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P1 - Brain-gut connectivity is dysregulated in disgust.

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Disgust is a basic emotion that helps to avoid ingesting potential toxins. Disgust has a characteristically visceral (stomach) response, typically accompanied by changes in gastric state (proto-nausea. Previous research has explored brain and stomach responses to disgust separately. But recent experimental work suggests that gastric state has a causal role in disgust experience. However, it remains unclear how brain and stomach communicate in the experience of disgust. This is particularly salient given the presence of a resting-state gastric network in the brain, which we hypothesised would be interrupted in the experience of disgust.

In the present study, we aimed to explore bidirectional stomach-brain connectivity during disgust, specifically whether and when stomach and brain signals impact each other. Participants (*N*=44) were exposed to blocks of neutral and core disgust stimuli in a passive-viewing task. Brain and stomach activity were measured using electroencephalography (EEG) and electrogastrography (EGG), respectively. Self-report disgust sensitivity and facial expression landmarks were also recorded.

Consistent with existing literature, we found normogastric power was reduced in response to disgust, whereas bradygastric and tachygastric power increased. Granger-causality revealed asynchronous connectivity between stomach and brain. Fronto-central regions of the brain predicted differences in stomach activity at an early lag, but during disgust this signal was attenuated. At later lags the stomach predicted changes in similar brain regions, which also reduced during disgust. Additionally, we found that self-reported disgust sensitivity was significantly positively correlated with somatosensory reductions in Granger-causality, indicating that higher disgust sensitivity was associated with a more dysregulated state. As a whole, these findings highlight the interaction between body-derived and brain-derived signals, with disgust serving as a model system for studying interoception. These present findings also indicate a clear relation between higher level constructs, such as disgust sensitivity, and low-level physiological processing of stimuli. Findings are discussed in the context of an active inference approach and views of exteroceptive vs. interoceptive processing.

P2 – Early Life Stress Impact on Anxiety-Related Behaviors and Anterior Insula Activity In Adult Mice

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The anterior insular cortex (anterior insula) is a critical hub for emotional integration and interoception, which was shown to be hyperactive in individuals with pathological anxiety. Early life stress is a major risk factor for anxiety disorders, yet its long-term effects on insula function remain poorly understood. In this study, we investigated how early life stress influences the dynamics of anterior insula pyramidal neuron during exposure to anxiogenic environments in adulthood.
Male and female C57BL/6J mice were subjected to a limited bedding and nesting (LBN) protocol during the early postnatal period from P02 to P09. In adulthood, pyramidal neuron activity was recorded using calcium fiber photometry during behavioral assays including the Elevated-Plus Maze (EPM), Elevated-Zero Maze (EZM), Light-Dark Box (LDB), Novelty-Suppressed Feeding Test (NSFT), social interaction tasks and a social valence assay.
The LBN early life stress increased anxiety-related behaviors of adult mice in multiple assays, along with a strong increase with locomotor activity and speed. As previously showed in our lab, mice exhibited a significant increase in anterior insula calcium activity when mice are navigating in exposed zones, such as the open arms of the EPM or the center of the OFT, reflecting heightened neural responses in dangerous contexts. Interestingly, although early life stress impacted behavioral outcomes, it did not change the amplitude of the anterior insula activity in response to dangerous areas, suggesting neurobiological compensatory mechanisms.

P3 - A hypothalamic circuit linking food odor perception to AgRP neuron suppression

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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.

P4 - Prefrontal cortex interoceptive tuning can encode emotional state

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Increasing evidence indicates that bodily states support emotional regulation[1,2,3]. But how does the brain "read out" body feedback to recognize the current emotional state and implement adaptive behaviors? The prefrontal cortex (PFC), positioned at the intersection of emotional and autonomic regulation[4], is well-suited to investigate this question. We recorded n=317 single units in the PFC of freely moving mice undergoing homecage sleep sessions, neutral exploration sessions and spatial fear conditioning.

We found that PFC neurons exhibit tuning to breathing (45%) and heart rate (35%), with either monotonic tuning or tuning peaking at a preferred intermediary frequency. Using generalized linear models to control for motion variables, we identified a subset of neurons specifically encoding cardiorespiratory signals, independent of movement. At the population level, breathing and heart rate could be accurately reconstructed from neural activity (cross-validated $R^2 = 0.86$ and 0.50, respectively). Remarkably, models trained on neutral wake states generalized well to stress ($R^2 = 0.74$) and sleep ($R^2 = 0.46$) for breathing. Cardiac frequency models trained in this way across wake states but not sleep. This suggests that the PFC more robustly encodes breathing—consistent with its strong respiratory phase modulation[1,5].

These observations provide strong evidence that specific prefrontal neurons encode cardio-respiratory frequency invariant to behavior and brain state, independent of motion variables with single-unit tuning curves that are reminiscent of classical senses such as audition or vision

These units provide a potential mechanism for the PFC to track bodily and emotional states. We therefore tested their functional relevance in emotional states differing in their breathing and heart rate profiles. Using our recent discrimination of two fear-related states characterized by immobility[6]—classical freezing (breathing >4Hz, high stress) and a novel recovery state (slow breathing ~2Hz, boosting resilience)—we found that PFC activity robustly discriminates between these states (89% accuracy). Importantly, the role of individual neurons in emotional state coding can be predicted from their interoceptive tuning. Accordingly, training a decoder to discriminate between high and low breathing states defined in other wake or sleep states is sufficient to decode the emotional state (76%). This demonstrates that interoceptive encoding in the PFC can support the encoding of different emotional states, providing a sensory mechanism for the brain to monitor ongoing emotional states and adapt behavior accordingly.

1. *Bagur, S. et al. Nat. Commun. 12, 2605 (2021).*
2. *Hsueh, B. et al. Nature (2023).*
3. *Klein, A. S et al. Science (2021).*
4. *McKleeven, J et al. Journal of Neuroendocrinlogy (2015)*
5. *Karalis, N. et al Nat. Commun. (2021).*
6. *Maheo et al, bioRxiv (2025)*

P5 - TaqIA polymorphism role in reward-associated disorders: new insights from a humanised murine model.

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The over-consumption of energy-dense foods is nowadays identified as one of the main causes of obesity. However, there is a substantial body of evidence that obesity and related disorders also result from an interaction between specific genetic polymorphisms and the modern food environment. In this context, the addiction-susceptibility TaqIA polymorphism is of particular interest. TaqIA is a single nucleotide polymorphism causing a change in amino acid in the gene coding for the kinase ankyrin repeat and kinase domain containing 1 (Ankk1) located in the in the vicinity of the dopamine 2 receptor (Drd2) gene. This polymorphism leads to 2 variants: A1 and A2. Approximatively 30% of the world population have one or two copies of the A1 allele. The function of the Annk1 protein remains unclear yet, but the presence of A1 leads is associated with 30% less DRD2 receptors in the striatum as well as an increased vulnerability to neurological and psychiatric disorders, eating disorders and obesity. The A1 allele is ancestral, while the A2 allele appeared more recently with the Homo taxon, impeding the understanding of its causal role in neuropsychiatric disorders.
We have then generated a single-point mutation to humanise mice with the A2 allele. This unique model offers significant translational value, allowing us to study how the A1 and A2 variants affect reward-associated disorders in a developmental context similar to humans.
Motivation of male and female mice of both homozygous for A1 or A2 allele, 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). 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, and lost when the cost to get the reward is higher (FR5).
These data confirm the importance of the role of the TaqIA polymorphism in reward-related behaviours. Our humanised murine model will then be of great importance to understand its causal role in the susceptibility induced by the TaqIA polymorphism.

P6 - Mechanisms underlying cortical processing of gustatory information

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The primary function of the sensory cortex is to analyze incoming stimuli from the periphery, distinguishing and interpreting them to guide behavior. Among sensory stimuli, gustatory information enables animals to analyze food identity and recognize the nutritional and hedonic values (e.g., palatable as sucrose, versus aversive as citric acid) to avoid poisons and regulate feeding behaviors, making it crucial for survival. Despite the importance of gustatory processing, our knowledge of the underlying neuronal circuits and their activity remains remarkably incomplete, especially compared to other sensory modalities (e.g., somatosensation, vision, olfaction, and audition). Here, we employ a combination of slice electrophysiology, optogenetics, and activity reporters to characterize the morphology and electrophysiological properties of layer 5 pyramidal neurons in the gustatory cortex, together with their synaptic inputs from the gustatory thalamus (which provides information regarding tastant identity) and amygdala (which provides information regarding palatability). We aim to disentangle how gustatory information is integrated and processed in the mouse gustatory cortex at the synaptic and circuit levels.

P7 - The role of addiction-susceptibility polymorphism TaqIA in metabolism and metabolic-associated disorders.

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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, leading to two alleles, A1 and A2. Approximatively 30% of the world population has one or two copies of the A1 allele. The presence of this allele increases the likelihood of developing neurological and psychiatric disorders, as well as an increased risk of obesity, indicating a role for this gene in energy homeostasis. While the A1 allele is the ancestral variant, the derived A2 variant has appeared with the Homo taxon, impeding the understanding of its causal role in neuropsychiatric and metabolic disorders. We have then generated a single point mutation to humanise mice for the A2 allele. This unique model brings strong translational value and allows us to profile how A1 and A2 variants affect energy homeostasis in a context of developmental expression of the mutation, similar to humans. Metabolism of male and female mice of both A1/A1 and A2/A2 genetic backgrounds was assessed in indirect calorimetry cages. Interestingly, only A2/A2 males displayed higher energy expenditure under both chow and habituation to a high-fat diet conditions compared to their A1/A1 counterparts, though a longer exposition to the high-fat diet makes this difference disappear. A2/A2 male mice also displayed better glucose regulation than A1/A1, maintaining similar glycaemic responses after the high-fat diet exposure. No such differences were observed in female mice. Metabolism of female mice was then assessed in different thermal conditions: room temperature, thermal neutrality and cold stress. Strikingly, A2/A2 female mice displayed higher energy expenditure under a cold stress, compensated by a higher energy intake. Altogether, these data confirm the importance of the role of the TaqIA polymorphism in the regulation of energy homeostasis, and underscore a sexual dimorphism in this context.

P8 – Dopamine D2R-neurons of the Paraventricular Thalamus Govern Feeding, Energy Balance and Body Homeostasis

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The central control of feeding behavior has been classically ascribed to the hypothalamus, but recent studies suggest that extra-hypothalamic structures could modulate feeding behavior. The paraventricular thalamus (PVT) is a midline structure located above the hypothalamus. It is described as an interface between limbic structures which integrate and sends multiple signals in order to regulate emotional behavior and/or cognitive process. Despite many connections with the hypothalamus and other satiety nuclei (PBN and NTS), PVT is still poorly understood in feeding behavior. Here, by taking advantage of cell-type specific strategies via viral approaches, whole cell patch clamp, fiber photometry and indirect calorimetry methods, we found that PVT and notably, the neurons expressing the dopamine D2 receptor (D2R) control food intake, energy balance and body homeostasis in both physiological and obesogenic contexts. Unraveling extra-hypothalamic brain circuits, such as PVTD2R neurons, may pave the way to new insights and may provide new therapeutics solutions to fight obesity dysfunctions or metabolic disorders.

P9 - Uncovering the neuro-immune mechanisms driving the “memory of obesity”

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Weight regain after weight loss represents a medical challenge for the long-term treatment of obesity. We have recently established (*Léon S et al., Diabetes 2025*) a dietary mouse model characterized by persistently higher body weight set-point and altered metabolic responses after an episode of diet-induced obesity. We have hypothesized that these lasting changes may be related to modifications in the hypothalamus-adipose tissue axis involving changes in immune cells (microglia in the brain, macrophages in the adipose tissue) and sympathetic nervous system (SNS) functions.
Initial immunostaining analysis of different adipose tissue depots for the tyrosine hydrolase (TH) has confirmed alteration of the SNS, particularly at the level of the subcutaneous adipose tissue. We therefore tested whether the inhibition of the EPAC pathway, which is supposed to re-establish SNS function in adipose tissue (*Valentine et al., J Clin Invest 2022*) can correct the body weight set-point in previously obese mice. Our data show that this treatment significantly reduces body weight in our model. Molecular analyses in adipose tissue and hypothalamus are currently ongoing to define changes in pathways of interest. Additionally, by carrying out bulk RNAseq in both brain microglia and adipose tissue macrophages, we found molecular signatures that persist altered in previously obese mice. Additional studies are currently ongoing to explore the role of microglia in the modification of the body weight set-point and in the alteration of SNS function. These set of findings, altogether provide novel information on the modification of the body weight set-point after an episode of obesity.

P10 - Leveraging linear models to correct interoceptive tuning for motion related activity

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The correlation between emotions and bodily state has long been established, and feedback from the body actively contributes to affective behaviors. Recent studies in mice have provided direct evidence that manipulating respiratory[1] (Bagur 2021) or cardiac[2,3] (Hsueh 2023, Klein 2021) feedback modifies fear behavior. The interoceptive system is thought to process these afferent visceral signals and integrate them into affective brain-body interactions. However, the precise neural encoding of interoceptive variables like heart or respiratory rate remains unknown. This may be due to the difficulty of evaluating the specific contribution of interoceptive variables to neural activity given their correlation with each other and behavioral variables. Computational approaches can help disentangle the contribution of each parameter.
In this work, we develop a framework to extract interoceptive tuning while correcting for motion biases. The data consists of prefrontal single unit activity (n=317) recorded simultaneously with motion (position, speed, head motion) and interoceptive (heart and breathing rate) variables in freely moving mice. Using Generalized Linear Models, we quantify the amount of variance explained by each measured variable as a proxy for neural sensitivity. Heart and breathing rate explain respectively 2,5 and 2% of the variance on average. Each motion variable explains around 2% of the variance, in agreement with previous studies[4,5]. This shows that interoceptive variables contribute with similar importance as motion variables to prefrontal coding. We then compute interoceptive tuning curves, defined as the firing rate of each neuron in response to specific ranges of heart or breathing rates. We observe that 35% and 45% of units are significantly tuned to heart and respiratory rate respectively. These curves shed light on the precision of single neuron interoceptive encoding. Using the motion related coefficients extracted by the linear model, we correct the firing rate of each unit for the contribution of motion activity. This yields movement corrected tuning curves. Interestingly, we find that in some units, the motion correction abolished the apparent tuning calculated from the uncorrected data, while preserving others intact. This work sheds light onto the contribution of interoceptive variables to prefrontal coding and shows the importance of correcting for misleading correlations to specifically address interoceptive related activity.

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P11 - Lateral habenula as a novel mechanism regulating systemic immune responses

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Mood can have a great impact on our physical health. In our everyday life, stressful events increase our chances of becoming sick. In clinical settings, patients suffering from mood disorders such as depression have increased risk of developing comorbid inflammatory diseases, such as arthritis, diabetes, autoimmune diseases. This strongly indicates that depressed patients may have an underlying dysfunctional immune system. Understanding how brain specifically modulate the peripheral immune system in the context of depression is scarcely explore. My research is aimed at understanding how, and which brain regions can modulate systemic inflammation and peripheral immunity during affective disorders. I particularly focus on the role of the lateral habenula (Lhb), a brain region that is critical for encoding and integrating aversive signaling. Dysregulation of Lhb circuitry has been proposed to mediate depressive symptomatology in humans and rodents. Therefore, my hypothesis is that increased neuronal activity in Lhb can lead to maladaptive changes in the peripheral immunity. To address this, I used an optogenetic approach to selectively activate Lhb neurons and then evaluated the immune system function by triggering an immune challenge with LPS. Repeated optogenetic activation of Lhb induced a negative affective state in both male and female mice. It also potentiated the inflammatory response to LPS in females while dampening it in males. To understand the peripheral mechanism, we tested whether the sympathetic nervous system was involved. Sympathectomy completely blocked the increased inflammatory response to LPS in females. This data indicates that persistent activation of Lhb can induce maladaptive immune responses in a sex-specific manner. Overall, this study provides a novel neuronal mechanism regulating systemic immune responses during negative affective states.

P12 - Dopamine transmission in the anterior insula shapes the neural coding of anxiety

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Anxiety is an adaptive response of individuals exposed to potentially dangerous contexts. However, anxiety can persist at elevated levels regardless of the environment, becoming pathological (Belzung & Griebel, 2001). Although anxiety disorders are the most prevalent psychiatric conditions, their underlying neurobiology remain poorly understood. Numerous studies have revealed the involvement of various neuromodulators, including dopamine, in the regulation of anxiety (de la Mora et al., 2010; Hjorth et al., 2021). Concurrently, imaging studies have shown that the insular cortex (insula), particularly its anterior part, is hyperactivated in individuals with anxiety disorders, and preclinical studies showed it has anxiogenic properties (Buff et al., 2016; Nicolas et al., 2023). While it is established that dopaminergic transmission regulates anxiety levels, its specific impact on the insula remains elusive. This work explores how dopaminergic transmission within the anterior insula regulates anxiety processing.

First, we revealed a higher density of neurons expressing the type 1-like dopamine receptor (D1) in the anterior compared to the posterior insula, with a density seven times greater than those expressing dopamine type 2-like receptor (D2). Furthermore, we observed that only a few neurons coexpress D1 and D2 receptors in the anterior and posterior insula. Finally, we found that D1 neuron projection pattern closely resembled those of the overall glutamatergic population.

Second, we observed a specific increase in dopamine release within the anterior compared to the posterior insula when mice are located in exposed areas. Interestingly, while dopamine release onto both D1 and D2 neurons increased in the anterior insula when mice are in exposed areas, the amplitude of this release was positively correlated with anxiety levels only in the D1 population. Finally, we pharmacologically demonstrated that D1 signaling in the anterior insula bidirectionally regulates anxiety levels, establishing a direct causal link between dopaminergic signaling in the anterior insula and anxiety.

Finally, we examined individual neuron correlates of anxiety in the anterior insula. Using deep-learning tools, we identified distinct coding profiles when mice were in exposed or safe zones. Notably, D1 activation increased anxiety levels and concomitantly sharpened the coding specificity for exposed areas as anxiety increased.

To conclude, our findings provide a new model of neural population coding of anxiety, unravelling a D1-dependent coding mechanism of anxiety in the mouse anterior insula.

P13 - Environmental Enrichment Modulates HPA Axis Reactivity and Anxiety in a Chronic Stress Model: Adaptive or Overloaded?

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Chronic stress is a major risk factor for anxiety disorders[1] and disrupts neuroimmune balance through HPA axis hyperactivation[2,3] and elevated glucocorticoids, such as corticosterone (CORT) in rodents[4,5]. This dysregulation affects brain-body communication, promoting neuroinflammatory responses[6,7]. Environmental enrichment (EE) has been shown to buffer these effects, enhancing stress resilience[8,9,10]. Exploring how EE shapes neuroimmune outcomes under stress may reveal links between psychological stress and immune dysfunction in anxiety. For this, *Swiss* male mice were assigned to one of two environmental conditions: non-enriched (NE) and enriched (EE). On PND70, mice were either exposed to or spared from Chronic Unpredictable Mild Stress (CMS), creating 4 groups: (1) NENS: non-enriched and non-stressed; (2) NEST: non-enriched and stressed; (3) EENS: enriched and non-stressed; and (4) EEST: enriched and stressed. Mice were subjected to Open Field (OF), Elevated-Plus Maze (EPM) and Light-Dark Box (LDB) tests to evaluate anxiety-related behaviors. To assess HPA axis activity, CORT was measured at 3 time points: post-acclimation, after 21 days of EE, and 24 h after the last stress. On both OF and LDB, EE reduced locomotor activity, irrespective of stress exposure. On the EPM, EEST mice exhibited anxiety-like behavior, suggesting adaptive vigilance and nuanced behavioral response to stressors. EE alone initially did not alter CORT, indicating no early HPA axis modulation. However, extended EE significantly increased CORT, an effect not observed in EEST animals, suggesting that CMS blunted this increase. While prolonged HPA axis activation is often linked to neuroimmune disruption, elevated CORT in EE mice may reflect adaptive responses to complex stimuli rather than dysfunction. The increased anxiety in EEST mice may indicate functional coping rather than a pathological response. This decoupling between behavior and endocrine reactivity may signal a buffered stress response, characteristic of resilience, rather than vulnerability. Overall, our data suggest that EE promotes resilience via adaptive mechanisms involving the neuroimmune and HPA axis interplay. These results highlight the neuroendocrine systems' role in brain-body stress regulation.

[1]Hammels et al., 2015; [2]McEwen B.S., 2007; [3]Santos-Rocha et al., 2018; [4]Adams et al., 2003; [5]Heim et al., 2008; [6]Hassamal, 2023; [7]Peng et al., 2022; [8]Lehmann & Herkenham, 2011; [9]Novaes et al., 2017; [10]Zanca et al., 2015.

P14 - Chemogenetic manipulation of insular cortex projections to the ventral striatum attenuates obesogenic diet-induced anxiety like behaviours

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Obesity, mainly due to excessive consumption of energy-dense food, is a risk factor for cardiometabolic disorders but also to brain dysfunctions with a higher prevalence of anxiety disorders compared to the general population. Clinical studies revealed that obesity and anxiety disorders are both associated with insular cortex dysfunctions. Similar to humans, rodent models of obesity induced by chronic high-fat high-sugar diet (HFSD) intake exhibit enhanced anxiety-like behaviours and using *in vivo* calcium imaging our preliminary results indicate that the neuronal activity of anterior insular cortex is higher in anxiogenic environments in HFSD-fed mice. However, it is not yet clear whether insula dysfunction causally contributes to HFSD-induced anxiety. We therefore use chemogenetic strategies to decrease insular activity and evaluate the effect on anxiety-like behaviours. Anxiety-like behaviours of adult mice, exposed to either standard diet or HFSD for 12 weeks, were assessed using elevated plus-maze, open-field, light-dark task and novelty suppressed feeding test (NSFT). Our results indicate that decreasing activity of principal neurons in the anterior insular cortex normalized anxiety-like behaviours in HFSD-fed mice, and strikingly so in NSFT. Additional controls indicate a specific effect on anxiety-like behaviour and not on motivation to eat in NSFT. As ventral striatum dysfunction mediates anxio-depressive behaviours in HFSD-fed mice, we then used an intersectional viral strategy to chemogenetically inactivate projections from insular cortex to ventral striatum. Our very preliminary data indicate that decreasing activity in this pathway also normalized anxiety-like behaviours in HFSD-fed mice. Our results indicate that insular circuit-specific neuronal populations display an increased activity after HFSD, which causally increases the level of anxiety.

P15 - Olfaction and feeding behaviour: neuronal substrates underlying odour modulation of neuronal circuits regulating food intake

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A growing part of the population is aging. One of the major health concerns in elderly is decreased-food intake-associated malnutrition which can accelerate cognitive decline. Increasing feeding behaviour is a pertinent approach which could significantly improve cognitive capacities of elderly. The olfactory system plays a key role in nutrition and could offer a non-invasive approach for stimulating feeding. Food intake is mainly controlled by hypothalamic AgRP (orexigenic) and POMC (anorexigenic) neurons. We hypothesized that food-related odorant molecules modulate the activity of these hypothalamic neurons to increase food intake.
We identified diverse food-related odorant molecules which show innate attractivity in both male and female mice. Among them, bacon odour revealed a potent appetitive effect in increasing food intake measured using automated food intake monitoring experiments. Patch-clamp electrophysiological recordings from brain slices of mice exposed to bacon odour during 30 min show that it induces decreased firing of POMC neurons. No effect was observed on AgRP neuron activity despite changes in synaptic inputs. In vivo fiber photometry recordings show that bacon odour induces a rapid decrease in AgRP neuron activity and an increased activity of POMC neurons during active sniffing of this odorant.
These results replicated with other odorants suggest that attractive food-related odours modify the electrical activity of neurons within the melanocortin network. Future work will map the olfactory projections to arcuate nucleus and will investigate the efficiency of odorant stimulation in aged animals on food intake and cognitive capacities.

P16 - Lack of Single Amino Acids Transcriptionally Modulates Sensory Systems to Enhance Microbiota Intake

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Adequate intake of dietary essential amino acids (eAAs) is critical for protein synthesis and metabolic health. In *Drosophila melanogaster*, deprivation of any single eAA drives a compensatory increase in protein appetite. However, the neural, metabolic and sensory mechanisms that translate internal nutrient needs into targeted foraging behaviors remain poorly understood.
To investigate this transformation from metabolic "need" to behavioral "want", we generated transcriptomic profiles from the heads of flies subjected to individual eAA deprivations. While each condition elicited a distinct gene expression signature, we identified a core set of genes consistently regulated across multiple deprivation states. Among these, the ionotropic olfactory receptor *Ir76a* was consistently upregulated across all deprivation conditions.
Functional imaging and genetic manipulation revealed that *Ir76a* is essential for the exploitation of gut-associated bacteria, which improves host fitness during eAA scarcity. These findings uncover a direct role for olfactory plasticity in nutrient-specific foraging behavior and demonstrate that microbiota ingestion is an integral component of dietary adaptation.
Together, our work reveals how internal nutrient status reshapes olfactory functions to guide the search for ecologically relevant nutrient sources. This establishes a mechanistic framework for understanding how sensory circuits integrate internal metabolic signals to drive adaptive feeding decisions.

P17 - Sex-specific metabolic and behavioral effects of ketogenic diet in a neuromelanin-based mouse model of prodromal Parkinson's disease

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Parkinson's disease (PD) is the second most common neurodegenerative disorder, with prevalence increasing with age. While motor symptoms typically appear after 40–60% neuronal loss in the substantia nigra, non-motor symptoms, particularly gastrointestinal dysfunction, often precede them and are considered prodromal features of the disease. Our group has developed a novel transgenic mouse model of PD (tgNM), which overexpresses the tyrosinase enzyme gene under the tyrosine hydroxylase promoter, leading to neuromelanin (NM) accumulation in all catecholaminergic brain regions, as occurs in the human brain. NM buildup induces neurodegeneration affecting dopaminergic, noradrenergic, and cholinergic systems, resulting in both motor and non-motor symptoms. Disease progression in this model is defined by age as preclinical (3 months), prodromal (10 months), and early PD (18 months) stages[1]. Given recent evidence supporting ketogenic interventions as a promising non-pharmacological approach to neurodegenerative diseases[2], we evaluated sex-specific effects of a ketogenic diet (KD; 90% lipids—20% MCTs, 10% protein, 0% carbohydrates) administered for 5 months to 8-month-old tgNM mice. Results showed that tgNM males achieved deep nutritional ketosis, with elevated ketones and reduced glucose levels, while tgNM females reached only mild ketosis. They also presented different patterns of feeding regulation (water, food and calorie intake) affecting body weight. As a result of dietary adaptation, tgNM males developed a hypertrophic liver and a hypotrophic pancreas, while tgNM females exhibited the opposite pattern. Adipose tissue analysis revealed brown fat accumulation in tgNM males and white fat, in tgNM females. TgNM mice showed a trend to increase intestinal weight and reduced cecum and colon weight. Functionally, KD reduced the observed increase in intestinal permeability of tgNM mice without altering total transit time, fecal water content, or fecal output. Anxiety- and depression-like behaviors remained unchanged, but cognition improved, particularly in males. No improvements in general motor symptoms were observed. Notably, KD increased the number of vocalizations, a relevant finding since vocal impairment is common in PD. These findings highlight sex-dependent metabolic responses to KD and support the importance of personalized nutritional strategies in neurodegenerative diseases.

1 Laguna, A. et al. Modelling human neuronal catecholaminergic pigmentation in rodents recapitulates age-related neurodegenerative deficits. Nat Commun (2024)
2 Gough SM, et al. Neuroprotection by the Ketogenic Diet: Evidence and Controversies. Frontiers in Nutrition (2021).

P18 - The role of lipid metabolism and circulating miRNAs in the intergenerational transmission of the effects of parental adverse childhood experiences

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Introduction: Childhood trauma is an important risk factor for psychiatric and physical ailments during adulthood. Emerging evidence suggests that some of its behavioural and metabolic symptoms are transmissible across generations. Intergenerational transmission of the effects of trauma is postulated to involve changes in germline non-coding RNAs. However, it is unclear how childhood trauma affects ncRNAs in the gametes. Circulating ncRNAs, such as miRNAs, majorly carried by lipid-associated factors in the body fluids, appear as important candidates for carrying the trauma effects to the gametes for intergenerational transmission.
Aim(s): Synergizing investigation in a mouse model of ACE induced via unpredictable maternal separation and unpredictable maternal stress (MSUS) and cross-injection studies, we hypothesize that lipid-associated miRNAs communicate the effects of ACE to the germline for intergenerational transmission.
Method(s): Intergenerational behavioral and metabolic phenotyping was performed, supplemented with small RNA sequencing followed by qPCR. Cross-injections of lipid-associated carriers into the tail vein of mice performed.
Results: Offspring of both MSUS- and HFD-exposed male mice showed impaired glucose tolerance, depressive-like behaviour and anxiety. Cross-injections from MSUS into CTRL mice prolonged the offspring latency to enter open arms in Elevated Plus Maze test. Cross-injections from MSUS into CTRL mice recapitulated the offspring metabolic phenotype associated with MSUS in Glucose tolerance test. Cross-injections from VE mice into MSUS mice partially mitigated the metabolic MSUS phenotype.
Conclusions: Injections of MSUS-material is sufficient and necessary to induce the intergenerational metabolic phenotype associated with MSUS while lipid-modifying interventions can potentially alter the intergenerational metabolic MSUS phenotype. This research provides proof-of-concept for a role of lipids and circulating miRNAs in communicating the effects of ACE to the germline for intergenerational sequelae.

P19 - Miniature endoscope for high resolution electrical and optical investigation of the colon in live mice

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To address the need for in-vivo, longitudinal investigation of the functional and morphological status of the colon in preclinical research to advance our understanding of disorders of the gut-brain interaction we have developed a novel multimodal mini-endoscope for use in anesthetized small animals.
The 2mm endoscope can be inserted up to 3.5 cm into the colon of an anesthetized mouse. It has 128-channel electrode array for high-resolution electrophysiological recording from the luminal side. An inner channel allows for insertion of tools, e.g. fiber probes for Optical Coherence Tomography (OCT) imaging[1] of morphology or for neuronal optogenetic activation.
The safety and feasibility of mini-endoscopy to collect multimodal data has been so far confirmed in 30 normal mice and 3 mice with BAC-lesioned[2] colonic tissue. In vivo recordings revealed smooth muscle calcium action potentials orchestrated into complex spatiotemporal patterns, which could be modulated by intraperitoneal injections of drugs (e.g. donepezil). Morphology was imaged in-vivo with 20-microns resolution OCT visualizing changes of the gut's layers from the distal colon to rectum. After in-vivo recordings the mice were perfused the colon was collected for tissue clearing and targeted fluorescence microscopy. The origin of signals was confirmed in ex-vivo colon preparations[3] where tetrodotoxin (TTX) completely disrupted the spontaneously occurring waves. Similarly, both in-vivo functional and morphological recordings were altered following BAC treatment known to disrupt the enteric nervous system.
We believe this novel multimodal endoscopic approach represents a significant improvement over current standards (e.g. fecal pellet output). We hope that the capabilities of this device will enhance our understanding of gut function in the context of various diseases, as well as its modulation by nutrients, the microbiome, or pharmacological agents.

[1]Gora et al. Tethered capsule endomicroscopy enables less invasive imaging of gastrointestinal tract microstructure. Nat Med. 2013
[2]Qin et al. Benzalkonium chloride–treated anorectums mimicked endothelin-3–deficient aganglionic anorectums on manometry. *Journal of Pediatric Surgery*, 2010
[3]Costa et al. Characterization of alternating neurogenic motor patterns in mouse colon. *Neurogastroenterology & Motility*, 2021

P20 - Induced Neural Responses to Respiration-Synchronized Olfactory Stimuli in Human EEG

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This study introduces a novel, cost-effective olfactometer device that uses a nasal sensor to deliver olfactory stimuli synchronized with the natural respiration cycle. Using simultaneous electroencephalography (EEG) recordings, we assess the brain's response to olfaction without bio-behavioral paradigms that are (i) prone to within-subject variation on repeated testing and (ii) dependent upon cognitive, literary, and/or motor control abilities. Testing was conducted on subjects (N = 17) using a 128-channel Electrical Geodesics Inc EEG system. Subjects were presented with scented (peppermint, oregano, or citrus) or non-scented control (water) stimuli.

After standard EEG preprocessing, results demonstrate significant coupling between the phase of natural respiration and EEG amplitude in frontal regions within canonical frequency bands. This respiration–EEG phase–amplitude coupling (PAC) was validated against phase-shuffled null distributions, replicating prior findings that respiration can entrain cortical oscillations (Zelano et al., 2016). We then assessed condition-specific modulation of PAC by comparing each odor to the control using two-sided permutation tests. PAC was significantly enhanced in the lower gamma band (30–55 Hz) and significantly diminished in the alpha band (8-12Hz) during odor presentation compared to control (FDR-corrected $p < 0.001$), indicating that olfactory input modulates respiration–EEG coupling in certain frequency bands. To further characterize neural responses to odor, we applied mixed linear effects models independently at each time point to EEG data filtered in the lower gamma band. To isolate induced (non–phase-locked) activity, we extracted the amplitude envelope using the Hilbert transform applied to epoched EEG signals. This time-resolved modeling approach incorporated odor condition as a fixed effect and subject as a random effect, increasing sensitivity to subtle, temporally dynamic effects. This approach is consistent with prior literature implicating gamma oscillations in olfactory perceptual binding and integrative processing, suggesting that these signals reflect induced rather than purely evoked neural activity (Tallon-Baudry, 1999).

This olfactometer was designed with cost efficiency and accessibility for researchers in mind, focusing on odor presentation synchronized with a subject's natural respiration. Functionality was demonstrated at a reduced cost compared to all existing research and commercial olfactometers, allowing for application across a range of clinical and experimental contexts.

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2. Zelano et al., "Nasal Respiration Entrains Human Limbic Oscillations and Modulates Cognitive Function." Journal of Neuroscience, 2016

P21 - Nicotine-induced immobility in mice reveals a coordinated brain-body recovery state post-stress

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Understanding how brain–body systems transition from stress to recovery is crucial to investigate adaptive defensive behaviors. Here, we characterize the physiological and neural signatures of an immobility state induced by an anxiogenic dose of nicotine in mice (0.5 mg/kg IP)[1]. We administered nicotine in both home-cage and open-field contexts. Following injection, mice exhibited prolonged immobility and clear thigmotaxis behavior in the open field. During immobility, respiratory rate slowed to 2–3 Hz, and heart rate variability markedly increased. Concurrent hippocampal recordings revealed abundant sharp-wave ripples (SWRs). This coordinated pattern - slow breathing, high heart rate variability, and SWRs - unfolded within minutes of nicotine injection and closely mirrored the recovery immobility previously identified after acute stress[2] and classical freezing associated with 4–6 Hz breathing.

These findings suggest that nicotine can be used as a fast and replicable tool to probe recovery dynamics. This work may provide a new window into the temporal structure of defensive behavior and its resolution, bridging brain rhythms, autonomic physiology, and behaviour.

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P22 – The Effect of Sleep Deprivation and Nocturnal Light Exposure on Recovery Sleep and Morning Physiological Markers

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Sleep deprivation increases homeostatic pressure for sleep, whereas nocturnal light exposure may disrupt circadian rhythms and affect sleep architecture and other physiological processes. The aim of this study was to compare macrostructural parameters of recovery sleep following sleep deprivation in darkness and under light, and to examine their relationship with morning melatonin and glucose levels. Twelve healthy adults participated in a within-subject protocol conducted in a sleep laboratory, consisting of two experimental blocks. Each block included a baseline night, one night of sleep deprivation (either in light or in darkness), and a subsequent recovery night. Sleep was recorded using polysomnography during the baseline and recovery nights. Sleep stages (NREM1–3, REM, wake) were scored according to standard international criteria. Sleep latency, total sleep time, sleep efficiency, and the proportion of each sleep stage were compared across the four conditions using Friedman tests. Salivary samples were collected at 07:00 following each recovery night to analyze morning melatonin and glucose concentrations. Ongoing analyses include sleep microstructure, covering markers of homeostatic sleep pressure (amount and dynamics of slow-wave EEG activity during NREM sleep), arousal (high/low frequency EEG activity during NREM sleep), and autonomic function (heart rate variability).
Both light and dark sleep deprivation conditions led to increased total sleep time, reduced proportion of light sleep (NREM1), and increased deep sleep (NREM3) during the recovery night. The increase in NREM3 was more pronounced after deprivation in darkness. Recovery nights differed highly significantly in sleep onset latency: participants took longer to fall asleep after deprivation under light ($p < 0.0001$). Recovery sleep following deprivation under light conditions was also characterized by increased wakefulness during the sleep period and lower sleep efficiency ($p = 0.011$). Morning melatonin levels were significantly lower after the recovery night following sleep deprivation under light compared to the recovery night following deprivation in darkness ($p < 0.01$). Glucose levels were higher after deprivation under light than after deprivation in darkness, although the difference did not reach statistical significance.

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P23 – Differential involvement of the endocannabinoid system in obesogenic diet-induced memory impairments: influence of ovarian hormones

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In addition to cardiometabolic disorders, obesity is associated with cognitive dysfunction. This is particularly worrisome in the growing population of obese adolescents. In rodents, obesogenic high-fat high-sugar diet (HFD) consumption, in particular during adolescence, induces memory deficits. We recently demonstrated that alterations of the hippocampal endocannabinoid (ECB) system and its main receptor CB1R participate in HFD-induced memory deficits in male mice. Indeed, systemic blockade of CB1R or decrease of CB1R on hippocampal neurons improved object recognition memory task in HFD-fed males. Here, we investigated whether eCB-CB1R system contributes to HFD-induced memory impairments in females.

As in males, systemic CB1R blockade restored long-term memory in HFD-fed females, confirming its role in both sexes. However, unlike in males, hippocampal CB1R reduction failed to rescue memory deficits, while CB1R decrease in the medial prefrontal cortex (mPFC) improved memory. Our findings also revealed that hippocampal CB1R specifically on glutamatergic neurons mediated deficits in HFD-fed males, whereas mPFC CB1R on GABAergic neurons played a role in HFD-fed females. Higher levels of the eCB anandamide were found in the hippocampus and mPFC of males compared to females and systemic injection of an inhibitor of anandamide synthesis rescued memory deficits in HFD-fed males. We then investigated whether ovarian hormones mediate sex differences during puberty. Ovariectomy *per se* did not affect HFD-induced memory deficits but impede the beneficial effect of decreasing CB1R on mPFC. Remarkably, decreasing CB1R on hippocampal GABAergic neurons rescued HFD-induced memory deficits in ovariectomized females. Altogether our findings suggest that eCB-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.

P24 - Interoceptive regulation of the fear response by a glucose-sensing circuit in the insular cortex

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The brain relies on interoceptive mechanisms to adapt behavior to internal body states. While the contribution of subcortical circuits in the responses to metabolic challenges is well described, the involvement of cortical circuits remains less understood. Here, we identify a population of glucose-sensing neurons in the insular cortex that directly responds to hypoglycemia. This homogeneous population of large layer 5 pyramidal neurons projects to a subpopulation of PKCdelta positive cells in the lateral central amygdala (CeL). Reactivation of this cortical interoceptive pathway reduces innate defensive freezing behavior in response to a threat. Those findings reveal a direct role of the insular cortex in interoceptive sensing and in shaping emotional behavior depending of the body's energy status.

P25 – Astrocytic Panx1 Channels in the Dorsal Striatum Regulate Energy Balance and Feeding Behavior

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**Co-last and co-corresponding authors*

While the hypothalamus has long been regarded as the central regulator of energy homeostasis, emerging evidence points to a critical role for the dorsal striatum (DS), a key hub in reward-based decision-making, in modulating feeding behavior. Astrocytes, through their strategic positioning between neurons and blood vessels, are now recognized as active regulators of metabolic signaling and neuronal circuit function. In this context, our project explores the role of astrocytic pannexin1 (Panx1) channels in the DS, and how they contribute to the integration of metabolic and hedonic cues regulating energy balance.

Using a Cre-LoxP system in Panx1$^{flox/flox}$ mice, we generated astrocyte-specific Panx1 knockdown (KD) in the DS. Under short term exposure to high-fat high-sucrose (HFHS–1week) diets conditions, Panx1-KD mice exhibited decreased food intake and higher locomotor activity, associated with reduced fat mass, suggesting a change of energy expenditure regulation. Interestingly, brown adipose tissue temperature was reduced under ad libitum conditions in KD mice but increased after fasting, suggesting altered metabolic flexibility. Notably, feeding behavior following an 18 hours fast was comparable between genotypes across both CD and short term exposure to high-fat high-sucrose (HFHS – 1week) diets, pointing to a potential role of astrocytic Panx1 in modulating anticipatory or reward-driven feeding.

To dissect the underlying mechanisms, we implemented chemogenetic tools to manipulate astrocytic calcium signaling. DREADDs approaches are being used to assess how astrocyte excitability influences striatal network activity in control and Panx1-KD mice. Complementary to these studies, in vivo fiber photometry recordings of dopamine dynamics using GRAB-DA sensors in the DS revealed that astrocytic activation modulates dopaminergic responses to palatable food and associated cues. These findings support a model in which astrocytes in the DS influence feeding strategies by regulating dopamine dynamics in response to metabolic states and reward signals.

Our ongoing work aims to define the interplay between astrocytic calcium dynamics, Panx1 activity, and dopamine signaling in the DS. These insights may uncover novel glial mechanisms underlying obesity and maladaptive feeding behaviors.

P26 – GABAergic neurons of the preBötzinger complex in the brainstem contribute to the generation of respiratory-cardiovascular coupling

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The respiratory and cardiovascular systems act together to maintain the body's homeostasis. Their physiological efficiency is improved by respiratory-cardiovascular coupling (RCC), where heart rate (respiratory heart rate variability, RespHRV) and blood pressure (Traube-Hering waves, TH waves) oscillate in phase with respiratory activity, which optimizes pulmonary gas exchanges and cardiac energetic cost. RCC is mainly due to an interaction between neurons generating the respiratory command and neurons regulating cardiovascular activity, which are located in the brainstem. Specifically, it was shown that preBötzinger complex (preBötC) neurons, the group that generates the inspiratory rhythm, also directly modulate the activity of autonomic neurons that regulate heart rate and blood pressure. The preBötC is a highly heterogenous neuronal group, with excitatory and inhibitory neurons. Previous studies suggested that the inhibitory GABAergic neurons of the préBötC (preBötC^{GABA}) participate in the generation of RCC. To test this hypothesis and characterize preBötC^{GABA} neurons, we combined anatomical and functional approaches. Fluorescent in situ hybridization revealed that preBötC^{GABA} neurons consist of two subpopulations: neurons exclusively GABAergic and neurons co-expressing GABA and glycine. To investigate their connectome and functional roles, we injected adeno-associated viruses carrying floxed expression cassettes into the preBötC of GAD-Cre rats, allowing for selective expression of proteins for neuronal tracing (tdTomato and synaptophysin-GFP) or for bidirectional optogenetic modulation (somBiPOLES) in preBötC^{GABA} neurons. We found that preBötC^{GABA} neurons make presynaptic contacts with neurons in autonomic regions involved in regulating cardiovascular activity. Using the *in situ* Working Heart-Brainstem Preparation and *in vivo* anesthetized rats, photostimulation of preBötC^{GABA} neurons decreased the amplitude of TH waves, RespHRV, phrenic nerve inspiratory discharge, and lowered mean arterial pressure, whereas photoinhibition induced opposite effects. Systemic injection of the muscarinic antagonist atropine blocked the heart rate effects but not the blood pressure effects. This work shows that preBötC^{GABA} neurons regulate major physiological functions and contribute to their coupling through modulation of autonomic cardiovascular neurons. RCC alterations are characteristic of cardiovascular diseases, the leading cause of death worldwide. Understanding how RCC is generated under physiological conditions is essential to addressing these dysfunctions and hopefully correcting them.

P27 - Hippocampal reactivation of aversive experience enables safety learning and slow-breathing state for stress recovery

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Animals face a dual challenge when confronted with threats such as predation or conspecific aggression. First, they deploy a cascade of defensive behaviours to avoid capture, such as freezing, avoidance, escape, or attack[1,2]. These strategies are essential to avoid physical harm but induce bodily and psychological stress that disrupts normal behaviours[3]. This leads to the second challenge: recovering from the stress induced by these events to restore homeostasis[4]—an underexplored process. Focusing solely on behavioural markers may overlook critical aspects of the aspects of the recovery process, such as bodily states including cardiovascular and respiratory parameters which are increasingly recognized as active participants in coping with threat. For instance, slow breathing can be artificially induced in mice to reduce stress[5] and is widely used as a relaxation technique in humans[6].
Therefore, whether animals engage in active processes of bodily and cognitive regulation leading to recovery remains unknown and their neural bases elusive.
Using a novel two-location fear conditioning paradigm in mice, we have identified a slow-breathing immobility state that emerges when animals identify safe environments after threat avoidance and participate in post-stress recovery. This immobile state was characterized by 2-4 Hz breathing and replay of the aversive experience in the hippocampus. Suppressing hippocampal sharp-wave ripples (SWRs) inhibited the emergence of this recovery state, suggesting their role in learning safe locations. Anxiolysis with diazepam directly promoted the recovery state while suppressing SWRs, showing this treatment to be a double-edged sword that facilitates immediate relief but impairs long-term safety learning. These results demonstrate the emergence of a coordinated brain-body active recovery state in which hippocampal replay plays a central role in emotional resilience and safety learning.

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P28 - The paraventricular thalamus regulates energy metabolism and glucose homeostasis

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The control of energy homeostasis is essential for adaptation and survival. Its regulation involves a complex and dynamic process which highly depends on genetic, physiological, neurobiological, and environmental factors. Unfortunately, this homeostatic process is nowadays constantly challenged by the abundance and consumption of high-caloric meals which lead to metabolic and psychiatric disorders. While the hypothalamus and brainstem are traditionally considered as key regulators of feeding behaviors and energy homeostasis, recent studies have suggested a key role of extra-hypothalamic structures. Indeed, the paraventricular thalamus (PVT) has recently emerged as a powerful relay for cognitive, homeostatic, and visceral stimuli, therefore playing a crucial role in processes like arousal, stress, emotional memories, and drug addiction. However, its specific role in regulating feeding behavior and energy homeostasis remains poorly understood. The main objective of this study is to understand the involvement of the anterior PVT (aPVT) in scaling energy balance in both physiological and pathophysiological (obesity) conditions. Using several in vivo approaches (behavioral outputs and indirect calorimetry) combined with cell type-specific strategies (chemogenetics) and cutting-edge technologies (Ca2+ imaging), we have found that aPVT-neurons (1) dynamically respond to nutritional and metabolic states, (2) regulate nutrients partitioning and energy metabolism, (3) scale in vivo glucose dynamics and (4) are connected to hypothalamic subregions involved in the control of body's homeostasis.
In conclusion, our results uncover a new role for thalamic neurons in the coordination of homeostatic functions, therefore leading to a new understanding of unconventional brain circuits involved in metabolic disorders.

P29 - Hypothalamic PTH1R Signaling: New Therapeutic Perspectives for the Treatment of Obesity and Metabolic Disorders

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Obesity, a major public health issue, results from an imbalance between energy intake and energy expenditure, and is accompanied by metabolic comorbidities such as fatty liver disease. The need to elucidate the mechanisms behind obesity and associated pathologies has sparked interest in the development of appropriate therapeutic strategies. The hypothalamus, the central regulator of energy metabolism, represents a preferential target thanks to its ability to integrate nutritional and energetic signals from peripheral organs. AgRP-neurons in the arcuate nucleus (Arc) of the hypothalamus play a central role in regulating this balance, notably via intracellular calcium signaling. One of the molecules involved in calcium homeostasis, and potentially in the regulation of food intake and energy metabolism, is the parathyroid hormone (PTH) via its receptor PTH1R.
The aim of our study is to determine the role of PTH1R signaling in AgRP-neurons in the modulation of energy metabolism in an obesity-related pathological context.
C57BL6/J mice were fed a high-fat diet (HFD) for 8 weeks. They were then stereotactically injected into the Arc with an adeno-associated virus (AAV) expressing a shRNA against Pth1r (sh-Pth1r) under the control of the AgRP neuron-specific AgRP promoter. The metabolic impact of this modulation was assessed 5 weeks after injection.
Our results show that selective down-regulation of Pth1r in AgRP-neurons in mice fed with HFD, induces a significant decrease in body weight, along with a reduction hepatic steatosis and improved glucose tolerance associated with enhanced pyruvate tolerance. The positive effect of this modulation could offer a potential new therapeutic tool for obesity and associated metabolic disorders.

P30 - Time and Mind: Electrophysiological Mechanism of Interval Timing

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Time perception is one of the main organizational principles of cognition shaping human life and behavior.
Temporal cognition plays a fundamental role in structuring human perception, thought, and behavior. It allows us to organize events in time, anticipate future outcomes, plan actions, and coordinate movement and speech. Time is also central to the representation of the self. The continuity of self-experience across time—often referred to as autonoetic consciousness—enables us to reflect on the past, envision the future, and maintain a stable sense of identity.
Recent research focuses on the study of oscillatory dynamics as a unifying principle for timing networks in the brain.
The present study focuses on interval timing, which involves processing durations from milliseconds to a few seconds. We investigated whether power in individual frequency bands or phase-amplitude coupling (PAC) correlates with temporal precision and accuracy in a Pair-Comparison Task. Using data from the first session, we built a linear regression model with frequency band power/PAC as predictors of temporal precision/accuracy. We then tested this model on data from a second session with the same participants.

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P31 – How does the TAQ1A/ANKK1 Polymorphism Influence Reward Related Behaviours ?

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Psychiatric disorders, such as psychotic and affective disorders, as well as eating disorders, are clinically distinct but share similar symptomatic dimensions, suggesting comparable pathophysiological mechanisms. In particular, decreased motivation, increased impulsivity, and impaired behavioral flexibility are common behavioral features that are linked to a dysfunction of the mesocorticolimbic dopaminergic transmission. In addition to environmental factors, vulnerability to the development of mental disorders has been largely attributed to genetic variants. However, whether and how they impact behavioral dimensions of reward processes remain poorly explored.

Increased risk of obesity and addiction is associated with the Taq1A/Ankk1 polymorphism, a single-nucleotide variant (T→C, A2) in the ANKK1 gene next to the dopamine D2 receptor (D2R) gene. Present in 30–80% of the population, homozygous A1 allele carriers show a 30–40% reduction in striatal D2R. One common symptom found in these psychiatric diseases is cognitive inflexibility. Interestingly, even in non-pathological conditions, A1 carriers display alteration in reversal learning task, a well-established way to assess cognitive flexibility. Preclinical data show that Ankk1 loss-of-function, particularly in D2R-expressing neurons, disrupts dopamine signaling, reward processing, and procedural learning. However, although alterations such as cognitive inflexibility have been observed in humans carrying the Taq1A polymorphism, these behavioral dimensions remain poorly characterized at the phenotypic level in mouse models mimicking this genetic variation.

To examine how Taq1A/Ankk1 polymorphism affects reward processes, we are using a novel transgenic mouse model expressing either the A1 or A2 Taq1A variant, allowing a direct investigation of genotype-specific effects on behavior. By using an operant conditioning-based reversal learning task to assess behavioral flexibility, we found that while the A2 variant did not alter associative learning, A2/A2 mice outperformed A1/A1 individuals in a reversal learning task, suggesting enhanced cognitive flexibility. We are currently assessing other components of reward processing and executive functions in this mouse model such as motivation, impulsivity and value-sensitive behaviors.

These findings highlight the potential of the Taq1A/Ankk1 polymorphism to modulate dopamine-dependent executive functions, thereby contributing to individual vulnerability to psychiatric disorders.

P32 - Implication of neural circuits of the insular cortex in diet-induced anxiety

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Anxiety is an essential emotion allowing animals to avoid harmful situations. However, anxiety can become pathological, when persistent independently of the environment. In fact, anxiety disorders represent the most prevalent psychiatric conditions with an estimated yearly prevalence of 18% and a lifetime prevalence reaching 28% among adults. Although the etiology of anxiety disorders remains largely unknown, risk factors have been identified. For example, 20% of obese subjects develop an anxiety disorder. Interestingly, clinical and pre-clinical observations showed that the insular cortex (insula) is altered in patients and animal models of both obesity and anxiety disorders. Thus, we hypothesize that the insula contributes to obesity-induced anxiety.

To assess the impact of overweight on anxiety, we subjected 8-weeks-old C57BL/6J male and female mice to high caloric diet (HCD) for 12 weeks. We evaluated the anxiety level of standard-diet (SD)-fed mice or HCD-fed mice by using the elevated plus maze (EPM), the open field test and novelty suppressed feeding test. Interestingly, HFD-fed mice spent less time in open arms of the EPM, meaning they are more anxious compared to SD-fed mice. These results confirmed that HCD increases anxiety-related behaviors.

To define the role of insula circuits in HCD-induced anxiety, we used calcium imaging to record the activity of excitatory neurons of the anterior or posterior insula as well as neurons of the anterior insula projecting to the nucleus accumbens or to the basolateral amygdala (insula-NAc and insula-BLA), in both SD-fed and HCD-fed mice. As shown previously, in SD-fed mice, the activity of insula neurons was higher when mice were in open arms, selectively in the anterior insula. Interestingly, this response was amplified in HCD mice, and this activity correlated with mice anxiety levels.

Consistently, using *ex vivo* electrophysiological recordings we found that anterior, but not posterior insula pyramidal neurons were more excitable in HCD-fed mice. Overall, our work supports the hypothesis of a crucial contribution of glutamatergic neurons of the anterior insular cortex in HFD-induced anxiety in mice.

P33 - Effect of Western Diet on Sensory Representation During Food Intake in the Mouse Olfactory Cortex

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Obesity is a complex metabolic condition increasingly linked to alterations in brain function, including changes in olfactory processing, which may influence eating behavior and energy regulation. In the current project, we aimed to investigate whether consumption of a western style obesogenic diet, i.e., a High-Fat and High-Sucrose (HFHS) diet, has an effect on sensory neuronal representations during feeding in the primary olfactory cortex, more precisely the anterior piriform cortex (aPC), in mice. In addition, we aimed to characterise the representation of isolated macronutrients (fat and sugar) alongside a combination solution (Ensure) in the piriform cortex. Utilizing *in vivo* Ca^{2+} imaging of excitatory neurons in the aPC, we demonstrated that, at a population level, there is feeding rate dependent modulation of aPC activity, replicating previous findings (Lo et al., 2025), and that this modulation is similar across Ensure, lipid and sucrose solutions. The representation (i.e., peak amplitude of activity) of the subset of neurons which were either activated or suppressed in response to the delivery of Ensure, lipid or sucrose solutions, seemed to scale with the caloric content of the solutions. Our findings thus suggest that the piriform cortex may also represent macronutrients such as fat and sugar, at a sensory level. A key finding of the current study was that consumption of HFHS was linked to a strong devaluation of feeding during the recording session during the period with *ad libitum* access to HFHS in the home cage, which recovered when access to the standard chow diet (SD) was restored. Exploratory and ongoing analyses on the impact of HFHS diet on sensory representations in primary olfactory cortex (aPC), in fasted conditions, were conducted, with an increase in peak amplitude of activation of Ensure responsive neurons at week 4 of HFHS consumption, however this needs to be supplemented and confirmed with increased sample size. The project sheds insight on the interplay between metabolic states and sensory systems, highlighting how metabolic states might modulate the sensory representations during food intake.

Reference:
Lo et al. (2025). Feeding-Induced Olfactory Cortex Suppression Reduces Satiation. *Neuron,* accepted 27th June 2025.

P34 - Cardiac interoception and insular cortex: a pathway to understanding social deficits in Autism

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Interoception, the brain's ability to process internal bodily signals, plays a crucial role in regulating physiological states and adaptive behavior. The insular cortex, particularly its posterior region (pIC), is a key hub for integrating interoceptive and sensory information. Disruptions in these processes have been implicated in neurodevelopmental conditions, including autism spectrum disorder (ASD), where altered sensory integration and autonomic regulation are observed.
This study investigates how neuronal populations within the pIC encode interoceptive signals and their role in shaping behavior. Using a combination of in vivo imaging, behavioral paradigms, and physiological recordings in a mouse model, we examine the relationship between neural activity and cardiac dynamics in both typical and altered conditions. By identifying the circuits involved in interoceptive processing, this research may provide insights into mechanisms underlying sensory and social deficits in ASD and related disorders.

P35 - Burnout and interoceptive awareness, an exploratory research

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Interoception, which is the ability to perceive, integrate, interpret and regulate internal signals (Chen et al, 2021) is implicated in various psychopathological disorders such as anxiety symptomatology, depression, panic disorders or eating disorders (Tsakiris et al., 2019). Although it is considered as a transdiagnostic process (Monestes et al., 2016), interoceptive awareness, defined as the conscious level of interoception with its multiple dimensions (Mehing et al., 2018), has received little attention in the context of burnout (BO).

The BO has been defined by the French National Authority for Health (HAS) as physical, emotional and mental exhaustion resulting from prolonged involvement in demanding work situations. According to the ICD-11, it is characterized by three criteria: (1) a feeling of exhaustion and fatigue; (2) a mental distance from one's work; and (3) a feeling of inefficiency. However, research suggests that there are several profiles of BO manifestation, some more focused on symptoms specific to BO (Berjot et al., 2017), and others, closer to certain comorbid disorders such as depression (Bauernhofer et al., 2018).

In the present research, we explore interoceptive awareness as a potential avenue to better understand the heterogeneity of BO. Indeed, as BO develops, a form of distance may emerge between the mental sphere (preoccupations, personal standard) and the perception of bodily signals (fatigue, somatization). According to Maslach (1997), during emotional exhaustion, avoiding strategies as hyperactivity can be developed to decrease the signals of fatigue. During the stage of escalation ("engrenage") and when facing a lack of performance, more cognitive and motivation efforts can be provided to trying achieving goals, and that, by ignoring or overpassing body exhaustion or pain signals (Pezé, 2022).

We hypothesize that various interoceptive modalities in term of perception, integration, interpretation or regulation, could be correlated with different profiles of BO manifestation. An initial qualitative study is currently underway to explore interoceptive awareness in women undergoing reconstruction after burnout. Initial data are currently being analyzed. We expect that an interoceptive mode combining body signals perception, attentional regulation, integration and interpretation capacities will be more expressed in people in an advanced phase of reconstruction

P36 – Implication of Mesocoticolimbic Dopamine Transmission in Behavioral Flexibility : a Role for Dopamine and NMDA Receptor Hetromers

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Executive function impairments are a common symptom of many psychiatric pathologies. They are correlated with impaired dopaminergic transmission originating from the midbrain within the medial prefrontal cortex (mPFC). This mesocorticolimbic dopamine transmission is believed to be a key modulator of goal-directed behaviors and reward processing through its action on dopaminoceptive neurons expressing either D1 (D1R) or D2 receptors (D2R) in target structures. However, the precise mechanisms by which this dopamine transmission modulates goal-directed behavior remain unclear. Through a chemogenetic approach, we show that the mesocorticolimbic dopaminergic pathway is required when the animal has to adapt to changes in the association between actions and outcomes. Accordingly, using dopamine sensor coupled with fiber photometry, we show that medial prefrontal dopamine release is observed mainly during the reversal of action-outcome associations. From a mechanistic standpoint, we demonstrate, using interfering peptides, that mPFC D1/NMDA and D2/NMDA receptor heteromers constitute a central mechanism to mediate the effects of dopamine on behavioral flexibility, as their blockade spares action-outcome learning and expression but selectively impairs the animal's ability to adapt to changes in action-outcome associations. Using a calcium sensor approach coupled with fiber photometry, we characterized the neural signature of mPFC dopaminoceptive neurons expressing D1R or D2R during Pavlovian and operant conditioning paradigms and the effect of heteromer blockade on these activities. We identified specific patterns of activity during discrete cue, action and consumption phases, and found that blockade of either D1/NMDA or D2/NMDA heteromers strongly impacts activity patterns during the reversal of associations. These data provide a better understanding of the underlying mechanisms of behavioral adaptations and suggest that medial prefrontal D1/NMDA and D2/NMDA heteromers could be prime targets for the development of more specific therapeutic treatments for psychiatric symptoms.

P37 - The translational functional architecture of cardiovascular interoceptors

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Cardiovascular interoception plays a key role in emotional behavior. Its alteration has been linked to emotional dysregulation and anxiety. Cardiovascular states and blood composition are monitored by specialized receptors located in large vessels and the heart. However, it is unclear whether those receptors are altered in disease states linked to interoceptive dysregulation. In addition, their cellular and molecular structure is poorly characterized in humans. In this work we leveraged large scale human tissue clearing and multiplexed immunostaining to provide a detailed mapping of human cardiovascular interoceptors. We showed that they are more widely distributed and heterogeneous than presented in previous descriptions. We also traced their innervation to better understand the pathways linking them to the brain. Eventually, we studied with a similar approach equivalent structures in mice. Altogether, our data provides a detailed, functionally-relevant 3D cellular map of cardiovascular interoceptors in mice and humans which can serve as a base for mechanistic and translational research on interoception and interoceptive pathology.

P38 - *Phascolarctobacterium faecium* reverses gut motility impairment in mice with diet-induced obesity

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The human intestinal bacterium *Phascolarctobacterium faecium* has anti-obesity properties in an animal model of diet-induced obesity (DIO) by promoting an anti-inflammatory response in the gut. Nevertheless, its impact on other intestinal pathways relevant for the energy homeostasis control, such as the modulation of the enteroendocrine system and the enteric nervous system (ENS), remains unexplored. Here, we investigated in mice whether *P. faecium* could affect these intestinal systems under an obesogenic diet and its effects on food intake, gut motility and postprandial metabolism. We demonstrated that *P. faecium* prevents hyperphagia through the anorexigenic gut hormone PYY. Independently of caloric intake, the bacterium accelerates gastrointestinal transit and reduces postprandial glycemia and intestinal lipid absorption. Immunofluorescence analysis of the ENS revealed a protective effect exerted by the bacterium on enteric neurons within the colonic myenteric plexus of mice exposed to a high-fat high-sugar diet. This study identifies the enteroendocrine system and the ENS as novel underlying targets through which the human intestinal bacterium, *P. faecium*, confers protection against obesity.

P39 - Hippocampal endocannabinoid system mediates obesogenic diet-induced memory impairments in male mice

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Obesity is a global health crisis, associated with cardiometabolic consequences but also with adverse cognitive outcomes. Adolescent obesity is increasing at a rate twice that of adults since 1990 and understanding its impact during this critical developmental period is essential, particularly on the cognitive aspect. Juvenile obesity can be modeled in rodents through high-fat and high-sugar diet (HFSD) exposure from weaning to adulthood. It is now well established that periadolescent exposure to HFSD has a detrimental effect on memory function. However, the mechanisms underlying these memory deficits remain to be elucidated. The brain endocannabinoid system and type-1 cannabinoid receptors (CB1R) control memory processes and are upregulated in obesity. In this study, we assessed in male mice whether the effects of obesogenic diet consumption on memory function are dependent on this system.

Using a pharmacological approach, we found that a systemic blockade of CB1R rescued HFSD-induced deficits of long-term object recognition memory (ORM), while also normalizing training-induced hippocampal c-Fos over-activation and aberrant in vivo long-term potentiation in CA1 of HFSD-fed mice. Following ORM training, we found an increase of endocannabinoid levels (anandamide), CB_1R expression and CB1R-dependent activation of the mTOR pathway in the hippocampus of HFSD-fed mice. Decreasing the expression of CB_1R expression on glutamatergic neurons in the hippocampus or inhibiting mTOR pathway rescued diet-induced long-term recognition memory deficits.

Together these results demonstrate that obesogenic diet consumption alters the endocannabinoid system of the hippocampus in male mice resulting in impaired activity and synaptic plasticity and eventually leads to memory deficits.

P40 - How adolescent obesity impacts social memory: the role of hippocampal CA2 and oxytocinergic system

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Obesity is a global health crisis, with adolescent obesity increasing twice as fast as in adults since 1990. Given its long-term metabolic, psychosocial, and cognitive consequences, understanding its impact during this critical developmental period is essential. Juvenile obesity can be modeled in rodents through adolescent high-fat and sugar diet (HFSD) exposure, a widely used model to study its cognitive effects. While HFSD impairs spatial, relational, contextual, and object-based memory, emerging evidence suggests it also disrupts social recognition memory (SRM). However, the underlying neural and molecular mechanisms remain unclear. We recently focused on the hippocampal CA2 area, known to be crucial for social memory, and found that HFSD-fed mice exhibit CA2 pyramidal neuron hyperactivity. Chemogenetic inhibition of these neurons rescues HFSD-induced SRM deficits. These deficits are also linked to reduced oxytocin (OT) signaling in CA2, as OT infusion during encoding restores SRM in HFSD-fed mice. However, as these findings were primarily obtained in males, we are currently investigating whether similar mechanisms are present in HFSD-fed females. Preliminary data suggest that, unlike males, HFSD-fed females show hippocampal hypoactivation and chemogenetic activation of the dorsal hippocampus rescues SRM deficits, indicating sex-dependent regulatory mechanisms. To further investigate these differences, we will assess in females SRM combined with biochemical, fiber photometry, chemogenetic, and pharmacological approaches to evaluate CA2 activity and OT signaling. Given the recent evidence implicating the supramammillary nucleus (SUM)-CA2 pathway in social novelty processing, we will also explore its role in HFSD-induced SRM deficits in both sexes. Identifying these mechanisms will underscore the importance of considering sex differences in cognitive research and may help developing future strategies to mitigate the neurocognitive impact of adolescent obesity.

P41 - Mapping the descending sympathetic innervation of spleen and pancreas

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To maintain homeostasis, the immune system must trigger complex, multiorgan responses. Previous studies suggest that the nervous system regulates spleen immune function not only through peripheral circuits, but also through a broader neuronal circuitry involving the brain. The sympathetic neuronal circuits involved, and the mechanisms underlying this immune regulation, remain largely unknown.
Our whole-organ imaging revealed dense sympathetic innervation of the spleen and pancreas. Tracing studies using Cholera Toxin subunit B (CTB) demonstrated largely distinct populations of celiac-mesenteric ganglia (CMG) sympathetic neurons innervating each organ. We hypothesize that different neuronal populations exhibit distinct transcriptional profiles that correlate with their target organ's function. To investigate this, we defined CMG neuronal populations using single-nucleus sequencing and are currently characterizing those innervating spleen and pancreas.
To identify the second-order, preganglionic CMG spinal neurons, we injected CTB into the CMG. We mapped these neurons to known sympathetic regions of the thoracic spinal cord. Using a monosynaptic rabies virus approach, we identified third-order neurons in the brain projecting to preganglionic CMG spinal neurons. As expected, we found a direct communication with neurons emerging from the brainstem and hypothalamus. Surprisingly, we also observed a substantial descending cortical innervation, originating not only from the prefrontal and sensory cortices but also from the motor cortex. We found anatomical evidence of descending motor cortical axons synapsing with preganglionic CMG neurons in the spinal cord. We are exploring whether motor cortex activity modulates CMG neuronal activity and immune responses.
Taken together, our findings reveal that distinct neuronal populations in the CMG innervate almost exclusively the spleen or pancreas and receive input from specific preganglionic spinal neurons. These are innervated by third-order neurons projecting not only from the brainstem and hypothalamus but also from the cortex. We hypothesize that descending circuits from the motor cortex may influence the function of organs beyond muscles, including the spleen

P42 - Contribution of the anterior insular cortex in anxiolysis induced by a single injection of psychedelics

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Anxiety is a natural, evolutionarily conserved response to perceived danger, essential for survival across species. However, when chronically high independently of the environment, it can become pathological. Anxiety disorders affect up to 18% of adults worldwide. Despite their prevalence, treatment options remain limited. SSRIs are commonly prescribed but often cause side effects, and around 30% of patients do not respond. The serotonin (5-HT) system, particularly its 1A and 2A receptor subtypes, plays a key role in mood and anxiety regulation. Psychedelics such as TCB-2 and 5-MeO-DMT, which act on these receptors, have recently gained attention for their potential to induce long-lasting anxiolytic effects. The anterior insular cortex (insula), enriched in 1A/2A receptors and involved in anxiety processing, may mediate these effects. We investigated the role of the anterior insula in the long-term anxiolytic actions of psychedelics.

Adult male and female mice (14 weeks old) received TCB-2 (3 mg/kg) or 5-MeO-DMT (20 mg/kg) intraperitoneally. Psychedelic activity was assessed by quantifying head-twitch responses over 60 minutes. Anxiety-like behaviors were measured using the elevated plus maze (EPM) and light-dark test (LDT) after short-term (60 min) and long-term (7 days) intervals.

In the short term, TCB-2 increased the time mice spent in the open arms without affecting behavior 7 days later, suggesting a transient effect. In contrast, 5-MeO-DMT showed a trend to decrease the time mice spent in the open arm in the short term ($p=0.1$) and significantly increased it after 7 days, indicating a sustained anxiolytic effect.

To explore the insula's involvement, we used fiber photometry to monitor calcium dynamics in anterior insula neurons expressing 1A or 2A receptors. 5-MeO-DMT increased the frequency of large amplitude transients (giant 'transients') in both populations, persisting at 7 days post-injection. To assess cell-type specificity, we used dual-color photometry to record glutamatergic neurons with jRGECO and monitored extracellular 5-HT with GRAB-5HT. Preliminary data suggest these giant transients are not systematically expressed by glutamatergic neurons, suggesting a contribution of GABAergic neurons.

We also performed *in vivo* electrophysiology to assess the neural impact of psychedelics. Twelve male and female mice were implanted with 16-channel electrodes to record local field potentials (LFPs) and spiking activity during behavior. Spectral analysis showed increased gamma-band power (30–80 Hz) shortly after 5-MeO-DMT injection. Single-unit analysis revealed enhanced spike–gamma phase coupling.

These findings suggest that 5-MeO-DMT induces lasting changes in anterior insula dynamics and circuit function, contributing to its anxiolytic effects and enhancing our understanding of psychedelic action on anxiety-related networks.

P43 - neuroIGNITOR: A flexible technology platform for stimulating and sensing peripheral nerves

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The development of more advanced and selective peripheral nerve stimulation technologies is essential for precisely modulating brain-body communication pathways, enabling deeper insights into neurophysiological mechanisms and more effective interventions for related disorders. We present a flexible stimulation and sensing benchtop system called neuroIGNITOR that is tailored to enable closed-loop neuromodulation experiments in pre-clinical settings. At the core of the system, we have developed an application specific integrated circuit (ASIC) that supports high voltage compliance (22V) and high stimulation currents (up to ±10.22mA) on 2 independent current sources that can be multiplexed to 16 output channels to enable a wide variety of peripheral nerve stimulation approaches (Xin et al. 2025). Furthermore, the ASIC provides both active and passive charge balancing capabilities and enables arbitrary waveforms along with novel, high frequency stimulation paradigms, such as i^2CS (Rossetti et al. 2025) or kHz-stimulation (up to 42kHz) in a safe manner. In order to enable closed-loop paradigms, it is integrated in a benchtop system that features additional 8 recording channels with advanced artifact blanking, built-in impedance monitoring and several digital lines for interfacing with other external devices. Finally, the hardware is controlled via a dedicated graphical user interface (GUI) for stimulation and recording, including on-the-fly visualization and pre-processing as well as a Python-based software development kit (SDK) for maximum flexibility to enable custom experimental protocols. We present results from validation experiments to showcase the potential of the system for research and pre-clinical studies by demonstrating stimulation of the medial and lateral giant fibers (MGF/LGF) in an earthworm model and simultaneous recording of the resulting evoked compound action potentials (eCAPs). Furthermore, we discuss the system components and possible applications in the neuromodulation space.

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P44 - Translational study of the protective role of indoles in psychiatric illnesses.

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Background: By 2030, psychiatric disorders are expected to become the leading cause of disability worldwide (Feng et al., 2020). Inflammatory processes are increasingly linked to psychiatric disorders and are known to be influenced by the gut microbiota. Among gut-derived metabolites, tryptophan-derived indoles have drawn attention for their immunomodulatory properties and potential effects on brain function (Qian et al., 2024). This project takes a translational approach to investigate the relationship between indoles, inflammation, and mood-related pathology.
Methods: Preclinical studies included *in vitro* experiments in which a selection of indoles were applied to BV2 microglial cells under inflammatory conditions (LPS) to assess anti-inflammatory effects. *In vivo*, dopaminergic activity in the nucleus accumbens was recorded via fiber photometry during a Pavlovian conditioning task to evaluate motivation-related neural dynamics. Mice received indole-3-lactic acid (ILA) either orally, through drinking water, or via intraperitoneal injection. Brain and blood samples were collected to assess ILA bioavailability and central penetration. In a clinical cohort of psychiatric patients with varying levels of depressive symptoms, circulating indole levels were measured alongside inflammatory and metabolic markers.
Preliminary Results: Data collection is ongoing. The study aims to characterize how peripheral indole levels relate to inflammation and psychiatric symptom severity in patients, assess the efficiency of brain delivery via different ILA administration routes in vivo, evaluate indole-related modulation of dopaminergic activity during reward processing, and determine the immunomodulatory effects of various indoles on microglial inflammatory responses in vitro.
Conclusion: This work integrates clinical, preclinical, and cellular approaches to examine gut-brain interactions in relation to psychiatric illness. By exploring mechanistic and translational aspects—including alternative routes of ILA administration—this project aims to study indoles potential as modulators of neuroinflammation and candidates for therapeutic development.

References
Feng et al., 2020; Qian et al., 2024

P45 - Exploring salivary and emotional responses triggered by exposure to real foods

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Our body works in a highly organized and coordinated manner to be physiologically prepared to receive food and for optimal nutrient processing - this happens even before food enters our mouth.
For example, when we see and smell a delicious chocolate cake, a cascade of different psychophysiological responses are triggered, including an increase of salivation, secretion of food-related hormones or changes in autonomic nervous system activity. These anticipatory events, collectively known to be part of the cephalic phase of digestion, play a crucial role in ingestive behaviour, may enhance appetite and encouraging us to eat.
Previous work, including studies from our lab, have reported changes at saliva secretion rate and composition level in response to visual food cues presented as pictures [1] and food odors (e.g., the smell of bread [2], vanilla and lemon [unpublished data]). These data suggest that the rapid release of saliva into our mouth, we experience during exposure to food stimuli, reflects changes in terms of composition that appear to vary according to the sensory characteristics and hedonic value of the food stimulus.
Notably, the same food stimuli may also evoke changes in our emotional states, indicating a complex interplay between physiological regulation and affective processing.
Investigating potential changes triggered by different real foods on salivary and emotional responses may provide valuable insights to elucidate physiological mechanisms underlying the regulation of ingestive behavior.
To further investigate these aspects, a total of sixteen healthy adults, from both sexes, took part in a within-subject experiment assessing salivary and emotional responses to real food stimuli.
Participants were asked to collect saliva samples, immediately before and during a 3-minute exposure to three foods, representing different calorie content and hedonic value (chocolate donut, white grapes and cream crackers) and a non-food item – a toy (car). Galvanic skin response, heart rate variability and facial expressions were also assessed to infer emotional arousal and detect affective responses. Additionally, participants self-report liking, desire to eat and rate the emotions evoked by each stimulus in study. The main results will be presented and discussed, correlating the changes in salivary biochemical composition with the activation of autonomic nervous system in response to foods.

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P46 - Infra-slow Frequency Oscillations Propagating through Multiple Organs Convey Information on Phase-specific Timing for Self-Initiated Actions

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Cognitive functions crucial for voluntary actions fluctuate with infra-slow frequencies (ISF, <0.2 Hz), indicating their potential impact on self-driven behavior. ISF's involvement in brain–body interaction suggests that the link between ISF oscillations and self-initiated actions can be explored through low-frequency physiological readouts in peripheral organs.

We investigated whether ISF in peripheral systems relates to spontaneous motor activity. Pupillary hippus, heart rate variability (HRV), and respiration were analyzed against self-paced button presses across ISF frequency bands in 16 participants (Discovery dataset) and validated in an independent sample of 25 healthy individuals (Validation dataset).

Self-initiated actions significantly clustered within a specific phase of the slow3 ISF band (0.073–0.198 Hz) across all three organ systems ($p \leq 0.001$). Moreover, we observed phase-locking of slow3 oscillations among pupillary hippus, HRV, and respiration, indicating synchronized ISF propagation throughout the body.

These findings demonstrate that spontaneous action timing is not random: it preferentially occurs at particular phases of slow3 oscillations detectable in the autonomic nervous system. This suggests that inherent ISF rhythms modulate the propensity to act, uncovering a unified brain–body mechanism underlying the initiation of voluntary movements. Further exploration of this pathway could deepen insights into the complexities of conscious action initiation.

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P47 - Restoring effect of voluntary exercise on obesogenic diet-induced social memory deficits: emphasis on the oxytocin signaling in the CA2 area of the hippocampus

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Obesity has emerged as a significant global health issue, with the prevalence among children and adolescents rising to 20% in 2022. During adolescence, a critical period for brain development, obesogenic diets have been shown to induce structural, cellular, and molecular alterations in multiple brain regions, particularly the hippocampus. Moreover, these diets also impair social recognition memory (SRM) which relies on the oxytocinergic system. Notably, the CA2 subregion of the hippocampus, characterized by a high expression of oxytocin (OXT) receptors, is regarded as a key hub for SRM. However, the specific role of OXT in the CA2 region on the SRM deficits induced by an obesogenic diet during adolescence remains unclear. Preliminary findings in the lab suggest that exercise during adolescence prevents these deficits, suggesting that the OXT signaling in the CA2 may be a key regulator.

The study aims at addressing the broad question of how exercise could mitigate obesity-related cognitive dysfunction.

First, we have established a dose-response of L368,899, an OXTR antagonist, in the CA2 area of control diet-fed mice in order to determine the suboptimal dose (preserving SRM) and the optimal dose (blocking SRM). Then, we locally administered these doses to assess their impact on exercise-induced SRM recovery in adolescent high-fat diet-fed mice. Besides, CA1-dependent spatial memory has been assessed via the object location memory test to evaluate the specificity of the observed effects.

Our results show that the pharmacological blockade of the OXTR in the CA2 induces deficits in the preference for social novelty but not spatial memory in control mice and that the oxytocinergic system may be involved in the beneficial effects of exercise.

P48 - Unravelling the contribution of glial cells in the insular cortex after obesogenic-diet induced anxiety

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Anxiety is an essential emotion that enables animals to avoid potentially harmful situations. However, when persistent and disproportionate in regards of the environment, anxiety becomes pathological. Anxiety disorders are the most prevalent psychiatric conditions, with an estimated 12-months prevalence of 14% [1]. Although the etiology of anxiety disorders remains largely unknown, several risk factors have been identified. Notably, patients suffering from obesity show a 1.4 higher risk to develop anxiety disorders [2].
Obesity is increasingly recognized as a state of chronic low-grade inflammation, which may contribute to neuropsychiatric comorbidities [3]. Glial cells, including microglia and astrocytes, play a crucial role in mediating neuroinflammation and modulating neuronal function, thereby influencing brain circuits involved in anxiety [4]. Clinical and preclinical studies have shown alterations in the insular cortex (insula) in both obesity and anxiety, suggesting a shared neural substrate [5,6]. Based on this, we hypothesize that the insula contributes to obesity-induced anxiety.
To investigate the behavioral consequences of diet-induced obesity, we exposed 8-week-old male and female C57BL/6J mice to either a high-caloric diet (HCD) or a standard diet (SD) for 12 weeks. Anxiety-like behaviors were evaluated using the elevated plus maze (EPM). Concurrently, we examined neuroinflammatory changes in the anterior and posterior insula by quantifying both the number and morphology of microglia and astrocytes to assess their activation state.
HCD-fed mice exhibited significant weight gain and demonstrated increased anxiety-like behavior, spending less time in the open arms of the EPM compared to SD controls. In the insula, we observed a significant increase in microglial density across all cortical layers, whereas astrocyte numbers remained unchanged. This increase in microglia density following a HCD diet appears to be mainly driven by the anterior insula, with lower effect size in the posterior part. Detailed morphological analysis of these glial cells revealed an obesity-induced neuroinflammatory phenotype. Taken together, our result suggest that obesity induced anxiety is linked to microglia specific neuroinflammation in the insula. Further research will focus on elucidate the mechanisms of how neuoninflammation in the insula modulates anxiety.

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P49 - Investigating how lung cancer alters behavior via regulating the internal sensory system

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The brain receives vital sensory information from internal organs and regulates critical autonomic functions such as breathing. As such, it has been observed that lung cancer patients display an array of behavioral alterations, traditionally regulated by the nervous system, with pain being the most common one. We hypothesize that lung tumors dysregulate interoceptive signals from the lung to the brain, driving cancer-induced visceral pain.

Given that rodents cannot articulate their experiences, we use an array of behavioral tools to assess their pain state. We assess spontaneous behaviors, including body posture, facial grimace and digging in $Kras^{G12D/+};p53^{-/-}$-driven lung adenocarcinoma mice across tumor development. Using a 3D imaging and behavioral platform termed Keypoint-MoSeq, we discovered that cancer mice show more hunching and stationary movement while engaging in "turning" behaviors requiring upper body movement less frequently than healthy mice. We also employed PainFace, a deep neural network, to assess grimace in healthy and lung tumor-bearing mice as another measure of spontaneous pain. We find that lung cancer mice exhibit significantly higher grimace scores in comparison to healthy controls. Finally, digging behaviors, recently linked to visceral pain, are also altered in lung cancer mice compared to healthy mice.

To identify brain regions involved in lung cancer-associated pain, we employed chemogenetic activation of peripheral sensory neurons. Selective activation of specific lung-innervating sensory neurons was sufficient to induce pain-like behaviors that mimic those observed in lung cancer. Brain c-Fos analysis revealed that this activation drives distinct neural activity in specific regions of the brainstem, which is critical for processing visceral sensory input. Similarly, c-Fos mapping in lung cancer-bearing mice revealed overlapping patterns of brain activation. By comparing the brain regions engaged by chemogenetic nociceptor stimulation and those altered in the context of lung cancer, we identified shared circuits that likely underlie cancer-associated pain. Ongoing studies are assessing whether inhibiting these circuits with chemogenetics can reverse pain behaviors and influence tumor growth and survival.

In conclusion, we are integrating advanced behavioral tools, cellular biology methods, and lung cancer mouse models to unravel the mechanisms behind cancer-induced visceral pain, offering a novel perspective on cancer biology. Our goal is to deepen our understanding of how visceral pain signals are transmitted and to pave the way for innovative therapies in lung cancer treatment.

P50 - Neuromodulation in the posterior insular cortex maintains fear balance

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Maintaining emotions in an adaptive range is important for survival. Our group has previously shown, that the posterior insular cortex (pInsCtx) plays a crucial role in keeping fear in balance upon extinction learning [1]. Surprisingly, we found that the pInsCtx exerts both, a fear extinction impeding, but also facilitating role depending on the strength of the acquired fear levels. However, we lack mechanistic understanding which factors may enable the dual role of the pInsCtx on fear extinction learning.

The neuromodulators noradrenaline (NA) and acetylcholine (ACh), are known to be released in response to sensory stimuli, as well as upon changes in affective states. Furthermore, they have been implicated in fear and extinction learning, as well as the regulation of bodily functions. Given these roles, we here aimed at investigating a potential contribution of these neuromodulators to the role of the pInsCtx in keeping fear in balance.

To understand the potential recruitment of NA and ACh within the pInsCtx during fear learning and extinction, we characterized their release using GRAB sensors during classical auditory fear conditioning in freely moving mice, as well as in head-fixed animals, where we obtained physiological readouts of heart rate, pupil and other arousal signals. Our results reveal specific differences in the dynamics of NA and ACh release in response to different fear-related sensory stimuli, changes in autonomic readouts and emotional behaviors. We found that NA release in the pInsCtx supports emotional learning and the maintenance of fear state, while ACh release is tightly coupled to bodily signals. Strikingly, interference with neuromodulatory release in the pInsCtx during fear extinction via optogenetic terminal inhibition resulted in bidirectional effects. While inhibition of NA terminals impaired fear extinction, inhibition of ACh terminals facilitated fear extinction. Importantly, these effects were contingent upon the fear state of an animal.

Together, our findings suggest that NA and ACh in the pInsCtx are crucial in regulating the adaptive balance of fear maintenance and extinction learning. This equilibrium is facilitated through the cholinergic integration of exteroceptive and interoceptive signals, alongside the noradrenergic encoding of fear state.

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