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Marchaland, F., Martinat, M., Di Miceli, M. et al. (2026) Maternal dietary n-3 PUFA deficiency leads to sex-specific alterations in placental and cerebral fatty acid profiles and in oxylipin profiles in the developing mouse brain. Biochimie. ISSN: 0300-9084

https://doi.org/10.1016/j.biochi.2026.07.010

Title: **Maternal dietary n-3 PUFA deficiency leads to sex-specific alterations in placental and cerebral fatty acid profiles and in oxylipin profiles in the developing mouse brain**

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This work has been performed in the frame of the international network Foood4BrainHealth

Funding sources:

This work was supported by INRAE Food4BrainHealth; Fondation pour la Recherche sur le Cerveau CONNECT (SL), Fondation pour la Recherche Médicale PRINSS DEQ 20170336724 (SL); Aquitaine Region AUTISME 2019-1R3M08 (SL) and ExoMarquAge 13059720-13062120 (SL, JCD); ANR IBRAA (SL); ANR-21-JPW2-0004-05 SOLID (SL); PhD extension grant FRM FDT202204014903 (MM); Agence Nationale de la Recherche [ANR-11-LABX-0021-01], INRAE, French "Investissements d'Avenir" Program, Conseil Régional Bourgogne, Franche-Comté (PARI grant), the FEDER (European Funding for Regional Economical Development).

1. Introduction:

The brain is highly enriched in fatty acids, including saturated (SFA), monounsaturated (MUFA) and polyunsaturated fatty acids (PUFAs) (1), which are mainly delivered to the brain *via* the bloodstream following dietary intake (2). Grey matter is particularly enriched in n-6 and n-3 long-chain PUFAs (LC-PUFAs) (3), with arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3) being the predominant species esterified on phospholipids of neuronal and glial cell membranes (1, 4, 5), while eicosapentaenoic acid (EPA, 20:5n-3) is mainly incorporated into microglial membranes (6, 7). In mammals, AA, EPA and DHA can be synthesized from dietary precursors found in plant sources, namely linoleic acid (LA, 18:2n-6) and α-linolenic acid (ALA, 18:3n-3). These LC-PUFAs can also be directly provided in their preformed state, through the consumption of terrestrial animal products or seafood (8, 9). Overall, both dietary precursors and preformed LC-PUFAs contribute directly to the levels of LC-PUFAs in the brain (1). Importantly, the highest accumulation of LC-PUFAs in the brain occurs during the perinatal period. In humans, this accretion is particularly intense from the third trimester of gestation to two years of age (10-12), and in rodents, from late gestation to the end of the third postnatal week (13). During this perinatal period, LC-PUFAs are initially transferred to the embryo *via* the placenta and subsequently to the offspring through breast milk, including delivery to the developing brain (14, 15). The hippocampus undergoes a major phase of neuronal circuit refinement during the third postnatal week (between P14 and P21), which corresponds to the late juvenile period. This period, during which the hippocampus undergoes functional synaptic maturation (16), represents a critical window for the establishment of hippocampal-dependent memories (17, 18), a process we found to be disrupted in male offspring from n-3 PUFA deficient diets at P21 (19, 20). Around the time of weaning (P21), the brain is already near adult size in many regions, yet major developmental processes, particularly the maturation and refinement of neuronal networks, including myelination and synaptic pruning, remain actively ongoing (21). Regarding the hippocampus, proliferation and migration of pyramidal neurons are completed before birth in mice, while neuronal circuit formation and maturation extend through the first postnatal weeks. Notably, the late juvenile period

represents a major phase of hippocampal circuit refinement (16) and a critical window for the establishment of hippocampal-dependent memories (17, 18). Overall, a deficiency in LC-PUFAs and/or an imbalance between n-3 and n-6 PUFAs can impair neurodevelopment (14, 15). Premature birth or cesarean delivery disrupts materno-fetal LC-PUFA transfer, leading to reduced availability compared to full-term infants, which may compromise neurodevelopment (22, 23). Moreover, low-birth-weight infants have reduced adipose stores of LC-PUFAs and are consequently at a higher risk of neurodevelopmental disorders (24). In rodents, maternal dietary n-3 PUFA deficiency during the perinatal period reduces brain DHA levels by embryonic day 17 (E17) (25), impairs memory and synaptic plasticity in the hippocampus from postnatal day 21 (P21) (19, 26, 20) and increases offspring vulnerability to the detrimental effects of early-life inflammatory challenges (25, 27). However, the mechanisms linking altered PUFA profiles to impaired brain development remain poorly understood. An additional key aspect of PUFA function in the brain involves their bioactive metabolites. Oxylipins, which form a major subclass of lipid mediators enzymatically derived *via* cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP450) pathways, play important signaling roles (28, 29, 30). They are present in the adult brain, with their levels and profiles strongly influenced by inflammatory stimuli and dietary PUFA status. Indeed, hundreds of oxylipins can be synthesized from a limited set of PUFA precursors, mainly DHA, EPA and AA (30, 31, 32, 33, 34, 35). This is particularly important since oxylipins derived from n-6 and n-3 PUFAs are key regulators of numerous brain processes, including synaptic plasticity, neuronal morphology, neurotransmission, cerebral blood flow and neuroinflammation (2, 7, 29, 30, 36, 37, 38, 39). Notably, oxylipins derived from n-6 PUFAs (e.g., prostaglandins, leukotrienes, thromboxanes, and lipoxins) and those derived from n-3 PUFAs (e.g., specialized pro-resolving mediators, SPMs) often exert opposing effects on inflammation and neuroinflammation (29, 40). Recent studies, including our own, have shown that, in a context of maternal dietary n-3 PUFA deficiency, AA and its metabolite 12-HETE (12-Hydroxyeicosatetraenoic acid) altered postnatal maturation of neuronal networks in the hippocampus *via* their specific effects on the activity of microglia (19), the brain resident phagocytic immune cells essential for synaptic pruning (41). This further supports the notion that oxylipins play a crucial role in brain

development. These findings highlight the importance of dietary PUFA composition in shaping the brain's oxylipin profile and potentially its functional outcomes.

Only a few studies have investigated sex differences in the composition of PUFAs and oxylipins in the brain, most of which have focused on adulthood. In rats and mice maintained under physiological conditions and fed a standard diet, brain fatty acid composition, including AA and DHA, as well as brain oxylipin profile, did not differ between sexes (42, 443, 44, 45). Recent data have shown that early-life exposure to a LA-rich diet differentially affects the adult brain PUFA profile in male and female rats, particularly with regard to AA levels (46). However, sex-dependent variations in fatty acid and oxylipin profiles during brain development, and their potential modulation by dietary n-3 and n-6 PUFAs, remain largely unexplored. We hypothesized that maternal consumption of different dietary LA/ALA ratios, from gestation through weaning, would alter both PUFA and oxylipin profiles in the developing brain and that these effects might differ by sex.

2. Materials and Methods:

2.1. Animals and diets

Animal housing and experimental procedures were performed in accordance with the European Union directive (2010/63/EU) and validated by the ethics committee (approval #2022031116224183). All experiments were conducted using CD1 mice (Janvier Labs, Le Genest-Saint-Isle, France). Animals were housed under standard conditions with controlled temperature (23 ± 1 °C) and humidity (40-50%), and maintained on a 12-hour light/dark cycle (7:30-19:30). Food and water were available *ad libitum*. Eight-week-old male and female mice were mated overnight. The successful mating was confirmed by the presence of a vaginal plug the following morning that was designated as embryonic day 0.5 (E0.5). Before mating, mice were maintained on a standard A04 diet. At mating, they were randomly assigned to either an n-3 PUFA-sufficient or -deficient diet and maintained on these diets throughout gestation and lactation, as previously described (19, 25, 20, 47). These diets, manufactured by the INRAE unit (Jouy-en-Josas, France),

contained 5% of fat in the form of sunflower oil, rich in LA (n-3 PUFA-deficient offspring) or in the form of canola oil, rich in ALA (n-3 PUFA-sufficient offspring) (Tables 1 and 2). We used a 5% fat content, consistent with the AIN-76A standard (48), in order to maintain consistency with established perinatal n-3 PUFA deficiency protocols previously validated in our group and others (1, 7, 19, 25, 26, 20, 27, 47, 49, 50, 51, 52, 53). Pregnant females were housed individually throughout gestation and lactation. To avoid cage effects, pups used at each developmental stage were selected from distinct litters, with each dam contributing a maximum of two litters to the study. In total, 5-6 mothers per experimental diet were used. For each mother, different pups from the same litter were randomly assigned to each developmental time point. For example, in a litter of approximately 16 pups, 2 males and 2 females were allocated to P0, 2 males and 2 females to P7, 2 males and 2 females to P14, and 2 males and 2 females to P21. Thus, at a given developmental time point, 4 to 6 pups per diet group (originating from 2 different mothers) were analyzed and no individual pup was sampled repeatedly across ages. Sample sizes (number of pups per experiment) are specified in the figure legends. No significant effect of diet on litter size or sex ratio was observed (data not shown).

2.2. Tissue collection

Placentas and brains from individual embryos were collected at E17.5 for lipid analysis. As the mouse is a multiparous species, each embryo has its own placenta. Samples were collected following maternal anesthesia with Bupaq solution (Centravet), diluted to 1:30 in water for injectable preparations and euthanasia using Euthasol Vet solution (Centravet), diluted to 1:10 in water for injectable preparations. For each solution, 10 µl per gram of mouse was injected. A tail sample was also collected from each embryo for determination of sex (see below). At later developmental stages, pups were anesthetized with Bupaq solution and euthanized with Euthasol Vet solution, using the same dilutions and injection volumes described above. Brains were then rapidly extracted and either frozen whole (P0 and P7) or processed for hippocampus dissection (P14 and P21). All tissue collections were performed on ice and samples were immediately stored at -80 °C until further processing. Each brain and hippocampal sample was divided into two equal parts: one

for lipid analysis, the other for oxylipin quantification. At E17.5, P0, and P7, whole brains were collected as the hippocampus could not be reliably isolated at these early developmental stages. At P14 and P21, hippocampi were dissected with sufficient anatomical precision.

2.3. Sex identification at E17.5

To determine embryo sex, genomic DNA was extracted from tail samples and used for Rbm31 genotyping (Tunster, 2017). Briefly, tail tissue was digested in 200 µl of 0.05 M NaOH during 10 min at 100 °C. Then, 50 µl of 1 M Tris-HCl (pH 8.0) were added to the mix. After centrifugation for 5 min, the supernatant containing DNA was collected and stored at 4 °C. Two µl of DNA extract were used for each PCR reaction. Each 20 µl PCR reaction mix also contained 5 µl of deoxynucleotide mix, 10 µl of 2X PCR mix (Promega, WI, USA), 0.1 µl of homemade Taq polymerase, and primers (5'-CACCTTAAGAACAAGCCAATACA-3' and 5'-GGCTTGTCCTGAAAACATTTGG-3'). PCR amplification in the thermocyler was performed using the following program: 2 min at 94 °C, 30 cycles of 20 s at 94 °C, 20 s at 60 °C, 30 s at 68°C, 5 min at 72 °C, then a cool down to 4 °C. Amplified PCR products were run through a 2% agarose gel and visualized using SafeView (Applied Biosystems, Carlsbad, CA) on UV table with gel imager (EBox CX5, Vilber, Collégien, France).

2.4. Lipid analysis

Lipids were extracted from placentas (E17.5), whole brains (E17.5), half-brains (P0 and P7) and half-hippocampi (P14 and P21) at the Eye & Nutrition Research Group laboratory (CSGA, INRAE, Dijon, France) and further processed for fatty acid measurement. Briefly, total lipids were extracted according to the Folch procedure using a chloroform/methanol mixture (54). The fatty acids were methylated (55) and the composition of the resulting fatty acid methyl esters (FAMEs) and dimethyl acetals (DMAs) was determined by gas chromatography coupled to flame ionization detection (GC-FID) using a Trace 1310 gas chromatograph (Thermo Scientific, Courtaboeuf, France), equipped with a split/splitless injector, a flame ionization detector, and a CPSIL-88 capillary column (100 m x 0.25 mm internal diameter; 0.20 µm film

thickness; Varian, Les Ulis, France). Hydrogen was used as the carrier gas at an inlet pressure of 210 kPa. The temperature program of the oven was set as follows: 60 °C for 5 min, increased to 165 °C at 15 °C/min (held for 1 min), then to 225 °C at 2 °C/min, with a final hold at 225 °C for 7 min. Injector and detector temperatures were set at 250 °C and 280 °C, respectively. FAMEs were identified by comparison with commercial and synthetic standards. The data were computed using the Chromeleon software (version 7.1.10 ES, Thermo Scientific). Results are expressed as the percentage of total FAMEs and DMAs.

2.5. Oxylipin quantification

Free (non-esterified) oxylipins derived from LA, DGLA, AA, DHA and EPA were isolated from the remaining half-brain or half-hippocampus samples and analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) at the METATOUL platform (MetaboHUB, INSERM UMR 1048, I2MC, Toulouse, France) according to the LC-MS/MS method published by Le Faouder et al. (56) (Table 3). Results were expressed as picograms per milligram of protein (pg/mg) and represented as Z-scores for heatmap visualization.

2.6. Statistical analysis

Statistical analyses were performed using GraphPad Prism software (version 10.3.1; GraphPad Software, Boston, MA, USA). Oxylipin and fatty acid levels were analyzed separately at each developmental stage using a 2-way ANOVA (sex x diet), followed, when appropriate, by Fisher's Least Significant Difference (LSD) post hoc tests. Heatmaps of oxylipin levels (expressed as Z-scores) were generated using R software (version 4.4.1) within the RStudio environment (version 2024.09). To allow easier visualization of oxylipin concentrations, data were standardized across samples separately for each sex and developmental stage by computing Z-scores for each individual oxylipin, as previously described (19). This normalization involved centering the concentrations around the mean and dividing by the standard deviation, resulting in values with a mean of zero and a standard deviation of one for each oxylipin. Given that whole brain and hippocampal fatty acid and oxylipin profiles reflect distinct levels of regional specificity, no statistical

comparisons across developmental stages were performed and analyses were conducted independently at each developmental timepoint.

3. Results:

3.1. Early-life exposure to diets differing in their LA/ALA ratio altered placental and embryo brain PUFA profiles

The impact of maternal n-3 PUFA dietary intervention was first assessed on fatty acid composition of the placenta and embryonic brain at E17.5. Among fatty acids measured, PUFAs were the most affected by early-life exposure to an n-3 PUFA-deficient diet in the placenta (Supplementary Table 1) and brain (Supplementary Table 2) of both males and females. In particular, n-6 PUFAs were significantly increased (Fig. 1A; LA, 20:2n-6, AA, 22:4n-6 and 22:5n-6) while n-3 PUFAs significantly decreased (Fig. 1B; ALA, EPA, 22:5n-3, DHA) in the placenta of n-3 PUFA-deficient males as compared to n-3 PUFA-sufficient males. Accordingly, in the brain, n-6 PUFAs were significantly increased (Fig. 1G; LA, 20:3n-6, AA, 22:4n-6, 22:5n-6) and n-3 PUFAs decreased (Fig. 1H; EPA, 22:5n-3, DHA) in n-3 PUFA-deficient males as compared to n-3 PUFA-sufficient males. Overall, early-life exposure to an n-3 PUFA-deficient diet similarly affected female placenta and brain, with significantly increased n-6 PUFAs (Fig. 1D for placenta; LA, 18:3n-6, 20:2n-6, 20:3n-6, 22:4n-6, 22:5n-6; Fig. 1J for brain; LA, 20:3n-6, AA, 22:5n-6) and significantly decreased n-3 PUFAs (Fig. 1E for placenta; ALA, EPA, 22:5n-3, DHA; Fig. 1K for brain; EPA, 22:5n-3, DHA) in n-3 PUFA-deficient females as compared to n-3 PUFA-sufficient females. Of note, EPA was significantly higher in the brain of n-3 PUFA-deficient females as compared to n-3 PUFA-deficient males (Supplementary Table 2). Overall, the n-6/n-3 PUFA ratio was significantly increased in the placenta and brain of male (Fig. 1C, 1I) and female (Fig. 1F, 1L) embryos from dams fed an n-3 PUFA-deficient diet as compared to an n-3 PUFA sufficient diet.

3.2. Early-life exposure to diets differing in their LA/ALA ratio altered brain PUFA and oxylipin profiles at birth

Fatty acid and oxylipin profiles were then determined in the brain of offspring at birth. Among fatty acids, PUFAs were the most impacted by early-life exposure to an n-3 PUFA-deficient diet (Supplementary Table 3). Especially, n-6 PUFAs were significantly increased in males (Fig. 2A; LA, 22:5n-6) and females (Fig. 2D; LA, 20:2n-6, 22:5n-6), while n-3 PUFAs were significantly decreased in males (Fig. 2B; EPA, 22:5n-3, DHA) and females (Fig. 2E; EPA, DHA), resulting in a significant increased n-6/n-3 PUFA ratio (Fig. 2C, 2F). Of note, in n-3 PUFA-deficient brains, 20:2n-6 was significantly higher in females, whereas 22:5n-6 and total n-6 PUFAs were significantly lower, as compared to males (Supplementary Table 3). Furthermore, oxylipins levels were altered by early-life exposure to n-3 PUFA deficiency (Supplementary Table 4). Particularly, LA-derived 9-HODE and 13-HODE were significantly increased in the brain of males (Fig. 2G) and females (Fig. 2H). Moreover, AA-derived oxylipins LxA4, 14,15-EpETrE, 11,12-EpETrE, 8,9-EpETrE, 15-HETE, 8-HETE and 5-HETE were significantly increased by the n-3 PUFA-deficient diet in the brain of males, but not in females (Fig. 2G). Of note, in n-3 PUFA-sufficient brains, 5-HETE was significantly higher in females than in males (Supplementary Table 4). Additionally, DHA-derived 17-HDoHE and 14-HDoHE were significantly reduced in the brain of n-3 PUFA-deficient females (Fig. 2H).

3.3. Early-life exposure to diets differing in their LA/ALA ratio altered brain PUFA and oxylipin profiles at post-natal week 1

One week after birth, among fatty acids measured, PUFA were the most affected by the n-3 PUFA-deficient diet (Supplementary Table 5). Especially, n-6 PUFAs were significantly increased in males (Fig. 3A; LA, 20:2n-6, AA, 22:4n-6, 22:5n-6) and females (Fig. 3D; LA, AA, 22:4n-6, 22:5n-6), while n-3 PUFAs were significantly decreased in males (Fig. 3B; EPA, 22:5n-3, DHA) and females (Fig. 3E; 22:5n-3, DHA). Overall, this led to a significant increase of the n-6/n-3 PUFA ratio in the brain of n-3 PUFA-deficient males (Fig. 3C) and females (Fig. 3F). Of note, 20:2n-6 was significantly higher in the brain of n-3 PUFA-deficient

females as compared to males (Supplementary Table 5). Moreover, early-life exposure to n-3 PUFA deficiency impacted brain oxylipin profile (Supplementary Table 6). In fact, LA-derived 9-HODE and 13-HODE were significantly increased in the brain of males (Fig. 3G) and females (Fig. 3H). In addition, AA-derived 15-HETE was significantly increased in the brain of males (Fig. 3G), while AA-derived 6kPGF1a and 15-HETE were significantly increased by the n-3 PUFA-deficient diet in the brain of females (Fig. 3H). Of note, in n-3 PUFA-deficient brains, AA-derived LxB4 was significantly higher in females than in males (Supplementary Table 6). Concerning n-3 PUFA-derived oxylipins, early-life exposure to n-3 PUFA deficiency significantly decreased levels of DHA-derived 17-HDoHE and 14-HDoHE, but only in the brain of males (Fig. 3G). In addition, levels of both 17-HDoHE and 14-HDoHE were significantly higher in the brain of males compared to females (Supplementary Table 6).

3.4. Early-life exposure to diets differing in their LA/ALA ratio altered hippocampus PUFA and oxylipin profiles at post-natal week 2

Among fatty acids measured in the hippocampus at P14, PUFAs were the most affected by the early-life exposure to an n-3 PUFA-deficient diet (Supplementary Table 7). Accordingly, n-6 PUFAs were significantly increased in males (Fig. 4A; LA, 20:3n-6, AA, 22:4n-6, 22:5n-6) and females (Fig. 4D; LA, 20:3n-6, AA, 22:4n-6, 22:5n-6), while n-3 PUFAs were significantly decreased in males (Fig. 4B; EPA, 22:5n-3, DHA) and females (Fig. 4E; EPA, 22:5n-3, DHA). Consequently, a significant increase of the n-6/n-3 PUFA ratio was measured in the hippocampus of offspring from n-3 PUFA-deficient mothers (Fig. 4C, 4F). Of note, in n-3 PUFA-sufficient hippocampi, LA was significantly higher in males than in females (Supplementary Table 7). In addition, early-life exposure to n-3 PUFA deficiency altered oxylipin profile in the hippocampus (Supplementary Table 8). Indeed, AA-derived 5,6-EpETrE was significantly increased in n-3 PUFA-deficient females as compared to n-3 PUFA-sufficient females (Fig. 4H). Moreover, DHA-derived 17-HDoHE and 14-HDoHE were significantly decreased in males (Fig. 4G) and females (Fig. 4H).

3.5. Early-life exposure to diets differing in their LA/ALA ratio altered hippocampus PUFA and oxylipin profiles at post-natal week 3

Finally, among fatty acids measured in the hippocampus at P21, the n-3 PUFA-deficient diet had the most influence on PUFAs (Supplementary Table 9). Indeed, significant increases of n-6 PUFAs were measured in the hippocampi of males (Fig. 5A; LA, 20:3n-6, 22:4n-6, DPA n-6) and females (Fig. 5D; LA, 20:3n-6, 22:4n-6, DPA n-6) as well as significant decreases of n-3 PUFAs in the hippocampus of males (Fig. 5B; EPA, 22:5n-3, DHA) and females (Fig. 5E; EPA, 22:5n-3, DHA). Overall, this led to a significant increase of the n-6/n-3 PUFA ratio in the hippocampus of n-3 PUFA-deficient males (Fig. 5C) and females (Fig. 5F). Additionally, oxylipin profile in the hippocampus was impacted by the n-3 PUFA-deficient diet (Supplementary Table 10). In particular, levels of AA-derived LxA4 were significantly increased in males (Fig. 5G), while those of AA-derived 6kPGF1a were significantly increased in females (Fig. 5H). Moreover, DHA-derived 17-HDoHE and 14-HDoHE were significantly decreased in males (Fig. 5G) and females (Fig. 5H).

4. Discussion:

In this work, we investigated the impact of perinatal exposure to diets sufficient or deficient in n-3 PUFAs on profiles of fatty acids and their metabolites (oxylipins) in the developing brain of male and female offspring, from embryonic life to weaning, a period during which pups are dependent on maternal PUFA supply. By assessing the impact of early-life exposure to diets with altered n-6/n-3 PUFA ratios on PUFA and oxylipin profiles in the pup brain at E17.5, P0 and P7, as well as in the pup hippocampus at P14 and P21, our study covers nearly the full trajectory of brain and hippocampal development. To our knowledge, these are the first data examining the impact of maternal n-3 PUFA dietary intervention on brain PUFA and oxylipin profiles from late embryonic life to postnatal weaning, taking into account sex. Overall, our study brings new insights on the effect of maternal dietary n-3 PUFA intake on offspring brain PUFA profiles, altered as early as E17.5, and oxylipin profiles, impacted from birth, in both males and females.

Maternal PUFAs are crucial for fetal brain development and for optimal fetoplacental growth. The placenta plays a central role in shaping the *in utero* environment through gas exchange, nutrient and hormone transport as well as secretion of signaling molecules that regulate both maternal physiology and fetal development. The placenta functions not merely as a passive conduit but actively adapts its transport and signaling in response to maternal and fetal cues, thereby affecting fetal growth trajectories and long-term health outcomes. Disruptions in placental function, due to maternal diet, disease, or suboptimal environmental conditions, can induce metabolic reprogramming and epigenetic changes in the fetus, thereby affecting disease susceptibility later in life (57). In this study, we reported that at E17.5, an n-3 PUFA-deficient diet initiated at E0 strongly impacted both placenta and brain PUFA profiles, as compared to an n-3 PUFA-sufficient diet. Several n-6 PUFA species were significantly increased, while several n-3 PUFAs were significantly decreased in both placenta and brain following exposure to the n-3 PUFA-deficient diet, resulting in an increase of the n-6 to n-3 PUFA ratio in the placenta and brain of both male and female offspring. Our findings also showed that n-6 PUFAs were predominantly present in the placenta, with LA and AA displaying the highest levels in both male and female placentas (around 4% and 17% respectively in n-3 PUFA-sufficient pups; around 8% and 17% respectively in n-3 PUFA-deficient pups). These concentrations were observed regardless of diet. In contrast, n-3 PUFA levels were lower, with DHA being the predominant n-3 PUFA (about 6% in n-3 PUFA-sufficient pups; about 3% in n-3 PUFA-deficient pups), while ALA was detected at the lowest levels (around 0.1% in n-3 PUFA-sufficient pups; around 0.07% in n-3 PUFA-deficient pups). These results are in accordance with our previous study reporting modulation of fatty acid content in the placenta and fetal brain according to the diet content in n-3 PUFAs (25). They are also in accordance with other reports describing such differences in placental fatty acid profiles in mouse (58, 59) and human (60) according to the diet. However, these previous analyses did not distinguish between males and females. Here, we showed that the same PUFA species were affected in both the placenta and brain of male and female pups. Only EPA levels were differentially impacted by sex in the brain of n-3 PUFA-deficient pups on E17.5 (Supplementary Table 2). The majority of LC-PUFAs transported from maternal blood across the placenta to the embryo, including its brain, originate from the maternal liver,

although adipose tissue can also contribute (61). Maternal PUFAs are transferred to the fetus exclusively *via* the placenta, facilitated by specialized fatty acid transporters including FATPs, FAT/CD36, FABPpm as well as Mfsd2a which contributes to the unidirectional transfer of DHA from the mother to the fetus (62, 63). In line with our results, several PUFA transporters are altered in the placenta of pregnant mice depending on dietary n-3 PUFA levels. Indeed, low maternal dietary n-3 PUFA intake downregulates placental genes involved in fatty acid transport, such as Mfsd2a, thereby reducing DHA transfer to the fetal brain and limiting neurotrophic signaling (64). Conversely, a maternal diet adequate in n-3 PUFAs increases Mfsd2a mRNA expression in both the placenta and fetal brain, correlating with higher DHA accumulation in the fetal brain (64). However, pregnant mice fed an n-3 PUFA-deficient diet also exhibit an increase in placental FABP expression, suggesting a compensatory mechanism to limit the decreased n-3 PUFA transfer to the embryonic brain (58, 59). More recently, a specific transcriptional program in the maternal liver, that promotes the esterification of DHA into phospholipids, has been identified as an additional mechanism supplying LC-PUFAs to the embryo, complementing the dietary LC-PUFAs derived from triglycerides and cholesterol esters (65). However, despite the activity of this endogenous synthetic pathway in the maternal liver during pregnancy, a decrease in maternal dietary n-3 PUFAs strongly impacts fetal brain DHA content, as seen in the present study and in previous studies (25, 66). This early decrease in brain DHA, accompanied by a compensatory increase in DPA n-6, starting as soon as 17 days of exposure to the n-3 PUFA-deficient diet, persists throughout postnatal life (19, 47), including adulthood (1, 25), as we previously described in male mice. Here, we further showed that it also occurs in the female brain (see Fig. 2 to 5). Overall, the same PUFA species were affected in the brains of both males and females, with an increase in n-6 PUFAs and a decrease in n-3 PUFAs under the n-3 PUFA-deficient diet. Only a few PUFA levels were significantly influenced by sex during postnatal development under n-3 PUFA deficiency: 20:2n-6 levels were approximately two-fold higher in females than in males at birth and P7, whereas DPA n-6 levels were around 1.4-fold higher in males than in females at birth (see Supplementary Tables 3 and 5).

We also measured oxylipin profiles derived from n-6 (LA, AA) and n-3 (DHA, EPA) PUFAs in the offspring's brain at P0 and P7 and in the hippocampus at P14 and P21 of males and females from mothers

fed a diet low or high in n-3 PUFAs, using a targeted oxylipidome approach, with results presented as Z-scores. Interestingly, oxylipin profiles displayed some age- and sex-related differences, not attributable to dissection duration known to influence brain oxylipin concentrations (67). Our results particularly pinpoint that 9-HODE and 13-HODE, LA-derived oxylipins previously identified in the adult brain (33, 44), were upregulated in the brain at P0 and P7 in both n-3 PUFA-deficient males and females, but not in the hippocampus at P14 and P21. These oxidized LA metabolites are produced enzymatically by LOX enzymes and belong to the OXLAMs, a class of oxidized LA derivatives generated through the enzymatic activity of LOX, CYP450, and soluble epoxide hydrolase (sEH) (68, 69, 70, 72). OXLAMs have also been detected in the developing brain, where they represent the most abundant oxylipins compared to those derived from other PUFAs. This specific pattern is no longer observed in the adult brain (37). Among OXLAMs, 13-HODE is the most abundant, followed by 9-HODE (36, 37, 71). Interestingly, both 9-HODE and 13-HODE have been shown to modulate the morphogenesis of rat cortical neurons *in vitro* in a sex-dependent manner, preferentially affecting dendritic and axonal growth while not affecting synapse formation (37, 39). 13-HODE has also been shown to modulate neurotransmission and synaptic function in the brain (36). In addition, 9-HODE and 13-HODE bind to lipid receptors such as PPARγ and G2A (GPR132), which are expressed on nociceptive neurons (73, 74). GPR132 has also been implicated in the 9-HODE-induced increase in astrocyte migration (75). Notably, recent studies indicate that low plasma levels of 9-HODE predict the severity of brain damage in patients with multiple sclerosis (92). Altogether, these findings suggest that the LA-derived oxylipins 9-HODE and 13-HODE contribute to neuronal network establishment and exert neuroprotective effects, in addition to their known anti-inflammatory and metabolic effects (93). However, whether their increase in the developing brain, linked to dietary increases in LA, is beneficial for neurodevelopment remains unclear, as previous studies have reported that LA-rich diets impair developmental brain wiring (19). This question is particularly relevant given that the LA content of infant formulas ranges from 9% to 20% of total fatty acids (76). Our results also revealed that dietary n-3 PUFA deficiency modulated lipoxin A4 (LxA4) levels in a sex-dependent manner. In males, LxA4 was increased in the brain at birth but decreased in the hippocampus at P21, whereas no significant changes were measured

in females. LxA4 is an AA-derived oxylipin involved in the resolution of inflammation, including in the brain (77), and has also been suggested to act as a signaling molecule regulating axonal and dendritic outgrowth *via* the formyl-peptide receptor 2 (FPR2) (78). On the other hand, several AA-derived metabolites were increased in the developing male brain, but not in females, particularly at birth. The bioactive species upregulated by maternal dietary n-3 PUFA deficiency included epoxyeicosatrienoic acids (EpETrEs), generated by CYP450 epoxygenases, and hydroxyeicosatetraenoic acids (HETEs), produced by CYP450 hydroxylases and LOX enzymes. HETEs are well known for their inflammatory properties and have been associated with brain disease severity and neurodegenerative processes (79), while EpETrEs are recognized for their anti-inflammatory and neuroprotective effects (80, 81). However, the presence and role of these metabolites in the developing brain has been poorly addressed. We previously reported that 12-HETE, which is increased in microglia of the developing male brain at weaning under a maternal n-3 PUFA-deficiency, impairs hippocampal wiring and memory by altering microglial phagocytosis (19). Furthermore, it was shown that EpETrEs, are produced endogenously by embryonic cortical neurons and that they stimulate axonal growth (82). Additional studies are necessary to further understand the cellular sources and functions of HETEs and EpETrEs, which are increased in the developing male brain by maternal n-3 PUFA-deficient dietary intervention. We also found that DHA-derived metabolites 17-HDoHE and 14-HDoHE were reduced in the n-3 PUFA-deficient brain at P0 and P7 in a sex-dependent manner, being reduced exclusively in females at P0 and exclusively in males at P7. In the hippocampus at P14 and P21, these hydroxydocosahexaenoic acids were decreased in both male and female n-3 PUFA-deficient mice. 14- and 17-HDoHE are derived from DHA *via* the 12- and 15-LOX pathways and have been reported to increase in the brain of adult mice and rats fed a diet rich in n-3 LC-PUFAs, particularly EPA and DHA (33, 83, 84). This positive association between these hydroxydocosahexaenoic acids and dietary n-3 PUFA levels is consistent with our findings in the developing brain. 17-HDoHE and 14-HDoHE are synthesized from their hydroperoxy precursors 17-HpDoHE and 14-HpDoHE, respectively. HpDoHEs are also converted to several SPMs, notably D-series resolvins and protectins as well as maresins, which have been described as pro-resolving in inflammation (1, 28) but are rarely detected in the brain (31). However, whether

fluctuations in HDoHE levels reflect neuroinflammatory conditions remains to be determined. These metabolites, along with other AA-derived oxylipins, are also detected in human cerebrospinal fluid and fluctuate in response to neuroinflammatory events such as surgery (85). However, to our knowledge, the relationship between oxylipin profiles and dietary PUFA intake in humans remains poorly investigated. Interestingly, during pregnancy, DHA-derived oxylipin levels are increased in the blood of women receiving n-3 LC-PUFA supplementation (86), as well as in the breast milk of lactating women consuming a DHA-rich diet (87). However, the impact on the offspring's oxylipin profile remains to be determined. Beyond our own findings, several studies support the notion that sex modulates oxylipin profiles in the brain. In rats, the large majority of oxylipins examined were higher in males than in females (88). Specifically, approximately 25% of the oxylipins identified showed a sex difference: of the 17 oxylipins concerned, 15 were higher in males and were derived from LA, DGLA, AA, ALA and DHA, whereas the two remaining were AA-derived and higher in females. These sex differences were largely unaffected by dietary manipulation of n-6 and n-3 PUFA, suggesting tight regulation of brain oxylipin levels independent of dietary intake. Whereas n-6 PUFA-derived oxylipins were minimally affected by the diets, effects on n-3 PUFA-derived oxylipins were driven primarily by n-3 PUFA-enriched diets and were most pronounced for EPA-derived oxylipins, which nonetheless remained higher in males than in females (88). In a mouse model of Niemann–Pick type C disease, only females exhibited a significant increase in free pro-resolving fatty acid epoxides from the CYP450 pathway in the cerebellum (89). Moreover, esterified mono- and dihydroxy lipid mediators derived from the LOX and sEH pathways were mainly increased in NPC females, suggesting enhanced sequestration of pro-inflammatory LOX and sEH metabolites (89). These findings support sex-specific adaptations in inflammation resolution pathways in NPC, with females exhibiting distinct inflammatory responses that may drive sex-related differences in disease pathogenesis (89). In addition, DPA n-6-derived oxylipins were not quantified in the present study, as the oxylipin panel used did not include them. Previous studies have reported that DPA n-6-derived oxylipins possess anti-inflammatory properties (90). However, to our knowledge, these oxylipins have not yet been detected in the brain, despite the substantial levels of DPA n-6 and their variations in response to n-3 PUFA-deficient diet consumption

in both adult and developing brains. Further studies are needed to measure these oxylipins and determine whether their levels vary across neurodevelopmental stages.

A limitation of this study is that the n-3 PUFA-deficient diet corresponds to a high LA/ALA dietary ratio, resulting in an elevated n-6/n-3 PUFA ratio in all tissues studied, which does not allow us to determine the exact dietary PUFA species involved in the observed effects. Of note, the experimental diets differed not only in their n-3 and n-6 PUFA contents but also in their SFA and MUFA compositions, as shown in Table 2. Since some SFAs and MUFAs are significantly increased in the brain of pups fed the n-3 PUFA-deficient diet (see Supplementary Tables) and given that some of these fatty acid species regulate enzymes involved in oxylipin synthesis (30), they may contribute to the observed changes in the brain oxylipin profile. In addition, only free (non-esterified) oxylipins were quantified in the present study. Since the majority of oxylipins in brain tissue exist in esterified form within membrane phospholipids (91), the results may differ depending on the oxylipin pool analyzed. Indeed, acute hypercapnia/ischemia has been shown to alter oxylipin concentrations differentially depending on whether the free or esterified fraction is considered (91). Furthermore, in a rat model of increasing dietary LA intake, total oxylipin concentrations (including both free and esterified fractions) in the cerebral cortex did not change significantly, whereas significant changes were observed specifically in the free fraction (71). Together, these data suggest a differential regulation of bioactive oxylipin availability in the brain depending on the dietary context. Future studies should therefore consider both the free and esterified fractions to provide a more complete characterization of the brain oxylipin profile under conditions of maternal n-3 PUFA deficiency.

In conclusion, our data indicate that maternal n-3 PUFA deficiency, introduced at mating, affects brain PUFA levels in a broadly similar manner in male and female offspring, with alterations occurring as early as E17.5. In contrast, the metabolism of these PUFAs into oxylipins appears to be differentially influenced by sex under n-3 PUFA-deficient conditions, particularly in early postnatal life. Together, these findings suggest that adequate maternal n-3 PUFA intake during the perinatal period helps maintain favorable PUFA

and oxylipin profiles, which may be relevant for fetal and postnatal brain development. However, additional studies are needed to further understand whether sex-specific changes in oxylipins contribute to neurodevelopmental outcomes.

Data availability:

All data are contained within the manuscript.

Acknowledgments:

We thank CIRCE, the animal housing facilities of INRAE UMR1286 NutriNeuro, funded by INRAE, GPR BRAIN_2030, and the Université de Bordeaux. We are grateful to all the zootechnicians of UMR1286 NutriNeuro for breeding our mouse colonies. We thank the MetaToul-MetaboHUB Lipidomic platform for oxylipin quantification and analysis, and the CSGA laboratory for fatty acid measurement and analysis.

Author contributions:

FM, MR, MM, LM, AA, AS, SG generated the data; FM, SG, NA, SL analyzed the data together with the other authors; MDM, NA, CJ and RPB critically contributed to the discussion; SL conceptualized all studies and supervised the work; SL and FM wrote the manuscript and all authors edited and approved the final version of the manuscript.

Declaration of interests:

The authors declare no competing interests.

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Figure 1: Placental and brain PUFA profiles in male and female embryos: (A-C) Placental levels of n-6 PUFAs (A), n-3 PUFAs (B) and n-6/n-3 PUFA ratio (C) in male embryos. (D-F) Placental levels of n-6 PUFAs (D), n-3 PUFAs (E) and n-6/n-3 PUFA ratio (F) in female embryos. (G-I) Brain levels of n-6 PUFAs (G), n-3 PUFAs (H) and n-6/n-3 PUFA ratio (I) in male embryos. (J-L) Brain levels of n-6 PUFAs (J), n-3 PUFAs (K) and n-6/n-3 PUFA ratio (L) in female embryos. Data are represented as mean ± SEM (% of total FAMEs and DMAs). N = 6 mice/group. Statistical comparisons were performed for each fatty acid using a 2-way ANOVA (sex x diet), followed by Fisher's LSD test in case of significant interaction. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure 2: Brain PUFA and oxylipin profiles in the brain of male and female offspring at birth: (A-C) Brain levels of n-6 PUFAs (A), n-3 PUFAs (B) and n-6/n-3 PUFA ratio (C) in male offspring. (D-F) Brain levels of n-6 PUFAs (D), n-3 PUFAs (E) and n-6/n-3 PUFA ratio (F) in female offspring. Data are represented as mean ± SEM (% of total FAMEs and DMAs). N = 3-5 mice/group. (G, H) Heatmaps of oxylipin profiles in the brain of male (G) and female (H) offspring expressed as Z-scores. Rows represent individual oxylipins and columns individual samples. Oxylipins are annotated by their PUFA precursor. Color scale reflects relative abundance (red = higher; blue = lower). Asterisks indicate oxylipins significantly different between groups. Statistical comparisons were performed for each fatty acid and each oxylipin using a 2-way ANOVA (sex x diet), followed by Fisher's LSD test in case of significant interaction. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure 3: Brain PUFA and oxylipin profiles in the brain of male and female offspring at P7: (A-C) Brain levels of n-6 PUFAs (A), n-3 PUFAs (B) and n-6/n-3 PUFA ratio (C) in male offspring. (D-F) Brain levels of n-6 PUFAs (D), n-3 PUFAs (E) and n-6/n-3 PUFA ratio (F) in female offspring. Data are represented as mean ± SEM (% of total FAMEs and DMAs). N = 5 mice/group. (G, H) Heatmaps of oxylipin profiles in the brain of male (G) and female (H) offspring expressed as Z-scores. Rows represent individual oxylipins and columns individual samples. Oxylipins are annotated by their PUFA precursor. Color scale reflects relative abundance (red = higher; blue = lower). Asterisks indicate oxylipins significantly different between groups. Statistical comparisons were performed for each fatty acid and each oxylipin using a 2-way ANOVA (sex x diet), followed by Fisher's LSD test in case of significant interaction. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure 4: Hippocampal PUFA and oxylipin profiles in the brain of male and female offspring at P14: (A-C) Brain levels of n-6 PUFAs (A), n-3 PUFAs (B) and n-6/n-3 PUFA ratio (C) in male offspring. (D-F) Brain levels of n-6 PUFAs (D), n-3 PUFAs (E) and n-6/n-3 PUFA ratio (F) in female offspring. Data are represented as mean ± SEM (% of total FAMEs and DMAs). N = 5 mice/group. (G, H) Heatmaps of oxylipin profiles in the hippocampus of male (G) and female (H) offspring expressed as Z-scores. Rows represent individual oxylipins and columns individual samples. Oxylipins are annotated by their PUFA precursor. Color scale reflects relative abundance (red = higher; blue = lower). Asterisks indicate oxylipins significantly different between groups. Statistical comparisons were performed for each fatty acid and each oxylipin using a 2-way ANOVA (sex x diet), followed by Fisher's LSD test in case of significant interaction. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure 5: Hippocampal PUFA and oxylipin profiles in the brain of male and female offspring at P21: (A-C) Brain levels of n-6 PUFAs (A), n-3 PUFAs (B) and n-6/n-3 PUFA ratio (C) in male offspring. (D-F) Brain levels of n-6 PUFAs (D), n-3 PUFAs (E) and n-6/n-3 PUFA ratio (F) in female offspring. Data are represented as mean ± SEM (% of total FAMEs and DMAs). N = 5 mice/group. (G, H) Heatmaps of oxylipin profiles in the hippocampus of male (G) and female (H) offspring expressed as Z-scores. Rows represent individual oxylipins and columns individual samples. Oxylipins are annotated by their PUFA precursor. Color scale reflects relative abundance (red = higher; blue = lower). Asterisks indicate oxylipins significantly different between groups. Statistical comparisons were performed for each fatty acid and each oxylipin using a 2-way ANOVA (sex x diet), followed by Fisher's LSD test in case of significant interaction. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.