Brain in the Body

Neuroscience at Institut Pasteur

November 25th 2024

Amphithéâtre Duclaux, Institut Pasteur Paris

Abstracts booklet

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Talk abstracts

Talk abstract

Thomas BOURGERON

Human Genetics and Cognitive Functions Lab, Department of Neuroscience, Institut Pasteur, Université Paris Cité, CNRS, IUF

The genetic architecture of autism: from medicine to neurodiversity

The genetic contribution to autism is high (>80% of heritability), but its architecture involves a complex combination of rare and common variants. Autism shares genetic variations with other conditions such as attention deficit hyperactivity disorders (ADHD), intellectual disability, and epilepsy, but little is known about the factors that contribute to the diversity of the clinical trajectories. Remarkably, if rare variants with strong effects are most often associated with intellectual disability, common variants taken altogether are in contrast positively associated with intelligence. In this presentation, I will introduce recent results that shed new light on the inheritance of autism and on some of the underlying mechanisms. For example, I will illustrate how genes associated with autism shape brain connectivity by regulating gene expression and synaptic function. Finally, I will present how we are currently studying Resilience to understand why some carriers of genetic variants seem to be protected from adverse symptoms while others have more difficulties to thrive in the society.

Keywords : Genes, Synapses, Autisme

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Talk abstract

Pauline SPEDER

Structures and Signals in the Neurogenic Niche Lab, Department of Developmental and Stem Cell Biology, Institut Pasteur

Drosophila neural stem cells enter a protective state under acute systemic stress

The neural stem cells (NSCs) are responsible for building, maintaining and reparing the central nervous system throughout life. As such, how they respond to environmental variations is crucial to brain health. Yet, little is known about the diversity of NSCs' responses upon environmental stress: protective, adaptive, or pathological. Here we propose to investigate NSCs' response to pathogenic infection. While clinical studies have indeed pinpointed a link between brain infections early in life (in utero and perinatal), when neurogenesis is high, and neurological sequelae later in life, its cellular basis and mechanisms remain poorly known.

We use the Drosophila larval brain as a model to study the effect of acute infection on NSCs in a developing brain. Drosophila larval NSCs share some core principles with mammalian neurogenesis. This includes self-renewal via asymmetric division, switch from quiescence to proliferation, glial and neuronal progeny of well-defined lineages and extrinsic control of proliferation.They also exist within an architecturally complex niche.

We have previously established a model of brain infection by mammalian pathogens in Drosophila, combining whole brain explants with in vivo systemic infection (1–3). In particular, we have shown that Group B Streptococcus (GBS), a leading cause of meningitis in neonates, can infect the fly brain by hijacking physiological barrier mechanisms. We also found that NSCs exhibit a striking phenotype in response to GBS infection, characterized by proliferation arrest ; loss of fate markers; DNA remodelling close to the nuclear lamina; an resistance to apoptosis. In contrast, neurons undergo apoptosis. We are now characterizing this distinct NSC state, which we call Zombie, and which we identified as a conserved response to several acute pathological states of the host organism. We aim to understand the molecular mechanisms supporting the transmission of acute systemic stress to NSCs, and where the NSC response lies between protective and pathological. Our study will shed light on potential modulators of NSC response to stressful signals, and also provide a paradigm on how NSCs manage acute environmental stress, a poorly explored domain.

Keywords : Neural stem cell, Stress, Drosophila

Talk abstract

Miria RICCHETTI
Molecular Mechanisms of Pathological and Physiological Ageing Lab, Department of Developmental and Stem Cell Biology, Institut Pasteur

Neural organoids to model a disease that combines neurodevelopmental and neurodegenerative defects

Cockayne syndrome (CS) is one of the rare diseases that combine neurodevelopmental defects and neurodegeneration, the former being pre- or peri-natal and the latter generally associated with an advanced age. This is likely the case because CS is also characterized by severe premature ageing. We explore the hypothesis that the two defects, normally occurring at opposite ends of the age range, are correlated.
Neurodegeneration is associated with some but not all progeroid syndromes that are normally due to monogenic defects, and displays the most dramatic features in CS, where it is characterized by severe and progressive cognitive and motor impairment.
To study these defects, we face major challenges: i) poor or no recapitulation of the disease in animal models, ii) large CS clinical heterogeneity that cannot be explained by simple genotype/phenotype correlation iii) poor and finite availability of patient-derived material. To overcome these difficulties, we have developed neural organoids (NOs) from iPSCs reprogrammed from cells of patients with different clinical severity, and include a case where, despite the mutation as in CS, no neurodegeneration or premature aging were observed.
Our results show a remarkable correlation between NOs defects and the clinical condition of the original patient, thereby providing a robust model system to study neural and premature ageing defects of CS. Multiple CS-NOs alterations lead to defective neural differentiation. We also developed isogenic models to study the role of the mutation per se in the severity of CS. We are investigating whether the type and the extent of CS-NOs defects allow to predict post-differentiation degenerative processes. This is of particular relevance since we succeeded in largely rescuing the neural defects in CS-NOs.

Keywords : Human neural organoids, Neurodevelopmental defects, Precocious ageing

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Talk abstract

Chiara ZURZOLO
Membrane Traffic and Pathogenesis Lab, Department of Cell Biology and Infection, Institut Pasteur

Inflammation, autophagy and mitochondrial dysfunction regulate tunneling nanotube (TNT)-mediated microglia-neurons crosstalk in neurodegenerative diseases

The neuroimmune system of the brain majorly constitutes microglia, the tissue-resident macrophages of the central nervous system (CNS). These cells tile the brain and function in close proximity to neurons and other glial cells, thereby playing a crucial role in maintaining brain homeostasis. In “resting” state, these cells survey the brain parenchyma to sense any pathophysiological changes, which if detected can bring about “activated” microglial states. Reactive microglia are a pathological hallmark of several neurodegenerative diseases, which can be induced by, and negatively affect, neuronal health. Although secretion-mediated communication between neurons and microglia have been well established, contact-mediated communication between these two cell types remain elusive. Such long-distance interactions are mediated by thin, F-Actin rich structures called Tunneling nanotubes (TNTs). TNTs facilitate the transfer of aggregated proteins such as Prions, α-Synuclein, tau, and mutant Huntingtin, as well as intracellular components like mitochondria between connected cells. Previous reports have demonstrated efficient directional transfer of α-Synuclein (α-Syn) aggregates from neuronal cells to microglia. The reason behind such directionality, however, remains unknown. Using quantitative fixed- and live-cell microscopy, we observed differential localization of aggregates on lysosomes of neuronal and microglial cells. Although lysosomal biogenesis increased for both neuronal and microglial cells upon exposure to aggregates, the ability of microglia to target lysosomes for degradation via lysophagy was significantly higher than neuronal cells, both at a basal level and in the presence of aggregates. Further autophagy inhibition in neuronal cells led to heightened aggregate transfer to microglia, also increasing the number of homotypic TNTs between cells. Interestingly, aggregate transfer is also elevated in an inflammatory environment, a neuroimmune phenotype of neurodegenerative diseases. Thereby, we propose a framework of impaired proteostasis and inflammation in mediating intercellular communication between neurons and microglia.

Keywords : Nuron-glia interactions, Neurodegenerative diseases, Organelles

Talk abstract

Claire PUJOL
Mitochondrial Biology Lab, Department of Cell Biology and Infection, Institut Pasteur

Tackling the complexity of mitochondrial diseases

Our project aims to tackle the complexity of mitochondrial neurological diseases by studying genetic mechanisms in spinocerebellar degeneration driven by mutations in the gene SPG7 and to identify modifier genetic variants explaining phenotypic variability. SPG7 encode mitochondrial matrix AAA (m-AAA) protease functionally interacting with AFG3L2 in one complex as part of the mitochondrial proteostasis system that is acting as quality control in mitochondria1. While initially attributed to recessive hereditary spastic paraplegia type 7 (SPG7) its associated phenotype is large with spasticity, cerebellar ataxia, optic neuropathy, cognitive impairment and parkinsonism2. Loss of m-AAA proteases affect mitochondrial protein synthesis and respiration and leads to mitochondrial fragmentation, which is an easily accessible microscopic readout. We started by using a powerful high-throughput imaging-based phenotypic screening pipeline3 to identified genes whose absence modified the mitochondrial phenotype of relevant cell models. We are combining sequencing data from patients of interest and proteomic analysis to shortlist those candidate genes.
Using the C. elegans model we will confirm or refute the effects of these candidates on mitochondrial biology. The nematode is particularly relevant to gain insight into the pathomechanistic consequences of the mitochondrial dysfunction observed in human diseases, thanks to the availability of a variety of tools: small size, transparency allowing in vivo visualization of fluorescently labeled proteins and the fact that RNAi can be activated in C. elegans by simply feeding them bacteria that express dsRNA corresponding to part of the gene we wish to silence. The dsRNA enters cells through the intestine and is recognized by the RNAi machinery spreading from cell to cell in the entire body.

Keywords : Mitochondria

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Talk abstract

Sandrine ETIENNE-MANNEVILLE

Cell Polarity, Migration and Cancer Lab, Department of Cell Biology and Infection, Institut Pasteur

Cytoskeletal crosstalk: from cell mechanics to glioblastoma progression

Glioblastoma multiforme is the most common and aggressive malignant brain tumor, characterized by a poor prognosis and the absence of curative therapies. The intratumoral heterogeneity and invasive behavior of glioblastoma cells significantly contribute to tumor aggressiveness and therapeutic failures. Cell invasion, a hallmark of cancer, is driven by cell intrinsic mechanical properties and mechanotransduction, a multi-step cellular and gene regulatory process that governs cellular responses to mechanical stimuli. Due to their physical properties, cytoskeletal components are crucial in modulating cell mechanical and invasive properties, enabling tumor cells to respond to physical stresses encountered during cancer progression. In this presentation we will explore how variations in the expression of cytoskeletal components influence tumor cell plasticity and resistance to treatment, highlighting potential therapeutic targets to improve patient outcomes.

Keywords : Glioblastoma, Invasion, Mechanobiology

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Talk abstract

Sedigheh DELMAGHANI
Progressive Sensory Disorders, Pathophysiology & Therapy Lab, IHU-Reconnect, Hearing Institut, Institut Pasteur, Inserm, Université Paris Cité, AP-HP

Navigating the complexity of causes behind progressive hearing impairment

Hearing is essential for every major activity of daily life, ranging from communication, mobility and autonomy to an appreciation of music, art and nature. Today, about 466 million people suffer from serious hearing impairment worldwide (https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss).
Congenital hearing loss affects 26 million people worldwide, with 60% (~ 15 million) attributed to genetic factors. However, an increasing number of cases (> 440 millions of cases), inherited or acquired, are postnatal and progressive. Untreated hearing decline severely impacts the quality of life is dramatic, impeding communication first, and in adults, leading to social isolation, depression, and reduced physical and cognitive functions. While the disease mechanisms and functional pathways involved in postnatal and/or progressive hearing impairment remain elusive, it is believed to involve a complex interplay of genetic, environmental, and lifestyle factors. Understanding the underlying mechanisms is crucial for developing effective interventions to slow or even prevent the progression of hearing decline.
Ongoing work show that deaf animal models, particularly clarin-deficient mice with inherited postnatal progressive hearing impairments, are valuable tools for elucidating the origin of progressive hearing loss. In-depth phenotyping of these mice models has revealed precise structural and molecular alterations in both hair cells and the auditory neurons. OMIC approaches, such as transcriptomics and proteomics, were carried out on distinct clarin-deficient mouse models that depict various clinical situations observed in humans. Our findings point the involvement of various cellular pathways in hearing decline, including neuronal and synaptic function, oxidative stress, and inflammation pathways. We also showed that gene therapy efficiently restores hearing and balance abilities in clarin-deficient mice.
Overall, the integration of detailed phenotyping with OMIC approaches allows identification of key insights into the underlying mechanisms of late-onset, progressive hearing impairments. Moreover, the identification of risk-conferring pathways holds great promise for the prevention and treatment of progressive hearing impairment.

Keywords : Progressive hearing impairment, Synaptopathy & Pathogenesis phenotyping, Gene therapy

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Talk abstract

Didier DULON
Hearing Institut, Institut Pasteur/Inserm (UA06)

The importance of otoferlin alternative splicing isoforms in auditory hair cell synaptic transmission

Mutations in the OTOF gene cause one of the most frequent cause of auditory hair cell neuropathy/synaptopathy (DFNB9). Otoferlin is expressed in sensory hair cells where it serves as a calcium-sensor controlling synaptic vesicle exocytosis (Leclère and Dulon, 2023). Two alternatively spliced forms of the otoferlin C-terminal transmembrane domain (TMD), encoded by either exon47 or exon48, have been described. Exon48-encoded otoferlin is thought to be the major isoform expressed in IHCs, while exon47 isoform is mainly found in the brain. Notably, hearing loss has been reported in some patients bearing mutations in exon47 (ClinVar), but the functional role of this TMD otoferlin isoform in hair cells remains unknown.

To address this question, we generated a knock-in mouse model (Otof exon47-mScarlet-flx/flx) in which exon47 is tagged with the red fluorescent protein mScarlet and flanked by two loxP sites, allowing its specific deletion by Cre/lox recombination. Remarkably, direct observation of live organs of Corti freshly dissected from Otof exon47-mScarlet-flx/flx mice showed specific fluorescent expression of m-Scarlet-tagged otoferlin in inner hair cells (IHCs), in particular at the ribbon synaptic regions. Furthermore, Otof exon4-mScarlet flx/flx-Myo15 Cre+/- mice, in which exon47 is specifically excised in hair cells, displayed apparent normal ABRs and DPOAEs thresholds. However when analyzing ABR wave-1 amplitude as a function of sound intensity, these mice showed a significant reduction of wave-1 at high sound levels above 60 dB SPL, suggesting an "hidden-like" IHC synaptopathy. These exon47 deleted IHCs displayed reduced Ca2+ currents associated with a defect in sustained exocytosis. Confocal immuno-microscopy analysis showed a 30% reduced number of ribbon synapses as compared to wild-type controls. Also, these hair cells lacking exon47 displayed smaller presynaptic ribbons associated with larger postsynaptic AMPAR clusters as compared to wild-type mice.

Overall, our results underline the importance of the exon47 TMD isoform of otoferlin in IHCs and suggest that this isoform is essential for the function and maintenance of a particular subtype of ribbon synapses, presumably the ones associated with the high threshold fibers. These findings should have important implications for future clinical diagnosis of otoferlin neuropathies and the design of efficient AAV rescue strategies.

Keywords : Deafness, Otoferlin, Hair cell synaptic transmission

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Talk abstract

Paul AVAN
Hearing Institut, Center for Research and Innovation in Human Audiology

Sound-processing disorders in the human auditory pathways: challenges for their detection

The processing of sound in the auditory system starts with several elementary stages that involve the cochlea, auditory nerve and brainstem nuclei. Frequency content, temporal fine structure, envelope, intensity, source direction are essential features whose combined analysis normally leads to the identification of sources in 'soundscapes' of hardly limited complexity. Sensorineural hearing impairment severely limits this ability. One current shortcoming of audiology is the restricted set of stimuli used to diagnose a disorder, that is, pure tones, short transients, broadband noise and lists of simple words, despite the fact that patients' disability is best revealed in ecologically relevant situations. What should be a relevant set of tests allowing precise personalized solutions to be implemented?

Auditory disorders show a large diversity of perceptual consequences, the most frequent one being loss of audibility of some frequency intervals due to cochlear pathology – easy to compensate but prone to distortions of the sensation of loudness. The loss of ability to process time cues by synapses or neurons is less frequent but increasingly worrisome because some of its versions are difficult to detect objectively. Furthermore, disorders can be isolated or combined, and they may induce obvious perceptual distortions (e.g., uncomfortable loudness) or more subtle ones such as excessive saliency of background sounds; changes in timbre; exaggerated detrimental effects of noise.

Research protocols conducted at CeRIAH attract cohorts of volunteer participants for tackling these issues, improve the accuracy of detection to suggest proper compensation strategies, evidence-based with the help of careful big-data analysis.

Keywords : Auditory processing, Sensorineural hearing loss, Audiological diagnosis

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Talk abstract

Nicolas WOLFF

Signaling and Dynamics of Receptors Lab, Department of Neuroscience, Institut Pasteur

Molecular organisation of the Usher2 complex related to deafness and blindness

THearing relies on the capacity of specialized sensory hair cells in the cochlea to transduce sound-induced vibrations into electrical signals that are transmissible to the brain. Hair cells possess actin-filled stereocilia structured into staircase-shaped bundles deflected by sound-waves. Large protein complexes are found at the anchoring sites of extracellular links that interconnect stereocilia. Mutations of these proteins are responsible for hereditary sensory diseases, notably the Usher syndromes. The Usher syndrome of type 2 (Usher 2) is the most common form genetic cause of combined congenital deafness and progressive blindness. The Usher 2 protein complex, involved in the morphogenesis of the hair bundles, encompasses two large transmembrane proteins, usherin and the G protein-coupled receptor (GPCR) ADGRV1, with very large extracellular domains forming fibrous links between the stereocilia. These two membrane proteins possess a cytoplasmic region in interaction with the scaffolding proteins whirlin and PDZD7, which in turn associate to actin-binding proteins. Usher proteins contain numerous protein-protein interaction domains necessary to the intricacy of the network, but the network's assembly remains elusive, thus leaving the effect of mutations detected in patients to speculation.The underlying molecular mechanisms being unknown, we have proposed to elucidate the composition, structure, regulation and downstream signaling of the Usher 2 complex. To this end, we have implemented an integrative approach to study the molecular assembly of Usher proteins in vitro, in cell and in dissected cochlea using notably state-of-the-art biochemistry (production of soluble, multidomain membrane proteins), biophysics, NMR, SAXS, X-ray diffraction as well as single particle cryo-electron microscopy analysis (Structure 2017; PNAS & J. Mol. Biol. 2020; BMC Bioinformatics 2021; Front. Mol. Science 2022). We are also developing soft X-ray and cryo-tomographies as well as high resolution STED fluorescence approaches on dissected tissues, in order to characterize complex assemblies in situ, and unveil complexes intricacy in their relevant cellular environment. Altogether, the obtained results aim at understanding the physiopathology of mutations associated to the Usher 2 syndrome.

Keywords : Hearing, Usher syndrome, Integrative biology

Talk abstract

Morgane BESSON
Integrative Neurobiology of Cholinergic Systems Lab, Department of Neuroscience, Institut Pasteur

Nicotinic modulation of vulnerability to mental disorders

Mental disorders are complex diseases whose development progressively recruits a large set of brain areas and neurotransmission systems. Moreover, there are inter-individual differences in the vulnerability to develop these pathologies. Such vulnerability can be conceptualized and characterized through several levels including genetic, environmental and affective/psychiatric ones, which are interconnected. Nicotinic acetylcholine receptors (nAChRs) are homo- and hetero-pentameric cationic ligand-gated ion channels composed of α and β subunits that can co-assemble in various combinations of distinct brain distribution and functional properties. There is a growing body of evidence linking alterations in nAChR number and/or function to several mental conditions such as substance use dirsorders, Alzheimer's disease or schizophrenia. Here I will briefly describe the translational research we have accomplished in recent years to unravel how the nicotinic system may contribute to such conditions. In particular, we have characterized the impact of a polymorphism of α5 containing nAChRs, previously identified in smokers, on a set of processes associated not only with nicotine but also cocaine, alcohol and possibly food addiction, as well as with social behavior and agressiveness. In parallel, we have developed novel approaches to refine our understanding of the role of α7 containing nAChRs in neuropsychiatric endophenotypes. Finally, we have been interested in environmental predisposition to nicotine addiction and established a link between the gut microbiota and the effects of nicotine on the mesolimbic system.

Keywords : Nicotinic receptors, Addiction, Mental disorders

Talk abstract

Stefano SUZZI
Perception and Action Lab, Department of Neuroscience, Institut Pasteur

Deciphering body periphery-to-brain communication in depression

Major depressive disorder is a prominent economic and societal burden. Its unclear pathophysiology complicates clinical management and research through animal modelling. Here we hypothesize that continuous perturbation of homeostasis in the body's periphery may have enduring consequences on brain function. Specifically, the association between some autoinflammatory disorders and depression prompted us to investigate systemic inflammation as a leading cause of depression. Using repeated intraperitoneal injections of a pro-inflammatory cytokine to induce systemic inflammation in mice, we observe depression-like behavioural manifestations. Conversely, a single injection has no effect. While both sexes are affected by the treatment, male mice respond more robustly. Analysis of the peripheral immune cell landscape in blood and spleen via multi-dimensional flow cytometry reveal specific rearrangements with repeated injections. Additionally, Bio-Plex multiple immunoassays demonstrate that repeated injections are associated with distinct cytokine profiles for blood and brain. To clarify how peripheral immune perturbations translate into impaired brain functions associated with mood disorders, we considered various routes through which peripheral inflammation could lead to central changes. In particular, we studied the fate of the choroid plexus, the anatomical and functional barrier between the blood and the brain via the cerebrospinal fluid. Further routes including the vagus nerve and the meninges will also be scrutinized. Our study will characterize the peripheral immune-related changes associated with depression in an inflammatory setting, shedding light on body-brain axes that may be implicated in depression pathogenesis.

Keywords : Depression, Cytokines, Brain borders

Talk abstract

Justus Ninnemann
Microenvironment and Immunity Lab, Department of Neuroscience, Institut Pasteur

Impact of chronic inflammation on sickness behaviors

The brain senses inflammatory signals upon infection and responds by inducing sickness behavior, which is characterized by fever, lethargy, social withdrawal and reduced appetite. This coordinated response of the immune system and the brain is a strategy to control infection in the host, as well as at the population level. However, it is unclear how behavior and metabolism are affected during chronic inflammation. We are investigating the influence of chronic inflammation on behavior and metabolism by utilizing programmable, refillable micro-infusion pumps. By measuring behavioral parameters in real time, we found that prolonged systemic inflammation increases the energy expenditure to critical threshold levels. To maintain viable metabolism, physical activity is reduced, and core body temperature occasionally drops to very low levels (torpors), leading to new states of equilibrium (allostasis). Our data show that chronic inflammation imposes critical energetic thresholds that force the brain to regulate new states of equilibrium (allostasis) in order to maintain vital body functions.

Keywords : Chronic inflammation, Sickness behaviors, Metabolism

Talk abstract

Pierre-Jean CORRINGER
Signalization and Receptor Dynamics Lab, Department of Neuroscience, Institut Pasteur

Designing allosteric modulators of the 5th subunit of nicotinic receptors

The nicotinic acetylcholine receptors (nAChRs) are pentameric complexes belonging to the superfamily of pentameric ligand-gated ion channels (pLGICs), mediating excitatory cholinergic communication between cells in the nervous system. In the brain, the major nAChR is made by the association of the α4 and β2 subunits, and a minor population also contains the α5 subunit (α4β2α5 nAChRs). Recent genomic and epidemiologic data have demonstrated a link between a highly prevalent (single-nucleotide) polymorphism (SNP) of the α5 subunit and both smoking addiction and lung cancer. Since this α5SNP generates a loss of function of α4β2α5 nAChRs, it is expected that activating specifically α4β2α5 nAChRs by positive allosteric modulator targeting the α5 subunit (PAMα5) would be a treatment of smoking dependence. However, α5 is an « orphan » subunit for which no ligand has been found at present.
To discover de novo a PAMα5, we targeted a unique binding site at the interface between the α5 and α4 subunits. This α5/α4 site is homologous to the ACh binding site located at the α4/β2 interface, but shows significant differences in amino-acid composition and does not bind ACh and nicotine. Using a fragment-based drug-discovery approach, we generated a series of PAMs and NAMs with far reaching potential for the treatment of not only addiction, but also cognitive impairment.

Keywords : Drug design, Nicotinic receptor, Allostery

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Talk abstract

Thomas SCHWARZ
Department of Neurology, Boston Children's Hospital

Mitochondria dynamics from neuronal cell biology to translational science

Mitochondrial dynamics are complex and highly regulated; they include long-range movements as well as fission and fusion. These dynamics are particularly crucial for neurons as a means of distributing adequate energy and metabolic supply to every part of the cell and adjusting to changing cellular conditions. Defects in the proteins that underly these dynamics often cause neurological disorders and one well-studied example is Autosomal Dominant Optic Atrophy, which arises from mutations in Opa1 – a catalyst of the fusion of inner mitochondrial membranes. We have made a mouse model of ADOA and uncovered a likely avenue for therapeutic intervention – inhibition of the enzyme SARM1. We are also studying a novel function for axonal transport of mitochondria – the cotransport of selected mRNA species that are tethered to the surface of the mitochondrion by binding to synaptojanin2. Mutations of the RNA Recognition Motif within synaptojanin2 prevents the transport of mRNA, including that encoding PINK1, into axons and dendrites.In consequence, the PINK1/Parkin pathway cannot be activated in distal axons, synaptic respiration is reduced, and the synaptic metabolome is altered. RNA transport via mitochondria and synaptojanin2 are thus an adaptation by which neurons can support local protein synthesis far from the soma.

Sylvain LEVALLOIS
Biology of Infection Lab, Department of Cell Biology and Infection, Institut Pasteur

Neurolisteriosis impact on microglia and cerebral functions

Central nervous system infections are severe, often resulting in death or neurological impairment. The bacterium Listeria monocytogenes (Lm) is a model pathogen and the causative agent of listeriosis, a foodborne infection. Upon entry into the central nervous system (CNS), it is responsible for neurolisteriosis, one of the most severe forms of brain infection. Neurolisteriosis has a poor prognosis, both in terms of mortality, with a lethality rate of 30% even under adequate antimicrobial treatment, and cognitive sequelae among survivors, which occurs in around 50% of cases (1). However, its pathophysiology remains poorly understood and the mechanisms responsible for long-term brain damage occuring after resolution of the infection are also unknown.

Using a humanized mouse model and clinically relevant neuroinvasive Lm strains, we show an increased susceptibility of the CNS to Lm infection compared to other systemic organs. Consistent with the brain being described as an immunoprivileged organ (2), we show that this results from a less efficient innate immune response in the brain compared to other organs. Upon infection by Lm, we observe that microglia, the resident brain macrophages, rapidly die from necroptosis, while bone-marrow derived monocytes enter the CNS to repopulate the brain parenchyma. To assess the impact of monocyte engraftment on the neurological sequelae of neurolisteriosis, we treated infected mice with antibiotics and followed them after infection resolution. We observe that these monocytes differentiate into microglia-like cells, partially contribute to microglia repopulation, and express T-cell recruiting chemokines, leading to the entry of IFN-γ producing CD8+ T-cells into the CNS. In line with the inflammatory effect of IFN-γ on macrophages, endogenous microglia display significant changes of their transcriptomic and protein expression profile weeks after infection resolution. Microglia are essential in maintaining cerebral homeostasis (3), and accordingly, their change in phenotype after neurolisteriosis is associated with changes in the behavior of previously infected mice.

Therefore, we plan to describe the neurological sequealae following neurolisteriosis resolution and to identify the precise mechanisms by which neuro-immune alterations after neurolisteriosis are responsible for cerebral impairments.

Keywords : Infection, Microglia, Listeria

Talk abstract

Aleksandra DECZKOWSKA
Brain-Immune Communication Lab, Department of Neuroscience, Institut Pasteur

Immune-brain communication via the CSF

The niche of the bone marrow present in the skull bone is connected to the brain territory via ossified channels. Recent publications demonstrate that the CSF enters the skull marrow niche to shape hematopoiesis, and the immune cells produced in the marrow infiltrate the dural layer of the meninges in physiology, and the brain territory in infection and acute injury. In the marrow, the hematopoietic output critically depends on the stromal cells of the niche, which nourish the dividing cells and regulate their differentiation. We investigate the activity of the skull marrow stroma under physiological conditions and its possible role in maintaining brain inflammation in aging and Alzheimer's disease.

Keywords : CSF, Choroid plexus, Bone marrow

Talk abstract

Guilherme DIAS DE MELO
Lyssavirus Epidemiology and Neuropathology Lab, Global Health Department, Institut Pasteur

Long Covid in the hamster model

It is increasingly clear that SARS-CoV-2 infection does not only affect the airways, but also the central nervous system (CNS), sometimes leading to long-lasting signs, including neuropsychiatric manifestations and cognitive deficits. These and other persistent symptoms constitute a novel entity called long Covid or Post-Acute COVID-19 Syndrome (PACS). However, it still lacks definitive diagnostic criteria and a universally accepted definition, as well as a fully comprehensive view of its causal mechanisms. Our working hypothesis is that SARS-CoV-2 and the related inflammatory response can trigger a central mechanism in the CNS leading to symptoms persistence. We previously demonstrated that different variants of SARS-CoV-2 could invade the brain via the olfactory bulbs. We are now focusing on the brainstem and the occurrence of neuropsychiatric and cognitive symptoms in the post-acute phases. To that, we developed and characterized a long Covid model in golden hamsters based on sex, severity of disease, and variant of SARS-CoV-2 in an 80-day timeframe. As observed in human patients, Wuhan SARS-CoV-2 and the variants Delta and Omicron/BA.1 induced prolonged, sometimes relapsing, behavioral changes including anxiety, depression and memory impairment. In the acute phase, the brainstem suffers from viral replication and an unbalanced innate immune response. It disturbs the controlled brain metabolism, affecting neurogenesis, cellular communication, and neuronal survival. In later phases, a RNAseq study revealed a massive impairment of dopaminergic and glutamatergic synapses, and of other pathways related to neurodegenerative processes including mitochondrial and proteasome dysfunction. Remarkably, while infectious virus was not detected in the lungs in the post-acute phase, some brainstems were still infected. Overall, this work will improve our understanding of the spatiotemporal dynamics of SARS-CoV-2 infection, from entry into the brain to long-term CNS alterations. Unveiling these fundamental mechanisms should be of broad interest to the scientific community, as these results may be applicable to other, less understood, neuroinvasive pathogens, whose infectious process may result in neuropsychiatric symptoms and cognitive impairment.

Keywords : Behavior disorders, Neuroinfection, SARS-CoV-2

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Talk abstract

Maroun ABI YOUNES
Neuroinfection and Immunity Lab, Neuroscience Institute of Paris Saclay

Exploring the neurological deficits of viral infection in the zebrafish central nervous system

Viral invasion of the Central Nervous System (CNS) poses severe risks, potentially leading to cognitive deficits in early life while the brain is still developing (1). Additionally, recurrent infection by neurotropic viruses has been linked to the occurrence of some neurodegenerative diseases (2). Vertebrates counter viral infections by activating the interferon (IFN) signaling pathway, thereby inducing the transcription of cytokines and IFN stimulated genes (ISG) (3), that can exacerbate CNS damage in some cases (4). In this study, we are infecting zebrafish larvae with Sindbis virus (SINV) (5) for RNA viruses and herpes simplex 1 virus (HSV-1) for DNA viruses to study immune cell dynamics, infected brain regions, neural network components, neural activity, behavioral phenotypes, and potential harm from ISGs due to the interferon response.

Pericardial injections of SINV into 3 dpf zebrafish larvae establishes viral infection in the periphery; the CNS, specifically the hindbrain and occasionally the midbrain, is invaded 2 days later via the vagal nerve. This results in a sustained IFN response evident in the expression of the ISG mxa in infected regions. CNS infection resulted in reduced swimming frequency, suggesting motor deficits. We are currently studying the changes in synapse density, neuronal activity and viability, and their link to behavioral changes. Furthermore, we are exploring the specific role of microglia in these phenotypes using transgenic lines or mutants to deplete macrophages. Furthermore, we are exploring the potential for long term CNS infection with HSV-1 by using autophagy- and macrophage-deficient larvae.

These results, in addition to results obtained by a parallel project in the lab studying the direct effect of recombinant IFN on neuronal activity and behavior, should allow us to distinguish between virus- and inflammation-induced neurological deficits.

Keywords : Viral infection, Encephalitis, Zebrafish

Talk abstract

Brice BATHELLIER
Auditory System Dynamics and Multisensory Processing Lab, Hearing Institut, Institut Pasteur

Toward auditory cortical implants for hearing restoration

Despite the enormous success of cochlear implants, achieving complete hearing restoration is still a challenge. In this presentation, I will cover our preclinical research on new avenues to provide auditory information at the level of the central brain in the auditory cortex. Our approach combines modern machine learning techniques with new methodologies to stimulate the brain and provide auditory information much beyond the density of current devices.

Keywords : Deep learning, Optogenetics, Prostheses

Talk abstract

Saaid SAFIEDDINE
Technologies and Gene Therapy for Deafness Lab, Hearing Institut, Institut Pasteur

Gene therapies for restoring hearing in deaf children: are we there?

Deafness caused by mutations in the otoferlin gene, known as DFNB9, accounts for 2 to 8% of genetic deafness cases. We have developed a therapeutic vector that provides the first proof of concept that viral gene therapy can effectively treat hearing impairment in a preclinical model of human DFNB9 deafness. The human version of this therapeutic vector is currently in successful phase II clinical trials for DFNB9 patients. I will outline the development journey of this vector, from its conceptualization to its application in treating DFNB9 patients. Additionally, I will discuss how our recent research demonstrated that this vector's application could be extended to atypical forms of DFNB9 caused by in-frame mutations of otoferlin, thereby offering treatment options spanning the entire spectrum of DFNB9-related hearing loss.

Keywords : DFNB9, Deafness, Viral, Gene therapy

Talk abstract

Nicolas MICHALSKI

Plasticity of Central Auditory Circuits Lab, Hearing Institut, Institut Pasteur

The cerebrovascular system: the missing link between hearing loss and dementia ?

People with hearing loss have two to five times more risk of developing dementia later in life than people without hearing loss. However, the biological processes linking hearing loss to dementia are not known. This lack of mechanistic knowledge represents a missed opportunity for the treatment of some forms of dementia, as hearing loss is the most significant potentially reversible risk factor for dementia (9% of patients). The vasculature plays an essential role in the neurodegenerative pathophysiological process of dementia. We have previously shown that auditory deficits triggers vessel loss in auditory areas of the brain. By combining the expertise of the Michalski (Institut Pasteur) and Renier teams (Paris Brain Institute, we obtained precise 3D whole brain reconstructions of the cerebrovascular network in mouse models of deafness. These data revealed that cerebrovascular deficits in deaf mice, initially confined to auditory areas, spread to other brain regions (prefrontal cortex, hippocampus, midbrain) during late adulthood. Moreover, we measured a significant brain-wide protection of these deficits when hearing was restored through gene therapy. We propose that the cerebrovascular network may be the Achilles heel linking hearing loss and dementia and that cerebrovascular deficits may be reversible upon hearing restoration.

Keywords : Cerebrovascular system, Hearing loss, Dementia

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Talk abstract

Florent HAISS

Neural Circuit Dynamics and Decision Making Lab, Department of Neuroscience, Institut Pasteur

Sensory coding and correlates of decision making in primay sensory cortex

During perceptually guided decisions, correlates of choice are found as upstream as in the primary sensory areas. However, how well these choice signals align with early sensory representations, a prerequisite for their interpretation as feedforward substrates of perception, remains an open question. We designed a complex percpetual decision making task in which male mice compared stimulation frequencies applied to two adjacent vibrissae. The optogenetic silencing of individual columns in the primary somatosensory cortex resulted in predicted shifts of perception , demonstrating that perception depends on focal, early sensory representations. Functional imaging of hundreds of single neurons in cortex revealed mixed coding of stimuli, choices and engagement/motivation in the task. From trial to trial, representation of stimuli and choice varied substantially, but mostly orthogonally to each other, suggesting that perceptual variability does not originate from primary somatosensory cortex fluctuations but rather from downstream higher cortical areas. Together, our results highlight the role of primary sensory areas in forming a reliable sensory substrate that can be used for flexible downstream decision processes.

Keywords : Perceptual decision making, Neural circuits, Two-photon imaging

Talk abstract

Yannick GOULAM HOUSSEN
Bioimaging Facility, Hearing Institut, Institut Pasteur

A facility for head-mounted two-photon microscopy in freely moving animals

Understanding the mechanisms of cognition and behavior necessitates broad and precise insights into neuronal activity during the performance of complex tasks in naturalistic settings. Over the past two decades, two-photon (2P) microscopy has significantly advanced, expanding the number of neurons that can be simultaneously recorded in awake, behaving animals and offering unmatched precision in determining neuronal location and genetic identity. Nevertheless, conventional 2P microscopy requires head-fixation of the subject, imposing significant constraints on the range of behaviors that can be studied and their relevance to natural conditions. A recent innovation by the Moser lab (Kavli Institute - Trondheim - Zong et al., Cell, 2022) has overcome these limitations, enabling 2P microscopy to be conducted in freely moving, behaving mice. Despite being open-source and requiring relatively modest investment, this technology remains complex to establish and operate.
We have implemented a head-mounted 2P microscope within the imaging facility at the Institut de l'Audition (IdA), which will benefit several Pasteur & UPC teams and further research projects in IdF region. This open facility will be the first of its kind in the IdF region and will enable the emergence of cutting projects in the field of neuroscience to decipher the neuronal underpinnings of perception across brain states or complex behavioral situations and of cognitive processes such as navigation, flexibility, social interactions, and complex motor skills. At IDA, it will be employed to investigate the effects of brain states across sleep and wakefulness on auditory processing, aiming to elucidate the mechanisms underlying sound perception during wakefulness and its attenuation during sleep. And within the region, we have started several collaborations within the Parisian neuroscience community. The projects are covering different studies from hippocampus imaging to temperature perception in the olfactory bulb.

Keywords : Imaging, Freely-moving, Behavior

Talk abstract

Alexandre BLANC
Decision & Bayesian Computation Lab, Department of Neuroscience, Institut Pasteur

A facility for head-mounted two-photon microscopy in freely moving animals

Understanding the mechanisms of cognition and behavior necessitates broad and precise insights into neuronal activity during the performance of complex tasks in naturalistic settings. Over the past two decades, two-photon (2P) microscopy has significantly advanced, expanding the number of neurons that can be simultaneously recorded in awake, behaving animals and offering unmatched precision in determining neuronal location and genetic identity. Nevertheless, conventional 2P microscopy requires head-fixation of the subject, imposing significant constraints on the range of behaviors that can be studied and their relevance to natural conditions. A recent innovation by the Moser lab (Kavli Institute - Trondheim - Zong et al., Cell, 2022) has overcome these limitations, enabling 2P microscopy to be conducted in freely moving, behaving mice. Despite being open-source and requiring relatively modest investment, this technology remains complex to establish and operate.
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Keywords : Imaging, Freely-moving, Behavior

Talk abstract

Jane FOSTER
Center for Depression Research and Clinical Care, Peter O'Donnell Brain Institute, UT Southwestern, Dallas

Advancing human microbiome research in the context of psychiatry

It is time for a paradigm shift in biomarker discovery in psychiatry. The need for biologically based models to understand clinical heterogeneity to improve treatment outcome in psychiatry is gaining momentum. Integrating the microbiome into biomarker discovery is advantageous as it provides an accessible and biologically based approach to generate more precise, clinically relevant biomarkers that consider the host and the environment in a comprehensive way. Preclinical research has linked microbiome to neurodevelopment, neurotransmission, neuroplasticity, neuroimmunology, and behavior .
This presentation will highlight preclinical studies that demonstrate the importance of microbiome-T cell signaling to brain function and behavior. In addition, recent clinical findings that suggest the microbe-host relationships in animal studies are mirrored in individuals with depression. These translational studies demonstrate the importance of considering the microbiome in mental health research. This presentation will conclude with a discussion of the potential benefitis and opportunities related to microbiome-related biomarker discovery for therapeutic development and precision medicine approaches.

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Talk abstract

Jean-Pierre CHANGEUX

Allosteric modulation of pentameric receptor channels and relevance to Covid 19,
Department of Neuroscience, Institut Pasteur

Louis Pasteur et les neurosciences à l'Institut Pasteur

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Poster abstracts

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Poster abstract
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Aïda YAKHLEF SANCHEZ
Progressive Sensory Disorders, Pathophysiology & Therapy Lab, IHU-Reconnect, Hearing Institut, Institut Pasteur, Inserm, Université Paris Cité, AP-HP

Characterization of inflammatory mechanisms underlying progressive and age-related hearing impairments: insights from clarins

Congenital hearing loss affects 26 million people worldwide, with 60% (~ 15 million) attributed to genetic factors. However, an increasing number of cases (> 440 millions of cases), inherited or acquired, are postnatal and progressive. Among these, age-related hearing loss (or presbycusis) is one of the most prevalent and debilitating condition that significantly impact the quality of life with 1 in 3 adults over the age of 65 experiencing some degree of hearing loss. Untreated hearing decline impedes communication leading to social isolation, depression, and reduced physical and cognitive functions. Although, the disease mechanisms and functional pathways involved in late-onset and/or progressive hearing loss remain elusive, it is increasingly recognized that inflammation plays a crucial role in the development and progression of hearing disorders, whether genetic, infectious, noise-related or age-related.

Our project aims at investigating the molecular pathways related to inflammation using animal models with progressive hearing loss or with altered inflammatory homeostasis. Ongoing work shows that clarin-deficient mice with inherited postnatal progressive hearing impairments, are valuable tools for elucidating the origin of progressive hearing loss. In-depth phenotyping of these mice models allowed us to establish precise structural and molecular alterations in both auditory hair cells and neurons. OMIC approaches, such as transcriptomics, were carried out on distinct clarin-deficient mice that depict various clinical situations observed in humans. Preliminary analyses have identified several molecular pathways in hearing decline, including oxidative stress, vascular and inflammation pathways. Ongoing analyses of our OMIC data pinpoint specific inflammatory pathways and mediators that are dysregulated during the progression of hearing loss. Through the characterization of these pathways in health and disease conditions, we aim to provide key insights into the molecular mechanisms linking inflammation to age-related hearing decline. Understanding the molecular and cellular mechanisms involved in the cochlea will pave the way to targeted therapeutic opportunities to selectively modulate cochlear inflammation, mitigate hearing damage, and restore auditory function.

Keywords : Progressive hearing impairments, Inflammation, Clarin-deficient mice, Omic approaches

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Poster abstract 2

Ali EL CHEIKH

Progressive Sensory Disorders, Pathophysiology & Therapy Lab, IHU-Reconnect, Hearing Institut, Institut Pasteur, Inserm, Université Paris Cité, AP-HP

Sensorimotor Synchronization in Children: Developmental Trajectories from Ages 4 to 7

Temporal synchronization between motor and sensory systems is crucial for fluent speech perception and production. In adults, this synchronization is most effective at a temporal rhythm corresponding to the average syllable rate. Interestingly, adults who are better synchronizers also show improved performance in word learning tasks. In this study, we aim to determine if a similar effect influences speech learning in children. We measured the ability of children aged 4 to 7 years to produce speech in rhythm with an auditory signal presented at 4.5 Hz. We hypothesize that synchronization performance will correlate with the children's vocabulary levels. We expect that better temporal synchronization between motor and sensory systems will be associated with higher overall language skills in children. In this poster, we will present the study results, which are currently being collected, to explore the relationship between motor-sensory synchronization and language learning in children.

Keywords : **Synchronization, Speech perception, Speech production, Motor and Sensory systems**

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Poster abstract 3

Allan MULLER
Hearing Institut, Institut Pasteur

Conservation of sensory coding in the primary auditory cortex during NREM sleep

Sensory disconnection during sleep contrasts with the evidence for largely preserved stimulus responses in the sensory cortex, in particular for sounds. Here, we followed spontaneous and sound-evoked activity in the mouse auditory cortex across sleep and wakefulness using two-photon calcium imaging. We observed that, despite a reduction in population responses, the structure and identity of sound representations is almost unaffected during sleep, contrary to what is observed under anesthesia. Moreover, while under anesthesia spontaneous and evoked activity are confounded in the same population activity subspace, both in wakefulness and sleep spontaneous and evoked activity live in distinct subspaces, indicating that spontaneous cortical activity in sleep is neither a masker nor a systematic replay of sound-driven activity. These results indicate that auditory disconnection in sleep depends on mechanisms that are downstream of the auditory cortex, leaving specific cortical feature selectivity intact for acoustic surveillance.

Keywords : Sleep, Auditory cortex, Two-photon imaging

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Poster abstract 4

Ana BLAS-MEDINA
Brain-Immune Communication, Neuroscience and Immunilogy departments

Microbial signals shape postnatal development of the choroid plexus and the brain

Postnatal development is a critical window of increased brain circuit remodeling coinciding with colonization of mucosal surfaces by microbial communities. A growing body of evidence suggests that perturbations of the microbiome-brain communication in the perinatal window are a risk factor for neurodevelopmental disease onset. Holding a strategic position to mediate such microbiome-brain crosstalk, the choroid plexus (CP), primary producer of cerebrospinal fluid (CSF), shapes brain function and completes its maturation postnatally, yet the extent of microbial product influence on this process remains to be studied. Using a transcriptomic approach, we show that CP development was accelerated and altered between postnatal days 10 and 15 when microbial factors are absent, coinciding with the dysregulation of genes involved in extracellular matrix organization, cell proliferation, stress pathways, and glucocorticoid responses. Furthermore, our study revealed abnormalities in brain and third ventricle volume in adult germ-free mice, likely responding to changes in CSF flow or composition. Overall, our findings shed light on a new pathway of microbiome-brain communication, suggesting that the cognitive abnormalities observed in adult germ-free mice may be partially caused by alterations in postnatal CP development. Therefore, early interventions aimed at modifying the microbiome-CP crosstalk may help prevent neurodevelopmental disease onset.

Keywords : Microbiome, Choroid plexus, Postnatal development

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Poster abstract
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Anna PEPE
Membrane Traffic and Pathogenesis, Department of Cell Biology and Infection

Mechanisms of tau spreading related to Alzheimer's disease progression

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by extracellular accumulation of amyloid-β and intracellular formation of hyperphosphorylated tau protein inclusions. The propagation of pathological tau proteins follows a prion-like mechanism, involving its seeding and transfer along connected neurons. However, important aspects of tau biology remain still open questions: (i) the mechanisms involved in tau transfer; (ii) which type of tau assemblies (oligomers or fibrils) is mostly transferred and has the highest seeding activity; (iii) in which cell compartment tau seeding take place. Recently, we have shown Tau aggregates transfer between neurons via Tunneling Nanotubes (TNTs), actin-rich open channels connecting cells. This project aims to identify where tau fibrillation takes place, how tau spreads, and which assemblies are transferred. The understanding of these mechanisms is pivotal to developing effective therapies.

Keywords : Amyloid proteins, Tau TNTs

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Poster abstract 6

Amy BLONDEAU

Microenvironment and Immunity, Immunology departement & Perception and action, Neuroscience department

Deciphering the contribution of the aging of the skull bone marrow to brain aging and neurodegeneration in Alzheimer`s Disease

We are what we breath; breathing shapes our whole body state via oxygenation but is also a strong tool to regulate our mental state. The lungs and the brain are strongly connected to assure this essential function. One of the way to look at this connection is to study the neuroimmune interactions in the lung. Being exposed to air, the lung is naturally exposed to all sorts of threats such as potential pathogens, chemical agents, pollutants, and allergens. Therefore, the lung must be able to maintain the integrity of the tissue barrier function while ensuring the essential gas exchanges for our survival. The nervous system plays an important role in this challenge relaying information produced by the lung and its immune system to the brain via sensory neurons and, in turn, regulates lung immunity through parasympathetic and sympathetic neurons. This entire regulatory loop has been little explored, and its study would allow us to better understand the extent of the brain's role in lung physiology and pathophysiology. More precisely, we want to define how are the immune challenges of the lungs perceived in the brain and identify regions of the brain that are specifically activated by immune challenges of the lungs. We want to understand if these regions are able to imprint these challenges and are then recall when the challenge reoccurs.

Keywords : Lung, Neuro-immune interactions

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Poster abstract
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Astrid NILSSON
Decisions and Bayesians computations lab, Department of Neuroscience, Institut Pasteur

Neuromodulation at the single neuron scale: from experiments to neural models

Animals' internal states change behavioural priorities and thus influence even decisions unrelated to these internal states. Hence, for example in feeding state information, how this information about hunger, is transmitted to non-feeding-related circuits and the circuit mechanisms involved in biasing non-feeding-related decisions remain an open question. Here, we explore neuromodulation experimentally and theoretically. Experimentally, using the Drosophila larva as a model system, combining calcium imaging, neuronal manipulations, behavioural analysis and computational modelling, we determined that the competition between different aversive responses to mechanical cues is biased by feeding state changes. We found that this is achieved by differential modulation of two reciprocally connected inhibitory neurons promoting opposing actions. Theoretically, we show, using toy machine problems, the structural consequences of allowing neuromodulation in neural networks, both purely feedforward and recurrent.

Keywords : Neuromodulation, Circuit mechanisms, Drosophila larva

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Chiara CIMMARUTA
Molecular Mechanisms of Pathological and Physiological Ageing Lab, Department of Developmental and Stem Cell Biology, Institut Pasteur

Unraveling the pathogenesis of Cockayne Syndrome: insights from patient-derived neural organoids

Cockayne syndrome (CS) and UV-sensitive syndrome (UVSS) share defective repair of UV-induced DNA damage but exhibit dramatically distinct clinical phenotypes. While both conditions share UV-induced skin photosensitivity, only CS presents with premature aging and neurodegeneration. Our previous investigation detected mitochondrial dysfunction and oxidative/nitrosative stress in CS but not in UVSS fibroblasts, suggesting their probable role in CS pathophysiology (1). However, the impact of these factors on CS neurological defects remains unexplored.
Given the lack of suitable animal models and the clinical heterogeneity of CS, we developed patient-derived neural organoids to investigate mitochondrial dysfunction and ROS/RNS mismanagement in CS pathogenesis. Neural organoids represent a remarkable advancement for disease modeling, enabling us to recapitulate key CS clinical features (i.e. microcephaly, hypomyelination) in correlation with the phenotypic severity within an in-vitro system (unpublished).
In our study, we aimed to elucidate the impact of oxidative stress on the developing human brain and assess the therapeutic potential of antioxidant and anti-RNS (nitrosative stress) treatments. Notably, our findings revealed that antioxidant and anti-RNS treatments rescued identified neural defects in CS cerebral organoids, highlighting a potential critical role of oxidative stress in CS pathogenesis.
By leveraging patient-derived neural organoids, we provide novel insights into the neuropathological features of CS and offer promising avenues for therapeutic intervention in this life-threatening condition. This study underscores the importance of innovative modeling approaches in unraveling the complex pathogenesis of rare genetic disorders like CS.

1. Chatre L. et al; PNAS, 2015; doi:10.1073/pnas.1422264112

Keywords : N**eural organoids, Oxidative stress, Neurodegeneration, Disease-modeling**

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Poster abstract
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Chloé BOUARAB
Integrative Neurobiology of Cholinergic Systems Lab, Department of Neuroscience, Institut Pasteur

Investigating the role of α5 containing nicotinic acetylcholine receptors in eating disorders

Nicotinic acetylcholine receptors (nAChRs) are pentameric ionotropic receptors composed of a combination of α and β subunits. Human genetic association and preclinical studies have shown a key role of α5 containing nAChRs (α5*nAChRs) in the risk to develop nicotine addiction. Tobacco smoking is highly comorbid with bulimia nervosa and binge eating disorders. Interestingly, genetic variation at CHRNA5 has also been associated with higher body mass index (BMI) in never smokers, but lower BMI in current smokers, and increased appetence for food in rodents. In this project we sought to investigate the role of α5*nAChRs in eating disorders with a compulsive component in a rat model. Using an intermittent limited access to high fat diet protocol, we observed that rats with limited and daily access to margarine for several weeks develop a binge eating-like behavior. Interestingly, galantamine, administered at a dose proposed to induce α5*nAChR allosteric modulation, reduced margarine intake in bingeing rats. To better characterize the role of α5*nAChR in these observations, we next assessed the effects of galantamine on binge-like and compulsive-like eating in rats knockout for Chrna5. Remarkably, using quantitative PCR, we further identified alterations in the expression of Chrna5, but not of other nicotinic subunit genes, specifically in the dorsomedial striatum and the prefontal cortex of bingeing rats, brain regions crucially involved in executive behavioral control. Altogether, our data emphasize the role of α5*nAChRs in the loss of control over eating and suggest that they may represent interesting therapeutical targets notably for more favorable outcomes in smokers with comorbid issue.

Keywords : Eating disorders, Nicotinic receptors, Rat

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Poster abstract
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Claire-Hélène DE BADTS
Perception and Action Lab, Department of Neuroscience, Institut Pasteur

BLA circuits underlying emotional biases in a male and female mouse model for depression

Depression is the single largest contributor to disability worldwide, affecting 300 million people annually, and twice more women than men. Beyond reduced activity and motivation, depression has been shown to be associated with a negative bias of valence: patients find sensory stimuli less pleasant. In rodents, basolateral amygdala (BLA) circuits play a major role in valence assignment, with specific pathways responding to positive or negative stimuli. Using a mouse model for depression of Unpredictable Chronic Mild Stress (UCMS), we showed that BLA-to-NAc neurons, that preferentially respond to positive stimuli, are less active in depressive-like male mice, and BLA-to-CeA neurons, that preferentially respond to negative stimuli, tend to be more active. These alterations are not restored by chronic treatment with Ketamine, a novel and fast-acting antidepressant, even if depressive-like behavior is largely rescued. In females however, depressive-like mice present a higher activation of BLA-to-NAc neurons than controls, which is restored by Ketamine, even if the treatment has very limited antidepressant effects in females. Of note, all studies investigating the preferential response of BLA-to-NAc neurons to positive stimuli used male individuals. So, this work highlights the possibility that BLA circuits may have a sex-specific role in valence assignment and thus be differently involved in the physiopathology of depression.

Keywords : Basolateral amygdala, Mouse model for depression, Ketamine, Antidepressant, Sex-specificity

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Poster abstract
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Eli BARTHOME
Human genetics and cognitive funcitons Lab, Department of Neuroscience, Institut Pasteur

Contribution of regulatory variants to brain related traits

Autism concerns 1-2% of the population and is characterized by atypical social interactions, and repetitive behaviors/interests. Autistic individuals display a high clinical heterogeneity, and often co-occurs with other psychiatric and medical conditions, such as intellectual disability (ID) or epilepsy. Autism heritability is estimated around 80%, and studies on rare variants impacting protein structure have pointed towards differences in synaptic and chromatin remodelling pathways. Genetic variants found more frequently in the general population also contribute (with smaller individual effects) in an additive manner to the development of neurodevelopment conditions (NDC), but their specific impact on autism and NDC susceptibility remains unclear.
In this study, we investigated the collective contribution of common variants in more than 40 brain-related traits. Using a dataset of over >50,000 expression quantitative trait loci (eQTL) detected in fetal brain, adult cortex, and cerebellum samples, we examined how the additive effect of these variants affect gene expression and biological pathways in different traits and conditions. We compared common variants identified in autism and other neuropsychiatric conditions, such as attention-deficit/hyperactivity disorder, intellectual disability or epilepsy and characterized their effect on gene regulation. Our findings shed new lights on the frequent regulatory and coding common variants that are shared among neurodevelopment conditions or among psychiatric. Characterizing the genes that are up or downregulated in the different traits will contribute to a better understanding of the genetic basis of these conditions.

Keywords : Human genetics, Brain development, Autism

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Poster abstract
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Elvira INFANTE
Cell Polarity, Migration and Cancer Lab, Department of Cell Biology and Infection, Institut Pasteur

Mechanoregulation of glioblastoma cell survival

Glioblastoma (GBM) is one of the most aggressive and common brain tumours, with a very poor prognosis. The standard therapeutic approach is surgical resection - which remains difficult due to the risk of post-resection neurological deficits - followed by radiotherapy and treatment with temozolomide. Nevertheless, virtually all patients with GBM suffer a relapse. Understanding the molecular mechanisms that characterise this cancer's aggressiveness, progression and resistance to current treatments is essential to developing effective therapies. It is now recognized that the interaction between the microenvironment and the mechanical properties of GBM influences cellular adaptation, tumour heterogeneity and resistance to treatment. Among the best characterized molecular player that respond to mechanical forces exerted on and by the cells is the intermediate filaments vimentin. Vimentin provide structural and mechanical support to cells and maintain the shape of cells and nuclei. Single-cell transcriptomic analysis of glioblastoma previously identify alterations in vimentin expression in GBM patients. Here, by combining multidisciplinary techniques, we discovered an unconventional impact of cell compression in promoting GBM cell survival to DNA damage and revealed the key role of vimentin in buffering compression-induced nuclear responses.

Keywords : Glioblastoma, Vimentin, Mechanical compression, DNA damage

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Poster abstract
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Etienne GOSSELIN
Auditory system dynamics and multisensory processing Lab, Hearing Institut, Institut Pasteur

Massive perturbation of sound representations by anesthesia in the auditory brainstem

Keywords : Sensory systems, Anesthesia, Brainstem

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Poster abstract
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Gabriela FERREIRA DE MEDEIROS
Integrative Neurobiology of Cholinergic Systems Lab, Department of Neuroscience, Institut Pasteur

Unravelling the role of prefrontal alpha7 nicotinic acetylcholine receptors in inhibitory control: a behavioral investigation using touchscreen technology

Dysfunctional α7 nicotinic acetylcholine receptors (α7*nAChRs) and their genetic regulation have been associated with several neuropsychiatric diseases, including schizophrenia and Alzheimer's disease (AD). Preclinical studies revealed that α7*nAChR ligands can improve executive function, commonly impaired across neuropsychiatric disorders. Yet, a translational gap prevents these findings from resulting into clinically effective treatments. To tackle this translational gap, we combine approaches such as transgenic rats, viral vector-mediated local gene expression, touchscreen-based behavioral assays, and pharmacological manipulations, to study the role of these receptors with region-specific resolution. Our findings show that knockout rats for the α7 subunit gene (α7KO) present a general deficit in inhibitory control as observed in the continuous performance task and the differential reinforcement of low-rates of responding task, which seems unrelated to deficits in attention, learning or motivation, and unlikely to be due to compensatory alterations in non-α7 nAChR subunits' expression. We further aim at unravelling the importance of α7*nAChRs expressed in the infralimbic cortex and in the anterior cingulate cortex (ACC) in the modulation of cognition by re-expressing these receptors specifically in these regions in α7KO rats. Finally, we aim at identifying the contribution of α7*nAChRs to the development of cognitive deficits in the context of neuropsychiatric disorders, and, in particular, the putative interaction between these receptors and the amyloid beta peptide in a rat model of AD. So far, our approach has revealed a crucial role of α7*nAChRs in response inhibition and represents a promising tool to screen new α7*nAChR ligands for therapeutical purposes.

Keywords : α7 nicotinic acetylcholine receptors, Neuropsychiatric disorders, Inhibitory control

Jean David RIANDRIANALY
Antibody Engineering Platform, Department of Structural Biology and Chemistry, Institut Pasteur

Toxicity of Aβ (intracellular pool) in Alzheimer's disease toward new therapeutic approaches developement

One of the pathophysiological model in Alzheimer's disease is the amyloid cascade hypothesis, where the accumulation of Aβ peptides leads to the formation of amyloid plaques, causing inflammation, synaptic loss, secondary tauopathies, neuronal death and clinical deficits.
The aim of this work is to test the efficacy of VHHs to target extracellular and intracellular deposits of Aβ and to assess their therapeutic potential in an AD mouse model.
Our team has developed a VHH, R3VQ, capable of specifically recognizing Aβ. The first part of the project involves optimizing and designing different formats of R3VQ (monomer, dimer, addition of an Fc fragment) and evaluating their in vivo efficacy in APP-PS1-KI mice developing severe brain amyloidosis.
Two enhanced immunotherapy strategies will then be tested on the mice model.
The effect of the treatments will be evaluated through behavioral tests and neuropathological analysis of mice.
Results:All R3VQ formats have been engineered.
ELISA indicated that the different R3VQ formats can detect both fibrillar Aß, the major constituent of amyloid plaques, and soluble (HFIP-treated) Aß species that are known to exert strong synaptotoxic effects.
We performed Thioflavin-T assay to follow fibrilization of Aβ 1-42 over time in presence of our anti amyloid VHH.Stereotaxic injections in the brain of living APP/PS1 KI mice showed that monomeric and dimeric VHHs can label both intra and extra cellular Aβ deposits and diffuse largely in brain tissue. Same experiments performed with a standard anti-Aß IgG underlined reduced diffusion of the antibody in brain parenchyma.Enhanced immunotherapy first results indicate that iv injected monomeric VHH can cross the BBB, diffuse in brain parenchyma and bind to amyloid plaques and enter in neuronal cells.We expect that the results of this study will provide a better understanding of the pathogenicity of the (extra- and intra-cellular) Aβ peptide and test the preclinical efficacy of R3VQ using original passive immunotherapy designs.

Keywords : Alzheimer's disease, VHH, Amyloid beta, Immunotherapy, APP/PS1 KI mouse

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Poster abstract
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Léa HAMON
Perception and Action Lab, Department of Neuroscience, Institut Pasteur

Investigation of the role of GDF11 as a potential blood-brain barrier rejuvenating factor

The blood-brain barrier (BBB) is composed of brain endothelial cells (BECs) that selectively restrict molecular exchange between the blood and the brain. In the neurogenic niche, BBB helps to support and regulate neural stem cell (NSC) self-renewal, proliferation, differentiation and migration. However, with aging, this barrier can deteriorate, resulting in increased permeability and structural changes, including a decline in tight junction proteins. Such BBB disruption can facilitate the invasion of toxins and pathogens and consists of a hallmark of many age-related disorders. Using the organ-on-chip technology, we have successfully recreated features of both young and aged neurogenic niche physiology by integrating murine NSCs and microvascular BECs that exhibit age-dependent characteristics in a 3D construction. Barrier integrity assays in this model reveal increased BBB permeability in the aged organ-on-chip compared to young. Previous studies have indicated a decrease in GDF11 levels in the blood plasma of aged mice, and intravenous administration of GDF11 has been shown to induce blood vessel regeneration. Treating aged BECs with GDF11 demonstrated significant effects both at the cellular level and within the organ-on-chip model, resulting in reduced permeability in the aged model upon GDF11 treatment. These findings suggest that GDF11 has the potential to rejuvenate the BBB by restoring its function.

Keywords : Systemic blood factors, GDF11, Organ-on-chip, Blood-Brain-barrier, NSCs

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Alessio QUARESIMA
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Inhibitory control and excitatory connectivity cooperate in the activation of sequence-selective populations

The auditory cortex (AC) is crucial for processing complex sound patterns [Ceballo et al., 2019, Dalmay et al., 2019] and different AC populations activate when the same sounds are presented in different orders [Bagur et al., 2023]. This suggests that the AC transforms spatio-temporal codes into population codes, though the details of this transformation are still unclear. Previous theories propose that order-dependent memories emerge from specific neural structures (sequence detection networks, SDNs) [Knoblauch & Pulvermüller, 2005]. These memories depend on short-term mechanisms like dendritic memory or synaptic plasticity. In prior work, we showed that networks with dendritic non-linearities and inhibitory plasticity (iSTDP) on the dendritic compartments allow to form such memories [Quaresima et al., 2023]. However, the model requires tight inhibitory control, which limits the formation of these memories in an unsupervised setting, as seen in passive listening experiments in vivo.

In this study, we investigate how pre-existing network structures and synaptic plasticity enable the formation of sequential memories. The model consists of 1000 neurons with dendrites with excitatory and inhibitory STDP, and synaptic connections modulated by the E/I balance. During learning, the network is exposed to overlapping sequences. Recognition is tested based on the firing of sequence detector populations. We find that weak inhibitory control of the dendritic compartment and low LTP thresholds favor the formation of sequence detector populations that allow for recognition of sequence identity ($\kappa \sim 0.6$). The network's initial structure also influences recognition, with networks embedding latent cell-assemblies yielding higher accuracy ($\kappa = 0.7$). These results indicate that the modulation of E/I balance enables the formation of sequential memories which provide stable readouts to communicate across cortical areas.

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Role of Synemin in glioblastoma cell invasion

Glioblastoma multiforme (GBM) is the most common and aggressive malignant brain tumors, and represents a significant challenge in oncology. Despite considerable progress in medical research, effective treatments for these cancers remain elusive. This is due to the highly invasive properties and intra-tumoral heterogeneity of GBM. Cytoskeletal components, including intermediate filaments (IFs), are key players in cell mechanics and migration. Recent results from our laboratory show that the intermediate filament network is crucial for GBM invasion. This project focuses on the specific role of Synemin, a type IV IF protein expressed in some GBM cells. The aim of this project is to determine the functions of Synemin and its interactors in mechano-transduction, mechanosensitive cell adhesion, migration and invasion of GBM cells. To carry out this project, different Synemin knock-out and knock-in cell lines were generated from a commercial glioblastoma cell line expressing Synemin. We are currently evaluating the adhesion, mechanosensitive migration, and invasion of Synemin knock-out and wild-type GBM cells, to reveal the impact of Synemin expression in primary GBM cells. Subsequently, biochemical, biophysical and omics approaches will be used to elucidate the molecular mechanisms involved in the functions of Synemin and their implication in GBM progression.

Keywords : Cell biology, Intermediate filament, Glioblastoma, Synemin

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An invertebrate model to identify virulence and neuro-damaging factors during pathogenic infection by Toxoplasma Gondii

Diseases of the central nervous system (CNS) are highly debilitating and often fatal. In all cases, they are challenging to treat, owing to the complexity of the tissue and its shielding behind strong physiological barriers. Identifying the mechanisms mediating the access and impact of these diseases to the CNS is key to identifying therapeutic targets at multiple levels, including blood-brain barrier permeability, virulence mechanisms and neurodegeneration. Our biological model, the Drosophila larval central nervous system, provides a compromise between in vitro cellular systems and mammalian models, serving as a fast and cost-eMicient platform to identify: i) eMects on the nervous system; and ii) factors crossing or mediating the passage of the blood-brain barrier. Toxoplasma gondii, the cause of toxoplasmosis, is an obligate intracellular parasite. Toxoplasmosis is usually transmitted to humans by domestic animals, by ingesting undercooked meat or by contaminated water. If acute T. gondii infection occurs during pregnancy or in immunocompromised people, its consequences are devastating. In pregnant women, it can cause miscarriage or congenital anomalies that aMect the brain and eyes. Additionally, T .gondii can establish a chronic and latent infection in the brain and 30% of the world's population actually carries this parasite. For both acute and latent forms, a prerequisite for cerebral T. gondii infection is the passage across the protective barriers of the brain, in particular the blood-brain barrier. Therefore, primary objective is to understand how T. gondii penetrates and resists in the brain environment. Additionally, latent forms in the brain are suggested to cause neurological disorders at diMerent time scales, although a demonstration and supporting mechanisms remain to be provided. Thus, our project proposes to use T. gondii infection as a proof-of-concept to identify molecular factors and cellular mechanisms of therapeutic interest for prevalent yet poorly understood neurological diseases with link to mental health.

Keywords : Nervous system, Brain infection, Drosophila melanogaster, Toxoplasma gondii, Infection protocol

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Role of mTORC1 on prefrontal inhibitory plasticity during memory consolidation

Memory consolidation is an essential process for our everyday lives. Memory representations are initially encoded in the hippocampus before being consolidated in the neocortex by synaptic plasticity processes that depend on protein synthesis. Within prefrontal cortex (PFC), inhibitory interneurons are critical in gating incoming hippocampal inputs and shaping pyramidal neuron responses. However, how molecular pathways affect synaptic signaling during memory consolidation is unclear. We hypothesize that mechanistic Target Of Rapamycin Complex 1 (mTORC1), a central regulator of protein synthesis, plays an essential role in inhibitory signalling between the hippocampus and the prefrontal cortex. To test this hypothesis, we first evaluated the role of mTORC1 in memory consolidation using a PFC-dependent spatial object recognition task. We found that infusion of rapamycin, a selective mTORC1 inhibitor, into the PFC immediately but not 3 hours after training disrupted long-term memory expression. Then, we evaluated the role of different prefrontal inhibitory interneurons during memory consolidation. We observed that chemogenetic inactivation of parvalbumin-positive (PV) but not of somatostatin-positive interneurons (SOM) after training enhanced memory performance. Finally, we assessed the effect of silencing mTORC1 in different interneuronal subclasses using shRNA strategies. We found that specific mTORC1 downregulation in PV but not SOM interneurons led to long-term memory expression impairments. Overall, our results suggest a key role of mTORC1 in controlling prefrontal inhibitory interneuron plasticity.

Keywords : Memory consolidation, Prefrontal cortex, Interneurons, mTORC1, Protein synthesis

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Deciphering the contribution of the aging of the skull bone marrow to brain aging and neurodegeneration in Alzheime's Disease

Neurodegenerative diseases are a key unaddressed medical need in modern society. The most prevalent among them is Alzheimer's Disease (AD). Progression of AD has been linked strongly to inflammation, which naturally occurs in tissues in aging. Recent studies have shown that the skull bone marrow directly interacts with the brain through specialized channels, allowing myeloid and B cells to access brain territory. Particularly, the meninges host B cells precursors that are skull bone marrow-derived and differentiate thanks to local factors. Recent studies suggest that cerebrospinal fluid can influence hematopoiesis within this unique niche. Simultaneously, marrow cavities in other locations were shown to undergo aging-related changes related to inflammation as well. Here we characterize the changes in the skull bone marrow niche in Alzheimer's disease (AD). Our study shows that B cell development in the skull bone marrow in AD is impaired. Elucidating the mechanisms underlying skull bone marrow influence on the central nervous system could provide new insights into AD and other neurodegenerative disorders, as well as inform potential therapeutic strategies targeting these interactions.

Keywords : Skull bone marrow, Alzheimer's Disease, Neuroimmunology

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Mauricio SAENZ
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Differential hearing restoration in the DFNB9 mouse model through AAV gene therapy with human and mouse cDNA

Deafness caused by mutations in the otoferlin gene, known as DFNB9, accounts for 2 to 8% of genetic deafness cases. Our team developed and characterized a DFNB9 murine model, demonstrating that otoferlin is crucial for the final steps of synaptic exocytosis, ensuring ultrafast vesicular neurotransmitter release at inner hair cell (IHC) ribbon synapses. This finding led to the conclusion that DFNB9 deafness is a genetically linked auditory synaptopathy. Notably, the team developed a therapeutic vector that provides the first proof of concept that viral gene therapy can effectively treat hearing impairment in a preclinical murine model of human DFNB9 deafness. The human version of this therapeutic vector is currently in successful phase II clinical trials for DFNB9 patients. One of the main unresolved questions in both fundamental and clinical research is whether the preclinical mouse model treated with DFNB9 gene therapy achieves similar hearing recovery and sound signal processing regardless of whether the administered vector delivers human or mouse cDNA. To address this issue, we administered either sequence at two different time points, before (P2) and after hearing onset (P15) using a dual-AAV approach. Thereafter, hearing function was evaluated at different time points, using auditory brainstem responses (ABR), startle reflex, and pre-pulse inhibition (PPI). Following auditory screening, the correct expression and localization of both proteins in the cochlea were confirmed with immunohistochemistry. Our results using murine cDNA validated previous results obtained with gene replacement therapy for DFNB9: ABR thresholds were restored to wildtype levels and the startle reflex and PPI were fairly rescued. Conversely, we found that treatment with human cDNA was not sufficient to elicit the same degree of auditory recovery, ABR thresholds were higher, wave I amplitudes were lower, and latencies were increased. Similarly, we observed an impaired startle reflex and absence of PPI when using the human cDNA. These results suggest that there is an intrinsic functional deficit of human Otoferlin protein when expressed in the murine cellular environment. This hypothesis was supported by IHC membrane capacitance measurements, demonstrating that Ca2+-dependent synaptic exocytosis was only partially recovered after treatment with human OTOF.

Keywords : Gene therapy, Deafness, DFNB9, Inner ear, Translational research

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In vivo study of truncated and zero-layer mutations of the C-terminus of SNAP25 reveals its direct role in auditory hair cell ribbon synaptic exocytosis

SNAP-25, a component of the SNARE complex, is central to synaptic vesicle exocytosis in neurons and neuroendocrine cells. We recently untangled the implication of SNAP-25 in inner hair cells (IHC) synaptic transmission by demonstrating that its targeted deletion in IHC results in profound deafness and cell degeneration. However, one key question was whether the loss of SNAP-25 triggers synaptic dysfunction leading to degeneration, or if SNAP-25 is responsible for another form of dysfunction that indirectly leads to the exocytic defects. To answer this question, we implemented a strategy for inducing in vivo AAV-mediated overexpression of mutated forms of SNAP-25 fused with GFP, within IHC.
We choose two AAV constructs: i) SNAP-25Δ9, which lacks the C-terminal nine amino acids, strongly inhibiting transmitter release, ii) SNAP-25Q174L, a point mutation which disrupts the protein's zero layer, resulted in only a moderate alteration in neurotransmission. The main objective was to investigate their impact on IHC synaptic exocytosis, mirroring findings reported in vitro.
After injection, all SNAP-25 constructs fused with GFP were mainly targeting the plasma membrane of IHC. In mice injected with GFP-SNAP-25Δ9, a profound deafness occurred due to the disruption of the rapid and sustained phases of IHC synaptic exocytosis despite near normal calcium current. This finding is consistent with what has been reported in vitro.
Remarkably, injection of GFP-SNAP-25Q174L into the cochlea led to a moderate hearing loss that progressed to a severe level but did not reach the profound deafness observed in the case of GFP-SNAP-25Δ9. While assessing IHC exocytosis via capacitance measurements, we detected a distinct reduction specifically in the sustained exocytotic phase.
Taken together, these findings uncouple the IHC exocytotic defect and the subsequent deafness from cellular degeneration, underscoring the critical role of SNAP-25 in IHC synaptic transmission.

Keywords : Hearing, Exocytosis, SNAP25, Ribbon synapse, Inner hair cell, AAV

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The study of the human specific nicotine receptor subunit, CHRFAM7A, in hiPSC derived microglia

The CHRNA7 gene codes for the alpha 7 nicotine acetylcholine receptor (alpha7-nAChR) subunit, which plays an anti-inflammatory role in microglia. The alpha7-nAChR is also involved in the phagocytosis of amyloid beta (ABeta) oligomers, an early marker of Alzheimer's Disease (AD). A human specific duplication of CHRNA7 led to the formation of a new gene; CHRFAM7A. The gene product of CHRFAM7A, dup-alpha7, codes for a truncated subunit and is thought to negatively modulate the functions of alpha7-nAChR. The aim of the project is to comprehend how dup-alpha7 expression modulates alpha7-nAChR mediated functions in human microglia. A CHRFAM7A-TdT lentivirus is used to overexpress CHRFAM7A in human induced pluripotent stem cells (hiPSC), which are subsequently differentiated via hematopoietic progenitor cells (HPC) into microglia-like (MGL) cells. In vitro, the effect of CHRFAM7A expression on the inflammatory response is assessed by exposing the MGL cells to liposaccharide (LPS) and ABeta oligomers. To translate these effects to in-vivo conditions, the hiPSC-derived HPC are transplanted into the lateral ventricles of the neonatal mouse brain, in which the human cells will differentiate further into microglia. LPS will be applied systemically in these chimeric mice to analyze the morphological response of the human microglia and whether CHRFAM7A expression modulates this response. This could give insights into the human specific response of microglia to pathological insults, and to the understanding of the pathogenesis of AD.

Keywords : CHRFAM7A, hiPSC, Microglia, Xenotransplantation

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MINXING ZHAN

Membrane Traffic and Pathogenesis Lab, Department of Cell Biology and Infection, Institut Pasteur

Impact of SARS-CoV-2 infection on neurogenesis and neurodegeneration

Following Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), many patients have reported long-term manifestations, now called Long-COVID syndrome, often including neurological symptoms. A range of evidence suggests that SARSCoV-2 can infect the human brain highlighting the potential of direct viral involvement in neurological symptoms in COVID-19 patients. Furthermore, COVID-19 has been associated with an increased risk of Alzheimer's disease (AD) and Parkinson's disease (PD). In contrast to adult neurons, it has been shown that neuronal progenitor cells (NPCs) are permissive to SARS-CoV-2 infection in vitro, which might have detrimental consequences even years after initial infection. Given that NPCs are the primary regenerative cells after CNS injury, I hypothesize that SARS-CoV-2 infection might disrupt neurogenesis and lead to neurological anomalies that pave the way to neurodegeneration. Here, we aim to shed light on the mechanism by which SARS-CoV2 invades the nervous system, elucidating its spreading pathway from the nasal mucosa to the brain and evaluating whether and how SARS-CoV2 infection can affect neurogenesis and increase the risk of neurodegenerative diseases (NDs).

Keywords : SARS-CoV-2, Neurons, TNTs

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Clarin-1 and Clarin-2, key tetraspan players in inner ear mechano-electrical transduction

Hearing impairment is the most frequent sensory deficit in humans of all age groups. More than half of congenital deafness are hereditary in nature. The other major causes of deafness, which also may have genetic predisposition, are aging, acoustic trauma, ototoxic drugs such as aminoglycosides, and noise exposure. Our perception of sound depends on the mechanoelectrical transduction (MET) process occurring in the mechanosensitive hair bundle, which is present at the apical surface of the
sensory auditory hair cells of the inner ear. Deafness is often linked to irreversible damage to the mechanosensitive hair cells. Our team worked on molecular mechanisms underlying progressive hearing impairment, using two mouse models of human deafness genes, CLRN1 and CLRN2, which encode the clarin tetraspan-like protein family members. We demonstrated that clarin-1 and clarin-2 are both necessary for normal MET in auditory hair bundles and for synaptic transmission. To understand the roles of clarins in the MET process, we investigated the protein interactions of clarins with the proteins in this complex. We used a biomolecular fluorescence complementation assay to study protein-protein interactions in mammalian cells. We found out that both clarin-1 and clarin-2 are interacting key proteins in the MET complex but differently, clarin-1 is also interacting with the channel protein TMC-1. Our findings showed that clarin-1 and clarin-2 can compensate for each other but not entirely. The clarins may be important to maintain the MET complex together for proper function.
Understanding the precise mechanisms that underly clarin-mediated hearing loss will help us to develop therapeutic approaches to prevent and/or slow down progressive hearing loss.

Keywords : Hearing loss, Mechano-electrical transduction, Protein-protein interactions

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Biometric evaluation of the effects of background music listening on emotional and autonomous responses

Keywords : **Music listening, Autonomous responses, Emotion**

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Najate BENAMER
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Peripheral gene therapy restores hearing and central auditory processing in an atypical DFNB9 mouse model

Background: Sound encoding relies on synaptic transmission between cochlear inner hair cells (IHC) and afferent fibers of the primary auditory neurons. This process requires otoferlin, a Ca2+-binding transmembrane protein featuring six C2 (C2A-F) domains and acting as a calcium sensor in IHC for exocytosis. Indeed, upon Ca2+ binding otoferlin triggers the final steps of synaptic exocytosis by ensuring rapid release of vesicular neurotransmitter at IHC ribbon synapses. DFNB9 deafness, caused by otoferlin gene mutations, accounts for 2 to 8% of all inherited cases. In a preclinical deaf mouse model due to truncated otoferlin gene variants, we demonstrated that Adeno-associated virus (AAV) gene therapy successfully restored hearing, as assessed by auditory brainstem response (ABR) recordings. However, it remains to be demonstrated that this approach can address fluctuating DFNB9 deafness from mild to profound linked to non-truncating variants and restore central auditory processing essential for speech understanding, as a normal ABR does not ensure normal hearing perception.
Methods: Using homologous recombination in mouse embryonic stem cells, we created a knock-in mouse model carrying the E1799del otoferlin mutation, which mirrors the human E1804del variant linked to atypical DFNB9 deafness, characterized by moderate-to-profound deafness during febrile episodes in affected individuals
Results: The mouse model exhibited abnormal otoferlin distribution, failure of synaptic transmission in inner hair cells, and profound hearing loss, all of which were restored to normal by AAV gene therapy. Notably, we conducted objective behavioral testing to provide the first compelling evidence that peripheral gene therapy can restore frequency discrimination, indicating the recovery of central auditory processing. This was achieved even when treatment was administered late at the end of the critical period, a time when the central auditory circuit had been deprived of the peripheral input needed for its maturation
Conclusions: In conclusion, these findings indicate that peripheral gene therapy can address the entire spectrum of DFNB9 hearing loss, and that profound deafness during critical period may not impede the restoration of normal central auditory processing.

Keywords : Otoferlin, Deafness, Gene therapy, Sound processing

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Alex BARBIER CHEBBAH
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Embedding-based generative models for connectome analysis

Full insect brain connectomes have recently been obtained, providing access to the complete connectivity matrix between neurons. Due to the amount of connections and possible patterns, using latent space representations is crucial to explore underlying biological properties and structures. Additionally, they hold considerable significance for extracting statistically relevant features from connectomes, which are generally obtained as a single instance per species, making it challenging to establish a null model or reference.
To this end, we propose a novel embedding approach, specifically tailored for small neural connectomes. Hence, we focus on three main properties: 1) Extract a low-dimensional latent representation of the connectome. 2) Identify specific structures hidden in the latent space that may reveal biological properties such as underlying neural architecture or neuron types. 3) By leveraging kernel functions, introduce a generative aspect to the latent space, enabling the creation of artificial connectomes with learned and tunable properties.

Keywords : **Connectome, Embedding, Generative kernels, Low dimensional representation**

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Structures and Signals in the Neurogenic Niche, Department of Developmental and Stem Cell Biology, Institut Pasteur

Do neural stem cells communicate with each other in the developing Drosophila central nervous system ?

Neural stem cells (NSCs) are the multipotent progenitors building, maintaining and repairing brain tissue. To do so, their activity is tightly controlled by intrinsic and extrinsic cues. Whether they can sense and compensate for alterations in their population, and regenerate lost tissue, is little known. Moreover, NSCs inhabit a complex cellular microenvironment, the niche, which supports their function. The close association of the niche with NSCs makes it an indispensable mediator of the signals exchanged between NSCs. Yet, the role of the niche in signal transmission, and ultimately in NSC communication and coordination, is poorly known. My PhD project proposes to investigate how NSCs exchange information in their population, and the role of the niche in this process.
To do so, I am using the Drosophila developing central nervous system (larval stage) as an in vivo model with unrivalled genetics. It contains well-characterised and tractable NSCs (called neuroblasts) found in a genuine niche. In particular, the membranes of the cortex glia (CG) infiltrate the NSC intercellular space, creating a plastic network spanning the entire central nervous system, while individually enwrapping NSCs along with their neuronal progeny. I take advantage of striking preliminary data showing that NSCs can detect a local, mosaic stress in their population and set up a CG-dependent compensatory response. Relying on a combination of unbiased transcriptomics and targeted candidate screen, I aim to identify the cellular and molecular signals sent and received by these NSCs via the niche. I will also ask the question of the functional relevance of such NSC response for the tissue and the host. All together, these approaches will shed light on how NSCs share information within the niche, an exciting while poorly explored field with impact on regenerative mechanisms upon injury.

Keywords : Communication, Neural stem cells, Neurogenic niche, Drosophila melanogaster

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Rough sounds processing: effects on autonomic, behavioral and neural responses in population with heightened sensitivity to sounds

Being able to catch other's attention is the foremost purpose of vocal communication. Baby cries, city alarms and screams share a common property that confers sounds a rough sonic texture inducing unpleasant sensations and increasing attention in humans. This "rough" texture is characterized by amplitude modulations of the temporal envelope of sounds between 30 Hertz (Hz) and 150 Hz. In humans, behavioral studies show that aversiveness to click train is maximal in the roughness range. Recent intracranial recordings have revealed that this response profile is hardly compatible with the sole recruitment of the classical auditory system but arguably targets non-primary auditory pathways such as deep temporal and limbic structures involved in salience and affective processing. Here we test the hypothesis that enhanced excitability in these central, salience related pathways, may lead to hypersensitivity to these sounds.
We recruited 20 normal hearing controls and 17 tinnitus participants. Participants performed a subjective rating task during which they assessed the aversion perceived in responses to click trains of varying frequency (1 to 250 Hz) and intensity (40 to 70 dB SPL). Through simultaneous measurements of cardiac activity (via electrocardiography), muscular/ocular reflex activity (via electromyography), and brain responses (using electroencephalography), we explore the relationship between autonomic changes and emotional/behavioral/neural responses to rough stimuli in control and tinnitus participants.
Our primary observations suggest sensitivity to roughness i.e. stronger aversion to sounds in the roughness range strongly varies between participants, commensurate with their degree of anxiety. Also, participants with tinnitus exhibit heightened aversion to roughness, as well as heightened anxiety levels compared to controls participants. Our results support the idea that tinnitus may enhance sensitivity to roughness, possibly reflecting exaggerated autonomic response and enhanced excitability of non-classical/salience auditory pathways. The rough sounds may therefore provide a useful means to assess the excitability of these circuits and their link to heightened sensitivity and anxiogenicity to sounds. By studying the variability of responses to roughness in a population of normal hearing and tinnitus participants, these results provide useful insights for the neural mechanisms involved in auditory hypersensitivity.

Keywords : **Roughness, Salience Pathways, Tinnitus**

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miR-124 mediated regulation of actin remodeling pathways affecting TNT formation in Parkinson's disease models

TNTs are specialized F-actin based membrane protrusions which mediate cell-to-cell communication and are instrumental in transfer of toxic protein aggregates like a-Synuclein between neuronal and glial cells, thereby aiding in progression of Parkinson's disease (PD). Inhibition of actin remodelers like ROCK2, Rac1 and Arp2/3 complex have been implicated in TNT formation in neuronal cells. Reactive Oxygen Species (ROS) too, have been shown to induce TNT biogenesis. However, how TNT formation is regulated in PD is not yet known. Here, we studied the regulation of TNT formation in neuronal SH-SY5Y cells with Rotenone, a neurotoxin commonly used to mimic PD in vitro and in vivo. Interestingly, a time-dependent response to TNT biogenesis upon Rotenone treatment was observed, with an increased TNT formation till 8hrs followed by a decrease after 16hrs of treatment. Concomitantly, we observed a gradual increase in cellular ROS with increasing treatment-time while induction of cellular apoptosis was noted after 8hrs of treatment. This suggests that generation of ROS may lead to an increased TNT formation which is possibly counteracted by induction of cellular apoptosis. Next, immunoblotting of actin regulatory proteins revealed a decrease in pCofilin/Cofilin levels with increasing treatment-time which indicates a destabilization of actin polymers with increasing cellular stress. To understand the time-dependent regulation of Rho/ROCK/Cofilin pathway, we checked the expression of miR-124, a brain-enriched microRNA known to have protective roles in PD by regulating apoptosis pathways. Interestingly, we found an increase in miR-124 levels at early time-points with a drastic decrease at 16h of treatment, corroborating with the time-point of TNT formation. Bioinformatic analysis also predicted regulatory binding sites of miR-124 to the 3'UTR of ROCK2, RhoA and Cofilin2 genes. Thus, our results so far suggest a possibility of miR-124 mediated regulation of Rho/ROCK/Cofilin pathway in TNT formation in Rotenone induced oxidative stress model of PD.

Keywords : **Tunneling nanotubes, microRNAs, Actin cytoskeleton, Parkinson's disease, Oxidative stress**

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Mitochondrial dysfunction as a cue for tunneling nanotube-mediated intercellular communication between neurons and microglia

Tunneling nanotubes (TNTs) represent a major route of intercellular communication in vitro. These thin, membrane- and actin-rich conduits can reach long distances (up to 100 µm) that facilitate material exchange between connected cells, with cargoes ranging from small ions (Ca2+) to large organelles and protein aggregates. In the context of Parkinson's Disease (PD), α-Synuclein (α-Syn) aggregates increases TNTs in both neuronal and microglial cells, the reason of which remains largely unknown. Using a bottoms-up, targeted approach to determine the effect of inflammatory stimuli on TNT formation, we found that both neuronal cells and microglia respond to pro-inflammatory stimuli (LPS, IL-1α, IL-1β, and TNFα) by increasing the number of connections in an NF-κB-dependent manner. α-Syn localizes to mitochondria in both the cell types, causing organellar fragmentation. Additionally, mitochondrial membrane potential is reduced and permeability transition pore (mPTP) is opened. Aggregate-induced mitochondrial damage leads to concomitant activation of the innate immune pathway, cGAS-STING. Pharmacological activation of STING upregulates TNTs for both neuronal and microglial cells, and specifically inhibiting STING (using H-151) blocks such an upregulation. Interestingly, inhibition of NF-κB activation upon activation of STING also prevents increase in the number of connections, providing a functional framework of mitochondrial damage and innate immune activation as a trigger for intercellular communication between neuronal and microglial cells.

Keywords : **Mitochondria, Inflammation, Tunneling Nanotubes**

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Gene Therapy for Clarin-2, a New Deafness Gene in Humans and Mice

Hearing impairment is one of the most prevalent sensory disorders worldwide, affecting social interaction, cognition, education and employment, and increasing the risk of dementia. Current treatments are limited to cochlear implants, unable to restore quality hearing function. Adeno-associated virus (AAV)-mediated gene therapy has emerged as a promising alternative, though some key hurdles remain. We used Clarin-2 deficient mice, a transgenic model of progressive hearing loss, to address some of these challenges, namely the effective window for intervention and the long-term efficacy of AAV-mediated gene supplementation.

We delivered AAV9-PHP.eB coding for human or murine Clarin-2 locally into the inner ear of Clrn2-/- mice. Injections were done at postnatal day 1, 5, 10 or 14 and beneficial outcomes assessed up to 6 months after treatment. Gene transduction efficiency was evaluated by qRTPCR, RNAscope and confocal microscopy. Scanning electron microscopy was used to monitor the architecture of hearing sensory hair cells. Auditory brainstem responses (ABR), distortion product otoacoustic emissions (DPOAE), along with mechano-electrical transduction (MET) and capacitance measurements were used to assess hearing sensitivity, hair cell MET and synaptic activity.

Our AAV injections lead to robust transgene expression in inner and outer hair cells, and prevent all the defects described in the Clrn2−/− inner ear. The structure of sensory hair bundles is preserved, as is the function of their MET channels and synapses. The ABR and DPOAE thresholds of treated mice remain normal over time. We found that early neonatal injections allowed for the best therapeutic outcomes, with effectiveness decreasing with intervention age. To confirm the pathogenicity of the c.494C>A CLRN2 mutation detected in deaf patients, we demonstrated that, unlike the wild-type human allele, its variants T165K and 146fs*26 were unable to rescue hearing in Clrn2-/- mice.

Our work shows that AAV-mediated gene supplementation substantially and durably preserves normal hearing when applied before symptom onset, underscoring the promising potential of gene therapy for auditory restoration.

This study was recently published in Molecular Therapy (PMID: 38243601).

Keywords : **Progressive Hearing Loss, Gene Therapy, Clarin-2**

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The role of aTAT1-mediated Microtubule Acetylation in Glioblastoma Cellular Responses to Radiotherapy

Keywords : Glioblastoma, Radiotherapy, Cell invasion

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Dual AAV gene therapy restores cochlear function and auditory processing capabilities in a DFNB16 mouse model

DFNB16 is an autosomal recessive form of deafness, considered the second cause of hearing loss. DFNB16 resulted from mutations in Stereocilin (Strc) gene encoding Stereocilin protein (STRC). STRC expressed exclusively on the hair bundles of Outer Hair Cells (OHCs, sensory cells responsible for sound amplification) and is required for the hair bundles cohesion and maintenance. Mutated STRC results in the detachment and degeneration of hair bundles leading to DFNB16 characterized by moderate to severe deafness. So far, there is no curative treatment for DFNB16. We aimed to develop an AAV-based gene therapy to replace the mutant gene with a wild type copy of it in a mouse model of DFNB16 . Due to the size of Strc coding sequence exceeding AAV packaging capacity, a hybrid dual vector strategy was used to deliverer Strc cDNA. Intracochlear injections of dual AAV-vector in Strc−/− mice resulted in a robust expression of STRC protein at the tip of the OHC stereocilia indicating the restoration of stereociliary links. Additionally, the OHC bundles showed a normal morpho-structure, leading to the durable restoration of distortion product otoacoustic emissions and auditory brainstem responses with hearing thresholds comparable to the wild-type mice.

Keywords : Hearing loss, DFNB16, Stereocilin, Gene therapy, AAV

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Optimizing the simultaneous identification of the three type I spiral ganglion neuron subtypes in models of genetic forms of deafness.

Auditory neuropathies disrupt the transmission of sound information from the ear to the brain by affecting type I spiral ganglion neurons or the synapses they form with sensory inner hair cells. Afferent type I spiral ganglion neurons (SGNs) form three physiologically distinct subtypes, which have been defined based on their spontaneous rates (SRs). Moreover, it has been found that type I SGNs also form three molecularly distinct subtypes, which are thought to largely correspond to the three functionally defined subtypes. The heterogeneity of type I SGNs is crucial in allowing for the encoding of sound over a wide range of intensities, and these three subtypes have shown differences in their susceptibility to aging. However, little else is known regarding the impact that genetic, molecular, or pathological factors might have on the differentiation of type I SGNs, in part due to the technically challenging nature of simultaneously identifying the three molecularly defined populations in an easily quantifiable manner. Here, we optimized a triple immunohistochemistry protocol to identify all three type I SGN subtypes using a 1% sodium dodecyl sulfate (SDS) solution for antigen retrieval and antibodies targeting Calb1, Calb2, and Pou4f1. With this method, we characterized type I SGN distributions in models of genetic forms of deafness, thus revealing how deafness may differentially affect type I SGN subtypes. This protocol can also be applied more widely across mouse models for auditory research, making it a valuable tool for understanding the roles that type I SGN subtypes play in the pathophysiological mechanisms of auditory neuropathies.

Keywords : Cochlea, Spiral ganglion differentiation, Hearing loss, Immunohistochemistry

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Brain function regulation by circadian rhythm at the choroid plexus

Recent studies linked prolonged circadian disruption with an increased risk of developing dementias, the most prevalent being Alzheimer's disease (AD; Bokenberger K, et al. 2018). Intriguingly, in the brain, the day/night cycle is most strongly pronounced at the choroid plexus (CP; Myung et al. 2018), the epithelial structure critical for brain maintenance. It is currently unknown whether the circadian function of the CP is key for maintaining brain homeostasis, and whether its dysregulation may promote brain aging and disease.
Preliminary data of bulk RNA-Seq from CPs of wild-type 3 month-old (mo) mice taken at ZT-0, 6, 12 and 18 identified 1032 cycling genes (corrected p value < 0,05 and fold change > 1,5) grouped into 6 clusters. In contrast, in wild-type 8 mo mice this rhythmicity was lost. In the AD mouse model (5XFAD) of 8 mo, analysis of the CP transcriptome revealed aberrant rhythmicity, with a similar number but different cycling genes as the WT 3 mo. Taken together, our results suggest that aging and neurodegeneration negatively shape CP rhythmicity.
Surprisingly, in 3 mo mice, cluster 3 featured neuronal genes peaking at ZT-12. The presence of neurons at the CP has only been explored in the context of peripheral innervation and whether neuroglial cells are present at the adult CP remains unknown. Using immunostainings, we have identified Sox2, Pax6, NeuroD2 and NeuN-positive cells at the CP, while the levels of NeuN peak at ZT18, in accordance with the RNA-seq analysis. snATAC-Seq of CP at ZT-0 and -12 showed a NeuroD2+/FoxJ1+ cluster and a different NeuroD2+/NeuN+ cluster. These results suggest the presence of a previously unidentified neuro-glial cluster at the CP. Our future experiments will investigate its origin and contribution to CP and brain physiology in health and AD. In addition, we plan to use a CP-specific disruption of the molecular clock to reveal whether circadian rhythmicity of this compartment is critical for brain maintenance in health and AD.

Keywords : Choroid plexus, Circadian rhythm, Alzheimer's disease

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Are presycusis patients better audio-visual integrators ?

In clinical practice, speech comprehension is often assessed through the auditory modality alone, whereas in ecological situations, it relies on the potentiation of the auditory and visual components. Whereas audio-visual (AV) integration is well documented in profound deafness and implantation, it is less in acquired hearing loss like presbycusis subjects. Thus, knowing whether these latter are better AV integrators than normal hearing (NH) pears is still a matter of debate. To address this, we tested participants equalizing the difficulty of the auditory and AV tasks. The first objective was to determine whether hearing-impaired individuals exhibit enhanced AV integration skills, in lip-reading and/or AV synergy, possibly due to deafness-driven plasticity. The second objective was to explore the impact of age on these variables. We tried to disentangle the effects of acquired hearing loss and age on AV integration.
This study was carried out on 65 participants aged 56 to 85 (70.4 years ± 7.6) with hearing ranging from normal to moderate (mean PTA, 44 dB HL ± 6).
AV sentences in background noise were used to assess participants' auditory, visual, and AV performance (AV version of the French Matrix Sentence Test). An adaptive procedure was used for the auditory and AV modalities, with a Speech Reception Threshold of 80% (SRT80). The visual-only modality was assessed with silent sentences in fixed background noise to test lip-reading skills. The Cognitive MoCA test was performed.
Partial correlations and mixed linear models were used to dissociate the effect of hearing loss and age on our variables of interest.
The results of this study indicate that hearing loss has no effect on lipreading ability. However, it was found to have a positive effect on AV gain ($r=0.55$, $p<10\text{-}3$). This improvement was observed to begin with moderate hearing loss. In contrast, age was found to negatively influence lipreading ($r=-0.34$, $p<10\text{-}2$) but has no effect on the AV gain.
In conclusion, acquired hearing loss does not improve lip-reading ability but does improve the interaction between visual and auditory information. However, age seems to degrade this audio-visual interaction as well as lip-reading ability in normal hearing listeners.

Keywords : **Audio-visual integration, Hearing loss, Lip-reading, Age effect**

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Assessing the presence and functionality of tunneling nanotubes in vivo using novel genome integrating tools

Tunneling nanotubes (TNTs) are tubular membranous conduits representing a novel direct way of communication between cells, shown in vitro to transfer genetic material, organelles and different pathogens. However, their physiological relevance is unclear because their existence in vivo has not yet been explicitly demonstrated. We hypothesize that TNTs could represent an early feature of cell-to-cell communication in the developing nervous system which predates classical synaptic transmissions, and be instrumental for the emergence of functional mature neuronal networks. I am currently investigating the presence and functionality of TNTs in the cerebellum, spinal cord and retina of chicken and mouse embryos by a multidisciplinary approach. Taking advantage of the fact that TNTs mediate the transfer of organelles between cells, I developed reporter systems to detect such transfer using the iOn genetic switch, a new transgenic expression approach based on DNA transposition. I designed different transgenes that efficiently mark the mitochondria and membrane of adjacent neural cells with distinct colors, creating a mosaic labeling ideal to directly track or report a posteriori mitochondria transfer between neighboring cells, and to visualize their membrane protrusions. After validating these new tools and establishing conditions to express them and visualize them in vivo by electroporation and multi-color confocal microscopy, I am applying them to investigate instances of organelle transfer and the existence of TNTs in the developing nervous system.

Keywords : **Transposon systems, Lineage tracing, Mosaic analysis, TNTs, Intercellular communication**

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Unraveling the interplay between Tau aggregates and autophagy-lysosomal dysfunction

Neurodegenerative diseases like Alzheimer's and Parkinson's have been associated with the pathological aggregation of misfolded proteins. In both diseases, respectively, Tau and α-synuclein seed and spread from cell-to-cell in a prion-like manner. Previous data suggests that aggregate-containing cells are dysfunctional in the autophagy-lysosomal pathway, leading to aggregates persistence and neurodegeneration. More precisely, we and others have shown that exogenous α-synuclein fibrils accumulate in lysosomes in human and mouse neuronal cells (SH-SY5Y and CAD cells), resulting in their swelling and decreased activity (measured by lysotracker labelling and cathepsins activity measures). However, in the case of Tau, we previously reported that endogenously formed repeated-domain (RD)-Tau aggregates were recognized as autophagic cargos but failed to be delivered to lysosomes. Yet, whether aggregates are not degraded because they are intrinsically resistant to degradation or because they impair the autophagy-lysosomal pathway still remains an open question. Our study aims to better characterize the fate of full-length (FL)-Tau aggregates and whether these cause autophagy-lysosomal disruption. In human SH-SY5Y neuronal cells, we stably overexpressed soluble or aggregated P301S-FL-Tau-mClover3 based on a Tet-off system. Using immunofluorescence and western blotting approaches, we show that in these cells lysosomes are affected in their morphology (bigger), positioning (more peripheral). However, unlike in the presence of α-synuclein aggregates, they are still labeled with lysotracker, suggesting that their acidification is not impaired. Intriguingly, we found that FL-Tau-mClover3 silencing by doxycycline doesn't revert this lysosomal phenotype, suggesting that the simple overexpression of FL-Tau modifies lysosomes irreversibly. Moreover, we observe that aggregates are more stable than soluble proteins and are not targeted to autophagy-lysosomal degradation. We are currently studying the mechanisms governing Tau aggregate formation, maintenance, and downstream effects on lysosomes, notably via lysosome purification and immunoprecipitation, in comparison to α-synuclein.

Keywords : **Neurodegenerative diseases, Protein aggregation, Tau, Autophagy-lysosomal dysfunction**

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Deciphering the role of HIPK2 in TDP-43-mediated neurodegeneration

Keywords : **Neurodegeneration, Protein aggregation, Neuroinflammation**

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Deficits in spike timing and transmission of auditory information in a mouse model lacking ribbon synapses

Keywords : **Inner hair cells, Ribbon synapse, Frequency modulations**

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Functional and Morphological Analysis of Interhemispheric Neurons in Somatosensory Cortex: A Study Using Two-Photon Ca2+ Imaging and high-Resolution Light Sheet Microscopy in the Expanded Brain

Exploration of the environment and making decisions is essential for survival across the animal kingdom. Mice, for instance, use multiple whiskers to generate a tactile map of their surroundings. To generate this tactile map and organize coherent behaviors, the brain must integrate information from whiskers located on both head sides. The primary brain region encoding this tactile map is the Barrel Cortex (BC), where information from each single whisker is computed in a matching columnal circuit. However, the neural mechanisms underlying whisker integration from both brain hemispheres are not well understood.

To study the modulation between barrels of the opposite hemisphere, a retropropagated virus expressing CRE (CAV-cre) was injected into the left hemisphere and into the contralateral Cre-dependent virus expressing GCaMP7s, labelling only neurons that had been transduced with both viruses and consequentially projecting from one hemisphere to the opposite hemisphere. Robust whisker-evoked responses from the BC are obtained through Ca2+ live imaging and are acquired with a 2-photon microscopy thanks to a window implantation in head-fixed mice where the stimuli occur through piezoelectric stimulation on both ipsi and contralateral whiskers. Furthermore, morphological characterization was performed using two different volume-imaging protocols: iDISCO, a classic clearance protocol in which the refractive index matches that of the surrounding medium, and ExA-SPIM protocol. The latter is a new technique in which the clearance and expansion of the tissue are combined with an objective and camera sensor derived from the metrology industries, resulting in nanoscale imaging of centimeter-scale samples with a higher speed, reducing the sectioning, which is the ultimate goal when tracing long projecting neurons.

Our results show that labeling neurons projecting from the BC located on the right hemisphere to the left one are distributed throughout layers I to V/VI (LI to LV/VI). Morphological characterization of those neurons reveal anatomical differences on neuron size in LII/III suggesting the presence of two population ensembles. Finally, physiological characterization using in vivo calcium imaging shows that these neurons exhibit stereotyped responses to adaptation and frequency changes to ipsilateral or contralateral whisker stimulation.

Keywords : **Long-Range Projecting Neurons, Whiskers, Barrel Cortex, Interhemispheric Connection, High Resolution Light-Sheet Microscopy, Calcium imaging, Whole-mounting Brain Immunostaining**

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Understanding the influence of the gut microbiome on the mesolimbic system and its response to nicotine

While emerging evidence suggests a role for gut bacteria in the pathophysiology of substance use disorders (SUD), studies of their impact on brain and behavioral responses to drugs have been very limited so far. We previously showed that gut dysbiosis enhances the nicotine-induced activation of the mesolimbic system and alters nicotine's motivational properties in mice. However, the mechanisms linking gut bacteria to the mesolimbic system to influence its response to nicotine remain unidentified. Microbial products are suspected to play a role in this process by altering gene expression, host immune and glial activation and synaptic signalling. In particular, short-chain fatty acids (SCFAs), the major microbial by-products of dietary fiber fermentation, are considered important targets for understanding the role of the gut microbiome in SUD as they notably regulate the secretion of gut hormones and can cross the blood-brain-barrier and affect epigenetic signaling in the brain. Therefore, we investigated the role of SCFAs in the consequences of several types of gut dysbiosis on the mesolimbic system function in mice. We notably show that SCFAs supplementation in mice with a gut microbiota depletion rescues the enhanced nicotine-evoked neuronal activation in the ventral tegmental area and the nucleus accumbens shell. We are currently further investigating the contribution of SCFAs-modulation of gut hormones and epigenetics in these effects. Our findings will contribute to identifying the mechanisms by which gut microbiome alterations modulate the brain response to nicotine with the potential to improve our understanding of individual propensity to develop nicotine addiction.

Keywords : Gut dysbiosis, Nicotine, Mesolimbic system, Short-chain fatty acids.

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Genotype-phenotype correlations in Phelan-McDermid syndrome : an on-going study

Genotype-phenotype correlations in Phelan-McDermid syndrome : an on-going study Phelan-McDermid Syndrome (PMS – OMIM#606232) is a rare severe neurodevelopmental disorder associated with intellectual deficiency (ID), epilepsy, catatonia, autism-like behavior, hypotonia and sleep disorder. All pathogenic variants have been identified on the 22q13 locus, including simple small to large deletions, unbalanced translocations, ring chromosome formation and deleterious point variations in SHANK3 (OMIM#606230). SHANK3 is a multidomain protein scaffold protein of the postsynaptic density that connect neurotransmitter receptors and other membrane proteins to the actin cytoskeleton and G-protein-coupled-signaling pathway. SHANK3 is also involved in synapse formation and dendritic spine maturation. Clinical features of patients are very diverse but, to date, no concrete genomic-phenotype correlations have been established to explain this disparate symptoms-onset. This project aims to better understand the physio-pathological mechanisms underlying PMS and the variety of clinical features, through genotype-phenotype correlations. A total of 90 PMS patients have been recruited, with clinical data and whole genome sequencing. To better study this cohort, a “matched” cohort has been established from an autism/ID cohort without variation in SHANK3, matched on ancestry, ID status, family status and sex. All patients harbor deleterious variants impacting SHANK3, 64 copy number variants (deletions), and 26 high impact single-nucleotide variants/indels. Most of the small variations are found in exon 22 of the gene. Interestingly, out of 64 deletions, 7 of them lead to the formation of a ring chromosome.
To study genomic data from both cohorts, and unaffected siblings, 3 gene-lists have been established in the team: high confidence genes involved in neurodevelopmental disorders (HC-NDD), medium confidence genes involved in neurodevelopmental disorders (Cand-NDD), and high confidence genes involved in epilepsy (HC-Epi). Using this last list of genes, PMS patients seem more likely to harbor variations involving a HC-Epi gene, which can create a pro-epileptic genetic environment. Interestingly, no non-epileptic matched individuals harbor variations in these genes.

Keywords : **Genetic, Syndrome, Intellectual disability, Whole genome**

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Altered Neural Entrainment in Young Adults with APOE4: Towards Early Identification of Alzheimer's Risk

Recent studies have suggested that prodromal stages of AD are accompanied with central auditory system dysfunction (Swords et al., 2018), which may be used as early indicators of disease onset and progression. In AD patients of 60 years old and more, atypical patterns of oscillatory entrainment to repetitive sound transients have been reported and suggested as potential neuromarker of Alzheimer's disease (van Deursen et al., 2011). Whether such alterations of auditory functions relate to genetic risk factor of AD (APOE4) at an early age (<30) is unknown.
Here we used EEG recordings to measure auditory responses to repetitive sounds (1 second click trains presented at various frequencies between 10 and 250 Hz) in 34 young normal hearing participants with no known neurological impairments. To test whether auditory responsivity is affected by AD risk factor, we compared auditory brain responses from 17 APOE3 (age mean=21.6, sd=1.8) and 17 APOE4 carriers (age mean=23.6, sd=4.9). Comparing the magnitude of auditory event related potentials (ERPs) we observe that APOE4 carriers exhibit slightly lower P2 and P3 ERP responses compared to APOE3 carriers, with a consistent delay starting from the N1 component. Focusing on ASSR power across frequencies (10–90 Hz), we observed that APOE3 carriers exhibit reliably stronger neural entrainment than APOE4 carriers (Cohens' d = 0.8, 'large' effect size). This difference was sustained across stimulus time course and seems mostly frontal and at low stimulus frequencies.
Overall, these results suggest that central auditory differences can be detected very early in at-risk populations. Studying these signals could help identify early AD pathology and provide an entry point for therapeutic interventions against neurodegeneration.

Swords, G. M., Nguyen, L. T., Mudar, R. A., & Llano, D. A. (2018). Auditory system dysfunction in Alzheimer disease and its prodromal states: A review. In Ageing Research Reviews. https://doi.org/10.1016/j.arr.2018.04.001

van Deursen, J. A., Vuurman, E. F. P. M., van Kranen-Mastenbroek, V. H. J. M., Verhey, F. R. J., & Riedel, W. J. (2011). 40-Hz steady state response in Alzheimer's disease and mild cognitive impairment. Neurobiology of Aging, 32(1), 24-30. https://doi.org/10.1016/j.neurobiolaging.2009.01.002