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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 reactivity. 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 programming 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].

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

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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 on metabolic outcomes [76]. In humans, the perilipin gene (*PLIN*) is located in chromosome 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 components, resulting in increased risk for maladaptive behaviors. Here, using an integrative model, we investigate 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, demonstrating 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 the study visits, as well as collection of material for genetic 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.

2.2. Measures

2.2.1. Anthropometrics

In this research, we used fetal growth as a proxy of the quality of the fetal environment. Fetal growth was based on the birth weight ratio (BWR), which is the ratio between the infant birth weight and the sex-