**Prénom, Nom**

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**Titre**

ROLE DES ACIDES GRAS POLYINSATURES DANS LE DEVELOPPEMENT CEREBRAL NORMAL ET PATHOLOGIQUE

**Abstract**
**POLYUNSATURATED FATTY ACIDS ROLE IN NORMAL AND PATHOLOGICAL BRAIN**

**DEVELOPMENT**

The perinatal dietary intake in n-3 and n-6 polyunsaturated fatty acids (PUFAs n-3 and n-6), also known as ‘omega-3’ and ‘omega-6’, is essential for brain development. As these lipids cannot be *de novo* synthesized by the body, they must be provided by the diet according to a ratio of one n-3 PUFA for four n-6 PUFAs. Western diet has dramatically evolved over the past 70 years, towards excessive omega-6 consumption and reduction in omega-3 intake. This correlated with an increasing number of children with neurodevelopmental pathologies. However, the link between perinatal nutrition and neurodevelopment remains poorly understood.

The main objective of my thesis was to study the cellular and molecular mechanisms by which a reduction in perinatal n-3 PUFA dietary intake alters neural networks shaping, focusing on the interactions between glial cells (namely microglia and oligodendrocytes) and

neurons.

Our results show that perinatal n-3 PUFA deficiency leads to 1) an alteration of microglial and oligodendrocytes functions during brain development; 2) an increase in microglia-mediated dendritic spines pruning and deficits in myelination process; 3) the establishment of dysfunctional neural networks in the hippocampus and prefrontal cortex; 4) deficits in learning, sociability and occurrence of anxiety behaviors.

Moreover, n-3 PUFA deficiency during the perinatal period exacerbates the deleterious effects of a prenatal maternal immune activation (MIA). Low n-3 PUFA intake 1) increases the maternal and fetal inflammatory response to MIA; 2) increases the duration and extent of MIA effects on neuronal morphology and microglia-neuron interactions; 3) alters the inflammatory reactivity of intestinal lymphocytes, that persists at adulthood 4) induces memory deficits and hyperactivity in offspring in adulthood.

Overall, the present work specified some of the mechanisms by which n-3 PUFA deficiency affects the developing brain by highlighting its detrimental effect on microglia andoligodendrocytes function and showing how its sensitizes the brain to other

developmental insults.

**KEY WORDS:** PUFA, BRAIN DEVELOPMENT, MICROGLIA, OLIGODENDROCYTE,

NEURAL NETWORKS, BEHAVIOR, PRENATAL INFLAMMATION.

**Jury**

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**Lieu et date de la soutenance**

ENSCBP (Campus Talence) Auditorium du bâtiment B - 14 Septembre 2018 à 14h

**Publications**

1- Labrousse VF\*, **Leyrolle Q\***, Delgado I, Delpech JC, Madore C, Amadieu C, Aubert A, De Smedt-Peyrusse V, Grégoire S, Bretillon L, Coutureau E, Joffre C, Gressens P, Nadjar A, Layé S (2018). Dietary omega-3 deficiency exacerbates inflammation and reveals spatial memory deficits in mice exposed to lipopolysaccharide during gestation. *Brain Behavior and Immunity.* Jun 4. doi: 10.1016/j.bbi.2018.06.004.

2- Nadjar A, **Leyrolle Q**, Joffre C, Layé S (2017). Bioactive lipids as new class of microglial modulators: when nutrition meets neuroimmunology**.** *Prog Neuropsychopharmacol Biol Psychiatry*. Oct 3;79(Pt A):19-26. doi: 10.1016/j.pnpbp.2016.07.004. Epub 2016 Jul 5.

3- Madore C\*, **Leyrolle Q\***, Lacabanne C, Benmamar-Badel A, Joffre C, Nadjar A, Layé S (2016). Crosstalk between gut and microglia in ASD: the role of n-3 PUFAs. *Neural Plast.*2016:3597209. Epub 2016 Oct 20. Review.

4- Abiega O, Beccari S, Diaz-Aparicio I, Sánchez-Zafra V, Deudero JP, Brewster AL, Anderson AE, Nadjar A, **Leyrolle Q**, Layé S, Zaldumbide L, Galbarriatu L, Marinas A, Vivanco M, Maletic-Savatic M, Matute C, Encinas JM, Sierra A (2016). Microglial phagocytosis coupling dictates apoptosis readout in the healthy and epileptic brain. *Plos Biology*. May 26;14(5):e1002466. doi: 10.1371/journal.pbio.1002466. eCollection 2016 May.

5- **Leyrolle Q**, Layé S, Nadjar A (2016). N-3 PUFAs and neuroinflammatory processes in cognitive disorders. *Oilseeds & fats Crops and Lipids.* doi: 10.1051/ocl/2015064. Review.

**Book Chapter:**

6- Nadjar A, **Leyrolle Q**, Joffre C, Layé S (2017). Anti-inflammatory properties of dietary n-3 polyunsaturated fatty acids protect against cognitive decline in aging and neurodegenerative diseases. Book: Role of the Mediterranean Diet in the brain and neurodegenerative diseases.

**Soumis**

7- Madore C£, **Leyrolle Q**£, Morel L£, Lacabanne C, Bosch-Bouju C, Greenhalgh AD, Bourel J, Thomazeau A, Delpech JC, Hopperton KE, Beccari S, Sere A, Aubert A, De Smedt-Peyrusse V, Lecours C, Bisht K, Fourgeaud L, Gregoire S, Bretillon L, Grant NJ, Badaut J, Gressens P, Sierra A, Butovsky O, Tremblay ME, Bazinet RP, Joffre C, Nadjar A\*, Layé S\*. Polyunsaturated fatty acids tune microglial shaping of neuronal circuits in the developing brain (£ co-first authors, \* co-last authors).