was exploratory in nature and future research is needed to extendthese findings.

Data Availability statement

Data available on request from the authors

Table 1.

Demographic and Symptomatic Characteristics of the Total Sample (n=287)

	M	SD
Demographics		
Age (years)	19.12	4.56
Gender *% female*	55.1	
Race		
%Caucasian	82.2	
%Black or African American	1.7	
%Asian	12.5	
%Other	3.1	
Study site		
%Melbourne	35.2	
%Vienna	23.3	
%Jena	12.2	
%Copenhagen	5.2	
%Singapore	5.2	
%Amsterdam	4.5	
%Zurich	4.5	
%Sydney	3.8	
%Hong Kong	3.5	
%Basel	2.4	
IQ estimate	102.65	14.66
Education or training (years)	10.31	3.25
Smoking status *%smokers*	55.4	
BMI *M(SD)*	23.97	5.27
Subjective health	3.79	1.00
Symptomatology		

Positive symptoms (BPRS-P)	8.25	2.64
Negative symptoms (SANS)	18.35	13.08
Depressive symptoms (MADRS)	19.46	9.02
Functioning (SOFAS)	53.46	11.96

Note. *M* = mean, *SD* = standard deviation, BMI = Body Mass Index, BPRS-P = Brief Psychotic Rating Scale Psychotic, SANS=Scale for the Assessment of Psychotic Symptoms, MADRS = Montgomery Asberg Depression Rating Scale, SOFAS = Social and Occupational Functioning Scale. The 22 participants who did not have PUFA data were compared to those who did on neurocognitive and demographic measures. Participants without PUFA data were significantly older, $t(285)=2.57$, $p=011$, M_2-$M_1=2.58$, and had lower IQ, $t(277)=2.37$, $p=.025$, M_2-$M_1=-5.05$.

Table 2.

Means and Standard Deviations of the Total Sample on Baseline Neurocognitive Z-Scores and Biomarker levels.

	N	M	SD
Neurocognition	287		
Verbal Memory		-0.24	1.62
Working Memory		-0.41	1.11
Motor Speed		-0.44	1.10
Verbal Fluency		-0.47	1.21
Attention and Processing Speed		-0.28	1.24
Executive Function		0.16	1.21
Composite Score		-0.45	1.39
PUFAs	265		
Omega-3 Total *(%mol)*		12.03	2.03
EPA *(%mol)*		0.97	0.33
DHA *(%mol)*		6.46	1.63
ALA *(%mol)*		0.17	.06
Omega-6 Total *(%mol)*		35.72	2.58
Omega-6:Omega-3 ratio		3.07	.60

Note. M = mean, SD = standard deviation, EPA = eicosapentaenoic acid, DHA = docosahexaenoic Acid, ALA =alpha-linolenic acid.

Table 3.

Pearson's Correlations between PUFA Markers and Neurocognition Scores

	VM	WM	MS	VF	A-PS	EF	C
n3-PUFA	-0.08	**-.13***	0.01	-0.05	-0.12	-0.06	-0.11
EPA	-0.04	-0.11	0.02	**.13***	-0.04	-0.03	-0.02
DHA	-0.09	-0.05	0.02	**-.20****	-0.09	-0.08	**-.13***
ALA	0.06	0.05	-0.10	**.19****	-0.05	-0.01	0.04
n6-PUFA	0.12	0.10	0.12	-0.09	0.10	-0.04	0.07
n6/3-PUFA	0.09	**.15***	0.005	0.003	0.12	0.07	0.11

Note. VM =Verbal Memory, WM = Working Memory, MS = Motor Speed, VF = Verbal Fluency, A-PS = Attention and Processing Speed, EF = Executive Functioning, C = Composite Score, n3= Omega-3 Total, EPA = eicosapentaenoic acid, DHA = docosahexaenoic Acid, ALA =alpha-linolenic acid, n6= Omega-6 Total, n6:n3 = Omega-6:Omega-3 Ratio. *p<.05. **p<.01.

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