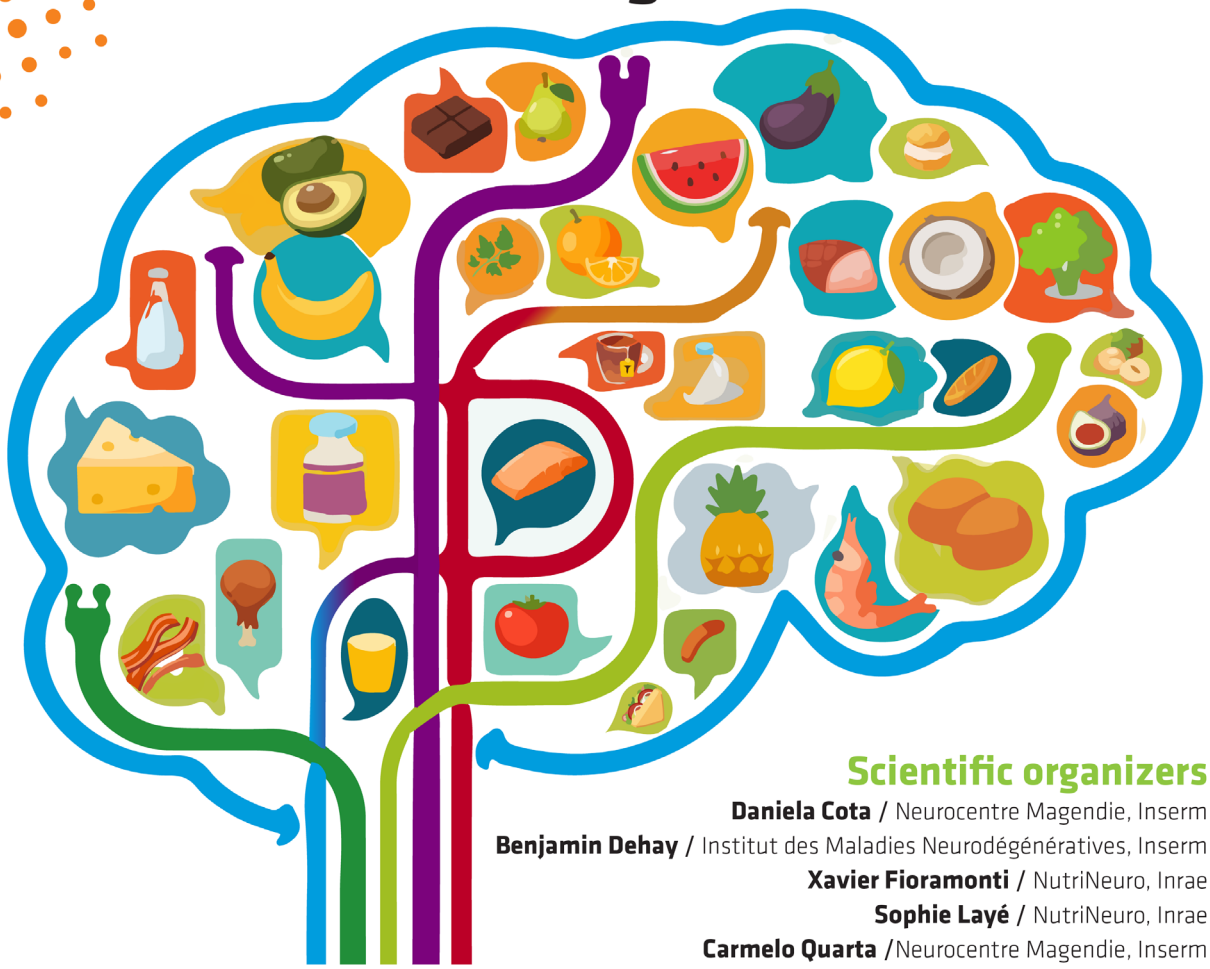
10TH BORDEAUX NEUROCAMPUS CONFERENCE

16-18 October 2024

Bordeaux, France

NeuroFood

Brain-Nutrition interactions: From metabolic to psychiatric and neurodegenerative diseases



Scientific organizers

Daniela Cota / Neurocentre Magendie, Inserm

Benjamin Dehay / Institut des Maladies Neurodégénératives, Inserm

Xavier Fioramonti / NutriNeuro, Inrae

Sophie Layé / NutriNeuro, Inrae

Carmelo Quarta /Neurocentre Magendie, Inserm

Abstract book

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About the conference

Eating hypercaloric food, rich in saturated fats and sugars and lacking essential nutrients, vitamins, and fibers, is associated with brain non-communicable diseases, including depression, anxiety, Alzheimer's, and Parkinson's, often co-morbid with obesity and type-2 diabetes. Complex intertwining exists between these different pathologies and our diet. An appropriate energy supply in quantity and quality is crucial for healthy brain functioning. Consequently, the brain is the main victim of changes in diet-induced energy disposal and metabolism, ultimately leading to pathology. On the other hand, nutrients and micronutrients represent potential tools to protect/correct brain diseases, and can be used to design new nutritional strategies for personalized medicine.

This conference will gather recognized French and International experts, who will provide overviews on advances made in understanding the impact of nutrition on psychiatric, neurodegenerative, and metabolic disorders, from molecular to behavioral neuroscience, up to human clinical trials and interventions. Presentations from established scientists will be combined with short talks and posters from younger researchers. The speakers' list includes young and more experienced scientists, respecting diversity and gender balance.

Scientific Organizers

Daniela Cota, Inserm, Neurocentre Magendie
Benjamin Dehay, Inserm, Institut des Maladies Neurodégénératives
Xavier Fioramonti, Inrae, NutriNeuro
Sophie Layé, Inrae, NutriNeuro
Carmelo Quarta, Inserm, Neurocentre Magendie

About Bordeaux Neurocampus international conferences

The Bordeaux Neurocampus Conferences are a series of 3-day neuroscience meetings that take place every year in autumn at the University of Bordeaux, France, since 2014.
The purpose of the conferences is to present and discuss recent findings in a topic field in Neuroscience, bringing together leading international experts and young researchers.

Invited speakers


Richard BAZINET


Nicholas BETLEY


Frédéric CALON


Lucile CAPURON


John CRYAN


Sophie LECLERCQ


Marcelo DIETRICH


Joël DORÉ


Sadaf FAROOQI


Christina GARCIA-CACERES


Tatiana KOROTKOVA


Serge LUQUET


Michel NEUNLIST


Sophie NICKLAUS


Soyoung PARK


Vincent PREVOT


David RUBINSZTEIN


Cécilia SAMIERI


Sandrine THURET


Matthias TSCHÖP

> More details

Program preview

Wednesday 16 October

8:30 - Welcome coffee
9:00 - Plenary lecture
10:00 - Coffee break
10:30 - Session 1: *New insights on neurobiological mechanisms of motivation and decision-making to eat*
12:30 - Commercial talk
12:35 - Lunch
13:00 - Poster session
14:00 - Session 2: *Central control of body weight and* metabolism (coffee break at 15:30)
17:00 - Plenary lecture
18:00 - Wine and cheese + poster session

Thursday 17 October

8:30 - Welcome coffee
9:00 - Session 3: *Nutrition and mental health* (coffee break at 10:00)
11:30 - Poster session
12:30 - Lunch break
14:00 - Session 4: *Nutrition and Neurodegenerative diseases: Where are we at?*
16:00 - Coffee break
16:30 - Plenary lecture
19:00 - Gala diner at the Château Labottière

Friday 18 October

9:00 - Welcome coffee
9:30 - Session 5: *Nutrients-brain interaction in disease: therapeutic perspectives* (coffee break at 11:15)
12:30 - Closing remarks
12:45 - Lunch

Conference in french

Tuesday 15 October at 6pm

"*Les additifs alimentaires nous montent-ils à la tête ?*", by Eric Houdeau (Toulouse)

Location : Cap Sciences – Hangar 20 – quai de Bacalan

Sponsors

Organization

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This project has received financial support from the French government within the framework of the France 2030 programme IdEx université de Bordeaux.

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For the general public

“Les additifs alimentaires nous montent-ils à la tête ?”

Tuesday 15 October at 6pm

In French

By Eric Houdeau

Directeur de recherche
Inrae – Laboratoire Toxalim (Toulouse)
Expert en toxicologie alimentaire

Location

Cap Sciences – Hangar 20 – quai de Bacalan

Résumé

Environ 350 additifs alimentaires sont autorisés en Europe. Autant d’évaluations par les Autorités sanitaires (ANSES en France, EFSA pour l’Europe) lorsqu’il s’agit de santé publique et d’alimentation, une démarche qui nécessite leur réévaluation régulière à la lumière de nouvelles données scientifiques. Si le titre se veut à double sens, c’est qu’il s’inscrit dans un process de transformation des aliments frais (multi-étapes et à différents degrés) pour rendre les produits finis toujours plus attractifs et gustativement meilleurs (colorants, agents de brillance, exhausteurs de goût), faciles à conditionner et à préparer (texturants, antiagglomérants), tout en les conservant plus longtemps (conservateurs, antioxydants). Le consommateur le souhaite-t-il systématiquement ? A-t-il été concerté ? Si l’ajout d’additifs respecte les réglementations en vigueur, leur déploiement est plus ou moins large selon le degré de transformation des denrées, très souvent en mélange et parfois… avec quelques contournements ! La recherche en toxicologie alimentaire et les agences déploient des moyens considérables dans le but d’aider les pouvoirs publics à faire le tri entre ce qui peut être effectivement autorisé pour être consommé au quotidien et le risque éventuel d’une trop forte ou trop longue exposition selon l’âge du consommateur (bébés, enfants, adultes). Entre les notions de « danger » (par défaut supposé, donc à tester avant autorisation) et de « risque » (risque t-on cet éventuel danger selon notre niveau d’exposition ?) existe tout un monde complexe fait de « lignes directrices », de doses journalières dites « admissibles » et de durées d’exposition (aigues ou chroniques) dans lequel le consommateur doit placer toute sa confiance… jusqu’à quel point ? Pourquoi tant d’alertes dans les médias ? Y a t-il des failles dans le système ? Entre l’innocuité réelle à être consommé (la plupart des additifs sont effectivement safe !), la notion de « principe de précaution » et les incohérences entre Autorités sanitaires de divers pays… il y a de quoi se perdre !

Cette conférence s’appuiera sur des questions d’actualité en prenant l’exemple des additifs alimentaires contenant des nanoparticules (particules ultrafines de dimension inférieure à 100 nanomètres), leur devenir et leurs effets dans l’intestin une fois consommées avec des aliments communs (plats préparés,

confiserie, pâtisseries etc…), leur passage dans le sang et vers d'autres organes et… pourquoi pas vers le cerveau justement ! Quelles sont les questions posées par leur taille et leur nature chimique (titane, silice…) ? Notre organisme peut-il les éliminer ? L'enfant à naître peut-il être contaminé par l'alimentation de sa mère pendant la grossesse ? En prenant l'exemple bien connu du dioxyde de titane (colorant blanc E171), pourquoi cet additif est-il aujourd'hui interdit en Europe (depuis 2022) et non dans d'autres pays ? Et pourquoi seulement dans l'aliment et les compléments alimentaires, mais pas dans les médicaments et dentifrices ? Enfin quid des autres additifs nanoparticulaires, pourtant tout autant consommés sinon plus ? Autant de questions où il est difficile pour le consommateur de faire la part des choses et de se rassurer sur « sa façon de manger » au quotidien.

Biosketch

Eric Houdeau est Directeur de Recherche INRAE au Centre de Recherche en Toxicologie Alimentaire (TOXALIM, Toulouse). Formé en physiologie, endocrinologie et toxicologie, il a créé et dirige l'équipe ENTeRisk (Endocrinologie et Toxicologie de la barrière intestinale) dédiée aux risques émergents dans l'alimentation humaine (nanoparticules, perturbateurs endocriniens). En 2010, il a été le premier à démontrer les effets du bisphénol A (BPA) sur l'intestin et son système immunitaire, avec des impacts à vie lorsque l'exposition commence *in utero*. Depuis 2013, il développe des programmes nationaux/internationaux en Nanotoxicologie sur le devenir et les effets de nanoparticules utilisées dans le secteur agroalimentaire, dans l'exemple du dioxyde de titane (additif alimentaire E171). Ses recherches ont permis d'interdire en France le BPA dans les matériaux en contact avec les aliments (2010 dans les biberons, 2015 dans tous les plastiques alimentaires), puis du E171 dès 2020. Expert à l'ANSES et membre du Panel d'experts EFSA dédiés aux additifs alimentaires, il contribue à fournir des données scientifiques nécessaires à l'évaluation des risques liés aux substances chimiques présentes dans l'alimentation et à l'élaboration de politiques publiques communes dans l'UE en matière de sécurité sanitaire.

Programme

Wednesday 16 October

From 8:15 Registration + welcoming coffee

9:00 Welcoming speech

Plenary lecture

Chair:
. Carmelo Quarta

9:05 - 10:00 **Matthias Tschöp**
Overcoming obesity: the discovery of multi receptor drugs

10:00 - 10:30 **Coffee break**

Session 1
New insights on neurobiological mechanisms of motivation and decision-making to eat

Chairs:
. Carmelo Quarta
. Xavier Fioramonti

10:30 - 11:00 **Tatiana Korotkova**
State-dependent regulation of feeding by complementary neuronal populations in the lateral hypothalamus

11:00 - 11:30 **Serge Luquet**
Brain lipid sensing and adaptive response to modern food environment?

11:30 - 12:00 **Soyoung Park**
Body-brain interaction as driving force for human adaptation

12:00 - 12:30 **Short talks:**
Victor Jouque
Beyond satiety: new roles for POMC neurons in feeding
Cristina Miralpeix
Hypothalamic POMC neurons control competing behaviors

12:30 - 14:00 Lunch + sponsor booths

13:00 - 14:00 Poster session (from 1pm)

Session 2
Central control of body weight and metabolism

Chairs:
. Daniela Cota
. Benjamin Dehay

14:00 - 14:30 **Nicholas Betley**
A cerebellar memory of a meal: adaptive control of food intake

14:30 - 15:00 **Marcelo Dietrich**
Early life transitions in the regulation of energy metabolism

15:00 - 15:30 **Cristina Garcia Caceres**
Hunger Timing Influence by Hypothalamic Astrocytes

15:30 - 16:00 Coffee break

16:00 - 16:30 **Vincent Prevot**
Tanycytic Shuttles: Guardians of Lipid and Glucose homeostasis for Healthy Aging

16:30 - 17:00 **Short talks :**
Jean-Charles Nicolas
New insights in the Functional heterogeneity of POMC neurons
Louise Eygret
Olfaction and feeding behaviour: Neuronal substrates underlying odour modulation of food intake regulating neuronal circuits

Plenary lecture

Chair:
. Sophie Layé

17:00 - 18:00 **Joël Doré**
Gut microbiome resilience: strategies for intervention

Wine & cheese + Poster session

18:00 - 20:00

Thursday 17 October

8:30 - 9:00 Welcome coffee

Session 3
Nutrition and mental health

Chairs:
. Xavier Fioramonti
. Sophie Layé

9:00 - 9:30 **Sophie Nicklaus**
Development of eating behavior during the first 1000 days: mechanisms, consequences on health outcomes, and public health communication

9:30 -10:00 **Lucile Capuron**
The role of diet in modulating immune function and influencing mental health

10:00 - 10:30 Coffee break

10:30 - 11:00 **John Cryan**
The Diet-Microbiota-Gut-Brain Axis- A Key Regulator of Brain and Behaviour Across the Lifespan

11:00 - 11:30 **Short talks:**
Quentin Leyrolle
The gut-derived metabolites as a new tool to improve mental health
Flore Marchaland
Neurobiological mechanisms protecting FAT-1 offspring from memory impairment induced by maternal dietary n-3 polyunsaturated fatty acid deficiency

11:30 - 12:30 **Poster session** + sponsor booths

12:30 - 14:00 Lunch + sponsor booths

Session 4
Nutrition and Neurodegenerative diseases: Where are we at?

Chairs:
. Daniela Cota
. Benjamin Dehay

14:00 - 14:30 **Sandrine Thuret**
Dietary modulation of adult hippocampal neurogenesis: Implications for cognitive ageing and dementia

14:30 - 15:00 **David Rubinsztein**
Regulation of mTORC1 and autophagy by nutrients

15:00 - 15:30 **Michel Neunlist**
Microbiota contribution to gut brain dysfunctions in neurodevelopmental diseases

15:30 - 16:00 **Short talks :**
Marie-Laure Arotçarena
Boosting autophagy through trehalose production as a potential therapeutic strategy for Parkinon's disease

Fabien Ducrocq
Reduced local GABA transmission onto ventral tegmental area dopamine neurons underlies vulnerability for hyperactivity in a mouse model of Anorexia Nervosa

16:00 - 16:30 - Coffee break

Plenary Lecture

Chair:
. Daniela Cota

16:30 - 17:30 **Sadaf Farooqi**
Neural regulation of human body weight

Gala dinner at the Château Labottière

From 19:00

Friday 18 October

Session 5: Nutrients-brain interaction in disease: therapeutic perspectives

Chairs:
. Sophie Layé
. Carmelo Quarta

9:30 - 9:45 **Short talk:**
Liam Bary-Carroll
Investigating the role of extracellular vesicles in the relationship between n-3 polyunsaturated fatty acid status and cognitive abilities

9:45 - 10:15 **Sophie Leclercq**
Role of the gut microbiota in alcohol use disorder: experimental approaches and clinical perspectives

10:15 - 10:45 **Richard Bazinet**
New methods lead to new findings regarding how diet and the liver regulate brain fatty acid levels

10:45 - 11:15 Coffee break

11:15 - 11:45 **Frédéric Calon**
Exploring Nutraceutical Treatment Options for Neurodegenerative Diseases

11:45 - 12:15 **Cécilia Samieri**
The food exposome of brain aging and dementia: epidemiological approach

12:15 - 12:30 **Short talk:**
Wassilios Meissner
Trial of the GLP-1 receptor agonist lixisenatide in Parkinson's disease

12:30 **Closing remarks**

12:45 Lunch

Invited speakers

Click on the name to get to the details!

Richard Bazinet, University of Toronto, Canada
Nicholas Betley, University of Pennsylvania, USA
Frédéric Calon, Université de Laval, Québec
Lucile Capuron, Inrae, University of Bordeaux, France
John Cryan, University College Cork, Ireland
Marcelo Dietrich, Yale University, USA
Joël Doré, Inrae, University of Paris-Saclay, France
Sadaf Farooqi, University of Cambridge, UK
Cristina Garcia-Caceres, Helmholtz Zentrum München, Institute for Diabetes and Metabolism, Germany
Tatiana Korotkova, University of Köln, Max Planck Institute for Metabolism Research, Germany
Sophie Leclerq, Université catholique de Louvain, Belgium
Serge Luquet, CNRS, University of Paris, France
Michel Neunlist, Inserm, University of Nantes, France
Sophie Nicklaus, Inrae, Univiersity of Dijon, France
Soyoung Park, DIFE, Germany
Vincent Prévot, Inserm, University of Lille, France
David Rubinsztein, University of Cambridge, UK
Cécilia Samieri, University of Bordeaux, France
Sandrine Thuret, King's College London, UK
Matthias Tschöp, Helmholtz Zentrum München, Germany

Richard Bazinet

Department of Nutritional Sciences, University of Toronto
https://nutrisci.med.utoronto.ca/faculty/richard-bazinet

New methods lead to new findings regarding how diet and the liver regulate brain fatty acid levels

Abstract

Docosahexaenoic acid (DHA; 22:6n-3) is prevalent in the brain, playing a crucial role in regulating cell survival, neurogenesis, and neuroinflammation. While DHA can be obtained through dietary sources, particularly fish, it can also be synthesized from alpha-linolenic acid (ALA; 18:3n-3), a plant-based precursor, via a series of desaturation and elongation reactions in the liver. The efficiency of DHA synthesis from ALA remains a topic of considerable debate, particularly important in light of ecological concerns regarding fish stocks and an increase in non-fish eating populations. Compounding this issue is a limited understanding of human DHA requirements. In this presentation, I will discuss new isotopic methods that have revealed several unexpected insights into DHA metabolism, including a feedback inhibition mechanism whereby DHA suppresses its own synthesis in the liver. These and other findings will be contextualized within the framework of human development, DHA requirements and controlled trials investigating the effects of DHA intake on brain function.

Biosketch

Dr. Bazinet received his BSc from the University of Western Ontario and completed his PhD under the supervision of Dr. Stephen Cunnane at the University of Toronto in 2003. Dr. Bazinet then completed a postdoctoral fellowship in Dr. Stanley Rapoport's Brain Physiology and Metabolism Section at the National Institute on Aging, National Institutes of Health. Dr. Bazinet joined the University of Toronto in 2006, where he is currently a Professor and Canada Research Chair in Brain Lipid Metabolism as well as the acting Chair of the Department of Nutritional Sciences. Dr. Bazinet is the recipient of several awards, including the Early Career Award from the International Society for the Study of Fatty Acids and Lipids; the Jordi-Folch-Pi Memorial Award from the American Society for Neurochemistry; the Future Leaders Award from the International Life Sciences Institute, the Young Scientist Award for the American Oil Chemists' Society, the Early Researcher Award from the Canadian Society for Nutrition, the Ralph Holman life time achievement award from the Oil Chemists' Society and most recently the Chevreul Medal from the French Society for the Study of Lipids. Dr. Bazinet sits on several editorial boards and is currently Editor-in-Chief of Prostaglandins, Leukotrienes and Essential Fatty Acids as well as a Senior Associate Editor of Lipids. The overall goal of Dr. Bazinet's research program is to identify the mechanisms that regulate brain lipid metabolism (signaling) and to identify the role of brain lipid metabolism in the pathogenesis of neurodegenerative diseases and neuropsychiatric disorders. Dr. Bazinet has published over 200 papers, largely in the field of brain fatty acid metabolism and is co-author of the joint WHO/FAO joint expert consultation on dietary fats and the central nervous system during aging and disease and was previously the president of the International Society for the Study of Fatty Acids and Lipids (ISSFAL).

Nicholas Betley

University of Pennsylvania, Associate Professor of Biology
https://web.sas.upenn.edu/betley-lab/

A cerebellar memory of a meal: adaptive control of food intake

Abstract

How is it possible to appropriately regulate the calories an individual consumes, given the varied food types available? We have recently identified a role for the cerebellum in influencing food intake. However, unlike canonical hunger and satiation centers, we believe that this center functions as a comparator between expected and consumed calories. I will present emerging evidence from the lab that suggests the cerebellar role in food intake is similar to cerebellar function in motor circuits and provide an outlook for how this regulation interfaces with canonical feeding centers.

Biosketch

Dr. J. Nichoals Betley attended Columbia University where he worked with Thomas Jessell to investigate the developmental programs that determine synaptic partners during circuit formation. To better understand how neural circuits influence behavior he moved to Janelia Research Campus and worked with Scott Sternson to examine the structure and function of neural circuits that influence feeding behaviors. He moved to the University of Pennsylvania in the Fall of 2015 and is interested in exploring how the brain guides behavior in a dynamic world. The Betley lab has a long-term research goal of understanding how the brain coordinates adaptive behavioral responses by integrating signals from the body. To this end, my laboratory investigates how neural networks that influence consumption choices are regulated by hunger, food cues and feeding to try and reconstruct the circuits influence food seeking and consumption. His lab has contributed to understanding how the brain integrates signals of hunger with other needs and has recently uncovered a novel role for the cerebellum in regulating food intake. His talk here will focus on emerging evidence for the role of the cerebellum in regulating meal size.

Frédéric Calon

Professeur titulaire, Faculté de Pharmacie de l'université Laval, Québec, Canada
Chercheur, Centre de Recherche du CHU de Québec-Université Laval
Co-directeur, Laboratoire international associé OptiNutriBrain (NutriNeuro-INAF)
Membre, Institut sur la nutrition et les aliments fonctionnels (INAF)

www.pha.ulaval.ca/faculte/repertoire-du-personnel/frederic-calon/page
www.crchudequebec.ulaval.ca/recherche/chercheurs/frederic-calon/

Linkedin

Exploring Nutraceutical Treatment Options for Neurodegenerative Diseases

Abstract

There is increasing interest in the use of food-derived products with potential health benefits for the prevention of age-related diseases. Although nutritional epidemiology studies often report associations between diet and the risk of developing neurodegenerative diseases, the outcomes of most clinical trials have been inconclusive. In this presentation, we will focus on the rationale of studying omega-3 fatty acids in Alzheimer's disease (AD) or Parkinson's disease (PD). We will show recent data from preclinical research conducted in animal models, post-mortem analyzes from human samples, and fluid measurements in individuals experiencing early-stage cognitive decline. We will critically assess the current evidence and show published and unpublished data from our research group. While available data is insufficient to recommend specific dietary interventions, the potential benefits may outweigh the risks for those with strong preclinical evidence and low toxicity, such as omega-3 fatty acids.

Biosketch

Dr Frédéric Calon's expertise focuses on neurodegenerative diseases (Alzheimer's and Parkinson's), the blood-brain barrier and the development of treatments, including nutritional approaches. He and his team contributed to the discovery of a neuroprotective effect of omega-3 fatty acids in brain diseases. He is co-author of more than 167 publications, cited more than 16,000 times. He also contributes to preclinical studies using animal models and clinicopathological studies based on brain samples. For less than a year, Dr Calon has been co-director of the Consortium for the Early Identification of Alzheimer's Disease - Quebec (CIMA-Q), involving a cohort of more than 400 participants. With Sophie Layé from Bordeaux, he has been co-director of the OptiNutriBrain International Associated Laboratory (LIA) and the Food4BrainHealth International Research Network (RRI) for almost a decade. Through these different multidisciplinary approaches, his research aims to discover new therapeutic targets, with the ultimate goal of preventing the progression of neurodegenerative diseases.

Lucile Capuron

Laboratory of Nutrition and Integrative Neurobiology, INRAE – Bordeaux Neurocampus - University of Bordeaux

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The role of diet in modulating immune function and influencing mental health

Abstract

Imbalanced diet and obesity have been associated with deleterious mental health outcomes. While the mechanisms underlying this relationship remain to be determined, mounting data suggest the involvement of inflammatory processes. We conducted a set of studies to assess the association of dietary habits, obesity and lipid status with neuropsychiatric vulnerability and depressive morbidity in healthy subjects and samples of patients with depression or obesity. Biological assays included the measurement of markers or inflammation and related pathways. Findings indicate that obesity and obesogenic dietary habits are associated with increased levels of peripheral inflammatory markers together with a greater risk of neuropsychiatric symptoms. Interestingly, inflammation-driven alterations in monoamine metabolism correlate with neuropsychiatric comorbidities in subjects with obesity. Finally, lipid status, notably as it relates to omega-3 fatty acids, predicts depressive symptoms and their clinical response to standard antidepressants in patients with major depressive disorder. These findings provide new insights on the pathways and mechanisms linking nutrition and mental health.

Biosketch

Dr. Lucile Capuron is a tenure 1st class Research Director at INRAE, Director of the laboratory of Nutrition and Integrative Neurobiology (NutriNeuro INRAE 1286–Univ Bordeaux), and head of the team Nutrition and Neuropsychiatric Symptom Dimensions, NutriPsy. She received her PhD, specialty health psychology/psychoneuroimmunology, in 1999 from the University of Bordeaux, France. Dr. Capuron was appointed Assistant Professor of Psychiatry from 2002-2005 in the Department of Psychiatry at Emory University School of Medicine, Atlanta, USA, where she still holds an adjunct faculty position. Her main research activity focuses on understanding the relationships between inflammation and neuropsychiatric symptoms in clinical/human settings and their modulation by nutritional and metabolic factors. She has an internationally recognized experience in the investigation of the central/mood effects of inflammatory factors in medically ill patients and the pathophysiological mechanisms underlying these effects. Dr. Capuron has authored more than 100 peer-reviewed publications in the fields of psychoneuroimmunology, psychiatry, neuroscience, and metabolism/nutrition. She is Associate Editor of Brain, Behavior & Immunity–Health; and Frontiers in Neuropharmacology, and serves on the Editorial Board of Brain, Behavior and Immunity. Dr. Capuron was awarded the Marcel Dassault Prize for Research in Mental Disorders 2018, and the Scientific Innovation Award of the “Académie des Sciences, Belles-Lettres et Arts de Bordeaux” in 2019.

John F. Cryan

University College Cork, Cork, Ireland

Website
X

The Diet-Microbiota-Gut-Brain Axis- A Key Regulator of Brain and Behaviour Across the Lifespan

Abstract

The prevalence of brain disorders, including stress-related neuropsychiatric disorders and conditions with cognitive dysfunction, is rising. Poor dietary habits contribute substantially to this accelerating trend. Conversely, healthy dietary intake supports mood and cognitive performance. Recently, the communication between the microorganisms within the gastrointestinal tract and the brain along the gut–brain axis has gained prominence as a potential tractable target to modulate brain health.

The microbiota and the brain communicate with each other via various routes including the immune system, tryptophan metabolism, the vagus nerve and the enteric nervous system, involving microbial metabolites such as short-chain fatty acids, branched chain amino acids, and peptidoglycans. Many factors can influence microbiota composition in early life, including infection, mode of birth delivery, use of antibiotic medications, the nature of nutritional provision, environmental stressors, and host genetics. At the other extreme of life, microbial diversity diminishes with aging. Stress, in particular, can significantly impact the microbiota-gut-brain axis at all stages of life. Much recent work has implicated the gut microbiota in many conditions including autism, anxiety, obesity, schizophrenia, Parkinson's disease, and Alzheimer's disease. Animal models have been paramount in linking the regulation of fundamental neural processes, such as neurogenesis and myelination, to microbiome activation of microglia. Moreover, translational human studies are ongoing and will greatly enhance the field. Future studies will focus on understanding the mechanisms underlying the microbiota-gut-brain axis and attempt to elucidate microbial-based intervention and therapeutic strategies for neuropsychiatric disorders.

The composition and function of the gut microbiota is robustly influenced by dietary factors to alter gut–brain signalling. To reflect this interconnection between diet, gut microbiota and brain functioning, we recently proposed that a diet–microbiota–gut–brain axis exists that underpins health and well-being and represents an uncharted frontier for brain health diagnostics and therapeutics across the lifespan.

Biosketch

John F. Cryan is Professor & Chair, Dept. of Anatomy & Neuroscience, University College Cork and was appointed Vice President for Research & Innovation in 2021. He is also a PI in APC Microbiome Ireland. Prof. Cryan has published over 650 peer-reviewed articles and has a H-index of >160 (Google Scholar). He is a Senior Editor of Neuropharmacology and of Neurobiology of Stress and is on the editorial board of a further 10 journals. He has co-edited four books and is co-author of the bestselling "The Psychobiotic Revolution: Mood, Food, and the New Science of the Gut-Brain Connection". He has received numerous awards including from European College of Neuropsychopharmacology (ECNP), European Behavioural Pharmacology Society(EBPS), British Association of Pharmacology, Physiological Society, American Gastroenterology Association and Neuroscience Ireland and FASEB. He was awarded an honorary degree from the University of Antwerp in 2018 and has been on the Highly Cited Researcher list in 2014 and from 2017 to the present. He was elected a Member of the Royal Irish Academy in 2017. A TEDMED speaker in 2014, TEDx Speaker in 2017 and he is a Past-President of EBPS. He was a Member of the 2022 Fens Forum Programme Committee and Chairs the Scientific Programme Committee of ECNP for 2022-2024.

Marcelo Dietrich

Department of Comparative Medicine, Yale School of Medicine

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Early life transitions in the regulation of energy metabolism

Abstract

All mammals transition from breastfeeding to independent feeding during the lactation period. In humans and other mammals, this critical transition is important for later in life metabolic control and, consequently, for the incidence of many chronic conditions. Here, Dr. Dietrich will discuss the function of hypothalamic neurons involved in homeostatic control during the transition from breastfeeding to independent feeding. His presentation will highlight novel properties of hypothalamic neurons in early life and adolescence, suggesting mechanisms by which early life events shape homeostatic regulation throughout the individual's lifespan.

Biosketch

Marcelo O. Dietrich is an Associate Professor with joint appointments in the Departments of Comparative Medicine and Neuroscience at Yale University School of Medicine. He joined the Yale faculty in 2014 after earning his M.D. and Ph.D. from Universidade Federal do Rio Grande do Sul in Brazil, with additional training at the Cajal Institute and Yale. Marcelo's research investigates how infants transition to adulthood and how experiences during this developmental stage influence their maturation. His laboratory studies the molecular, cellular, and systems mechanisms governing the development of physiological and behavioral processes in infant mammals. His work integrates fields like neurobiology, metabolism, genetics, and behavior. A central focus is the social attachment bond between infants and caregivers that provides all the essential needs for infants and impacts their survival and future health. By researching these early life transitions and their biological bases, Marcelo aims to gain insights into fundamental developmental processes relevant to promoting healthy human development across the lifespan.

Joël Doré

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https://www.micalis.fr/poles-et-equipes/pole-ecosystemes-alimentaires-et-digestifs/fonctionnalite-de-l-ecosysteme-intestinal-nicolas-lapaque

Linkedin

Gut microbiome resilience: strategies for intervention

Abstract

Like most eukaryotes living on earth, humans are microbial, ecosystems and symbioses. In humans, this intimate relationship starts at birth, making the first 1,000 days a sensitive period in the life cycle. Each adult individual interacts with 50 trillion bacteria and many other microbes present on the skin and at all the body's mucosal interfaces, providing essentially protective functions that make them a key element in maintaining health and well-being. However, the human-microbiota symbiosis is fragile, and recent changes in our lifestyles may have favored an alteration in this symbiosis, frequently associated with chronic disorders and diseases whose incidence has been increasing, uncontrolled, for several generations. It is in this context that microbiota science is today documenting an invisible erosion of our microbiomes that is accompanying the 6th extinction of living organisms. In many of the chronic conditions of modern society, the loss of richness in our intestinal microbiota is accompanied by intestinal permeability, inflammation and oxidative stress, which can mutually support each other in a vicious circle. Such dysregulation can tip the system into a state of pre-disease or disease, sustained by circular causalities and impossible to resolve by current therapies which only manage symptoms, and more often than not in an organ-centric way. A technological revolution in microbiota science has taken place over the past 20 years, leading to the era of metagenomics - the characterization of microbiota by massive sequencing. It consolidated earlier observations on gut microbiota diversity and inter-individual heterogeneity. It has documented new concepts such as enterotypes, stratifying the human population into several major intestinal ecologies. Finally, it has confirmed the existence of altered microbiota in a large number of clinical indications and chronic disorders, and highlighted low gene richness as a risk predictor with obvious relevance for decision support in medical management. A causal link has in some cases een evidenced by microbiota transfer in animals and humans. There are two imminent prospects for innovation in preventive nutrition and therapy. Diagnosis of the state of the symbiosis will be a tool in the service of a medicine that integrates lifestyle, as soon as practitioners can prescribe and, and access via a biology laboratory to 'microbiota and host' data positioning any individual in the landscape of the general healthy and sick population. This perspective will benefit from large-scale projects such as ‘Le microbiote français’ (lefrenchgut.fr), which aims to recruit 100,000 volunteers in the general population. Nutritional prevention and precision medicine of the “microbial human” will also emerge. Epidemiology documents the highly significant protective effects of the Mediterranean diet, whose characteristics are in line with the concept of a holistic approach to preserving the host-microbes

symbiosis. Recent work on animal models demonstrates that nutritional ingredients targeting all the levers of an altered symbiosis can be just as effective as chemical treatments for depression. Clinical trials are currently underway (OptiMood, ICAN) to validate their relevance in patients. While nutrition and supplements based on the combination of dietary ingredients may have their place in a global approach to prevention and therapeutic support, there remain contexts of unmet medical needs where nutrition will not be the major recourse. In these situations, where the patient's survival is threatened and medicine has no solution, rebuilding symbiosis by transferring fecal microbiota from healthy donors to patients may be an option. In conclusion, many innovations are expected from emerging knowledge on host-microbes symbiosis, for a new medicine of the "microbial human", interestingly also aligned with the challenges of sustainability of living systems and planetary health.

Biosketch

Joël Doré joined INRAE in 1983 and received his Ph.D. from the University of Illinois Urbana-Champaign in the U.S. in 1988. Trained in microbial ecology, he developed intestinal metagenomics for diagnostic applications and tools used to study interactions between food, microbiota, and their hosts. Joël Doré devoted his carreer to scientific research on the gut microbiome and their applications. He aimed to contribute to a better understanding of the symbiosis between humans and microbes to improve prevention and treatment. With more than 250 publications (H-index of 90), Joël Doré received LABIP's International Science Award in 2008 ; the Simone and Cino del Duca Foundation's Grand Prize in Science (along with S.D. Ehrlich) In 2014, the Dupont Nutrition & Health Science Medal for Excellence in Microbial Research in 2016 ; and the prize Benjamin Delessert in 2024. He is scientific coordinator of the project https://lefrenchgut.fr. Cofounder and scientific advisor of MaaT Pharma, Novobiome and GMT, Joël Doré is science coordinator of the digital platform https://www.gutmicrobiotaforhealth.com.

Sadaf Farooqi

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Neural regulation of human body weight

Abstract

Using genetic approaches, we have shown that disruption of multiple genes in the leptin-melanocortin pathway can cause human obesity. These molecules regulate signaling through hypothalamic circuits which project widely throughout the brain. By coupling genetic, molecular and physiological studies we are discovering key regulators of human eating behaviour. Some of these molecules regulate anxiety/fear responses, social interaction and maternal care, demonstrating the critical role of these circuits in human innate behaviour.

Biosketck

Sadaf Farooqi is a Wellcome Principal Research Fellow and Professor of Metabolism and Medicine at the University of Cambridge, UK. She is an internationally leading Clinician Scientist who has made seminal contributions to understanding the genetic and physiological mechanisms that underlie obesity and its complications. The work of Sadaf Farooqi and her colleagues has fundamentally altered the understanding of how body weight is regulated. With colleagues, she discovered and characterised the first genetic disorders that cause severe childhood obesity and established that the principal driver of obesity in these conditions was a failure of the control of appetite. Her work is often cited as an exemplar of how the translation of research into the mechanisms of disease can lead to patient benefit. She has received a number of awards including the 2024 Outstanding Clinical Investigator Award from the Endocrine Society. In 2021, she was elected as a Fellow of the Royal Society in recognition of her exceptional contribution to science.

Cristina Garcia Caceres

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Hunger Timing Influence by Hypothalamic Astrocytes

Abstract

Obesity is linked to compromised brain health, affecting food reward pathways, hormone-sensing neuronal activity, and brain connectivity. The arcuate nucleus (ARC) of the hypothalamus, a key hub for metabolic signals, traditionally thought to be regulated by neurons, is now known to involve astrocytes—non-neuronal cells that play a significant role in metabolic control. Unlike astrocytes in other brain regions, hypothalamic astrocytes respond uniquely to energy-dense food intake, modulating synaptic connectivity and influencing brain-peripheral communication. However, how the molecular mechanisms by which astrocytes regulate hunger circuits, remains unclear. In this talk, I will discuss ongoing studies focused on how astrocytes communicate with neighboring neurons in the ARC to regulate feeding. Using two-photon excitation imaging and electrophysiological recordings combined with genetically encoded fluorescence indicators, cell manipulation, and pharmacology in ex vivo brain slices from mouse models, we observe that the consumption of high-caloric meals boosts the calcium-dependent release of glutamate from astrocytes, which in turn increases the firing rate of AgRP/NPY neurons by activating NMDARs located at extrasynaptic sites. Furthermore, our data show that astrocyte calcium activity and the spontaneous firing rate of AgRP/NPY neurons exhibit similar daytime-linked activity patterns—i.e., low activity at the beginning of the day (fed state) and high activity just before the night cycle (non-satiated state). In sum, our findings suggest that glutamate-mediated astrocyte gliotransmission in the ARC could be a key mechanism governing the natural, temporal regulation of hunger, which may be altered under a hypercaloric diet, contributing to the hyperphagia associated with obesity.

Biosketch

Prof. Dr. Cristina Garcia Caceres earned her Ph.D. in Madrid, Spain, and completed academic internships at Yale University, USA, and Göteborg University, Sweden. After her doctoral studies, she conducted postdoctoral research at Helmholtz Munich and the Technical University of Munich in Germany. In 2015, she established the Astrocyte-Neuron Network Unit at the Institute for Diabetes and Obesity. Currently, she is a W2 Professor at Ludwig Maximilian University and serves as Head of Research and Deputy Director at the Institute for Diabetes and Obesity at Helmholtz Munich.

For over 16 years, Prof. Dr. Garcia Caceres has focused on understanding how the hypothalamus controls energy balance, particularly through astrocytes. Her research aims to uncover the cellular mechanisms underlying obesity and metabolic disorders. Her pioneering work, awarded with ERC Starting Grant, has shown that the brain's control of energy and glucose metabolism involves astrocytes. By exploring the interactions between neurons, astroglia, and blood vessels, she seeks insights to inform strategies for obesity prevention and treatment, including associated conditions like hypertension. Additionally, her recent research extends to understanding how the brain integrates peripheral endocrine cues into hypothalamic circuits, critical for metabolic adaptation in diet-induced obesity. Overall, her discoveries challenge traditional obesity treatment models and underscore the importance of considering sex as a biological variable in addressing this health issue.

Tatiana Korotkova

Institute of Systems Physiology, Faculty of Medicine, University of Cologne, Germany

https://physiologie.uni-koeln.de/vegetative-physiologie/research/research-groups/korotkova

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State-dependent regulation of feeding by complementary neuronal populations in the lateral hypothalamus

Abstract

Feeding is largely regulated by neuronal populations in the lateral hypothalamus, an evolutionarily conserved brain region. Animals must coordinate and prioritize multiple, sometimes competing, basic needs to ensure survival and reproduction. The fulfillment of nutritional needs has to be balanced and weighed against competing needs such as mating and voluntary exercise. Using optogenetics, chemogenetics, deep-brain calcium imaging, and electrophysiology in freely behaving mice, we investigated the neuronal mechanisms enabling state-dependent representation and orchestration of multiple innate drives. We identified neuronal populations and circuits that act in a complementary manner to enable the flexible fulfillment of multiple essential needs.

Biosketch

Tatiana Korotkova is a full professor and Director at the Institute of Systems Physiology, Faculty of Medicine, University of Cologne, Germany. Her lab investigates neuronal mechanisms of innate behaviors, including feeding, social interactions and voluntary locomotion. The overall goal of her studies is to unravel functions of hypothalamic neuronal circuits in health and disease. These studies are supported by ERC consolidator grant and by the German Research Organization (DFG). Tatiana Korotkova studied biology with a focus on human and animal physiology at Lomonosov Moscow State University. She did her Ph.D. under the supervision of Dr. R.E. Brown and Prof. H.L. Haas in Dusseldorf, Germany, and her postdoctoral studies in the labs of Prof H. Monyer in Heidelberg, Prof. T. J. Jentsch in Berlin. T. Korotkova was a junior group leader at the FMP Institute/Neurocure Cluster of Excellence in Berlin, and a Max-Planck group leader at Max Planck Institute for Metabolism Research in Cologne. She was a holder of the DFG and Schering foundation research stipends, and was awarded the Human Frontier Science Program (HFSP) Grant as well as the Junior Brain Prize by Lundbeck Foundation. She supervised 13 Ph.D, 12 M.Sc. students and 8 postdocs.

Sophie Leclercq

Université catholique de Louvain, Institute of Neuroscience, Laboratory of Nutritional Psychiatry, Brussels, Belgium

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Role of the gut microbiota in alcohol use disorder: experimental approaches and clinical perspectives

Abstract

Alcohol use disorder (AUD) is a global health problem with limited therapeutic options. The biochemical mechanisms that lead to this disorder are not yet fully understood. Alterations of the gut microbiota composition and function are well established in AUD patients, and we have shown that intestinal "dysbiosis" in these patients was associated with the severity of the psychological symptoms (depression, anxiety, alcohol craving and social impairments). In order to demonstrate a causal link between the gut microbiota and behavior, we used two different experimental strategies. First, we used a model of fecal microbiota transplantation (from humans to mice) and showed that mice receiving AUD microbiota exhibited changes in behavior (depression-like behavior, reduced sociability) and brain functions (neuroinflammation, myelination, neurotransmission). Secondly, we conducted a randomized, double-blind, placebo controlled clinical study to test the effect of a prebiotic supplementation on behavior during a detoxification program. We showed that social impairments were improved in AUD patients upon prebiotics exposure. Overall, these experimental and clinical data strongly suggest a link between the gut and the brain in AUD. Recent metabolomics data explore the potential gut-brain communication pathways in order to help finding new targets in the management of alcohol addiction.

Biosketch

Sophie Leclercq investigates the role of the gut microbiota in the regulation of emotions and cognitive functions in patients suffering from psychiatric diseases. In 2014, she obtained her PhD in Biomedical Sciences in UCLouvain, Belgium. During her thesis, she studied the gut-brain axis in alcohol use disorder patients. She then moved to McMaster University (Hamilton, Canada) for a post-doctoral training, during which she investigated the long-term effects of early life antibiotic exposure on brain functions and behavior in a mouse model. In 2022, Sophie was appointed FNRS research associate and created the laboratory of Nutritional Psychiatry in the Institute of Neuroscience of UCLouvain. Her team mainly conducts clinical study to test the impact of nutritional compounds on mental health and to decipher the mechanisms underlying gut-brain interactions. In 2023, she was awarded the ESBRA Nordmann Prize for her significant contribution in alcohol-related biomedical research.

Serge Luquet

Unité "Biologie Fonctionnelle & Adaptative" - Université Paris Cité, CNRS UMR 8251
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Brain lipid sensing and adaptive response to modern food environment?

Abstract

In the brain, neurons and glial cells are equipped with the necessary machinery to transport and metabolize nutritional lipids. Since neurons only uses glucose as energy substrate it has been postulated that lipids might act as signaling molecule. Lipid sensing was initially described in hypothalamus, and alter described in various brain structures including the reward dopaminergic system which is is instrumental to encode the reinforcing/rewarding aspects of feeding. In the reward circuit, DA-producing and dopaminoceptive neurons specifically express the lipoprotein lipase (LPL), an enzyme able to hydrolyze the dietary form of lipids, namely the triglycerides (TG), suggesting that circulating TG might modulate the activity of dopaminergic and dopaminoceptive neurons. By using in vivo central TG delivery, which mimics post-prandial increase of TG specifically in the brain, we have discovered that circulating TG act directly onto DA-D2 (DR2) receptors expressing neurons modulating the reinforcing and motivational values of feeding. In humans, we discovered that the neural responses to food cues show a significant correlation between postprandial increases in TG and the presence of Drd2/Taq1A genetic polymorphism. Taq1A polymorphism is one of the most commonly studied in psychiatry. TaqIA is located in the gene that codes for the Ankyrin repeat and kinase domain containing 1 kinase (ANKK1) near the dopamine D2 dopamine receptor (DR2) gene. It affects 30 to 80% of the population and its homozygous expression of the A1 allele correlates with a 30 to 40% reduction of striatal DR2, a typical feature of addiction, over-eating and other psychiatric pathologies. Using genetic approaches, we revealed that Ankk1 loss-of-function in dorsal and ventral striatum leads to alteration in learning, impulsive, and flexible behaviors resembling the endophenotypes described in A1 carriers. We also observed an unsuspected role of ANKK1 in striatal DR2-expressing neurons in the regulation of energy homeostasis and documented differential nutrient partitioning in humans with versus without the A1 allele. We are now investigating the consequences of an engineered point mutation in mice to produce humanized TaqIA mutation. Altogether, our data indicates that genetic variant of TaqIA greatly influence how the reward system response to modern food environment and particularly nutritional lipids to control behavior and metabolism.

Biosketch

Serge Luquet received his undergraduate degree in Biology &Biochemistry from the University of Nice Sophia Antipolis, France in 2003. During his PhD training he was interested in the role of the fatty-activated transcription factor PPAR delta in adipose and muscle cell differentiation. He published seminal paper showing the role of PPAR delta in the controls of muscle development and oxidative capability. In 2003 he joined the laboratory of Pr Richard Palmiter (Howard Hughes Medical Institute &

Department of Biochemistry) at the University of Washington, Seattle for his post-doctoral training. He studied the role of hypothalamic neurons that produce Agouti related protein in the control of feeding behavior. He was recruited at researcher by the French CNRS in 2006 and was awarded a young investigator research program that led him to conduct an independent research. His group is established at the University Paris Cité. The core approach of his team (https://bfa.u-paris.fr/equipe-5/) is to leverage the power of modern molecular genetic tools and mouse models using integrated approaches in order to dissect out the role of discrete neural circuit elements in the control of different aspect of energy balance including feeding behavior & energy expenditure.

Michel Neunlist

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Microbiota contribution to gut brain dysfunctions in neurodevelopmental diseases

Abstract

Over evolution, gut and brain have closely evolved together in order to accomplish fundamental tasks such as species survival and adaptation to their environment. Permanent and dynamic interactions between gut and brain, two neurological organs, set the basis for the gut-brain axis. Over the past years, the gut microbiota has been identified as a fine and profound regulator of the gut-brain axis. In particular, gut microbiota plays a central role in the development of gut nervous system as well as brain structures and ultimately organ functions, via the production of metabolites such as short chain fatty acids or bacterial cell wall components. Conversely, mounting evidences suggest that alterations of gut microbiota composition as well as microbiota metabolism could play a central role in the development of chronic diseases of the brain such as behavioral, neurodevelopemental and in neurodegenerative diseases. In this context, key functions of gut microbiota in gut brain axis development and neurodevelopemental diseases, in particular in autism spectrum disorders will be summarized in this talk.

Biosketch

Michel Neunlist received an Engineering Degree in Physics from the Ecole Nationale Supérieure de Physique of Strasbourg. He obtained a PhD in electrophysiology from the University of Strasbourg. He spent a 5 years research training period in the Department of Biomedical Engineering of the Johns Hopkins School of Medicine where he developped optical recording methods to measure cardiac activity. He next spen 5 years at the Veterenary School of Medecine in Hannover (Germany) where he trained in the field of enteric neurobiology. He joined in 2000 the Institut of Digestive Diseases of the University Hospital of Nantes where he developed a translational research program centred on the study of the role of the enteric nervous system in digestive and brain chronic diseases. He is currently the head of the Inserm Unit of TENS (The enteric nervous system in gut and brain disorders) composed of over 40 members.

Sophie Nicklaus

Centre des Sciences du Goût et de l'Alimentation, UMR CNRS, INRAE, Institut Agro, Université de Bourgogne, France
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Development of eating behavior during the first 1000 days: mechanisms, consequences on health outcomes, and public health communication

Abstract

During this presentation, I will first explain the main factors enabling and leading to the development of eating behavior during the first thousand days of life, related in particular to sensory development, milk and complementary feeding experience and psychosocial environment. Then I will explain the consequences of eating behavior and dietary intake during this period on health outcomes (growth, allergic diseases and neurodevelopment). Finally, I will describe which can be the implications of this accumulating knowledge for public health communication, and how in turn research can build on communication regarding healthy eating during the first thousand days.

Biosketch

Sophie Nicklaus, PhD is a Senior Scientist at INRAE (the French National Research Institute for Agriculture, Food and Environment), in the Centre des Sciences du Goût et de l'Alimentation (Center for Taste and Feeding Behavior) in Dijon, France. She received her PhD in Food Science from the University of Burgundy (Dijon, France) in 2004; and her Habilitation in 2013. She has been studying children's eating behavior (food preferences; control of food intake) for the past 20 years, looking at the role of food-related inputs (sensory properties, energy density) in the development and evolution of infants and children's liking and food intake, using experimental and epidemiological approaches (in particular in two birth cohorts, OPALINE and ELFE). She is especially interested in understanding the impact of early eating experiences on later eating behavior, and their contribution to health status (obesity, allergy). She led the team 'Determinants of eating behavior across the lifespan, relationships with health' from 2017 to 2023. In 2018, she was awarded the Danone International Prize on Alimentation. In 2020, she took over the scientific lead of the 'Dijon, Alimentation Durable 2030' ('Dijon, sustainable food system 2030'), a systemic development project coordinated by the Municipality of Dijon, aimed at demonstrating the pathway toward sustainable agrifood system with a network of more than 20 local stakeholders. She is also engaged with the French public health agency, to contribute to the promotion of healthy eating habits toward the lay public. Since 2024, she joined the "Food and bioeconomy" Scientific Direction of INRAE.

Soyoung Park

German Institute for Human Nutrition & Charité - Universitätsklinik Berlin

https://www.dife.de/en/research/departments-and-labs/decision-neuroscience-and-nutrition/
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Body-brain interaction as driving force for human adaptation

Abstract

What food to eat and when to eat can impact the dynamics of neurotransmitter systems, such as dopamine, thereby modulating brain function and resulting behavior. On the other hand, such food preferences are shaped by diverse intrinsic and extrinsic factors. Here I present a series studies that show how the body and the brain interact to enable human adaptation.

Biosketch

Soyoung Q. Park is a professor of Nutrition Neuroscience at the Charité – Universitätsmedizin Berlin and heads the department of Decision Neuroscience and Nutrition at German Institute for Human Nutrition. Her research focuses on the metabolic, neural and social mechanisms underlying human decision making, with the ultimate goal to develop novel intervention strategies to shape and optimize choices. Here, the reward-based decisions, such as consumer decisions and decisions in social contexts are at focus. She studied Psychology at the Institute of Technology Berlin (Germany) and received her PhD in Neuroscience from the Free University of Berlin, after her stay as a stipend holder at the Berlin School of Mind and Brain at the Humboldt University. After her PhD, she moved to Switzerland for a postdoctoral research training at the department of economics at the University of Zurich. Before moving to Berlin/Potsdam, she was a professor for social psychology and decision neuroscience at the University of Lübeck, Germany, where she was headed the Psychology degree program (B.A. and M.A.).

Vincent Prevot

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Tanycytic Shuttles: Guardians of Lipid and Glucose homeostasis for Healthy Aging

Biosketch

I am currently Senior Research Director at the Inserm (the French National Institute of Health and Medical Research) and Head of the "Development and Plasticity of the Postnatal Brain" laboratory at the Lille Neuroscience & Cognition Research Center in Lille, France, since 2007. The two principal focuses of my research are the Central Control of Energy Homeostasis and the Neurobiology of Reproduction. Among my recent pioneering studies is the demonstration that tanycytes, specialized ependymoglial cells lining the floor of the third ventricle, transport circulating metabolic signals such as leptin, as well as anti-obesity drugs like liraglutide, across brain barriers into the hypothalamus to regulate energy homeostasis.

David Rubinsztein

University of Cambridge and UK Dementuia Research Institute

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Autophagy, a nutrient-regulated pathway, and its roles in neurodegeneration

Abstract

Intracellular protein aggregation is a feature of many late-onset neurodegenerative diseases, including Parkinson's disease, tauopathies, and polyglutamine expansion diseases (like Huntington's disease (HD)). Many of these mutant proteins, like that causing HD, cause disease via toxic gain-of-function mechanisms. Therefore, the factors regulating their clearance are crucial for understanding disease pathogenesis and for developing rational therapeutic strategies. We showed that autophagy induction reduces the levels of mutant huntingtin and attenuated its toxicity in cells, and in Drosophila, zebrafish and mouse HD models. We have extended the range of intracellular proteinopathy substrates that are cleared by autophagy to other related neurodegenerative disease targets, like alpha-synuclein in Parkinson's disease and tau in various dementias and Alzheimer's disease. In this talk, I will discuss how genetic lesions causing neurodegeneration impact autophagy at different stages of the pathway and will describe some of our attempts to identify therapeutic targets. I will describe how nutrients, particularly amino acids like leucine, regulate autophagy via mTORC1 across different timescales, and how these pathways are involved in disease.

Biosketch

David Rubinsztein is Professor of Molecular Neurogenetics and a UK Dementia Research Institute Group Leader at the University of Cambridge. He is Deputy Director of the Cambridge Institute for Medical Research. Dr. Rubinsztein earned his MB ChB, BSc(Med)Hons, and PhD degrees from University of Cape Town. He came to Cambridge in 1993 as a Senior Registrar in genetic pathology and was the first person to complete formal training in this field in the UK. His research is focused in the field of autophagy, particularly in the context of neurodegenerative diseases. His laboratory pioneered the strategy of autophagy upregulation as a possible therapeutic approach in various neurodegenerative diseases, and has identified drugs and novel pathways that may be exploited for this objective. He has made contributions that reveal the relevance of autophagy defects as a disease mechanism and to the basic cell biology of this important catabolic process. Rubinsztein was elected Fellow of the Academy of Medical Sciences (2004), EMBO member (2011), Fellow of the Royal Society (2017) and membership of Academia Europaea (2022). He was awarded the Graham Bull Prize (2007), Thudichum Medal (2017), Roger de Spoelberch prize (2017) and the Goudie Medal (2020).

Cécilia Samieri

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The food exposome of brain aging and dementia: epidemiological approach

Abstract

Healthy nutrition is a critical determinant of healthy brain aging. However, a challenge remains to decipher the very specific aspects of nutrition most likely to modify substantially the risk to develop brain aging pathologies. As dementia develops silently over years before diagnosis, epidemiology is a unique tool to characterize early risk factors and long-evolving brain aging pathways through biomarkers. Epidemiology also allows to study complex exposures such as nutrition with a holistic perspective – the food exposome, from candidate nutrients to a global approach of diet patterns. Moreover, there is substantial inter-individual variability in the metabolic and neurobiological responses to diet and deciphering such heterogeneity - the foundation of precision medicine – with precision epidemiology may help refine nutritional interventions for the prevention of dementia. Hence, the development of high-throughput technologies applied to biological matrices has fostered characterization of the molecular architecture underpinning such heterogeneity across individuals, allowing to refine knowledge on how specific elements of the food matrix may impact pathways leading to dementia. A critical step in precision epidemiology is also to interrogate effect modification by some biological modulators that may define individualized vulnerability profiles. This presentation will provide an overview of current epidemiological knowledge on the relation of the food exposome with brain aging and dementia and review several novel methods for population research in diet, including how to better study diet patterns and vulnerability factors in nutritional epidemiology by exploration of the food metabolome. The final goal is to find for each individual the optimal pathway-modifying diet prescription likely to modulate brain aging trajectories and avoid dementia.

Biosketch

As a director of research at INSERM (the French National Institute for Health), Cécilia Samieri leads a group on the “exposome of brain aging and dementia” in the Bordeaux Population Health research center. She studies the epidemiology of brain aging, with the aim of understanding how the environment influences the etiology of dementia, developing original approaches to address lifestyle and brain health with a holistic vision, from diet patterns to molecular markers of the exposome. Trained as a veterinary and then as a neuro-epidemiologist in Bordeaux and as a Fulbright post-doctoral fellow at Harvard School of Public health in Boston, she leveraged large French and US cohorts to evidence associations of healthy diets and optimal cardiovascular health, with healthy brain aging. She served as academic co-chair of the Alzheimer’s Association's Professional Interest Area group on Nutrition and Metabolic Diseases from 2019 to 2021. In 2022 she has set up a new population-based cohort of your seniors after age 55 as a unique tool to evaluate, with high-throughput molecular and imaging-based epidemiology, the exposome and early signs of neuropathology. The overarching goal is to inform next-generation public health policies, integrating behaviors with contextual factors for the precision prevention of cognitive aging.

Sandrine Thuret

King's College London, England

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Dietary modulation of adult hippocampal neurogenesis: Implications for cognitive ageing and dementia

Abstract

Research over the last 20 years has firmly established that learning and memory abilities as well as mood can be influenced by diet. Although the underlying mechanisms by which diet modulates mental health are not fully understood. One of the brain structures associated with learning, memory and mood is the hippocampus. Interestingly, the hippocampus is one of the rare structures in the adult brain where the formation of newborn neurons -or neurogenesis- persists. The level of neurogenesis in the adult hippocampus is altered with age and has been linked directly to cognitive performance and mood. Therefore, modulation of adult hippocampal neurogenesis by diet emerges as a possible mechanism by which nutrition impacts on mental health. During this talk I will present evidence of alteration of neurogenesis during ageing and evidence of cognition and mood being modulated by dietary parameters, which are also responsible for adult hippocampal neurogenesis regulation. This will inform a discussion on the important translational concept that diet, a modifiable lifestyle factor, holds the ability to modulate brain plasticity and function.

Biosketch

Professor Sandrine Thuret is Head of the Neurogenesis & Mental Health Laboratory and Head of the Basic & Clinical Neuroscience Department at the Institute of Psychiatry, Psychology & Neuroscience within King's College London, UK. She is Director of the UKRI Medical Research Council Doctoral Training Partnership in Biomedical Sciences, and co-Director of the Wellcome-funded PhD programme in Mental Health Research for Health Professionals. Professor Thuret has a background in bioengineering, molecular, cellular, behavioural and ageing biology. She graduated from the University of Heidelberg, Germany with a PhD in Neuroscience and then did her postdoctoral research at the Salk Institute with Prof. F.H. Gage, CA, USA, where she investigated the role of stem cells in the mammalian central nervous system. Her lab (thuretlab.com) is investigating environmental and molecular regulatory mechanisms controlling the production of new neurons in the adult brain and how these impact mood and memory, in health and disease. Overall, she has made significant novel contributions to our understanding of neural stem cell biology in the context of regeneration, neurodegeneration, mental health and neurogenesis with over 9,000 citations. She is a TED speaker with 14 million views and currently leading two international research consortia on cognitive aging, Alzheimer's disease and brain plasticity.

Matthias Tschöp

Helmholtz Munich, Technical University of Munich, Germany

www.helmholtz-munich.de/en/board-of-directors/matthias-tschoep
Linkedin

Overcoming obesity: the discovery of multi receptor drugs

Abstract

On our mission to overcome the obesity pandemic by discovering highly effective medicines, we hypothesized that chemistry based on more than one endocrine factor may be required to significantly reduce body fat without causing severe side effects. We selected combinations of afferent gut hormones acting in the CNS as the most likely path toward efficacy comparable to bariatric surgery benefits. Over the last 20 years, we combined advanced in vivo preclinical biology with state-of-the-art peptide chemistry to achieve such synergistic gastrointestinal hormone pharmacology. What proved successful was the unprecedented approach of fully integrating two and three mechanisms of biological action at a potency that matched the individual native hormones into single molecules. The resulting peptides are analogous to master keys, structurally nearly identical to natural gut hormones, but delivering multiple metabolic action profiles. We discovered multiple dual and triple hormone-like chimeric peptides from a set of intestinal hormones and chemically refined these for medicinal purposes to possess suitable time action and physical properties to support infrequent subcutaneous dosing. This new class of drugs was then validated by showing unprecedented improvements in glycemic control and body weight reduction in multiple rodent models of obesity and insulin resistance. Aiming at efficient translation into clinical medicine, we designed and supervised the validation of the rodent observation with first-generation forms of these poly-agonists in non-human primate studies and subsequently in the first clinical trials. The results triggered numerous pharmaceutical interests and led to multiple competitive dual and triple agonist versions now advancing in mid and late-stage clinical trials, reflecting medicinal importance of the discovery and validating the reproducibility of their pioneering science. Tirzepatide/Mounjaro/Zepbound (Eli Lilly & Co) represents one of the initial members of the newly discovered class of dual agonist drugs and was FDA-approved last year for treating type 2 diabetes. It synergistically integrates GIP and GLP-1 receptor agonist pharmacology into a single molecule, as we had first discovered and reported in 2013. The GIP/GLP-1 dual agonist Tirzepatide/Mounjaro/Zepbound has been approved for treatment of obesity and diabetes by the regulatory agencies and achieves an average of 22.5% weight loss in clinical obesity, a milestone achievement previously thought to be impossible. Multiple other versions of such dual and triple agonist classes of drugs are successfully underway including several in clinical phase III trials.

Biosketch

Matthias Tschöp is the CEO of Helmholtz Munich, Vice President of the German Helmholtz Association and Alexander-von-Humboldt Professor at the Technical University of Munich. Tschöp unraveled fundamental gut-brain signals to discover the first highly effective drugs for human obesity in

collaboration with the chemist Richard DiMarchi - the dual and triple gut hormone multi-agonists. A first representative is FDA-approved, others are successfully progressing through clinical trials. Tschöp has received numerous honors and awards, including the Banting Medal (2023), the Heinrich Wieland Prize (2023), the Schering Prize (2023), the EASD-Lilly Centennial Prize (2022) and the Ernst Jung Prize (2021). He holds an adjunct professorship at Yale University and an honorary doctorate at Leipzig University. He was elected a member of the German, Bavarian, and European Academies of Sciences, the American Society for Clinical Investigation and the Association of American Physicians.

Short talks

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Marie-Laure Arotçarena

Institut des Maladies Neurodégénératives

Boosting autophagy as potential therapeutic strategies for Parkinson's disease

Synucleinopathies are neurodegenerative diseases characterized by the presence of α-synuclein-positive intracytoplasmic inclusions into the central nervous system. Increasing evidence indicates that impairment of lysosomal function may contribute to the pathogenesis of the synucleinopathies, including Parkinson's Disease and Multiple system atrophy. We and others have shown that inducing autophagy, through chemical and/or genetic approaches, is an effective and promising therapeutic strategy for synucleinopathies.

Liam Barry-Carroll

NutriNeuro

Investigating the role of extracellular vesicles in the relationship between n-3 polyunsaturated fatty acid status and cognitive abilities

Dietary supplementation with n-3 polyunsaturated fatty acids (PUFAs) has been proposed as an attractive therapeutic strategy for maintaining cognitive function. Preclinical studies indicate that n-3 PUFAs can partially mitigate the deleterious effects of aged-related cognitive decline in the elderly. Additionally, n-3 PUFAs are crucial during fetal and early postnatal development, as deficiencies during this period can result in cognitive abnormalities that persist into adulthood. Although the mechanisms by which n-3 PUFA status on cognitive health are not fully understood, they appear to affect the interactions between neurons and the brain's support cells, microglia, leading to altered neuronal activity. This study investigates the role of of extracellular vesicles (EVs) in n-3 PUFA mediated modulation of brain function. EVs are nano-sized, lipid bound particles secreted by all cell types, involved in cellular signalling and pathogenesis. Due to their ability to reflect their cell of origin, plasma-derived EVs are proposed as prognostic and diagnostic biomarkers for various pathologies. This study aims to characterize the impact of n-3 PUFA status on both plasma and brain EV signatures in relation to cognitive abilities.

Methods

This double-blinded, randomized, and placebo-controlled study involved 80 healthy individuals aged 60-70 years, who underwent a 12-month supplementation with 340 mg of n-3 PUFAs. Plasma collection and cognitive evaluations were performed before and after supplementation. EVs were isolated from plasma and analyzed using nanoscale flow cytometry to investigate the surface expression of CD9 and CD41. To understand the impact of n-3 PUFA deficiency, mice were fed diets either deficient or sufficient

in n-3 PUFAs from gestation until 3 months old. EV extracts from the whole brain were assessed using proteomic analysis and applied to microglia in vitro to evaluate their functional impact.

Results

Dietary n-3 PUFA supplementation significantly improved visuospatial working memory and increased circulating levels of docosahexaenoic acid (DHA) in elderly individuals. A notable reduction in the percentage of EVs expressing CD9 and CD41 (markers of platelet-derived EVs) was observed in a subset of individuals receiving n-3 PUFA supplementation, which negatively correlated with their memory performance. This suggests that increased n-3 PUFA consumption modulates platelet activity, associated with improved brain function. In mice, brain-derived EVs from n-3 PUFA sufficient and deficient diets contained differentially expressed proteins related to synaptic remodeling and metabolic pathways. These EVs had opposing effects on microglia in vitro, with n-3 sufficient EVs promoting a pro-proliferative response, whereas n-3 deficient EVs increased microglial phagocytic activity.

Discussion

These findings suggest that dietary n-3 PUFAs modulate the signatures of plasma and brain-derived EVs, associated with changes in EV functionality that may mediate neuronal activity linked to cognitive function.

Fabien Ducrocq

Nutrineuro

Reduced local GABA transmission onto ventral tegmental area dopamine neurons underlies vulnerability for hyperactivity in a mouse model of Anorexia Nervosa

Hyperactivity is a persistent symptom of anorexia nervosa (AN) that often precedes occurrence of the disease, and constitutes a major barrier to recovery. Alteration of mesolimbic dopamine transmission has been hypothesized as a critical factor for the development and maintenance of AN and hyperactivity. However, the nature of dopamine dysfunction in AN, and the underlying mechanisms remain unclear. We therefore aimed at i) characterizing the impact of the activity-based anorexia (ABA) model on ventral tegmental area dopamine (VTADA) neurons and ii) determining whether restoring activity of VTA neural network is protective in the ABA model. Using ex-vivo electrophysiology in mice exposed to the ABA model, we found that VTADA neurons displayed increased firing frequency. This was paralleled with reduced GABAergic inputs onto VTADA neurons. This reduction was at least in part attributable to local VTAGABA neurons. Indeed, using electrophysiological recording coupled with optogenetic manipulations, we found that VTAGABA neurons were less excitable, displayed a lower firing frequency and a reduced probability of release onto VTADA neurons. Restoring the excitability of VTAGABA neurons via chemogenetic activation rescued mice from starvation by decreasing hyperactivity. In summary, we found that caloric restriction together with running leads to dysregulation of VTAGABA

transmission on VTADA neurons that reinforces maladaptive behaviors such as hyperactivity. This study uncovers new mechanisms linked to the disturbed dopamine system characterizing AN, identifying a role of decreased local GABAergic control over VTADA neuron output in this process.

Louise Eygret

NutriNeuro

Olfaction and feeding behaviour: Neuronal substrates underlying odour modulation of food intake regulating neuronal circuits

A growing proportion of the population is having problems maintaining a stable body weight. Therapeutic drug strategies deployed to modulate food intake are often accompanied by side effects. Olfactory system plays an important role in food intake, thus it could offer safer alternative strategies to regulate eating behaviour. Food intake is essentially regulated by the hypothalamic neurons of the melanocortin network: AgRP (Agouti Related Peptide) and POMC (Pro-opiomelanocortin) neurons, respectively orexigenic and anorexigenic. Previous studies showed that the presentation of food rapidly modulates the activity of these neurons in mice even before eating suggesting the involvement of sensory cues in this modulation. However, the determinants of this modulation have not been identified. Our study presents the modulatory effects of appetitive odorant molecules on hypothalamic neurons involved in the control of food intake.

We selected attractive food odorants on both males and females based on investigating times in individual cages. Food intake was quantified in automated monitoring cages to characterize the appetitive effect of the chosen odours. This led us to identify attractive food odours that increased food intake in mice namely without preliminary association with food. The electrical activity of POMC and AgRP neurons was recorded in brain slices obtained from mice exposed to these odorants or to the solvent only. The POMC neurons from animals exposed to appetitive odours showed a modulation of their electrical activity with a lower spontaneous action potential firing. In AgRP neurons, odour exposure had less impact. Using fiber photometry coupled to breathing activity monitoring, we measured a decrease of activity in AgRP neurons when animals were actively sniffing appetitive odours. Our results highlight the appetitive effect of some food odours, some of which show an innate effect on food intake. Electrophysiological and fiber photometry recordings suggest that odours are capable of modulating the electrical activity of neurons in healthy melanocortin networks. Future work will attempt to identify the olfactory projections involved in this modulation of the arcuate nucleus of the hypothalamus.

Victor Jouque

Neurocentre Magendie

Beyond satiety: new roles for POMC neurons in feeding

Eating is a process essential for life. Therefore, powerful brain mechanisms have evolved to allow not only the matching of the organism's energy needs with energy intake, but also the recognition of food rich in calories to guarantee survival under variable environmental food sources. In this context, neuronal circuits classically aiming at integrating information about the organism's energy status must interact with networks regulating the rewarding aspect of food intake. Little is known about how such communication is set in place and the neuronal substrates underlying this phenomenon. Hypothalamic pro-opiomelanocortin (POMC) neurons are classically viewed as the mediators of satiety by the release of a-MSH in response to metabolic and hormonal cues. However, recent evidence demonstrates that POMC neurons are highly heterogeneous, can stimulate feeding under specific conditions, and become active before food consumption, therefore challenging the traditional view of their satietogenic function. Here, we provide new insights on the implication of hypothalamic POMC neurons in decoding food caloric value.

Quentin Leyrolle

NutriNeuro

The gut-derived metabolites as a new tool to improve mental health

Gut microbiota has been associated with mental health that can be influenced by several neurobiological processes including brain inflammation. Until now mechanisms remained poorly understood. In this regard, gut-derived metabolites (GDM) are interesting compounds that are produced by gut bacteria and, for some of them, can reach the brain and influence brain inflammation and behaviour. Thus, the aim of our work was to select GDM that are decreased in mental health disorders and to test whether a supplementation can have a protective effect in preclinical models against brain inflammation and behavioural disturbances by using microglia cultures and chronic social defeat stress (CSDS) model. We observed that a phenolic GDM is able to alleviate proinflammatory cytokines production under lipopolysaccharides stimulation in primary microglia culture. We also observed that oral supplementation with this GDM was able to rescue CSDS-induced weight gain as well as anxiety and depressive-like behaviour. Our results revealed that phenolic GDM can efficiently modulate microglia inflammatory activity in vitro and prevent chronic stress induced behavioural disturbances.

Flore Marchaland

NutriNeuro

Neurobiological mechanisms protecting FAT-1 offspring from memory impairment induced by maternal dietary n-3 polyunsaturated fatty acid deficiency

N-3 and n-6 polyunsaturated fatty acids (PUFA) are essential fatty acids whose precursor forms are provided by plant foods. Once consumed, they are metabolized into long chain PUFA, notably docosahexaenoic acid (DHA, n-3) and arachidonic acid (ARA, n-6), which are the most abundant PUFA in the brain, esterified into neuronal and glial cell phospholipids. During perinatal period, they are transferred through placenta during gestation and milk during lactation. Thus, n-3 and n-6 PUFA levels accreted in the developing brain are highly reliant on maternal PUFA dietary intake. As a result, maternal dietary n-3 PUFA deficiency reduces n-3 PUFA and increases n-6 PUFA accretion in offspring's brain. We previously found that this imbalance between n-3 and n-6 PUFA leads to long-lasting alterations of spatial memory, morphological and functional parameters of hippocampal neurons, and hippocampal-cortical network connections in male offspring. These experimental findings are corroborated by clinical observations reporting a positive correlation between maternal n-3 PUFA status and children's cognitive performance. However, mechanisms by which n-3 PUFA impact brain development and cognitive trajectory, considering sex, remain poorly understood. Thus, by combining nutritional and genetic approaches, we developed a model allowing the maintenance of n-3 PUFA levels in offspring developing in a n-3 PUFA-deficient maternal environment, thanks to the fat-1 gene. This gene, not present in mammals, comes from C. elegans and converts n-6 into n-3 PUFA. We mated FAT-1 homozygous fathers with wild-type (WT) mothers to generate FAT-1 heterozygous offspring developing in a WT mother. Our findings show that perinatal exposure of these WT mothers to a n-3 PUFA-deficient diet decreases n-3 PUFA levels while increases n-6 PUFA levels in the brain of their WT pups, not their FAT-1 pups, who maintain n-3 PUFA levels similar to those of WT offspring from WT mothers fed a diet balanced in n-6/n-3 PUFA. This imbalanced PUFA ratio also impact cerebral levels of their bioactive derivatives, oxylipins, whose analysis reveals different profiles depending on the genotype and sex of the offspring. Moreover, at weaning, n-3 PUFA-deficient WT offspring display spatial memory impairment, in contrast to n-3 PUFA-deficient FAT-1 or n-3 PUFA-sufficient WT offspring. In addition, hippocampal pyramidal neurons display higher density of mature dendritic spine in n-3 PUFA-deficient FAT-1 compared to WT offspring. Finally, transcriptomic analysis of the hippocampus and cortex of the offspring reveals a significant down-regulation of mitochondrial metabolic pathways in n-3 PUFA-deficient FAT-1 compared to WT offspring. Overall, our results suggest that perinatal maintenance of n-3 PUFA levels mitigates alterations induced by maternal n-3 PUFA deficiency on neurodevelopment, in both male and female offspring, potentially explained by mitochondrial metabolism involvement.

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Wassilios Meissner

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Trial of the GLP-1 receptor agonist lixisenatide in Parkinson's disease

Background: Lixisenatide, a glucagon-like peptide-1 receptor agonist used for the treatment of diabetes, has shown neuroprotective properties in a mouse model of Parkinson's disease.
Methods: In this phase 2, double-blind, randomized, placebo-controlled trial, we assessed the effect of lixisenatide on the progression of motor disability in persons with Parkinson's disease. Participants in whom Parkinson's disease was diagnosed less than 3 years earlier, who were receiving a stable dose of medications to treat symptoms, and who did not have motor complications were randomly assigned in a 1:1 ratio to daily subcutaneous lixisenatide or placebo for 12 months, followed by a 2-month washout period. The primary end point was the change from baseline in scores on the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (range, 0 to 132, with higher scores indicating greater motor disability), which was assessed in patients in the on-medication state at 12 months. Secondary end points included other MDS-UPDRS subscores at 6, 12, and 14 months and doses of levodopa equivalent.
Results: A total of 156 persons were enrolled, with 78 assigned to each group. MDS-UPDRS part III scores at baseline were approximately 15 in both groups. At 12 months, scores on the MDS-UPDRS part III had changed by -0.04 points (indicating improvement) in the lixisenatide group and 3.04 points (indicating worsening disability) in the placebo group (difference, 3.08; 95% confidence interval, 0.86 to 5.30; P = 0.007). At 14 months, after a 2-month washout period, the mean MDS-UPDRS motor scores in the off-medication state were 17.7 (95% CI, 15.7 to 19.7) with lixisenatide and 20.6 (95% CI, 18.5 to 22.8) with placebo. Other results relative to the secondary end points did not differ substantially between the groups. Nausea occurred in 46% of participants receiving lixisenatide, and vomiting occurred in 13%.
Conclusions: In participants with early Parkinson's disease, lixisenatide therapy resulted in less progression of motor disability than placebo at 12 months in a phase 2 trial but was associated with gastrointestinal side effects. Longer and larger trials are needed to determine the effects and safety of lixisenatide in persons with Parkinson's disease.

Authors : cf. https://pubmed.ncbi.nlm.nih.gov/38598572/

Cristina Miralpeix

Neurocentre Magendie

Hypothalamic POMC neurons control competing behaviors

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Survival in natural habitats forces animals to constantly adapt their behavior according to their intrinsic needs and environmental conditions. This situation can put basic physiological responses in competition, forcing the animal to make a choice. For instance, a hungry animal in a threatening situation will favor fear responses over their motivation to eat to ensure survival. However, in this context, how the brain senses the inner state and a threatening situation to orchestrate an optimal survival response has been poorly studied. Within the hypothalamus, pro-opiomelanocortin (POMC)-expressing neurons classically promote satiety during energy surfeit and have a role in the physiological adaptations that occur during stressful and fearful events. Recent findings from our lab have demonstrated that POMC neurons activity is regulated by cannabinoid type 1 (CB1) receptors, key physiological determinants of synaptic and behavioral functions. Here, we hypothesized that CB1 receptor-dependent signaling in POMC neurons is at the intersection of fear and feeding responses. Mice lacking CB1 in POMC neurons POMC-CB1-KO, did not show any relevant change in food intake in basal condition compared to their control littermates. However, when POMC-CB1-KO mice were fasted and in a fearful situation (using fear-conditioning protocol), they displayed higher motivation for eating and decreased fear response than their control littermates. Immunofluorescence and chemogenetic studies showed that POMC activation is necessary for suppressing the motivation to eat in a threatening situation. However, POMC neurons without CB1 are in a hyperactive state, possibly impairing proper decision making. In addition, POMC neurons are a heterogeneous population that can express both inhibitory and excitatory neurotransmitters. We have observed that mice with impaired release of GABA in POMC neurons, also favor eating behavior over fear responses. Thus, these results suggest that CB1 receptors and GABA release in POMC neurons are key to balancing fear and feeding behaviours. Finally, since a threatening situation can activate the stress response and POMC neurons modulate stress hormones release through CRH neurons, we evaluated corticosterone plasma levels observing that corticosterone levels of POMC-CB1-WT and KO correlate with their eating behaviour and fear response. Therefore, we are now deciphering a POMC-to-CRH neurons circuit as possible key to control competing behaviors.

Jean-Charles Nicolas

Neurocentre Magendie

New insights in the functional heterogeneity of POMC neurons

Obesity results from an imbalance in energy homeostasis and maladaptive central changes in the perception of peripheral energy state signals, with POMC neurons in the arcuate nucleus (ARC) playing a key role. Accumulating data from our laboratory suggest that the extracellular matrix (ECM), in particular perineuronal networks (PNNs), are critical regulators of POMC neuronal biology. PNNs, composed of molecules such as chondroitin sulphate proteoglycans (CSPGs), surround a subset of POMC neurons at the ARC-median eminence junction and contribute to the intrinsic functional heterogeneity of this neuronal population. Understanding how PNNs modulate POMC neuronal activity may provide new insights into the molecular mechanisms of obesity, with potential implications for the development of novel therapeutic strategies to treat metabolic disorders.

Posters

P1 - A ketogenic diet enriched with omega-3 fatty acids alleviates primary mitochondrial disease in mice.
Luciano Willemse - North-West University, South-Africa

P2 - Long-term effects of an egg-protein hydrolysate on cognitive performance and vascular function: a randomized controlled trial in adults with elevated subjective cognitive failures
Micah Adams - Maastricht University, The Nethelands

P3 - Modulation of melanocortin-3-receptor neurons during stress affects feeding behavior
Jiajie Zhu - Universität Potsdam, Germany

P4 - Fasting changes the activity of melanocortin-3 receptor (MC3R) neurons in the paraventricular thalamus (PVT)
Robert Chesters - German Institute for Human Nutrition, Germany

P5 - The gut-brain vagal axis governs mesolimbic natural and recreational reward dynamics.
Oriane Onimus - Univ. Paris Cité, France

P6 - Neuroprotection through gut microbiota modulation in neonatal hypoxia-ischemia Study on a rat model
Pierre Goudeneche - Univ. of Bordeaux, France

P7 - Activation of NAc in response to dietary and genetic changes specifically focused on the role of MC3R neurons
Tsendmaa Tsengenbayar - Universität Potsdam, Germany

P8 - Involvement of FGF21 in the crosstalk between brown fat thermogenesis activation and hypothalamic endocannabinoids in obesity
Rosalia Rodriguez-Rodriguez - Universitat Internacional de Catalunya, Barcelona, Spain

P9 - Early hypothalamic inflammation induces central insulin resistance
Sebastian Zagmutt - Universitat Internacional de Catalunya, Barcelona, Spain

P10 - Nurturing the next generation: Unraveling the role of gut-derived short-chain fatty acids in offspring metabolism and neurodevelopment
Nadia Elshareif - Univ. of Lausanne, Switzerland

P11 - Tanycytic transcytosis inhibition disrupts energy balance, glucose homeostasis and cognitive function in male mice
Eleonora Deligia - Univ. of Lille, France

P12 - Constitutive activation of YAP in tanycytes triggers proliferation and impairs energy homeostasis
Mathilde Roux - Univ. of Lille, France

P13 - Insulin regulates energy substrate switching in astrocytes
Bouchra Taib - Univ. Ibn Tofail, Morocco

P14 - A randomised controlled trial to investigate the cognitive, mood and metabolic effects of acute oyster mushroom intervention in older adults (oysaco study).
Sara Cha - Reading, UK

P15 - GnRH, a fertile new pathway for the regulation of food intake
Alicia Sicardi - Univ. of Lille, France

P16 - TaqIA polymorphism role in reward- and metabolic-associated disorders: new insights from a humanised murine model.
Simon Benoit - Univ. Paris Cité, France

P17 - Dopamine d2r-neurons of the paraventricular thalamus govern feeding, energy balance and body homeostasis.
Bertrand Benoit- Univ. Paris Cité, France

P18 - Insulin signaling in astrocytes plays a role in the brain-liver axis and the control of glucose production.
Elena Garcia Clave - Helmholtz Zentrum, Munich, Germany

P19 - Circulating triglycerides scale the activity and functions of the dopamine reward system depending on metabolic states.
Guangping Li - Univ. Paris Cité, France

P20 - Impact of Omega-3 Polyunsaturated Fatty Acids on Emotional, Cognitive and Biological Alterations in Alcohol Use Disorder
Marie Mornard - UCL, Louvain, Belgium

P21 - Sex difference in cognitive deficits and hippocampal alterations induced by n-3 polyunsaturated fatty acid deficiency
Ivan Marniquet - Univ. of Bordeaux, France

P22 - The Gut Microbiota Influences Hypothalamic Blood-CSF Barrier Structure and Function
Marialetizia Rastelli - Univ. of Lille, France

P23 - Depression phenotypes, dietary habits, and biological pathways: An overall assessment of the Gut-Brain-Axis
Simon Van Haverbeke - UCL, Louvain, Belgium

P24 - Differential involvement of cb1 receptors in obesogenic diet-induced memory deficits in male and female mice
Mylène Potier - Univ. of Bordeaux, France

P25 - CB1 receptors located on hippocampal glutamatergic neurons control obesogenic diet-induced memory impairment in male mice
Eva-Gunnel Ducourneau - Univ. of Bordeaux, France

P26 - Human 3D-cerebral organoids: phenotypic & functional characterization to study brain-nutrient interactions in vitro.
Milan Boulaire - Univ. of Bordeaux, France

P27 - Astrocytic hemichannels are involved in hypothalamic control of energy balance
Caroline Léger - Univ. of Paris Cité, France

P28 - Adverse effects of adolescent obesity on recognition memory performances in an fMRI task
Anaïs Bouvier - Univ. of Bordeaux, France

P1 - A ketogenic diet enriched with omega-3 fatty acids alleviates primary mitochondrial disease in mice.

Luciano Willemse[1], Karin Terburgh[1] and Roan Louw[1]

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Background: Leigh syndrome is a mitochondrial disorder characterized by neurodegeneration, neurometabolic disease, inflammation, and hyperactivation of the mammalian target of rapamycin (mTOR). The ketogenic diet (KD), known for its high fat and low carbohydrate composition, inhibits the mTOR pathway and alters the cellular redox state. High omega-3 (ω-3) diets also show potential in regulating mTOR activity, reducing inflammation, and delaying neurodegeneration in animal models. The study explored the impact of a dietary intervention, specifically a high ω-3 KD, on mTOR activity, inflammation, and disease progression using the Ndufs4 knock-out (KO) mouse model.
Methods: Dietary intervention was initiated on postnatal day 24 for each group (n=12). The study evaluated disease phenotype and survival rates in knockout (KO) mice, comparing those fed a control diet to those on a high ω-3 KD. Phenotypic assessment involved monitoring survival, clasping onset, locomotor activity, and grip strength. Biochemical and metabolic analyses were conducted on both wild-type (WT) and KO mice, with each group receiving either the control diet or the high ω-3 KD. Assessment of mTOR activity via western blotting and systemic inflammation via flow cytometry was performed on brain tissue and serum, respectively. Neurometabolism was further evaluated using untargeted metabolomics (1H-NMR, GC-TOF-MS) and lipidomics (Synapt G2-Si).
Results: KO mice fed a high ω-3 KD showed significant improvements in survival and a decrease in clasping behavior compared to those on a control diet. However, no significant differences were observed in locomotor activity and grip strength between the two groups. Moreover, while no significant effect was detected in brain mTOR activity, there were significant changes in inflammation levels in the serum. Additionally, metabolic and lipidomic profiling unveiled significant alterations in numerous metabolic pathways following consumption of the high ω-3 KD, indicating a potential metabolic reprogramming effect.
Conclusion: These results shed light on the influence of a high ω-3 KD on mTOR activity, as well as neuro- and systemic inflammation, underscoring its role in systemic metabolism. The study provides valuable insights into the therapeutic potential of a ω-3 KD in alleviating metabolic and inflammatory conditions, such as neurodegeneration and metabolic syndrome. Further research is needed to explore the potential advantages of this dietary intervention in translational and clinical studies of mitochondrial dysfunction, neurodegenerative diseases, and metabolic disorders.

Keywords: Ketogenic diet; Omega-3; mTOR; Western blot; Flow cytometry; metabolomics; lipidomics.

P2 - Long-term effects of an egg-protein hydrolysate on cognitive performance and vascular function: a randomized controlled trial in adults with elevated subjective cognitive failures

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Age-related chronic diseases including dementia and cardiovascular disease are a growing concern. An impaired vascular function is considered an important common denominator of these co-morbidities. We previously reported that short-term intake of the egg-protein hydrolysate Newtricious (NWT)-03 improved cognitive performance, but underlying mechanisms and long-term effects are unknown. Our aim was, therefore, to assess the long-term effects of NWT-03 in participants with elevated subjective cognitive failures (SCF) on cognitive performance, cerebral blood flow (CBF) - a marker of brain vascular function, and vascular endothelial function. A 36-week randomized controlled trial (RCT) was conducted with 40 (n=23 men, n=17 women) overweight or obese adults experiencing elevated SCF. Participants consumed 5.7g of NWT-03 or maltodextrin placebo powders daily. Cognitive performance was evaluated using a neurophysiological test battery (CANTAB). CBF was quantified by magnetic resonance imaging perfusion method Arterial Spin Labeling. Vascular endothelial function was assessed using brachial artery flow-mediated vasodilation (FMD) and carotid artery reactivity (CAR). A one-way ANCOVA, using the baseline measurements of the outcome variables as covariates and intervention as a fixed factor was conducted to determine differences in responses between intervention and placebo groups.

No overall intervention effects were observed on cognitive performance or CBF in the whole group, but post-hoc analyses revealed greater improvements in executive function in women compared to men. Women experienced a 74 ms reduction in reaction latency on the multitasking task (95%CI: -134, -15; p=0.02) and a 9-point reduction in total errors (95%CI: -15, -3; p<0.001) on the spatial working memory task. There were no sex differences in CBF or vascular endothelial function. In the whole group, beneficial effects on FMD nearly reached statistical significance (0.34 percentage points (pp), 95%CI: -0.1,0.7; p=0.08) and a significant improvement in CAR (0.70 pp, 95%CI: 0.1,1.3; p=0.03) responses was observed. Among women with elevated SCF, long-term NWT-03 consumption enhanced executive functioning in women, while vascular endothelial function improved for both sexes. Brain vascular function remained unaffected, suggesting that other mechanisms may explain the observed improvements in executive function.

P3 - Modulation of melanocortin-3-receptor neurons during stress affects feeding behavior

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Stress is a common trigger for inappropriate eating behaviors within modern society, yet the neural mechanism responsible for this is poorly understood. The central melanocortin system is the key regulator of energy homeostasis and feeding behavior, and functions by signaling to a family of five G protein–coupled melanocortin receptors; MC1R - MC5R. Of these receptors, only MC3R and MC4R are expressed in the brain.
Our focus has been on the role of MC3R neurons and their role in stress responses. A modified social defeat test was chosen to mimic a social stressor in mice. We first used DREADD mouse model to either activate or inhibit MC3R cells in the entire animal. Further, we modulated region specific MC3R neurons using stereotaxic surgery and virus-mediated expression of DREADDs specifically in the brain. We assessed food intake, body weight change and brain activity using immediate early gene markers as well as a behavioral readout using DeepLabCut and SIMBA analysis.
We observed that activation of whole body MC3R cells protected the animals from stress-induced body weight loss by inducing more food intake. Assessment of the neuronal activity marker c-Fos, demonstrates a sex difference with females showing a more profound pattern of neuronal activation in response to DREADD mediated activation of MC3R cells. We also show that during the acute phase of social defeat test, animals exhibited specific behavioral patterns that differ between treatment groups. In conclusion, modulation of MC3R cells using DREADD receptors results in unique and significantly changes to feeding behavior in response to a social stressor. This response also is sex specific, warranting the further study of the MC3R in females as a marker of stress mediated changes to eating.

P4 - Fasting changes the activity of melanocortin-3 receptor (MC3R) neurons in the paraventricular thalamus (PVT)

Robert A. Chesters[1], Selma Yagoub1,2,4, Bethany M. Coull[1], Lea Baumer[1], Katrin Ritter[1], Rachel N. Lippert[1,3,4]

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The brain exerts control over energy homeostasis by regulating food intake through signaling within the melanocortin system. Whilst we understand the role of the hypothalamus within this system, how extra-hypothalamic brain regions are involved in the control of energy balance, and how the development of these systems might be perturbed due to early influences, remains under investigation.
The melanocortin-3 receptor (MC3R) is implicated in modulating feeding behavior and body weight changes under different nutritional challenges, and MC3R deficient animals show a defective fasting response. The MC3R is highly expressed in the paraventricular nucleus of the thalamus (PVT): a brain region that integrates information about internal energy state with environmental stimuli to determine feeding and reward behaviors. Understanding the role and the development of MC3R neuronal activity within the PVT could present as an interesting nexus for food intake regulation in various contexts.
In this study we show that, in adult ad-libitum fed mice, MC3R-PVT neuronal activity follows a circadian pattern of activity. Moreover, this fluctuation of activity is dependent on food availability, as a 16-hour overnight fast alters this rhythm. Upon refeeding, however, this activity significantly increases to that seen under fed conditions. To further explore these effects in the PVT, we identified a role of early maternal overnutrition in impacting the development and maintenance of projections to the PVT and assessed changes in neuronal response to fasting established in the non-maternal diet manipulated paradigm outlined above.
In conclusion, we have identified circadian fluctuations in PVT-MC3R neuronal activity. These fluctuations are significantly impacted by energy state, as fasting results in changes to the activity pattern. We also show significant changes to the PVT in adult animals exposed to early maternal overnutrition. Further in-depth analysis of PVT MC3R neurons may yield advanced understanding of feeding-related behaviors.

P5 - The gut-brain vagal axis governs mesolimbic natural and recreational reward dynamics.

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Reward-related disorders, elicited by recreational psychoactive drugs (cocaine, amphetamine) or natural rewards (food), are associated with functional, structural, and long-lasting alterations of the brain dopamine (DA) reward system. Despite their intrinsic differences, drugs of abuse and palatable food lead to (mal)adaptive modifications of the DA system that can ultimately drive compulsive and addictive behaviours with severe health and social impacts, collectively increasing the urgent need for innovative therapeutic strategies.
Visceral and interoceptive information through the vagal axis, classically described for its main role in feeding and energy homeostasis, also modulates the reward system. However, the functional underpinnings of such modulation in reward processing and associated disorders are unknown. Here, we provide evidence showing that the gut-brain vagal axis serves as an integrative lever for gating the hedonic and homeostatic effects of both natural and recreational stimuli, thereby playing a permissive role in the development of reward-based dysfunctions such as eating disorders (binge eating, obesity) and drug addiction. By taking advantage of multi-scale approaches (from integrative physiology to neuronal networks dynamics) and complementary cutting-edge techniques (neuronal morphology, electrophysiology, in vivo imaging) to decipher the complex role of the vagus nerve in reward/addictive behaviours, we demonstrate the existence of an extended reward system, and we highlight the functional and structural adaptations of DA-neurons and dynamics within the mesolimbic system.
In conclusion, we propose a novel conceptual framework that sees in the interoceptive vagal axis a major player in the development of reward dysfunctions, thus providing evidence for a new therapeutic target.

P6 - Neuroprotection through gut microbiota modulation in neonatal hypoxia-ischemia – Study on a rat model

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Neonatal hypoxia-ischemia (NHI) is a major cause of perinatal death and long-term disability. The only therapeutic solution is hypothermia but half of newborns does not respond favorably to this standard of care. Therefore, development of new therapeutic approaches is a priority. Our team has shown, in a rat model of NHI, a neuroprotective effect of a nutritional maternal supplementation with resveratrol (RSV, polyphenol present in grapes), in the context of NHI, characterized by a decrease in brain lesion volumes and preservation of sensorimotor skillsA. However, RSV has low bioavailability, limiting its translation to humans. In this context, we evaluated the benefice of a maternal supplementation with a polyphenolic cocktail (RSV + viniferin + pterostilbene)B,C in order to obtain a synergy effect. This maternal supplement provided better neuroprotection than supplementation with RSV alone in pups that underwent NHI. At the mechanistic level, we demonstrated that the neuroprotective effects of these polyphenols involved the stimulation of brain energy metabolismA. Brain is not an isolated organ, a systemic implication has therefore been questioned, particularly at the level of the gut-brain axis. The aim of this new project was to determine the role of the gut microbiota in the neuroprotection of maternal polyphenolic supplementation, in the context of NHI, on a rat model. Rat pups whose mothers were not supplemented were force-fed, for 7 days, with fecal transplants from females supplemented with polyphenolic cocktail. These pups then underwent NHI. The effect of fecal transplantation on NHI-induced damage was assessed multimodally by diffusion MRI and behavioral tests. Our results showed for the first time that modulation of the maternal microbiota by consumption of polyphenols was involved in neuroprotection, in the context of NHI.

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P7 - Activation of NAc in response to dietary and genetic changes specifically focused on the role of MC3R neurons

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Within the brain, the hypothalamus is well known to be responsible for nutrient status and appetite control via the action of the central melanocortin system. The nucleus accumbens (NAc) has a neural interface between motivation and action in the feeding behavior and is known to be functionally modulated by melanocortin system activation. However, studies have not fully understood the neuronal connections between brain regions which are responsible for motivation and decision making in eating behavior at the level of the potentially linked melanocortin system neurons. Interestingly, dorsal to the hypothalamus, the paraventricular thalamic nucleus (PVT) has recently been implicated in coordinating metabolic signals in the whole animal and thus might be functioning to integrate the melanocortin system signaling into the whole animal behavior. In this, we have investigated and established some of the basic understanding of neuronal connections between PVT and NAc using various novel methods in the mouse brain.

P8 - Involvement of FGF21 in the crosstalk between brown fat thermogenesis activation and hypothalamic endocannabinoids in obesity

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The endocannabinoid (eCB) system in the hypothalamus plays a critical role in the regulation of energy homeostasis and in obesity. However, the exact dynamics of endocannabinoids in the hypothalamus and their interplay with peripheral tissues during obesity development remain poorly understood. Our group has previously described a temporal profile of hypothalamic eCB levels during obesity development, closely associated with brown adipose tissue (BAT) thermogenesis activation. In our study, induction of BAT thermogenesis by the β3-adrenergic agonist CL 316,243 triggered a substantial increase in hypothalamic eCB levels. However, acute intracerebroventricular administration of the two main eCBs did not induce BAT thermogenesis. This finding led us to hypothesize a link from BAT thermogenesis to hypothalamic eCBs. Since FGF21 is a batokine secreted upon thermogenesis activation, it is a potential candidate for mediating the BAT-hypothalamus crosstalk. Here, we aim to explore the involvement of FGF21 in this crosstalk.
Our results show that, in response to the intraperitoneal injection of the β3-adrenergic agonist in WT and FGF21-KO mice, BAT thermogenesis was similarly activated by the drug in both WT and KO mice, but only led to an increase in hypothalamic eCB in WT mice. In contrast, hypothalamic eCBs in FGF21-KO mice remained unchanged. The changes in hypothalamic eCB levels were also supported by the analysis of the expression profile of the enzymes involved in synthesis/degradation of eCBs, with particular alterations in the metabolism of AEA. Similar results in hypothalamic eCB dynamics were observed following intraBAT administration of the β3-adrenergic agonist, confirming the specificity of BAT signaling.
Altogether, these preliminary results suggest that FGF21 is involved in the signaling between BAT and hypothalamus. Our study is revealing a new signal in the endocannabinoid system within the hypothalamus and could therefore contribute to a better understanding of the pathophysiology of obesity.

P9 - Early hypothalamic inflammation induces central insulin resistance

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Obesity is defined as excessive fat storing resulting from a chronic surplus of energy intake relative to energy expenditure. The main region of the brain controlling energy balance is the hypothalamus, composed of a series of nuclei containing a sophisticated neuronal network that regulates functions such as food intake and satiety. Therefore, obesity can be considered a metabolic disorder associated with hypothalamic dysfunction.
Over the past two decades, obesity has been associated with chronic low-grade inflammation in various peripheral tissues, but despite the significant advances in molecular mechanisms, hypothalamic inflammation occurring during obesity has been less explored. Studies have shown that diet-induced inflammation initially and preferentially affects the medial basal hypothalamus, but little is known about the microglial dynamics that trigger this inflammation and the underlying events.
Here, we explore the effects of a high-fat diet in hypothalamic microglia dynamics during early stages of diet-induced obesity in male and female mice.
Results: Three days of a high-fat diet (HFD) are sufficient to increase the number of microglia in the paraventricular nucleus of the hypothalamus, whereas no changes are observed in astrocyte activation. This result is accompanied by an increase in the expression of proinflammatory cytokines in the hypothalamus. Characterization of microglial polarization reveals that after one day of HFD, there is an increase in M2 marker expression that decreases over the exposure to the diet. Seven days of HFD induces strong central insulin resistance that precedes peripheral insulin resistance. Our results reveal that the early inflammatory events occurring in the hypothalamus could be the initial triggers of metabolic imbalance at the peripheral level.…

P10 - Nurturing the next generation: Unraveling the role of gut-derived short-chain fatty acids in offspring metabolism and neurodevelopment

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The rising prevalence of obesity and type 2 diabetes necessitates innovative approaches to address metabolic dysfunction. Western dietary habits, characterized by high saturated fat, sugar, and low fiber, disrupt the gut microbiome, impairing vital gut-brain signaling pathways and exacerbating metabolic imbalances. Although the gut microbiota's role in metabolism is acknowledged, the precise molecular mechanisms of regulating host physiology are not well defined. Fermentation of dietary fiber produces short-chain fatty acids (SCFAs), namely acetate, propionate, and butyrate, exhibit promising effects on glucose regulation and mood modulation via the gut-brain axis.1 However, the specific involvement of SCFAs and free fatty acid receptors (FFARs), in metabolic and neuronal regulation requires further elucidation.

Recent research has highlighted the pivotal role of maternal gut microbiota in offspring metabolic resilience where maternal propionate production emerges as a critical determinant shaping embryonic metabolic and neural systems, influencing glucose homeostasis and energy balance during post-natal development and through adulthood.2 Offspring lacking maternal gut microbiota, and in term, short chain fatty acids, display heightened susceptibility to metabolic disturbances and autonomic dysregulation, a phenomenon observed in FFAR3 knockout offspring despite maternal high fiber intake. Based on these findings, we hypothesize that maternal gut-derived SCFAs and neuronal FFAR3 mediate these effects.

Here, unravel mechanisms underlying SCFA and FFAR-mediated protection against neuro-developmental and metabolic dysfunction by manipulating maternal diet during pregnancy and evaluating expression profiles of FFAR3 and downstream targets. Using cre-lox mouse models, we identify neuron-specific roles of FFAR3 in the protective mechanisms of SCFAs and their long-lasting effects. These efforts aim to identify novel therapeutic targets by manipulating maternal nutrition to prevent offspring metabolic disease.

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P11 - Tanycytic transcytosis inhibition disrupts energy balance, glucose homeostasis and cognitive function in male mice

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Western diets high in fats and sugars, have significantly contributed to the obesity epidemic and its associated health issues. The disruption of communication between the body and brain—essential for maintaining glucose and energy balance—results from both obesogenic and genetic factors, leading to metabolic disorders. In this study, we explore the role of hypothalamic tanycyte shuttles between the pituitary portal blood and the third ventricle cerebrospinal fluid in regulating energy balance.
The release of molecules mediated by vesicle-associated membrane proteins (VAMP1-3) in tanycytes was inhibited by expressing botulinum neurotoxin type B light chain (BoNT/B) in a Cre-dependent manner.
In male mice on a standard diet, targeted expression of BoNT/B in adult tanycytes blocks leptin transport into the mediobasal hypothalamus amd leads to central obesity characterized by increased food intake, abdominal fat accumulation, and elevated leptin levels, though body weight remains largely unchanged. Additionally, BoNT/B expression in tanycytes promotes fat storage, leading to glucose intolerance and insulin resistance. Remarkably, these metabolic disruptions occur despite a compensatory increase in insulin secretion, observed in response to both exogenous glucose administration in vivo and isolated pancreatic islets. Interestingly, these metabolic changes are also linked to impaired spatial memory in BoNT/B-expressing mice.
These findings emphasize the critical role of tanycytes in the communication between the brain and the periphery, suggesting their potential involvement in the development of type 2 diabetes and cognitive decline with age. Our tanycytic BoNT/B mouse model offers a valuable tool for studying the progression of these conditions and the specific contribution of tanycytes to their onset. Recognizing the impact of tanycytic transcytosis on hormone transport opens up new possibilities for developing targeted therapies that could address both metabolic disorders and their associated cognitive impairments, which often emerge or worsen with age.

P12 - Constitutive activation of YAP in tanycytes triggers proliferation and impairs energy homeostasis

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In the adult mammalian brain, the hypothalamus has been identified as a neural stem cell (NSC) niche, in which newborn neurons integrate circuits controlling energy homeostasis. Putative NSCs of this niche are the tanycytes, specialized radial ependymoglial cells lining the 3rd ventricle (3V), which are also key components for the regulation of energy balance. A proposed candidate for the regulation of tanycyte NSC properties is the Hippo pathway (HP), a major signaling pathway involved in organ growth and stem cell control. Previous work of the lab has shown that all core components of the HP are expressed in adult mouse tanycytes. We therefore thought to explore whether the HP controls tanycyte NSC properties and impacts energy metabolism.

To do so, we used an in vivo model of hyperactivation of Yes-associated protein (YAP), the main effector of the pathway, in tanycytes, thanks to the intracerebroventricular injection of an adeno-associated virus 1/2 coding for a constitutively active mutant form of YAP (YAPCA) driven by the tanycyte-specific deiodinase 2 promoter. Mice were subsequently injected with the thymidine analog bromodeoxyuridine (BrdU) and sacrificed after 2 months in order to assess cell proliferation and differentiation. Immunodetection of BrdU showed that the expression of YAPCA in tanycytes markedly stimulated cell proliferation in the mediobasal hypothalamus, associated to increased vimentin staining along the 3V border, suggesting a disorganization of the tanycyte border. Co-immunodetection of different lineage markers (Sox2 for progenitors, HuC/D for neurons, S100 for astrocytes, Olig2 for oligodendroglial lineage cells) was performed to determine the fate of newborn cells and showed that most remained in a progenitor state, and that YAPCA did not favor the entrance in any cell lineage over the others. In agreement with neuroanatomical data, RT-qPCR analysis on tanycytes isolated by fluorescence-activated cell sorting revealed that YAPCA enhanced the expression of genes involved in cell cycle progression such as cyclin dependent kinase 6 or cyclin D1. YAPCA expression in tanycytes also increased mice bodyweight and fat mass, while glucose homeostasis was not affected.

Altogether, our results show that YAP regulates the proliferation of adult tanycytes and that forced activation of tanycyte proliferation impacts energy homeostasis.

P13 - Insulin regulates energy substrate switching in astrocytes

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The β-oxidation of fatty acids is thought to be limited in brain. This notion has been challenged by recent data showing that under conditions of high neuronal activity the toxic accumulation of fatty acids is circumvented by transporting fatty acids to astrocytes for β-oxidation. We found that insulin induces the uptake of glucose and fatty acids in astrocytes while shifting their metabolic preference from glucose to fatty acids through a sequential shift in the expression of genes associated with fatty acid uptake, synthesis, transport and metabolism. Fatty acids are converted into TCA cycle intermediates in sufficient quantity to satisfy astrocyte energy demands. Under these conditions, pyruvate derived from glucose is directed away from the TCA cycle to accelerate the production of lactate that is a preferred fuel for neurons. This shift in astrocyte energy substrate preference is required for insulin to enhance long-term potentiation in the Schaffer collateral. These findings establish a homeostatic mechanism where insulin promotes LTP by switching the energy substrate preference of astrocytes to fatty acids. This allows glucose in astrocytes to be shuttled to the production of lactate that is the preferred fuel for neurons.

P14 - A randomised controlled trial to investigate the cognitive, mood and metabolic effects of acute oyster mushroom intervention in older adults (oysaco study).

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The aim of this double-blind randomised cross-over study was to investigate whether ergothioneine-rich oyster mushrooms induce benefits to cognitive performance and mood in the immediate post-prandial period. Healthy adults (n=33) aged 60-80 years old consumed a noodle soup containing the equivalent of 0.5 (OM0.5), 1 (OM1) and 2 (OM2) servings of freeze-dried oyster mushroom powder, or a calorie-matched control soup (OM0), on four separate occasions each separated by one week. Cognitive function and subjective mood were assessed at baseline (-1h, prior to administration of the intervention) and then at 2h, 4h and 6h post-consumption on each test day. A serum blood sample was taken at 6h, to measure metabolic, neurotrophic and inflammatory markers. Results revealed tentative benefits to positive affect (PA) and mental fatigue (MF), driven primarily by a statistically significant decline in PA and concomitant increase in MF over the test day after consuming OM0. This pattern was not seen following mushroom treatments OM0.5, OM1, or OM2, possibly suggestive of a protective effect. Cognitive findings were mixed with no consistent pattern of effects seen following mushroom treatments compared to placebo on executive function and memory measures. Unexpectedly, brain derived neurotrophic factor (BDNF) in serum at 6h post-treatment was found to be dose-dependently lower after consuming the mushroom treatments compared to OM0. At the same timepoint analysis of the inflammatory markers revealed significantly lower levels of nitrite, nitric oxide (NOX) and inducible nitric oxide synthase (iNOS), following mushroom treatments compared to OM0. However, no significant between-treatment differences were observed for the metabolic markers. Overall, this study has shown that healthy adults tentatively experienced a protective mood effect, up to 6h post-consumption of ergothioneine-rich oyster mushrooms. However, the observed differences in BDNF and inflammatory markers require further investigation to understand how these actions may contribute to the observed behavioural effects. Future studies should explore the impact of oyster mushrooms after repeated daily consumption over several weeks.

P15 - GnRH, a new fertile pathway for the regulation of eating behaviour

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Eating disorders are multifactorial and complex diseases with no effective long-term treatment. Patients suffering from these pathologies show severe alterations in their reproductive function such as dysmenorrhea and fertility problems even after remission. The hypothalamus is the seat of regulation of many vital functions including reproduction and energy metabolism. An interconnection exists between them. The reproductive function is orchestrated by GnRH neurons. The way in which metabolic state can modulate the function of GnRH neurons is well documented. Indeed, it is known that in the presence of a disturbed energy balance due to both an excess and a lack of energy reserves, reproduction and hence GnRH neuronal activity is shut down. In contrast, the existence of an inverse link is much less clear. To investigate whether GnRH neurons can regulate metabolism, we generated mice in which activity-dependent exocytosis, including GnRH secretion, is blocked by the Cre recombinase-dependent expression of the Clostridium botulinum neurotoxin serotype B light chain (Gnrh1::cre; iBot). Gnrh1::cre; iBot mice show a drastic decrease in food intake as well as deregulation of body weight and other metabolic parameters. A 15-day treatment restoring the physiological rhythm of GnRH secretion in these mice rescues these alterations. Beyond state-of-the-art approaches, such as ultrahigh field 17.2T magnetic resonance imaging, as well as more classical neuroanatomical and physiological approaches are being used to untangle the role of GnRH in the regulation of eating behaviour. Overall, our results show an involvement of the reproductive hormone GnRH in the regulation of eating behaviour and raise the intriguing possibility that pulsatile GnRH therapy holds potential for the management of eating disorders.

P16 - TaqIA polymorphism role in reward- and metabolic-associated disorders: new insights from a humanised murine model.

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While the over-consumption of energy-dense foods is now clearly identified as one of the main causes of obesity, there is a large body of evidence supporting that the development of obesity and related disorders is also the result of an interaction between specific genetic polymorphisms and the modern food environment. In this context, the addiction-susceptibility TaqIA polymorphism is of particular importance. TaqIA is a single nucleotide polymorphism located in the Annk1 gene, corresponding to three variants: A1/A1, A1/A2, and A2/A2. The function of the Annk1 protein is yet unknown. However, the presence of the A1 allele increases the likelihood of developing psychiatric disorders, such as attention deficit, hyperactivity, or eating disorders. In addition, carriers of the A1 allele have an increased risk of obesity, also indicating a role for this gene in regulating metabolism. While the A1 allele is the ancestral variant, the derived A2 variant has only recently appeared with the Homo taxon, impeding the understanding of its causal role in neuropsychiatric and metabolic disorders.
We have now generated a CRISPR-engineered single point mutation in rodent to humanise mice for the A2 allele. This unique model will bring strong translational value by allowing us to profile how A1 and A2 variants affect the development of reward- and metabolic-associated disorders in a context of developmental expression of the mutation – similar to the human context.
Motivation of male and female mice of both A1/A1 and A2/A2 genetic backgrounds was assessed in operant cages where reward is a 30s-access to feeders filled with chow food. Females A2/A2 mice significantly increased their number of active presses in a Fixed-Ratio (FR) 1 paradigm compared to their A1/A1 counterparts. However, this effect is lost when the cost to get the reward is higher (FR5) or when the reward is more palatable (high-fat high-sucrose diet, HFHS diet). Males A2/A2 significantly increased their number of feeders visits compared to their A1/A1 counterparts despite no differences in active lever press. This phenotype is heightened where the reward is more palatable (HFHS diet), and lost when the cost to get the reward is higher (FR5). Metabolism of male mice of both A1/A1 and A2/A2 genetic backgrounds was then assessed in indirect calorimetry cages. Interestingly, males A2/A2 displayed higher energy expenditure under both chow and habituation to a high-fat diet conditions that the A1/A1 counterparts.
Altogether, these data confirm the importance of the role of the TaqIA polymorphism in the regulation of reward-related behaviours and energy homeostasis. Our humanised murine model will then be of great importance to understand its causal role in the susceptibility induced by the TaqIA polymorphism.

P17 - dopamine d2r-neurons of the paraventricular thalamus govern feeding, energy balance and body homeostasis.

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The paraventricular thalamus (PVT) has recently emerged as a critical hub involved in the regulation of cognitive processes but also in the integration of homeostatic and visceral signals, thus controlling adaptive and food-seeking behavioural responses. However, despite growing evidence, the neural mechanisms by which the PVT neurocircuitry gates feeding, energy balance and nutrients partitioning remain largely unknown.
Here, we show that a specific population of PVT-neurons, notably those expressing the dopamine D2 receptors, promptly and bidirectionally (activation/inhibition) gate feeding behaviours, body homeostasis and energy balance, thereby contributing to the control of energy-related adaptive responses in both physiological and obesogenic contexts. In addition, by combining complementary cutting-edge strategies (virally mediated activation/inhibition, ex vivo electrophysiology and in vivo fiber photometry) to functional metabolic readouts, we describe PVT D2R-neurons as gatekeepers of hunger and satiety in lean and obese animals. This project may lead to a new understanding of unconventional brain circuits involved in food-related disorders and may provide new therapeutic solutions to counterbalance obesity-associated dysfunctions.

P18 - Insulin signaling in astrocytes plays a role in the brain-liver axis and the control of glucose production.

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The prevalence of obesity and its comorbidities have exponentially increased within the last years, and, despite the effort, no successful long-term anti-obesity drug has been developed to counteract such metabolic disturbances. While the central nervous system stands as a promising target, prevailing evidence predominantly fixates on neurons, neglecting other essential brain cells. Astrocytes, previously seen as mere structural support, have emerged as pivotal contributors to energy homeostasis and early responders to obesogenic diets. These glial cells express several receptors and transporters that allow them to respond to blood-born metabolic cues and communicate with neighboring neurons. Our preceding research showed that eliminating the insulin receptor in astrocytes reduces brain exposure to insulin and glucose, subsequently dampening glucose-dependent neuronal activation.
In pursuit of deeper insights, we have used transgenic mice lacking both insulin and insulin growth factor 1 receptors in astrocytes, resulting in a comprehensive blockage of insulin signaling in these glial cells. Our results demonstrate that this alteration reduces insulin-driven glucose uptake into the brain and decreases neuronal activation across multiple brain regions, with the arcuate nucleus of the hypothalamus being particularly affected. As a result, these transgenic mice show altered peripheral insulin responses, notably impairing liver insulin sensitivity and the regulation of gluconeogenesis. Interestingly, despite a marked reduction in overall body fat, the mice exhibit lipid droplet accumulation in the liver.
As research unfolds, it becomes increasingly apparent that astrocytes play a fundamental role in central insulin signaling, thereby influencing whole-body glucose homeostasis. These revelations offer a promising path for understanding and potentially mitigating the complex interplay between astrocytes, insulin, and metabolic health.

P19 - Circulating triglycerides scale the activity and functions of the dopamine reward system depending on metabolic states.

Guangping Li[1], Julien Castel[1], Anthony Ansoult[1], Benoit Bertrand[1], Claire Martin[1], Giuseppe Gangarossa[1,2], Serge Luquet[1,2]

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The modern dietary environment is saturated with energy-dense and palatable diets, which has largely contributed to the global obesity epidemic. The brain's reward circuitry, specifically dopamine (DA) transmission, plays a crucial role in regulating feeding behavior by integrating energy signals with cognitive and motivational components. Obesity and a high-fat diet disrupt DA signalling, leading to reward dysfunction and overeating. Recent studies have shown that dietary lipids, especially triglycerides (TG), which represent conserved postprandial metabolic signal, act as functional modulators of DA circuits, potentially contributing to obesity-related maladaptations.

Using behavioral and in vivo imaging approaches we demonstrate that brain-specific TG delivery modulates feeding response and produce behavioural reinforcement in lean but not in obese mice. In addition, in vivo calcium recordings revealed that brain lipid delivery decreases the activity of dopamine-2 receptor (DRD2) neurons in the nucleus accumbens (NAc) specifically in response to food cues in obese but not in lean mice while preserving DRD2-neurons response to non-food cues. In addition, central TG delivery did not affect NAc DA dynamics in response to food-reward.

These results suggest that TG can modulate the response of DRD2-neurons to DA- and non-DA-dependent signals in the processing of food-related signals in a metabolic-dependent context.

Our work reveals a role for TG in DA-mediated reward and feeding behaviors, provides new insights into the pathophysiology of obesity, and highlights potential targets for therapeutic intervention.

P20 - Impact of Omega-3 Polyunsaturated Fatty Acids on Emotional, Cognitive and Biological Alterations in Alcohol Use Disorder

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Alcohol use disorder (AUD) is a major public health problem with huge economical, psychological and social impact.

For several years now, research has been showing that the intestinal microbiota appears to play an essential role in the body's proper functioning. Many factors, including diet, influence microbial composition.

In the context of AUD, numerous studies have shown that alcohol and its metabolites alter this intestinal microbiota, leading to an increase in inflammation associated with psychological disturbances.

The main aim of our research is to test whether and how a nutritional intervention could improve the mood, cognition and social behaviour of AUD patients. Omega-3 polyunsaturated fatty acids are already well known for their role in regulating inflammation and for their beneficial on depressive symptoms. However, their role in AUD has not yet been studied.

We will conduct a randomised, placebo-controlled, double-blind study testing the impact of Omega-3 supplementation on AUD patients undergoing a detoxification program at St-Luc academic hospital. 100 AUD patients will be enrolled and tested over 3 periods: T1 (2nd day of withdrawal), T2 (18th-19th day of withdrawal) and T3 (after 3 months of withdrawal).

We hope to see a beneficial effect of omega-3 on social, emotional and cognitive deficits. We will investigate the mechanisms involved, namely changes in the composition of the intestinal microbiota, reduced systemic inflammation, and the production of bacterial metabolites with immune or neuroactive properties.

P21 - Sex difference in cognitive deficits and hippocampal alterations induced by n-3 polyunsaturated fatty acid deficiency

Ivan Marniquet[1], Flavie Crespo[1], Heena Brown[1], Liam Barry-Carroll[1], Sophie Layé[1], Jean-Christophe Delpech[1]

[1] *Univ. Bordeaux, INP Bordeaux, INRAE UMR 1286, Nutrineuro*

The rise in the elderly population is leading to an increase in the number of people suffering from cognitive decline, causing major socio-economic stress on the healthcare system. Among the environmental factors, nutrition and in particular polyunsaturated fatty acids (PUFAs) appear to be crucial. Dietary changes over the last few decades have led to an increase in the number of people deficient in n-3 PUFAs, in favor of an increase in n-6 PUFAs. This n-6 PUFA/n-3 PUFA disbalance is linked to an increased risk of cognitive alterations. Preclinical studies have shown that early deficiency leads to impaired working memory at weaning in males, and that supplementation with n-3 PUFAs in old animals restores their working memory. However, the cognitive dimensions affected and the underlying neurobiological mechanisms remain poorly understood. I am interested in the cognitive changes in the subject in relation to his n-3 PUFA intake, and the mechanisms involved as a function of sex.
To do this, I use a nutritional approach involving gestational deficiency in n-3 PUFAs in C57Bl6/J male and female mice. In adulthood (3-month-old), I am studying multiple behavioral dimensions such as anxiety, spatial working memory and associative spatial and temporal memories. Spatial working memory tested with object location memory is impaired in deficient n-3 PUFA of both sexes (N=28-32; 3 cohorts). We used delayed fear conditioning to assess contextual memory at 24 hour and 10 days. Our results show an impaired contextual memory at 24h in deficient females (N=20; 2 cohorts) and only after 10 days in males (N=16-18; 2 cohorts). Anxiety tested in elevated plus maze and open field was not increased in deficient animals (N=28-32; 3 cohorts). Electrophysiological recording in whole cell patch clamp of pyramidal neuron of the dorsal CA1 were performed to assess neuronal excitability (N=6). In deficient animals, those neurons were more excitable but with an increase resting membrane potential in males and a decrease action potential threshold and rheobase in females. We characterized kinases activity of the hippocampus (N=8) with PAMGENE microarray. Kinases involved in synaptic organization were increased in female mice and decreased in male animals. This was linked to a decrease in vesicular glutamate transport 1 (VGlut1) and postsynaptic density protein 95 (PSD-95) colocalization in males but not females.
My results indicate that early n-3 PUFA deficiency alters hippocampal-dependent memories in both sexes, linked to sex-dependent change in neuronal excitability. These results may pave the way to better understand sex-dependent cognitive alterations due to abnormal nutritional intake.

P22 - The gut microbiota influences hypothalamic blood-csf barrier structure and function

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A complex neuronal network in the hypothalamus regulates appetite and energy expenditure. To maintain energy homeostasis, hypothalamic neurons must rapidly sense and integrate a variety of peripheral signals (*e.g.,* hormones and nutrients). This is possible because of the close vicinity of hypothalamic neurons with the median eminence (ME), a circumventricular organ containing a specialized interface called the blood-cerebrospinal fluid (CSF) barrier. The ME blood-CSF barrier is characterized by fenestrated vessels, which are highly permeable to blood-borne molecules. It is also composed of tanycytes, which are specialized hypothalamic glial cells that line the floor of the 3rd ventricle and are joint together by tight-junction complexes to create a physical barrier with a typical honeycomb structure that prevents the diffusion of molecules from the ME parenchyma to the rest of the brain via the CSF. The gut microbiota is a complex and dynamic community of bacteria living within the gastrointestinal tract of the host. It is now well established that the gut microbiota plays an essential role in maintaining host energy homeostasis. Increasing amount of evidence also suggests that the gut microbiota may affect brain function and development, as well as blood brain barrier integrity. However, whether the gut microbiota influences the structure and function of the hypothalamic blood-CSF barrier is still unknown. To address this question, we examined the structure and function of the hypothalamic blood-CSF barrier using two complementary animal models with altered gut microbiota: the germ-free (GF) mice and mice in which the gut microbiota composition was altered during adulthood using oral administration of a cocktail of antibiotics (ABX). Immunohistochemical labeling and confocal microscopy was used to visualize the organization of the tight-junction protein zonula occludens-1 in relation to the blood-CSF barrier of the ME. Additionally, we assessed the diffusion function of the ME blood-CSF barrier by quantifying the penetration of Evans Blue dye in the hypothalamic parenchyma. The results indicate that the organization tanycytic honeycomb structure is disrupted in GF and adult ABX mice. The structural reorganization of the ME barrier was associated with the altered diffusion of the circulating Evans Blue dye into the parenchyma of the hypothalamus. Together, our results suggest that the gut microbiota plays an essential role in maintaining the structure and diffusion function of blood-CSF in the adult mouse hypothalamus.

P23 - Depression phenotypes, dietary habits, and biological pathways: An overall assessment of the Gut-Brain-Axis

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INTRODUCTION: Major Depressive Disorder (MDD) is a prevalent mental health condition, yet a sizeable percentage of patients diagnosed with MDD do not achieve full remission after receiving antidepressant treatment.
In line with the increased knowledge of the microbiota-gut-brain axis, emerging evidence from observational and interventional studies suggests that dietary patterns may play a significant role in the prevention and treatment of MDD, giving rise to the field of Nutritional Psychiatry. This burgeoning discipline aims to understand how specific dietary components affect depressive symptoms and to identify the biological pathways that mediate these associations. Such insights could lead to the development of personalised dietary interventions.

OBJECTIVES: The objective of this project is to investigate the clinical and biological correlations between dietary habits and MDD. To achieve meaningful results, we will integrate precise clinical characterization, dietician-led dietary assessment and analyses across multiple biological levels, including omics. We expect our findings to contribute to the development of personalized dietary interventions in psychiatric units.

METHODS: Our multicentric study will adopt a cross-sectional design. Patients will be recruited on admission for MDD treatment from two psychiatric units at Cliniques Universitaires Saint-Luc (CUSL) and Hôpital Psychiatrique Le Beau Vallon. In total, we hope to have a sample of 100 inpatients in each psychiatric unit and a control group of 50 individuals. The psychometric assessments will involve completing questionnaires and solving computer-based tasks. Dietary data will be collected using a 72-hour recall method. Biological analyses will require collecting blood, stool and saliva samples to examine the composition (metagenomics) and function (metabolomics) of the microbiota, inflammation, hypothalamic-pituitary-adrenal axis activity, oxidative stress, neurogenesis, and the integrity of the intestinal barrier and endothelium.

P24 - Differential involvement of cb1 receptors in obesogenic diet-induced memory deficits in male and female mice

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In addition to metabolic and cardiovascular disorders, obesity is associated with cognitive dysfunction in humans. Similarly, an obesogenic high-fat diet (HFD) consumption in rodents, in particular during adolescence, induces memory deficits. Alterations of the hippocampal endocannabinoid system (ECS) and its main receptor CB1R, well known to regulate brain plasticity and memory processes, participate in HFD-induced memory deficits in male mice. Indeed, systemic blockade of CB1R or decrease of CB1R on hippocampal glutamatergic cells improved memory in HFD-fed males. Nevertheless, recent findings indicate that this may not be true for female mice.
Our goal was to identify whether the ECS-CB1R contribute to HFD-induced memory deficits in females and to explore whether similar mechanisms (brain structures and cell types) are implicated.
As in male mice, systemic injection of a CB1R antagonist (Rimonabant) reversed long-term object recognition memory deficits in HFD-fed female, indicating that CB1R signaling regulates the impact of HFD on memory function in both sexes. Contrary to males, infusion of the viral vector carrying the Cre recombinase (with an ubiquitous CAG promoter) in the hippocampus of CB1-flox female mice did not improve memory deficits despite a similar reduction in hippocampal CB1R expression. Interestingly, decrease of CB1R in the medial prefrontal cortex (similar in both sexes) rescued memory deficits in females, but not males. Thus, our findings revealed a double dissociation in the hippocampal and prefrontal CB1R regulation of HFD effect on memory in females and males. Moreover, hippocampal CB1R on glutamatergic (but not GABAergic) neurons were involved in memory deficits of HFD-fed males while prefrontal CB1R on GABAergic (but not glutamatergic) neurons were involved in HFD-fed females. Subsequently, we investigated whether these sexual differences could be mediated by ovarian hormones during puberty. For this purpose, we evaluated whether ovariectomy (OVX) renders HFD-fed females sensitive to CB1R decrease in the hippocampus. Whereas OVX did not affect HFD-induced memory deficits, decreasing hippocampal CB1R improved memory deficits in HFD-OVX females. Altogether our findings suggest that ECS-CB1R system contributes to the HFD-induced memory deficits in both sexes but that brain structures and cells types involved differ between males and females through a modulation from ovarian hormones.

P25 - CB1 receptors located on hippocampal glutamatergic neurons control obesogenic diet-induced memory impairment in male mice

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Obesity is associated with adverse cognitive outcomes, particularly those depending on hippocampal function, in humans as well as in animal models. As the endocannabinoid system participates in obesity and regulates memory processes, we address its causal involvement in memory deficits induced by obesogenic high-fat diet (HFD) intake during adolescence in mice. Using a pharmacological approach, we demonstrated that a systemic blockade of the main cannabinoid type 1 receptor (CB1R) rescued HFD-induced deficits of long-term object recognition memory but also normalized training-induced hippocampal c-Fos over-activation as well as aberrant in vivo long-term potentiation in CA1 of HFD-fed mice. We then found enhanced CB1R expression and endocannabinoid levels (specifically anandamide) in the hippocampus of HFD-fed mice trained with novel objects in a novel environment and showed that decreasing hippocampal CB1 expression abolished HFD-induced long-term recognition memory deficits. We then investigated which neuronal types (GABA or glutamate) carrying CB1R are responsible for memory impairments in HFD-fed mice. While the absence of CB1R from GABAergic neurons had no effect, the specific CB1R deletion on hippocampal glutamatergic cells alleviated HFD-induced long-term recognition memory deficits. Moreover, this CB1R deletion rescued other memory deficits induced by HFD, i.e. social memory and object-in-place memory, and this effect was dependent on CB1R located at the plasma, but not mitochondrial, membranes of glutamatergic cells. These results demonstrate that, despite carrying only 5% of hippocampal CB1R, glutamatergic neurons mediate endocannabinoid-induced alterations of hippocampal function in HFD-fed mice.

P26 – Human 3D-cerebral organoids: phenotypic & functional characterization to study brain-nutrient interactions in vitro.

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Studying the human brain at the molecular and cellular level is challenging. However, human 3D-cerebral organoids, derived from induced pluripotent stem cells (IPSCs), are emerging as a novel in vitro model to study brain-environment interactions. Indeed, they have been shown to replicate some key aspects of human brain development, making them ideal models to investigate human brain development & its mechanisms in health and disease (Lancaster & Knoblich., 2014). Here, we have been developing human 3D-cerebral organoids in vitro using unguided differentiation protocol. We adapted and refined different versions of Lancaster's protocols to promote differentiation of IPSCs into complex neural tissues at different ages of development. We have characterized our model by 1) gross morphometric analysis, 2) molecular assessment using transcriptomic, protein and lipid analysis, 3) spectral flow cytometry and immunohistochemistry for cellular diversity and microscopic cellular organization (neural rosettes) and 4) functional assessment in response to an immune challenge. This novel model will serve our questions in order to determine the influence of environmental factors such as nutrients on the human brain in vitro.

P27 - astrocytic hemichannels are involved in hypothalamic control of energy balance

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[2] *Collège de France, Centre Interdisciplinaire de recherche en biologie, Paris, France,*
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* Co-last and co-corresponding authors

Hypothalamic astrocytes are strategically positioned to integrate key signals from hormones and metabolites carried through the bloodstream, thereby playing a vital role in the management of energy metabolism and the control of food intake (Kim1 et al. 2014).
The hypothalamus is a brain region that plays a pivotal role in maintaining body weight and directly influencing feeding behavior and metabolic processes. While neural input from hypothalamus are critical of metabolic control, recent research has increasingly focused on elucidating the role of astrocytes, a crucial subset of glial cells, in regulating energy homeostasis and their potential contribution to obesity (García-Cáceres et al. 2019). The work from our lab recently highlighted a pivotal role of astrocyte in the paraventricular nucleus of the hypothalamus (PVN) in the control of food intake, energy expenditure, and glucose metabolism (Herrera Moro Chao et al. 2022). Astrocyte's hemichannels are critical to support astrocyte-astrocyte and astrocyte-neuron communication we therefore investigated the role of Pannexin1 (Panx1), a non-junctional hemichannel protein, in the adaptive response of astrocyte-neuron dialogue in the response to obesogenic environment.
To investigate the role of astrocytic Panx1 in vivo, we used floxed Panx1 mice in combination with viruses to delete Panx1 in astrocytes of the PVN. We found that, in lean but not obese mice, selective knock out of Panx1 in PVN astrocyte leads to enhanced circulating corticosterone associated with impaired glucose homeostasis as assessed by oral glucose tolerance test. These results suggest that Panx1 integrity in PVN astrocyte exert a control on the Hypothalamic–pituitary–adrenal axis and metabolic output. The mechanism linking astrocyte Panx1 with PVN corticotropin-releasing factor (CRF) is currently investigated together with the adaptive response that uncoupled astrocytic control of HPA axis in obesogenic context.

García-Cáceres, et al. 2019. *Nature Neuroscience*. https://doi.org/10.1038/s41593-018-0286-y.
Herrera Moro Chao, et al. 2022. *Cell Metabolism*. https://doi.org/10.1016/j.cmet.2022.09.002.
Kim1, et al. 2014. *Nature Neuroscience*. https://doi.org/10.1038/nn.3725.

P28 – Adverse effects of adolescent obesity on recognition memory performances in an fMRI task

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Cognitive dysfunctions and brain modifications have been reported in adolescents with obesity (Maayan et al, 2011; Pearce et al, 2019). However, it remains unclear if recognition memory is affected in obese adolescents and related to brain functional changes. Here we evaluated the impact of obesity during this critical period of development on recognition memory and its associated brain activation.
We developed an event-related functional magnetic resonance imaging task to test recognition memory in 11 obese male adolescents and 15 healthy adolescents (mean body mass index: 33.65 $\pm$ 5.45 kg/m² and 18.10 $\pm$ 3.37 kg/m² respectively) aged 9 to 17 years old, presenting no other diagnosed comorbidity. At the beginning of the fMRI task, during the encoding phase, subjects were shown a series of 48 different trials comprising a background image of an every-day life situation (airport's halls, bridges…), followed by a combined image of a portrait from the Karolinska Directed Emotional Faces database superposed onto the background. No explicit encoding guidelines were given. After ten minutes, subjects had to retrieve, amongst 3 faces, the one that was presented previously over an already shown background for the 48 trials. Facial recognition memory performance was calculated from the last phase of the task during which response rates and times were recorded. Functional neuroimaging analyses were performed on the encoding and retrieval phases.
Although both groups had similar response rates, obesity in male adolescents was associated to significantly reduced facial recognition performances in comparison to their age-matched controls (Student One-tailed t-test, $p=0.039$). Additionally, obese subjects were significantly faster to answer than their peers whether the faces were accurately or falsely retrieved (Two-way ANOVA, Group effect, $p<0.001$). Whole-brain fMRI statistical analyses ($Z>2.3$; cluster corrected $p<0.05$) revealed similar activated encoding and retrieval networks in successful or failed trials in both groups. Further whole-brain analyses revealed during encoding, a hypoactivation of the right hippocampus and parahippocampal gyrus and a hyperactivation of the left cerebellum in the adolescents with obesity in comparison to the control group and during retrieval, a higher activation of the precuneus in adolescent obesity. In the whole adolescent group, the level of activation in the precuneus was negatively correlated with the recognition memory performance (Pearson's correlation $r= -0.39$, $p =0.048$).
Our study indicates that lower recognition memory performances are associated with cerebral and cerebellar functional modifications in obese adolescents, confirming that recognition memory is affected in obese adolescents and suggesting its neural bases.

References: Maayan et al, 2011 doi:10.1038/oby.2011.15 Pearce et al, 2019 doi:10.1016/j.dcn.2019.100727

Practical Information

Venue

Centre Broca Nouvelle-Aquitaine – **Bordeaux Neurocampus**
Campus Carreire - University of Bordeaux
Bordeaux, France

Location on Google map:
Search for “Centre Broca”
https://goo.gl/maps/p4JE9mnJVMQ9hzz5A

How to get there?

Access details:
https://www.bordeaux-neurocampus.fr/en/centre-broca-nouvelle-aquitaine/

By taxi

Closest campus entrances :
40 rue Albert Marquet or 14 rue Eugène Jacquet

GPS: 44.810012 / -0.59645

By tram

Closest tram stop: "**Saint-Augustin**".

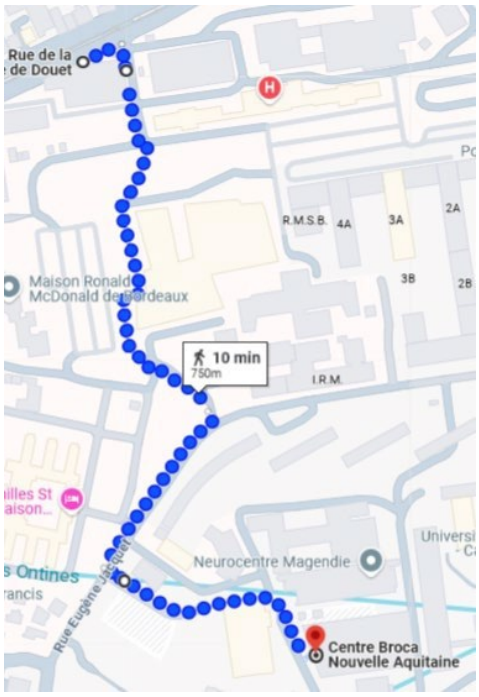
From the airport: (20 minutes)
Take the tram A.

From the city center (around 15 minutes from the city center)
Take the tram A, direction “Mérignac”, “Le Haillan”, “Pin Galant” or “Aéroport”.

> Walking from the tram station

The Broca Centre is at around 8 min from the tramway station.

Take the **street under the chimney** and **follow the pedestrian white path** and the arrows “Centre Broca”.



By bus

Bus 24, 55 (Stop: Campus Carreire)
Bus 8, 20, 73, 80 (Stop: Bordeaux Carreire)

Transportation in the city

You can use your smartphone with the app TBM.

DISPONIBLE SUR App Store

DISPONIBLE SUR Google play

You can also buy a “m-ticket” before entering tram or bus.

All details on https://www.infotbm.com/en

To use your “m-ticket”, just validate each time you get into the tram or bus.

Practical information

Posters

Sessions are organized during lunch breaks and the wine and cheese.
All posters will be presented during all sessions.

Luggage

“VIGIPIRATE” safety instructions strongly recommend to the participants to avoid to come with their luggage.
Exceptionally, the bags can be left at the front desk after being screened by a security officer.

Wifi

Wifi connection will be available.
Access through Eduroam will be possible.

Coffee and lunch

A welcome coffee will be served between every morning before the talks.
Coffee, tea and refreshments will be available during morning and afternoon breaks.
Lunches will be taken at the conference venue.

Goodies

We will not distribute notebooks, pens or totebags. Do not hesitate to go to our sponsor booths to get some!

Gala dinner

Thursday, October 17th - From 7:00PM

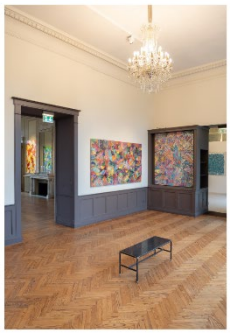
Château Labottière - Bernard Magrez Cultural Institute

5 rue Labottière, Bordeaux

No specific dress code, but an elegant attire is welcome.

The Bernard Magrez Cultural Institute, a private artistic patronage foundation, is a place where arts and knowledge intersect and respond to each other. Founded by the patron and owner of Grands Vignobles, Bernard Magrez, the Cultural Institute offers a varied and eclectic program composed of monographic and collective exhibitions, of emerging or established artists.

Each year is also punctuated by concerts, conferences, cultural events and charity evenings.
Installed in the wooded setting of **Château Labottière** since 2011, the Bernard Magrez Cultural Institute creates a dialogue between neo-classical architecture and the contemporary artistic creation that it houses. If the exhibitions have taken on a Street Art look for several years, the walls of Château Labottière remain above all the home of the 550 works from the Collection of the Cultural Institute. A true quest for singular emotions, this Collection testifies to the view and esteem that collector Bernard Magrez has for the artists of his time.
The Cultural Institute testifies to the values of sharing, transmission and support of creation, carried by a founder wishing to allow all audiences access to art and knowledge.



How to get there?

5 rue Labottière

Location:https://maps.app.goo.gl/7DxKvnvwP7i3AWeD7

- By tram :
Tram D: Barrière du Médoc stop / Tram C: Camille Godard stop
- By bus : But 23 - Croix de Seguey stop, then 8min of walk

Contact:
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