Mechanisms underlying brain programming by early-life adversity and nutrition

Reemst, K.

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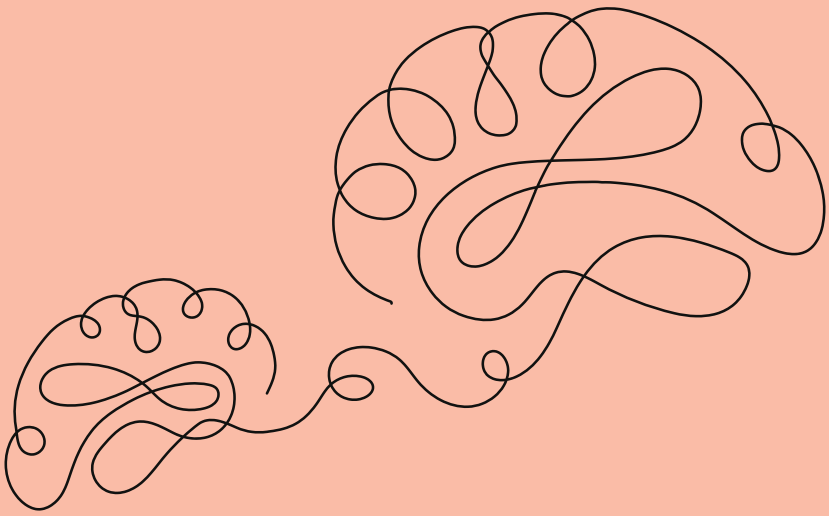

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Mechanisms underlying brain programming by early-life adversity and nutrition

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Table of contents

Preface

Shaping the brain by early-life adversity and nutrients

The development of several mental (e.g. depression and anxiety disorders) and metabolic (e.g. obesity and inflammatory bowel disease) disorders relies on the interaction between a genetic vulnerability factor and exposure to (early) environmental factors, so called gene-environmental (GxE) interactions. Such environmental factors are for example stress exposure and dietary intake during the early life period, and both contribute to the risk of developing such pathologies[1–7]. In humans, the first 1000 days of life, from the moment of conception until 2 years of age, are considered the brain's 'window of opportunity'. During this critical period, the brain, body and immune system grow and develop significantly, setting the foundation for our lifelong health[8]. This is often referred to as the "developmental origins of adult disease" (DOHAD) hypothesis, and assumes a critical interaction between early developmental plasticity and the early environment, that determines the risk for later-life health and disease[9,10]. The concept that early environmental experiences can shape the offspring *for life*, is also referred to as "early programming". Brain-programming describes the process through which exposure to environmental stimuli during critical phases of development leads to permanent changes in brain structure and function.

Programming by early-life adversity/stress

As the brain is still extremely plastic and displays extensive growth during the early phases of life, exposure to extreme stress in this period, referred to as early-life adversity (ELA) or early-life stress (ELS), can adversely influence brain development and have long-term consequences for later-life functions. ELA has for example been associated with an increased risk for several diseases, including cognitive impairment in adulthood. Unfortunately, ELA is very common, in the United States approximately 61% of all adults have experienced one or more forms of adversity during their early life period, including parental death/illness, abuse (physical, sexual or emotional) and/or parental neglect[11–14]. Prevention of ELA is often not feasible and currently no intervention strategies are available to protect or rescue a vulnerable population from the lasting consequences of ELA. Therefore, increased understanding is needed of the processes involved in brain programming by ELA.

Nutritional programming

Nutritional programming refers to the idea that in particular the nutrition (quality, composition and/or quantity of specific nutrients) received during early life is an important determinant of later life health. The brain develops more quickly during the first 1000 days than at any other stage of life, and nutrition provides the fuel that drives much of this early brain growth and development[8]. It is therefore not surprising that food intake during

early-life influences brain development. These early developmental alterations can also lead to lasting effects and mal- and undernutrition have indeed been associated with an increased risk for later mental and metabolic disease[2,15]. In particular, dietary omega (ω)3 polyunsaturated fatty acids (PUFAs) are important for the brain; they are key for normal brain development[16,17], have a positive influence on cognition, especially when provided already early in life[18–20], and have anti-inflammatory properties[21–24]. In the last century, the relative proportion of PUFAs consumed by the general population in the western world has shifted towards a relative higher intake of especially ω6 linoleic acid (LA; ω6 PUFA) and lower amounts of ω3 α-linolenic acid (ALA; ω3 PUFA), which has resulted in a higher ω6/ω3 ratio[25]. This is believed to be another environmental factor that contributes to the increased risk for mental health disorders and chronic metabolic diseases such as for example depression and obesity[26–30]. Notably, while ELA is hard to prevent, nutrition is a key modifiable factor for later-life health. Increased understanding of the biological underpinnings of nutritional intake and of the functions of nutrients in the brain can therefore potentially aid the development of nutritional interventions to further support a healthy development and possibly counteract detrimental effects of ELA.

Mechanisms underlying brain programming by ELA and dietary PUFAs

The implications of the concept "programming" are considerable as they imply that, once we understand the processes involved in programming by ELA and dietary PUFAs, we can potentially intervene and prevent the detrimental outcomes of ELA, possibly via non-invasive nutritional interventions. **Our lab has previously shown in a rodent model, that ELA induced later cognitive impairments[31], alterations in inflammatory signaling in an Alzheimer's disease mouse model[32], and triggered metabolic alterations in the adipose tissue and leptin system[33]. Additionally, we demonstrated that an early dietary intervention with a reduced ω6/ω3 PUFA (LA/ALA) ratio, protected against the cognitive deficits in adulthood, but did not rescue the metabolic alterations induced by ELA[34].** Currently, the mechanisms underlying the cognitive effects of ELA, or of the diet, remain poorly understood and may be multi-factorial. Therefore, in this thesis we address some of the biological mechanisms that could mediate these effects.

Importantly, long-term programming by early-life environment also depends on the later-life environment. The 'two-hit' hypothesis suggests that ELA represents a first "hit", that then increases sensitivity to later-life challenges, i,e, the "second hit", and only then the earlier programmed changes are 'unmasked', that are not otherwise apparent under basal circumstances[35]. Due to the effects of ELA and PUFAs on (neuro-)inflammatory processes, we choose in this thesis a secondary inflammatory challenge to better understand if and how i) ELA and/or dietary PUFAs affect inflammatory signaling in adulthood, and ii) whether an inflammatory challenge can 'unmask' any programmed effects of ELA and diet.

Neuroinflammation

Both human and rodent data show that exposure to ELA affects the neuro-immune system and inflammatory signaling. In particular the role of microglia has remained obscure. They are the macrophages of the brain, and likely play important roles in the effects of adverse (early-life) experiences on the maturation of those brain circuits that are involved in cognition and later-life brain function[36,37]. In addition, dietary PUFAs too are modulators of inflammatory signaling and can modulate microglial functions[22]. Therefore in this thesis, we explore the role of neuroinflammation and microglia in the ELA and diet induced effects, both under basal and inflammatory conditions.

microRNAs and gene expression

Epigenetic mechanisms play a crucial role in adaptive and maladaptive processes by regulating gene expression without changing the genome[38]. They have been strongly implicated in mediating at least some of the effects of early life adversity on the offspring. Recently, small noncoding RNAs have emerged as key controllers of gene expression and play important roles in the development of various (brain) diseases. Specifically, microRNAs (miRNAs) are studied most in this respect which were shown to be important regulators of e.g. neuronal plasticity[39]. Recently, few studies have started to describe the role of miRNAs in the ELA-induced structural and functional brain changes and whether these processes are associated with the ELA-induced risk for later-life disease[40,41]. In addition, there is evidence for PUFAs and their derivatives too to affect miRNA expression in the brain[42,43]. However, how exactly miRNAs are involved in ELA and diet induced effects is unknown. Therefore, in this thesis we examine miRNAs and their target genes in mediating the effects of ELA and dietary PUFAs on the brain, both under basal and inflammatory conditions.

Brain lipids

There is increasing evidence that dysregulation of lipids is important for the pathophysiology of brain diseases, such as depression and Alzheimer's disease[44]. Interestingly, both ELA and malnutrition are predisposing factors of such brain diseases. It remains currently unknown, however, whether the lipid dysregulation associated with these disorders might have an early-life origin. We therefore address if and how the brain lipid profile in adulthood is modulated by ELA and early dietary PUFAs.

The gut microbiota

In recent years there has been a rise in studies investigating the role of the gut microbiota as a modulator of general health. Drastic changes in the composition of the gut microbiota have been shown to influence normal physiology and even contribute to normal brain functions as well as to diseases ranging from inflammatory bowel disease to Alzheimer's disease to depression[45–47]. Importantly, accumulating data indicates that the

gut microbiota communicate with the CNS seemingly via neural, endocrine and immune pathways, thereby influencing brain function and ultimately behaviour[48,49]. While the relation between stress, nutrition and the gut microbiota has gained increased attention over the years[47,50–52], specifically how ELA and a dietary ratio of ω6/ω3 PUFAs in the early diet can program the gut microbiota, was unknown, and will therefore be investigated in this thesis.

Comorbidity and sex-specificity in ELA induced risk for disease

There is abundant evidence showing far reaching effects of ELA on both peripheral measures (e.g. body weight and insulin sensitivity)[15,53] and on behaviour (e.g. cognition and depression)[54,55]. Both rodent and human researchers however are often refrained to a limited study design, therefore unable to study all components that might matter for ELA effects on brain and metabolic outcomes. In this thesis, we will therefore take a broad perspective and try to bring together all readouts of the many changes induced by ELA itself, in as much as they are relevant and have consequences for later metabolic and brain health (chapter 7).

Firstly, exposure to ELA is a major risk factor for both mental and metabolic disorders[3,53,54,56]. In the general population these disorders are often comorbid, however so far they were mostly studied separately and not simultaneously or in relation to each other. As a result, it is so far unclear whether ELA plays a role in the co-occurrence of these diseases. Secondly, whereas there is a strong male bias in rodent research (as in this thesis), the above mentioned disorders exhibit clear sex differences in their prevalence and presentation[57,58]. In addition, several studies have reported sex-specific effects of ELA[59–65], making it crucial to gain more insights also in ELA's sex-specific risk for disease. Thirdly, while in this thesis we mainly focus on early postnatal stress, there is plenty of evidence that also stress exposure prenatally/in utero, affect the development of the offspring and later-life risk for disease, stressing the importance of understanding in what way timing of ELA matters for brain development and later-life outcomes. Lastly, it is key to understand to what extent the above mentioned ELA-induced effects are consistent across human and rodent literature to assess and value the translational aspect of rodent research. So far, a comprehensive review on human and rodent ELA (pre- and postnatal) studies examining mental or metabolic health in both sexes was still missing, which is why it will be addressed in this thesis.

Aims and thesis outline

The main aims of this thesis are to; i) address the biological mechanisms that could mediate brain programming effects of ELA and early dietary PUFA intake, ii) study these mechanisms under basal and inflammatory conditions, iii) understand to what extent exposure to ELA during critical developmental periods (prenatally or

early postnatally) in either rodents or humans, contributes to the vulnerability to later mental and metabolic disorders, to their comorbidity and their sex-dependent prevalence.

The following underlying mechanisms will be addressed: microglia and (neuro-) inflammation, (epi-)genetics, brain lipids and the gut microbiota. To study such cellular and molecular processes, we use a **mouse model of chronic early-life adversity (ELA)**. In this model, chronic ELA is caused by fragmentation of maternal care, that is induced by limited amounts of nesting and bedding material[31,32,34]. **The dietary intervention we use in this thesis is based on modulation of the ratio between ω6 and ω3 PUFAs**; high ω6/ω3 ratio = 15 and a low ω6/ω3 ratio = 1.1, with the low ratio leading to more ω3 fatty acid availability in the brain[34]. In several studies, we have used a **secondary inflammatory challenge in the form of intraperitoneal (i.p.) lipopolysaccharide (LPS) injection**. In this thesis, we will mostly focus on ELA induced cognitive impairment, a common trait of many different psychopathologies[66–68] and a consistent outcome of the mouse model we use[31,34].

In **chapter 1,** we start off with describing the effects of stress on neurons and glial cells focusing on glucocorticoid (GC) signaling. Next to stress exposure during the early life period, also exposure to chronic stress in adult life, is a risk factor for developing mental disorders. One hallmark of stress-related pathologies is a dysregulated hypothalamic-pituitary-adrenal (HPA-axis), which has intensified research efforts into the neurobiology of stress. However, while the impact of GCs has been mainly examined on neurons, evidence shows cell-type (neurons, microglia, astrocytes)-specific effects of stress. In this chapter, we therefore focus on GCs effects on the morphology and functionality of both neurons and glia.

In **chapter 2,** we discuss the various roles of glial cells, microglia and astrocytes, during normal brain development. Although both cells are fundamentally different in origin and function, they often affect the same developmental processes such as neuro-/glio-/angiogenesis, axonal outgrowth, synaptogenesis and synaptic pruning, processes known to be affected by ELS and dietary PUFAs. Due to the instructive roles glial cells play in these processes, dysfunction of microglia or astrocytes during brain development could contribute to neurodevelopmental disorders and potentially also to later-life neuropathology. A better understanding of the origin, differentiation process and developmental functions of microglia and astrocytes will help to fully appreciate their roles both in the developing as well as in the adult brain, in health and disease.

Neuroinflammatory processes have been implicated in the ELS-induced negative health outcomes, but how exactly ELS impacts microglia, the macrophages of the central nervous

system is largely unknown. Therefore, the role of microglia in the ELS-induced effects is studied in **chapter 3**. Specifically, we study the impact of ELS on morphology and gene expression of hippocampal microglia from young and adult mice. Due to the involvement of microglia in inflammatory signaling, and in order to understand whether a secondary challenge might unmask earlier ELS programmed effects in adult mice, we test the effect of ELS on microglia both under basal and inflammatory conditions in adult animals.

Chapter 4 is aimed at elucidating the molecular mechanisms underlying the effects of ELS and dietary PUFAs on hippocampal functioning, both under basal conditions and in response to an adult inflammatory challenge. Several studies have demonstrated a crucial role for miRNAs in the translation of environmental cues into adult health outcomes, but if and how early-life exposures such as ELS and dietary PUFAs affect gene expression through modulation of miRNAs, and which molecular pathways are involved, is not precisely known. In this chapter, we test; i) whether miRNAs and their target genes mediate the protective effects of an early diet with low ω6/ω3 ratio against the ELS-induced cognitive deficits, and ii) whether this relates to inflammatory signaling. We test this both under basal conditions and in response to an inflammatory challenge in adulthood.

In chapter 5, we study the involvement of brain lipids as mediators of the effect of ELS and early dietary PUFA's on the brain. Brain lipid dysregulation is increasingly believed to be a key characteristic of several brain diseases, like depression and Alzheimer's disease, which are also marked by chronic inflammation. While ELS and dietary intake of PUFAs are known to contribute to the risk of developing such pathologies, little is still known as to whether this also lead to brain lipid dysregulation. Therefore, we set out to study if and how ELS and early dietary FAs modulate the brain lipid and oxylipin profile, both under basal conditions and in response to an inflammatory challenge in adulthood.

Much of our research has been focused specifically on central mechanisms, however in the last decade a prominent role of the microbiota has been emerging as key modulator of mental health. The gut-brain axis has long been appreciated as an essential bi-directional communication system between the central and the enteric nervous system, thereby linking emotional and cognitive centers of the brain with specific peripheral intestinal functions. Over the past 15 years, specifically the gut microbiota (i.e. the trillions of microorganisms within the gut) have emerged as important regulators of the gut-brain axis, leading to the concept of "the microbiota-gut-brain (MGB) axis. The MGB axis can be affected by numerous environmental factors including (early-life) stress and diet. **Chapter 6** focuses on the impact of ELS and dietary PUFAs on the gut microbiota. We study the involvement of the gut microbiota in ELS- and diet-induced long-term effects and how microbiota changes relate to cognitive, metabolic and fatty acid profiles.

Finally, as mentioned earlier, ELS increases the risk for both mental as well as metabolic disorders. It is important to note that in the general population these disorders are often comorbid and exhibit sex differences in their prevalence and presentation. However, if and to what extent ELS contributes to this comorbidity and sex-specific prevalence of these disorders, remains unclear. Therefore, in **chapter 7** we comprehensively review and integrate human and rodent ELS studies that examined mental or metabolic health in both sexes. Importantly, while in the other chapters we focus on early postnatal stress, also stress exposure prenatally will be included in this review. In addition, we discuss the placenta and breastmilk as key mechanisms translating maternal effects to the offspring.

In **chapter 8**, the general discussion, the main findings of this thesis are highlighted and discussed in a broader perspective.

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