MODERATING EFFECT OF PLIN4 GENETIC VARIANT ON IMPULSIVITY TRAITS IN 5-YEAR-OLD-CHILDREN BORN SMALL FOR GESTATIONAL AGE

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Abstract

Poor fetal growth is associated with long-term behavioral, metabolic and psychiatric alterations, including impulsivity, insulin resistance, and mood disorders. However, the consumption of omega-3 polyunsaturated fatty acid (n-3 PUFA) seems to be protective for this population, improving inhibitory control and behavioral re- activity. We investigated whether the presence of the A allele of rs8887 SNP (PLIN4 gene), known to be associated with increased sensitivity to the consumption of n-3 PUFAs, interacts with fetal growth influencing inhibitory control. 152 five-year-old children were genotyped and performed the Stop Signal Task (SSRT). There was a significant interaction between birth weight and the presence of the A allele on SSRT performance, in which lower birth weight associated with poorer inhibitory control only in non-carriers. These results suggest that a higher responsiveness to n-3 PUFAS protects small for gestational age children from developing poor response inhibition, highlighting that optimizing n-3 PUFA intake may benefit this population.

1 Introduction

Nutrition has great influence on health both in childhood and adulthood. The current western diet, related to epidemic childhood obesity rates[1], has been implicated in programing cognitive[2] and metabolic alterations[3] throughout the lifespan. Recent evidence suggests that the brain may be particularly vulnerable to the effects of obesogenic diets during early life[2], reinforcing the importance of the quality of perinatal environment for preventing metabolic disease [4-6] and neuropsychopathology [7-13]. High dietary intake of omega 6 fatty acids (n-6 FAs) as occurs today in the western diet promotes the occurrence of many inflammatory and autoimmune diseases [14], whereas increased levels of omega 3 polyunsaturated fatty acids (n-3 PUFAs), exert suppressive effects [15, 16]. This balanced ratio of n-6 to n-3 is critical to human development during pregnancy and lactation, in the prevention of chronic diseases and in their management [17, 18]. Furthermore, '*in vitro*' and experimental research have shown that n-3 PUFAs influence regulation of gene expression in a number of pathways [19], supporting the relevance of these components and their genetic interactions. Recent evidence suggests that dietary FAs, influenced by genetic variation in FA metabolism, contribute to poor central nervous system functioning in children, with long-lasting outcomes [20]. Investigations on mental health and disease highlighted the importance of omics [21] (lipidomic, metabolomic, and genomic) for identification of risk biomarkers in subjects with vulnerable phenotypes, revealing biochemical abnormalities, such as the association with FA levels and psychological outcomes [22] [23, 24] [25].

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Evidence suggests that exposure to an insult during early development modifies tissue differentiation through adaptive responses [26, 27]. Neurobiological systems are especially susceptible to both organizing and disorganizing influences, sometimes resulting in neuroadaptation impairments [28], particularly in sensitive pathways controlling the executive function (EF) [29]. EF is the group of self-regulatory processes composed by cognitive flexibility, working memory, and inhibitory control [30]. Inhibition underpins self-control and delayed gratification, and in early childhood is positively associated with later outcomes in academic achievement, health, risk-taking, happiness and socioeconomic status [31-33]. Impulsivity is comprised by a complexity of constructs and is commonly linked to a variety of psychiatric disorders [34-37] and with the development of obesity [38, 39]. Inefficient inhibitory control and heightened impulsivity are risk phenotypes associated with unhealthy eating in children [40]. Interestingly, a recent review demonstrated that deficits in inhibitory control/impulsivity are associated with a more obesogenic eating in young children compared with those who have disorders only in attention control/shifting and working memory dimensions [41]. Longitudinal studies found that general alterations in EF play an important role in the weight development of children [42], reinforcing the well-documented association between inattentive and impulsive behaviors with unhealthy eating [43-46] and with attention-deficit hyperactivity disorder (ADHD) and obesity [47]. Birth weight adjusted for gestational age is a predictor for ADHD, internalizing and externalizing problems [48, 49], and associated endophenotypes, including altered feeding behavior, overweight and obesity [50]. Small-for gestational age (SGA) individuals are more impulsive towards food rewards [50, 51], a phenotype associated with non-adaptive feeding behavior, characterized by enhanced food fussiness in childhood and external eating in adolescence [52, 53], which were linked to negative outcomes later in life. Recent studies by our research group have demonstrated that n-3 PUFAs exert a protective effect in small-for gestational age individuals by limiting impulsive eating [52, 53]. Although not the scope of this work, it is necessary to highlight that the family is an important social context where children learn and adopt eating behaviors, in which parents play the role of health promoters, role models, and educators in the lives of children, influencing their food cognitions and choices. This effect was well documented in a systematic review and meta-analysis, demonstrating that a number of parental behaviors are strong correlates of child food consumption

behavior[54].

EFs depend on efficient processing in frontal and pre-frontal cortical regions and their sub-cortical connections. It is known that adequate intake of long chain PUFA (LC PUFA, fatty acids that contain > 12 carbon atoms) is important for proper neural development during prenatal and postnatal periods up to 2 years of age [55-57]. Linoleic acid (LA, n−6) and α-linolenic acid (ALA, n−3) are essential fatty acids (EFAs), as humans cannot synthesize them. In the human body, EFAs give rise to arachidonic acid (ARA, n−6), eicosapentaenoic acid (EPA, n−3), and docosahexaenoic acid (DHA, n−3) that play key roles in regulating body homeostasis. The n-3 PUFAs are involved in neural development and functioning [58-60], being essential in the regulation of neurochemical and behavioral aspects related to stress responses, mood [61], aggressiveness and impulsivity reactions [62, 63] , and modulating neurotransmitter systems such as the dopaminergic mesocorticolimbic pathway [64, 65]. DHA is the dominant n-3 PUFA in the brain [66] and accumulates, in areas associated with learning and memory, such as the cerebral cortex and hippocampus [67, 68]. DHA is incorporated into glycerophospholipids of the neuronal membrane where it regulates many neuronal and glial cell processes, including neurogenesis, neuroplasticity, neurite outgrowth, synaptogenesis and membrane fluidity, influencing signal transduction and neurotransmission [69-73]. DHA also improves vascular tone resulting in increased cerebral blood flow [74], and regulates the movement of glucose in endothelial cells [73]. Moreover, DHA is a natural ligand for various nuclear receptors that regulate gene expression and are precursors of neuroprotectins and resolvins that can buffer neuroinflammation and oxidative stress, increasing neuronal survival [69, 70, 75].

The A allele of human *PLIN4* single nucleotide polymorphism (SNP) rs8887 is associated with enhanced sensitivity to dietary n-3 PUFAs, showing protective effects of on metabolic outcomes [76]. In humans, the perilipin gene (*PLIN*) is located in chromosomal 15q26 [77], a region previously linked to obesity, hypertriglyceridemia, and diabetes [78, 79]. The PLIN4 protein, previously referred to S3–12, belongs to the PAT family [80] comprised of PLIN1/perilipin (PLIN), PLIN2/ADRP (adipose differentiation related protein), PLIN3/ TIP47 (tail interacting protein 47), and PLIN5/LSDP5 (Lipid Storage Droplet Protein 5) [80]. In humans, the expression of

PLIN4 protein is limited to white adipose tissue, heart and skeletal muscle, and its role is not well-characterized [81], but it appears to participate in triglyceride synthesis, acting as a co-activator [82] of the nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ), an essential transcriptional regulator of adipogenesis [83]. In the basal state, PLIN4 is located throughout the adipocyte cytoplasm, but when stimulated by insulin and oleic acid, lipid droplets coated with PLIN4 form and relocate to the periphery of the adipocyte [84]. Taken together, this evidence [19, 76] have demonstrated anti-obesity effects of n-3 PUFAs which are thought to mediate their effects by modulating the activity of various transcription factors important to lipid metabolism.

Therefore, it may be assumed that neurocognitive functions could be nutritionally programed in early in life by a combination of both dietary and genetic compounds, resulting in increased risk for maladaptive behaviors. Here we to investigate with an integrative model, the interplay between external and internal variables, such as associations with the early environment, a genetic variant and their phenotype correlates. Our hypothesis is that subjects born with reduced fetal growth and carrying the A allele of the SNP rs8887 have enhanced sensitivity to dietary n-3 PUFAs levels, presenting a protective effect on impulsivity traits.

2 Material and Methods

The study sample included 600 children recruited in Montreal (Quebec-CA) or Hamilton (Ontario-CA), as part of a prospective cohort established in 2003, the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) Project [85]. MAVAN is a multidisciplinary and collaborative study designed to examine the consequences of fetal adversity as a function of the quality of the postnatal environment, focusing on mother-child dyad interactions. The study recruited pregnant women in the second trimester of pregnancy, older than 18 years, from the Montreal and Hamilton areas (Canada), in obstetric clinics and hospitals. Exclusion criteria were serious obstetric complications during pregnancy or birth, extreme low birth weight, prematurity (gestational age <37 weeks), and congenital diseases. The pregnant women were interviewed between 24 and 36 weeks of gestational age; the children were evaluated at 3, 6, 12 and 18 months postpartum and annually from 24 months to 6 years of age. Several behavioral questionnaires and cognitive assessments were performed during study visits, as well as collection of material for laboratory biochemical, genetic and epigenetic analysis. At the

time of this analysis, 152 MAVAN participants included had completed the Cambridge Automated Neuropsychological Test Battery (CANTAB) at 60 months of age and had genotype data available for this SNP.

2.1. Ethical considerations

The study was approved by the hospitals and universities involved: ethics committees of McGill University, Université de Montréal, Royal Victoria Hospital, Jewish General Hospital, Hospital de l'Université de Montréal, Hôpital Maisonneuve-Rosemount, St Joseph's Hospital and McMaster University. MAVAN Project was approved by the Research Ethical Board of Douglas Mental Health Research Institute (number 03/ 45), and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from the participants.

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Table 1 - Descriptive characteristics according to participants' genotype.

Sample characteristics	**rs8887 A allele carriers (n=103)**	**Non-carriers (n=49)**	**P**
Females (%)	43 (41.7%)	29 (59.2%)	0.056
Birth weight (g)	3364±0.05	3299±0.06	0.405

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Gestational age (weeks)[a]	38.98±0.11	39.06±0.18	0.697
Maternal smoking during gestation (%)[b]	12 (12.9%)	5 (11.1%)	1.000
Maternal education below 10 years of schooling (%)[b]	4 (4.2%)	2 (4.2%)	1.000
Family income below LICO (%)[b]	26 (25.7%)	15 (30.6%)	0.561
Exclusive breastfeeding (weeks)[a]	12.30±0.99	11.21±1.42	0.532
Mean daily n-3 PUFAs intake between 48-72 months (g)	2.27±0.26	1.52±0.34	0.107
Body mass index (kg/m^2) z-scores at 60 months[a]	0.28±0.10	0.15±0.18	0.534
SSRT at 60 months	480.24±16.44	557.62±26.64	0.011

[a]Student's t-test and [b]Chi-square test. Data are expressed as mean±SEM, or proportions (percentages). LICO=Low Income Cut Off.

specific mean birth weight for each gestational age for the local population. Children are classified as IUGR if they have a BWR of < 0.85 [86]. Birth weight and gestational age were assessed using birth records obtained directly from the birthing units, and a Canadian reference was used [87]. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2), measured by trained researchers, during visits to the laboratory up to 60 months of life.

.2.2. Food frequency questionnaire

We used the semi-quantitative Food Frequency Questionnaire (FFQ) valid for the Canadian population [88]. It was applied to mothers at 48 and 72 months of age, containing 45 types of foods with the portion size and frequency consumed (times per day, per week or per month). This is a standard procedure used to assess eating behavior and habitual consumption in children [89,90]. Mothers were invited to report their children's food intake on a typical day, with the help of a food photo album and measures to estimate the portion size of each food [91]. Based on these reports, the quantitative analysis of total caloric and macronutrient intake, as well as n-3 PUFAs consumption, was derived using NutriBase software (Version NB7 Network) [Phoenix, AZ, US].

2.2.3. Stop-signal task

The Stop-signal Reaction Time (SSRT) is a measure derived from the Stop Signal task, part of CANTAB battery that measures the ability to exert volitional control over a response that has already been initiated rather than choice selection [92–95]. During the task, individuals are asked to press a button when they perceive a GO stimulus on a screen (i.e., an arrow pointing left or right), unless they hear a 300 Hz sound stimulus (the STOP signal) after the GO signal, which occurs approximately once every four tests. This establishes a conflict between the reaction time for the initial task, which is to press the button in response to the GO stimulus, and the inhibitory process triggered by the sound (STOP stimulus). Depending on the speed of the stopping process of an individual (with faster stopping responses allowing faster inhibition) and the delay between the GO stimulus and the start of the STOP signal (signal stop delay-SSD), the responses to the signal GO on a given STOP test will be successfully deleted or not. The SSD for a given individual is calculated around the 50% performance level, increasing or decreasing depending on the primary inhibition response. When the percentage of successfully repressed responses is 50%, the difference between the SSD and the mean reaction time for correct GO assays when there is no STOP signal is an estimate of SSRT, with higher values indicating a less robust inhibitory process [96]. The stop-signal test was administered as part of a larger testing protocol done at or within a few weeks of each child's 60-month birthday. Mothers were instructed to arrive at the laboratory for testing between 0900 and 1000 hours.

2.2.4. Genotyping

Genotyping for rs8887 was extracted from the PsychArray/ PsychChip from Illumina, according to the manufacturer's guidelines, with 200 ng of genomic DNA derived from cells of the oral mucosa.

2.2.5. Statistical analysis

We categorized the sample into two groups according to the presence of allele A of the SNP rs8887. Descriptive statistics were per- formed comparing children groups including sex, birth weight, gestational age maternal smoking during gestation, maternal education

and family income, duration of exclusive breastfeeding, BMI at 60 months and mean n-3 PUFAs intake from 48 and 72 months FFQ data using Student's t-tests (for continuous variables) and chi-squared tests (for categorical variables). Sex was included in the regression model. Pearson's chi-square test was used to assess Hardy-Weinberg equilibrium (HWE). A linear regression model was performed to investigate the interaction between BWR and the presence of the A allele in the SSRT task, adjusted of not by ADHD symptoms from the Child Behavior Checklist applied at 48 months [97].

Analyzes were performed using the Statistical Package for the Social Sciences (SPSS) 22.0, considering significant values when $p < 0.05$.

3. Results

There were no significant differences between the A allele carriers and non-carriers on the main confounders such as birth weight, gestational age, breastfeeding duration, maternal schooling and income, smoking during gestation and n-3 PUFAs intake in infancy, as shown in Table 1. Sex rate almost reach significance for being different between the genotype groups (p=0.056), therefore sex was included in the subsequent models. PLIN4 genotype was in HWE for the A allele in the population study, with the frequency of 44% (P = 0.712) (Table 2). As depicted in Table 1, non-carriers of the A allele had less robust inhibitory process on SSRTs than the carriers group (Student's T Test, t (150) = 2.572, p = 0.011), in agreement with the work of Richardson et al.[76], in which the protective effect appears only for the A allele carriers of the rs8887 SNP.

As hypothesized, there was a significant interaction between BWR and the presence of the A allele on SSRT task performance (p= 0.014) in the predicted direction, such that an association between lower birth weight and poorer inhibitory control was seen only in the non-carrier subjects (B=-586.81, beta=-1.452, t=2.019, p=0.045), as depicted in Figure 1. Thus, the rs8887 SNP may protect small for gestational age children from developing poor response inhibition early in life. Adjusting the analysis for ADHD symptoms did not change the results (B=-708.01, beta=-1.827, t=-2.41, p=0.017).

Table 2- Genotypic and allelic distribution of SNP PLIN4 rs8887

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Plin 4 (*rs8887*) G>A				
Genotype	n (%)	**Allele**	n (%)	P
GG	49 (32.2%)	G	177 (58.23%)	0.712
GA	79 (52%)	A	127 (41.77%)	
AA	24 (15.8%)			
Total	152			

Data expressed in absolute (n) and relative (%) frequencies. A: Adenosine G: Guanine.

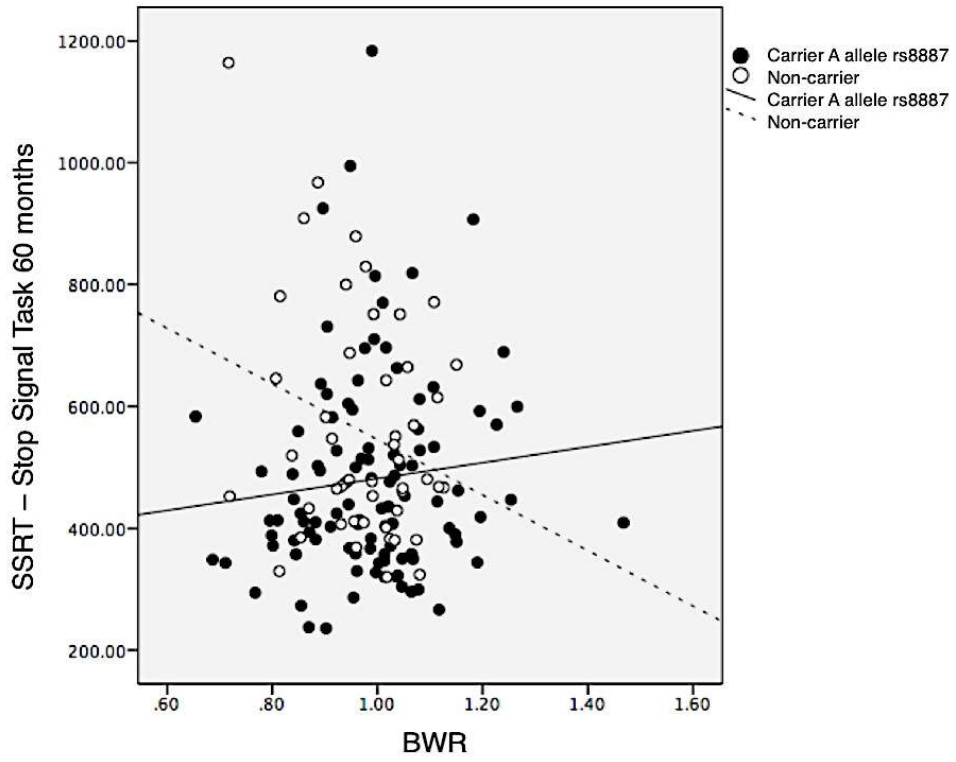

Figure 1. Interaction between BWR and the presence/absence of the A allele of the *rs8887* SNP

4 Discussion

The current study identified an interaction between the genotype and fetal growth in response to the inhibitory control task. In accordance with previous studies [52, 53, 98, 99], we found a negative correlation between fetal growth rate and SSRT performance for non-carriers of the A allele of the rs8887 SNP, in which the lower the birth weight,

the worse the performance in the inhibitory control task (longer SSRTs). We also report an important new finding for A allele carriers, who do not exhibit an association between fetal growth and worse inhibitory control, suggesting a protective role of this genetic variant in this sub-population. Our findings provide important clues for the comprehension of variables involved in early neural programming.

Early neural development is central to current models of mental health and disorder. Understanding both intrinsic and environmental risk factors for mental disorder requests a relational system of psychobiological development in a temporal dimension [100]. In this study, we analyzed developmental outcomes as a consequence of the interaction of at least two components (environmental and genetic) of the system on a specific temporal dimension.

In the intrauterine period and up to six months after birth, the child depends on the maternal transfer of LC PUFAs through umbilical cord and breast milk [101, 102], because placenta lacks the delta-5 and delta-6 desaturases to convert EFAs into LC PUFAs, and the enzymatic activity in the fetus and child under six months is very limited. As a compensatory mode, during pregnancy, the placenta tends to prioritize the transport of LC PUFAs into the fetal blood, demonstrating a preference for blood enrichment by DHA> AA> ALA> LA [103]. Maternal glucocorticoid exposure is considered a model of prenatal stress [104], as such as chronic stress and/or maternal dietary factors during pregnancy has been associated with increased risk for the development of mental illness later in life[105, 106]. High glucocorticoid exposure during pregnancy has been associated with higher incidence of neuropsychopatology[107], and new evidence has shown alterations in placental LC PUFAs metabolism in human IUGR (intrauterine growth restriction) [108]. Fetal LC PUFA supply during pregnancy is of major importance, particularly DHA, that is an essential component of the nervous system cell membranes with direct effects on neural and visual development [57]. DHA can alter brain development and function through effects related to neurogenesis, dendritic arborization, synaptogenesis, selective pruning and myelination [109], acting at molecular levels for neuronal cell growth and differentiation and in neuronal signaling [105, 110, 111] . The large membrane surface areas of neural cells, astrocytes, oligodendrites and microglia, with branch of dendrites that continuously change shape and length during development and learning suggests that inadequate DHA levels alter brain development through effects associated to cellular structures [112]. Recent evidence

suggests associations with early insult and altered placental LC PUFAs metabolism in IUGR individuals, with altered expression of FA transport proteins (FATP), translocases and the cytosolic protein perilipin [108]. Integrated analysis of multivariate imaging and genetic data suggests a relationship between PPAR signaling and variability in preterm white matter development, with functional networks enriched for the PLIN1 gene [113]. Moreover, experimental and cell culture studies have shown alteration in the expression of PLIN proteins related to aging or with anti-inflammatory astrocytic activity, suggesting that *PLIN* genes are implicated in lipid metabolism during stress and inflammatory activity [114-116]. This suggests a mechanism for modulation of DHA and PLIN genes induced by early life neural programming and insults, with individuals carrying the minor allele of the *PLIN4* had buffered the undesirable effects of early neurodevelopmental programming, with enhanced sensitivity for n-3 PUFAs.

Self-regulatory abilities such as inhibitory control and capacity to delay gratification are crucial in regulating reward-driven behavior. Impulsive individuals, often deficient in self-regulation, are more prone to engage in reward-driven behaviors than non-impulsive ones [117]. In addition, early life inhibitory control combined to birth weight appear to be quite predictive of outcomes throughout life [50, 118]. The mesocorticolimbic system, comprising DA cells within the ventral tegmental area (VTA) that mainly project to the nucleus accumbens (NAc) and prefrontal cortex (PFC), has an important role in value attribution and inhibitory control [119], considering that frontal lobes and basal ganglia inhibit ongoing responses derived from Stop-signal tasks [120]. As a consequence of prenatal adversities comprised by altered neurochemical signaling [121], the fetal nervous system undergoes neuroadaptations [122], with late behavioral changes, by altering the response to rewarding stimuli [123, 124]. Moreover, DHA deficiency is strongly associated with changes in mesocorticolimbic dopaminergic activity [64, 65, 125]. Evidence from human neuroimaging studies further suggests that psychiatric disorders initially emerging in childhood and adolescence associated with low peripheral DHA levels are characterized by frontal circuit deficits compared with healthy developing youth [126-128]. A recent methylome-wide study [129] suggests that altered early life methylation in the peroxisomal network, which is essential in DHA formation, could contribute to an impulsivity phenotype, including ADHD. This suggests that our current results, in agreement to our previous findings, corroborate to the idea that n-3 PUFAs are important moderators of the association between IUGR and impulsivity [52,

53], possibly through involvement of the PPAR signaling pathway[82, 130], inferred with the *PPAR* network regulating *PLIN* genes[130]. Richardson et al. meta-analysis of *PLIN4* SNPs detected for the minor allele of *PLIN4* rs8887 an association with increased adiposity and a interaction with omega-3 PUFA, such that higher omega-3 PUFA intake was associated with lower anthropometric traits, which suggests possible molecular mechanism involving the creation of a new micro RNA regulatory binding site (miR-522) [76, 131] by the *PLIN4* variant regulated n-3 PUFA through PPAR mediated pathways [82].

Despite of studies describing the effect of the minor allele of *PLIN4* rs8887 on anthropometric traits in association with n-3 PUFA [76], the role of this SNP is still not fully understood. Our genetic result of a moderating action on impulsivity traits adds a new function to the minor allele of this *PLIN4* variant, and supports previous work from Richardson *et al*.[76], reinforcing the integrative approach of genetic and environmental developmental systems. As we did not detect between-group differences in the consumption of n-3 PUFAs, we suggest that for the same amount of n-3 dietary intake, the A allele carriers are more sensitivity to the consumption of these dietary lipids. The mechanism of this association is unknown, and there are controversial results for the association of the PLIN4 variant protein expression. Moreover, experimental studies have demonstrated anti-obesity effects of n-3 PUFAs by modulating the activity of various transcription factors important to lipid metabolism [19].

Limitations of this study include the coexistence of more than one SNP for the *PLIN4* gene in the same subject, and the possible triple interactions with sex, for which our sample size does not have the necessary power to explore. The use of a food frequency questionnaire, an indirect dietetic measure to determine n-3 PUFAs consumption, may not be ideal for quantifying the intake of specific nutrients. Many efforts have been made to identify genetic involvement on complex common diseases and genome-wide plus candidate-genes studies have identified numerous disease-related SNPs, but many of these associations were not replicated in part because of methodological differences [132]. For neurobehavioral research it is a challenge to identify relevant gene–environment interactions regarding specific developmental outcomes and the appropriate investigation method.

5 Conclusion

The current research can be considered as a neuroscience based clinical candidate gene study, examining an important SNP which could have significant implications for informing novel early intervention strategies in primary prevention of conditions associated with inhibitory control deficits in this population.

Conflict of interest

The authors declare no conflict of interest.

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