2018 NutriNeuro annual meeting

January 16th

9h30-10h50 session 1 From metabolism disorders to brain dysfunction
Chair: Lydie, Quentin, Roman, Hugo

Lison Huet: Role of impairment of Tryptophan metabolism in the pathophysiology of depressive symptoms in obese patients.

Eugene Cameron: Role of glucocorticoids in cognitive alterations in type-I diabetes.

Ines Delgado: Diet and stress-induced alterations in gut microbiota: relationship with metabolic health and depressive risk in obesity.

Camila de Avila: Sex-specific effect of rln3 on food intake and effect of estradiol levels on brain rln3/rxfp3 system in rats.

10h50-11h10 coffee

11h10-12h30 session 2 Nutrition and neuropathology
Chair: Fabien, Mathieu, Andrea, Ines

Pierre Cardinal: The role of brain IDO in the resistance to Escitalopram treatment

Essi Biyong: Effect of vitamin A supplementation in the prevention of Alzheimer's disease modelled in mice.

Mathilde Chataigner: Impact of marine-derived products on age-related cognitive decline prevention.

Andrew Greenhalgh: Macrophage control of Microglia during brain injury.

12h30 - 13h30 lunch

13h30-13h45 2018 Master 2 presentation

13h45-15h00 session 3 Nutrition and brain circuits – part 1
Chair: Pierre, Essi, Mathilde, Andrew

Lydie Morel: Role of the microglia in synaptic pruning during development and effects of the PUFAs as immunomodulators

Quentin Leyrolle: Early-life PUFAs modulate myelination during development.

Roman Walle: Interaction between membrane lipids and the functionality of accumbal medium spiny neuron: impact on mesolimbic dopaminergic transmission.

Hugo Martin: Unravelling the role of brain insulin action in diabetes-related depression.

15h15-16h15 session 4 Nutrition and brain circuits – part 2
Chair: Lison, Eugene, Camila

Fabien Ducrocq: Modulation of mesolimbic dopamine transmission by brain lipid composition: consequences on reward processing.

Mathieu Di Miceli: Role of DHEA, a DHA-derived endocannabinoid, in synaptic plasticity.

Andrea Contini: Impact of ω-3 long-chain polyunsaturated fatty acids on the functionality of the mesocorticolimbic dopaminergic pathway.

ABSTRACTS

1.1 Role of impairment of Tryptophan metabolism in the pathophysiology of depressive symptoms in obese patients

Lison Huet [ab], Ines Delgado[ab], Sandra Dexpert[ab], Cédric Beau[cd], Patrick Ledaguenel[cd], Agnès Aubert[ab], Damien Forestier[cd], Eric Magne[cd], and Lucile Capuron[ab].

a INRA, Nutrition and Integrative Neurobiology (NutriNeuro), UMR 1286, 33076 Bordeaux, France
b Univ Bordeaux, Nutrition and Integrative Neurobiology (NutriNeuro), UMR 1286, F-33076 Bordeaux, France
c Service de Chirurgie Digestive et Pariétale, Clinique Tivoli, F-33000 Bordeaux, France
d Clinique Jean Villar, F-33520 Bruges, France

Obesity represents a public health problem that is reaching pandemic proportions worldwide. In addition to being associated with an increase risk of chronic diseases such as cardiovascular pathologies, obesity is also associated with neuropsychiatric comorbidities including depression. Recent data suggest that inflammation may contribute to this effect. Chronic inflammation is a fundamental characteristic of obesity and it is now well established that inflammatory processes play a critical role in the pathophysiology of depression. This effect may rely on the ability of pro-inflammatory cytokines to modulate the activity of neurotransmitter systems, including the serotonin system, which is a key player in mood regulation. In particular, cytokines activate the enzyme Indoleamine 2,3 dioxygenase (IDO), which is responsible for the degradation of tryptophan (TRP), the primary precursor of serotonin, within the kynurenine pathway leading to the production of neurotoxic metabolites including 3-hydroxykynurenine (3-HK) and quinolinic acid (QA). Albeit the activation of this pathway has been shown to contribute to depressive symptoms in patients with chronic inflammation and/or in depressed patients, its involvement in the pathophysiology of comorbid depression in obesity remains to be determined.
The aim of this work was to determine the role of inflammation-driven alterations in TRP metabolism in depressive symptoms in patients with severe obesity. For this purpose, a sample of 80 patients with severe obesity and 20 lean control subjects were recruited. Depressive symptoms were assessed using the Mini International Neuropsychiatric Interview (MINI) and the Montgomery-Asberg Depression Rating Scale (MADRS). Fasting blood samples were collected for the measurement of inflammatory markers and metabolites of the kynurenine pathway.
Results indicate significantly higher concentrations of inflammatory markers (CRP, IL-6) together with increased concentrations of metabolites of the kynurenine pathway in obese patients compared to healthy controls. Interestingly, obese patients with higher levels of inflammation (CRP>5mg/l) were those who exhibited the highest levels of kynurenine metabolites. Whereas, TRP levels remained comparable across the two groups, kynurenine levels and the ratio of kynurenine/TRP
were higher in obese patients, indicative of an increased degradation of TRP along the kynurenine pathway in obesity. Depressive symptoms were associated with reduced TRP levels in obese subjects. The association with neurotoxic metabolites is still under investigation.

1.2 Role of glucocorticoids in cognitive alterations in type-I diabetes.

Eugene Cameron

Le diabète de type 1 est en augmentation constante chez les enfants. Il est associé à une plus grande fréquence de la dépression et de l'anxiété et à des troubles de l'apprentissage et de la mémoire. Des modifications d'activité de l'axe corticotrope et des volumes cérébraux, notamment de l'hippocampe, ont été également rapportées.

Nous faisons l'hypothèse que le diabète de type 1 de l'enfant peut être associé à une hyperactivité de l'axe corticotrope *via* une augmentation de la biodisponibilité locale des hormones glucocorticoïdes. Nous pensons

que cette hyperactivité pourrait contribuer au développement de troubles cérébraux et participer aux altérations tissulaires de l'hippocampe constatés en cas de diabète

Le diabète de type 1 dont la fréquence augmente chez les enfants, est globalement associé à une hyperactivité délétère de l'axe corticotrope (AC). Parmi les causes possibles de celle-ci, on trouve des dérégulations de la biodisponibilité des GC *via* les enzymes 11β-hydroxystéroïde-deshydrogénases (HSD1&2) responsables des désactivation/réactivation réversibles des GC. Le diabète, en modifiant l'activité des HSD dans les tissus où elles s'expriment, induirait des anomalies locales de concentration de GC qui seraient responsables d'une partie des conséquences du diabète. Ces anomalies pourraient en effet contribuer au développement de troubles cognitifs & mnésiques et aux altérations tissulaires de l'hippocampe constatées en cas de diabète.

Le projet propose l'exploration des mécanismes biologiques responsables de potentiels désordres cérébraux induits par le diabète et consistera à ; l'analyse des résultats d'un étude clinique, approfondir les hypothèses élaborée chez l'humain et l'animal par des études sur un modèle de rats diabétiques juvéniles, et explorer *in vitro* les effets de l'insuline et du glucose sur l'activité des 11β-hydroxystéroïde-deshydrogénases dans des cellules d'origine cérébrales et périphériques.

1.3 Diet and stress-induced alterations in gut microbiota: relationship with metabolic health and depressive risk in obesity

Ines Delgado

Chronic psychological stress and unbalanced diets in modern societies represent potent risk factors for the development of obesity and related comorbidities including depression. Risk of obesity-related depressive comorbidity was suggested to be reduced in subjects with metabolically healthy obesity (MHO) compared to individuals with metabolically unhealthy obesity (MUHO). The gut microbiota, which is modulated by diet and stress, is thought to underlie those obesity phenotypes and disease risk. However, this has not been systemically assessed in experimental studies. The aims of this work are 1) to study the effects of diet and related-microbiota composition on stress reactivity and neuropsychiatric risk in a group of healthy subjects (Ambrosiac Study); and 2) to identify microbial and metabolic biomarkers of metabolic health and assess their association with depressive symptomatology in obese subjects (HealthMark Study). In the Ambrosiac Study, psychological stress will be induced by the Trier Social Stress Test in healthy volunteers stratified on the basis of their diet habits (healthy *versus* unhealthy) as assessed by the PNNS. Salivary cortisol levels will be collected to measure stress reactivity and fecal samples to analyze gut microbiota composition. In the HealthMark Study, severely obese patients awaiting bariatric surgery will be recruited on the basis of their metabolic health (MHO *versus* MUHO). MUHO is defined as obesity with at least two metabolic alterations, including low HDL cholesterol, high fasting glucose, hypertriglyceridemia, high blood pressure and increased systemic inflammation, according to the Adult-Treatment-Panel-III. Serum and urine samples will be collected to assess metabolic and inflammatory markers and fecal samples to analyze microbiota composition and function. Depressive symptoms will be measured through a comprehensive neuropsychiatric evaluation. All measurements will occur before and six-months after bariatric surgery.
This work will allow to decipher the role of the gut microbiota in obesity-related metabolic health and neuropsychiatric risk.

1.4 SEX-SPECIFIC EFFECT OF RLN3 ON FOOD INTAKE AND EFFECT OF ESTRADIOL LEVELS ON BRAIN RLN3/RXFP3 SYSTEM IN RATS.

de Ávila Camila1, Calvez Juliane1, Lenglos Christophe1, Timofeeva Elena1, Cifani Carlo2.

1 CRIUCPQ, Department of Psychiatry and Neuroscience, Université Laval, Québec - Canada. 2 School of Pharmacy, University of Camerino, Italy.

Relaxin-3 (RLN3) is a neuropeptide expressed in the nucleus incertus (NI) of the brainstem. RLN3 binds to its cognate receptor relaxin-like family peptide receptor 3 (RXFP3). Previously we demonstrated that, the intracerebroventricular injection of RLN3 increased chow intake in satiated rats and this effect was stronger in

females. The present study was designed to investigate possible role of estrogen in higher sensitivity to RLN3 orexigenic effects in female rats. We first confirmed the well-known oscillation of food intake across the estrous cycle and the effects of ovariectomy (OVX) and estrogen replacement (OVX+E) on feeding. We used in-situ hybridization to assess the expression levels of RLN3 and RXFP3 mRNAs in the NI and parvocellular hypothalamic nucleus (PVN) of female rats across estrous cycle and in OVX and OVX+E as well as in the brain of male. Expression of RLN3 mRNA was significantly decreased in female during proestrus and estrus phases compared to diestrus suggesting the increased levels of estradiol suppress expression of RLN3 and thus may regulate food intake across estrous cycle. The subcutaneous injection of estradiol in OVX rats decreased expression of RLN3 in the NI. Detection of expression of RXFP3 in the parvocellular hypothalamic nucleus (PVN) revealed higher levels of expression of RXFP3 in female compared to male. Across estrous cycle, expression of RXFP3 decreased at diestrus and increased at proestrus, estrus, and metestrus. These results suggest RLN3 may mediate the effects of estradiol on food intake in female rats.

2.1 The role of brain IDO in the resistance to Escitalopram treatment

P. Cardinal, Monchaux C., Lasselin J., Vancassel S., Castanon N., Capuron L.

Depression is a serious disorder in our modern societies, reaching lifetime prevalence as high as 21% of the general population in some developped countries. Despite a plethora of approved medications, patients with major depressive disorder continue to suffer from lack of remission or response from currently available antidepressants (AD). Thus, the need for new treatments is critical.

Among the co-morbidities associated with resistance to AD drugs is chronic low-grade inflammation, a state of constant activation of the peripheral immune system. It has been previously shown that this leads to the activation of peripheral and brain indoleamine 2,3 dioxygenase (IDO), shifting the tryptophan metabolism from serotonin synthesis to the kynurenine pathway, which is thought to play a role in the resistance to AD therapy.

Using the acute model of depression-induced inflammation with the administration of lipopolysaccharide (LPS), we will evaluate the role of IDO in the resistance to AD treatment. By administering an AD concomitantly (or not) with 1 methyl tryptophan (1-MT), an inhibitor of IDO, after LPS administration, and evaluate depressive behavior with different behavioral paradigms such as the Forced swim test or Splash test. Our goal is to reverse the resistance to AD by LPS-induced inflammation with 1-MT. Immunological status will be evaluated, as well as inflammatory state in brain regions of interest such as the hippocampus or the prefrontal cortex.

2.2 Effect of vitamin A supplementation in the prevention of Alzheimer's disease modelled in mice.

E. Biyong; F. Dumetz; S. Alfos; C. Bosch-Bouju; V. Pallet

Alzheimer's disease (AD) etiology is still not fully understood but is associated with specific histological lesions: extracellular aggregates of beta amyloids (the amyloid pathology) and intracellular accumulation of neurofibrillary tangles (the tau pathology). Both phenomenons lead to neuronal damage and death causing cognitive impairments, especially learning and memory processes.

Body of evidence shows both aging and the onset of AD is associated with a downregulation of retinoid signaling at peripheral and central levels. The ligand-activated retinoic acid receptors (RAR) control the expression of genes implicated in the clearance of beta amyloid aggregates, as well as in the phosphorylation of Tau. Thus, a decrease of retinoic acid synthesis participates in the enhancement of the amyloidogenic process. Moreover, an increase of hypothalamic pituitary adrenal (HPA) axis activity has been described in Alzheimer patients and animal models, which is also admitted to be associated with the retinoid signaling downregulation.

As current therapeutics have a limited efficacy, it is of top priority to better understand the mechanisms underlying the development of AD and to find strategies to prevent their occurrence, especially through the action of nutritionnal vitamin A, a crucial molecule for the maintenance of learning and memory processes. Indeed, nutrition is a promising and non-invasive way to target a wider population being at risk to develop the disease.

The goal of this project is to better understand the ability of nutritional vitamin A to avoid neurobiological, endocrine and cognitive disorders specific to AD, on a mouse model induced by a single i.c.v. injection of beta amyloid peptide. We will focus on molecular aspects related to HPA axis activity, on pathways associated with the activation of RARs, and on the specific pathological features underlying AD.

2.3 Impact of marine-derived products on age-related cognitive decline prevention.
Mathilde C.

Normal brain aging leads to a decline of the cognitive functions which can result in the development of neurodegenerative pathologies. It is associated with well-defined physiopathological characteristics such as the decrease in the level of docosahexaenoic acid (DHA), the induction of low-grade chronic inflammation, as well as the modulation of neurogenesis due to mitochondrial dysfunctions leading to increased oxidative stress. Polyunsaturated long chain fatty acids (PUFA-LC) derived from n-3, and in particular DHA, have immunomodulatory properties reducing the production of inflammatory cytokines, thus representing a preferred prevention for the delay of cognitive decline. Bioactive peptides found in fatty fishes have a number of biological properties including anxiolytic, anti-inflammatory and antioxidant activities are also promising in term of prevention of cognitive decline. Therefore, due to their individual or synergistic effects, the aim of this project is to study mechanisms by which DHA, phospholipids and the bioactive peptides can potentially protect against aged-related cognitive alterations.
Several experimental approaches will be used. The first one will be realized *in vitro* to evaluate the neuroprotective and anti-inflammatory impact on neuronal (SH-SY5Y) and microglial (BV2) cultures. Then effects on cognitive abilities, longevity and aging biomarkers of aged-mice (C57Bl/6J) will be investigated. These approaches will be followed by a clinical study to do the synergistic effect's proof of concept of their efficiency in human.

2.4 Macrophage control of Microglia during brain injury
Andrew Greenhalgh

Microglia are the resident immune cell of the brain and a critical component of CNS injury and disease. It is currently controversial whether microglial responses are beneficial or detrimental to the brain. To this end, I propose a new endogenous mechanism of control over microglia, performed by a distinct immune cell population, infiltrating monocyte-derived macrophages.

Our previous data suggests that invading macrophages act as a cellular switch to control microglial responses in a context-dependent manner, and that lipids and their derivatives may mediate this control.

Here, I will investigate macrophage-lipid control of microglia in a model of juvenile brain injury. This is an important context as brain injury is the leading cause of disability among young adults and children in Europe and a risk factor for dementia. In addition, I will assess dietary lipid deficiencies as an additive risk factor for neurodegenerative disease.

The approach will consist of novel in vivo strategies to manipulate brain-infiltrating macrophages and their lipid profile in a cell-specific manner during brain injury. RNA-sequencing (including single-cell) and lipidomics will assess microglia/macrophage responses. We will also modulate macrophage-derived lipids with clinically relevant strategies to improve acute and long-term outcomes after dietary deficiencies and brain injury.

This project will provide wide-ranging mechanistic insight to into juvenile brain injury, test multiple clinically relevant treatment options and assess poor diet as a risk factor for worse outcome.

3.1 PUFAs modulate microglia-mediated synaptic pruning during development
Lydie Morel, Quentin Leyrolle, Agnès Aubert, Alexandra Sere, Véronique DeSmedt-Peyrusse, Fabien Ducrocq, Pierre Triffilief, Corine Joffre, Agnès Nadjar, Sophie Layé

During development, the many cells of the central nervous system (CNS) interact to allow the maturation of a functional network. Amongst the necessary remodeling events is the synaptic pruning, during which certain synaptic terminals are removed to guaranty the efficiency of the neuronal signaling. This elimination activity is performed by microglia, the innate immune cell of the brain which is capable of phagocytosis. Polyunsaturated fatty acids (PUFAs) are immunomodulators and key regulators of brain innate immune system processes. Our group showed that by changing the ratio of oméga-3/omega6 PUFAs in the diet, their levels in the brain and in the composition of the microglia membrane were altered. Functional analyses and high-resolution imaging revealed that microglia-dependent synaptic pruning is inversely correlated to the n-3/n-6 PUFA ratio. Additionally, the deleterious effect of dietary n-3/n-6 PUFA was inhibited by blocking microglial CR3 a key component of the complement pathway.

This part of the study uses in vitro models to better understand the mechanisms of this dysregulation. By providing microglial cell culture with a pH-sensitive fluorescent substrate we can monitor their phagocytic phenotype by FACS. This in vitro model allows us to apply different treatments on the microglia and access their effect on phagocytosis. Which PUFAs affects the phagocytic function of the microglia? Is it through their integration in the membrane or as lipid mediator? Which elements of the complement pathway are regulated by the PUFAs ? At which level: gene expression, protein function? We are just starting to answer those questions…

3.2 Early-life PUFAs modulate myelination during development.

Quentin Leyrolle[1,2,3*], Fanny Decoeur[3], Agnès Aubert[3], Alexandra Seré[3], Anne-Karine Bouzier-Sore[4], Marie-Eve Tremblay, Pierre Gressens[1,2,], Cyril Dejean[5], Corinne Joffre[3], Sophie Layé[3*] and Agnès Nadjar[3*]
[1]*Inserm, U1141, Hôpital Robert Debré, Paris, France*
[2]*Université ParisDiderot, Sorbonne Paris Cité, Paris, France*
[3] *NutriNeuro, INRA – University of Bordeaux , France*
[4] *RMSB, CNRS – University of Bordeaux, France*
[5] *Neurocentre Magendie, INSERM - University of Bordeaux, France*

Early-life nutrition is a decisive factor in brain development in such a way that perinatal malnutrition notably affects behavior throughout life. In the last trimester of gestation in humans, the brain accelerates its accumulation of fatty acids, especially in their polyunsaturated form (PUFAs). PUFAs are essential fatty acids that the developing brain obtains through the maternal diet. They subdivide in two categories, the n-6 PUFAs (omega-6) and the n-3 PUFAs (omega-3), among which docosahexaenoic acid (DHA) and arachidonic acid (AA), are the most represented in the brain. PUFAs and their mediators regulate several neurodevelopmental processes within the brain and clinical trials have shown that early-life imbalance in AA or DHA intake is an environmental risk factor for neurodevelopmental disorders such as autism or schizophrenia. These pathologies have been associated with myelination abnormalities. Moreover n-3 PUFAs levels have been associated with myelination deficits in schizophrenia. In this study, we investigate the role of early-life PUFAs on myelination process that is crucial to ensure optimal brain function.

We designed a rodent model in which we controlled early-life DHA/AA ratio by manipulating maternal lipid intake so as to resemble human situation. After mating, CD1 female mice were fed with an n-3 deficient or balanced diet. We observed that early-life n-3 PUFAs increased diffusion tensor imaging (DTI) signal at P35 suggesting deficits in myelination in n-3 deficient mice. We confirmed these data by immunostaining MBP(a protein of myelin structure). We also observed that such myelination deficits were transient since there was no more difference in n-3 deficient and n-3 balanced adults. However, we found that functional connectivity between hippocampus and prefrontal cortex was disrupted by using *in vivo* electrophysiological measurements in adult offspring. These results uncover a previously unrecognized role of early-life PUFAs in the myelination process.

3.3 Interaction between membrane lipids and the functionality of accumbal medium spiny neuron: impact on mesolimbic dopaminergic transmission

Roman Walle[1], Fabien Ducrocq[1], Asma Oummadi[1], Sophie Layé[1], Peter Vanhoutte[2, 3,4], Véronique De Smedt-Peyrusse[1], Pierre Trifilieff[1]

[1] INRA, Nutrition et Neurobiologie intégrée, UMR 1286, 33076 Bordeaux, France ; University of Bordeaux, Nutrition et Neurobiologie intégrée, UMR 1286, 33076 Bordeaux, France
[2] INSERM, UMR-S 1130, Neuroscience Paris Seine, Paris, France; [3]CNRS, UMR 8246, Neuroscience Paris Seine, Paris, France; [4]Sorbonne Universités, UPMC Université Paris 06, UMR-S 8246, Neuroscience Paris Seine, Paris, France

N-3 polyunsaturated fatty acids (n-3 PUFA) are decreased in several psychiatric disorders, however the implication of such endophenotype in the etiology of psychiatric symptoms is unclear. We and others have shown in rodents that n-3 PUFA deficiency leads to impaired dopamine signaling in the nucleus accumbens (NAc), a central structure for reward processing and motivation. The NAc is mainly composed of medium spiny neurons, divided into those expressing the dopamine D1 receptor (D1R), and those expressing the D2 receptor (D2R). Several studies highlight a central role of D2R-expressing neurons of the NAc in the physiopathology of the reward system. Nevertheless, their role in motivated behaviors and the impact of PUFA composition on their functionality are still unclear.

In a first step, we manipulated the activity of D2R-expressing neurons of the NAc through pharmacogenetic approaches and downregulation of D2R by interfering RNAs. Using operant conditioning tasks in mice, we observed that activation and inhibition of these neurons decreases and increases motivation, respectively. In a consistent manner, downregulation of D2R selectively impaired motivation. Importantly, these manipulations had no effect on hedonic reaction.

In a second step, we showed that developmental n-3 PUFA deficiency leads to impaired motivation that is not reversed by postnatal n-3 PUFA supplementation. N-3 PUFA deficient animals displayed blunted responses to amphetamine and D2R ligands in motivational tasks, supporting an implication of D2R-expressing neurons in this deficit. Aiming at directly testing this hypothesis, we used pharmacogenetics to manipulate the activity of D2R neurons of the NAc. Interestingly, n-3 PUFA deficient animals were insensitive to pharmacogenetic manipulation.

These observations – together with other data from the group – highlight a central role of membrane PUFA composition on the functionality of G protein-coupled receptors and support the idea that n-3 PUFA decrease in psychiatric disorders could directly participate to some symptoms.

3.4 Unravelling the role of brain insulin action in diabetes-related depression

***Hugo MARTIN**, Xavier FIORAMONTI*

Type 2 diabetes (TD2), notably characterized by insulin-resistance, and major depressive disorder (MDD) represent two of main concerns for public health worldwide. Epidemiological studies indicate that patients suffering from T2D are more likely to struggle with MDD. In accordance with these clinical observations, it was recently demonstrated that naïve mice fed a high fat diet (HFD) harbour metabolic abnormalities reminiscent insulin resistance accompanied by the expression of some hallmarks of anxiety and depression-like symptoms. Despite these data, it is still unclear if these T2D-associated mood disorders are due to change in brain and/or peripheral insulin sensitivity. The serotoninergic (5-HT) system, which originates from the dorsal raphe nucleus (DRN), is highly involved in mood regulation/disorders. Therefore, our main hypothesis is that insulin regulates mood through a central modulation of the serotoninergic system.

According to previous results showing expression of the insulin receptor (InsR) in the DRN, we will determine which neurons subtypes expressed this receptor in the DRN. Functionality of InsR will be then evaluated by using *in vitro* electrophysiology to appreciate how insulin can directly or indirectly module DRN 5-HT neurons electrical activity. Moreover, signalling pathways arising from InsR activation will be evaluated using immunoblotting. In a second step, by using a genetic mice model of central insulin-resistance specifically in DRN 5-HT neurons, we will decipher in details the role of insulin trough behavioural experiments and assessment of electrical activity. We will then explore to what extent the regulation of DRN 5-HT neurons in response to insulin is altered in wild-type mice exposed to long-term high fat diet, a model of T2D-associated mood disorders. In

these mice, we will conduct *in vitro* electrophysiology to evaluate the electrical and synaptic activity of DRN 5-HT neurons in response to insulin. Finally, we will examine how metabolic-related anxiety-like and depression-like symptoms can be reversed by insulin sensitizing enhancement.

4.1 Modulation of mesolimbic dopamine transmission by brain lipid composition: consequences on reward processing.

Fabien Ducrocq, Roman Walle,AsmaOummadi, Clementine Bosch-Bouju, Suzanne van der Veldt, Tarson Tolentino-Cortez, Agnès Aubert, Rolando Meloni, Gabriel Barreda, Sophie Layé, David Ma, VéroniqueDeSmedt-Peyrusse and Pierre Trifilieff

Various,though distinct psychiatric disorders, such as Schizophrenia, bipolar disorder or majordepression are associated with a dysfunction of the reward system linked to an alteration of dopamine transmission. Furthermore, these pathologies are also accompanied by changes in brain lipid composition and in particular a decrease in the content of docosahexaenoic acid (DHA), the main n-3 polyunsaturated fatty acid (PUFA) in the brain. However, despite that n-3 PUFA supplementation seems to improve or prevent some psychiatric symptoms, the implication of brain lipid composition in the etiology of psychiatric endophenotypes has been overlooked.

Using operant conditioning tasks in mice, we show that developmental n-3 PUFA deficiency leads to motivational deficit that is not reversed by postnatal n-3 PUFA supplementation. Supporting a unique sensitivity of mesolimbic dopamine transmission to PUFA manipulations,n-3 PUFA deficient animals display blunted responses to amphetamine and dopamine D2-receptor (D2R) ligands in motivational tasks. Moreover, n-3 PUFA deficiency leads to alterations in electrophysiological properties of medium spiny neurons (MSNs) in the nucleus accumbens (NAc) that could account for the behavioral deficits. Indeed, D1-MSNs displayed a decrease in neuronal excitability in parallel with an increase of inhibitory input onto these neurons that are reversed by the D2R agonist quinpirole, suggesting an increase of the inhibitory input of D2-MSNs on D1-MSNs within the NAc.

Accordingly, using a transgenic approach that allows the expression of the fatty acid desaturase FAT1 in a cre-dependent manner, we show that rescuing appropriate PUFA levels in D2R-expressing neurons selectively, is sufficient to reverse both the motivational deficits and alterations in electrophysiological properties of MSNs induced by n-3 PUFA deficiency. We demonstrate that alteration of PUFAs in discrete neuronal population can alter neuronal function and associated behavior.

4.2 Role of DHEA, a DHA-derived endocannabinoid, in synaptic plasticity.

Mathieu Di Miceli, *Louisa Linders, Clémentine Bosch-Bouju & Sophie Layé.*

Background: Dietary poly unsaturated fatty acids (PUFAs) and its metabolites endocannabinoids have been implicated in anxiety and depressive disorders. We previously demonstrated that chronic social defeat stress in mice induces anxiety-like behaviours associated to a loss of endocannabinoid-dependent synaptic plasticity in the nucleus accumbens. In addition, we showed that n-3 PUFA enriched diet prevents anxiety-like behaviour and plasticity loss in mice submitted to social defeat stress. Dietary intake of PUFAs directly modulates the levels of the derived endocannabinoids and it has been shown that dietary DHA (docosahexaenoic acid) increases brain levels of its endocannabinoid derivative, DHEA. We thus hypothesise that n-3 PUFA enriched diet, by increasing levels of DHEA, preserves synaptic plasticity following chronic stress.

Objectives: Our objective is to characterise how DHEA affect synaptic transmissions in the murine nucleus accumbens, to better understand its potential role in preventing anxiety-like behaviour.

Material and Methods: Whole cell patch clamp electrophysiology was performed on sagittal brain slices of Bl6C57/J male mice. Medium spiny neurons (MSN) were identified and recordings were acquired using standard methods. Excitatory post-synaptic current were recorded in neurons following stimulation of glutamatergic fibers and DHEA (1-10 µM for 10 minutes) was bath-applied. Current amplitudes were compared 10 min before and 30 min after DHEA application.

Results: Preliminary findings show that bath application of DHEA induces long-term depression (LTD) of excitatory post-synaptic current in MSN, an effect that was not observed following vehicle applications (0.002%

ethanol, v/v).Pharmacological blockade of classical endocannabinoid receptors did not prevent the effect of DHEA on synaptic transmission. However, we have found that pharmacological antagonism of GPR55 cannabinoid receptors prevented DHEA-induced LTD.

Conclusion: Our preliminary study suggests that DHEA strongly impacts local neurotransmission within the nucleus accumbens. We have also demonstrated the role of GPR55 in endocannabinoid-dependent plasticity.

4.3 Impact of ω-3 long-chain polyunsaturated fatty acids on the functionality of the mesocorticolimbic dopaminergic pathway.

Andrea Contini, Fabien Ducrocq, Roman Walle, Asma Oummadi, Sophie Layé, Guillaume Ferreira,Véronique De Smedt-Peyrusse, Pierre Trifilieff

Long-chain polyunsaturated fatty acids (PUFAs) are a class of essential lipids that are crucial for neurodevelopment andsynaptogenesis, and an adequate accretion of ω-3 PUFAs is critical for the normalphysiology of the brain and the maturation of multiple neuronal systems. Indeed, ω-3 PUFAsare essential component of the neuronal membrane phospholipids, where they regulate the activity of membrane associated proteins and neurotransmission.Reduced levels of ω-3 PUFAs have been found in patients withmajor depression, bipolar disorder and schizophrenia. These neuropsychiatric conditions are allcharacterized by a dysregulation of the cortico-limbic dopaminergic system, which leads to an impairment in reward-related processes. A substantial body of evidence has shown that this pathway is particularly sensitive to a deficiency inω-3 PUFA, since animal models of ω-3 PUFA deficiency display1) altered activity of dopamine D2 receptors and expression of monoamines' transporter (VMAT2), and 2) alteredextracellular dopamine levelsin both nucleus accumbens and prefrontal cortex. The Trifilieff's team has recentlydemonstrated that deficits in reward processing under ω-3 PUFA deficiency originate from a dysregulation of the activity of dopaminoceptive MSNs in the nucleus accumbens.The aim of this project is toimplement the above findings byfurther characterizing the impact of n-3 PUFA deficiency on the integrity of the cortico-limbic pathway and its implication in the development of the psychotic-like state. For this purpose, I will employ sophisticated behavioral paradigms to assess cognitive performance and sensory functionalities inω-3 PUFA deficient mice. I will combine advanced neurochemical, transgenic and pharmacogenetic procedures in order toidentify the neuronal populations of the mesocorticolimbic pathway that are directly responsible for ω-3 PUFA-induced behavioral deficits.