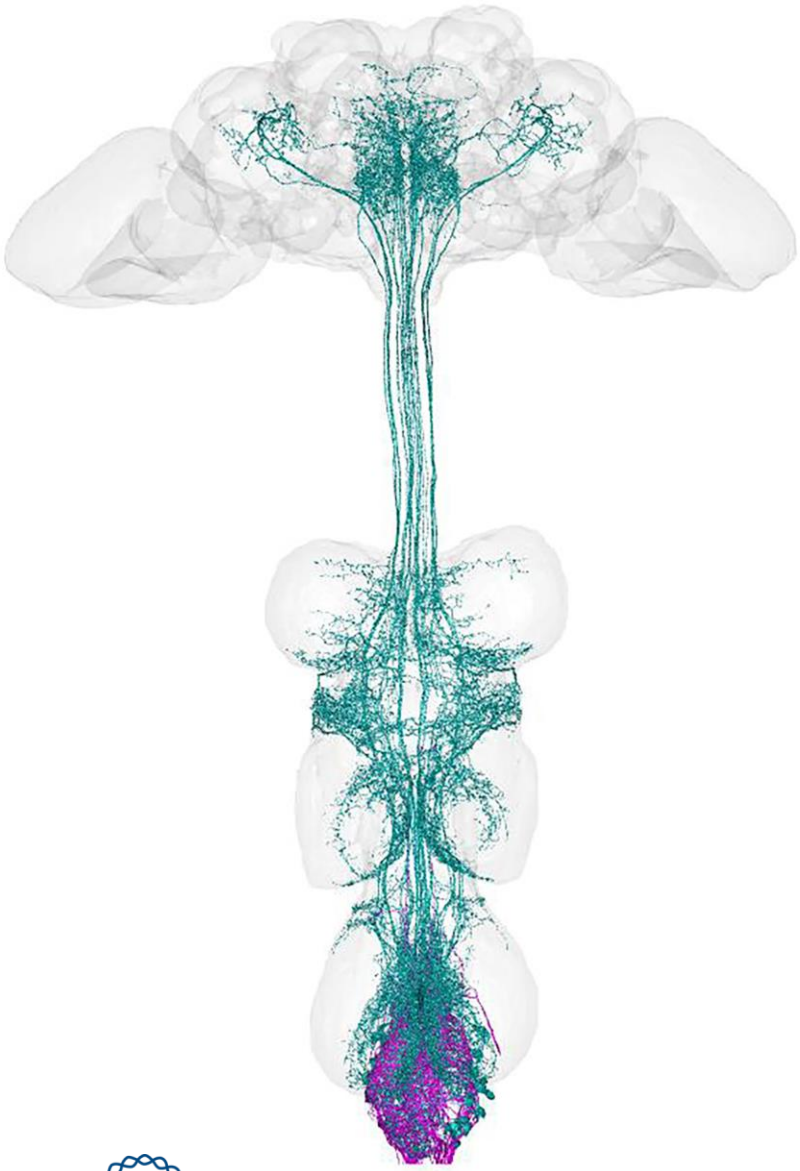
Abstracts of papers presented
at the 2026 meeting on

BRAIN BODY PHYSIOLOGY

May 12–May 16, 2026



Cold Spring Harbor Laboratory
MEETINGS & COURSES PROGRAM

Abstracts of papers presented
at the 2026 meeting on

BRAIN BODY PHYSIOLOGY

May 12–May 16, 2026

Arranged by

Kara Marshall, *Baylor College of Medicine*
Carlos Ribeiro, *Champalimaud Centre for the Unknown, Portugal*
Asya Rolls, *Tel Aviv University, Israel*

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MEETINGS & COURSES PROGRAM

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Front cover: Reconstructions of ascending body-brain circuitry from the maleCNS *Drosophila* connectome. Sensory neurons of the abdomen in magenta, and top ascending outputs in turquoise. - Rory Beresford, Inês de Haan Vicente, and Arina Dygay, Ribeiro Lab, Champalimaud Centre for the Unknown.
Back cover: Illustration of the mouse gut-brain connection and the spinal and sensory neurons that connect them. Britya Ghosh, Baylor College of Medicine.

BRAIN BODY PHYSIOLOGY
Tuesday, May 12 – Saturday, May 16, 2026

Tuesday	7:30 pm – 9:30 pm	**Session I:** Opening Session **Keynote Speaker**
Wednesday	9:00 am – 12:00 pm	**Session II**
Wednesday	12:00 pm – 12:10 pm	**Flash Talks I (a):** Tools and Diverse Systems
Wednesday	2:00 pm – 4:30 pm	**Session III**
Wednesday	4:45 pm – 5:00 pm	**Flash Talks I (b):** Sex and Reproduction
Wednesday	5:00 pm	*Wine & Cheese Party*
Wednesday	7:30 pm – 10:30 pm	**Poster Session I**
Thursday	9:00 am – 12:00 pm	**Session IV** **Keynote Speaker**
Thursday	12:00 pm – 12:10 pm	**Flash Talks II (a):** Cancer and Reproduction
Thursday	2:00 pm – 4:45 pm	**Session V**
Thursday	4:45 pm – 5:00 pm	**Flash Talks II (b):** Cardiac and Immune Preview
Thursday	7:30 pm – 10:30 pm	**Poster Session II**
Friday	9:00 am – 12:00 pm	**Session VI**
Friday	2:00 pm – 5:00 pm	**Session VII**
Friday	6:00 pm	*Cocktails and Banquet*
Saturday	9:00 am – 11:00 am	**Session VIII:** Closing Session
Saturday	11:15 am – 12:00 pm	**Panel Discussion**

All times shown are US Eastern: Time Zone Converter

Mealtimes at Blackford Hall are as follows:
Breakfast 7:30 am-9:00 am
Lunch 11:30 am-1:30 pm
Dinner 5:30 pm-7:00 pm

Bar is open from 5:00 pm until late

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PROGRAM

TUESDAY, May 12—7:30 PM

SESSION I: OPENING SESSION

Chairpersons: **Kara Marshall,** Baylor College of Medicine, Houston, Texas
Carlos Ribeiro, Champalimaud Centre for the Unknown, Lisboa, Portugal
Asya Rolls, Tel Aviv University, Israel

Welcome and Meeting Overview
by Organizers

KEYNOTE SPEAKER

Misha Ahrens
HHMI Janelia Research Campus

SESSION II

Chairpersons: **Maayan Levy,** Stanford University, California
Nadine Gogolla, Max Planck Institute of Psychiatry, Munich, Germany

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WEDNESDAY, May 13—12:00 PM

FLASH TALKS I-a: Tools and Diverse Systems

WEDNESDAY, May 13—2:00 PM

SESSION III

Chairpersons: **Sinisa Hrvatin,** Whitehead Institute, Massachusetts Institute of Technology, Cambridge
Jessica Osterhout, University of Utah, Salt Lake City

WEDNESDAY, May 13—4:45 PM

FLASH TALKS I-b: Sex and Reproduction

WEDNESDAY, May 13—5:00 PM

Wine and Cheese Party

WEDNESDAY, May 13—7:30 PM

POSTER SESSION I

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THURSDAY, May 14—9:00 AM

SESSION IV

Chairpersons: **Yoav Livneh,** Weizmann Institute of Science, Rehovot, Israel
Stephen Liberles, Harvard Medical School, Boston, Massachusetts

KEYNOTE SPEAKER

Rui Costa
The Allen Institute

Lineage and organ cues sequentially build organ intrinsic nervous systems
I-Uen (Yvonne) Hsu, Jia Zhao, Yingxin Lin, Yunshan Guo, Qian J. Xu, Yuancheng Shao, Ruiqi L. Wang, Dominic Yin, Kakali Ghoshal, Rida Mourad, Ambra Pozzi, Carmen M. Halabi, Lawrence H. Young, Hongyu Zhao, Le Zhang, Rui B. Chang.
Presenter affiliation: Yale University School of Medicine, New Haven, Connecticut. 20

Preoptic neurons that control entry into hibernation
Adrian J. Martinez, Christopher M. Reid, Aurora J. Lavin-Peter, Wenhui Li, Andrew S. Lee, Eric C. Griffith, Siniša Hrvatin.
Presenter affiliation: Whitehead Institute, Massachusetts Institute of Technology, Cambridge; Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, Massachusetts. 21

Synthetic torpor to discover novel metabolic vulnerabilities in breast cancer
Alexandria Battison, Adrian Gomez, Sonam Tamrakar, Jeremy Balsbaugh, Jennifer Liddle, Marina Sherman, Jill Habel, Yue Wu, Patrick Wertimer, Michael Lukey, Jeremy Borniger.
Presenter affiliation: Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. 22

The maternal body-brain connection—Investigating the role of mammary gland-innervating sensory neurons in lactation
Briana G. Nixon, Sasha L. Fulton, Ishmail Abdus-Saboor.
Presenter affiliation: HHMI, Columbia University, New York, New York. 23

Wireless, cell-type-specific magnetomechanical control of vagal gut–brain circuits
Ye Ji Kim, Nasim Biglari, Cameron Forbrigger, Scott Matchen, Emmanuel V. Panigua, Karen Pang, Jessica Slaughter, Jacob Beckham, Keisuke Nagao, Elizabeth Whittier, Polina Anikeeva.
Presenter affiliation: Massachusetts Institute of Technology, Cambridge, Massachusetts. 24

Extreme glucocorticoid levels in deer mice emerge from an evolutionary arms race
Jennifer R. Merritt, Sophie Lockwood, Natalie Niepoth, Hyatt Taylor, Serena Cooper, Grace Kaprielian, Esther Carlitz, Wei Gao, Clemens Kirschbaum, Andrés Bendesky.
Presenter affiliation: Columbia University, New York, New York. 25

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FLASH TALKS II-a: Cancer and Reproduction

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Susana Delgado Ocana *poster p. 96*
Raquel Nóbrega *poster p. 97*

SESSION V

Chairpersons: **Zachary Knight,** University of California, San Francisco
Jens Brüning, Max-Planck Institute for Metabolism Research, Cologne, Germany

Intracolonic optogenetic stimulation of vagal innervations increases exploratory behaviors in freely moving mice
Karen Ka Lam Pang, Rajib Mondal, Sharmelee Selvaraji, Magdelena Slowikowski, Hua Fang, Gari Eberly, Atharva Sahasrabudhe, Polina Anikeeva.
Presenter affiliation: Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts. 31

Nociceptors regulate hair plucking-induced inflammation and regeneration
Shir Keret, Nadav Goldberg, Yael Kashash, Tamar L. Ben-Shaanan.
Presenter affiliation: Weizmann Institute of Science, Rehovot, Israel. 32

Sympathetic-epithelial crosstalk governs tissue-resident memory T cell immunosurveillance in the skin
Peng Zhang, Juju Miao, Haoyue Yu, Hualin Yu, Chao Liu, Luming Zhao, Ping Yang, Ting Zhou, Bing Zhang.
Presenter affiliation: Westlake University, Hangzhou, China. 33

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FLASH TALKS II-b: Cardiac and Immune Preview

THURSDAY, May 14—7:30 PM

POSTER SESSION II

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Chairpersons: **Ritchie Chen** University of California, San Francisco
Sung Han, Salk Institute for Biological Studies, La Jolla, California

FRIDAY, May 15—2:00 PM

SESSION VII

Chairpersons: **Mark Andermann,** Beth Israel Deaconess Medical Center, Boston, Massachusetts
Ruslan Medzhitov, HHMI, Yale University School of Medicine, New Haven, Connecticut

FRIDAY, May 15—6:00 PM

COCKTAILS and BANQUET

SESSION VIII: CLOSING SESSION

Chairpersons: **Holly Ingraham,** University of California, San Francisco
Zuri Sullivan, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge

SATURDAY, May 16—11:15 AM

PANEL DISCUSSION

Organizers and Invited Speakers

POSTER SESSION I

POSTER SESSION II

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A BRAINSTEM HUB FOR THE CONTROL OF GASTROINTESTINAL MOTILITY

Naz Dundar[1,2], Ilayda Alkislar[2], Ho Namkung[1], Brooke C Jarvie[1], Kathryn Xie[1], Mahek Kaur[1], Longhui Qiu[1], Zachary A Knight[1,2]

[1]University of California, San Francisco, Department of Physiology, San Francisco, CA, [2]University of California, San Francisco, Neuroscience Graduate Program, San Francisco, CA

Gastric emptying and intestinal transit must be precisely coordinated to ensure effective digestion. One example of this coordination is the suppression of gastric emptying to prevent excessive duodenal filling, while intestinal contents continue to move distally. Although the dorsal vagal complex is strongly implicated in gastrointestinal motility, the specific neuronal populations within this region that coordinate gastric and intestinal dynamics remain poorly understood. Here, we identify neuropeptide FF (Npff) neurons in the subpostrema as a critical brainstem node controlling gastrointestinal motility. Npff neural activity increases with duodenal filling and decreases with gastric distension, consistent with a role in preventing the overfilling of either the stomach or the proximal intestine. Optogenetic activation of Npff neurons inhibits gastric emptying while simultaneously accelerating small intestinal transit. Moreover, Npff neurons bidirectionally regulate feeding behavior, with activation suppressing food intake and inhibition increasing consumption. Anatomical and pharmacological manipulations further suggest that these effects are mediated through cholinergic vagal motor output. Together, these findings identify Npff neurons as a brainstem hub that coordinates gastric and intestinal motility and couples gastrointestinal state to the control of feeding behavior.

THE NEURAL CIRCUITRY AND CODING OF INTEROCEPTION

Catherine E Gallori[1,2], Tianxiao X Huang[1], Yandan Wang[2], Shiqi Wang[1], Alex Hiroto[1], Showmick Paul[1], Seeun Park[1], Verina Leung[3], Tianbo Qi[3], Bohan Lin[1], Lauryn Guan[1], Li Ye[3], Stephen D Liberles[2], Chen Ran[1,2]

[1]The Scripps Research Institute, Department of Neuroscience, La Jolla, CA, [2]Harvard Medical School and Howard Hughes Medical Institute, Department of Cell Biology, Boston, MA, [3]The Scripps Research Institute and Howard Hughes Medical Institute, Department of Neuroscience, La Jolla, CA

The nucleus of the solitary tract (NTS) in the brainstem serves as the brain's primary interoceptive hub. It integrates and processes convergent sensory inputs from visceral organs via the vagus nerve and spinal cord, transmitting signals to higher-order brain regions to regulate behavior, physiology, and metabolism. Despite its importance, the principles by which the NTS organizes peripheral information to mediate these complex responses remain poorly understood. Here we develop a novel in vivo two-photon brainstem imaging platform, which allows us to record the activities of thousands of NTS neurons simultaneously. We discover that the NTS creates a map of internal organs that takes the shape of a "visceral homunculus". This topography requires brainstem inhibition, as blockade of inhibition broadens neuronal tuning and disrupts spatial organization. Combining brainstem imaging with genetic strategies to label targeted populations of NTS neurons, we show that the NTS creates parallel viscerosensory pathways. These pathways are distributed across the topographic map of internal organs and are similarly tuned to respond to various viscerosensory stimuli but differentially control behavior and metabolism. Our work establishes the conceptual framework of the organizational logic of the brainstem interoceptive circuits.

RETROSPECTIVE REACTIVATION OF AMYGDALA FLAVOR REPRESENTATIONS UNDERLIES POSTINGESTIVE LEARNING

Christopher A Zimmerman*[1,2], Julie M Fabre*[2], Ilana B Witten[2,3]

[1]University of Utah, Department of Neurobiology, Salt Lake City, UT,
[2]Princeton University, Princeton Neuroscience Institute, Princeton, NJ,
[3]Howard Hughes Medical Institute, Princeton, NJ

We form lifelong aversions to the foods that make us sick. This single-trial learning is among the most robust and evolutionarily conserved forms of associative memory, yet it poses a fundamental computational challenge: the brain must determine what food caused the illness, despite the delay between eating and experiencing food poisoning symptoms (gastric malaise). We recently found that malaise drives the amygdala into a neural state resembling flavor consumption, which could help an animal bridge the delay between the recently consumed flavor and the subsequent illness experience (Zimmerman et al., 2025). However, it remains unclear if this illness-driven reactivation simply reflects a hardwired overlap in flavor and malaise encoding in the amygdala, or if it reflects a retrospective process underlying associative learning. To test this, we examined two conditions in which mice consume a flavor and experience illness but do not form an association. First, we reversed the temporal order of flavor and illness: when illness precedes rather than follows novel flavor consumption (backwards conditioning), animals do not learn a flavor aversion. We found that while malaise still recruited flavor-coding amygdala neurons during backwards conditioning, it did so non-selectively — neurons from other functional clusters were recruited equally, rather than flavor-coding neurons being selectively activated. This implies that the selective activation of flavor coding neurons by malaise is retrospective. Next, as a second behavioral manipulation to block associative learning, we pre-exposed mice to the flavor before conditioning (familiar conditioning). This also produced a less selective reactivation of the flavor representation by malaise, implicating flavor novelty — in addition to temporal order — as a critical gate on selective reactivation of amygdala flavor representations during illness. After conditioning, amygdala flavor responses weakened in backward-conditioned or familiar-conditioned mice — resembling habituation across repeated flavor exposures in mice that did not experience malaise — whereas flavor responses were relatively stable in forward-conditioned mice. Together, these findings support a model in which illness drives retrospective and novelty-dependent reactivation of amygdala flavor representations, which in turn serves to strengthen flavor representations in support of associative learning.

CONTROL OF INGESTION BY THE CAUDAL BRAINSTEM

Zachary A Knight

University of California, San Francisco, Physiology, San Francisco, CA

The question of why we stop eating is one of the fundamental problems in physiology. This process has traditionally been explained in terms of negative feedback from the stomach and intestines, which gradually intensifies as a meal progresses and is integrated in satiation circuits in the caudal brainstem. However, this idea has never been tested by recording the activity of these circuits while animals eat. I will describe our work investigating how the sensory feedback generated during a meal is encoded in the brainstem and used to control behavior.

A NEUROHUMORAL AXIS REGULATING MEAL SIZE AND TIMING

Alexander R Nectow

Columbia University, Department of Medicine, Division of Cardiology, New York, NY

Hunger and satiety signaling ensure the maintenance of proper energy stores and are therefore required for survival. While the brainstem is known to play a key role in orchestrating the behavioral and physiologic adaptations to changing energy stores, the molecular, cellular, and circuit mechanisms through which this is achieved is incompletely understood. In recent work, we have demonstrated that the brainstem's dorsal raphe nucleus (DRN) plays a key role in regulating appetite through acute changes in meal size and timing. Here, we describe recent studies building on this work, characterizing how the DRN's molecular and cellular heterogeneity gives rise to complex and surprising changes in feeding behavior. We find that functionally opponent populations of neurons in the DRN monitor ongoing ingestive behavior, by tracking similar orosensory and gut-borne ingestive signals, which these neurons then use to stochastically initiate or terminate a meal. We then leverage a specialized gut preparation to demonstrate the specific macronutrient classes that are capable of driving changes in activity across molecularly-distinct DRN cell types. Using in vivo imaging, we also demonstrate a gating mechanism through which the DRN simultaneously tracks internal state, information which is integrated with ongoing ingestive information and then leveraged to make important decisions about when to start and stop a meal. Together, these findings are helping us better understand how distinct central and peripheral signals are integrated by the brainstem to decide when (or when not) to eat.

SENSORY CIRCUMVENTRICULAR ORGANS DECODE INFECTION DURING SICKNESS

Jessica A Osterhout

University of Utah, Department of Neurobiology, Salt Lake City, UT

During infection, the brain generates a stereotyped set of sickness symptoms to aid in pathogen clearance and increase survival. How the brain can detect and process immune signals to coordinate this critical response is still poorly understood. Circumventricular organs (CVOs) are sensory regions of the brain with well-documented roles in metabolic control, hormonal regulation and physiological health. Each is strategically positioned near brain areas that govern key homeostatic set points and innate behaviors. We propose that specialized cell types within CVOs play an essential role in detecting circulating immune signals and relaying immune status to nearby neuronal populations responsible for modulating physiology and behavior during infection. To investigate this hypothesis, we have utilized single-cell approaches for molecular characterization to systematically map the cell types and gene expression profiles within CVOs in response to bacterial- and viral-like immune challenges. Our analysis has revealed that CVO regions exhibit unique cellular and transcriptomic profiles compared to control regions. CVO-enriched cell types include infiltrating immune cells, suggesting these regions represent a unique immunological niche within the brain. Moreover, we find specific upregulation of immune genes encoding immune mediators within these regions and the profile of immune gene expression is dependent upon the bacterial- or viral-like stimulant. Finally, we find activation of neuronal cell types within these regions. Using matching ligand-receptor-based analyses, we find stimulant-specific, immune-mediated interactions between non-neuronal cell types and local neurons. Together, these results suggest that specialized CVO cell-types sense systemic immune signals and can distinguish among different types of infection to affect local neuroimmune environments.

A DIRECT NEURONAL PATHWAY DRIVING ANTICIPATORY INSULIN RELEASE UPON FOOD SWALLOWING

Rory J Beresford[1], Martina Held[2], Haluk Lacin[3], Rituja S Bisen[4], Ibrahim Tastekin[1], Marcelo Dias[1], Igor Siwanowicz[5], Carlos Ribeiro[1], Jan M Ache[2]

[1]Champalimaud Research, Neuroscience, Lisbon, Portugal, [2]University of Würzburg, Neurobiology and Genetics, Würzburg, Germany, [3]University of Missouri Kansas City, Biology and Biomedical System, Kansas City, MO, Max Planck Institute for Metabolism Research, Metabolism, Cologne, Germany, [5]HHMI Janelia, Neuroscience, Ashburn, VA

Insulin secretion is classically recognised as an evolutionarily conserved homeostatic response to elevated circulating glucose, ensuring optimal uptake and storage of nutrients. However, both theoretical predictions and experimental evidence from mammalian studies suggest that secretion can also be engaged pre-emptively in response to sensory cues. Despite these indications, neuronal circuits that mediate such anticipatory release remain poorly understood.

In *Drosophila*, insulin is released by a population of Insulin-Producing Cells (IPCs) in the brain. Here, we characterize a neuronal pathway that drives insulin release upon feeding initiation. In-vivo calcium imaging revealed that swallowing rapidly excites IPCs, a response that is reminiscent of mammalian Cephalic Phase Insulin Release. Combining connectome analyses with functional connectivity experiments, we show that IPCs receive strong, monosynaptic excitatory input from a population of neurons (Pi neurons) which encircle the esophagus and express the mechanosensory channel, nanchung.

Optogenetic activation of these neurons increased feeding, while knockdown of nanchung in Pi neurons reduced feeding. Knocking down nanchung in Pi neurons also reduced the rapid response of the IPC population to sucrose feeding, and abolished their response to water feeding, suggesting a crucial role of Nanchung sensing in this response. This is highly indicative of Pi neurons, via Nanchung, sensing and relaying the mechanical forces generated by swallowing, and relaying this information to the IPCs to enact insulin signalling. Importantly, this pathway is critical for homeostasis, since optogenetic manipulation of Pi or IPC activity drastically reduces starvation resistance and survival. Our findings thus reframe swallowing as a metabolic commitment point: the signal that nutrients have been ingested and that insulin release should be engaged without delay.

HYPOTHALAMIC CONTROL OF METABOLISM

Jens C Bruening

Max Planck Institute for Metabolism Research, Neuronal Control of Metabolism, Cologne, Germany

The brain integrates hormonal, nutritional, and sensory cues to regulate feeding, energy expenditure, and glucose metabolism. Recent advances, including the identification of PNOC neurons as additional players in leptin- and diet-responsive pathways, highlight that the diversity and specialization of hypothalamic neuron populations are far greater than previously appreciated. These emerging circuits, together with the coordinated actions of classical AgRP and POMC neurons, illustrate how the hypothalamus orchestrates metabolic homeostasis through distributed and interconnected networks. In parallel, rapid brain-liver communication shows how sensory food perception can anticipate metabolic needs by adjusting hepatic mitochondrial and glucose responses. Collectively, these findings reshape our understanding of neuroendocrine control of metabolism.

DORMANT HYPOTHALAMIC CIRCUITS CONTRIBUTE TO BRAIN-BODY AGING

Michael S Segel, Xianyu Hao, Jennifer Yi, Denny Lu, Bryce Tiglon

Harvard University, Department of Stem Cell and Regenerative Biology, Cambridge, MA

Not all cells age equally—some are selectively vulnerable to aging and may set the health for the rest of the organism through secreted factors and paracrine signaling. My lab hypothesizes that homeostatic circuits of the central nervous system, including in the brainstem and hypothalamus, serve as the cellular bottlenecks on organismal healthspan. To test this, we have paired blood-serum proteomics, lightsheet microscopy, and single nuclei sequencing on the aging hypothalamus and brainstem and have uncovered critical neuronal circuits, particularly those involved in the hypothalamus involved in circadian rhythm and metabolism, that become functionally dormant under homeostatic conditions. Importantly, these neurons are not gone and short term time-restricted feeding can reactivate some, but not all, "youthful" molecular signatures of hypothalamic circuit activity, as determined by single nuclei sequencing. Directly reactivating these circuits in aged mice using chemogenetics or G-protein couple receptor agonists can powerfully modulate aging-associated inflammation and thereby improve resilience of aged mice to peripheral immune stressors such as lipopolysaccharide. Together, our work provides evidence to support the hypothesis that hypothalamic neuron dormancy is an important hallmark of aging and a contributing factor to aspects of innate immune-system aging with potential relevance to the timing, onset, and prevention of aging-associated disease.

FEELING THE PRESSURE: AGING-RELATED BLADDER MECHANOSENSORY DECLINE AND ITS RESCUE BY DIETARY FATTY ACIDS

Yasmeen M Hamed[1], Vikram Joshi[2], Kevin Wilhelm[3], Luis O Romero[4], Valeria Vásquez[4], Olivier Lichtarge[3], Arthur Beyder[2], Kara L Marshall[1]

[1]Howard Hughes Medical Institute, Dept. of Neuroscience, Baylor College of Medicine, Houston, TX, [2]Dept. of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, [3]Dept. of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, Dept. of Biochemistry and Molecular Biology, University of Texas Health Science Center at Houston, Houston, TX

Mechanical cues are a fundamental mediator of brain–body communication. PIEZO ion channels are specialized mechanosensors embedded in the plasma membrane that transduce mechanical forces into biological signals—a critical mechanism for various physiological processes. Many of these processes, including urinary function, deteriorate with age, substantially contributing to morbidity and mortality, yet the role of mechanosensation in aging-associated dysfunction remains poorly understood. Our human genotype–phenotype association analyses identified a *PIEZO1* gain-of-function variant as a risk factor for early-onset neuromuscular bladder dysfunction. Like humans, aged mice exhibit urinary dysfunction characterized by increased frequency, urgency, and incontinence. We first asked whether changes in overall bladder innervation are associated with urinary dysfunction but found no significant differences between young and aged mice. The mechanosensitivity of neurons and urinary reflexes are ultimately driven by tissue mechanics at nerve endings embedded within the bladder, thus, we focused on understanding how the bladder wall muscle itself changes with age. We found that smooth-muscle–specific *Piezo1* deletion protects against aging-related urinary dysfunction in mice via preserving bladder wall muscle functional integrity. To explore non-invasive strategies for modulating PIEZO activity, we investigated whether altering cellular biomechanical properties via dietary supplementation with membrane-stiffening fatty acids (FAs) can attenuate PIEZO activity and ameliorate urinary dysfunction in aged wild-type mice. Indeed, electrophysiological recordings from FA-enriched dorsal root ganglia (DRG) sensory neurons revealed reduced mechanocurrent densities and elevated displacement thresholds, consistent with PIEZO inhibition. Behavioral analyses further demonstrated decreased voiding frequency and improved continence after four-five weeks of FA-enriched diet compared with chow. Together, these findings identify PIEZO channels as key mediators of aging-related urinary dysfunction and demonstrate that dietary modulation of membrane biomechanics offers a powerful approach to probe mechanosensation and a promising therapeutic avenue for mechanosensory disorders.

PSYCHEDELICS MODULATE ENTERIC OXIDATIVE STRESS INDUCED BY BRAIN-GUT ASSOCIATIVE LEARNING.

Eugene L.Q. Lee, H. Robert Horvitz

HHMI, MIT, Dept. Biology, Cambridge, MA

Learning is classically described as a singular neurally modulated response by an organism. Nonetheless, organisms are capable of expressing a wide range of responses mediated by different tissues or neural circuits. How are learned responses coordinated across different organs within an individual to execute appropriately adaptive actions? Nervous systems which are the loci of learning, are themselves composed of sub-networks, as exemplified by the clear distinction between the central and enteric nervous systems. In the nematode *Caenorhabditis elegans*, the pharyngeal neurons that control feeding are organized analogously to the mammalian enteric nervous system with a bounded neural circuit distinct from the rest of the nervous system. We have trained worms to modulate their feeding behaviors through associative conditioning in which a neutral odor is paired with an aversive light stimulus. Specifically, we trained *C. elegans* to inhibit its feeding behavior in response to a once neutral odor, revealing a capacity for plasticity in the enteric nervous system. The same associative pairing task resulted in learned locomotory avoidance to the odor. An analysis of individual worm responses revealed that feeding and locomotor learning occurred independently of each other with differential magnitudes and kinetics. These observations reveal that a single associative relationship can produce separate learned behaviors across distinct brain-body neural sub-networks within an individual animal. We further found that this training paradigm induced a physiological response in addition to the learned behaviors of feeding inhibition and locomotory avoidance – associative learning triggered a robust oxidative stress response in the gut. While exploring the neurochemical bases of these various responses, we discovered that psychedelics affected both behavioral and physiological enteric responses. Psychedelics specifically inhibited learned feeding behavior, while sparing learned locomotory avoidance. Psychedelics also either enhanced or diminished learned enteric stress depending on the temporal order in which the psychedelics were applied with respect to the learning episode. Our observations of enteric system-associated learning reveals that a viscera-associated nervous system is capable of expressing experience-dependent behavior that extends beyond a purely reflexive nature and that classically cognitive processes (e.g. learning) can induce profound effects in non-neural tissues such as the gut.

MECHANISMS OF BODY-BRAIN COMMUNICATION

Stephen D Liberles

Harvard Medical School / HHMI, Boston, MA

Body-brain sensory neurons monitor the status of internal organs, drive behaviors to alleviate physiological need, and communicate with brain-body motor neurons to conduct a symphony of body biology. The vagus nerve is a key instrument of the body-brain axis that ensures organ homeostasis and controls vital functions of our respiratory, cardiovascular, digestive, and immune systems. It helps orchestrate the rhythms of our heart and lungs, blood pressure and digestion, reflexes like cough, gasps, and swallows, survival behaviors like feeding and drinking, and physiological states like satiety and nausea. The vagus nerve controls such fundamental physiology; yet, it has been poorly understood at a molecular and cellular level. This stands in stark contrast to our external senses where discoveries of sensory receptors for smell, touch, taste, vision, and hearing were landmark achievements. Over recent years, my lab initiated the use of molecular and genetic approaches in mice to deconstruct the vagus nerve. Our studies of vagal sensory neurons in the airways, cardiovascular system, and gut have revealed additional body-brain reflexes, sensory receptors and mechanisms underlying classical reflexes, and key features of how inputs from the interoceptive nervous system are organized in the brain. Defining the repertoire of body-brain communication pathways and underlying signaling mechanisms will uncover basic principles of neurophysiology and may provide new ways to treat autonomic disease.

THE 'LITTLE BRAIN' ON THE HEART --- INTRINSIC CARDIAC NERVOUS SYSTEM IS ESSENTIAL FOR CARDIAC FUNCTION AND SURVIVAL ACROSS CONDITIONS

Qian J Xu[1,2,3], Marissa Applegate[1,2], Ruiqi Wang[1,2,3], I-Uen Hsu[1,2], Omar A Hafez[1,2,3,4], Pam E Rios Coronado[2], Rachel P Kogan[6], Lawrence Young[2,5], Xing Zeng[7], Le Zhang[6], Rui Chang[1,2,3]

[1]Yale University, Department of Neuroscience, New Haven, CT, [2]Yale University, Department of Cellular and Molecular Physiology, New Haven, CT, [3]Yale University, Interdepartmental Neuroscience Program, New Haven, CT, Yale University, M.D.-Ph.D. Program, New Haven, CT, [5]Yale University, Department of Internal Medicine, New Haven, CT, [6]Yale University, Department of Neurology, New Haven, CT, [7]University of Texas Southwestern Medical Centre, Department of physiology, Dallas, TX

The intrinsic cardiac nervous system (ICNS) is a key node in the heart-brain communication and an emerging target for cardiac therapy, yet its physiological importance and functional organization remain poorly understood. Here, we show that the ICNS is essential for cardiac performance and survival across conditions. We identify two molecularly distinct intrinsic cardiac neuron (ICN) subtypes that differ in extrinsic inputs, projection architectures, and functional roles. Npy^+ ICNs preferentially receive vagal input and mediate parasympathetic control of heart rate and coronary perfusion, and their ablation leads to fatal cardiac failure. In contrast, $Ddah1^+$ ICNs receive sympathetic input and are required to preserve electrical stability and prevent sudden cardiac arrest under extreme stress, with their activation providing cardioprotection. Together, these findings establish the ICNS as a critical determinant of cardiac survival and reveal a division of labor among molecularly defined ICN subtypes, providing a framework for precise, cell type–targeted neuromodulatory therapies.

FEMALE GUT PAIN: ESTROGEN HIJACKS A GUT PARACRINE PATHWAY

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Visceral pain disorders like irritable bowel syndrome disproportionately affect women, yet the underlying mechanisms remain poorly understood. Enhanced signaling between enterochromaffin (EC) cells in the gut epithelium and nearby sensory nerve fibers likely drives this sex difference. We identified an estrogen-regulated paracrine pathway linking two enteroendocrine cell types — PYY-expressing L cells and serotonergic EC cells — that amplifies gut sensitivity in females. Estrogen signaling upregulates the short-chain fatty acid receptor Olfr78 on colonic L cells, boosting their responsiveness to the bacterial metabolite acetate and increasing PYY secretion. Elevated PYY then acts on neighboring EC cells via NPY1R receptors, enhancing serotonin release and promoting gut pain signaling. We propose that hormonal fluctuations, combined with internal factors such as stress or environmental factors such as diet, amplify this estrogen-sensitive colonic circuit, driving maladaptive visceral hypersensitivity in females.

*Eric E Figueroa and Archana Venkataraman are co-first authors of this work.

AN INTERORGAN NEUROIMMUNE CIRCUIT PROMOTES VISCERAL HYPERSENSITIVITY

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Visceral pain disorders such as interstitial cystitis/bladder pain syndrome (IC/BPS) and irritable bowel syndrome (IBS) often manifest concurrently in the bladder and colon. Yet, the mechanistic basis of such comorbidities and the transmission of neural hypersensitivity across organ systems have remained a mystery. Here, we identify a mast cell-sensory neuron circuit that initiates bladder inflammation and simultaneously propagates neural hypersensitivity to the colon in a murine model of IC/BPS. We unveil anatomic heterogeneity of mast cells in relation to nociceptors in the bladder and their critical dependence on Mas-related G protein-coupled receptor B2 (MrgprB2) to promote visceral hypersensitivity. Employing retrograde neuronal tracing, spatial transcriptomics, in vivo calcium imaging, and intersectional genetics, we characterize a population of polyorganic sensory neurons that simultaneously innervate multiple organs and exhibit functional convergence. Importantly, using humanized mice, we demonstrate that pharmacological blockade of mast cell-expressed MRGPRX2, the human ortholog of MrgprB2, attenuates both bladder pathology and colonic hypersensitivity. Our studies reveal evolutionarily conserved neuroimmune mechanisms by which immune cells can directly convey signals from one organ to another through un-silencing polyorganic sensory neurons, in the absence of physical proximity, representing a new therapeutic paradigm.

BRAIN-BODY INTERACTIONS: SENSATIONS AND PREDICTIONS IN THE INSULAR CORTEX

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The brain and body are in a continuous dialog that is essential for our physical and mental health. Yet we still do not have a neurobiological understanding of how this dialog is achieved. How do cortical activity patterns give rise to specific interoceptive sensations? How are internal and external information streams integrated to form specific interoceptive predictions? How are learned predictions transformed into top-down signals that prepare the body for anticipated physiological changes? I will present our recent work addressing these questions using non-invasive gut optogenetics for quantitative interoceptive psychophysics, combined with two-photon cortical imaging, optogenetics, and endocrine measurements. We use this combined approach to uncover a neural basis for perception of internal sensations in the insular cortex, as well as mechanisms of learning interoceptive predictions. I will further show that insular cortex predictions are essential for anticipatory physiological control, and for subsequent long-term maintenance of metabolic homeostasis.

DIRECT INTEROCEPTIVE INPUT TO THE INSULAR CORTEX SHAPES LEARNED FEEDING BEHAVIOR

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The insular cortex (insula) is an interoceptive hub, which senses internal states such as hunger, thirst, pain, and emotions. Interoceptive information arrives at the insula indirectly, either through the vagus nerve's connections or through peripheral hormonal signals to the hypothalamus. Previous studies, however, suggest that the insula directly senses internal states, but the mechanisms remain elusive. We identified a novel population of glutamatergic leptin receptor-positive (LepR+) cells with a unique morphology in the insula (INSLepR). Based on leptin's known role in signaling adiposity levels, we hypothesized that INSLepR neurons detect internal states and thus regulate food intake and body weight. Accordingly, we found that leptin administration in the insula increases intrinsic excitability of INSLepR cells, suppresses feeding, and reduces body weight. Moreover, optogenetic stimulation of INSLepR cells suppresses learned operant feeding and leads to avoidance in a real time place preference context. We also found that INSLepR neurons encode operant feeding bouts, and their activity is modulated specifically by hunger, but not thirst, states. Single-nuclei sequencing and ribosome profiling revealed that INSLepR is expressed on both Layer 6 neurons and on vascular cells, suggesting that leptin can be delivered directly through receptor-mediated transport through the blood brain barrier into the insula. INSLepR neurons form mainly local connections within the insula and an external projection to the basolateral amygdala (BLA), and optogenetic stimulation of BLA terminals also regulated learned operant feeding. Moreover, we found that administration of leptin alters insula neural dynamics in response to feeding, but not drinking, behavior, and reshapes the transcriptome, suggesting that internal state information provided by leptin is used by the insula to coordinate feeding behavior. Taken together, our data supports a model for direct interoceptive input to the insula, in which INSLepR cells integrate adiposity level signals to regulate feeding and body weight in a learned manner.

HYPOTHALAMIC NEURAL REPRESENTATION FOR FLEXIBLE INNATE BEHAVIORS UNDER INTERACTING INTERNAL STATES: HUNGER AND AGGRESSIVE INTERNAL AFFECTIVE STATES

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Animals must continually integrate signals from the body and brain to adaptively balance competing motivational drives. Physiological states such as hunger and emotional states such as anger interact strongly to shape decision-making and survival behaviors. Although hunger often enhances irritability—producing the colloquial “hangry” state—the underlying neural mechanisms governing this interaction remain unclear. Here we show that different levels of food deprivation oppositely influence aggression in male mice, revealing a bidirectional coupling between metabolic and affective states. Moderate starvation (18 h) potentiated attack behavior, whereas prolonged starvation (40 h) suppressed it. Using a previously described line attractor dynamic in the hypothalamic nucleus VMHvl as a neural correlate of aggressive intent, we found that hunger modulated both the stability and persistence of this attractor. These biphasic effects were recapitulated by graded chemogenetic activation of hypothalamic AgRP neurons, implicating body-derived hunger signals in reshaping the neural landscape of aggression. Importantly, in moderately starved mice, aggression-related VMHvl activity remained stable even during short feeding bouts, suggesting an adaptive mechanism that maintains defensive and territorial readiness while energy stores are being replenished. Together, these findings reveal how interactions between metabolic and affective circuits enable the brain to prioritize behavioral drives across changing physiological contexts, providing a mechanistic framework for understanding body–brain integration in motivational flexibility.

A SIGNALING HUB IN THE MOSQUITO RECTUM COORDINATES HOST-SEEKING AND BLOOD NUTRIENT UTILIZATION

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Female Aedes aegypti mosquitoes require a blood meal to develop eggs and are highly motivated to feed on humans, transmitting pathogens in the process. However, host seeking is transiently suppressed after a female feeds to repletion and remains low until egg laying several days later. Building on our previous finding that conserved Neuropeptide Y-related signaling suppresses human attraction after blood feeding, we investigated how Neuropeptide Y-like Receptor 7 (NPYLR7) regulates this behavioral switch. NPYLR7 is most closely related to mammalian receptors that signal satiety and suppress feeding.

Although npylr7 mutant females consume normal-sized blood meals, they fail to properly provision their eggs with protein and exhibit persistent host seeking and blood feeding after a nutritive meal, consistent with a loss of satiety signaling. Using a transgenic driver line, we identified npylr7-expressing cells and found that, unlike related receptors in other species, Aedes aegypti npylr7 expression is highly restricted to the rectal pads, a poorly characterized hindgut tissue. In cell-based assays, NPYLR7 responds to multiple peptide ligands, including RYamide. RYamide-expressing neurons project from the ventral nerve cord to the rectal pads, and npylr7-expressing cells show RYamide-induced calcium responses that are abolished in mutants. These cells also respond to amino acids, suggesting potential integration of nutrient and neuropeptide signals.

Despite being non-neuronal, rectal pad cells display neuron-like features, including calcium excitability and expression of secretory and neurotransmitter synthesis machinery. Electron microscopy reveals structural changes consistent with vesicle release following blood feeding. Together, these findings identify a previously unknown gut-based signaling system in which neuron-like rectal pad cells use NPYLR7 to regulate host-seeking behavior, revealing a novel peripheral-to-brain pathway controlling mosquito biting and reproductive investment.

LINEAGE AND ORGAN CUES SEQUENTIALLY BUILD ORGAN INTRINSIC NERVOUS SYSTEMS

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Organ intrinsic nervous systems (OINSs) are critical components of the body–brain axis, coordinating visceral organ function with systemic physiological control. Despite their importance, how these distinct neural architectures arise from a common neural crest cell (NCC) origin has remained unclear. Here, we present a systems-level, cross-organ analysis of OINS development, integrating lineage tracing, 3D imaging, single-cell transcriptomics, and genetic perturbations across heart, pancreas, intestine, and lungs. We show that differences in NCC migratory trajectories prefigure the spatial architecture of OINSs, laying the foundation for organ-specific patterning. In contrast, molecular identity emerges largely in response to local environments, indicating that extrinsic cues play a major instructive role. Using in vitro co-cultures, we demonstrate that organ-derived cues reprogram intrinsic neurons toward organ-specific transcriptional profiles and direct neuronal differentiation, with extracellular matrix (ECM) contact identified as a central mediator. In vivo, ECM–integrin signaling supports intrinsic cardiac neuron neurogenesis, while ECM crosslinking stabilizes their stereotyped ganglionic organization. Together, these findings reveal that OINS diversity arises through a dual logic: lineage programs prefigure spatial frameworks, while organ-specific cues instruct final molecular identities and architectural precision. This work establishes a conceptual paradigm for how organs actively build their own nervous systems, illuminating principles that underpin body–brain integration (Hsu et al., Nature, forthcoming).

PREOPTIC NEURONS THAT CONTROL ENTRY INTO HIBERNATION

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Evolution of seasonal hibernation has enabled mammals to survive harsh conditions by entering a state of prolonged hypometabolism and hypothermia with body temperatures as low as 0-4°C. Despite decades of physiological studies, the genetic tools to study hibernation have remained limited and the mechanisms that induce hibernation entry are still unknown. Focusing on the brain, we map state-dependent neuronal activity across the hibernation cycle in Syrian hamsters and identify the hypothalamic anterior preoptic area (aPOA) as a key regulator of hibernation entry. Single-nucleus RNA and chromatin profiling provided a map of neuronal populations present in the hamster POA and enabled the discovery and design of an enhancer AAV that selectively targets hibernation-associated aPOA subpopulations. Using this genetic approach, we show that Samd3-positive aPOA glutamatergic neurons are necessary for entry into hibernation and that their activation is sufficient to induce a prolonged hypothermic state with associated nesting behavior. Together, we identify the first neuronal population that controls entry into hibernation, opening new avenues for investigating and manipulating the metabolic and physiological mechanisms underlying this extreme state of “suspended animation” and its potential applications in aging and disease.

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SYNTHETIC TORPOR TO DISCOVER NOVEL METABOLIC VULNERABILITIES IN BREAST CANCER

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Cancer growth induces large metabolic strain on the body, with tumors being immensely energetically demanding. We therefore wondered if, given its role in integrating the nervous and endocrine system, hypothalamic modulation could induce a whole-body metabolic shift, and how that may impact tumor growth and resiliency. Mammalian torpor is a controlled hypometabolic state characterized by marked reductions in metabolic rate, core body temperature, and locomotor activity, enabling energy conservation during periods of environmental stress such as winter. Previous work has identified a group of QRFP neurons ("Q neurons") within the preoptic area of the hypothalamus which can induce a torpor-like state when activated. Given the hypermetabolic demand of cancer cells we sought to investigate if torpor/hibernation benefits cancer-related outcomes. We found that DREADD-mediated stimulation of Q neurons stifled the growth of orthotopic EO771 breast tumors and B16/F10 melanoma tumors, as well as reduced the metastatic burden of lewis-lung carcinoma (LLC) cells, suggesting a globally suppressed metabolic state improves cancer-related outcomes. To understand systemic changes that occur due to both the hypometabolic and tumor-state within the body, we performed untargeted metabolomics, lipidomics, and proteomics analysis on the tumor, visceral organs, and plasma. We show that the hypometabolic state induced by activation of Q-neurons to induce a single bout of torpor (4-6 days) was sufficient to significantly reduce or completely eliminate breast tumors, with over 50% of mice showing a complete elimination of tumors, while those that remained showed a reduction tumor weight from 0.20g to .02g. We analyzed >250 tissue samples across all conditions and timepoints and obtained metabolomics, lipidomics, and proteomics samples from each tissue. This allowed identification of ~2,000 analytes per tissue type and over 4,000 tumor proteins by DIA-PASEF analysis. Comprehensive analysis of the data highlights several pathways that are aberrantly regulated in cancer cells, leaving them vulnerable to the hypometabolic shift induced by torpor. Torpor forces an obligatory whole-body shift to fatty acids as a fuel source, which is not sufficient to sustain cancer cells' heightened growth.
Our data show that this shift results in aberrant activity of the carnitine, beta-oxidation, and lipid peroxidation pathways, and points towards mechanisms driving torpor-induced cancer cell death.

THE MATERNAL BODY-BRAIN CONNECTION: INVESTIGATING THE ROLE OF MAMMARY GLAND-INNERVATING SENSORY NEURONS IN LACTATION

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The ability of a parent to provide nutrition for their young is critical for the survival of the species. In mammals, the process of lactation has evolved to meet this demand: mothers provide their neonates with milk, which is produced and secreted by the mammary gland. Lactation involves multisensory interactions between mother and offspring, with touch being a critical sensation. While the mammary gland is highly innervated, the molecular identity and function of its afferent sensory neurons and how they integrate with circuits of the central nervous system remains poorly understood. My project aims to determine how molecularly-defined subsets of mammary gland-innervating sensory neurons detect tactile stimuli, respond to and impact their tissue microenvironments, and contribute to the process and experience of lactation.

Thus far, I have generated a neuroanatomical map of murine mammary gland innervation by dorsal root ganglia (DRG) sensory neurons using fluorescent retrograde neuronal tracers. Additionally, I have performed preliminary histological characterizations of mammary gland-innervating neuronal projections, including purported nociceptors and mechanoreceptors. To better understand the makeup of the microenvironments these sensory neuron projections reside in, and how this changes during pregnancy and lactation, I have performed single-nuclei sequencing on the mammary gland across physiological conditions. This has uncovered potential ligand-receptor interactions between neurons and other cell types that may influence neuronal activation as well as lactation. In addition, I am generating a cell atlas of mammary gland-innervating neurons, which will elucidate the genetic heterogeneity among these cells. Leveraging these datasets, I am currently working to employ mouse genetics to target, characterize, and manipulate genetically defined neuronal subsets in this organ. These manipulations are being coupled with behavioral assays measuring various aspects of maternal behavior. Overall, this work hopes to help elucidate the contributions of these sensory neurons to mammary gland biology and maternal physiology.

WIRELESS, CELL-TYPE-SPECIFIC MAGNETOMECHANICAL CONTROL OF VAGAL GUT–BRAIN CIRCUITS

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Brain–body signaling through vagal sensory pathways plays a central role in regulating motivated behaviors and energy balance, yet the anatomical dispersion and cellular heterogeneity of these circuits pose challenges for causal investigation using rigid, localized implants. We present a wireless, implant-free strategy for cell-type-specific modulation of vagal sensory neurons using magnetite nanodiscs (MNDs) tethered to genetically defined populations in the nodose ganglia. Systemic viral delivery of membrane-anchoring moieties enables stable membrane association of MNDs, and slowly varying magnetic fields induce mechanical movement of the nanodiscs, generating membrane torque that depolarizes vagal sensory neurons via endogenous mechanosensitive ion channels. Selective stimulation of neurons expressing the glucagon-like peptide-1 receptor (Glp1r) or oxytocin receptor (Oxtr) in the left nodose ganglion suppresses food intake in mice and activates downstream brainstem circuits in the nucleus tractus solitarius, consistent with recruitment of satiety pathways. These findings establish magnetomechanical neuromodulation as a precise and scalable platform for interrogating and modulating gut–brain communication without implanted hardware.

EXTREME GLUCOCORTICOID LEVELS IN DEER MICE EMERGE FROM AN EVOLUTIONARY ARMS RACE

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Glucocorticoids are among the most widely prescribed type of drugs in the world because of their immunosuppressive effects, but chronic, high glucocorticoids lead to adverse metabolic and psychiatric effects. It is thus surprising that extreme glucocorticoid levels have independently evolved in mammals at least six times, suggesting that elevated glucocorticoids are tolerated or even beneficial under certain conditions. In the genus *Peromyscus*, oldfield mice have a 10-fold higher level of circulating corticosterone – their primary glucocorticoid – than their sister species, the deer mouse. To understand the genetic basis and phenotypic consequences of elevated corticosterone levels in oldfield mice, we generated 769 F_2 deer x oldfield hybrids and quantified corticosterone levels as well as immune, metabolic, and behavioral phenotypes. Quantitative genetic mapping revealed two loci that contribute to corticosterone levels, the glucocorticoid receptor (GR) and the corticosteroid binding globulin (CBG), both of which contain novel amino acid variants. Through biochemical modeling and in vitro assays, we found that both genes have reduced binding affinity to corticosterone, rendering the oldfield mouse resistant to glucocorticoids. To study these loci in detail, we generated congenic mice with the oldfield GR and CBG alleles on a common deer mouse genetic background. The oldfield alleles of these genes enhance social approach in a resident-intruder task but reduce circulating immune cells. These data indicate that the alleles promoting social behavior may come at the cost of immune function. Moreover, the effects of GR and CBG depended on one another, suggesting an evolutionary arms race in the HPA axis. Together these findings suggest that oldfield mice maintain chronically elevated glucocorticoids not by accident, but as an adaptive gamble – trading immune robustness for heightened sociality. More broadly, they reveal how extreme glucocorticoid phenotypes can repeatedly evolve and how far organisms will push the HPA axis to balance competing physiological demands. Because glucocorticoid signaling is ancient and conserved, this work shows how easily the HPA axis can be rewired, and how profoundly physiology can change when a new hormonal setpoint takes hold.

BEYOND THE BRAIN: HOW THE GUT SHAPES OUR MIND

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The gut-brain axis has emerged as a critical mediator of cognitive function, yet the peripheral mechanisms driving brain aging and cognitive decline remain poorly understood. Here, we present evidence that disrupted gut-brain signaling represents a shared pathological pathway underlying hippocampal dysfunction and memory impairment across two distinct conditions: aging and post-infection syndromes. In aged mice, the accumulation of gut bacteria producing medium-chain fatty acids, exemplified by Parabacteroides goldsteinii, promotes peripheral inflammation and attenuates interoceptive input to the hippocampus. In post-acute sequelae of COVID-19 (PASC), viral infection and interferon-driven inflammation deplete peripheral serotonin, similarly impairing vagal nerve activity and hippocampal function.
Using complementary approaches, targeted restoration of gut-brain communication rescues memory in both models. Together, these findings establish interoceptive dysfunction as a convergent mechanism of cognitive decline and suggest that interventions targeting the gut-brain axis may offer broadly applicable therapeutic strategies.

GUT BACTERIA-DERIVED SUCCINATE INDUCES ENTERIC NERVOUS SYSTEM REGENERATION

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Enteric neurons control gut physiology by regulating peristalsis, nutrient absorption, and secretion. Disruptions in microbial communities caused by antibiotics or enteric infections result in the loss of enteric neurons and long-term motility disorders. However, the signals and underlying mechanisms of this microbiota–neuron communication are unknown. We studied the effects of microbiota on the recovery of the enteric nervous system after microbial dysbiosis caused by antibiotics. We found that both enteric neurons and glia are lost after antibiotic exposure, but recover when the pre-treatment microbiota is restored. Using murine gnotobiotic models and fecal metabolomics, we identified neurogenic bacterial species and their derived metabolite succinate as sufficient to rescue enteric neurons and glia. Unbiased single-nuclei RNA-seq analysis uncovered a novel neural precursor-like population marked by the expression of the neuronal gene Nav2. Genetic fate-mapping showed that Plp1+ enteric glia differentiate into neurons following antibiotic exposure. In contrast, Nav2+ neurons expand upon succinate treatment and indicate an alternative mode of neuronal regeneration under recovery conditions. Our findings highlight specific microbial species, metabolites, and the underlying cellular mechanisms involved in neuronal regeneration, with potential therapeutic implications for peripheral neuropathies.

MATERNAL MICROBIOME-TARGETED INTERVENTION PREVENTS OFFSPRING SOCIAL DYSFUNCTION IN A MOUSE MODEL FOR NEURODEVELOPMENTAL DISORDERS

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The reduction in neural tube defects (NTDs) following formal guidance for dietary folate intake during the periconceptional period reveals the prophylactic potential of targeting maternal nutrition to improve neurodevelopmental outcomes in children. Like NTDs, neurodevelopmental disorders originate *in utero*. Emerging evidence links the maternal gut microbiome, also determined by diet, to risk for neurodevelopmental disorders. Data collected from large, independent mother-child cohorts show maternal Western Dietary Pattern during pregnancy increases the likelihood of neurodevelopmental disorder diagnoses, including for autism spectrum disorder (ASD), and symptom severity in children. In contrast, healthy prenatal dietary adherence significantly decreases risk. Consistent findings in preclinical animal models demonstrate that obesogenic maternal diets can disrupt offspring brain development and behavior in ways that resemble neurodevelopmental disorders and phenotypes characteristic of genetic models for them, encompassing alterations in DNA methylation, gene expression, neural circuit function, and behavior.

Despite broad availability of prenatal nutrition recommendations, longitudinal studies reveal persistent low diet quality throughout pregnancy and postpartum across diverse sociodemographic groups and geography. It is thus imperative to leverage recent insights into how maternal obesogenic diets drive molecular-to-circuit level dysfunction underlying maladaptive behavior to develop effective interventions even when optimal dietary adherence is not achieved. Ideally, an approach as straightforward as prenatal vitamins.

Here, we investigated whether precision targeting of the maternal gut microbiome during pregnancy can improve neurobehavioral outcomes in a preclinical environmental mouse model for ASD, maternal overnutrition. We developed a novel seven-strain maternal probiotic cocktail (MPC) comprised of microbes that dominate the healthy breastfed-infant gut and found antenatal administration reduces social dysfunction among maternal high-fat diet offspring *via* modulation of a microbially-associated biosynthetic pathway. Notably, we reproduced the MPC-mediated rescue pharmacologically in our model. Our data identify precision targeting of the maternal gut microbiome as a promising approach to reducing risk for adverse outcomes in pregnancies affected by environmental exposures, including maternal diet-induced obesity.

MATERNAL DIET REWIRES REWARD CIRCUITS THROUGH GUT-SEROTONIN-MICROGLIA SIGNALING

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Serotonin (5-HT) is a critical signaling molecule regulating proper circuit development, and serotonergic dysfunction is commonly observed across neurodevelopmental disorders. High maternal weight is epidemiologically linked with increased risk for neurodevelopmental disorders, suggesting that maternal diet shapes offspring serotonin circuit wiring. Here, we identify a projection-specific developmental mechanism linking maternal diet to long-term reward circuit remodeling.

Maternal exposure to a high saturated-fat diet (mHFD) from gestation through weaning selectively disrupts postnatal wiring of dorsal raphe-->nucleus accumbens (DNR-->NAc) serotonin projections, while sparing DRN-->orbitofrontal cortex projections. This structural rewiring is accompanied by reduced microglial phagocytosis of serotonin fibers, persistent increases in serotonergic synapse density, elevated serotonin release, and reduced intrinsic firing of DRN-->NAc neurons in adulthood.

We further identify region-specific microglial serotonin receptor heterogeneity, with NAc microglia enriched for functional 5-HT2C signaling and show that mHFD selectively increases NAc microglia 5-HT2C receptor expression during postnatal development. Behaviorally, these circuit changes are associated with enhanced reward-motivated learning and chemogenetic activation of DRN-->NAc serotonin neurons phenocopies this behavioral effect.

Finally, we link these neural changes to a concurrent developmental shift in the offspring gut microbiome, including downregulation of serotonin-producing microbes, suggesting that gut-derived serotonergic cues normally guide microglia-dependent circuit refinement. Together these findings reveal a previously unrecognized gut-immune-serotonin mechanism that confers projection-specific vulnerability of reward circuits to maternal diet.

HEARTBEAT SIGNALS IN THE BRAIN: INSULAR ENCODING OF CARDIAC INTEROCEPTION AND EMOTION

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Growing evidence suggests that cardiac information influences neuronal activity and fundamental brain functions across species. Yet, how the brain represents cardiovascular signals and how this may impact the processing of emotion states remains unclear. I will discuss recent data from my lab demonstrating that intracellular dynamics and single unit activity in the posterior insular cortex of the mouse are precisely regulated by cardiac signals, with individual neurons tuned to heartbeats in a frequency-dependent manner. Furthermore, heartbeat tuning in the insular cortex occurred preferentially during the first phase of the cardiac cycle, at systole. Heartbeat tuning increased during both appetitive and aversive emotion states, a process not simply explained by increases in heart rate. Manipulation of sympathetic cardiac arousal using beta-adrenergic blockade disrupted neuronal encoding of emotion states in the insula and blunted behavioral and bodily emotion expression. These findings reveal precise sensory coding of cardiovascular signals in the pInsCtx, which supports its role in encoding emotion states.

INTRACOLONIC OPTOGENETIC STIMULATION OF VAGAL INNERVATIONS INCREASES EXPLORATORY BEHAVIORS IN FREELY MOVING MICE

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Functional gastrointestinal (GI) disorders are often comorbid with anxiety symptoms. The vagus nerve (VN), a peripheral nerve connecting the brain and the GI tract, modulates motivated behaviors like reward. Yet, how colon-vagus-brain interactions contribute to the modulation of anxiety remains unclear. To address this, we (a) investigated the role of colonic vagal innervations in anxiety-like behaviors using wireless intracolonic optogenetics, (b) mapped the central circuits of colonic vagal afferents using transneuronal viral tracing and (c) examined the effects of colonic sensory signalling on the brain using fiber photometry coupled with gut optogenetics. We developed flexible multifunctional devices for optogenetic manipulation and temperature monitoring in the mouse proximal colon. Optogenetic stimulation of colonic VN increased exploratory behaviors in adult mice in common rodent anxiety assays, without affecting stress-induced hyperthermia. These results indicate that colonic VN modulates anxiety-like behaviors independently of physiological stress responses. We also found that colonic vagal stimulation was not valenced, suggesting input-specific modulation of motivated behaviors by the VN. To identify brain regions mediating this anxiolytic effect, we performed anterograde transneuronal circuit mapping by injecting a Cre-dependent herpes simplex virus (HSV,H129ΔTK-TT) into the proximal colon of adult Phox2b-Cre mice. 5 days post-injection, HSV expression was present in the nodose ganglia but not in dorsal root ganglia. With time, HSV labelling extended to the caudal medulla, the pons, hypothalamus and other regions. We validated these results using fiber photometry and showed that activating colonic VN modulated lateral hypothalamus activity. In summary, we present novel technology enabling region-specific optogenetic manipulation of the colon. Our findings suggest that colon-VN activity facilitates exploratory behavior and identify the central targets of colonic vagal afferents. Future work investigating how this colon-to-hypothalamus circuit is altered in disease contexts may offer insights into GI and affective comorbidities.

NOCICEPTORS REGULATE HAIR PLUCKING-INDUCED INFLAMMATION AND REGENERATION

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Mammalian hair and fur provide mechanical and thermal protection for the skin tissue, and their hair follicles (HFs) serve as compelling biological models due to their unique combination of complexity, functional autonomy, and regenerative potential. Importantly, HFs are also sensory organs, innervated by both mechanosensitive neurons responding to hair movement and specialized pain-generating nociceptors responding to hair pulling and plucking. Skin damage and noxious stimuli activate cutaneous nociceptive innervations, sending pain signals to the brain and stimulating the local release of neuropeptides and neurotransmitters. Notably, HF-innervating nociceptors exhibit unusually large receptive fields, interacting with multiple HFs simultaneously, suggesting a capacity to provide synchronized feedback across follicles. Inspired by this anatomy, our work aims to define how nociceptors coordinate the skin's cellular regenerative response to hair plucking.

Hair plucking is a painful experience that creates mild, repairable damage to the plucked HFs. Remarkably, plucking also promotes regeneration of neighboring unplucked follicles via CCL2-dependent recruitment of TNF-producing macrophages. Our data demonstrate that broad nociceptor ablation (achieved by crossing TRPV1Cre with DTA-floxed mice) profoundly disrupts this regenerative response. Specifically, nociceptor-ablated mice exhibit exaggerated edema, skin thinning, and keratinocyte loss, accompanied by increased frequency of Annexin V positive keratinocytes suggestive of apoptotic cell death. Hair plucking in nociceptor-ablated mice also alters the local inflammatory response, manifested by reduced recruitment of circulating monocytes and dermal macrophages alongside increased neutrophil frequency. These observations support the hypothesis that the activation of nociceptors, and potentially HF-innervating nociceptors, regulates monocyte/macrophage recruitment and shapes the epithelial cell compartment response to hair plucking. Indeed, local chemogenetic activation of cutaneous nociceptors in naïve skin triggers neurogenic inflammation, monocyte accumulation, and increased TNFα expression. These findings highlight the critical role of pain-mediating nociceptor innervation in activating downstream, tissue-specific cellular pathways essential for regeneration. Moreover, they suggest a link between pain sensation and the regenerative capacity of the skin and hair follicles.

SYMPATHETIC-EPITHELIAL CROSSTALK GOVERNS TISSUE-RESIDENT MEMORY T CELL IMMUNOSURVEILLANCE IN THE SKIN

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A central question in immunology is how local tissue immunity is calibrated. Although the cellular and molecular components of tissue immunity are well characterized, they are insufficient to explain the context-dependent variability of local immune protection. This suggests the existence of higher-order regulatory mechanisms. Emerging evidence indicates that neural activity can modulate immune function, and clinical studies link psychological stress to outcomes in cancer, infection, and chronic inflammation. We therefore asked whether the nervous system contributes to the control of local immunity.

To address this question, we focused on the skin, the largest barrier tissue, in which $CD8^+$ tissue-resident memory T cells (T_{RM}) act as key immune sentinels, providing rapid protection against infection and early malignancy. Here, we identify that sympathetic nerves (SN) engage with epidermal keratinocytes to regulate the local density of T_{RM}, thereby influencing regional cancer immunosurveillance. SN do not communicate directly with T_{RM}; instead, they form synapse-like structures near the basal keratinocytes and dynamically modulate epithelial-derived signals essential for T_{RM} formation via norepinephrine–ADRB2 signaling. Reduced sympathetic tone elevates epithelial-derived chemokine CXCL16 to promote T_{RM} development in the skin epithelium, while heightened sympathetic activity during acute stress dampens this process. Through this indirect mechanism, SN calibrate the size of the T_{RM} cell pool in the skin and consequently tune local immunosurveillance against nascent cancer cells.

Our findings highlight a synergistic interaction between the nervous and immune systems mediated by skin epithelium, revealing a neuro-epithelial-immune axis that adjusts tissue immunosurveillance strength according to systemic neural inputs. Elucidating this mechanism is crucial for understanding regionalized immunosurveillance and the earlier steps of tumor development. These insights could also inform new strategies to boost T_{RM} protection against infections, or to enhance immune containment of emerging cancers.

ESTROGEN-SENSITIVE NEURONS MODULATE THERMOREGULATORY RHYTHMS DURING PREGNANCY

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Pregnancy induces dynamic and conserved changes in body temperature, yet the neural mechanisms that integrate reproductive state with thermoregulation remain poorly understood. We tested the hypothesis that estrogen-sensitive neurons function as state-dependent modulators that tune thermoregulatory outputs across pregnancy. Using continuous temperature monitoring in mice, we quantified core temperature, its circadian amplitude, and its ultradian variability across gestation. We combined this physiological phenotyping with cell-type-specific tools to identify and manipulate estrogen receptor alpha (ERα)-expressing neuronal populations in the preoptic area that are implicated in thermoregulation. We find that pregnancy is characterized not simply by changes in average body temperature, but also by a dramatic dampening of its rhythms. During pregnancy, ERα-expressing POA neurons show enhanced estrogen signaling and hormone-responsive gene expression changes. Silencing ERα neurons or selectively deleting ERα in the POA attenuates pregnancy-induced decreases in Tc and its rhythmicity, leading to alterations in gestational length and/or birth weight. Together, these findings demonstrate that ERα signaling within the POA reshapes thermoregulatory rhythms during pregnancy, coordinating metabolic, circadian, and reproductive signals to stabilize maternal physiology. More broadly, our results support a model in which steroid hormone signaling tunes homeostatic circuits in a context-dependent manner to meet the energetic and developmental demands of pregnancy.

NEURAL CIRCUIT REMODELING UNDERLYING ENHANCED FEEDING DURING PREGNANCY IN MICE

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Pregnancy represents a unique physiological state marked by substantial adaptations influencing both behavior and metabolism. Alterations have been observed across multiple levels—from changes in cellular morphology, synaptic density, and neuroglial interactions to a brain-wide reduction in gray matter volume. While these adaptations are thought to support offspring survival and promote maternal physiological and psychological well-being, their functional significance remains largely unresolved. In particular, linking localized synaptic plasticity to a broader brain-wide circuit dynamics has posed a major challenge. Using virus-mediated screening in mice, we investigated the pregnancy-induced remodeling of the presynaptic landscape of paraventricular hypothalamic (PVH) oxytocin neurons, a central hub of maternal physiology. Here we show a selective and reversible elimination of excitatory synaptic inputs from the medial preoptic nucleus to PVH oxytocin neurons, displaying region-, cell-type-, and pathway-specificity. This reduction in excitatory drive attenuated the anorexigenic activity of oxytocin neurons during feeding, thereby promoting the increased food intake characteristic of pregnancy. These data demonstrate that the selective suppression of anorexigenic PVH oxytocin neuron activity plays a critical role in appetite regulation during pregnancy. More broadly, our data identify a pregnancy-associated remodeling of hypothalamic neural circuits with direct physiological relevance.

CHARACTERIZATION OF NIPPLE-INNERVATING SENSORY NEURONS IN LACTATING MICE

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Dorsal root ganglion (DRG) sensory neurons detect mechanical, thermal, and chemical stimuli and relay critical information from the body to the central nervous system, regulating physiological responses. Nursing provides a striking example of body–brain communication critical for survival of mammalian species. Suckling activates nipple-innervating DRG sensory neurons, triggering pulsatile oxytocin release from hypothalamic neurons to drive milk ejection and stimulating prolactin release from the pituitary to sustain milk production.

Despite the essential role of somatosensory input in initiating this neuroendocrine reflex, the sensory neuron subtypes required for this response and the spinal cord circuits they engage remain unknown. To address this gap, we are using genetic strategies to identify, monitor, and manipulate defined DRG neuron subtypes in vivo, aiming to: (1) define the molecular composition and heterogeneity of nipple-innervating sensory neurons; (2) characterize response properties to controlled and naturalistic suckling-related stimuli; and (3) identify subtypes required to drive neuroendocrine responses during lactation. Our ongoing genetic survey reveals that nipple-innervating neurons are heterogeneous, comprising multiple molecularly distinct somatosensory neuron subtypes. These include several C- and A high-threshold mechanoreceptors (HTMRs), as well as C- and A low-threshold mechanoreceptors (LTMRs) subtypes. Interestingly, these subtypes exhibit distinct spatial axon organizational patterns within the nipple, suggesting functional specialization.

To assess the functional contribution of C-fiber and subsets of Aδ-fiber innervation, we used Nav1.8-Cre; $ROSA^{LSL\text{-}DTA}$ mutant mice, in which these neurons are ablated. Pups nursed by mutant females grew normally up to postnatal day 2 (P2), however from P3 onward they exhibited reduced weight gain. The delayed onset of pup growth suggests that $Nav1.8^{+}$ sensory neurons play a role in scaling milk production as lactational demand increases. Alternatively, this phenotype could reflect broader systemic consequences of $Nav1.8^{+}$ neuron ablation, and ongoing studies are aimed at distinguishing between these possibilities. Together, this work reveals a high degree of nipple sensory neuron subtype heterogeneity and begins to define the contributions of select sensory populations to lactation physiology. These findings lay the groundwork for future studies of the central connectivity of nipple-innervating neurons and the circuits mediating sensory-evoked neuroendocrine responses.

A PUTATIVE NOVEL NEUROPEPTIDE INVOLVED IN REPRODUCTIVE FUNCTIONS

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Neuropeptides are potent signaling molecules that play critical roles in regulating physiology and behavior. While over 100 neuropeptides are known, more likely await discovery. Their small size and rapid evolutionary divergence hinder bioinformatic detection, and peptides expressed in highly specific cell types are difficult to identify using bulk RNA sequencing or mass spectrometry. Here, we implement a computational screen leveraging a protein language model to identify 18 putatively novel secreted peptides. From this set, we characterize one candidate neuropeptide, C2orf66, that is deeply conserved across vertebrates and highly expressed in a small population of cells in the preoptic area of the hypothalamus. C2orf66+ cells display sexual dimorphism and exhibit high expression of sex hormone receptors, suggesting a role in reproductive phenotypes. Functional analyses in knockout animals demonstrate that loss of C2orf66 disrupts pubertal onset and fertility. Together, these findings expand the known repertoire of neuropeptides and suggest that additional functionally important peptides remain to be discovered in the genome.

NEURAL ENCODING OF HOST DEFENSE PROGRAMS

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In nature, animals encounter diverse pathogens from across different domains of life that engage distinct peripheral host defense programs. Despite this diversity, the overwhelming majority of studies on sickness behavior rely on a single experimental mouse model in which lipopolysaccharide (LPS) induces an acute inflammatory state that mimics bacterial infection. This has skewed our understanding of sickness, thereby limiting our ability to discover host defense strategies that might be unique to different pathogens.

We hypothesized that, analogous to peripheral immune responses, different pathogens may elicit distinct sickness states encoded in the brain. Using models of bacterial, viral, and parasite infection, allergic immunity, and chronic inflammation, we assessed sickness across scales: organismal – animal behavior and physiology; cellular – brain-wide neural activity patterns; and molecular – single-cell spatially resolved transcriptomics in the hypothalamus, which regulates social and homeostatic behaviors altered during infection. Remarkably, these diverse immune challenges elicited unique patterns of whole-brain neural activity, hypothalamic gene expression, and repertoires of behavior. Distinct behavioral and physiologic changes across diverse immune challenges were accompanied by changes in the activity of molecularly-defined cell types known to regulate these organismal programs. These studies establish the existence of pathogen-specific sickness states generated by brain-immune system interactions, which parallels the pathogen-specific responses observed at the cellular and tissue scales of immunity. We predict that numerous other parallels exist between immunity across scales, and that understanding sickness through this lens will shape our understanding of sickness as a host defense strategy.

VISCERAL SIGNALING OF POST-INGESTIVE MALAISE DIRECTS MEMORY UPDATING IN DROSOPHILA

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Consolidation is a time when labile memories transition to a stable form. Malaise learning in
Drosophila reveals consolidation to also permit memory updating. Flies taught to associate one of two odors with toxin-tainted sugar initially express conditioned odor approach, that following consolidation switches to avoidance. Behavioral reversal emerges from dopaminergic update of parallel memories for the two trained odors. Differential serotoninergic modulation of specific aversive and rewarding dopaminergic neuron subtypes permits post-ingestive intoxication to suppress consolidation of initial odor-sugar memory and simultaneously invert reward memory plasticity into "safety" memory for the odor experienced without food. Fat body release of the Toll-ligand activating protease modSP, and resilience factor Turandot A, instruct malaise updates by triggering autocrine Toll signaling in the same brain dopaminergic neurons that form and consolidate initial sugar memory. This neural mechanism overcomes the credit assignment problem of delayed postingestive reinforcement by updating earlier memories of the trained odors.

FROM PERCEPTION TO REGULATION: ATTENTION CAUSALLY REGULATES ACUTE INFLAMMATION IN HUMANS

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Attention is a central mechanism for prioritizing and shaping sensory information. Shifting attention away from injury reduces perceived pain, but does this cognitive modulation also alter downstream biological processes? In animal models, nociception is critical for effective immune regulation, suggesting that sensing tissue disturbance serves functional biological roles beyond perception. Here, we test whether immune regulation in humans depends not only on nociceptive input, but on its cognitive modulation through attention.

Across three preregistered within-subject experiments using acute skin inflammation as a model system (total N=57), we induced localized inflammation via histamine skin prick and compared responses when participants focused attention toward sensations at the inflammation site versus when they were distracted. Distraction was induced both through videoclips (Study 1) and using an internal distraction task (Study 2), matching sensory input across conditions.

Directing attention inward consistently produced a more regulated, faster-resolving inflammatory response compared to distraction, despite the identical immune challenge within the same individual. The effect was strikingly robust: ~90% of participants across independent cohorts showed more regulated inflammatory responses under internal attention, with approximately 1.5-fold reduced magnitude relative to distraction.

Mechanistically, autonomic recordings across both studies revealed increased parasympathetic vagal activity without changes in sympathetic arousal, consistent with vagal-mediated anti-inflammatory regulation. In Study 3, we demonstrate that pharmacological attenuation of sensory signaling reduced, but did not eliminate, the attentional effect, implicating both sensory-dependent amplification of afferent input and sensory-independent top-down control.

These findings identify a neuroimmune mechanism in humans, demonstrating that voluntary attention directly regulates acute inflammation in real time. Extending animal work on nociception, we show that immune control depends not only on objective sensory input, but also on its cognitive modulation. Within predictive and allostatic models of brain-body regulation, these results reframe perception as biologically consequential rather than merely experiential, suggesting that sensing discomfort serves a regulatory function.

GHRELIN ACTS IN STRIOSOMES TO PRODUCE STATE-DEPENDENT CONFLICT DECISION-MAKING

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Most daily decisions require weighing potential costs against potential rewards, so-called “conflict” decision-making. Decisions depend on the external qualities of rewards and costs, but can also be influenced by internal states, including endocrine signals. However, the neural circuit mechanisms regulated by internal states are poorly understood. Ghrelin is a hormone that arises from the gut and is elevated by low energy states such as hunger or stress; ghrelin can cross the blood-brain barrier and influence behavior by acting on ghrelin receptors throughout the brain. Here, we sought to determine whether ghrelin, which can regulate the processing of aversive and rewarding stimuli separately, influences decision-making when aversive and rewarding stimuli are both present. We manipulated ghrelin receptor activity in healthy rats performing a series of non-conflict (offering a single aversive or rewarding stimulus) or conflict (offering a combination of reward with an aversive cost) decision-making tasks and found that stimulating ghrelin receptors enhanced cost sensitivity only during conflict decisions. We then examined expression of the immediate-early gene cFos across 50 brain regions after ghrelin receptor stimulation and found the striosomes and lateral habenula had, by far, the greatest increase in neuronal activity; we confirmed ghrelin-induced striosomal hyperactivity and neuronal synchrony using calcium imaging. We also examined regions within the striosomal circuit for neural inactivity following ghrelin receptor stimulation by measuring phosphorylated pyruvate dehydrogenase expression and found that ghrelin receptor agonism increased inactivity levels of dopaminergic neurons in the substantia nigra pars compacta. Quantitative analysis of ghrelin receptor expression levels within the striatum, as well as ghrelin binding, revealed surprisingly selective expression in striosomes of the dorsomedial striatum, with very low expression in the surrounding matrix. We thus used a striosome-specific OPRM1-cre transgenic rat line to chemogenetically manipulate striosomes and found that striosomal hyperactivity is necessary and sufficient for ghrelin-mediated modulation of choice behavior. Consequently, we propose a computational model wherein ghrelin acts on the DMS striosomes to narrow the processing of context-relevant information and, when elevated, enhances sensitivity to cost-related signals.

NEURAL CIRCUIT MECHANISMS OF NON-AUTONOMIC BREATHING REGULATION

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Breathing is often viewed as an automatic homeostatic process generated by brainstem rhythm generators, yet it is continuously shaped by emotional state, cognitive context, and voluntary behavior. In this talk, I will present our recent work identifying neural circuit mechanisms underlying this non-autonomic regulation of breathing. Using cell type- and projection-specific approaches in mice, we have uncovered distributed forebrain–brainstem pathways that couple respiration with affective pain, anxiety, panic-like responses, and top-down behavioral control. These findings reveal how emotional and cortical inputs can bidirectionally modulate breathing dynamics, from rapid defensive respiratory changes to slower, affect-associated breathing patterns, and suggest emerging mechanisms by which voluntary processes such as breath holding transiently override automatic respiratory rhythms. Together, these results highlight breathing as an actively regulated brain–body interface shaped by integrated neural circuits linking physiology, emotion, and behavior.

CONTROL OF FEAR STATES AND UNDERLYING NEURAL DYNAMICS BY RESPIRATORY INTEROCEPTION

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In both humans and animals, fear states are accompanied by marked physiological changes in breathing patterns. The central sensation of these bodily signals – respiratory interoception – has been proposed as a core component of emotion regulation. For example, fluctuations in respiration are correlated to emotional responses and adaptive behaviors, and individuals with anxiety disorders often report altered perception of breathing-related sensations. The neural substrates of interoception substantially overlap with the circuits regulating fear, including the prefrontal cortex and amygdala. However, it remains unclear how respiratory interoceptive signals shape activity in these fear-regulation circuits and whether they play a causal role in mediating fear behaviors.

To investigate the mechanisms of how respiratory interoception modulates fear-related behaviors and neural activity, we combine high-resolution behavioral assays, precise respiratory monitoring, circuit-specific manipulations, and large-scale neural recordings in mice. We found that respiratory rhythms are shaped by the animal's current fear state, allowing us to predict an animal's location in safe or aversive environments solely from its breathing rate. Moreover, chemogenetic interruption of respiratory interoceptive signals through targeted inhibition of specific preBötzinger complex neurons attenuates fear-related behaviors, providing causal evidence for a functional brain-body loop. Furthermore, both bulk and single-neuron recordings reveal that prefrontal and amygdala dynamics are tightly coupled to the respiratory cycle, with enhanced tuning during fear-associated cues.

Together, these data provide support for a mechanistic brain-body-brain loop in the regulation of anxiety and lay the groundwork for future investigations into how interoceptive signals such as breathing may be harnessed to influence emotional brain states.

CARDIAC INTEROCEPTIVE MODULATION OF AFFECTIVE BEHAVIOR

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Emotions such as fear and anxiety are associated with top-down changes in bodily physiology, including rapid fluctuations in heart rate. However, whether changing heartbeats alone can modulate affective behaviors remains unclear. The James–Lange theory of emotion proposes that bodily changes—for example, an elevated heart rate—can play a causal role in generating emotional states. A critical obstacle to testing this hypothesis is the lack of tools that can precisely control organ physiology without invasive or destructive procedures, while remaining compatible with behavioral studies.

We have developed optogenetic and chemogenetic approaches that enable nondestructive, highly precise control of cardiac activity. By leveraging the ultrapotent opsin ChRmine, we built an optogenetic pacemaker that controls individual heart contractions, allowing us to investigate how cardiac interoception influences brain states and behavior in mice. We found that optically induced tachycardia accentuated anxiety-like behavior in stressful environments, and that the posterior insula plays a functional role in mediating these cardiogenic changes in behavior. In more recent work, we found that chemogenetic induction of bradycardia was insufficient to induce anxiolysis, contrary to reports that descending brain-to-body reductions in heart rate can reduce anxiety-like behavior. Interestingly, bradycardia prolonged defensive behavior during fear learning, suggesting an important role for cardiac interoceptive feedback in modulating central threat-response pathways.

Collectively, these findings highlight the complex interplay between the body and the brain in shaping emotional states, and establish noninvasive approaches to dissect organism-wide brain–body interactions underlying behavior.

NEUROPEPTIDE SIGNALING IN THE VAGUS NERVE MODULATES FEAR RESPONSES AND REGULATES INSULAR CORTEX ACTIVITY

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Introduction: Stress-related conditions such as post-traumatic stress disorder (PTSD) are associated with impaired vagal parasympathetic regulation, contributing to exaggerated stress responses and maladaptive fear behaviors. The vagus nerve contains diverse neuropeptides with specialized functions. We found that pituitary adenylate cyclase-activating polypeptide (PACAP) is expressed in the nodose ganglion and regulates parasympathetic function and posterior insular cortex (pIC) activity under stress, highlighting the importance of cell- and gene-specific manipulation of the vagus nerve to modulate stress responses. We further show that PACAP-expressing nodose neurons project to visceral interoceptive neurons in the nucleus of the solitary tract (NTS), which relay to the pIC via the parabrachial nucleus to regulate it's neuronal activity.

Methods: We microinfused AAV8-hSyn-DIO-rM3D(Gs)-mCherry (N = 15) or AAV8-hSyn-mCherry control (N = 10) into the left nodose ganglion of Adcyap1(PACAP)-2A-Cre knock-in mice. Three weeks later, mice underwent stress-enhanced fear learning (SEFL). In one cohort, we quantified freezing across SEFL phases, including fear expression, extinction, recall, and extinction recall. In a second cohort, we assessed pIC neural activity using fiber photometry by microinfusing 500 nL AAV9-CaMKII-GCaMP6s into the left pIC, then measuring calcium dynamics during nodose-PACAP chemogenetic stimulation and SEFL. In a third cohort, we paired nodose-PACAP stimulation with pIC inhibition and assessed effects on SEFL behavior.

Results: Nodose-PACAP stimulation significantly reduced cFos labeling in the pIC following SEFL. Behaviorally, nodose-PACAP stimulation decreased fear recall and extinction recall compared with controls. Fiber photometry revealed that nodose-PACAP stimulation reduced pIC calcium activity during extinction recall. Finally, pairing pIC inhibition with nodose-PACAP stimulation also reduced fear recall and extinction.

Conclusions: These findings identify a nodose PACAPergic pathway that coordinates interoceptive processing under stress and modulates pIC activity to regulate fear behavior. More broadly, we highlight the nodose ganglion as a tractable target for cell- and gene-specific manipulation to influence interoceptive circuits and stress-related behavioral outcomes.

MOLECULARLY-DEFINED PATHWAYS OF AIRWAY REFLEXES

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Breathing requires continuous sensory surveillance of the airway surface to detect threats and trigger vital reflexes to preserve gas exchange. Disruption of airway barrier defense is common in respiratory disease and can be life-threatening, increasing vulnerability to infection, edema, and obstruction. We previously defined the molecular and functional properties of an airway sentinel cell type, the neuroepithelial bodies, that use mechanosensation to sense airway closure in cooperation with sensory neurons to evoke protective reflexes. However, the underlying molecular sensors of barrier integrity and epithelial-to-neuron mechanisms that engage adaptive defense programs remain poorly understood. Here, we investigate a neuro-sentinel cell signaling pathway critical for eliciting airway mucosal defense. In vivo vagal ganglion imaging revealed dedicated sensory neuron types tuned to distinct airway threats, and single-cell transcriptomics further delineated the cellular diversity of airway sentinel cell types. Live tissue imaging and new genetic strategies enabled selective targeting and recording of sentinel cell response properties. We characterized sentinel cells responses to disruptions of the air-tissue interface and identified a sensory receptor mechanism critical for airway function. Complementary neuronal manipulations and physiological assays demonstrated specific behaviors mediated by neuro-epithelial communication. Together, these findings define a neuro-sentinel cell reflex that ensures airway integrity and expands organizational principles of visceral sensory pathways.

DEFINING A LUNG-BRAIN NEUROENDOCRINE AXIS THAT CONTROLS ASTHMA-ASSOCIATED STRESS RESPONSE

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The lung is densely innervated by sensory neurons that continuously relay interoceptive information to the brain, yet how central circuits integrate respiratory signals to coordinate physiological and behavioral responses remains poorly understood. We recently identified the first complete interoceptive circuit linking the lung to the brainstem and back to the lung that mediates exaggerated airway constriction, a defining feature of asthma. These findings establish a functional neuro-respiratory axis regulating airway tone and provide the foundation for our current work.

Asthma is strongly associated with psychological stress, suggesting higher-order brain centers may integrate allergen-evoked respiratory signals with stress circuitry. Building on our prior work demonstrating that allergen exposure selectively activates *Dbh*$^+$ neurons in the nucleus of solitary tract (nTS) of the brainstem via vagal sensory inputs, we now show that allergen challenge robustly activates molecularly defined neurons in the paraventricular nucleus of the hypothalamus (PVN), a central neuroendocrine hub. Selective ablation of allergen-activated PVN neurons significantly attenuates both stress-related behaviors and airway hyperreactivity. Notably, we found that distinct type of PVN neurons differentially control these outputs: *Crh*$^+$ and *Avp*$^+$ PVN neurons regulate stress-related behaviors, whereas *Oxt*$^+$ PVN neurons specifically mediate allergen-induced airway hyperreactivity. These findings reveal that allergen exposure engages molecularly and functionally distinct PVN subpopulations to coordinate behavioral and respiratory outputs. Together, our work defines a previously unrecognized lung-brain neuroendocrine axis that becomes maladaptive following allergen exposure in the lung, providing a circuit-level framework for how organ-derived interoceptive signals are integrated in the brain to drive coordinated behavioral and physiological dysfunction.

THE FUNCTIONAL DIVERSITY OF MAMMALIAN SOMATOSENSORY NEURON REPERTOIRES

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Somatosensory neurons of the dorsal root ganglia (DRG) serve as the body's interface with the environment. Mammals inhabit a range of body forms and surfaces that reflect their diverse lifestyles and environmental niches, ranging from the dense fur of the chinchilla, adapted to the rocky, alpine peaks of the Andean mountains, to the furless skin of the fossorial naked mole rat, adapted to hot, arid tunnels underneath East Africa's deserts. Yet how the somatosensory neuron repertoires of mammals adapt to their diverse lifestyles and niches remains poorly understood.

Here we describe the functional diversity of mammalian DRG neuron repertoires from over a dozen mammals sampled from across rodents, primates, and Laurasiatherians by collecting and analyzing DRG neuron multi-omic data. We also generate and apply new enhancer-based viral approaches and tools to genetically access and functionally characterize conserved DRG neuron types (orthotypes) across Mammalia. Lastly, we provide our cross-species single-cell multi-omic datasets as a resource to the somatosensory neuron community.

While most orthotypes are conserved across mammals, orthotype proportions vary across species, notably, in tandem with body surfaces: for example, the proportion of hair follicle-innervating C-LTMR neurons tracks hair follicle density across rodents and primates. Mice, small rodents with dense fur, have proportionally the most C-LTMRs, while humans and naked mole rats, which have very little or no fur, have few or no C-LTMRs, respectively. Species with intermediate hair follicle densities have intermediate C-LTMR proportions. Further, optogenetic activation of C-LTMRs in mice and rats, enabled by new enhancer AAVs (eAAVs) that drive viral payload expression in both species, elicits wet dog shake behavior, while species without C-LTMRs fail to perform wet dog shake in response to naturalistic stimuli.

In addition to changes in orthotype proportions, sensory and immune receptor gene expression patterns are not conserved across species. Rather, they vary extensively within orthotypes across species, even between closely related species such as mice and rats, and especially within several polymodal C-fiber neuron types. This results in species-specific orthotype physiology that we characterize in vivo using new eAAVs that enable specific genetic access to Mrgprd+ neurons in mice and rats. Finally, polymodal C-fiber orthotypes also frequently diversify into physiologically distinct species-specific subtypes.

Together, our findings describe how a conserved set of DRG neuron types functionally diversify across Mammalia and help to subserve the somatosensory functions of mammals adapted to a wide range of different lifestyles and environmental niches. We also present a new approach and suite of viral tools for genetic access to and characterization of conserved somatosensory neuron types across mammals.

FROM ISOLATION TO INTEGRATION: MAPPING THE BRAIN-BODY INTERACTOME THROUGH SYMPATHETIC TAXONOMY AND CIRCUITRY

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Core biological functions depend on tight integration between the brain and peripheral organs. Traditionally, the sympathetic nervous system is known to broadcast states of stress for the “fight or flight” response, but it is increasingly recognized as a hub of brain-body communication that can precisely and independently regulate physiological responses such as heart rate, digestion and immune response. We report initial results towards an effort to construct a “brain–body interactome” focusing on the sympathetic nervous system. We used single-nucleus RNA-sequencing, single-nucleus epigenomics, retrograde labeling, and integration with published single-cell atlases to generate a preliminary transcriptomic taxonomy spanning most sympathetic ganglia. This analysis reveals distinct transcriptional cell types that fall into broad functional classes, including cardiovascular and digestive (“fight or flight”) neurons, secretomotor neurons, and non-adrenergic neurons such as cholinergic sudomotor cells. We investigated the pre- and postsynaptic pathways to the sympathetic neurons. We used monosynaptic retrograde labeling by rabies virus to identify the descending pathways from the brain through the spinal cord preganglionic to the sympathetic Celiac-Mesenteric Ganglia (CMG) neurons. Surprisingly, we identified not only brainstem and hypothalamic neurons but also corticospinal neurons in this circuitry. We traced neurons from the spleen and pancreas to the CMG and found that individual neurons typically innervate one organ or the other, and a small percentage of these innervate both. We are utilizing the transcriptomic taxonomy of CMG neurons to identify molecularly-defined populations innervating the spleen and pancreas. Together, these results establish a cellular taxonomy of the sympathetic nervous system and provide a foundation for developing a viral genetic toolkit and the connectivity map of the sympathetic nervous system. With these resources, we aim to enable precise manipulation of different brain–body pathways to advance basic research and new treatments for autonomic disorders.

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A NEUROPEPTIDE THAT REGULATES CELL NON-AUTONOMOUS PROTEIN HOMEOSTASIS.

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The coordination of protein homeostasis between the nervous system and peripheral tissues is essential for the health and survival of all animals. In *C. elegans*, glia coordinate organismal protein homeostasis and longevity via the unfolded protein response of the endoplasmic reticulum (ER-UPR). However, the identity of the intercellular signaling molecules required remained unknown. Here, we show that glial ER-UPR activation increased levels of specific neuropeptides. We performed loss and gain-of-function genetic screens and identified a single neuropeptide, FLP-17, as sufficient to induce cell non-autonomous activation of the ER-UPR and confer chronic ER stress resistance. FLP-17 deletion did not suppress glial-mediated activation of the ER-UPR, suggesting functional redundancy among neuropeptides. We determined that the G-protein coupled receptor EGL-6 partially mediates cell non-autonomous activation of the ER-UPR and ER stress resistance by FLP-17. Furthermore, both XBP-1 and PERK are required for maximal FLP-17-induced ER-UPR activation, though only XBP-1 was necessary for organismal ER stress resistance. In *C. elegans*, FLP-17 is secreted from a pair of sensory neurons in response to unfavorable feeding conditions to initiate an aversion behavior and to regulate intestinal lipid stores. Thus, FLP-17 is a critical neuropeptide that coopts an existing sensory-metabolic circuit to coordinate organismal ER stress resilience. This work reveals how the nervous system leverages pre-existing behavioral circuits to orchestrate organism-wide protein homeostasis in response to environmental challenges.

LINKING FUNCTIONAL AND TRANSCRIPTOMIC INFORMATION TO IDENTIFY SATIETY-PROMOTING NEURONS IN THE PARABRACHIAL NUCLEUS

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The parabrachial nucleus (PBN) in the brainstem integrates interoceptive signals such as thirst, hunger, pain, and temperature to bring about appropriate behavioral and physiological responses. However, little is known about how distinct channels of interoceptive information are integrated by PBN neurons. One possibility is that there is a mapping between the transcriptional identity of PBN neurons and the modality of interoceptive information that they encode. Testing this hypothesis has been challenging because most studies focus on a single PBN cell type at a time, thereby preventing a comprehensive understanding of how interoceptive stimuli are encoded across all PBN neuron subtypes. To address this issue, we have developed a 3D imaging pipeline to track the activity of thousands of neurons in PBN brain slices followed by EASI-FISH for multiplexed 3D mRNA labeling of dozens of genetic markers in each imaged neuron. We have combined this approach with optogenetic stimulation of axonal inputs to PBN that are known to carry specific types of interoceptive information (e.g. hunger, satiety), enabling identification of PBN subtypes that encode specific interoceptive modalities. Notably, optogenetic stimulation of satiety-promoting neurons could drive complex responses across the PBN, such as excitation of one PBN subregion followed by inhibition of another, suggesting differential gating of various interoceptive channels. In parallel with these efforts to define the functional properties of interoceptive modality-specific PBN neurons, we are now using all-optical approaches to determine their influence locally on other PBN subtypes, and on behavior. Collectively, these studies will uncover how different channels of interoception are integrated by the many subtypes of PBN neurons.

SOCIAL PHYSIOLOGY: HUMAN HOMEOSTASIS IS MORE EFFICIENT IN SOCIAL PROXIMITY

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Physiological homeostasis is classically defined as the regulation of bodily demands, traditionally treated as an individual process shaped by evolution to optimize the energetic efficiency of regulation. However, this individual-centric framework has obscured the possibility that, in social animals, sociality may itself be conserved in part because it promotes homeostatic efficiency. While the evolutionary role of sociality through cooperation or threat buffering is well recognized, it has not been tested whether social proximity enhances core homeostasis regulation in a manner that improves energetic efficiency, and in systems not traditionally viewed as socially sensitive. Glucose metabolism is one such system. In a set of preregistered experiments, we found that glucose homeostasis following a carbohydrate challenge is more efficient in a Social than an Alone condition, exhibiting lower perturbation amplitude and faster recovery (n=108). The social benefit in homeostasis replicated in thermoregulation during a cold challenge (n = 116) and in sympathetic regulation during stress in adults (n = 115) and infants (n = 56). Across systems, social proximity lowered the perturbations and accelerated the recovery, independent of stress reduction or touch. These findings demonstrate ***Social Physiology***: a cross-domain principle whereby physiological homeostasis is enhanced by social proximity. Beyond behavioral and ecological advantages, Social Physiology identifies a psycho-biological benefit of sociality that may contribute to the evolution and maintenance of social bonds. It further delineates a pathway through which social bonds exert their health benefits and shape long-term metabolic function and disease.

SENSORS FOR INTERNAL STATE AND EXPECTATION SIGNALS IN DROSOPHILA

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The maintenance of internal homeostasis relies on intricate coordination between peripheral sensory systems and central neuroendocrine circuits. While central regulatory mechanisms governing hormonal release are well established, the peripheral sensory pathways responsible for monitoring internal physiological states remain largely uncharacterized. Here, we describe a novel population of peripheral sensory neurons that innervate the anterior aorta in Drosophila. Their receptive fields are strategically positioned immediately downstream of neuropeptide release sites into the circulation, implicating these neurons in the direct sensing of systemic endocrine signals. These neurons likely detect metabolic cues including circulating sugars, gut-derived peptides, and adipose tissue–derived factors, situating them as critical mediators of systemic metabolic state to neural feedback integration.
Crucially, the principal downstream targets of these sensory neurons are the Insulin-producing cells and the dopaminergic neurons in the central brain, thereby establishing a defined peripheral-to-central neuroendocrine and "teaching" signal feedback loop. We observed this sensory neuron population to be conserved in both larval and adult stages, with downstream synaptic connectivity comprehensively mapped. Together with our previous work on the enteric serotonergic system, our analysis supports the view that dopamine and serotonin operate at successive stages of feeding behavior, the former signaling anticipation and the latter signaling successful completion, of swallowing food.

TOWARD THE VAGAL CONNECTOME: UNRAVELING THE INTEGRATED CIRCUIT MECHANISMS THAT CONTROL THE BODY

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The vagus nerve (cranial nerve X) is a bidirectional neural pathway that enables the brain to sense and control a wide range of bodily functions, including cardiovascular, digestive, and immune processes. Through these interactions, the vagus nerve plays a critical role in maintaining an animal's homeostasis while dynamically shifting behavioral states to fit the ever-changing needs of the body. Yet, in contrast to other neural systems such as the retina, where detailed circuit maps have illuminated the computational motifs that define their function, little is known about how the anatomical principles that dictate how the sensory, motor, and intermediary interneurons are organized.

Here we present progress toward a comprehensive vagal connectome in the larval zebrafish. Expanding from an initial volume of just the larval zebrafish brain that has been aligned to functional imaging data, we have appended an additional electron microscopy dataset that includes many of the vital organs that are innervated by the vagus nerve, including the gills, pharynx, pancreas, intestine, swim bladder, and heart. The targets of sensory neurons can be divided into two classes: 1) those that make local connections and are upstream of vagal motor neurons, and 2) ascending neurons that innervate distributed regions of the brain and may potentially influence higher-cognitive processing. Within the local circuitry, there exists a high degree of recurrent connectivity that spans hemispheres to promote symmetrical activity. Furthermore, subpopulations of these interneurons possess dendritic morphologies that recreate those of motor neurons, enable them to mirror their inputs and support synchronization of motor pools.

A prominent exception to these structural patterns is observed in the neurons that innervate the heart. These neurons are largely innervated by descending inputs, consistent with a hierarchical, top-down mode of regulation. These inputs are dominated by premotor neurons with activity that reflects tail action, suggesting a mechanism enabling cardiac output to be matched with locomotive actions. By integrating structure and function within the same animal, this work begins to uncover the organizational principles of the vagal systems and lays a foundation for building functional models that govern the body and how it interfaces with broader brain and behavioral states.

TUMOUR-BRAIN CROSSTALK RESTRAINS CANCER IMMUNITY VIA A SENSORY-SYMPATHETIC AXIS

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Body-brain communication has emerged as a key regulator of tissue homeostasis. Solid tumours are innervated by different branches of the peripheral nervous system, and increased tumour innervation is associated with poor cancer outcomes. However, it remains unclear how the brain and responds to tumours in peripheral organs, and how tumour-brain communication influences cancer immunity. Here, we identify a tumour-brain axis that promotes oncogenesis by establishing an immune-suppressive tumour microenvironment (TME). Combining genetically engineered mouse models with neural tracing, tissue imaging, and single-cell transcriptomics, we demonstrate that lung adenocarcinoma induces innervation and functional engagement of vagal sensory neurons, a major interoceptive system connecting visceral organs to the brain. Mechanistically, Npy2r+ vagal sensory nerves transmit signals from lung tumours to brainstem nuclei, driving elevated sympathetic efferent activity in the TME. This, in turn, suppresses anti-tumour immunity via β2-adrenergic signaling in alveolar macrophages. Disruption of this sensory to-sympathetic pathway through genetic, pharmacological or chemogenetic approaches significantly inhibited lung tumour growth by enhancing immune responses against cancer. Collectively, these results reveal a bidirectional tumour-brain communication involving vagal sensory input and sympathetic output that cooperatively regulate anti-cancer immunity; targeting this tumour-brain circuit may provide new treatments for visceral organ cancers.
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HORMONAL TUNING OF GUT–NERVE COMMUNICATION IN VISCERAL PAIN

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The gut epithelium acts as a sensory interface, continuously integrating dietary, microbial, and mechanical inputs into neural signals that encode interoceptive information. Specialized enteroendocrine cells (EECs) sparsely distributed along the intestinal surface detect luminal cues and secrete hormones that exert potent physiological effects. Enterochromaffin (EC) cells, a subtype of EECs, detect noxious stimuli such as distension, dietary irritants, and microbial signals and secrete serotonin (5-HT) in response. In prior work, we established that EC cells drive nociceptive signaling by transducing sensory information to 5-HT_3 receptor–expressing mucosal afferents, highlighting how pain sensing begins at the epithelium. Intriguingly, we also found that the EC-afferent circuit is differently tuned in males and females.

Here, using orthogonal experimental approaches across ex vivo, in vivo, and organoid systems, we identify an estrogen-dependent paracrine circuit that amplifies visceral sensitivity in females. We found that estrogen receptor-α (ERα) expression was confined to L cells, another EEC subtype, rather than EC cells, positioning L cells as the primary estrogen-responsive node within the intestinal epithelium. Estrogen enhances L cell responsiveness to the abundant colonic short-chain fatty acid (SCFA), acetate, by upregulating the SCFA receptor *Olfr78* and promoting peptide YY (PYY) release. PYY then acts on neighboring EC cells through NPY1R to potentiate 5-HT release and activate mucosal nociceptors, leading to intense visceral pain in females.

Together, we define a hormone-sensitive epithelial–neural pathway that amplifies visceral pain signaling and identify PYY as a previously unrecognized nociceptive signal within the gut–brain axis. We propose that fluctuations in estrogen dynamically calibrate sensory gain, providing a mechanistic framework linking sex hormones, microbial metabolites, and stress to sex-biased vulnerability in visceral pain disorders.

A SOFT, FLEXIBLE DEVICE FOR WIRELESS PHOTOMETRIC RECORDING OF GASTROINTESTINAL TRACT PHYSIOLOGY IN FREELY BEHAVING MICE.

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In the brain, optical techniques like fiber photometry enable the mechanistic study of neuronal circuits that underpin behavior. These techniques can be used to monitor the activity of genetically defined cell populations or track the release of specific neurotransmitters.

However, we lack similar techniques for recording the activity of peripheral neurons, like those in the gastrointestinal (GI) tract, limiting the mechanistic investigation of their role in GI physiology. These intestinal neurons make up the enteric nervous system (ENS), which coordinates intestinal motility, senses local mechanical and chemical signals, and communicates to the brain to influence behavior.

To record ENS activity during behavior and over long experimental timespans, implanted devices must withstand the constant motion of the GI tract without breaking, form close contact with the GI tract wall without impeding digestion, and be soft and flexible to avoid damage or rupture of the GI tract wall. Therefore, stiff silica probes common to brain photometry are not suitable for implantation in the GI tract.

In this work, we present a system that enables wireless photometric recording from the murine GI tract during behavior. This system includes a flexible, implantable device that consists of a micropatterned polyamide-copper substrate integrated with LEDs and photodetectors and enclosed within a soft silicone. An optical filter is coated over the photodetectors to block excitation light. Device function is wirelessly controlled using a custom detachable module that communicates with software that is used to set recording parameters and display data.

Furthermore, we demonstrate that these devices can be chronically implanted to wirelessly record fluorescent signals from within the murine colon. We show that these devices function for at least 3 weeks in vivo, with limited impact on animal locomotion, weight, and feeding behavior. Compared to alternative techniques for recording ENS activity, our system enables recording in freely behaving animals over several weeks and enables investigation of the role of the ENS in behavior and disease.

A BRAIN-BONE CROSSTALK ORCHESTRATES MOTOR COORDINATION THROUGHOUT LIFE

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Bone is a densely innervated organ, containing a complex network of sensory and sympathetic nerves that regulate bone mass and repair. However, it remains unknown whether this innervation influences the recently described endocrine functions of bone. Here, we identify a neural circuit in long bones whereby neuron-derived glutamate stimulates the endocrine release of osteocalcin (OCN) from osteoblasts. We show areas of enrichment of the vesicular glutamate transporter 2 (VGLUT2) on the neural side and the glutamate transporter GLAST, and members of the SNARE protein family on osteoblasts that represent the putative neuron-osteoblast junction. We propose that this specialized machinery allows osteoblasts to uptake neuron-derived glutamate, which prevents OCN to be carboxylated by the enzyme gamma-carboxylase. As a result, uncarboxylated, bioactive OCN can be released into the circulation. We demonstrate that this glutamatergic circuit is engaged during arousal states, including but not limited to acute stress, establishing that the nervous system governs the endocrine functions of bone. In an effort to assess the physiological significance of this neuroendocrine circuit, we modeled in mice symptoms observed in patients with loss-of-function mutations in EAAT1 (the human homologue of Glast), which cause episodic ataxia type 6 (EA6). This rare disease is characterized in part by episodes of severe motor incoordination triggered by stress. The absence of GLAST specifically in osteoblasts impairs the neuron-dependent release of OCN during arousal and recapitulates the motor incoordination phenotypes observed in EA6 patients. We further show that physiologically, OCN signals through the G protein-coupled receptor GPR158 in Purkinje cells of the cerebellum to increase their basal firing frequency, contributing in that way to proper motor coordination. Notably, as motor coordination declines with aging so does circulating OCN levels. Restoring circulating OCN in aged WT mice to levels seen in young mice prevents the appearance of and reverses an existing age-related motor incoordination phenotype. Together, our findings reveal a bone-brain axis in which neuron-derived glutamate signals in osteoblasts to release OCN, modulating motor coordination. We propose that this pathway may be harnessed to treat age-related decline motor incoordination.

INFLUENZA A VIRUS INFECTION REMODELS THE SPATIAL NEURO-IMMUNE LANDSCAPE OF THE OLFACTORY EPITHELIUM

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The olfactory epithelium (OE) presents a uniquely vulnerable interface where olfactory sensory neurons (OSNs) provide a direct axonal route for viruses to enter the central nervous system (CNS). OSNs connect to the olfactory bulb (OB) of the brain, which in turn connects to the olfactory cortex. In wildtype mice, Influenza A Virus (IAV) infects OSNs after intranasal infusion. However, neuroinvasion of the brain is typically restricted, suggesting the existence of a potent "nose–brain barrier." Using high-resolution Xenium spatial transcriptomic analyses, we characterize this barrier as a dynamic, multi-lineage defense system. At day 3 post-infection in wildtype mice, we observed a striking recruitment of immune cells to the OE, including a 46-fold increase in M1-like macrophages, alongside significant influxes of NK cells (7.7-fold), neutrophils (4.7-fold), and $CD4^+$ and $CD8^+$ T cells (1.4-fold and 1.8-fold, respectively). We quantitated spatial proximity of immune cells to infected OSNs and found that M1-like macrophages, $CD4^+$ T cells, and NK cells preferentially organize around infected OSNs. This recruitment is accompanied by a robust antiviral program. High levels of interferon-stimulated genes (ISGs), such as *Cxcl10*, *Cxcl9*, *Irf7*, and *Isg15* are induced not only in immune cells, but also across OSNs and even some OB neurons, including most without productive infection, creating a broad "shielding" effect. Concomitantly, the OE undergoes fundamental reprogramming, characterized by the downregulation of homeostatic genes, such as *Nqo1*, *Nr4a1*, and *Dnah5*, in infected OSNs.
The necessity of specific immune compartments was demonstrated through depletion models: while IAV remains confined to the OE in wild-type mice, chemical depletion of microglia/macrophages via CSF1R inhibitor PLX5622 permits viral spread into the OB. In lymphocyte-deficient RAG1 KO mice, the barrier failure is more extensive, with IAV infecting the olfactory cortex and the hippocampus, a region involved in memory and neurodegenerative pathology. Together, these findings demonstrate that while innate immune cells are essential for preventing initial entry into the OB, adaptive immune cells are critical for halting viral progression into deeper CNS structures, establishing the "nose-brain barrier" as an essential guardian of brain health.

MORE THAN JUST A PASSENGER: THE GUT MICROBIOME DRIVES TERRITORIAL CONFLICT IN GRYLLODES SIGILLATUS

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The gut microbiome is thought to shape host behavior through the gut-brain axis (GBA), changing host neurochemistry and social behaviors critical for reproduction and survival. However, determining whether and how the microbiome affects complex social behaviors can be challenging due to inherent noise in biological systems and limitations of quantitative methods to assess complex behavior. While high-throughput sequencing enables rapid profiling of microbial communities, measuring active dyadic interactions can be subjective and prone to bias. This study sought to overcome this challenge by modifying the gut microbiome to assess the effects on territorial aggression in the banded cricket, Gryllodes sigillatus. To increase precision in measuring aggression, we employed a novel markerless multi-animal pose estimation (maDLC) approach, paired with custom rule-based algorithms, to translate high-speed video to classify five discrete aggressive states: mutual avoidance, dominance, antennal fencing, mandible engagement, and grappling. We applied this framework on crickets exposed to three microbiome-modifying treatments, including a broad-spectrum antibiotic (vancomycin), a probiotic (Bifidobacterium longum BB536), and a serotonin precursor (5-HTP). We found that depleting the microbiome with vancomycin produced a hypo-aggression phenotype, resulting in significantly fewer fight wins, while serotonergic augmentation with 5-HTP shifted behavior toward peak aggression and increased grappling. These results suggest that the gut microbiome modulates aggression by interacting with the serotonergic system, suggesting microbiome health can shift an individual's competitive strategy. Furthermore, our pipeline eliminates the rate-limiting step in behavioral analysis, enabling integration of physical fight metrics with high-resolution genomic data. We anticipate that this approach will serve as a starting point to build more sophisticated models of the microbe-gut-brain axis in social behavior and help explain the regulation of aggression in insects and other animals, potentially informing future research into the microbial underpinnings of social disorders in humans.

MECHANISMS AND FUNCTIONS OF UTERINE NERVE REGRESSION DURING PREGNANCY

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Pregnancy triggers extensive remodeling of nearly every organ system including the brain and peripheral nerves. Strikingly, the sympathetic nerves that innervate the uterus regress dramatically by mid-gestation. The mechanisms driving this structural remodeling are unclear, and its potential functions remain sorely understudied. We are using mouse models to address these gaps in our understanding of healthy pregnancy. To determine whether pregnancy-induced uterine nerve regression is driven by systemic or local signals, we restricted embryo implantation to one side of the bicornuate mouse uterus. In unilaterally pregnant dams, we found that nerves on the pregnant side of the uterus regress as early as gestational day 10.5 (GD10.5), yet nerves on the non-pregnant side remain intact. This suggests that local cues, rather than systemic pregnancy hormones, trigger uterine nerve regression in pregnancy. We are now systematically elucidating the cellular and molecular signaling between the conceptus and the nerves that drive regression by combining perturbation of candidate pathways with unbiased transcriptomic profiling. To probe potential function(s) of sympathetic nerves in the pregnant uterus, we exposed pregnant dams to nociceptive stress on GD3.5-5.5, prior to the onset of pregnancy-induced nerve regression. Nociceptive stress activates sympathetic neurons which mediate vasoconstriction of uterine blood vessels. Although maternal stress did not affect the number of implantation sites per uterus, embryos from stressed dams developed fewer somites by GD9.5, suggesting that maternal stress delays or restricts embryonic growth. Together, our results suggest that local factors produced by the conceptus trigger pregnancy-induced nerve regression to protect the fetus from the vasoconstrictive effects of sympathetic nerves.

ESTROGENIC RE-MAPPING OF THE METABOLIC RESPONSE TO AN ENERGY DEFICIT

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In response to an energy deficit, mice conserve energy by entering torpor, a hypometabolic state. While torpor can be adaptive, it can also interfere with reproduction, suggesting energy homeostasis and reproduction must be carefully balanced during an energy shortage. In support of this notion, we found that fasting-induced torpor use naturally varies across the estrous cycle and is increased by ovariectomy. Together, these data demonstrate that torpor is modulated by reproductive signals from the ovaries. To test whether circulating estrogens were, at least in part, underlying this phenomenon, we treated female mice with 17β-estradiol (E2, a potent estrogen naturally produced by the ovaries). We found that E2 potently reduced torpor usage, keeping energy expenditure high even in the face of a dangerous energy deficit. The signaling mechanisms underlying this estrogenic re-mapping of the metabolic response to an energy deficit are unknown, however.

Estrogen-sensitive neurons in the medial preoptic area ($MPO^{ER\alpha}$ neurons) are central coordinators of torpor in mice, leading us to the hypothesis that circulating E2 may reduce torpor usage by acting directly on the MPO. To test this hypothesis, we first delivered E2 directly to the MPO to test the sufficiency of this pathway. E2 delivered to the MPO was sufficient to reduce torpor usage in gonad-intact female mice, but, surprisingly, not in ovariectomized females. Next, we knocked out estrogen receptors in the MPO to test the necessity of this pathway. Briefly, we found that knocking out estrogen receptor alpha alone, or in combination with estrogen receptor beta, in the MPO did not block the effect of E2 treatment on torpor in ovariectomized females. Together, these results suggest that the MPO is integrated into the regulatory circuit that mediates the effects of circulating E2 on torpor, although its contributions appear to be minor and dispensable.

We are currently using in vivo calcium imaging to test whether circulating E2 influences the activity of $MPO^{ER\alpha}$ neurons, either directly and/or indirectly. Ongoing analyses have revealed that $MPO^{ER\alpha}$ neurons have mixed responses during torpor and will determine if the relationship between torpor and neuronal activity is altered by E2 treatment.

In conclusion, our findings demonstrate that circulating estrogens reduce torpor usage and exclude the MPO as a direct mediator of this phenomenon. These results advance our understanding of how estrogens influence torpor in mice, a critical step towards the larger goal of understanding how estrogens influence energy balance across species.

NEUROTENSIN-EXPRESSING SYMPATHETIC NEURONS REGULATE SEXUALLY DIMORPHIC ADIPOSE TISSUE METABOLISM IN MICE

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The sympathetic nervous system (SNS) is essential for maintaining homeostasis in response to environmental challenges. This regulation is mediated by the spinal sympathetic preganglionic neurons (SPNs), which influence diverse organs via postganglionic neurons located in the sympathetic trunk and splanchnic ganglia. Despite classical studies suggesting selective organ control within SNS, the underlying neural circuit organization remains largely elusive. Recently, our team demonstrated a tight correlation between the transcriptomic types of SPNs and their output target specificity in the lower thoracic spinal cord.

White adipose tissue (WAT) plays a central role in energy homeostasis by storing energy via lipogenesis and releasing it through lipolysis. Sympathetic input is known to robustly regulates lipolysis. While previous studies have revealed detailed functions of WAT-projecting postganglionic neurons, the identities of the upstream SPNs that regulate these neurons remain elusive. In addition, although pronounced sexual dimorphism in WAT physiological is well documented, whether SNS-mediated control contributes to this phenomenon is unknown.

To address these questions, we generated a spatial transcriptomics (STx)-based activity atlas of SPNs in mice exposed to cold, a condition that robustly induces WAT lipolysis to mobilize energy stores. By combining immediate early genes (IEGs) detection, we identified two SPNs transcriptomic subtypes activated during cold exposure, one of which was characterized by expression of Neurotensin (Nts).

Anterograde axon tracing revealed that Nts expressing (+) SPNs in the lower thoracic spinal cord project selectively to the sympathetic trunk and the aorticorenal ganglia (ARG), both of which contain postganglionic neurons innervating inguinal and gonadal WAT (iWAT and gWAT). Functional manipulation and ablation experiments further showed that Nts+ SPNs exert pronounced control over WAT lipolysis and are essential for energy mobilization required for cold tolerance. Notably, both activation and ablation phenotypes of Nts+ SPNs were markedly female-biased.

Collectively, these findings identify Nts+ SPNs as key regulators of WAT lipolysis via the sympathetic trunk and ARG, and suggest that SNS-mediated control of lipolysis contributes to sexually dimorphic WAT physiology.

DEVELOPMENT OF THE SEXUALLY DIMORPHIC MOXD1 POPULATION

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Social behaviors are essential for species reproduction and survival. In mammals, these behaviors are supported by a set of interconnected regions collectively known as the social behavior network (SBN). The SBN displays major sexual dimorphisms, which arise from different hormonal environment during development: at birth, male testes release a surge of testosterone that is aromatized into 17β-estradiol (E2). This neural E2 acts through the estrogen receptor α (ERα) to drive brain sexual differentiation. This process is thought to contribute to the functional sex differences of the SBN, eventually leading to sex-variable behavioral repertoires. However, the precise mechanisms linking early life hormone signaling to the emergence of neural sex differences remain poorly understood.
To address this question, we focus on a recently identified transcriptomic population in the SBN, defined by the expression of Moxd1, as a model for studying sexual differentiation. In the posterior part of the bed nucleus of the stria terminalis (BNSTp), Moxd1 neurons display the highest number of sexually differentially expressed genes, and are more abundant in males that in females. A similar male-biased number is observed in other SBN regions, the preoptic area and the medial amygdala. We hypothesized that ERα signaling in Moxd1 neurons during the postanal period drives these sex differences. To test this, we generated a Moxd1-Cre driver to selectively label and manipulate these neurons.
We find that genetic deletion of ERα specifically in Moxd1 neurons profoundly disrupts male sexual behavior, with only 20% of them reaching ejaculation. In addition, the sexual dimorphism in BNSTp cell number is absent in these mutant males. This indicates that ERα in Moxd1 neurons is crucial for the male-biased cell number and the display of male sexual behavior. We now aim to trace the development of Moxd1 neurons connectivity, and link the actions of ERα at birth to the resulting sex differences in projection patterns. More broadly, our goal is to connect the perinatal ERα target genes to the emergence of sexual dimorphisms and, ultimately, to sex-specific behaviors in adulthood.

RE-INTERPRETING PROLACTIN AS A PERIPHERAL BRAIN–BODY STRESS RESPONSE AMPLIFIER: LESSONS FROM THE HAIR FOLLICLE

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From a Brain–Body Physiology perspective, prolactin (PRL) is increasingly recognized for pleiotropic functions well beyond lactation, yet its role as a peripherally produced stress response amplifier remains underexplored. PRL levels can increase under psychoemotional stress, with PRL being also generated locally in diverse tissues, including synoviocytes, immune cells, and hair follicles via a distinct extrapituitary promoter, enabling autocrine/paracrine amplification at the tissue level. This positions PRL to orchestrate energy trade-offs between growth and regression, immune activation and tolerance. We postulate this axis constitutes a brain–body interface redirecting cellular programs under stress, with pathology arising when this adaptive switch becomes chronically locked.

We introduce scalp hair follicles (HFs), uniquely accessible human mini-organs undergoing cyclic remodeling (growth–regression) to probe this hypothesis. We previously showed that HFs both produce and respond to PRL, which induces premature regression (catagen) in microdissected, organ-cultured, and thereby "stressed" male scalp HFs. We therefore now tested whether a generative AI-designed PRLR-antagonizing antibody (ABS-201) restores HF growth while preserving epithelial hair follicle stem cells (eHFSCs). Full-thickness temporofrontal male scalp skin was organ-cultured (serum-free, 6 days) with ABS-201 or IgG control, with/without exogenous PRL, preserving epithelial–mesenchymal interactions, resident immune cells, endogenous PRL production, and intact JAK/STAT signaling while eliminating systemic endocrine and neural confounders.

Quantitative (immuno)histomorphometry showed that ABS-201 inhibited PRLR-mediated STAT5 activation induced by high-dose PRL and significantly prolonged active hair growth (anagen), increased hair matrix keratinocyte proliferation, and elevated expression of key growth factors (IGF1, FGF7). ABS-201 protected and even expanded the $K15^+$ eHFSC pool by preventing PRL-induced apoptosis and supporting proliferation and $CD34^+$ progeny generation. Importantly, ABS-201 alone also promoted HF growth, indicating neutralization of endogenous intrafollicular PRL signaling.

These results provide the first direct evidence, in a translational relevant human peripheral mini-organ, that PRLR antagonism can break the proposed negative tissue-level amplifier function of PRL. Given that ABS-201 restores HF growth and stem cell resilience in androgen-sensitive scalp skin, we propose that androgenetic alopecia reflects, in part, a normally adaptive peripheral PRL-mediated stress program that has become chronically activated, which ABS-201 may rebalance. More broadly, our findings invite reconceptualization of peripheral PRL as an actionable neuroendocrine amplifier whose stress-driven dysregulation contributes to chronic tissue pathology, with the hair follicle serving as a clinically accessible window into brain-body stress-energy signaling.

THE ROLE OF PULMONARY INNERVATION IN BREAST CANCER LUNG METASTASIS

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In breast cancer, metastasis to distant organs and tissues is the primary cause of breast cancer-related death. The lungs are one of the most common locations for metastatic breast cancer and have been well characterized in terms of immune, structural, metabolic and genetic state during this process. Organs are innervated by the peripheral nervous system (PNS) which can regulate critical homeostatic processes such as immune defense and wound healing through their activity and arborization. With this in mind, we aim to answer the question of if and how pulmonary metastases impact the local PNS. Here, we delivered MMTV-PyMT breast cancer cells through intravenous tail-vein injections and we assessed the lungs for changes in innervation patterns using lightsheet microscopy. Antibody staining of iDISCO-cleared lungs for tyrosine hydroxylase, vesicular acetylcholine transferase, and sodium channel $Nav_{1.8}$ revealed the innervation patterns of sympathetic, parasympathetic, and sensory nerve populations in the metastatic lung. By imaging the neural projections alongside the MMTV-PyMT metastatic lesions in the whole lung, we reveal potential direct neurite-tumor interactions and find that sensory and parasympathetic neurites associate with the tumors. Peripheral nerves release neurotransmitters and neuropeptides in a calcium-dependent manner and these secondary messengers bind with their receptors that are expressed on many endothelial and immune cell populations. Neuropeptides mediate immune cell recruitment, vascular regulation, and stromal remodeling during injury, making them candidates for cancer regulation. To this end, we are investigating the secretion of neuropeptides from pulmonary nerve terminals and how this may affect MMTV-PyMT cell growth in vivo and in vitro. To test how nerve activity influences the local pulmonary metastatic environment in vivo, we chronically activated specific pulmonary nerves throughout the dissemination and seeding processes of lung metastasis. This project aims to answer two questions: (1) how does breast cancer pulmonary metastasis influence the local neural landscape and (2) does pulmonary innervation play a role in regulating this metastatic niche. Together, this project will disentangle the bidirectional crosstalk between the pulmonary metastatic microenvironment and local innervation, redefining breast cancer's understanding as a systemic disease with neural determinants and effects. This understanding may reveal novel therapeutic strategies to target the critical stages of cancer progression at distant organ sites.

GUT MICROBIOME DISRUPTION BY CEFTRIAXONE INDUCES NEUROBEHAVIORAL DYSREGULATION

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Introduction: The gut–brain axis integrates microbial, immune, and neural signaling to regulate behavior and cognition. Although antibiotics are clinically essential, they can disrupt gut microbial ecosystems and alter neuroimmune communication. We examined whether short-term ceftriaxone (CTX)-induced dysbiosis produces neurobehavioral and molecular alterations in the hippocampus, with attention to sex differences. We hypothesized that CTX-driven microbial depletion would impair cognition and disrupt synaptic and metabolic pathways.
Methods: Male and female C57BL/6 mice received CTX (200 mg/kg) or vehicle via oral gavage for four consecutive days. Fecal samples were analyzed using 16S rRNA sequencing. Behavioral assessments were conducted following treatment. Hippocampus, frontal cortex, and colon were harvested for immunoblotting and proteomic analyses; plasma cytokines were quantified; and immunohistochemistry was performed on half-brains.
Results: CTX significantly reduced microbial richness and diversity and altered community structure in both sexes. Treated mice exhibited cognitive deficits, reduced pain sensitivity, and anxiety-like behaviors, with stronger effects in males. Colonic calprotectin and IL-1β were elevated, indicating intestinal inflammation. Hippocampal proteomics revealed clear group separation and widespread remodeling of proteins involved in mitochondrial function, translation, vesicular trafficking, and synaptic regulation. Synaptophysin was reduced in the hippocampus of CTX-treated males, consistent with impaired synaptic integrity. Frontal cortex expression of microbial metabolite receptors (GPR109A, MCT-1) was decreased, and plasma fractalkine levels were reduced, suggesting disrupted gut-derived signaling and altered neuron–microglia communication.
Conclusion: Short-term CTX exposure induces gut microbial depletion coupled to intestinal inflammation, hippocampal proteomic reprogramming, and multidomain behavioral impairments. Altered synaptic and metabolic pathways support a mechanistic link between antibiotic-induced dysbiosis and disrupted neuroplasticity. Greater male vulnerability suggests sex-dependent modulation of microbiome–neuroimmune interactions. These findings demonstrate that even brief antibiotic exposure can perturb gut–brain signaling and influence cognitive and affective behaviors.

FOREST BATHING IN PATAGONIA AYSÉN: COMPARING IN-PERSON AND VIRTUAL EXPERIENCES ON AUTONOMIC NERVOUS SYSTEM MARKERS AND EMOTIONAL WELL-BEING IN MIDLIFE WOMEN

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Introduction: The lack of health interventions targeted at women within an age range close to the end of the reproductive stage has generated the need for complementary strategies to promote well-being. In this context, non-pharmacological interventions have gained relevance due to their accessibility, low risk, and therapeutic potential. Among them, an intervention known as forest bathing or shinrin-yoku has shown favorable effects on physiological and emotional parameters associated with stress, such as regulation of the autonomic nervous system and reductions in cortisol levels. However, access to natural environments is not always possible due to geographical, climatic, or mobility barriers, which has encouraged interest in studying alternative modalities such as virtual reality.
Methodology: The present study focused on evaluating and comparing the immediate physiological effects of a guided forest bathing session delivered through in-person and virtual modalities, using a pre-experimental design with pre- and post-intervention measurements in women aged 50 to 65 years, living in the city of Coyhaique, Chile. We recruited 21 volunteers, who repeated both modalities, on different days. Heart rate, frequency, arterial pressure, respiratory rate, temperature, heart rate variability, salivary cortisol, and mood state (by POMS scale) were assessed. Mann-Whitney and Kruskal Wallis tests were used for statistical analysis (Graph Pad Prism software), $p<0.05$ was considered statistically significant.
Results and discussion: The 30-minute forest bathing session showed differences according to the modality applied. In the virtual intervention, immediate physiological changes were observed, evidenced by decreases in heart rate (76.48 bpm to 69.38 bpm; $p<0.05$) and respiratory rate (17,57 rr to 15,24 rr; $p<0.05$) after completing the virtual session. The in-person modality showed no statistically significant changes. When comparing both interventions, certain conditions were identified that could explain the lack of effect of the in-person forest bathing session including the hour and day of the week on which each session was conducted, which apparently influenced the participants basal physiological state (significant differences between basal pNN50 in virtual vs. basal pNN50 on in-person intervention). Overall, these findings add evidence to the use of virtual forest bathing as a complementary practice for promoting well-being in women aged 50 to 65 years.

OPTICAL FIBER FLUORESCENCE ENDOSCOPY VISUALIZES ENTERIC NERVOUS SYSTEM ACTIVITY IN VIVO

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The enteric nervous system (ENS) innervating organs of the gastrointestinal (GI) tract not only regulates local functions including nutrient absorption and immune system activation, but also communicates bidirectionally with the brain. Increasing awareness of gut-brain axis activity, including its potential role in mediating GI comorbidities that commonly accompany psychiatric disorders, has motivated the development of neural monitoring tools to capture and characterize these interactions. Optical imaging of genetically encoded fluorescent indicators reporting neural activity has transformed our ability to visualize brain function, and stands to similarly empower scalable and specific ENS monitoring. However, barriers to accessing the delicate internal organs of the gastrointestinal (GI) tract have primarily limited previous work to the evaluation of ex vivo tissue, negating opportunities for longitudinal studies preserving extrinsic innervation.
To address these challenges, we have developed a miniature flexible endoscope using bundled polymer optical fibers to spatially resolve fluorescent indicators expressed by ENS neurons in the distal colon of anesthetized mice. Our minimally invasive and non-surgical approach critically leverages the systemic delivery of viral vectors to broadly express a variety of indicators and eliminate the need for localized injections or transgenic animals. By pairing our optical fibers with 3D-printed microlens housing, microfluidics, a multicolor back-end imaging system, and a signal processing pipeline including robust fluorescence amplification, filtering, and motion correction, we enable the stable recording of multifaceted signaling dynamics in response to pharmacological stimuli at near-cellular resolution.
To date, we have used our endoscopic imaging platform to temporally characterize the colonic expression of genetically encoded indicators and capture differential neuronal firing (calcium indicator) and neurotransmitter release (serotonin indicator) in response to diverse ENS agonists in healthy animals in vivo. We further deploy our platform to longitudinally characterize changes in neural activity, motility, and microvasculature that occur over time in a mouse model of colitis. In contrast to conventional ex vivo assays, we anticipate that our novel approach will uniquely enable long-term investigations of peripheral nervous system function under normal or pathological conditions in intact animals, broadening our understanding of the relationship between the ENS, brain, and behavior.

ADOLESCENT E. COLI HS COLONIZATION ALTERS BEHAVIOR AND BRAIN MATURATION IN A SEX-SPECIFIC MANNER

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The adolescent period is a time when brain circuits, cognitive functions, and behaviors mature and transition to their adult state. Not surprisingly, this period also represents a window of vulnerability during which various environmental factors can affect these ongoing processes, leading to long-lasting effects in brain physiology and pathology. Recently, a strong link between the early-life microbiome and behavioral and neuroanatomical outcomes in adulthood has emerged, including clinical and preclinical data associating adolescent microbiome perturbations with psychiatric conditions such as depression, autism, and anxiety. However, the molecular mechanisms underlying these alterations and their neurological consequences remain largely unknown. Therefore, the main goal of this project is to mechanistically evaluate how changes in the gut microbiome composition during adolescence impact ongoing brain maturation and behavior. Previous data from our lab have shown that in adult animals, increases in gut proteobacteria colonization result in glycine depletion in the host, altering rewarding and motivational behaviors. Based on this data, we hypothesized that increases in proteobacteria colonization in the adolescent period would have significant impacts on behavior and the maturation of dopaminergic circuitry through the same mechanism of glycine depletion. here we reset the adolescent microbiome in male and female mice using a brief period of antibiotic exposure followed by oral gavage with either the human commensal Escherichia coli strain HS or a fecal microbiota transplant (FMT) as a control. This strategy allows us to overrepresent E. coli HS in the microbiome during early adolescence (PND 22-25) in mice. Following microbiome manipulation, we performed behavioral, molecular, and metabolic analyses to assess the microbiome's impact on host physiology. As expected, we found that glycine levels in stool are significantly downregulated 1 week after E. coli HS administration, both in males and females. Behavioral evaluations (PND 34-36) revealed that E. coli HS colonization improves social recognition and blunts the behavioral response to amphetamine only in male mice. These changes are also associated with alterations in the expression of dopaminergic and glutamatergic proteins in the adolescent brain in areas of the dopaminergic pathway, including the prefrontal cortex, nucleus accumbens, and ventral tegmental area. Altogether, these results strongly indicate that during adolescence, increases in E. coli HS colonization can significantly alter host glycine levels, leading to sex-specific changes in behavior and brain physiology. Ongoing studies will determine whether these adolescent behavioral and molecular alterations persist into adulthood and whether the bacteria's sex-specific effects on brain physiology and behavior are similarly retained.

CXCL12 REGULATES NEURONAL MIGRATION AND EARLY GENE EXPRESSION IN HYPOTHALAMIC NEURONS

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Chemokines are key signaling molecules that regulate cell migration during development, with CXCL12 playing a central role in directing neuronal positioning in the embryonic brain. CXCL12 is a chemokine that guides stem cell migration and is essential for cerebellar granule cell movement during embryogenesis. Prenatal alterations in CXCL12 signaling, including increased expression of CXCL12 and its receptors CXCR4 and CXCR7 in the hypothalamic paraventricular nucleus (PVN), have been associated with altered neurodevelopment. Based on its established role in cell migration, we hypothesize that CXCL12 will stimulate neuronal migration and change the transcription of its associated genes.

To investigate this, a migration assay was used and showed that CXCL12 moderately to greatly stimulated migration between 3–24 hours after treatment with 50, 100, and 200 ng/mL CXCL12. Next, RNAseq was used to examine differential gene expression of hypothalamic neurons after 3 hours of treatment with CXCL12. The fastq files were aligned, counts determined, and differential expression analysis was conducted using the iDEP (integrated Differential Expression and Pathway analysis) web-based bioinformatics platform. Gene expression was analyzed using DESeq2 at three-fold-change (FC) thresholds (1.2, 1.5, and 2.0). Overlapping genes across treatments were identified.

At the 1.2 FC threshold, six overlapping genes were identified, including one upregulated gene and five downregulated genes. These genes included migration- and differentiation-related factors such as Gata2, Egr1, Smad6, Atoh8, Dok7, and Zfp839. However, at the 1.5 and 2.0 FC thresholds, no overlapping genes met the criteria for consistent regulation. The predominance of downregulated genes and absence of shared genes at higher thresholds indicate that CXCL12 induces only modest early transcriptional changes at 3 hours. Overall, these findings suggest that CXCL12 mildly stimulates both migration and migration-related gene expression in the hypothalamic neurons at this time point.

CORTICAL CONTROL OF ADAPTIVE IMMUNE RESPONSES

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Survival depends on the brain's ability to coordinate physiological, immunological, and behavioral responses. Abundant evidence shows that the brain and the immune system are in constant communication. While it is established that the brain can influence aspects of innate immunity, whether it can control more specialized adaptive immune responses is unknown. We addressed this question using a mouse model of house dust mite (HDM)-induced respiratory allergy. We sensitized and challenged mice intratracheally and confirmed a robust adaptive immune response in the lungs three days post-challenge. Using intravital imaging approaches and TRAP2 mice to label neurons activated during this response, we identified specific cortical populations engaged during the allergic reaction. First, we characterized their identity and projections. Next, to explore their functional role, we employed chemogenetics and viral tools to reactivate them after inflammation had resolved. Strikingly, this reactivation alone—without further allergen exposure—was sufficient to re-induce lung inflammation to levels matching the initial challenge. The response recapitulated the original challenge in both anatomical specificity and immunological identity, triggering an antigen-specific type 2 adaptive immune response. Notably, the response was mediated by the sympathetic system. These findings establish the cortex as a central regulator of local cellular adaptive immunity.

MULTISENSORY INTEGRATION BY BRAINSTEM PEPTIDERGIC NEURONS REGULATING ENERGY HOMEOSTASIS

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The brainstem functions as the central hub controlling moment-to-moment ingestive behavior. The ending of an ongoing meal is a major factor in determining meal size and, therefore, influences energy intake and body weight. Meal termination in an adaptive setting is called satiation, which is dissociable from satiety signaling (the state between two consecutive meals) and is regulated by a distinct set of neural circuits. While hypothalamic peptidergic neurons are crucial for regulating hunger-satiety dynamics, classic studies using decerebrate rats identified a satiation center in the brainstem. However, the specific cell types, circuits, and mechanisms that govern brainstem regulation of satiation remain poorly understood. In recent work, we describe the discovery of an obligate peptidergic population in the brainstem's dorsal raphe nucleus that controls satiation. These neurons express the anorectic hormone cholecystokinin (CCK) and an array of other peptides, while lacking classical fast neurotransmitters. Input-output mapping revealed that CCK neurons are ideally positioned to coordinate with other feeding-related brain areas. The regulatory effect of CCK neurons on feeding exhibits a built-in delay and persists for tens of minutes even after their activity ceases. To achieve this, CCK neurons integrate various ingestive signals. These signals include the sensory qualities of food, oropharyngeal signals from the bite, the chemical sensation of food macronutrients in the stomach, and gut-derived humoral factors. This multilevel sensory integration, with its delayed yet sustained effect on food intake, makes the CCK population a prime candidate for the elusive "satiation center" in the brainstem.

UTERINE-BRAIN COMMUNICATION DURING LABOR: TOWARD A CLOSED-LOOP FRAMEWORK FOR CHILDBIRTH

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Childbirth requires tightly coordinated communication between the uterus and brain, yet the neural architecture of this communication remains poorly understood. Clinically, labor induction and augmentation have remained largely unchanged for decades, relying on continuous systemic infusion of synthetic oxytocin (Pitocin) to stimulate contractions. This approach bypasses the endogenous, pulsatile oxytocin signaling that characterizes natural labor, which is frequently associated with stronger and more painful contractions, higher rates of Caesarean delivery, lactation difficulties, and postpartum hemorrhage. Yet, we lack a causal and quantitative framework that links uterine contraction dynamics to ascending sensory signaling and brain-mediated feedback. As a result, it remains unclear how current induction practices alter brain–body communication during labor.

This project tests the hypothesis that labor functions as a closed-loop feedback system between the uterus and brain, and that current induction practices disrupt this physiological control architecture. To address this, we quantify spontaneous and evoked pain-related behaviors in mice during natural and oxytocin-induced labor, providing a behavioral proxy for ascending sensory signaling during labor. In parallel, we use the MyoMatrix electromyography (EMG) array to record high-resolution uterine contractions in awake, behaving animals, allowing quantitative measurement of contraction strength, timing, and spatiotemporal propagation. To define the structural substrates of retrograde signaling, we performed uterine retrograde tracing to map afferent projections through dorsal root and vagal ganglia and have identified candidate brain regions involved in contraction-related sensory processing.

As a future direction, we will integrate these approaches into a closed-loop perturb-and-measure platform enabling spatiotemporally controlled, localized oxytocin delivery within the uterus while simultaneously recording contraction dynamics and behavioral outputs. Using a photoactivatable oxytocin analog, we control the timing and location of uterine oxytocin release with millisecond and micrometer precision, allowing systematic manipulation of contraction waveforms independent of systemic hormone exposure. This strategy will enable causal dissection of how defined peripheral contraction patterns shape ascending signaling and neuroendocrine feedback.

This work positions the uterus as an active signal generator within a distributed brain–body circuit rather than a passive effector of endocrine commands. By defining how peripheral contraction dynamics drive central sensory processing, this research reframes labor induction as a control problem in integrative physiology and points toward more physiologically informed, tunable strategies for labor management.

BEYOND THE BRAIN: THE GUT MICROBIOME AS A MODULATOR OF ADDICTION PHENOTYPES

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Addiction is a chronic, relapsing disorder characterized by compulsive drug use despite harmful consequences and remains a major global health challenge. Substance use disorders (SUDs) affect millions of individuals worldwide, yet currently available pharmacological and behavioral treatments show limited long-term success, underscoring the need to identify novel biological mechanisms that contribute to addiction vulnerability and relapse.

Emerging evidence indicates that the gut microbiome plays an important role in regulating brain function and behavior through gut–brain signaling pathways. Clinical studies have reported significant alterations in gut microbial composition in individuals with SUDs, and microbiome shifts have been observed during key stages of addiction, including the transition from recreational to compulsive drug use and during withdrawal. However, the specific microbial taxa involved and the molecular mechanisms mediating host–microbiome interactions in addiction remain largely unknown.

To address this gap, we use a multidisciplinary approach integrating neuroscience, microbiology, and behavioral pharmacology to investigate how psychostimulant exposure reshapes the gut microbiome and how these changes influence addiction-related behaviors. Our work examines drug-induced alterations in specific microbial populations and tests whether these microbiome shifts contribute to behavioral phenotypes associated with drug reinforcement and relapse.

Elucidating the mechanisms underlying microbiome–brain interactions in addiction may uncover previously unrecognized pathways contributing to substance use disorders and support the development of microbiome-informed therapeutic strategies.

WHOLE-BODY IMAGING OF IMMUNE, RESPIRATORY AND NEURAL INTERACTIONS IN DROSOPHILA

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Understanding how the brain coordinates organism-wide physiological responses remains a central challenge in brain–body physiology. Systemic stressors such as infection, diet, or ageing drive coordinated changes across multiple organs, yet current approaches make it difficult to capture these dynamics in intact adult animals at cellular resolution.
Here, we establish a proof-of-concept strategy to map the organisation of immune (haemocytes), neural and respiratory (tracheal) networks in adult Drosophila melanogaster. We developed a multimodal imaging pipeline combining tissue clearing, light-sheet microscopy and an in-house serial two-photon platform (BrainSaw), enabling high-resolution reconstruction of whole or hemi-dissected adult flies.
This approach enables quantitative analysis of tracheal architecture and haemocyte distribution across physiological conditions, including sex, ageing and metabolic perturbations. We then extract organism-wide features such as tracheal branching patterns, network organisation and haemocyte clustering. In parallel, we can test candidate neural circuits that may contribute to this remodelling, making it possible to examine whether defined neuronal populations influence haemocyte positioning and tracheal plasticity in response to physiological demand. Together, this work establishes a scalable platform for whole-body imaging at cellular resolution.

MICROBIAL METABOLITES UNDERLIE AGE-RELATED ENS SUSCEPTIBILITY TO DAMAGE

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The enteric nervous system (ENS) is sensitive to the trillions of microbes that inhabit the gastrointestinal tract, and disruption of microbial homeostasis, or dysbiosis, from antibiotic treatment induce intrinsic neuronal and glial death and associated dysmotility [1-3]. Although disruption of microbial colonization during weaning is associated with inflammatory diseases in both humans and mice, its effect on ENS development remains to be defined. We have discovered that susceptibility to antibiotic-mediated neuronal and glial loss begins at 4 weeks old, while younger mice are protected. This neuroprotection is due at least in part to the microbiome, as adult mice colonized with PedsCom, a consortium of preweaning bacteria [4], did not lose neurons or glia when treated with ampicillin. Conversely, weaning-age mice colonized with MM12, a gnotobiotic community representing the adult microbiome [5], do lose neurons and glia upon ampicillin treatment. We used LC/MS of polar metabolites in the cecum of SPF 3- and 4-week-old mice to identify microbially derived metabolites associated with neuronal loss and protection. There was a significant increase in the concentration of flavonoids, polyphenol secondary metabolites produced by plants, in the ceca of 4-week-old mice treated with ampicillin compared to their younger counterparts. Treatment with a mixture of flavonoids was sufficient to cause neuronal loss in adult SPF mice, and maintenance on a flavonoid-free diet attenuated ampicillin-mediated neuronal loss. In addition, markers of aerobic respiration and oxidative stress increased, and products of bacterial anaerobic respiration such as succinate, butyrate, and short-chain fatty acids (SCFAs) decreased, in 4-week-olds. Succinate and SCFAs in the gut promote neuronal recovery after injury and may protect them from death [4]. Indeed, single-nucleus RNA sequencing revealed an upregulation of genes associated with oxidative stress and programmed cell death in 4-week-old as compared to 3-week-old SPF mice treated with ampicillin. Taken together, these results suggest that ampicillin treatment in the mature microbiome removes neuroprotective metabolites and increases oxidative stress and the concentration of flavonoids, which cause neuronal death. In contrast, the unique metabolic functions of the early-life microbiome confer resilience to dysbiosis-mediated ENS injury, which may provide novel therapeutic interventions in other enteric degenerative conditions.

INTEGRATING REAL-TIME PHYSIOLOGY WITH BEHAVIOR TO MAP INTERNAL STATES IN FREELY MOVING MICE

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Background: Animal behavioral studies rely on observable behaviors as proxies for internal states. Freezing, grooming, and exploration are often interpreted as fear, anxiety, or motivation, providing a convenient but incomplete view. Current behavioral metrics may conflate distinct internal states with similar body movements. For example, resting and freezing can be scored similarly by automated platforms, despite reflecting different arousal states. Integrating spatiotemporal movement with concurrent physiology can provide a richer, time-resolved account of internal state as animals move through behavioral tasks.

Hypothesis: Aligning sub-second behavioral movements with autonomic physiology will improve internal-state inferences beyond behavior-only scoring and reveal the physiological structure of behavioral motifs.

Methods: We are developing a physiological–behavioral pipeline in freely moving mice that synchronizes wireless physiology (NeuroLux: heart rate, respiratory rate, body temperature) with video-based behavioral quantification (DeepLabCut; Keypoint-MoSeq). Physiological streams are aligned to behavioral "syllables" and analyzed with custom MATLAB tools to map autonomic signals onto behavioral syllable motifs and sequences. We compare behavior in field-standard versus customized NeuroLux-compatible mazes designed to accommodate wireless constraints while preserving core task features.

Results: Aligning physiology to behavior yields physiologically informed "signatures" of behavioral motifs, enabling temporal mapping of autonomic signals onto behavior at sub-second resolutions. Mice perform comparably across field-standard and NeuroLux-compatible mazes, supporting the feasibility of wireless physiology without substantially altering task performance.

Conclusions: This scalable framework interprets behavior through concurrent autonomic physiology, moving beyond coarse proxies toward multidimensional readouts of internal state and detection of subtle state changes missed by human observers or behavior-only automation.

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RETROSPECTIVE REACTIVATION OF AMYGDALA FLAVOR REPRESENTATIONS UNDERLIES POSTINGESTIVE LEARNING

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We form lifelong aversions to the foods that make us sick. This single-trial learning is among the most robust and evolutionarily conserved forms of associative memory, yet it poses a fundamental computational challenge: the brain must determine what food caused the illness, despite the delay between eating and experiencing food poisoning symptoms (gastric malaise). We recently found that malaise drives the amygdala into a neural state resembling flavor consumption, which could help an animal bridge the delay between the recently consumed flavor and the subsequent illness experience (Zimmerman *et al*., 2025). However, it remains unclear if this illness-driven reactivation simply reflects a hardwired overlap in flavor and malaise encoding in the amygdala, or if it reflects a retrospective process underlying associative learning.

To test this, we examined two conditions in which mice consume a flavor and experience illness but do not form an association. First, we reversed the temporal order of flavor and illness: when illness precedes rather than follows novel flavor consumption (backwards conditioning), animals do not learn a flavor aversion. We found that while malaise still recruited flavor-coding amygdala neurons during backwards conditioning, it did so non-selectively — neurons from other functional clusters were recruited equally, rather than flavor-coding neurons being selectively activated. This implies that the selective activation of flavor coding neurons by malaise is retrospective. Next, as a second behavioral manipulation to block associative learning, we pre-exposed mice to the flavor before conditioning (familiar conditioning). This also produced a less selective reactivation of the flavor representation by malaise, implicating flavor novelty — in addition to temporal order — as a critical gate on selective reactivation of amygdala flavor representations during illness. After conditioning, amygdala flavor responses weakened in backward-conditioned or familiar-conditioned mice — resembling habituation across repeated flavor exposures in mice that did not experience malaise — whereas flavor responses were relatively stable in forward-conditioned mice.

Together, these findings support a model in which illness drives retrospective and novelty-dependent reactivation of amygdala flavor representations, which in turn serves to strengthen flavor representations in support of associative learning.

NOVEL PATHWAYS IN CEREBROVASCULAR DISEASE

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Introduction: Stroke remains highly prevalent despite targeting classic risk factors, eg, hypertension (HTN), diabetes, and hyperlipidemia. We studied novel contributions to cerebral small vessel disease, a major cause of stroke and the most important contributor to vascular cognitive impairment. We focused on cerebral microhemorrhages (CMH), the most prevalent form of hemorrhagic small vessel disease, in models of chronic kidney disease (CKD) and periodontitis (PD), as well as HTN.
Methods: PD was induced by P. gingivalis-LPS injections between first and second maxillary molars bilaterally twice/week for six weeks. HTN was induced in 17 months old male C57BL/6J mice via infusion of angiotensin II (ATII) over 4 weeks. At end of six weeks, we collected mouse brains (N=5 each for HTN, PD, HTN+PD, and Control). 17-month-old mice were also treated with either 0.2% adenine diet to induce CKD, or angiotensin II (ATII) to induce HTN and compared with control mice. A subset of CKD mice was treated with rapamycin to inhibit mTORC1 signaling. After 4 weeks, RNA sequencing of mouse brain was done via Illumina NovaSeq 6000. Differentially expressed genes (DEGs) and enriched pathways were identified using the MsigDB Hallmark 2020 database. Pathway analysis was further examined using qPCR and immunohistochemistry staining. To assess CMH load, the average number, total area, and size of Prussian blue-positive deposits were quantified. Microglial activation was assessed by Iba-1 immunostaining and microglial morphology.
Results: In PD model, size of CMH doubled in presence of PD with HTN (10.58±2.55 μm2 per cm2 vs. 5.05±1.15 μm2 per cm2, $p < 0.05$). CKD mice had increased CMH (1.12 ± 0.10 vs. 0.85 ± 0.08 per cm2 in CKD vs. control mice, $p < 0.05$), and whole-brain RNA-seq showed significant alterations in mTORC1 pathway, with 18 DEGs involved in mTORC1 signaling in CKD compared with controls. qPCR and immunohistochemistry analysis confirmed CKD-associated upregulation of DNA damage-induced transcript 4 (DDIT4), upstream component of the mTORC1 pathway. ATII-induced HTN more than doubled CMH formation (CMH count 1.44 ± 0.17 vs. 0.61 ± 0.23 per cm2 in HTN vs. control mice, $p < 0.01$), without significant alteration of mTORC1 pathway. Treatment of CKD mice with mTOR inhibitor rapamycin significantly reduced brain CMH burden (16% reduction in CMH count; 52% reduction in CMH area, $p < 0.05$). CKD, PD, and HTN models all showed significant microglial activation, and microglial depletion in CKD and HTN models mitigated effects on CMH.
Conclusion: We demonstrate that PD enhances CMH in a HTN model, while CKD induces CMH formation with an mTORC1 signature that appears to be CKD-specific. These findings emphasize the importance of non-traditional risk factors and pathways for stroke and cerebrovascular disease.

GLUCOCORTICOID RECEPTOR SIGNALING PROMOTES ASTROCYTE MATURATION TO RESTRICT NEURONAL PLASTICITY

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Sensory experience shapes the development of neural circuits during early-life windows of heightened plasticity known as critical periods. This process has been extensively studied in the mammalian primary visual cortex (V1), where transient monocular deprivation in early life produces lasting cortical blindness for the deprived eye. Fast-spiking parvalbumin-expressing (PV+) interneurons, which innervate the soma of pyramidal neurons, gate the onset of critical periods by enabling plasticity within cortical networks. Although the molecular pathways that initiate critical period opening have been widely studied, the specific cues that terminate developmental plasticity remain poorly understood.

Here we examine the experience-dependent specification of mouse V1 across postnatal development using paired single-cell transcriptomic and chromatin accessibility sequencing. In addition to identifying the activity-dependent gene programs that emerge within each cortical cell type, we find that light exposure around eye-opening elevates circulating corticosterone (CORT) levels and promotes the recruitment of the glucocorticoid receptor (Nr3c1/GR) to chromatin selectively in astrocytes. Astrocyte GR signaling activates an extensive gene regulatory program that includes canonical astrocyte maturation genes and drives astrocyte morphogenesis. Features of this gene program are shared across other developing mouse brain regions and are conserved during human brain development. Selective deletion of GR in V1 astrocytes induces a neotenic state characterized by diminished formation and maintenance of perineuronal nets (PNNs) on neighboring PV+ neurons - a key hallmark of critical period closure - reactivation of axonal plasticity gene expression, and reopening of experience-dependent ocular dominance plasticity in adult animals. Collectively, these findings identify GR as a key regulator of astrocyte maturation that restricts developmental plasticity. Glucocorticoid regulation of astrocyte maturation may also mediate the effects of early-life stress across the brain, and the disruption of this process may contribute to neuropsychiatric disease.

THERAPEUTIC EXPOSURE TO AMPHETAMINE IN ADOLESCENCE ENHANCES SUSCEPTIBILITY TO INTESTINAL INFLAMMATION IN A SEX-DEPENDENT MANNER

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Adolescence is a critical developmental window during which neural, immune, and gastrointestinal systems undergo rapid maturation, and vulnerability to chronic disease increases. This period coincides with the rising incidence of inflammatory bowel disease (IBD). Although environmental factors are recognized as contributors to IBD initiation and relapse, the specific exposures that increase disease risk during these critical developmental windows remain poorly defined. Lately, the use of stimulant medications in the pediatric population has significantly increased, with amphetamine (AMPH) and related compounds are among the most frequently prescribed. Prior work from our laboratory and others has demonstrated that stimulant exposure increases gut permeability and alters microbiota composition, both of which are characteristic of IBD. However, whether AMPH exposure during this vulnerable developmental stage alters gut homeostasis or increases susceptibility to intestinal inflammation remains unknown. Therefore, here we tested the main hypothesis that therapeutic AMPH exposure during adolescence, by altering microbiota composition, can increase the vulnerability to intestinal inflammation. To this end, we exposed adolescent male and female mice to a low, clinically relevant AMPH dose and a mild dextran sulfate sodium (DSS) regimen, designed to create an inflammation-prone intestinal environment. Disease severity was evaluated by histopathology, inflammatory gene expression, and fecal lipocalin-2 levels, and 16S rRNA sequencing was performed to determine whether AMPH exposure was associated with shifts in microbial community. We found that, in contrast to saline-treated mice, AMPH exposure significantly exacerbated DSS-induced intestinal pathology only in female animals, demonstrating a sex-dependent effect under susceptible conditions. However, microbiome profiling unexpectedly did not reveal the anticipated compositional changes. Together, these findings identify adolescent psychostimulant exposure as a potential disease-modifying factor that can worsen intestinal inflammation and may contribute to IBD risk, highlighting a previously underrecognized and potentially modifiable contributor to disease susceptibility.

ANDROGEN SIGNALLING CONTROLS SEX DIFFERENCES IN THE NEURONS OF THE VENTRAL PREMAMMILLARY NUCLEUS

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Neurons in the hypothalamus sense peripheral factors through a semi-permeable barrier, establishing an interface between the blood and the brain. The ventral premammilary nucleus (PMV) of the hypothalamus is a cluster of neurons that is implicated in the control of sexual maturation, fertility and aggression. How PMV neurons control complex sex-biased physiological traits is poorly defined.

We first analysed the gene expression profile of PMV neurons in both sexes. To do this, we microdissected the area of interest using reporter mice that express the fluorescent tdTomato protein in a Cre-dependent manner (Tac1Cre-Ai14-loxP-STOP-loxP mice). Strikingly, RNA sequencing revealed that PMV neurons are clearly sex-biased, with over 500 genes differentially expressed between the sexes (p-value <0.01). In males, enriched pathways included numerous hormonal receptors, GPCR ligand-binding factors, as well as factors controlling feeding behaviour.

Next, we asked how sex differences in PMV neurons are established. To acquire sex-biased identity and control complex sex-biased physiological traits, PMV neurons may be responsive to gonadal steroids. Screening for candidate factors has revealed that PMV neurons express Androgen receptor (*Ar*), with AR protein levels considerably higher in males. Abolishing AR signalling using the Cre-loxP system (Arfl/y, Tac1-Cre) feminised the gene expression profile of PMV neurons: of 50 top male-biased genes, 40 were down-regulated in AR knock out males compared to controls. Further, out of the 50 genes downregulated in $AR^{Tac1Cre}$ males compared to control, over half were enriched in the PMV compared to bulk hypothalamus tissue, highlighting the role of AR signalling in establishing PMV neuronal identity.

Given the prior evidence that PMV neurons also express satiety hormone leptin receptor (LEPR), we asked if there is signalling crosstalk between leptin and adrogen signalling in the PMV. RNA hybridisation analysis showed that PMV neurons express both *Ar* and *Lepr*. Deleting LEPR using Tac1-Cre driver showed no difference in body weight, glucose, or insulin sensitivity under a standard chow diet provided ad libitum, and only minimal changes in the transcriptional profile. Challenging $Lepr^{Tac1Cre}$ mice with high-fat diet showed impaired insulin sensitivity in knock out males compared to controls, while insulin signalling in females appeared unaffected.

Together, these findings establish that PMV neurons show sex differences, that are largely controlled by androgen receptor signalling in males. Additionally, PMV neurons integrate nutritional status with gonadal steroid signalling to control complex sex-biased physiological traits.

CHANGES IN GUT-BRAIN INTERACTIONS FROM FASTED TO FED STATE

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Disorders of gut-brain interaction (DGBIs) are functional gastrointestinal diseases characterized by altered gastrointestinal motility and visceral hypersensitivity (Sperber et al., 2021). Functional Magnetic Resonance Imaging (fMRI) studies in these populations have identified altered connectivity of brain regions involved in afferent signaling, interoceptive awareness, and sensorimotor processing (Icenhour et al., 2017; Sclocco & Fisher, et al., 2022). These differences are likely due to increased integration between attentional, affective, and sensory processing of interoceptive visceral afference (Liu et al., 2015; Sclocco & Fisher et al., 2022). While assessment of connectivity in DGBIs has become more common, exploration of changes from fasted to fed states in healthy adults is limited.

Here we investigated resting functional connectivity using 3 Tesla fMRI in 17 healthy adults (mean age: 26). The nucleus of the solitary tract (NTS), responsible for relaying visceral afference, was used as a seed to estimate connectivity to the whole brain. Images were collected pre and post ingestion of a high-calorie contrast meal. Additionally, cinematic 4D volumetric gastric scans, were collected pre- and post-meal, segmented to isolate gastric volume, and used to assess gastric accommodation (gastric volume change/ volume ingested).

When contrasting fed and fasted NTS-to-whole brain connectivity, three clusters show significant change in connectivity ($p<0.05$, $Z>2.3$). Specifically, NTS connectivity to the right primary motor cortex and left primary somatosensory cortex show an increase in connectivity after the meal, suggesting that NTS connectivity to somatomotor regions increases immediately post meal. The third cluster, located in the medial prefrontal cortex (PFC), shows a decrease in connectivity. Further, we extracted the peak voxel z-statistic from each of the clusters and correlated it with gastric accommodation. We found a negative correlation between NTS-to-motor cortex connectivity and accommodation, i.e., greater connectivity was accompanied by lower gastric accommodation ($r=-0.55$, $p=0.035$).

Together, these findings suggest a shift whereby NTS connectivity switches from a higher order cognitive network to sensorimotor processing brain regions immediately post meal ingestion. Within the primary motor cortex, this shift corresponds to a lesser ability of the stomach to expand to accommodate the food volume, which may be due to altered top-down gastric signaling. Thus, future work should assess the impact of neuromodulatory, top-down treatments on NTS-to-sensorimotor connectivity post-meal.

SEMAPHORIN 6D MAINTAINS AMYGDALAR NEURAL INTEGRITY TO COORDINATE EMOTIONAL, METABOLIC AND INFLAMMATORY OUTPUTS

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The crosstalk among neural, metabolic, and immune systems is pivotal for maintaining physiological homeostasis. Recent studies highlighted the essential roles of this crosstalk in various peripheral tissues, such as liver, adipose tissue, and intestine. However, whether and how the brain regulates the coupling of these systems remains to be elucidated. Here we show that semaphorin 6D (SEMA6D), an axonal guidance molecule, maintains amygdalar neural integrity to coordinate emotional, metabolic and inflammatory outputs. Through genome-wide analyses, we found that SEMA6D is associated with both psychiatric and metabolic traits in human. To examine the roles of SEMA6D in neural, metabolic, and immune responses, we performed behavioral, metabolic and hematopoietic analyses of *Sema6d*$^{-/-}$ mice. First, *Sema6d*$^{-/-}$ mice showed increased anxiety. Second, high-fat diet feeding induced abnormal metabolic and hematopoietic responses in these mice, such as attenuated obesity and exaggerated myelopoiesis. Third, these metabolic and hematopoietic abnormalities in *Sema6d*$^{-/-}$ mice were due to due to enhanced sympathetic signaling via the *β3*-adrenergic receptor. Mechanistically, SEMA6D-mediated synaptic maturation and *γ*-aminobutyric acid transmission in the amygdala is responsible for coordinating emotional, metabolic and inflammatory outputs. In conclusion, these results highlight the essential role of amygdalar SEMA6D for coupling emotional, metabolic, and inflammatory responses.

A REAL-TIME IN VIVO PLATFORM TO STUDY GASTROINTESTINAL MOTILITY AND GUT–BRAIN INTERACTIONS

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A major barrier in gut-brain research has been the lack of tools to monitor gastrointestinal activity in vivo. Most assays of GI function measure a single time point, often after animal sacrifice, and therefore are poorly suited to study dynamic gut-brain interactions. X-ray fluoroscopy enables the continuous measurement of gut motility in behaving animals, but this technique has not been widely used to study body-brain signaling. Here, we have developed approaches to use x-ray fluoroscopy to monitor GI motility in behaving mice and integrate this with simultaneous neural recordings and circuit manipulations. We have validated this approach by examining how ingestion of different types of solutions differentially affects stomach and intestinal function. I will also describe how GI motility is altered by manipulating gut hormones, enteroendocrine cells, and the vagus nerve.

CXCL12 REGULATES HYPOTHALAMIC NEURONAL MIGRATION THROUGH RNA-MEDIATED POST-TRANSCRIPTIONAL MECHANISMS

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Cell migration is a fundamental process in embryonic brain development, orchestrated by tightly regulated signaling molecules that ensure proper neuronal positioning and circuit formation. Among these signaling factors, CXC motif chemokine ligand 12 (CXCL12) functions as a potent chemotactic cue that directs neuronal precursor movement during development. CXCL12 is produced by maternal tissues and can be transferred to the embryo during fetal development, where it guides stem and neuronal migration. During embryogenesis, CXCL12 regulates cerebellar granule cell movement and has been implicated in hypothalamic neurogenesis, particularly within the paraventricular nucleus (PVN). Neuronal migration is essential for establishing functional brain architecture, as newly generated neurons must travel from their site of origin to their final destination. Based on its established chemotactic properties, we hypothesized that CXCL12 stimulates neuronal migration without significantly affecting proliferation.

RNAseq was used to examine differential gene expression of hypothalamic neurons after 24 hours of treatment with 50, 100, and 200 ng/mL of CXCL12. FASTQ files were aligned, and splice variant counts were determined. The differential gene expression analysis was conducted using the iDEP (integrated Differential Expression and Pathway analysis) platform.

At the 1.2 FC threshold, 40 overlapping genes were detected (35 downregulated, 5 upregulated). At 1.5 FC, 39 genes were identified (35 downregulated, 4 upregulated), and at 2.0 FC, 38 genes were observed (35 downregulated, 3 upregulated). Among these targets, ENSRNOG00000063783 was alternatively spliced and demonstrated sequence similarity to Hnrnpa3, an RNA-binding protein functionally related to Cpeb4, a gene consistently found to be downregulated across all concentrations of CXCL12. Both Hnrnpa3 and Cpeb4 encode RNA-binding proteins that regulate alternative splicing and mRNA translation, processes essential for cytoskeletal remodeling, polarity establishment, and adhesion dynamics during neuronal migration. Post-transcriptional regulation of migration-associated transcripts enables neurons to rapidly adjust protein expression in response to chemotactic cues such as CXCL12. Downregulation of Cpeb4 and alternative splicing of Hnrnpa3-like transcripts suggest that CXCL12 may modulate neuronal migration partly through RNA regulatory mechanisms. Collectively, this analysis reveals additional RNA regulatory targets potentially involved in CXCL12-driven migratory processes and provides a foundation for future mechanistic studies of alternative splicing in embryonic neurogenesis.

MATERNAL HIGH-FAT DIET IS ASSOCIATED WITH MICROBIOME-LINKED METABOLOME SHIFTS AND HYPOTHALAMIC HISTONE MODIFICATIONS IN OFFSPRING

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Pregestational maternal obesity is a strong perinatal risk factor for neurodevelopmental disorders, including autism spectrum disorder (ASD). Despite strong epidemiological evidence, the underlying mechanisms by which the maternal metabolic state is translated into altered molecular programs in the offspring brain remain poorly defined. Our prior work using a mouse model for diet-induced obesity shows that perinatal maternal high-fat diet (MHFD) can induce ASD-like social behavior deficits and underlying synaptic deficits in offspring, which are associated with gut microbiota dysbiosis. Here, we are investigating the relationship between MHFD-induced changes in the offspring gut microbiome and microbially-associated metabolome with offspring brain epigenomic states.
Consistent with prior studies, fecal shotgun metagenomics revealed a distinct microbial community structure in MHFD *versus* MRD offspring, including differential representation of multiple species and separation in beta-diversity. In parallel, untargeted metabolomics followed by metabolite set enrichment analysis indicated remodeling of fecal and serum metabolic pathways, including pathways related to histidine and methylhistidine metabolism. We further quantified short-chain fatty acids, microbiota-linked metabolites known to influence chromatin state, and observed elevated serum butyrate and propionate in MHFD offspring.
To connect these peripheral shifts to central gene regulation, we used CUT&Tag, an epigenomic profiling method for histone modifications, to map H3K27ac (active) and H3K27me3 (repressive) modifications in adult hypothalamus and whole embryonic brain. We performed bulk RNA-seq on the same tissues. Pathway-level analyses of the epigenomic and transcriptomic datasets indicated alterations in gene programs related to synaptic function and metabolic regulation, which were more prominent in adult hypothalamus than in whole embryonic brain. In the context of ASD genetics, gene-set enrichment analysis using an ASD risk gene set curated from the SFARI Gene database revealed down-regulation of ASD risk genes in adult hypothalamus, whereas embryonic brain showed no enrichment.
Collectively, these data indicate that MHFD induces changes in circulating metabolites and brain histone modification programs in offspring that may causally contribute to ASD-like behavioral phenotypes by impacting the expression of ASD-risk genes. Moreover, the findings suggest that microbiome alterations may contribute to the observed metabolic and epigenomic changes.

24-HOUR TREATMENT OF HYPOTHALAMIC NEURONS WITH THE CHEMOKINE, CXCL12, SHOWS A DIFFERENTIAL GENE EXPRESSION PATTERN THAT CORRESPONDS TO MIGRATION

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Chemokines are key signaling molecules that regulate cell migration during development, with CXCL12 playing a central role in directing neuronal positioning in the embryonic brain. Prenatal alterations in CXCL12 signaling, including increased expression of CXCL12 and its receptors CXCR4 and CXCR7 in the hypothalamic paraventricular nucleus (PVN), have been associated with altered neurodevelopment. Based on its established role in cell migration, we hypothesized that CXCL12 will differentially affect genes associated with migration.

To investigate this, a migration assay was used and showed that CXCL12 moderately to greatly stimulated migration between 3 and 24 hours post-treatment with 50, 100, and 200 ng/mL of CXCL12. Next, RNAseq was used to examine differential gene expression of hypothalamic neurons after 3 hours of treatment with CXCL12. These concentrations of this chemokine show a graded increase in stimulating neuronal migratory behavior. The fastq files were aligned, counts determined, and differential expression analysis was conducted using the iDEP (integrated Differential Expression and Pathway analysis) web-based bioinformatics platform. Gene expression data from the 24-hour time point were analyzed using DESeq2 across three fold-change (FC) thresholds (1.2, 1.5, and 2.0), each assessed separately. Overlapping upregulated and downregulated genes were identified across the three treatments in comparison to the control.

At the 1.2 fold-change (FC) threshold, 9 overlapping genes were identified, including 3 downregulated genes (ENSRNOG00000063783, Cdhr2, and Dpp4) and 6 upregulated genes (Pmel, AABR07038881.1, Dct, Tyrp1, Syt4, and LOC100911361). When the threshold was increased to 1.5 and 2.0 FC, 8 overlapping genes were consistently detected, comprising the same 3 downregulated genes (ENSRNOG00000063783, Dpp4, and Cdhr2) and 5 upregulated genes (Dct, AABR07038881.1, Tyrp1, Syt4, and LOC100911361), with Pmel no longer meeting the stricter cutoff. These genes are involved in different aspects of neuronal migration. This indicates that CXCL12 promotes gene expression changes that are consistent with neuronal migration.

Overall, these findings support a role for CXCL12 as a key regulator of neuronal migration that is sustained 24 hours after treatment. Future studies will further investigate the specific molecular pathways underlying CXCL12-mediated migration and assess long-term functional outcomes of altered CXCL12 signaling.

COMPLEX INTERPLAY OF NEURONAL, HORMONAL RESPONSES BY GUT-BRAIN AXIS TO A DEFICIT IN ESSENTIAL AMINO ACIDS

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A deficit in protein can trigger a nutrient-specific appetite; however, the mechanism underlying this process remains poorly understood. Here, we found that a set of distinct neuronal and systemic mechanisms is activated in the microbiome-gut-brain axis to induce an essential amino acids (EAA)-specific appetite. In *Drosophila*, EAA deprivation increases the expression of CNMa in the gut enterocyte, which activates enteric neurons and ellipsoid body neurons in the brain to promote EAA intake through two complementary pathways: a rapid, direct neuronal gut-brain axis and a slower hormonal route. In parallel, CNMa suppresses the activity of sugar-sensing DH44 neurons, thereby reducing carbohydrate intake and biasing feeding toward EAAs. Similarly, protein deprivation in mice promotes EAA-specific appetite independently of FGF21 that required an intact spinal pathway. Together, these findings reveal multi-layered gut-brain mechanisms that regulate nutrient-specific feeding and maintain EAA homeostasis across species.

A GUT–BRAIN SEROTONERGIC AXIS REGULATES FOOD INTAKE

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Serotonin (5 hydroxytryptamine, 5 HT) has long been a key target for anti obesity therapy. Agents that boost 5 HT levels reliably suppress appetite and reduce body weight; for example, the weight loss effect of d fenfluramine, a component of Fen Phen, is partly mediated through 5 HT_2C receptors. Numerous studies show that 5 HT producing neurons in the dorsal raphe inhibit feeding via postsynaptic 5 HT receptors in the brain. Because 5 HT does not cross the blood–brain barrier, peripheral and central serotonergic systems were thought to function independently.

Here, we report a previously unrecognized gut–brain serotonergic axis that directly modulates feeding. Circulating 5 HT engages 5 HT receptors on circumventricular neurons within the median eminence, leading to reduced food intake. Ablation of these neurons or genetic deletion of 5 HT_1B and 5 HT_1A receptors markedly diminishes the anorectic effect. Conversely, stimulating 5 HT producing enterochromaffin cells in the gut is sufficient to suppress feeding. In addition, we show that enterotoxin induced food poisoning elevates circulating 5 HT and generates a prolonged reduction in appetite via circumventricular 5 HT receptors.

These findings unveil an alternative serotonergic pathway linking the gut and brain, establishing peripheral 5 HT acting on central 5 HT receptors as a critical regulator of feeding behavior.

VAGAL BLOOD VOLUME RECEPTORS COMPENSATE FOR HAEMORRHAGE AND POSTURE CHANGE

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Cranial nerves densely innervate the heart and vasculature, with sensory neurons reporting on blood pressure, respiratory gases and tissue damage. The roles of arterial baroreceptors in systemic physiology are well appreciated, but the functions of vagal cardiac mechanoreceptors have been more difficult to parse, in part due to the closed-loop structure of the cardiovascular system. Here we use genetic tools in mice to identify a small group of neurons that are acutely sensitive to circulating blood volume and initiate a reflex that compensates for decreased filling of the heart in an upright posture and haemorrhage. Vagal PIEZO2 neurons form characteristic end-net endings in the heart, lower blood pressure in response to optogenetic stimulation and display blood-volume-dependent responses with every heartbeat that are time-locked to atrial and ventricular systole. Knockout of Piezo2 and/or ablation of PIEZO2 neurons in vagal ganglia eliminates this heartbeat-coupled nerve activity, causes orthostatic hypotension and compromises cardiovascular stability during trauma-induced blood loss. Together, these findings demonstrate that vagal mechanoreceptors monitor the cardiac cycle and initiate a blood-volume-dependent reflex that defends the constancy of circulation.

CONTROL OF INGESTION BY THE AREA POSTREMA

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The area postrema (AP), traditionally known as the “nausea center”, contains specialized neurons that lie outside the blood-brain barrier and can sense circulating aversive signals to evoke nausea and sickness. Nevertheless, the AP can also directly detect hormones related to normal food intake and receives direct input from gut-innervating vagal afferents, raising the possibility that it also controls normal feeding. However, how the AP processes aversive and ingestive signals during behavior is unknown. Here, we performed calcium imaging in awake behaving mice to investigate how various genetically defined neuronal populations in the area postrema respond to an array of aversive and ingestive stimuli. We found that *CalcR* neurons responded minimally to aversive stimuli but were activated preferentially by food containing high sugar content. This preferential sugar response appears to be detected in the intestine as osmolarity-dependent stretch and leads to suppression of feeding. A second population, *Gfral* neurons, respond robustly to aversive stimuli, but surprisingly are also activated by fat ingestion but not by other macronutrients. Their activation by fat leads to changes in feeding and gastrointestinal motility. This selective fat activation is likely gated by endogenous anti-nausea *Gipr* neurons who silence Gfral neurons only during sugar consumption, but not during fat consumption. This suggests the existence of anti-nausea signals during the normal consumption of a meal. Altogether, our results indicate that the area postrema contains functionally heterogeneous cells that can respond to both aversive and ingestive stimuli. These findings suggest that brain regions traditionally associated with aversion may also contribute to encoding internal signals related to food intake.

DAYTIME WAKE IS ENHANCED BY AN EXTRA-CEREBRAL LIPID BINDING PROTEIN THAT BLOCKS LIGHT-INDUCED LIPID PEROXIDATION AT THE BLOOD BRAIN BARRIER, BODY SURFACE AND GUT

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We report a previously unrecognized brain vulnerability from visible light exposure that is exacerbated by high fat diets. Prior work in Drosophila identified daywake (dyw), a predicted lipid/hormone binding protein that stimulates wake only when animals are exposed to visible light. Herein we show that high fat diets (HFD) preferentially increase daytime sleep in dyw-null flies compared to wildtype flies, consistent with dyw's strong inducibility by HFD. This increased daytime sleep is causally linked to light-dependent reactive oxygen species (ROS) accumulation and lipid peroxidation at the blood brain barrier (BBB) and cortex region of the brain, events eliminated by return to darkness or dietary supplements with antioxidants. Although DYW is not detected in the brain it is produced in thousands of sensory neurons at or near the body surface and the gut where it also prevents the combination of light exposure and HFD to drive lipid peroxidation. Our findings suggest that blocking light-mediated lipid peroxidation at the surface and peripheral organs helps stimulate daytime wake by maintaining an antioxidant milieu for the brain to operate.

A DIETARY SWITCH PROMOTES SENSORY-NEURON DEPENDENT CANCER-ASSOCIATED CACHEXIA

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Sickness behaviors are seen in cancer cachexia and affect up to half of lung cancer patients, yet why certain patients develop this devastating syndrome remains largely unknown. We demonstrate that among the most common cancer mutations, loss of function of the tumor suppressor Lkb1 promotes a dramatic reduction in food intake and the development of cachexia in pre-clinical genetically engineered models of lung cancer. In an attempt to improve caloric intake by placing tumor bearing animals on high-fat, energy dense diets, we paradoxically observed a dramatic exacerbation in anorexia and cachexia only in animals harboring Lkb1-mutant tumors. We demonstrate this diet-induced cachexia is mediated through local, Ptges mediated production of prostaglandin E2 and the depletion of omega-3 eicosanoids, without impacting circulating factors. Genetic and pharmacological inhibition of tumor prostaglandin synthesis or dietary fueling with omega-3 eicosanoids improves anorexia and cachexia. Importantly, we demonstrate that local cachexia signaling is mediated by lung sensory neuron signaling as its abrogation by vagotomy and chemogenetic inhibition improves cachexia-associated sickness.
Our study establishes a role for localized signals to sensory neurons rather than circulating factors in the development of cachexia and highlights a novel role of the peripheral nervous system in cancer cachexia.

COCAINE-INDUCED GUT DYSBIOSIS FACILITATES ADDICTION-LIKE BEHAVIORS

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Addiction is a chronic, relapsing disorder characterized by compulsive drug use despite adverse consequences. Addiction and substance use disorders (SUDs) affect millions worldwide and cause substantial socioeconomic burdens. Although some pharmacological and behavioral treatments are available, their low success rates underscore the need for novel therapeutics. Lately, clinical and preclinical studies have reported alterations in gut microbial composition in animal models and individuals with SUDs. Furthermore, microbiome shifts have been associated with escalation of drug use and transitions into withdrawal or treatment, posing the microbiome as an exciting new avenue that can be used to modulate brain function and behavior. However, developing microbiome-based therapies requires a deeper understanding of the mechanisms behind these interkingdom interactions. To this end, we first assessed how cocaine exposure alters gut microbiome composition, then explored the contribution of specifically selected microbial members in addiction-like behaviors. We found that repeated cocaine exposure reshapes the gut microbiota in male mice, increasing the Firmicutes-to-Bacteroidetes ratio and altering alpha and beta diversity. Based on these results, using in vivo approaches in germ-free, antibiotic-treated, and conventional mice, we identified a specific Firmicutes taxon that strongly modulates cocaine-induced behavioral phenotypes. Furthermore, using pharmacology strategies and in vitro bacterial assays, we dissected not only a mechanism by which cocaine modulates the gut microbiome composition, but also a molecular pathway through which Firmicutes impact cocaine-induced plasticity and addiction-like behaviors. Overall, our findings advance the gut–brain axis field by identifying addiction-related microbiome–host interactions with translational relevance to cocaine use disorders.

OVARY-DERIVED SIGNALS COUPLE OOGENESIS TO NUTRIENT-SPECIFIC APPETITE

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Maintaining organismal homeostasis requires mechanisms that coordinate the metabolic needs of individual organs with whole animal nutrient intake. Although nutrient sensors and central pathways regulating hunger have been extensively characterized, how peripheral organ physiology influences nutrient specific appetites remains poorly understood. Here, we identify a previously unrecognized signalling axis, originated in the ovary, that modulates yeast appetite in *Drosophila melanogaster*. Through a targeted germline RNAi screen, we find that perturbations in oogenesis consistently and selectively increase yeast appetite without broadly altering sugar intake. These manipulations disrupt oogenesis progression, producing a shared signature of increased vitellogenic follicle accumulation and reduced number of mature (stage 14) oocytes. This shift is accompanied by decreased expression of the relaxin like hormone Dilp8, and loss of Dilp8 recapitulates the feeding phenotype. We show that this ovarian regulation of nutrient specific appetite is independent of amino acid state but requires mating, indicating integration with Sex Peptide–mediated reproductive activation. Together, our findings uncover a dual signal mechanism that couples oogenesis progression to nutrient selection, positioning the ovary as an active regulator of whole organism nutritional decisions. This work provides a conceptual framework for how reproductive tissues communicate their physiological demands and raises the possibility that analogous ovary derived signals may shape nutrient specific appetite and metabolic states in other animals.

PARSING THE PUMP: DISTINCT VAGAL SENSORS FOR CARDIAC PRELOAD AND AFTERLOAD

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At its core, the heart is a pump with two interfaces - preload, determined by venous filling, and afterload, imposed by the arterial load. This raises a central question: how does the body know when the heart is underfilled or overloaded? Here, we systemically identified vagal sensory neurons that respond to distinct cardiac signals using two-photon based *in vivo* calcium imaging of the nodose ganglion, and determined their molecular identities through post-hoc spatial transcriptomics. We found that cardiac preload was sensed by the vagal preload sensors. In contrast, cardiac afterload is monitored by vagal afterload sensors, and engagement of this pathway stabilizes cardiac contractility and rhythm during change in afterload. Together, these findings define the preload- and afterload-responsive vagal-cardiac pathways, revealing functionally distinct sensors that monitor mechanical state at the entry and exit of the heart.

COGNITIVE IMMUNITY: ANTICIPATORY BRAIN MECHANISMS IN THE REGULATION OF IMMUNE RESPONSES

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Effective defense against pathogens requires not only rapid immune responses but also mechanisms that anticipate potential threats. Traditional immunology has largely conceptualized host defense as a reactive process initiated after pathogen entry. However, accumulating evidence indicates that the nervous system can proactively modulate immune function. Within the scope of this project, we investigate the hypothesis that the brain can predict infectious threats and adjust immune responses in advance, an anticipatory process referred to here as cognitive immunity. This framework considers the central nervous system as a component of host defense that integrates sensory, social, and contextual information to influence physiological immunity prior to physical exposure to pathogens.

The project combines methods from neuroscience, immunology, and psychology to characterize neuroimmune interactions across behavioral, neural, endocrine, and cellular levels. Using immersive virtual-reality paradigms, pathogen-related scenarios are simulated while brain activity, neuroendocrine and hormonal signaling, and immune responses are measured in humans. Additionally, psychological mechanisms such as disgust, the core component of the behavioral immune system, are investigated in how they modulate these physiological responses. Together, this work examines whether predictive brain processes can translate into measurable changes in biological immune function. Our findings indicate that perceived infectious threats, even when virtual, can alter innate immune activity, including modulation of circulating immune cell subsets and inflammatory signaling. Neuroimaging results further suggest that multisensory brain networks representing the space immediately surrounding the body (i.e., Peripersonal Space - PPS) contribute to anticipating pathogen contact, together with areas of the salience network, and engage neuroendocrine/hormonal pathways via the Hypothalamus-pituitary-adrenal (HPA) axis. Individual differences in personality traits, such as disgust sensitivity, and social factors also shape these anticipatory responses, revealing variability in how cognitive and emotional processes regulate immunity. Ongoing work aims to map the full pathway from threat perception to immune activation by integrating brain imaging with molecular immune profiling in the same participants. Additional studies examine how pathogen contact prediction mechanisms translate into defensive motor behavior (motor preparation to approaching threats) and alterations in self-representation, as induced by virtual embodiment paradigms. Together, this research seeks to describe how predictive brain functions interact with physiological immunity.

BRAIN-ENGRAFTED MONOCYTE-DERIVED MACROPHAGES FROM BLOOD AND SKULL-BONE MARROW EXHIBIT DISTINCT PROPERTIES

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Microglia arise from yolk sac (YS) progenitors and are thought to persist throughout life with minimal input from adult hematopoiesis. However, whether brain-engrafted monocyte-derived macrophages (MDM) exist at homeostasis and during turnover, and how they function relative to yolk sac-derived microglia (YSM) remain unsettled. Here, we combine lineage tracing, pharmacological microglia depletion, and multi-omics profiling to define the ontogeny, identity, and function of MDM in the mouse brain. Despite sharing the parenchymal milieu, MDM display transcriptional and epigenetic landscapes distinct from YSM. Fate-mapping reveals that newly engrafted MDM transiently express CD206, echoing a developmental stage of embryonic microglial precursors. The engraftment and polarization of MDM are modulated by the CSF1R ligand IL-34 and the chemokine receptor CCR2. Furthermore, parabiosis and skull-flap transplantation reveal that both blood and skull marrow supply the niche via distinct routes, yielding origin-biased MDM states. Functionally, engraftment of MDM increases the number of demyelinated axons during cuprizone-mediated demyelination. Together, our study defines the cellular dynamics, core molecular features, heterogeneous origins, and context-dependent roles of brain parenchymal MDM across homeostasis, turnover, and CNS pathology.

SPATIAL TRANSCRIPTOMIC ATLAS OF SPINAL SYMPATHETIC NEURONS DELINEATES COLD-INDUCED NEURAL ACTIVATION PATTERNS

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The sympathetic nervous system orchestrates the regulation of diverse organ systems to maintain homeostasis and mediate responses to various stressors. Recentl advances in single-nucleus RNA sequencing (snRNA-seq) have enabled the classification of spinal sympathetic preganglionic neurons (SPNs) into distinct subtypes based on their transcriptomic profiles. However, the precise anatomical distribution of these subtypes across the thoracic, lumbar, and sacral segments of the spinal cord remains largely unresolved. Moreover, the mechanisms underlying the selective activation of discrete SPN subtypes in response to specific stressors are yet to be elucidated. Advances in spatial transcriptomics (STx) technologies now permit spatially resolved gene expression analysis at single-cell resolution, which is critical for examining the sparsely distributed SPNs. In this study, we reanalyzed existing snRNA-seq datasets of SPNs to refine subtype discrimination with a targeted probe panel for multiplexed in situ hybridization using the 10X Genomics Xenium platform. This enabled the generation of a comprehensive STx atlas of SPNs at single-cell resolution. This spatial atlas delineates the segmental localization of SPN subtypes along the spinal cord, revealing that certain subtypes exhibit segment-specific distribution patterns. To explore SPN activity under physiological stress, we applied the Xenium platform to mice subjected to cold ambient tempratures, a condition known to elicit thermogenic and metabolic responses via the SPN activation. We observed the induction of immediate early genes (IEGs) expression, a proxi of neuronal activation, in distinct SPN subtypes. Collectively, these findings demonstrate that SPN subtype activation is tightly regulated to facilitate physiological adaptations under stress and suggest that specific SPN subtypes are enriched within defined spinal segments, potentially regulating discrete target organs. This dataset establishes a basic resource for the targeted modulation of organ-specific functions, with potential implications for future therapeutic applications.

HIGH TONIC LOCUS COERULEUS ACTIVITY ACCELERATES MURINE TRIPLE-NEGATIVE BREAST CANCER PROGRESSION VIA SYMPATHETIC IMMUNE CROSSTALK

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Activity of sympathetic neurites in the breast cancer tumor microenvironment (TME) has been associated with increased inflammatory tone and poor anti-tumor immunity. These neurites are part of the sympathetic nervous system, which is activated by discrete CNS nuclei that regulate arousal, yet relationships between these systems in the context of cancer have not been explored. Here, we used polysynaptic retrograde tracing with Pseudorabies virus (PRV-614) injected into primary syngeneic E0771 triple-negative breast tumors in the inguinal mammary fat pad. We combined whole-brain immunofluorescence with iDISCO clearing of the thoracic spine and lightsheet imaging to simultaneously visualize the tumor-innervating neurons of the sympathetic chain and their inputs from the CNS. PRV-614 reached thoracic sympathetic chain ganglia (T10–12) ipsilateral to the tumor 72 hours post-injection, identifying this as the primary tumor-innervating population. After 144 hours, PRV-614 was visible in the noradrenergic locus coeruleus (LC-NE), indicating a polysynaptic connection between these populations. High tonic LC-NE population activity is closely associated with increased wakefulness, stress, and sympathetic tone. To observe the relationship between tonic LC-NE activity and tumor progression, we performed 24-hour fiber photometry at the LC-NE in unperturbed E0771-bearing mice throughout tumor development. We found that higher levels of tonic LC-NE activity prior to and during progression correlate with larger final tumor volumes. To measure the effect of high tonic LC-NE activity on E0771 tumors, we administered daily one-hour tonic frequency optogenetic stimulation of LC-NE and monitored tumor progression. LC-NE stimulation accelerated E0771 tumor development, resulting in larger lesions. Flow cytometry and single-cell RNA sequencing of tumors from LC-NE-stimulated mice revealed poorer overall immune infiltration and upregulation of inflammatory transcripts, including S100A8/A9 (calprotectin), Il1a, and CSF3 across cell types, indicating a pro-inflammatory shift in the TME. These findings implicate LC-NE as a modulator of breast cancer progression and anti-tumor immunity via a sympathetic–immune axis and link CNS arousal circuitry to inflammatory dynamics in murine breast cancer.

MULTISENSORY MATERNAL-INFANT INTERACTIONS UNDERLYING ATTACHMENT IN RODENTS

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Early interactions with caregivers are critical determinants of infant survival and social development. However, we know little about how the infant brain encodes parental information or how cues from the infant can promote parental behaviors. Infants develop strong attachments to maternal cues, and this preference endures into adulthood, a phenomenon termed imprinting. Imprinting thus provides a powerful model for studying how transient early-life experiences shape neural circuits and have long-lasting effects on animal behavior. Our study asks two questions: 1. What are the sensory cues from dams that determine imprinting in infants? 2. How do cues from the infant regulate maternal behavior?

We established an imprinting paradigm in which infant mice encode maternally associated odors and formed lasting preferences for these odors well into adulthood. Our data surprisingly revealed that male pups form greater preferences for odors associated with dams than female pups. To determine whether sex-specificity in imprinting is a result of differences in maternal care, we used high-resolution videography, finding that mouse dams lick male pups more than female pups. We hypothesize that gentle touch from the dam supports imprinting in mice. We discuss experiments to test whether the activity of specific gentle touch sensing neurons is required for imprinting in the infants.

How do dams distinguish male and female pups? Previous research has demonstrated sex-differences in the repertoire of pheromones released by male and female rodents. We hypothesize that differential pheromone release by male and female pups underlies behavioral differences in maternal care. Our experiments aim to identify the sensory mechanisms used by dams to distinguish male and female pups. Our data point to a chemosensory and behavioral loop between mothers and infants that might provide a paradigm to understand the development and evolution of mechanisms underlying attachment and social development.

PLACENTAL NEUROENDOCRINE CONTRIBUTIONS TO TRISOMY 21 NEURODEVELOPMENTAL OUTCOMES

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Placental abnormalities are associated with neurodevelopmental risk, yet the role of secreted placental factors in early brain development remains poorly understood. Down syndrome results from trisomy of chromosome 21 (T21), affecting 1 in 700 live births, and presents with variable phenotypic severity, including intellectual disability and increased risk for other neurodevelopmental disorders. The first trimester is a critical developmental window during which placental endocrine function is established and neuronal differentiation begins. In T21, structural and functional alterations emerge in the placenta and brain during this period. T21 placentas exhibit altered cytotrophoblast (CTB) fusion to form syncytiotrophoblast (STB), the major secretory cell type of the placenta, and aberrant endocrine function. T21 brains show reduced neural progenitor proliferation and altered neurogenesis, leading to abnormal cortical lamination. Despite clear placental dysfunction in T21, research has focused almost exclusively on cell-autonomous brain defects, leaving the contribution of placental neuroendocrine dysfunction to neurodevelopmental outcomes largely unexplored. Comprehensive characterization of the STB secretome and its abnormalities in T21 during early pregnancy has received limited attention. To better understand T21-associated STB abnormalities and identify key neuroendocrine factors that impact early human neurodevelopment, we derived trophoblast stem cells (TSCs) from T21 (n=4) and euploid (n=4) human induced pluripotent stem cells (hiPSCs) and differentiated them into STBs. Transcriptomic analysis of iPSCs, TSCs, and STBs revealed cell type-specific impacts of T21 on genome-wide gene expression and alterations in the TSC-to-STB differentiation trajectory, consistent with impaired TSC fusion in our iPSC-based model and prior first-trimester placental explant studies. Secretory proteomics analysis of STB-conditioned media identified peptide factors secreted by human STBs and changes to this signaling profile in T21. Computational cell-cell communication analysis of the secretome profiles generated candidate neuroendocrine factors that may modulate neurodevelopmental processes.
Our findings from the hiPSC-derived T21 placental model provide novel insights into the placenta's non-cell-autonomous contribution to neurodevelopmental outcomes. This work has broad implications for understanding placental-brain signaling and potential interventions for conditions with compromised placental function and increased neurodevelopmental risk.

APOE-DEPENDENT LIPID HANDLING BY MEDIAN EMINENCE MICROGLIA PRESERVES MYELIN INTEGRITY AND METABOLIC FUNCTION

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Microglia regulate hypothalamic control of systemic metabolism, but the mechanisms underlying their contribution remain unclear. We identified a distinct apolipoprotein E (ApoE)+ microglial population enriched in the median eminence (ME), a brain region involved in sensing peripheral cues and metabolic regulation. These microglia engage multiple functional programs related to lipid handling, interferon signaling, and stress responses that are differentially regulated within the ME. Consumption of a Western diet (WD) increased interferon signaling and lipid accumulation in ME microglia. Expression of the human APOE4 isoform in mice exacerbated microglial lipid dysregulation, interferon signaling, and impaired ME myelin organization. Deleting APOE in microglia attenuated their ability to couple lipid accumulation to interferon signaling, identifying microglial APOE as a cell-intrinsic determinant of interferon responses. Finally, selective activation of liver X receptor signaling using synthetic HDL nanoparticles restored microglial lipid homeostasis, improved hypothalamic leptin responsiveness, and limited weight gain in WD–fed mice. Together, these findings define an Apoe-dependent regulatory program in ME microglia that is therapeutically targetable and clarify how nutritional stress disrupts hypothalamic control of metabolic homeostasis.

MULTI-OMIC ASSESSMENT OF INSULIN RESPONSIVENESS IN HPSC-DERIVED NEURONS: A PATHWAY TO POTENTIAL THERAPEUTICS FOR METABOLIC DISORDERS.

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Insulin is a key neuroendocrine regulator of metabolic homeostasis. In addition to its role in peripheral glucose regulation, a target area of many clinically approved therapies, insulin signaling also exerts critical functions within the central nervous system (CNS). In the CNS, the hypothalamus serves as a regulator of metabolic homeostasis through insulin-mediated pathways. Dysfunction of the hypothalamus and impairments in insulin signaling cascades (commonly termed insulin resistance) are major risk factors for metabolic disorders such as type 2 diabetes, obesity, and Alzheimer's disease. While disruption of insulin signaling is the focus of many studies, the cellular mechanisms regulating these processes in human hypothalamic neurons remain poorly understood. Here we use human pluripotent stem cell (hPSC)-derived hypothalamic neurons to elucidate the mechanisms underlying insulin resistance. We characterized insulin-induced changes in transcriptomic and metabolomic profiles to identify potential mediators of insulin signaling. Integration of these multi-omic data and utilization of a recently developed drug identification pipeline aided in the identification of potential insulin-signaling modulators along with a list of clinically approved drugs that target these candidates. These candidate compounds will be evaluated in future studies to assess their ability to modulate insulin sensitivity in hypothalamic neurons. Together these findings will expedite identification of potential therapeutics for various metabolic disorders associated with insulin resistance.

TEMPORAL CONGRUENCY DRIVES THE MULTISENSORY INTEGRATION OF INTEROCEPTIVE AND EXTEROCEPTIVE INFORMATION

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The brain continuously processes signals from the external environment (exteroception) and internal bodily states (interoception) to shape our perception of the world and the body within. In the exteroceptive domain, multisensory integration across modalities such as vision and audition has long been recognized as a fundamental mechanism for forming unified percepts from distinct sensory inputs. Whether multisensory integration similarly links bodily signals with external sensory information, however, remains an open question. We used electroencephalography (EEG) and a novel heartbeat feedback task to investigate multisensory integration across interoceptive and exteroceptive channels in three independent studies. Specifically, we examined heartbeat-evoked potentials (HEPs) as objective markers of interoceptive processing, alongside stimulus-evoked potentials (SEPs) as markers of external sensory processing. We assessed how the temporal alignment between externally presented heartbeat cues and actual heartbeats modulates HEP and SEP amplitudes during the heartbeat task with auditory-visual feedback. In this task, a tone and a visually displayed heartbeat were phase-locked to an individual's cardiac cycle and periodically accelerated or decelerated. Our findings showed significant differences in HEPs, SEPs, and cardiac parameters (e.g., heart rate variability) when the stimulus was coupled to auditory-visual feedback compared to when it was uncoupled ("fasterStim HR" & "slowerStim HR"). These findings were replicated in three independent studies of healthy participants (total n= 110). Results suggest clear signs that interoceptive processing is altered by temporal locking with external information, and exteroceptive processing is altered by temporal locking with internal information. The neural and physiological markers we identified in healthy participants can inform future development of transdiagnostic biomarkers of multisensory integration and how it is altered in mental health disorders.

THE METABOLIC FUNCTIONS OF SENSORY NERVES IN ADIPOSE TISSUE

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Substantial knowledge gaps remain regarding adipose tissue sensory nerve functions and interoceptive signals from the tissue that promote afferent nerve communication to the brain. Prior work has demonstrated metabolic relevance of adipose sensory innervation through various tissue denervation methods. However, given the overlap in certain nerve markers between sensory and sympathetic and the evidence for nerve crosstalk, it remains unclear what distinct roles are carried out by adipose sensory nerves, the identify of axonal subtypes of sensory innervation, and the contributions of afferent synaptic communication to the brain versus neuropeptides released to the tissue. We have demonstrated that subcutaneous white adipose tissue (scWAT) sensory axons express classical markers of peptidergic nociceptors (Nav1.8, TRPV1, and calcitonin gene-related peptide, or CGRP), and that noxious stimuli, including inflammatory lipids, promoted afferent signaling via the dorsal root ganglia (DRG) and hypothalamus, concurrent with CGRP (sensory neuropeptide) release into the tissue. We revealed that the neuro-adipose nexus (NAN), a unique sensory nerve terminal on a subset of white adipocytes, are nociceptors. NANs consistently proliferated in number with inflammation independent of energy balance status, and even when adipose lost innervation. CGRP levels in scWAT were altered across numerous acute or chronic energy balance states, and remained chronically high in obesity even with some loss of sensory innervation of the tissue, indicating an overall sensory nerve dysfunction with metabolic disease. Viral-mediated knockdown of sensory axon TRPV1 (a prominent channel promoting CGRP release) in scWAT led to adipose dysfunction, including protection from diet-induced weight gain. CGRP impacted adipocyte lipolysis, independent of norepinephrine, and mice with an adipocyte-specific knockout of the CGRP receptor (RAMP1) had altered adiposity in a sex-dependent manner. Taken together, our studies identify interoceptive stimuli for sensory nociceptors in adipose tissue and reveal CGRP functions related to adipose tissue health and metabolic functions.

APPROACHES TO STUDY MENINGEAL MECHANISMS OF MIGRAINE

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Migraine is one of the most common neurological disorders, with a global prevalence of over 1 billion cases and 1-2% of people experiencing episodes more than 15 days per month. The meninges, a membranous structure surrounding the brain, houses branches of the trigeminal nerve that are a major source for pain sensation within the skull and thus is a focus for understanding mechanisms of headache in migraine. While the meninges exhibits an analogous structural organization to other peripheral barrier tissues like the skin and the gut, it is uniquely positioned adjacent to the brain to receive direct signals. So far, the relative contributions of meningeal cell types in causing activity in trigeminal afferents remain unclear: Although vasodilation and inflammatory signals (e.g. mast cell degranulation) have been implicated in exciting meningeal neurons, factors released by these neurons such as the neuropeptide calcitonin gene-related peptide (CGRP) have also been shown to stimulate vasculature and immune cells. Clarifying these cellular interactions and signaling events remains challenging because conventional techniques, such as cranial windows, cause trauma that alters the physiological cell states that we aim to study. For instance, surgical damage to the skull and meninges can trigger widespread mast cell degranulation, confounding baseline observations. To overcome these limitations, we refined an intact skull clearing approach that permits longitudinal optical access in awake animals for imaging and optogenetic studies. To identify regions of interest, we performed immunostaining of CGRP-positive afferents and mast cells in murine meningeal wholemounts. While these populations are found throughout the dura, we identified areas of increased axonal and cellular density, providing targets to guide in-vivo experiments. Using fluorescent reporters, we observed putative nerves and real-time blood flow that recapitulates known arterio-venous trajectories to the dural sinuses. Towards selectively stimulating meningeal afferents and understanding their contribution to migraine-like states, we validated transgenic mice display aversive behaviors upon exciting peripheral sensory neurons and customized gear for delivering light directly above the skull in freely moving mice. This emerging toolkit will enable detailed study of cellular interactions in physiologic and disease conditions that could aid in the design of improved migraine treatments.

REDUCTION OF CXCL12 DURING PREGNANCY WITH A HIGH-FAT DIET INDUCES SEXUALLY DIMORPHIC CHANGES IN OFFSPRING.

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Prenatal exposure to a high-fat diet (HFD) influences hypothalamic development, ingestive and emotional behaviors in offspring, and may be exerted through chemokine CXCL12. Prenatal HFD increases circulating CXCL12 levels in dams and upregulates its receptors in offspring's paraventricular nucleus (PVN). Prenatal CXCL12 administration mimics HFD effects, stimulating neurogenesis and enkephalin expression in PVN while increasing anxiety-like behaviors. These findings implicate CXCL12 in PVN as a mediator of prenatal HFD's effects on enkephalinergic neurons and emotional regulation. This study investigates CXCL12's role on hypothalamic development and behaviors by using a CXCL12-neutralizing antibody to block HFD effects. The dams were given HFD or HFD paired with intraperitoneal injections of CXCL12-antibody during hypothalamic development. Blood was collected and analyzed for CXCL12 levels in dams and postnatal day 0 (P0) offspring. Results reveal decreased CXCL12 levels in dams injected with antibody while HFD dams had increased levels. CXCL12 levels in P0 offspring were undetectable, suggesting maternal manipulation of CXCL12 is responsible for brain development changes. Postnatal behavioral measurements show sexually dimorphic differences in anxiety-like behavior and locomotor behavior that are reversed with the addition of the CXCL12-ab. Prenatal HFD caused males to increase locomotor activity and females to reduce anxiety-like behavior. These results show that maternal HFD-induced changes can be prevented by reducing the maternal CXCL12 signaling during development.

BRAIN HYPOGLYCEMIA DURING EXERCISE: DOES IMPAIRED GLUCONEOGENESIS LIMIT PERFORMANCE AND ALTER BRAIN METABOLISM?

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The brain relies heavily on glucose as its primary carbon source. During exercise, peripheral tissues such as skeletal muscle increase their fuel uptake to meet energy demands. Under normal physiological conditions during exercise, the body tightly regulates blood glucose levels, largely through hepatic gluconeogenic flux.
This led us to ask what occurs when the body becomes markedly hypoglycemic during exercise. Specifically, how is the brain—which requires glucose for its function—affected? Furthermore, is gluconeogenesis required to sustain exercise capacity, and is the brain involved in this regulation?
To address this, we utilized a liver-specific FBP1 (fructose-1,6-bisphosphatase 1) depleted mouse model with impaired gluconeogenesis. These mice appear normal under ad libitum feeding but become hypoglycemic more rapidly during fasting and exercise. In a treadmill endurance test, the FBP1-depleted mice fatigued significantly earlier than controls. However, there was no difference in voluntary running capacity, suggesting that their reduced exercise capacity is not due to motivational issues. Whole-brain metabolomics revealed reduced post-exercise abundance of aspartate, a TCA-linked metabolite. We are also mapping post-exercise activity patterns using whole-brain c-Fos imaging to see regional differences.
Together, these results suggest that when glucose is low, brain metabolism is affected during exercise. Ongoing work will test how these metabolic changes impact brain energy balance and the central regulation of fatigue and exercise performance.

ALTERED LEARNING IN CHRONIC PAIN: FROM BIAS IN REINFORCEMENT LEARNING AND RESPONSES TO HEARTBEATS

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Interoceptive signals — the brain's processing of internal bodily states — are closely tied to value-based decision-making. Cortical processing of cardiac activity preceding choice presentations, indexed by heartbeat-evoked potentials (HEPs), has been linked to subjective value encoding (Azzalini et al., 2021), suggesting that the heart-brain axis actively shapes how we learn and decide. Chronic pain, a condition characterized by profound alterations in bodily perception, may therefore disrupt value-based learning partly through aberrant interoceptive processing. We recently demonstrated that chronic pain patients shift reinforcement learning strategies away from global, context-independent value representations toward locally learned, context-dependent values — and that this shift is associated with pain duration but not intensity (Williams et al., 2025). Here we investigate whether interoceptive signals underlie this shift and vary across chronic pain conditions. Back pain (n = 29) and fibromyalgia (n = 18) patients and healthy controls (n = 24) completed a reinforcement learning task with simultaneous EEG. Behaviorally, overall learning performance was comparable across groups ($\chi^2(2, 72) = 3.56$, $p = 0.168$), but decision-making strategies were significantly different ($\chi^2(8, 72) = 17.32$, $p = 0.027$). Computational modeling across five models revealed that back pain patients relied significantly less on global value representations than controls and fibromyalgia patients, who did not differ from one another, demonstrating meaningful heterogeneity across pain conditions. We are now examining trial-by-trial interactions between pre-decision HEPs and computed option values across groups. We predict that larger HEP-value interactions will associate with greater reliance on global value representations, and that HEPs during learning will predict subsequent choice accuracy. These findings will illuminate how interoceptive processing shapes learning strategy selection in chronic pain, and how disrupted heart-brain communication may contribute to the formation of value representations.

HEALING TAKES SLEEP: A SLEEP-DEPENDENT FIBROBLAST STATE CONTROLS SKIN REPAIR

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Sleep is an evolutionarily conserved process essential for survival across nearly all species. However, its role in maintaining peripheral organs, particularly the skin, a barrier organ long anecdotally linked to sleep, remains largely unexplored.

Here, we demonstrate that sleep is required for skin wound healing. Under continuous sleep disruption (SD), the incisional skin wound enlarges and ulcerates, forming a chronic, non-healing ulcer with loss of diverse cell types and structures inside the wound bed. To identify the mechanism underlying this loss of regenerative capacity under sleep loss, we performed single-cell RNA sequencing to profile the cellular and molecular changes within the wound formed during SD or unperturbed sleep. We uncovered a distinct fibroblast population that arises in the wound bed only during SD. These SD-enriched fibroblasts downregulate extracellular matrix components and growth factors, while being enriched for pro-inflammatory cytokines and chemokines. Through an *in vivo* AAV-mediated functional screen, we identified that multiple pro-inflammatory cytokines derived from SD-enriched fibroblasts are sufficient to block wound healing and drive the formation of a chronic ulcer even under unperturbed sleep.

Taken together, we identified a sleep-dependent fibroblast state that emerges during sleep disruption and suppresses tissue regeneration through pro-inflammatory signaling. Importantly, the chronic ulcers formed under SD replicate key clinical features of human chronic wounds, a prevalent and burdensome public health issue affecting over 6.5 million people in the United States annually, with no FDA-approved drug to date. By uncovering the cellular and molecular pathways linking sleep loss to impaired tissue repair, our findings provide a conceptual framework and potential therapeutic targets for improving wound healing under SD and beyond.

RETHINKING THE PD GUT: A DECLINING MICROBIAL ECOSYSTEM?

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Parkinson's disease (PD) is a condition characterized by motor and non-motor symptoms such as tremor and gastrointestinal dysfunction, respectively. To more fully characterize the gut's role in PD, the gut microbiome has been a growing area of interest to researchers in the field. Previous studies on the PD gut microbiome have identified differences in the relative abundance of bacterial taxa between PD and non-PD. However, relative abundance measures are inherently proportional, meaning that an increase in one taxon leads to a perceived decrease in others, even if their absolute concentrations remain unchanged. This limitation hinders the ability to accurately quantify microbial dysbiosis and its potential mechanistic role in disease pathology. To address this gap, we measure total microbial load and absolute abundance differences in bacterial taxa between PD participants and non-PD controls.

Participants (n=112 PD, n=83 non-PD) were recruited from the Stanford Movement Disorder Clinic and local PD support groups to complete a lifestyle questionnaire and provide stool and blood samples. 96% of non-PD controls share a household with a PD participant, which helps disentangle the influence of the environment from the effects of the disease.

We found that total microbial load is decreased in PD participants compared to non-PD controls, as measured by total 16S rRNA bacterial copies per dry gram of stool ($p=0.00467$). In addition, the comparison of differential absolute abundance analyses with published differential relative abundance yielded both complementary and contradictory insights, underscoring the limitations of relying solely on relative abundance data.

For the blood samples, we performed bulk RNA sequencing on peripheral blood mononuclear cells (PBMCs). Our preliminary analyses suggest that in PD, the gut microbiome exerts a diminished regulatory influence on peripheral immune function compared to control conditions. These findings point toward a disruption in microbiome-immune crosstalk in the PD environment. We ultimately aim to provide insight into how microbial dysbiosis may contribute to PD pathogenesis and progression.

PRENATAL STRESS DYSREGULATES LUNG-BRAIN AXIS DEVELOPMENT AND IMMUNE SIGNALING

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The brain and the lungs are some of the first organs to begin developing during gestation and whose developments are not yet complete for many years after birth. Special sensory cells of the lung called pulmonary neuroendocrine cells (PNECs) are the only innervated cells of the lung epithelium and, critically, are the first specialized lung epithelial cells during development. Through secretion of signaling molecules like neurotransmitters, hormones and cytokines, PNECs signal to the brain via their vagal partners and direct local lung immune activity. Therefore, PNECs are positioned to influence the earliest communication between the lung and brain, yet it has not been described how the mechanisms of PNEC-vagal signaling might impact brain development.

One mechanism by which PNECs could impact brain development is via activation of the immune system in response to prenatal stress. Macrophages in the brain (microglia) and periphery, e.g. the gut, are known to shape nervous system development through synaptic pruning, and microglial pruning of synapses is highly sensitive to environmental perturbations, such as stress. Prenatal maternal experiences are known to impact fetal neurodevelopment and microglial inflammatory states. Understanding the roles pulmonary macrophages may play in shaping PNEC-vagal innervation and therefore lung-brain communication is a crucial gap in our understanding of the development of interoception.

Epidemiological studies demonstrate an increased risk of offspring developing adverse respiratory outcomes, such as asthma, after prenatal and early life stress. However, no studies have looked for lung-brain axis developmental differences after prenatal stress. Here we investigate the perinatal development of PNECs and their vagal innervations, as well as the inflammatory states of the lung and brain after prenatal stress. Our murine model of prenatal stress limits bedding and nesting for embryonic days 13.5-18.5 of gestation, and pups are born under control housing conditions. Using this model, we found that prenatal stress significantly increases expression of calcitonin gene-related protein—a major developmental and immune signaling molecule of PNECs—in the lung, which recapitulates clinical findings. Additionally, we report a significant increase in the pulmonary macrophage population of prenatally stressed offspring at P10. This prenatal stress also impacts developmentally regulated ultrasonic vocalization behavior of P10 pups.

With this model and preliminary data, we can now dissect the critical mechanisms directing development of the lung-brain axis. Specifically, we can explore how prenatal stress or perinatal macrophage activity impacts the organization of PNECs or their proximal neurons by early postnatal life. We hypothesize that by modulating lung-brain development, prenatal stress increases susceptibility to respiratory and neurodevelopmental disease comorbidity.

SELECTIVE HIPPOCAAMPAL HIF-1α ACTIVATION IN A MURINE MODEL OF ASTHMA–COPD OVERLAP AND ITS MODULATION BY OUABAIN

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Asthma–COPD overlap (ACO) is characterized by the coexistence of features of asthma and chronic obstructive pulmonary disease. Beyond lung pathology, accumulating evidence suggests that chronic airway inflammation may extend systemically and impact the CNS, potentially triggering hypoxia and oxidative stress–related alterations. In this context, HIF-1α, a key regulator of cellular adaptation to hypoxia, integrates inflammatory, metabolic, and redox responses, linking hypoxic signaling to immune modulation. Ouabain (OUA) an inhibitor of the Na^+/K^+-ATPase, has been described as a modulator of inflammatory and neural pathways, exerting neuroprotective effects under neuroinflammatory conditions. Therefore, this study investigated the impact of the ACO model on the CNS, focusing on hypoxia and oxidative stress mechanisms associated with stress, and evaluated whether ouabain modulates these responses. Female Balb/c mice. ACO groups were sensitized with ovalbumin(OVA)+ACF (sc,Day:0) and received EPP solution intratracheally on day 21. Challenged with OVA (intranasally) on days 22-24 and euthanasia on day 25. The ACO+OUA group was treated with ouabain (0.56 mg/kg) i.p. 1 hour before each challenge. ELISA quantified HIF-1α levels. Proteins of interest were quantified in the frontal cortex by Western blot. Data are expressed as mean±SEM by one-way ANOVA N=7(GraphPad). In the hippocampus, the ACO model significantly increased HIF-1α levels compared to the control group PBS (46±158 P<0,0070). In the frontal cortex, the ACO+OUA group decreased pNRF2 (0,1±0,2 P<0,0046), and increased IκBα levels (0,2±0,4 P<0,01) vs the PBS group. BNIP3, there was a decrease in the ACO with and without OUA compared to PBS (0,3±0,02 P<0,006). Our results suggest a region-specific CNS response in the murine ACO model, characterized by a significant increase in HIF-1α in the hippocampus, with no changes in the medulla oblongata, indicating selective rather than global hypoxia-driven activation. In the frontal cortex, reduced BNIP3 levels in both ACO and ACO+OUA groups suggest impaired mitochondrial adaptive responses. Additionally, decreased Nrf2 and increased IκBα in the ACO+OUA group indicate that ouabain modulates redox and inflammatory pathways. CEUA8314270721 FAPESP 2021/12906-0 2021/06009-6 2024/06058-5 CAPES-CNPq

INCREASED KLOTHO LEVELS INDUCED BY GESTATIONAL EXPOSURE TO VALPROIC ACID

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Valproic acid (VPA) is a drug used to treat epilepsy. Prenatal VPA exposure is linked to an increased risk of congenital malformations and neurodevelopmental disorders, characterized by cognitive and linguistic impairments, developmental delays, and an elevated prevalence of Autism Spectrum Disorder (ASD). The molecular basis of these alterations has yet to be fully clarified, necessitating the exploration of candidates such as the Klotho protein as potential mediators, given its known neuroprotective role. The objective of this study was to investigate the effects of VPA on behavior, and Klotho protein expression in cognitive-related brain regions of male mice offspring exposed to VPA in utero. Pregnant female mice (C57/BL6) were treated with VPA (300 mg/kg) or saline (vehicle) on embryonic days 10 and 12. At one month old, male offspring (n=15) were subjected to behavioral tests: the Elevated Plus Maze (EPM), Social Interaction (SI), and Social Preference (SP). After the behavioral tests, animals were euthanized, hippocampus, frontal cortex and cerebellum were dissected. ELISA assay (n=5) was performed to analyze soluble Klotho levels. Klotho was also evaluated through immunofluorescence assay (n=3) from cortical area (bregma −0.50 mm to −1.22 mm). Statistical analysis was performed using unpaired Student's T-Test, and Mann-Whitney in the GraphPad Prism. This study was approved by the Ethics Committee on the Use of Animals (CEUA nº 2945190521). In the EPM test, male VPA offspring showed an increase in time spent in the closed arms ($p=0.0147$) and a reduction in time spent in the open arms ($p=0.0174$) and in the number of entries into the open arms ($p=0.0146$). No differences were observed in the number of entries into the closed arms. In the SI test, the VPA group showed reduced interaction with an unfamiliar animal ($p<0.0001$) but a significant increase in interaction with an object ($p=0.0010$). In the SP test, the VPA group exhibited increased interaction with a familiar animal ($p<0.0001$) and more time spent in the familiar animal's compartment ($p=0.0016$). Klotho levels were increased in the VPA group in the frontal cortex in ELISA ($p=0.0045$) and immunofluorescence ($p<0.0001$) assays, while no differences were found in the hippocampus or cerebellum by ELISA. Our findings demonstrate anxiety-like phenotypes and altered social interaction/preference in male VPA offspring. Additionally, the observed increase in frontal cortex Klotho expression suggests a possible compensatory response to prenatal VPA exposure.
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INTEGRATION OF REPRODUCTIVE AND METABOLIC DEMANDS VIA TN-SST NEURONS AND ANDROGEN SIGNALING

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Somatostatin neurons in the tuberal nucleus of the hypothalamus (TN-SST) modulate food intake in mice. Specifically, activating these neurons increases food intake. However, the ablation of these cells results in sex- and context-specific effects. TN-SST ablation decreases food intake in females, but only when body fat is low and estrogens are high. It is unknown which peripheral hormonal cues control these effects and how the TN integrates these signals to modulate food intake. Here, we aim to elucidate the gonadal hormone(s) that mediate these effects. We hypothesize that TN-SST neurons sense changes in circulating gonadal hormones to modulate feeding behavior in a sex-dependent manner. To determine whether the sex difference in TN-SST neuronal ablation is driven by the presence of ovaries or a lack of testes, we ablated TN-SST neurons in combination with gonadectomy. Surprisingly, castration modulated the effects of ablating TN-SST neurons in males. This suggests the intriguing possibility that TN-SST neurons may directly sense and respond to changes in circulating testicular hormones to modulate food intake. Presently, we are examining the role of androgens on this phenotype. To do this, we are using TN-SST neuronal ablation in combination with testosterone replacement. Finally, we will investigate the role of the androgen receptor using an intersectional genetic strategy to ablate AR specifically in TN-SST neurons. Overall, this data suggests that decreases in food intake caused by the withdrawal of testicular hormones require TN-SST neurons. Together, these studies aim to pinpoint TN-SST neurons as sensors and integrators of reproductive and metabolic signals within the neural circuit that controls feeding. More broadly, this work furthers our understanding of how animals balance competing motivations for metabolic demands and reproduction.

MOLECULAR AND CELLULAR MECHANISMS OF AIRWAY SENSATION AND PROTECTION

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Every breath exposes our airways to potential threats - chemicals, gastric acid, food, or liquids - which can damage the respiratory epithelium, induce inflammation, and acutely impair breathing. Our airways have multiple sensory systems that detect these threats to trigger protective reflexes like coughing and swallowing. We found that rare epithelial cells in the trachea and larynx called neuroendocrine (NE) cells are sensitive to commonly aspirated noxious stimuli, water and acid, and upon stimulation release ATP to activate purinoreceptive sensory nerve fibers to initiate swallowing and cough-like reflexes. This work uncovered striking molecular and biophysical diversity of NE cells across the airways and revealed mechanisms by which these specialized cells serve as sentinels for activating airway protective circuits. We are now investigating whether other molecularly distinct sensory epithelial cell types contribute to airway protection, how their properties change in human airway disease, and whether dysregulation of these cells underlies disorders of airway hyper- or hyposensitivity.

ROLE OF A VENTRAL RESPIRATORY GROUP NEUROPEPTIDERGIC TONALITY IN FEAR AND METABOLIC RESPONSES

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Stress profoundly alters energy metabolism and cardiorespiratory function, yet the central circuits linking stress to peripheral metabolic regulation remain unclear. We have identified the ventral respiratory group (VRG), a brainstem respiratory rhythm-generating network, as a stress-responsive hub that coordinates breathing dynamics with whole body metabolic adaptation. The VRG contains heterogeneous neuronal populations, including the pituitary adenylate cyclase-activating polypeptide receptor PAC1R, which is known to regulate respiration and stress. We systematically investigated the role of VRG-PAC1R neurons in stress-induced metabolic and cardiorespiratory adaptation in mice. To do this, we used PAC1R floxed mice and ablated PAC1R in the VRG via viral Cre-mediated deletion (AAV2-hSyn-Cre). We then analyzed fear behavior and cardiorespiratory output using stress-enhanced fear learning (SEFL; n=20) coupled with telemetric recording. We further used c-Fos mapping (n=5), viral tracing (n=12), and spatial transcriptomics in the VRG (n=1), alongside metabolic profiling of brown adipose tissue (BAT; n=3) and liver (n=3), to evaluate central regulation of metabolism under stress. First, SEFL induced robust c-Fos expression in the VRG. Using retrograde viral tracing, we identified neuronal projections from VRG to BAT and the liver, with a subset of these neurons expressing PAC1R. Second, PAC1R ablation in the VRG, alone or with SEFL, increased freezing, while ablation plus SEFL elevated stress-induced respiration and heart rate. Third, under SEFL conditions, PAC1R ablation reduced sympathetic innervation to BAT, suppressed energy expenditure, impaired thermoregulation, and reprogrammed the BAT lipid metabolic pathways. We also observed shifts in hepatic transcriptional profiles toward amino acid metabolism and gluconeogenesis. Further, PAC1R ablation under SEFL increased glucose intolerance without alterations in insulin sensitivity. Spatial transcriptomics revealed a disrupted excitatory-inhibitory balance in the VRG after PAC1R ablation. Our findings for the first time reveal the VRG- PAC1R neuropeptidergic signaling as a key pathway in linking respiratory dynamics to stress-induced metabolic regulation.

EMPATHY BEYOND THE BRAIN: MICROBIOME AND IMMUNE SIGNATURES OF SOCIAL PAIN

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Empathy—the capacity to perceive and share another's internal state—is fundamental to social cohesion and mental health, and its dysregulation contributes to autism spectrum disorder, depression, and schizophrenia. Despite mounting evidence that the gut–brain axis influences mood and social behavior, how peripheral systems contribute to empathic processes remains unknown. We propose a fundamental reconceptualization: empathy is not solely a property of the brain, but an integrated brain-body phenomenon shaped by peripheral physiological systems.

Using our mouse model of social transfer of pain, we demonstrate that bystander mice rapidly adopt the sensory and affective state of a social partner experiencing inflammatory pain. After a brief social interaction, non-injured bystanders develop mechanical hypersensitivity, thermal aversion, facial grimace, and behavioral despair matching that of injected mice. This socially acquired pain activates the anterior cingulate cortex and nucleus accumbens, requires ACC neural activity, and is potentiated by serotonergic signaling. We now provide convergent evidence that the bystander's body is an active participant in the empathic response. First, $TRPV1^+$ dorsal root ganglion neurons are sensitized in bystanders following state matching, indicating peripheral nociceptive afferents are engaged during socially induced pain. Second, bystanders and pain partners show aligned gut microbiome shifts, with both groups demonstrating significant enrichment of Lachnospiraceae, DRG excitability, and peripheral immune tone. Third, bystanders show decreased 5-HT reuptake transporter expression on B cells, $CD4^+$ T cells, and $CD8^+$ T cells, reflecting peripheral remodeling of the 5-HT that tracks pain state matching. Fourth, untargeted serum metabolomics reveals separable profiles for bystanders with top features including microbial metabolites known to support neural health and affective regulation.

Together, these findings motivate a model in which state matching depends on a brain-initiated, peripherally amplified loop: autonomic signals reshape immune tone and remodel gut microbial composition; gut-derived metabolites and serotonin then sensitize $TRPV1^+$ DRG nociceptors, which project into spinal circuits and feed back to cortex. These studies establish the microbiome, immune system, and peripheral sensory neurons as critical regulators of empathic state sharing, and reveal novel interoceptomimetic targets for empathy dysregulation in chronic pain, depression, and ASD—accessible therapeutic entry points that bypass the CNS.

UNRAVELING CENTRAL MECHANISMS OF CLASSICALLY CONDITIONED IMMUNE-SUPPRESSION

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The brain can modulate immune responses through peripheral neuronal inputs to immune organs. Importantly, this modulation can be learned, as demonstrated by paradigms of conditioned immune suppression. During the acquisition phase of such paradigms, animals are exposed to a sensory stimulus paired with an immunosuppressive drug. Subsequently, in the evocation phase, presentation of the sensory stimulus alone is sufficient to suppress immune responses to an immune stimulant. Our goal is to dissect the mechanisms underlying conditioned immunossuppression, by comprehensively characterizing the immune responses involved and identifying the central brain regions—and the specific cell types within those regions—that orchestrate this learned immune response. Previous studies of conditioned immune effects have relied primarily on in vitro assessments, leaving the time course and magnitude of the in vivo response largely uncharacterized. To address this gap, we characterized the temporal dynamics of plasma cytokine changes following administration of an immune stimulatory challenge (concanavalin A, ConA), as well as their suppression by an immunosuppressant (cyclosporine A, CSA), in awake mice. This was achieved using implanted catheters that enable repeated blood sampling with minimal stress-free. We combined this approach with the Olink Target 48 cytokine panel, which allows simultaneous quantification of 43 immune-related proteins from small blood volumes. Using this methodology, we successfully demonstrated robust CSA mediated immune suppression in vivo. In parallel, we engineered an odor delivery system capable of precise and reliable presentation of olfactory conditioning stimuli, and preliminary conditioned immune suppression experiments are currently underway using this setup. Together, these foundational experiments establish the framework for investigating the central nervous system mechanisms underlying the learning and evocation of conditioned immune responses—brain pathways that can modulate immunity.

IN UTERO EXPOSURE TO MATERNAL PARASITIC INFECTION DRIVES DYSREGULATED RISK ASSESSMENT, SOCIAL DYSFUNCTION, AND CORTICOTHALAMIC CIRCUIT ALTERATIONS

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Chagas disease is a prevalent neglected tropical disease endemic to the Americas caused by the vector-borne parasite *Trypanosoma cruzi* (*Tc*). Acute *Tc* infection results in immune activation characterized by the induction of proinflammatory cytokines, including IL-6 and IL-17A, which play a complex role in host defense versus pathogenesis. Pathological activation of the IL-17A pathway is a proposed mediator of neurodevelopmental impairment in the maternal immune activation (MIA) model for autism spectrum disorder (ASD). MIA disrupts cortical lamination, perturbs network connectivity, and increases neuroinflammation, leading to ASD-like behavioral deficits in offspring. Given that the maternal proinflammatory response to *Tc* infection protects against neonatal infection but can also results in potentially pathogenic levels of circulating IL-6 and IL-17A, we hypothesized that *in utero* exposure to maternal *Tc* infection would adversely affect offspring neurodevelopment and behavioral outcomes irrespective of congenital transmission. Here, we report that periconceptional *Tc* infection drives expansion of the T helper 17 cell population while decreasing regulatory T cells in dams. Male and female *Tc*-exposed offspring demonstrate dysregulated risk assessment and altered social behavior in the absence of congenital infection. Analyses of cell type-specific and activity-dependent markers in the offspring brain and metagenomic sequencing of the maternal and offspring gut microbiome reveal mechanisms by which *in utero* exposure to maternal *Tc* infection alters offspring brain development and behavior. Our data identify *in utero* exposure to acute maternal *Tc* infection as a model with high construct and face validity for studying mechanisms by which maternal environmental exposures during pregnancy modify risk for neurodevelopmental and neuropsychiatric disorders in offspring and provide rationale for prioritizing women of childbearing age for vaccination against *T. cruzi*.

ROLE OF LOCUS COERULEUS PAC1 RECEPTORS IN MODULATING WHOLE-BODY ENERGY METABOLISM UNDER STRESS

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Introduction: Post-traumatic stress disorder (PTSD) is characterized by chronic dysregulation of the fear response in part due to heightened activation of the sympathetic nervous system (SNS). PTSD is also highly comorbid with metabolic disorders and is associated with maladaptive lifestyle factors, such as increased consumption of a high-fat diet (HFD). The locus coeruleus (LC) is a brainstem structure and primary regulator of the SNS that has been implicated in feeding and metabolism. However, the role of the LC in coordinating stress-induced metabolic dysregulation remains poorly understood. The LC expresses PAC1, a receptor for Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP), a neuropeptide associated with PTSD symptom severity and metabolism.
Methods: In order to investigate the role of LC-PAC1 neurons in coordinating stress and metabolism, mice with flanking loxP sites around the gene encoding PAC1 receptors (*Adcyap1r1*$^{loxP/loxP}$) were stereotaxically injected with either AAV2-hSyn-GFP control virus or AAV2-hSyn-Cre-GFP to knockdown PAC1 receptor expression in the LC. Following recovery from surgery, mice were placed on a HFD (60% kcal by fat) and underwent stress-enhanced fear learning (SEFL), a three-day stress paradigm that recapitulates key aspects of PTSD including increased fear expression. Mice were then separated into two groups: a group receiving 15 weeks of a single, once/week reminder shock (RS+), or no reminder shocks (RS-). Body weights were recorded weekly. Mice were then placed in metabolic chambers for 72h to perform indirect calorimetry. In a separate cohort of mice, Cholera Toxin Subunit B conjugated to Alexa Fluor 647 (CTB-AF647) was injected into the LC of PACAP-GFP mice. CTB is a monosynaptic retrograde tracer, allowing for PACAPergic projections to the LC to be identified via colocalization of AF647 and GFP.
Results: Cre-mediated knockdown of PAC1 in the LC was associated with increased freezing during weekly reminder shocks, as well as attenuation in weight gain. From indirect calorimetry, LC-PAC1 knockdown was predominantly associated with an increase in oxygen consumption (VO2), carbon dioxide production (VCO2), and energy expenditure (EE) in RS- groups. However, LC-PAC1 knockdown had the opposite effect in RS+ groups and was associated with a decrease in the same metabolic parameters.
Conclusion: These findings suggest that LC-PAC1 knockdown has inverse effects on basal (RS-) and stress-associated (RS+) whole body energy metabolism. Given the role of the LC in regulating the SNS, further studies will determine the role of the sympathetic response in mediating these metabolic effects.

CROSSTALK BETWEEN THE OVARIAN AND OLFACTORY SYSTEM IN MOUSE MODELS OF MENOPAUSE

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Ovarian failure is caused by a progressive loss of ovarian follicles and results in menopause in women around the age of 50. Although it is associated with various secondary co-morbidities, such as neurological complications including sensory alterations, the biological basis of these changes is still unclear and almost solely attributed to hormonal changes, especially a decrease in estrogen. In addition, most prior studies have focused on the central nervous system, particularly the hypothalamus where sensory information and internal states are integrated to regulate body physiology and behavior. Thus, it remains elusive if and how ovarian failure impacts peripheral sensory systems. Our recent work has revealed that olfactory sensory neurons (OSNs) in the mouse nose adaptively alter odor responses based on how active or inactive over hours to days. Such adaptation is achieved through coordinated changes in the expression of genes involved in neuronal physiology. This work also suggests the possibility that OSNs are sensitive to not just sensory stimuli but also signals that reflect internal states such as hormonal and life stages and tailor odor response patterns. In line with this idea, accumulating evidence has emerged that internal states (e.g., hunger, estrous stage, sexual experience) influence responses of peripheral sensory neurons in the nose. Based on these findings, we hypothesized that ovarian failure alters olfaction via the impacts on the peripheral olfactory system. To test this model, we used two mouse lines with accelerated ovarian failure that gradually lose ~100% or ~70% of ovarian reserve by 2 months of age, allowing us to characterize the effects of ovarian failure on olfaction independent of aging. In these mutants, we identified signatures of chronic inflammation in the nasal olfactory epithelium with increased T cell recruitment. Intriguingly, immune cell infiltration is restricted to the ventral domain of the olfactory epithelium, suggesting spatial differences in the responsiveness to hormonal and immune signals. We also observed ventral-specific increase in neurogenesis. Because OSNs undergo continuous turnover and the position in the olfactory epithelium determines the identity of odorant receptors to be expressed, changes in neurogenesis in a spatially organized manner could impact odor perception over weeks-long timescales. We further found that mutant OSNs exhibit a gene expression signature associated with low activity states, predicting their hypersensitivity to odors. We are currently investigating how ovarian failure affects OSN transcriptomes and neurogenesis as well as the patterns of neuronal and behavioral odor responses. Altogether, this study suggests that the olfactory epithelium plays unique roles in linking our brain and body by sensing signals from both the outside world and inside of the body.

PRENATAL ALCOHOL AND CANNABINOID EXPOSURE ALTERS THE GUT MICROBIOME AND METABOLIC SIGNALING: IMPLICATIONS FOR ADULT ADDICTION RISK

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Prenatal alcohol exposure (PAE) is a leading cause of neurodevelopmental disabilities, collectively termed, FASDs, including a spectrum of systemic and neurobehavioral deficits that adversely influence health across a lifespan. Alcohol is often co-used with other psychoactive substances like cannabis, each of which has been independently linked to neurobehavioral and developmental effects. However, there is a critical lack of understanding on the impact of PAE versus the interaction of PAE with other psychoactive substances. Emerging evidence links PAE to alterations in gut microbiome associated with anxiety-like behaviors, but how these early-life exposures shape gut and systemic metabolism and their association with addiction risk in adulthood remains unclear. We examined the persistent effects of prenatal alcohol, cannabinoid, or combined exposure on gut microbiota and metabolites and their associations with alcohol seeking behavior in adult offspring. Pregnant C57BL/6J mice were exposed to ethanol (95% vapor ethanol), cannabinoid (CP-55940), or simultaneous alcohol and cannabinoid at gestational days 12-15, corresponding to a critical period of cerebral cortical plate neurogenesis and angiogenesis. Adult alcohol seeking behavior was assessed between postnatal days 107-253. Fecal (from caecum) and plasma samples were collected at ~8.5 months (n=16-17/group). Shotgun metagenomics was performed on cecal samples, and global metabolomics was conducted on both plasma and cecal samples. We observed distinct microbial shifts in the co-exposure group, including reduced key butyrate-producing bacteria, suggesting impaired gut homeostasis. Plasma LPS levels were significantly elevated in the co-exposure group, indicating impaired gut barrier integrity and increased systemic inflammation. Distinct metabolomic profiles were observed with differential regulation of bile acids, lipid, amino acid, and xenobiotic-related metabolites across exposure groups. Correlation analyses identified several microbial taxa and metabolites associated with alcohol-seeking behavior in co-exposed animals, linking gut dysbiosis to behavioral vulnerability and highlighting a gut-brain axis link shaped by prenatal exposure. Prenatal exposure to alcohol and/or cannabinoid induces persistent alterations in the gut microbiome and metabolism in adult, influencing neurobehavioral health outcomes. By understanding these alterations, we could identify gut-derived biomarkers and potential targets for microbiome- or metabolite-based interventions to reduce neurobehavioral risks associated with adverse early life experiences.

GFRAL NEURONS MEDIATE INTESTINAL TYPE 2 IMMUNITY

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Increasing evidence highlights the importance of the central nervous system (CNS) in regulating allergic responses, also in the context of food allergies. While food allergies were once considered relatively uncommon, their prevalence has risen significantly in recent years among both children and adults. Recent studies have identified a critical function for growth differentiation factor 15 (GDF15) released in the intestine and acting on the brain, particularly in mediating avoidance behavior associated with food allergies. However, the exact neural circuits and mechanisms by which GDF15 contributes to the modulation of immune responses in the context of food allergy remain poorly understood. In this study, we focus on a specific population of neurons located in the area postrema (AP) and the nucleus of the solitary tract (NTS), these neurons uniquely express GDNF family receptor α-like (GFRAL), which to date is the only known receptor for GDF15. Here, we test the hypothesis that GFRAL-expressing neurons function as a brainstem immune-sensing node that links systemic type 2 inflammatory signals to intestinal immune remodeling and disease outcomes. Using models of food allergy and cytokine-driven type 2 inflammation, we show that GFRAL neurons are activated by antigen- and cytokine-mediated immune challenges. Through chronic genetic and viral strategies to enhance GFRAL neuron activity, we demonstrate that sustained GFRAL activation reshapes intestinal architecture, promotes tuft cell and goblet cell pathways, and alters nutrient absorption independently of food intake. Mechanistically, we identify a parasympathetic brain-gut circuit involving the vagus nerve that connects GFRAL neurons to the small intestine. Finally, we show that manipulating GFRAL neuron activity alters susceptibility to helminth infection, colitis, and allergic sensitization. Together, these findings reveal an unexpected role for GFRAL neurons in coordinating immune-neural communication along the brain-gut axis and identify a mechanism by which systemic type 2 immune signals influence intestinal immunity and disease progression. This neuro-immune pathway may represent a novel mechanism by which the brain contributes to type 2 immunity and represents a promising target for therapeutic intervention targeting neuro-immune communication.

NEUROIMMUNE MEMORY: MAPPING AND MANIPULATING INFLAMMATION ACROSS THE ZEBRAFISH BODY

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Our body and brain are in constant communication, this “inner sense,” called interoception, influences behaviours from feeding to fear responses. The brain constantly monitors the internal state of the body to maintain homeostasis. Among those internal signals, inflammation is an essential defence mechanism to protect organisms against tissue damage and infection. Recent work suggests the existence of immune memories in the brain, that can remember the inflammatory state of organs event once the inflammation is gone. However, it is difficult, in most animal models, to image both the subcortical brain regions through which the body signals are processed and the internal processes of the body in vivo.

We use transparent zebrafish larvae to image the activity of the brain to study how inflammation is represented using a chemical model of colitis. We have observed an increased activity using whole-brain activity mapping of ERK phosphorylation in the telencephalon and hypothalamus during inflammation. The hypothalamus is known to be involved in immune responses, and controls major physiological processes, such as feeding. The telencephalon of larvae is not yet fully developed, so claiming homology is premature, and we think that our future molecular fingerprinting will help make functional homology claims. We will use calcium imaging to identify with cellular resolution, which neurons respond to the acute gut inflammation, using in situ hybridization will allow us to identify post-hoc the molecular identity of those neurons. In the future, we will use light-based tools to trigger inflammation with high spatial accuracy to map any topographic or organocentric representation of inflammation in the brain. Understanding these immune memories would open the way to new ways to manage inflammatory disease, especially chronic inflammation.

THE DORSAL VAGAL COMPLEX IS INVOLVED IN MYOCARDIAL INFARCTION AND CHRONIC HEART FAILURE

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Myocardial infarction (MI) affects 3 million individuals worldwide yearly and carries a ~20% 5-year mortality. Post-MI sympathetic overactivation and parasympathetic withdrawal is a key driver of arrhythmias, heart failure (HF), and mortality. Despite existing therapies that target peripheral sympathetic pathways, mortality remains high. Understanding the contribution of specific brain circuits to post-MI autonomic dysfunction may identify new therapeutic targets, which is critical to address the urgent need for more effective therapies. In order to elucidate brain regions implicated in MI-associated HF, we mapped the central neural response to acute MI. MI was induced in adult male mice by surgical ligation of the left anterior descending artery (LAD). Brains were collected 90 minutes after LAD ligation or sham operation (n = 5/group). We used c-Fos immunohistochemistry (IHC) to quantify neuronal activation in regions of interest. We observed robust activation in the nucleus tractus solitarius (NTS) and the ventrolateral medulla (VLM), with the number of c-Fos positive cells present in each region almost three times higher after MI than after sham operation. Increased activity was also observed in the dorsal motor nucleus of the vagus (DMV) and the locus coeruleus (LC), and decreased activity was observed in the ventromedial hypothalamus (VMH), but these changes were not statistically significant. Activation in the dorsal vagal complex (DVC), comprising the NTS, DMV, and the area postrema (AP), was of particular interest due to its known involvement in cardiopulmonary modulation. The NTS is the primary central relay of cardiovascular afferent information and orchestrates the chemoreflex, baroreflex, and cardiac sympathetic reflex through projections to the VLM and DMV. These reflexes are altered in chronic HF. To further elucidate the involvement, if any, of the DVC in chronic MI-associated HF, we performed a qPCR panel on micropunches enriched for the NTS or the AP in mice 4 weeks after LAD ligation or sham operation. Expression of Slc2a3 and Mdh2 was reduced in the NTS, suggesting decreased neuronal glucose uptake and impaired oxidative metabolism. The AP exhibited reduced expression of Ndufs1 and Cox7b, indicating suppressed oxidative phosphorylation. These findings suggest not only acute activation but also chronic metabolic defects in the DVC after MI. Future studies will identify the connectivity of NTS neurons activated in MI by combining the described c-Fos methodology with VLM retrograde tracing. Additionally, we will leverage activity-dependent genetic labeling to test the contribution of dysfunctional cardiopulmonary reflexes at the level of the NTS to ventricular remodeling after MI. Through this work, we aim to enhance our understanding of the role of the brain in MI-associated HF and identify novel central therapeutic targets for HF.

THE RELATION BETWEEN GUT MICROBIOTA, BRAIN STRUCTURE AND COGNITIVE FUNCTION IN METABOLIC SYNDROME

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Background: Metabolic syndrome (MetS) can lead to accelerated brain aging and cognitive decline. Evidence has suggested the involvement of the microbiota-gut-brain axis in the relationship between MetS and cognitive dysfunction, but the underlying mechanisms are unclear.
Methods: Using magnetic resonance imaging and 16S rRNA gene amplicon sequencing, we collected data of brain structure and gut microbiome from 97 MetS patients and 103 healthy controls. Group differences in gut microbiome, brain structure, and cognitive function as well as their plausible interactive links in MetS patients were examined.
Results: We found that MetS patients exhibited impaired executive function and memory ability, both depleted short-chain fatty acids (SCFA)-producing bacteria and enriched inflammation-triggering bacteria, gray matter atrophy of several brain regions and microstructural integrity damage of multiple white matter tracts. Of more importance, correlation and mediation analyses demonstrated that the abnormal brain structure mediated the associations between the depleted anti-inflammatory bacteria (i.e., Clostridium XlVa, Kineothrix and Acetivibrio) and the impaired cognitive function in MetS patients.
Conclusions: Our findings not only point to new hypotheses about potential neurobiological pathways by which gut microbial dysbiosis may lead to cognitive dysfunction in the context of MetS, but also highlight the potential therapeutic value of targeting gut microbiota for cognitive impairments in MetS patients.

CENTRAL AMYGDALA MEDIATES BOTH POSITIVE REINFORCEMENT AND NEGATIVE AFFECT BY FENTANYL

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Opioid addiction is driven by a powerful cycle of positive reinforcement from drug intake and the emergence of negative affective states during abstinence, both of which fuel continued use and relapse. The central nucleus of the amygdala (CeA) is a critical hub in this process, containing an opioidergic microcircuit that integrates reward, stress, and neuromodulatory signals. However, how defined CeA cell types and their intracellular signaling mechanisms coordinated during fentanyl exposure remains poorly understood.

In this study, we utilize a mouse intravenous fentanyl self-administration (IVSA) model to investigate how CeA mediates these opposing motivational processes. Focusing on genetically defined PKC-δ, Pdyn and Cartpt neuronal populations, we combined longitudinal behavioral analyses spanning acquisition, extinction, and reinstatement with multimodal in vivo imaging. Using one-photon GRIN lens imaging, we monitored population-level activity and functional interactions among distinct CeA ensembles across different stages of addiction. To probe intracellular mechanisms underlying μ-opioid receptor (MOR) sensitization and opioid tolerance, we applied in vivo two-photon fluorescence lifetime imaging microscopy (2P-FLIM) to quantify key intracellular signaling changes at single cellular resolution over time. Furthermore, fiber photometry was employed to record real-time dopamine and acetylcholine signals across behavioral states.

Our findings reveal a functional divergence within the CeA, with PKC-δ, Pdyn, and Cartpt neurons differentially encoding the rewarding effects of fentanyl and the aversive states associated with abstinence. Crucially, cell-type specific deletion of MORs in the CeA PKC-δ neurons significantly attenuates negative affective behaviors. Together, these results demonstrate that the CeA serves as a critical site where cell-type specific circuit dynamics and MOR-dependent molecular plasticity converge to shape the trajectory of opioid addiction.

A VAGAL LIVER-BRAIN CIRCUIT FOR INFLAMMATION SENSING AND RESPONSE

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Maintaining energy homeostasis during infection or inflammation requires accurate sensing of internal states, coupled with mechanisms to effect adaptive behaviours and partition available resources. As the gateway between the gastrointestinal tract and internal circulation, the mammalian liver is uniquely positioned to sense and prepare the body for incoming immune threats originating from the gut, requiring functional coordination of the nervous and immune systems. However, the molecular identity and function of liver-innervating vagal afferents remain unclear, resulting in a poor understanding of how hepatic signals relay to the brain to regulate adaptive responses. Using the CUBIC tissue-clearing technique, we identified that Phox2b^{+} vagal nerves predominantly innervate the hepatic portal vein. Projection-based single-cell transcriptomic analysis revealed that liver-innervating vagal sensory neurons highly express prostaglandin receptors, which detect immune mediators released by liver macrophages during injury or inflammatory insult. Hepatic immune challenge robustly activates liver-innervating vagal sensory neurons and their synaptically connected downstream brain regions, including the nucleus of the solitary tract (NTS), paraventricular nucleus (PVN), and parabrachial nucleus (PBN), thereby modulating sickness behaviors, including reduced food intake, decreased locomotor activity, and alterations in the hepatic immune response. Importantly, we revealed that deletion of prostaglandin receptors in liver-innervating vagal sensory neurons under inflammatory challenges impairs the activation of this circuit and attenuates feeding suppression. Our findings reveal a molecularly defined neuroimmune feedback system by which peripheral immune challenges relay to the brain via the liver to control feeding behaviour and immune responses.

Key words: Liver-brain vagal axis; vagal sensory neurons; immune modulation; prostaglandin receptors; feeding regulation.

INTEROCEPTIVE NETWORK RESPONSES TO INFLAMMATORY CHALLENGE IN DEPRESSION

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Background: Peripheral inflammation generates interoceptive signals that convey changes in bodily state to the brain, producing adaptive behavioral responses collectively termed sickness behavior. These processes are thought to be mediated by interoceptive networks centered on the insular cortex, which map visceral signals, and the cingulate cortex, which integrates these signals with affective and regulatory processes. Although a subset of individuals with major depressive disorder (MDD) exhibit elevated circulating inflammatory markers, it remains unclear whether neural processing of immune-related interoceptive signals differs between depressed and healthy individuals.
Methods: Thirty-one adults with MDD and thirteen healthy controls (HC) received low-dose lipopolysaccharide (LPS; 0.8 ng/kg). Functional MRI was acquired at baseline and approximately two hours post-infusion, coinciding with peak cytokine response. During scanning, participants completed a visceral interoceptive awareness task contrasting attention to internal bodily sensations (heart/stomach) with an exteroceptive control condition (font-color changes). Serum cytokines were measured using MesoScale Discovery V-Plex assays. Given prior evidence implicating insula and cingulate cortex in immune-related mood and behavioral changes, analyses focused on diagnosis-by-time interactions within Brainnetome-defined subregions of these areas, controlling for age, sex, BMI, and head motion.
Results: The MDD group exhibited greater serum cytokine responses to LPS than HC, peaking approximately 1.5 hours post-infusion. In HC, LPS administration was associated with bilateral reductions in activation of posterior insular subregions (hypergranular and dorsal granular) and posterior cingulate cortex (ventral and dorsal area 23) during interoceptive attention. In contrast, individuals with MDD showed no such reductions and, in some regions, increased activation. Mixed-effects analyses revealed significant Diagnosis × Time interactions in posterior insula ($d = 0.69–0.79$) and posterior cingulate cortex ($d = 0.91$; all $p_{FDR} < .05$), reflecting larger post-LPS signal decreases in HC relative to MDD.
Conclusion: These preliminary findings suggest that MDD is associated with altered neural representation of inflammatory signals within posterior insula and posterior cingulate cortex during immune challenge. Disrupted central processing of peripheral inflammation may contribute to impaired resolution of immune responses and sustained depressive symptoms. Replication in larger samples is needed to clarify whether altered interoceptive immune–brain signaling represents a mechanistic pathway linking inflammation to depression.

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CODE OF CONDUCT FOR ALL PARTICIPANTS IN CSHL MEETINGS

Cold Spring Harbor Laboratory (CSHL or the Laboratory) is dedicated to pursuing its twin missions of research and education in the biological sciences. The Laboratory is committed to fostering a working environment that encourages and supports unfettered scientific inquiry and the free and open exchange of ideas that are the hallmarks of academic freedom. To this end, the Laboratory aims to maintain a safe and respectful environment that is free from harassment and discrimination for all attendees of our meetings and courses as well as associated support staff, in accordance with federal, state and local laws.

Consistent with the Laboratory's missions, commitments and policies, the purpose of this Code is to set forth expectations for the professional conduct of all individuals participating in the Laboratory's meetings program, both in person and virtually, including organizers, session chairs, invited speakers, presenters, attendees and sponsors. This Code's prohibition against discrimination and harassment is consistent with the Laboratory's internal policies governing conduct by its own faculty, trainees, students and employees.

By registering for and attending a CSHL meeting, either in person or virtually, participants agree to:

1. Treat fellow meeting participants and CSHL staff with respect, civility and fairness, without bias based on sex, gender, gender identity or expression, sexual orientation, race, ethnicity, color, religion, nationality or national origin, citizenship status, disability status, veteran status, marital or partnership status, age, genetic information, or any other criteria prohibited under applicable federal, state or local law.

2. Use all CSHL facilities, equipment, computers, supplies and resources responsibly and appropriately if attending in person, as you would at your home institution.

3. Abide by the CSHL Meeting Alcohol Policy (*see below)*.

Similarly, meeting participants agree to refrain from:

1. Harassment and discrimination, either in person or online, in violation of Laboratory policy based on actual or perceived sex, pregnancy status, gender, gender identity or expression, sexual orientation, race, ethnicity, color, religion, creed, nationality or national origin, immigration or citizenship status, mental or physical disability status, veteran status, military status, marital or partnership status, marital or partnership status, familial status, caregiver status, age, genetic information, status as a victim of domestic violence, sexual violence, or stalking, sexual reproductive health decisions, or any other criteria prohibited under applicable federal, state or local law.

2. Sexual harassment or misconduct.

3. Disrespectful, uncivil and/or unprofessional interpersonal behavior, either in person or online, that interferes with the working and learning environment.

4. Misappropriation of Laboratory property or excessive personal use of resources, if attending in person.

BREACHES OR VIOLATIONS OF THE CODE OF CONDUCT

Cold Spring Harbor Laboratory aims to maintain in-person and virtual conference environments that accord with the principles and expectations outlined in this Code of Conduct. Meeting organizers are tasked with providing leadership during each meeting, and may be approached informally about any breach or violation. Breaches or violations should also be reported to program leadership in person or by email:

- Dr. David Stewart, Grace Auditorium Room 204, 516-367-8801 or x8801 from a campus phone, stewart@cshl.edu
- Dr. Charla Lambert, Hershey Laboratory Room 214, 516-367-5058 or x5058 from a campus phone, clambert@cshl.edu

Reports may be submitted by those who experience harassment or discrimination as well as by those who witness violations of the behavior laid out in this Code.

The Laboratory will act as needed to resolve the matter, up to and including immediate expulsion of the offending participant(s) from the meeting, dismissal from the Laboratory, and exclusion from future academic events offered by CSHL.

If you have questions or concerns, you can contact the meeting organizers, CSHL staff.

For meetings and courses funded by NIH awards:

Participants may contact the Health & Human Services Office for Civil Rights (OCR). See this page for information on filing a civil rights complaint with the OCR; filing a complaint with CSHL is not required before filing a complaint with OCR, and seeking assistance from CSHL in no way prohibits filing complaints with OCR. You may also notify NIH directly about sexual harassment, discrimination, and other forms of inappropriate conduct at NIH-supported events.

For meetings and courses funded by NSF awards:

Participants may file a complaint with the NSF. See this page for information on how to file a complaint with the NSF.

Law Enforcement Reporting:

- For on-campus incidents, reports to law enforcement can be made to the Security Department at 516-367-5555 or x5555 from a campus phone.
- For off-campus incidents, report to the local department where the incident occurred.

In an emergency, dial 911.

DEFINITIONS AND EXAMPLES

Uncivil/disrespectful behavior is not limited to but may take the following forms:

- Shouting, personal attacks or insults, throwing objects, and/or sustained disruption of talks or other meeting-related events

Harassment is any unwelcome verbal, visual, written, or physical conduct that occurs with the purpose or effect of creating an intimidating, hostile, degrading, humiliating, or offensive environment or unreasonably interferes with an individual's work performance. Harassment is not limited to but may take the following forms:

- Threatening, stalking, bullying, demeaning, coercive, or hostile acts that may have real or implied threats of physical, professional, or financial harm
- Signs, graphics, photographs, videos, gestures, jokes, pranks, epithets, slurs, or stereotypes that comment on a person's sex, gender, gender identity or expression, sexual orientation, race, ethnicity, color, religion, nationality or national origin, citizenship status, disability status, veteran status, marital or partnership status, age, genetic information, or physical appearance

Sexual Harassment includes harassment on the basis of sex, sexual orientation, self-identified or perceived sex, gender expression, gender identity, and the status of being transgender. Sexual harassment is not limited to sexual contact, touching, or expressions of a sexually suggestive nature. Sexual harassment includes all forms of gender discrimination including gender role stereotyping and treating employees differently because of their gender. *Sexual misconduct* is not limited to but may take the following forms:

- Unwelcome and uninvited attention, physical contact, or inappropriate touching
- Groping or sexual assault
- Use of sexual imagery, objects, gestures, or jokes in public spaces or presentations
- Any other verbal or physical contact of a sexual nature when such conduct creates a hostile environment, prevents an individual from fulfilling their professional responsibilities at the meeting, or is made a condition of employment or compensation either implicitly or explicitly

MEETING ALCOHOL POLICY

Consumption of alcoholic beverages is not permitted in CSHL's public areas other than at designated social events (wine and cheese reception, picnic, banquet, etc.), in the Blackford Bar, or under the supervision of a licensed CSHL bartender.

No provision of alcohol by meeting sponsors is permitted unless arranged through CSHL.

Meeting participants consuming alcohol are expected to drink only in moderation at all times during the meeting.

Excessive promotion of a drinking culture at any meeting is not acceptable or tolerated by the Laboratory. No meeting participant should feel pressured or obliged to consume alcohol at any meeting-related event or activity.

VISITOR INFORMATION

EMERGENCY (to dial outside line, press 3+1+number)	
CSHL Security	**516-367-8870 (x8870 from house phone)**
CSHL Emergency	**516-367-5555 (x5555 from house phone)**
Local Police / Fire	**911**
Poison Control	**(3) 911**

CSHL SightMD Center for Health and Wellness ***(call for appointment)*** Dolan Hall, East Wing, Room 111 **cshlwellness@northwell.edu**	**516-422-4422** **x4422 from house phone**
Emergency Room **Huntington Hospital** 270 Park Avenue, Huntington	**631-351-2000**
Dentists Dr. William Berg Dr. Robert Zeman	 **631-271-2310** **631-271-8090**
Pharmacy Value Drugs 391 W. Main Street, Huntington	**631-427-2919**

GENERAL INFORMATION

Meetings & Courses Main Office

Hours during meetings: M-F 9am – 9pm, Sat 8:30am – 1pm
After hours – See information on front desk counter
For assistance, call Security at 516-367-8870
(x8870 from house phone)

Dining, Bar

Blackford Dining Hall (main level):
Breakfast 7:30–9:00, Lunch 11:30–1:30, Dinner 5:30–7:00
Blackford Bar (lower level): 5:00 p.m. until late

House Phones

Grace Auditorium, upper / lower level; Cabin Complex; Blackford Hall; Dolan Hall, foyer

Books, Gifts, Snacks, Clothing

CSHL Bookstore and Gift Shop
516-367-8837 (hours posted on door)
Grace Auditorium, lower level.

Computers, E-mail, Internet access

Grace Auditorium
Upper level: E-mail and printing in the business center area
WiFi Access: GUEST (no password)

Announcements, Message Board Mail, ATM, Travel info

Grace Auditorium, lower level

Russell Fitness Center
Dolan Hall, east wing, lower level
PIN#: **(On your registration envelope)**

Laundry Machines
Dolan Hall, lower level

Photocopiers, Journals, Periodicals, Books
CSHL Main Library
Open 24 hours (with PIN# or CSHL ID)
Staff Hours: 9:00 am – 9:00 pm
Use PIN# (On your registration envelope) to enter Library
See Library staff for photocopier code.
Library room reservations (hourly) available on request between 9:00 am – 9:00 pm

Swimming, Tennis, Jogging, Hiking
June–Sept. Lifeguard on duty at the beach. 12:00 noon–6:00 p.m.
Two tennis courts open daily.

Local Interest

Fish Hatchery	631-692-6758
Sagamore Hill	516-922-4788
Whaling Museum	631-367-3418
Heckscher Museum	631-351-3250
CSHL DNA Learning Center	x 5170

New York City
Helpful tip -
Take CSHL Shuttle OR Uber/Lyft/Taxi to Syosset Train Station
Long Island Railroad to Penn Station
Train ride about one hour.

TRANSPORTATION

Limo, Taxi

Syosset Limousine	516-364-9681
Executive Limo Service	516-826-8172
Limos Long Island	516-400-3364
Syosset Taxi	516-921-2141
Orange & White Taxi	631-271-3600
Uber / Lyft	

Trains

Long Island Rail Road	718-217-LIRR (5477)
Amtrak	800-872-7245
MetroNorth	877-690-5114
New Jersey Transit	973-275-5555

CSHL's Green Campus

Cold Spring Harbor Laboratory is pledged to operate in an environmentally responsible fashion wherever possible. In the past, we have removed underground oil tanks, remediated asbestos in historic buildings, and taken substantial measures to ensure the pristine quality of the waters of the harbor. Water used for irrigation comes from natural springs and wells on the property itself. Lawns, trees, and planting beds are managed organically whenever possible. And trees are planted to replace those felled for construction projects.

Two areas in which the Laboratory has focused recent efforts have been those of waste management and energy conservation. The Laboratory currently recycles most waste. Scrap metal, electronics, construction debris, batteries, fluorescent light bulbs, toner cartridges, and waste oil are all recycled. For general waste, the Laboratory uses a "single stream waste management" system, removing recyclable materials and sending the remaining combustible trash to a cogeneration plant where it is burned to provide electricity, an approach considered among the most energy efficient, while providing a high yield of recyclable materials.

Equal attention has been paid to energy conservation. Most lighting fixtures have been replaced with high efficiency fluorescent fixtures, and thousands of incandescent bulbs throughout campus have been replaced with compact fluorescents. The Laboratory has also embarked on a project that will replace all building management systems on campus, reducing heating and cooling costs by as much as twenty-five per cent.

Cold Spring Harbor Laboratory continues to explore new ways in which we can reduce our environmental footprint, including encouraging our visitors and employees to use reusable containers, conserve energy, and suggest areas in which the Laboratory's efforts can be improved. This book, for example, is printed on recycled paper.

Cold Spring Harbor Laboratory Bookstore & Gift Shop

Main campus, lower level of Grace Auditorium

Store Hours

Did you miss your chance to shop at the CSHL Bookstore and Gift Shop during the conference?

No problem! Visit our Online Bookstore and Gift Shop.

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cshlvirtualstore.com

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