**Thèse en co-tutelle Université de Bordeaux-McGill University**

**Sous la co-direction de Sophie Layé (NutriNeuro, Bordeaux) et Giamal Luheshi (Department of Psychiatry, McGill, Montréal)**

**Chloé Lacabanne**

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**Titre :** Inflammation and immune-mediated neurobehavioral alterations: a critical role for microglia

**Abstract :**

Recent research on microglia has uncovered a multitude of activities that extends the role of these cells well beyond their traditional function as immune sentinels. The most prominent of these newly described activities is an intricate role in neuronal network remodeling notably upon environmental challenge or during brain development, the disruption of which can result in long lasting consequences relevant to several psychopathologies. We sought, in the current thesis, to identify some of the mechanisms involved. First, we targeted the immune function of microglia, based on our previous findings linking systemic immunogenic challenge with lipopolysaccharide (LPS) in mice with the development of despair-like behaviour/depression. These studies were conducted in adult mice in which phagocytic microglia were depleted using a single injection of liposomal clodronate in the CA3 region of the hippocampus. Clodronate-mediated depletion attenuated most of the LPS-induced cytokine expression in the hippocampus and -depressive-like symptoms, providing a snapshot of the role of inflammation in the development of brain dysfunction mediated by microglia. In subsequent studies, we investigated the role of microglia activity in prenatal LPS-induced neurodevelopmental disorders. Our results demonstrated maternal LPS administration reduced the percentage of mature microglial population in the brain of embryos and impaired the offspring’s neonatal as well as adult social and repetitive behavior and memory, with a clear divergence along sex lines in adulthood. We then identified the role played by pro-inflammatory cytokines, particularly IL-1 in LPS-induced impairment of microglia in the brain of embryos in complex behaviours. In conclusion, the work presented in this thesis shows the role of microglia in mediating short- and long-term LPS-induced behavioural deficits. Notably, our results show that depletion of phagocytic microglia can attenuate LPS-induced despair-like behaviours while LPS-induced inflammation during embryonic development leads to the exhibition of sexually dimorphic traits and disrupted microglial development for which IL-1 appears to be the primary mediator.

**Jury**

Pr Pierre Gressens, Directeur de Recherche Inserm, Paris, France

Pr Lalit Srivastava, Full Professor, McGill University, Montréal, Canada

Dr Steve Lacroix, Research Director, Université Laval, Québec, Canada

Dr Thierry Alquier, Research Director, Université de Montréal, Montréal, Canada

Dr David Gosselin, Research Director, Université Laval, Québec, Canada

Dr Sophie Layé, Directrice de Recherche Inra, Bordeaux, France

Pr Giamal Luheshi, Full professor, McGill University, Montréal, Canada

Pr Josephine Nalbantoglu, Full Professor, McGill University, Montréal, Canada

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**Publications**

**Neuroinflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega 3, and Microbiota**

Charlotte Madore, Quentin Leyrolle, **Chloé Lacabanne**, Anouk Benmamar--Badel, Corinne Joffre, Agnès Nadjar and Sophie Layé

*(Published. Neural Plasticity, 2016 October • 2016:3597209)*

**Microglial Activation Enhances Associative Taste Memory through Purinergic Modulation of Glutamatergic Neurotransmission**

Jean-Christophe Delpech, Nicolas Saucisse, Shauna L. Parkes, **Chloé Lacabanne**, Agnès Aubert, Fabrice Casenave, Etienne Coutureau, Nathalie Sans, Sophie Layé, Guillaume Ferreira\* and Agnès Nadjar\*

*(Published. The journal of Neuroscience, 2015 February • 35(7):3022–3033)*

**Dietary n-3 PUFAs Deficiency Increases Vulnerability to Inflammation-Induced Spatial Memory Impairment**

Jean-Christophe Delpech, Aurore Thomazeau, Charlotte Madore, Clémentine Bosch-Bouju, Thomas Larrieu, **Chloé Lacabanne**, Julie Remus-Borel, Agnès Aubert, Corine Joffre, Agnès Nadjar and Sophie Layé

*(Published. Neuropsychopharmacology, 2015 November • 40(12):2774-87)*

**Interleukin-1β mediates the effects of prenatal LPS induced behavioral anomalies in the offspring through modulating microglia**

**Chloé Lacabanne**, Lourdes Fernandez de Cossio, Sophie Layé\* and Giamal N. Luheshi\*

*(In preparation)*