Encadrant **AGULHON Cendra**
mail cendra.agulhon@parisdescartes.fr

Equipes Glia-Glia And Glia-Neuron Interactions
Responsable AGULHON Cendra
Unité Integrative Neuroscience and Cognition Center (INCC)

Sujet **Astrocytic signaling in atypical visual information processing, perception and memory: implications for neurodevelopmental disorders**

Résumé

1. INTRODUCTION

• General context: This project aims at studying the cellular, molecular, and neural network mechanisms underlying cognition in physiology and neurodevelopment disorders (NDDs). It will be developed in C. AGULHON's Lab within the Integrative Neuroscience and Cognition Center, which brings together neuroscientists, psychologists and physicists, doing translational neuroscience research in animal models and humans.

• Project rationale: Astrocytes, the most numerous glial cell types in the central nervous system, express numerous G protein-coupled receptors (GPCRs). These cells are anatomically and functionally associated with synapses and can alter synaptic transmission and plasticity, via activation of their GPCR signaling, and subsequent release of neuroactive molecules. The Gq GPCR signaling (linked to Ca2+) has been the most studied. On the other hand, astrocytic Gs or Gi GPCR signaling (linked to cAMP) has been investigated only scarcely, although astrocytes exhibit a wide range of Gs/Gi GPCRs, including those activated by inflammatory and stress-related mediators (Monfared et al., 2021). Moreover, chronic activation of Gs GPCRs impairs long-term memory, suggesting an effect on synaptic transmission and plasticity (Orr et al., 2015). Additionally, activation of astrocytic Gi signaling can lead to the production of astrocyte-secreted proteins involved in synaptogenesis, thus altering excitatory synapse density/function and behavior (Nagai et al., 2019). Furthermore, disrupted synapse formation, maturation or density occurs in NDDs (Caldeira et al., 2019), and epidemiological studies point to a strong correlation between chronic inflammation and/or stress during brain development and the occurrence of NDDs (e.g. autism and schizophrenia, Jiang et al., 2018).

2. HYPOTHESIS

Abnormal chronic activation of astrocyte GPCR cAMP signaling during critical periods of brain development triggers an alteration in the production of astrocytic synaptogenic, maturation and/or pruning factors, which may subsequently alter neuronal circuit formation and activity, thus contributing to NDD etiology.

3. MAIN GOAL, SPECIFIC AIMS & TECHNICAL APPROACHES

The 1st goal is to test this hypothesis in vivo using chemogenetic tools to selectively activate astrocytic GPCR cAMP signaling during the critical period of mouse primary visual cortex (V1) plasticity. V1 undergoes major synaptogenic and pruning events during this period of postnatal cortical development, and its maturation is strongly influenced by environmental factors and sensory experience. Thus, V1 provides an excellent model to study how neuronal circuits form, are sculpted and function during brain development. V1 is also a relevant experimental system for the study of cortical circuit abnormalities in NDDs. Indeed, visual perception and cortical oscillations are impaired in patients with autism and schizophrenia (Robertson

& S. Baron-Cohen, 2017). It is thus conceivable that dysfunctional astrocytic GPCR cAMP signaling during V1 critical period is involved in such visual dysfunctions. To place our mouse model observations into a Human context, the 2nd goal is to develop a translational research.

To achieve both goals, the use of “chronic inflammation/stress” mouse models will be combined with genetics, in vivo electrophysiology & fiber photometry imaging, biochemistry, immunohistochemistry, and a unique mouse visual perceptual behavioral learning paradigm (Cooke et al., 2015). An adapted form of this paradigm will also be applied to neuro-typical and atypical human subjects using EEG and eye-tracking as well as immunohistochemistry and RNA profiling in human brain samples.

The PhD student will be involved in the following specific aims:
▪ AIM 1 (mouse models):
To (i) test whether chronic activation of astrocytic GPCR cAMP signaling during V1 critical period affects visual-induced information processing, a/b/t/g oscillations and perceptual memory, and (ii) characterize the involved cellular and molecular mechanisms downstream of cAMP signaling.
▪ AIM 2 (humans):
To determine whether similar visual-induced information processing, oscillations and perceptual memory as well as cellular and molecular features also occur in typical vs. atypical Humans.

4. CONCLUSION
Our findings may be of considerable significance for a better understanding of astrocytic GPCR signaling in neurophysiopathology, leading to potential new understanding and treatments of NDDs.

Encadrant **ALONSO Mariana**
mail malonso@pasteur.fr

Equipes Perception and Memory
Responsable LLEDO Pierre-Marie
Unité Gènes, Synapses et Cognition

Sujet **Neural circuits underlying emotional biases in male and female mouse model for depression**

Résumé Neural circuits underlying emotional biases in male and female mouse model for depression

Depression is the single largest contributor to disability worldwide, affecting 300 million people annually. Importantly, women suffer from depression nearly twice as frequently as men. Still, the origin of sex bias in depression is not well established. In psychiatric disorders, different affective states (e.g. depression, mania) are characterized by clinical criteria that hardly transpose to animal models. To overcome this issue, clinical criteria need to be translated into domains or basic functions alterations that can be measured both in humans and animals to be used for neurobiological multilevel analysis.

Assignment of a positive or negative valence to environmental and internal cues is a fundamental process that guides our emotional and behavioral responses. In fact, salient cues can trigger emotional responses depending on the value assigned to these stimuli. Expression of emotions is thought as a window into the internal affective state of an individual across species, from insects to humans. Importantly, emotional processing is an essential domain affected in mood disorders as negative emotional bias is a major characteristic of depressive episodes, leading patients to attribute more negative valence to salient environmental cues. Moreover, restoration of these emotional biases is predictive of the response to antidepressant treatment and essential for recovery from the episode. The use of animal models of mood disorder could thus be extremely important to unravel the psychopathology of these human diseases as well as to find new therapeutic approaches. However, great methodological improvement is needed for modelling affective states and measuring animal behavior in laboratory settings.

In humans, numerous studies have shown the involvement of the amygdala in the etiopathology of depression. Accordingly, recent findings in animals have highlighted how basolateral amygdala (BLA) circuits assign positive and negative valence to emotional stimuli. During associative learning, BLA neurons preferentially involved in either positive or negative valence coding can be distinguished according to their projection targets as well as spatial and genetic characteristics. BLA neurons projecting to the nucleus accumbens (NAc) mainly respond to positive stimuli and trigger approach behaviors, while BLA neurons targeting the centro-medial nucleus of the amygdala (CeA) mainly respond to negative stimuli, generating defensive responses. BLA playing a major role in valence processing, we hypothesized that the activity of BLA-to-NAc projecting neurons would be reduced in depressive states while BLA-to-CeA neurons would be more active. These dysfunctions could be responsible for emotional processing alterations associated with depressive states.

We recently evaluated odor valence assignment in an animal model for depression relying on chronic administration of corticosterone (CORT). We show spontaneous negative bias in depressive-like male mice which attribute more negative valence for both attractive and aversive odors, mimicking the bias observed in depressed patients. In addition, CORT treatment reduces BLA-to-NAc neuronal activity while increasing BLA-to-CeA, circuits known to be involved in respectively positive and negative valence encoding. Moreover, the precise causal mechanisms underlying these dysregulations in depressive states and their sex specificity are still unexplored. Besides, we do not know how these BLA circuit alterations could play a feedback function to maintain long-lasting maladaptive emotional states. We propose that the

modification of BLA neuronal activity could extend the expression of negative stimuli or conversely reduce the expression of positive ones, leading to durable changes in emotional processing. In this context, the goal of this project is thus to study emotional bias both in male and female mouse models for depression, the underlying mechanisms, and the response to treatments. To tackle these questions, this research program will include the following three main axes: 1) Study of emotional bias in mouse model for depression in both sex; 2) Evaluation of mechanisms behind emotional bias: BLA subpopulation activity and circuits manipulation; 3) Effect of antidepressant treatment on emotional bias.

Encadrant **ARNAL Luc**
mail luc.arnal@pasteur.fr

Equipes Cognition Auditive et Communication
Responsable ARNAL Luc
Unité Institut de l'Audition, unité de Génétique et Physiologie de l'Audition

Sujet **Deciphering the code of neural predictions in auditory sequence processing**

Résumé The mammalian brain is an expert at extracting sensory regularities to anticipate future events and proactively adapt behavior. In humans, for instance, this ability is apparent in vocal communication in noisy environments (e.g. cocktail party settings), where linguistic relationships and sequential regularities allow us to infer future utterances to improve comprehension. By enabling the efficient allocation of processing resources, predicting the timing ('when') and the content ('what') of upcoming inputs reduces sensory uncertainty, thereby enhancing the processing of noisy inputs.

According to the predictive coding hypothesis, predictions are generated at each level of the auditory hierarchy and propagate in a top-down manner to minimize bottom-up prediction errors at the hierarchical level below. However, the neural architecture subserving predictive processes is likely to be more complex, with diverse pathways and functions potentially contributing in parallel. To reduce both external and internal noise, the brain can arguably exploit any available source of prior knowledge to generate predictions (Rimmele et al., 2018). These priors can arise from regions with vastly diverse functions and expertise: the motor system for instance, owing to its exquisite temporal proficiency in fine movement planning, is thought to facilitate precise, time-based predictions. Memory systems belonging to temporal/limbic structures (e.g. the hippocampus) arguably contribute to convey predictive insights based on past experiences.

Although there exists many hints supporting the existence of predictive processes in the human brain, they have been mostly evidenced in an indirect way by means of measuring the outcome of such computations: prediction errors. To date, where predictions arise in the brain and which mechanism allows to predictively prepare sensory cortices to process expected sensory inputs is unknown. The goal of this project is to investigate the anatomical and functional origins and the neurophysiological mechanisms supporting top-down predictions before prediction errors are computed.

In a comparative study using intracranial electrophysiological recordings from human (co-supervision Benjamin Morillon, AMU) and non-human primates (collab. Chris Petkov, Newcastle), the PhD applicant will first aim at decoding prestimulus endogenous signals underlying 'what' vs 'when' predictions during sequence processing.

Using an auditory sequence processing paradigm, we will test the ability of participants to process sequences of four syllables, that will either be repeated multiple times (becoming fully predictable) or made of syllables presented in random order (unpredictable). Contrasting brain responses between recognized and unknown sequences, we will track how prior knowledge modulates auditory processing and related performance.

Using classification and temporal generalization algorithms to analyze spectrally resolved local field potentials (LFP) from iEEG recordings, we aim to uncover the neural signature of top-down predictions. Multidimensional classification algorithms and mutual information quantifiers will be used to decode predicted syllable in the time window preceding its occurrence. Exploring how prestimulus activity (high frequency LFP in human and spiking activity in monkey data) is impacted by expectations in primary auditory regions, we will decipher how the brain predictively organizes neuronal activity to optimize the allocation of processing resources and to

facilitate perceptual performance.
Based on these results we will then explore the putative anatomical and functional origins of predictions in the brain. In humans (epileptic patients undergoing intracranial recordings for clinical purposes), intracranial recordings are simultaneously recorded in other regions of the brain (including prefrontal, parietal and hippocampal regions) during the task. Extending the prestimulus classification analysis, we will explore the neuroanatomical sources of predictions along the many pathways (e.g. ventral, dorsal or limbic) involved in the predictive processes. With information theoretic and directed connectivity measures (Granger causality) approaches, we will uncover the key anatomical and functional nodes involved in anticipatory mechanisms and the neural mechanisms underlying ‘what’ versus ‘when’ predictions in humans and non-human primates.

Rimmele, Morillon, Poeppel, Arnal (2018). Trends in Cognitive Sciences

Encadrant **BARBOUR Boris**
mail boris.barbour@ens.fr

Equipes Neuronal Algorithms
Responsable BARBOUR Boris
Unité Institut de Biologie de l'Ecole Normale Supérieure (IBENS)

Sujet **Synaptic and network mechanisms underlying iterative learning**

Résumé

Many learning problems are difficult and can only be solved by animals after multiple repeats of the stimulus or behaviour. The Neuronal Algorithms group seeks to understand the synaptic, neuronal and network mechanisms of directed and undirected learning. We define directed learning as a process in which an objective function is available. One example is the optimisation of rapid, complex movements, in which the cerebellum is thought to play a central role. Conversely, we define undirected learning as the spotaneous emergence of beneficial network phenomena in the absence of reward or error signals. An example of undirected learning would be the ability to recognise and discriminate new, complex sensory stimuli after multiple repetitions. Such mechanisms are thought to involve the recurrent circuitry of the neocortex. We seek a student to work focus on one or more of these processes using computational and/or experimental approaches, with the latter potentially involving in vivo and in vitro (slice) electrophysiology.

Encadrant **BARTOLOMEO Paolo**
mail paolo.bartolomeo@gmail.com

Equipes PICNIC Lab (Physiological Investigations of Clinically Normal & Impaired Cognition)
Responsable COHEN Laurent / NACCACHE Lionel / BARTOLOMEO Paolo
Unité Institut du Cerveau et de la Moelle épinière

Sujet **VISIONARY: Brain Circuits of Visual Mental Imagery in Neurotypical, Stroke, and Alzheimer Populations**

Résumé We use Visual Mental Imagery (VMI) to relive our memories, enjoy a novel, or create a painting. Individuals vary in the subjective vividness of their VMI, including the complete lack of such experiences (known as aphantasia). Our work with stroke patients demonstrates that vivid VMI is possible even with no contribution from early visual areas, contrary to the dominant model, but can be impaired by left temporal damage (t.ly/CQm5). In a meta-analysis of neuroimaging studies (t.ly/yB0o), we found VMI-related activity in a previously undescribed functional region of the left ventral temporal cortex (VTC), which we called Fusiform Imagery Node (FIN). Our recent 7T fMRI evidence (t.ly/I7uCO) confirms the presence and location of the FIN in the left fusiform gyrus, both in typical imagers and aphantasic individuals. It also shows the activation of domain-preferring VTC regions, such as the fusiform face area or the visual word form area, for the corresponding VMI domains. We also found functional connectivity of the FIN with mainly left-hemisphere frontoparietal (FP) networks during VMI in typical imagers, but not in aphantasic individuals.

Our working hypothesis is that FIN activity is initiated and sustained by FP networks, and integrates amodal semantic knowledge processed in the anterior temporal lobe with high-level visual representations in domain-preferring VTC regions. VISIONARY will (1) identify laminar-specific activity in VMI-related regions using ultra-high field fMRI in neurotypical participants with varying degrees of subjective imagery vividness; and (2) establish the causal roles of specific cortical regions and white matter tracts using high-resolution neuroimaging in patients with focal or diffuse brain damage.

Methods: VISIONARY will integrate (1) participants' introspective reports of their experiences with (2) behavioral measurements using our multi-domain, enhanced Batterie Imagination Perception (eBIP) (t.ly/s7gq), and (3) brain mapping in neurotypical individuals and neurological patients.

Study 1: Laminar fMRI - Top-down and bottom-up influences act on distinct cortical layers. We will use ultra-high field laminar 7T fMRI with VASO sequences at Neurospin to observe laminar-specific activity in 15 typical imagers and 15 aphantasic subjects while they perform the eBIP. Laminar-specific VMI- and perception-related activity in different regions of the VMI network including the FIN, and in occipital visual areas will be explored. We predict that perceptual information should evoke activity in all the cortical layers, while VMI-related top-down feedback should mainly cause activity in superficial and deep layers, but little middle-layer activity. Laminar fMRI will allow us to assess whether congenital aphantasia is associated with abnormal top-down activity in FIN or other temporo-occipital regions.

Study 2: Neuropsychology of VMI - To establish the causal role of VMI-related cortical nodes and white matter pathways in specific VMI domains, we will use high-resolution MRI techniques to study VMI in brain-damaged patients. A first group, with a first unilateral vascular stroke in the occipito-temporal or FP cortex (30 patients), will provide information on the causal role of specific brain regions and networks linked by white matter tracts. We expect patients with left temporal damage including the FIN, or disconnecting it from more anterior regions, to show acquired aphantasia. A second group with semantic dementia, posterior cortical atrophy, or typical

Alzheimer's disease (30 patients) will help to identify the causal role in VMI of large-scale connected networks (e.g. semantic networks, default mode network), and of the medial temporal lobe. Neuroimaging will be performed at 3T at the CENIR in the Pitié-Salpêtrière hospital and will make it possible to assess lesion anatomy, patterns of white matter disconnection, resting-state functional connectivity, and fMRI using the eBIP.

The model resulting from VISIONARY findings will identify neural targets for neuromodulatory techniques such as neurofeedback and TMS. These developments will offer opportunities to treat conditions such as PTSD, characterized by inappropriate and intrusive VMI of the stressing event, or absence of VMI (congenital or acquired aphantasia). The results will also offer a deeper understanding of the subjective experiences of neurological patients, enabling clinicians to more accurately assess their cognitive profiles.

Encadrant **BENCHENANE Karim**
mail karim.benchenane@espci.fr

Equipes Memory, Oscillations and Brain states
Responsable BENCHENANE Karim
Unité Laboratoire Plasticité du Cerveau (LPC)

Sujet **Rôles des sharp-waves ripples hippocampiques et des oscillations liées à la respiration dans la panique et l'anxiété chez la souris.**

Résumé La peur est une émotion aux multiples facettes. Il existe un cadre théorique qui propose que l'adaptation à la menace et les réactions de défense s'organisent autour d'une seule dimension : l'"imminence de la prédation" (IP) (1) et les deux extrémités de ce spectre peuvent être qualifiées de "panique" (forte IP) et d'"anxiété" (faible IP). Ces deux systèmes de défense peuvent être discriminés à l'aide d'outils pharmacologiques tels que les panicolytiques et anxiolytiques utilisés pour traiter les troubles panique et l'anxiété chez l'homme.

Afin d'explorer pleinement l'éventail des comportements de peur non abordé par les tâches de peur classiques, l'équipe de Karim Benchenane a développé chez la souris un nouveau paradigme comportemental qui modélise explicitement l'imminence de la prédation chez la souris. Dans cette tâche d'apprentissage aversif, l'animal explore un environnement en forme de U et reçoit des chocs dans un des deux bras (bras de choc) et peut éviter les chocs en allant dans l'autre bras (bras sûr). Au cours de cette tâche, les souris font montre d'un large éventail de réactions de défense, notamment l'évitement, l'évaluation du risque et le freezing. Il est important de noter qu'elles présentent des périodes de freezing identiques comportementalement dans les deux extrémités du U-maze mais différenciable au niveau neurophysiologique. Du côté du choc (IP élevée), les animaux présentent un rythme dans le bulbe olfactif, lié à la respiration à environ 4 Hz, leur fréquence cardiaque est élevée et régulière (signe de stress). Du coté opposé aux chocs (coté sûr - IP faible), les animaux respirent à 2 Hz, leur fréquence cardiaque est faible et variable et l'hippocampe génère un grand nombre d'oscillations à haute fréquence dans l'hippocampe appelées «sharp-wave ripples» (ripples ou SWR).

Ces SWR sont liées à des réactivations de neurones dans l'hippocampe (HPC), ou dans le cortex préfrontal (CPF) correspondant à des expériences passées qui sont rejouées. Plusieurs des résultats préliminaires suggèrent l'implication des sharp-wave ripples dans le freezing côté sûr (IP faible). Tout d'abord, pendant les ripples du freezing dans le côté sûr, on a observé que l'activité des neurones du cortex préfrontal présentait une forte similarité avec celle observée quand l'animal recroît des stimulations aversives. Cela suggère que l'animal « rejoue » l'expérience aversive pendant ces ripples. Deuxièmement, l'administration de diazepam, un agent anxiolytique utilisé dans le traitement clinique de l'anxiété entraîne une forte diminution de la fréquence de ces ripples. Bien entendu, le diazepam pourrait avoir d'autres effets que l'inhibition des ripples. Du côté choc, on observe une oscillation à 4Hz très régulière liée à la respiration dans le bulbe olfactif et dans le cortex préfrontal. Cette oscillation a déjà été observée dans des tâches de conditionnement de peur classique et leur rôle était de maintenir le freezing(3). De façon intéressante cette oscillation est supprimée par des panicolytiques (fluoxétine chronique) et on observe une diminution du freezing.

Le but de cette thèse est d'aller au-delà de l'approche pharmacologique qui est toujours difficile à interpréter en agissant directement les patterns électrophysiologiques qui semblent impliqués dans les comportements observés. Les SWR seront inhibées directement par une interface cerveau-machine ou la détection automatique des SWR déclenchera une stimulation de la voie commissurale

hippocampique connue pour supprimer sélectivement les SWR(2). Les oscillations du bulbe olfactif seront manipulées par optogénétiques en activant des interneurones locaux a des fréquences permettant d'amplifier certaines oscillations ou au contraire de provoquer des interférences. Ces deux approches ont déjà été utilisées dans l'équipe(2,3).

Nous analyserons l'effet de ces manipulations dans la tâche du U-maze au niveau comportementales et électrophysiologique pour proposer une théorie sur les bases neurophysiologiques de l'efficacité des médicaments utilisés en clinique humaine pour traiter les désordres mentaux.

Références :
1. Perusini N., Fanselow MS. (2015) Learn. Mem. 22(9):417-25
2. Bagur, S., et al. (2021) Nat Commun 12, 2605
3. Girardeau G., Benchenane K., et al (2009) Nat. Neurosci. 12(10):1222-3

Encadrant
mail

BIRMAN Serge
serge.birman@espci.fr

Equipes
Responsable
Unité

Genes Circuits Rhythms and Neuropathology
BIRMAN Serge
Laboratoire Plasticité du Cerveau (LPC)

Sujet

Role of the vacuolar ATPase of dopaminergic neurons in the pathogenesis of Parkinson's disease studied in the Drosophila model

Résumé

Parkinson's disease is the most common neurodegenerative movement disorder, which is primarily characterized histologically by the dysfunction and loss of a significant proportion of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. The causes of the pathology are not yet sufficiently understood to allow the development of a real cure for this disease. An increase in oxidative stress related to mitochondrial dysfunction, a chronic neuroinflammation of ill-defined origin, and the disruption of cellular degradation processes, appear to be major determinants in Parkinson's disease pathogenesis.

The vacuolar ATPase (V-ATPase) is a highly conserved membrane-associated enzymatic complex, whose best-known function is to ensure an appropriate level of acidification in various intracellular organelles, such as the lysosomes and synaptic vesicles. Our team recently identified a novel neuronal protein, named VhaAC45-related protein (VhaAC45RP), as a specific regulator of the V-ATPase in Drosophila that is required for proper synaptic vesicle acidification and neurotransmitter release (Dulac et al., 2021). VhaAC45RP specifically interacts with subunits of the membrane (V0) domain of the V-ATPase, and in particular with ATP6AP2, whose mutations can cause juvenile-onset Parkinsonism in humans. One of the major proteins associated with Parkinson's disease, Leucine-rich repeat kinase 2 (LRRK2), was also shown to interact with the membrane domain of the V-ATPase, and appears to be a regulator of its function.

The purpose of this thesis project, will be to explore further the relationship between the function of V-ATPase in dopaminergic neurons and the progression of Parkinsonian symptoms in sporadic and genetic models of Parkinson's disease in Drosophila. Previous unpublished results from our team suggested that up- or down-regulation of VhaAC45RP can interfere with disease development in these models, suggesting a potential neuroprotective function. The specific aims will be to identify the molecular mechanisms and the organelles involved, and determine the respective roles of other Parkinson's disease-associated V-ATPase interactors, such as ATP6AP2 and LRRK2, in the pathogenesis. In particular, we will study the implication of the lysosomal V-ATPase of dopaminergic neurons, since we have shown in recent works that the autophagy-lysosomal pathway plays an essential role in in the progression of the disease in the Drosophila model (Issa et al., 2018; Rahmani et al., 2022).

Overall, this PhD work should pave the way for a better understanding of the molecular mechanisms relating the V-ATPase function to Parkinson's disease development in humans.

Related references of the team:

— Dulac A., Issa A.-R., Sun J., Matassi G., Jonas C., Rahmani, Z., Chérif-Zahar B., Cattaert D., Birman S. A novel neuron-specific regulator of the V-ATPase in Drosophila. (2021) eNeuro 8(5):ENEURO.0193-21.2021. doi: 10.1523/ENEURO.0193-21.2021

— Issa A.-R., Sun J., Petitgas C., Mesquita A., Dulac A., Robin M., Mollereau B., Jenny A., Chérif-Zahar B., Birman S. (2018) The lysosomal membrane protein LAMP2A promotes autophagic flux and prevents SNCA-induced Parkinson disease-like symptoms in the Drosophila brain. Autophagy 14(11):1898–1910. doi: 10.1080/15548627.2018.1491489

— Rahmani, Z., Surabhi, S., Rojo-Cortés, F., Dulac, A., Jenny, A., Birman, S. (2022) Lamp1 deficiency enhances sensitivity to α-synuclein and oxidative stress in Drosophila models of Parkinson disease. Int. J. Mol. Sci. 23(21), 13078. doi: 10.3390/ijms232113078

Encadrant **BOHL Delphine**
mail delphine.bohl@icm-institute.org

Equipes ALS: Causes and Mechanisms of Motor Neuron Degeneration
Responsable BOILLEE Séverine
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Human spinal cord organoids to study motoneuron-microglia crosstalk in Amyotrophic Lateral Sclerosis.**

Résumé Amyotrophic Lateral Sclerosis (ALS) or Charcot disease is the most common motor neuron (MN) disease in adults. ALS affects both upper MNs in the motor cortex and lower MNs in the spinal cord. Symptoms are progressive muscle atrophy and patients die most of the time by respiratory failure 3 to 5 years after diagnosis. Despite the discovery of several genetic causes, of numerous mechanisms involved in MN degeneration and despite many therapeutic trials based on these results, there is to date no curative treatment. Several reasons could explain failures of trials. First, ALS is a heterogeneous disorder both at the clinical level and at the genetic level with 90% of sporadic cases. Familial cases representing 10% of ALS cases allowed the identification of more than 25 causal genes, most of autosomal dominance, involved in different pathways. Second, there are still few animal models of ALS and the only patient's tissues that can be obtained are post-mortem ones which represent the end-stage of the disease. Third, while MNs are the major cell type dying in ALS, other cell types are involved in the pathology, and in particular microglial cells that we and others have shown implicated in ALS disease progression (Chiot et al., 2020. PMID: 33077946). As neuroinflammation is a common signature to all ALS patients, it represents an interesting therapeutic target for all patients.

In this context, my group is interested in the modeling of ALS with human induced pluripotent stem cells (IPSC), as this human model offers an opportunity to assess the cause and the progression of MN dysfunction, especially at the early stages of the disease. Thus, we developed several tools and protocols to model ALS with iPSC derived from patients with different ALS forms (genetic and sporadic) and control subjects. We compared ALS and control iPSC-derived MNs to study MN intrinsic defects and showed specific ALS MN phenotypes (Lefebvre-Omar et al., in revision). Next, we developed co-culture experiments between microglia and MNs to study the role of these inflammatory cells in MN death. We identified common but also distinct deregulations in microglia with different ALS forms (Liu et al. in preparation). However, the role of microglia in the pathogenesis and progression of ALS remains unclear. To go one step further, we need now to develop more complex models. In this context, the thesis project will consist of the generation of spinal cord organoids from ALS and control iPSC to study the contribution of microglia towards MN death in these 3D cultures. First, the PhD student will have to generate and characterize spinal cord organoids at different stages of maturation. The second objective will be to analyze whether pathological hallmarks of ALS are present in organoids. Finally, control or ALS iPSC-derived microglia will be injected into organoids to assess their interaction with ALS MN and their contribution to MN death. In conclusion, with the accumulating evidence for spatiotemporal regulation of microglia activation in ALS, we think that spinal cord organoids will be powerful models to better understand the crosstalk between MN and microglia.

Encadrant **BOUSLAMA OUEGHLAMI Lamia**
mail lamia.bouslama@upmc.fr

Equipes Myelin Plasticity and Regeneration
Responsable NAIT OUMESMAR Brahim / ZUJOVIC Violetta
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Deciphering the role of NF2 in the regulation of myelin plasticity in the adult central nervous system**

Résumé In the vertebrate central nervous system (CNS), myelin is produced by oligodendrocytes (OLs). This lipid-rich multi-layered structure surrounds specific portions of selected axons and is essential for the proper functioning of the nervous system. Myelin acts as an insulating sheath, increasing the speed of nerve impulse conduction. The position, thickness and length of the sheath therefore modulate the conduction of the action potential to synchronize neuronal communications. Myelin landscape is genetically predetermined but is refined through life depending on neuronal activity, allowing a constant adaptation of CNS circuits. Myelin is indeed a highly plastic structure: (i) maintenance of the sheath requires a continuous synthesis of myelin, and (ii) myelin landscape itself is modulated depending on experiences. This adaptive myelination is expressed in several manners: from the genesis of new OLs to the modulation of preexisting sheaths in terms of length and thickness. The molecular mechanisms underlying this adaptive myelination are not yet fully understood. Their elucidation will therefore increase our knowledge in the emerging field of myelin plasticity. Furthermore, it could lead to the identification of new therapeutic targets to normalize the myelin landscape and, consequently, the synchronization of neuronal circuits in several psychiatric disorders. In the lab, we have identified two key proteins, PAK1 (P-21 activated kinase) and NF2 (Neurofibromatosis 2), involved in the regulation of myelin wrapping, i.e. the regulation of the thickness of myelin sheaths. Indeed, we have shown that inhibition of PAK1 by NF2 in OLs results in deconstruction of the actin cytoskeleton, a key process in myelin wrapping (Baudouin, Adès et al., under preparation). In vivo, the conditional deletion of PAK1 in OLs (PAK1 cKO) increases myelin thickness during development, with no alteration of the differentiation of OL precursor cells (OPCs). We are currently studying the developmental myelination of Nf2 cKO mice and our first preliminary results show developmental hypomyelination, as expected by the reduced inhibition of PAK1 due to the absence of NF2. We then aim to establish the role of NF2 in myelin plasticity in adulthood and its subsequent effect on mouse behavior, and to identify the molecular pathways by which NF2 regulates myelin formation.

The main objectives of the proposed PhD project are to:

-Define the role of NF2 in the regulation of myelin plasticity and mouse behavior in adulthood. We are interested in determining whether NF2 could control adaptive myelination. To test this hypothesis, Nf2 deletion in OLs will be induced once the broad myelin landscape is formed in Nf2 cKO adult mice. An electron microscopy (EM) study will be performed to determine if the adult deletion of Nf2 prevents myelin maintenance and would consequently lead to a spontaneous loss of myelin thickness and/or myelin sheaths. Investigation of the role played by Nf2 in myelin plasticity will then be pursued by analyzing if this protein is required for the modulation of myelin landscape following experience. Specific learning tasks are associated with increased myelin formation in the hippocampus and motor cortex. Learning tests will therefore be performed in Nf2 cKO mice. Myelin state will be assessed following the learning paradigms to interpret the behavioral results. The thickness and density of the myelin sheaths will be analyzed, as well as the proliferation and differentiation of OPCs in the tested mice.

-Find the molecular mechanisms triggered by NF2 in the regulation of myelination. Our preliminary results suggest that the regulation of myelin formation by NF2 also involves other pathways than its inhibition of PAK1 kinase activity. Given that NF2 acts on its targets by binding, we are currently performing a proteomic analysis of its binding partners in the OLs. Based on the results of this analysis, an in-depth study of the most relevant candidates will be performed to validate them.

Overall, this study will lead to a better understanding of the undocumented role of Nf2 in the regulation of myelin plasticity and learning. It will also allow the discovery of new molecular mechanisms involved in these processes.

Encadrant **CASADO Mariano**
mail mariano.casado@ens.fr

Equipes Glutamate Receptors and Excitatory Synapses
Responsable PAOLETTI Pierre
Unité Institut de Biologie de l'Ecole Normale Supérieure (IBENS)

Sujet **Functional study of excitatory glycine receptors (eGlyRs), a recently discovered family of brain receptors, in the dopaminergic system**

Résumé Ionotropic glutamate receptors of the NMDA type (NMDARs) are key players of excitatory synaptic transmission and plasticity. NMDARs are tetramers made of two GluN1 subunits and two GluN2 or GluN3 subunits. GluN1 and GluN3 bind glycine while GluN2 binds glutamate. GluN1/GluN2 combinations produce "conventional" NMDARs, that are Ca-permeable, blocked by Mg and opened by the concomitant binding of glutamate and a coagonist (glycine or D-serine)6. NMDARs containing GluN3 subunits (GluN3A or GluN3B) are way less known. In the adult, GluN3B expression is restricted to brainstem and spinal motoneurons while GluN3A is more widely expressed, with strong expression in several regions of the forebrain7. GluN3 subunits were first thought to form exclusively GluN1/GluN2/GluN3 triheteromers7. Moreover, this subunit was supposed to play a role primarily during development at its peak of expression7. This view has been recently challenged by several laboratories, including ours. Our lab and others have shown that GluN1/GluN3A receptors; which were known to form glycine-gated receptors in recombinant systems, are bona fide neuronal receptors present in both the juvenile and adult brain2,4,5. These receptors are active in the medial habenula where they control aversive states5. They are also present in the basolateral amygdala where they participate in the stabilization of fear memories2. Furthermore, unpublished data from our lab establishes the presence of eGlyR in the ventral hippocampus. An overall view begins to emerge pointing to a particular enrichment of eGlyRs in regions involved in processing of emotional information in the adult brain.
The dopaminergic system is a key element in the elaboration of behaviors with motivational or emotional value. Besides, transcriptomic studies indicate the expression of GluN3A in these regions.
This project aims to characterize these new eGlyRs in the dopaminergic system. We will first evaluate their presence in the main dopaminergic structures, i.e. Substantia Nigra, Ventral Tegmental Area, hypothalamic nuclei and Zona Incerta. Then, we will tackle the issue of the mode of activation of eGlyRs and their potential regulation by neuromodulators.

Workplan
We will perform whole-cell patch clamp recordings on the different cell types of acute slices from adult mice. Cell types will be identified by the use of mouse strains expressing the Cre recombinase under the control of the DAT promoter (using Td-Tomato reporter mice for cell identification). We will monitor the presence of eGlyRs in our cells by puffing glycine in the presence of antagonists against conventional NMDARs (APV), GlyRs (strychnine), GABARs (bicuculline) and sodium channels (TTX). To improve the signal-to-noise ratio, GluN1-mediated desensitization can be precluded by GluN1 preferring antagonists1 like CGP-78608, identified in our lab as an enhancer of eGlyRs4. The nature of the recorded currents will be confirmed by the use of antagonists (CNQX, DCKA), GluN3A Ko and mice injected with viruses containing shRNA against GluN3A. In a second set of experiments, we may analyze the impact of receptor activation on neuronal firing. Acute activation (glycine plus CGP-78608), acute inactivation (DCKA) or semichronic inactivation (shRNA) approaches will be used.

The characterization of the neuronal expression of eGlyRs in the adult dopaminergic

nuclei is a first step in the project. Several aspects of eGlyR physiology will also be addressed, in particular the source of glycine and the roles of astrocytes: the involvement of receptors in phasic synaptic transmission is unclear, rather tonic activation is likely in brain structures largely lacking glycinergic inputs.
Last but not least, dopaminergic pathways are involved in physiological process including motor control, cognition, executive functions, reward, motivation, and neuroendocrine control. On the long run, we aim to explore whether eGlyRs participate in such functions or any related pathological condition, ie Parkinson's upon SN degeneration. With this project, we expect to provide critical insights on a novel family of brain receptors and their role in circuit function and behavior.

1 Awobuluyi et al 2007. Mol Pharmacol 71, 112
2 Bossi et al 2022. Neuron 110, 2438
3 Chatterton et al 2002. Nature 415, 793
4 Grand et al 2018. Nat Comm 9, 4769
5 Otsu et al 2019. Science 366, 250
6 Paoletti et al 2013. Nat Rev Neurosci 14, 383
7 Pérez-Otaño et al 2016. Nat Rev Neurosci 17,623

Encadrant **CAULI Bruno**
mail Bruno.cauli@upmc.fr

Equipes Cortical Network and Neurovascular Coupling
Responsable CAULI Bruno / LAMBOLEZ Bertrand
Unité Neuroscience Paris Seine

Sujet **Cell-type specific metabolic tuning of neuronal activity and neurovascular coupling**

Résumé Local regulation of cerebral blood flow and metabolism by neuronal activity is essential for brain function. This neurovascular and neurometabolic coupling (NVC/NMC) ensures the homeostasis of cerebral glucose and leads to a transient rise in extracellular lactate, the lack, but also the excess of which is deleterious and implicated in neurological disorders, notably in epilepsy and in Alzheimer's disease (AD).
We have recently shown that lactate consumed by neurons increases their activity through a closure of intracellular ATP-sensitive potassium channels. These observations suggest that lactate could favor vasodilation, but, when in excess, could induce a pathological hyperactivity of the cortical network. Our preliminary data also revealed that pyramidal cells and inhibitory somatostatin (Sst) interneurons, two neuronal types altered in AD, drive vasodilation and vasoconstriction at moderate and high firing frequencies, respectively. In physiological conditions, a feedback control of blood perfusion could therefore exist downstream of increased neuronal activity to limit an excessive lactate supply and thus attenuate cortical hyperactivity.
Based on our preliminary work and current knowledge, we hypothesize that lactate can tune NVC in an activity- and context-specific manner: at low activity levels, lactate may favor vasodilation, but at high levels may promote vasoconstriction to exert a feedback control on brain energy supply and network activity. Furthermore, Sst interneurons exhibit a much higher mitochondrial content than pyramidal cells. This greater oxidation capacity could allow them to be the first responders to a rise in lactate and thus inhibit the activity of the cortical neuronal network thereby providing an additional synaptic mechanism attenuating network hyperactivity. To explore these hypotheses, we will determine by ex vivo and in vivo approaches how lactate shapes neuronal activity and the NVC response controlled by pyramidal cells and Sst interneurons.
The precise control of the extracellular medium in cortical slices permits acute pharmacological manipulation, which allows unraveling the signaling mechanisms for NVC tuning by lactate. We will image Ca2+ signal, as a surrogate of spiking activity, in pyramidal cells or Sst interneurons in which the Ca2+ GCamp6f sensor will be expressed by crossing "floxed" GCamp6f mice with Emx1-Cre or Sst-Cre mice, respectively. Experiments will be carried out at rest and during thalamic fiber stimulations to recapitulate cortical network activity and the effect of different extracellular lactate concentrations will be studied. The contribution of Sst interneuron inhibition will be also evaluated by pharmacological manipulations. These experiments will determine the kinetics of lactate-sensing in pyramidal cells and SST interneurons and will deepen the understanding of how metabolic states influence neuronal network dynamics.
To characterize the role of pyramidal cells and Sst interneurons in lactate-tuned NVC, their activity will be selectively controlled by optogenetic stimulations. The actuator Channelrhodopsin-2 (ChR2) will be expressed by crossing "floxed" ChR2 mice with Emx1-Cre or Sst-Cre mice, respectively. We will monitor optogenetically induced NVC response in cortical slices in presence of different extracellular lactate concentrations. Lactate, through increasing neuronal activity, should dose dependently lower the frequency thresholds of vasodilation and vasoconstriction and increase NVC gain, and thus facilitate and enhance vasocontriction, respectively, as suggested by our preliminary data. These results will be confirmed in vivo where both neuronal

connectivity and blood perfusion are preserved using two-photon microscopy in collaboration with our partners at the Vision Institute.
Through complementary approaches combining multimodal imaging with optogenetic and pharmacological manipulations, we believe that this project will lead to a better understanding of NVC/NMC coordination. Moreover, since NVC/NMC is the physiological basis of functional imaging, this project will also contribute to a better interpretation of its signals. In the long term, it could also help to identify diagnostic and therapeutic targets and contribute to promote the adoption of a lifestyle adapted to neurological disorders in which neuronal, vascular and metabolic alterations overlap such as epilepsy and AD.

Encadrant **CHARRIER Cécile**
mail cecile.charrier@ens.fr

Equipes Development and plasticity of synapses
Responsable CHARRIER Cécile
Unité Institut de Biologie de l'Ecole Normale Supérieure (IBENS)

Sujet **Regulation of synaptic development by neurotransmitter receptors linked to human evolution**

Résumé The synapse is a nanoscale machine, which transfers, integrates and stores information in brain circuits. Its function relies on multimolecular networks of interactions whose composition and dynamics shape synaptic transmission. A large body of evidence indicates that synapses specialized in humans. Human synapses are more densely distributed along dendrites and their period of maturation is protracted compared to rodent or non-human primate synapses. The rules governing their plasticity also differ from the other mammalian species studied so far. These traits contribute to the formation and function of complex circuits supporting human cognitive abilities. Yet, the underlying molecular mechanisms are not known.

In the lab, we are investigating the regulation of synaptic development and plasticity by molecular pathways linked to human evolution. We have recently shown that the human-specific gene SRGAP2C (Slit-Robo Rho GTPAse-activating protein 2C) has contributed to the emergence of human features of synapses, including their protracted maturation and their increased density, by mediating regulations at the core of synapses. Our work on SRGAP2, in addition to recent advances in comparative genomics and developmental transcriptomics, has led us to identify several ionotropic neurotransmitter receptors that are differentially regulated in the human neocortex, including glutamate receptors of the delta and kainate subfamilies and serotonin receptors. Based on previous work and preliminary data from the lab, this project will characterize how the regulation of specific receptor subunits impact synaptogenesis and circuit assembly in the neocortex.

We will address these key issues using complementary mouse and human models, and a multiscale approach that goes from the molecule to the circuit. We will perform in vivo sparse manipulations in intact mouse brain circuits to interrogate gene function using high-resolution confocal microscopy and electrophysiology (whole-cell patch-clam recording). We will use proteomic approaches to identify molecular networks of interactions and decipher the mechanisms involved. We will engineer human cortical neurons derived from pluripotent stem cells (hPSCs) and transplantation into the rodent brain to access human-specific regulations in an integrated, physiological context.

This project will allow us to uncover fundamental mechanisms operating at the synapse and regulations specific to humans to better understand the uniqueness of the human brain at the cellular and molecular levels.

Publications:
- Assendorp N, Depp M, Fossati M, Dingli F, Loew D, Charrier C, CTNND2 moderates neuronal excitation and links human evolution to prolonged synaptic development in the neocortex, bioRxiv 2022.09.13.507776; doi: https://doi.org/10.1101/2022.09.13.507776
- Gemin O, Serna P, Zamith J, Assendorp N, Fossati M, Rostaing P, Triller A and Charrier C, Unique properties of dually innervated dendritic spines in pyramidal neurons of the somatosensory cortex uncovered by 3D correlative light and electron microscopy (2021) Plos Biology, 19(8): e3001375.

- Fossati M, Charrier C, Trans-synaptic interactions of ionotropic glutamate receptors (2021) Curr Opin Neurobiol, 66:85-92.
- Fossati M, Assendorp N, Gemin O, Colasse S, Dingli F, Arras G, Loew D and Charrier C, Tans-synaptic signaling via the glutamate receptor delta-1 mediates inhibitory synapse formation in cortical pyramidal neurons (2019) Neuron, 104(6):1081-1094.e7.
- Fossati M, Pizzarelli R, Schmidt ER, Kupferman JV, Stroebel D, Polleux F, Charrier C, SRGAP2 and its human-specific paralog co-regulate the development of excitatory and inhibitory synapses (2016) Neuron, 91(2):356-69.
- Charrier C, Joshi K, Coutinho-Budd J, Kim JE, Lambert N, de Marchena J, Jin WL, Vanderhaeghen P, Ghosh A, Sassa T and Polleux F, Inhibition of SRGAP2 by its human-specific paralogs induces neoteny during spine maturation (2012) Cell, 149(4):923-35.

Encadrant
mail

COHEN Laurent
laurentcohen2@gmail.com

Equipes
Responsable
Unité

PICNIC Lab (Physiological Investigations of Clinically Normal & Impaired Cognition)
COHEN Laurent / NACCACHE Lionel / BARTOLOMEO Paolo
Institut du Cerveau et de la Moelle épinière

Sujet

Music reading: MRI studies of cortical specialization and neural codes

Résumé

Most musicians master two distinct reading systems, one for words and one for music. Both systems rely on highly trained and specialized visual processing, which gives access to multimodal cerebral networks where language and music are represented. Using functional and anatomical brain imaging, our team made a first step towards unraveling the brain mechanisms of music reading and their relationships with word reading. We identified specialized but overlapping areas for words and for music within the visual cortex and showed that musical expertise modifies slightly the location of the word-selective area (Mongelli et al., 2017). We also showed that musical expertise has an impact on the functional lateralization of the visual cortex (Bouhali et al., 2017), but also on the anatomical connectivity between the visual cortex and broad networks subtending musical cognition (Bouhali et al., 2020).

In those studies, stimuli consisted of single bars of printed piano music, which did not allow us to manipulate and study the musically-relevant parameters of musical writing. This PhD project aims at studying the visual decoding of melodic, rhythmic, and harmonic patterns, and at comparing those phenomena between musicians and naïve participants, but also between musicians mastering monophonic or polyphonic instruments, differing in level of expertise, etc. In addition to readers of music and naïve controls, the experiments will involve musicians with no knowledge of the written musical code. We will use behavioral measures, including the recording of eye movements, 3 Tesla and 7 Tesla MR imaging.

The PhD project will follow a two-pronged strategy, addressing the connected issues of musical pattern complexity and of regional brain specialization.

As a first experiment on pattern complexity, we will focus on melodic structure, and generate sequences of 12 sounds of varying complexity, as defined by the algorithmic compressibility of the operations used to generate the sequences (Sablé-Meyer et al., 2021) (e.g. a ‘simple’ ascending scale results from the repetition of a “one step up” operation, while a ‘complex’ random sequence would require a long series of instructions). Those sequences will be used in a cross-modal paradigm, presented either first visually and then auditorilly, or in the opposite order, with a matching-to-sample decision task. Behavioral measures and MRI images will be acquired during this experiment. In the MRI signal, we will try to identify markers of melodic structure at different time points (during stimulus presentation, during the memory phase between sample and target, and during the response phase).

We recently found, using 7 Tesla imaging, that the visual cortex of bilingual individuals harbors distinct patches specialized for Chinese but not alphabetic reading (Zhang,… & Cohen, in press, Science Advances). Capitalizing on our experience, we will study the double specialization for word and music reading, by imaging at high resolution individuals varying in musical proficiency, while they are reading words and music, and when they are exposed to other categories of visual images, plus appropriate low-level control conditions. This will allow us to identify fine-grained specialization for music perception, and the dissociation or co-localization of the word and the music reading systems.

We will favor a candidate with strong musical competence, in addition to her/his interest for a cognitive neuroscientific approach to those topics, and if possible some experience in the field of experimental psychology, psychophysics, brain imaging, and adequate programming skills. Her/his task will be, under the close supervision of Laurent Cohen at the Paris Brain Institute, where 3T MRI is available and a 7T magnet will be running in 2 years, and in collaboration with the Neurospin imaging center (Stanislas Dehaene), to design experiments, to create experimental material, to recruit participants including expert musicians, to gather and analyze data and to write high-level articles.

References

Bouhali et al., 2020, Neuroimage, 212, 116666
Bouhali et al., 2017, Neuroimage, 156, 445-455
Mongelli et al., 2017, Cortex, 86, 260-274
Sablé-Meyer et al., 2021, PNAS, 118, e2023123118
Zhang et al., 2023, Science Advances, in press

Encadrant **COHEN-SALMON Martine**
mail martine.cohen-salmon@college-de-france.fr

Equipes Physiology and physiopathology of the gliovascular unit
Responsable COHEN-SALMON Martine
Unité Centre Interdisciplinaire de Recherche en Biologie

Sujet **Impact of pesticides on the gliovascular unit development**

Résumé The European population is daily exposed to pesticide residues found in the food. In particular, the French Food Report conducted by ANSES (TDS2, June 2011) has shown that the anilinopyrimidine (AnPy) fungicides cyprodinil, mepanipyrim and pyrimethanil are among the pesticides most commonly detected in our diet, especially in fruits (37%), vegetables (18%), fruit juices (25%) and alcohols (25%) 1. To protect food consumers from potential adverse effects, EU has defined an internationally accepted maximum residue limit dose in tap water (EU directive 80-778-EEC). However, it has been recently shown that chronic exposure to AnPy below this regulatory dose exacerbated the markers of Alzheimer's disease in the J20 mouse model 2 and altered neurogenesis in neonates following gestational exposure 3. Thus, the chronic exposure to AnPy results in brain damages which points out the need to evaluate the impact of these residues on brain development.
AnPy residues may access to the brain perinatally through the blood circulation and could first alter the gliovascular unit (GVU), a specific interface formed by astrocytes and the vascular compartment, where important brain functions such as the blood brain barrier (BBB), the immune homeostasis, the brain drainage and the neurovascular coupling are set 4. Our preliminary results indicate that cortical astrocyte distribution, morphology, and reactivity, as well as the vascular organization are changed in neonates upon AnPy gestational exposure.
The objective of this proposal is therefore to further investigate GVU pathophysiological modifications induced by AnPy chronic exposure to wild-type (WT) as well as genetically predisposed to autism spectrum disorder (ASD) mice. Indeed, ASD is a neurodevelopmental pathology which may result from genetic predisposition associated to environmental assaults 5. The ASD model explored here will be the Cntnap2-/- (contactin associated protein-like 2) deficient mouse model. Cntnap2 is a neuronal neurexin expressed at a critical period of time for astrogliogenesis and synaptogenesis and Cntnap2-/- mice display neuronal migration defects and core autism-related deficits 6.
WT and Cntnap2+/- females will be exposed to a low dose (EU regulatory limit range) of AnPy cocktail, or to an equivalent volume of DMSO (control) during mating, gestation and lactation. This protocol has been set by our collaborator Veronique Perrier (INM, Montpellier) 3. We will investigate in the cortex of male and female offspring (WT, Cntnap2-/- and Cntnap2+/+littermates):

• The interactions between astrocytes and the vascular compartment using a multicolor astrocyte imaging strategy (collaboration with Karine Loulier, INM, Montpellier) 7 from postnatal day (P)5 to P15 – the period we have identified as the time window for the development of astrocytic perivascular contacts (PvAP) 8, and in adults.

• The vascular organization (from embryonic day10 to adult) by immunolabelling all vascular and vascular-associated cells including PvAP on either cleared brains (collaboration with Ali Ertürk, München, Germany and with Axel Montagne, Edinburgh, Scotland) or brain sections.

• GVU molecular properties developing high throughput mass spectrometry and transcriptomic analyses on purified GVUs (our protocols 9);

• GVU functions such as BBB integrity by in situ brain perfusion (Collaboration with Salvatore Cisternino, Faculty of Pharmacy, Paris), immune quiescence (immunodetection of immune cells), blood flow and neurovascular coupling by functional ultrasound imaging, and brain drainage by MRI (Collaboration with Denis Vivien, Cyceron Caen).

This project will bring to light early pathophysiological modifications induced by pesticide chronic exposure to WT and genetically predisposed ASD brains. It will be crucial to understand the impact of pesticides on brain development and warn about their use. Importantly, it may also exemplify the deleterious link between ASD and environmental pollutants.

1. Nougadere A, et al. Environ Int. 2012 15;45:135-50.
2. Lafon PA, et al. Env. Health Perspect. 2020;128(1):17011.
3. Wang Y, et al. Environ Res. 2021;195:110829.
4. Cohen-Salmon M, et al. Glia. 2021;69(4):817-41.
5. Bolte S, et al. Cell Mol Life Sci. 2019;76(7):1275-97.
6. Penagarikano O, et al. Cell. 2011 30;147(1):235-46.
7. Clavreul S, et al. Nat Commun. 2019 25;10(1):4884.
8. Gilbert A, et al. Elife. 2021 1;10.
9. Boulay AC, et al. J Vis Exp. 2015; 105.

Encadrant **COLLINS Thérèse**
mail therese.collins@parisdescartes.fr

Equipes Vision
Responsable COLLINS Thérèse
Unité Integrative Neuroscience and Cognition Center (INCC)

Sujet **Serial dependence in brain and behavior**

Résumé Our subjective experience of the visual world is stable, continuous and seamless. How this phenomenology arises is one of the mysteries of cognitive science, because the outside world presents itself to our senses in a discontinuous manner. Visual input is particularly variable: object features change with perspective and lighting, and input is interrupted by blinks and modified by eye, head and body movements. Despite these discontinuities, we do not perceive objects to shift every time we move our eyes, or the physical characteristics of objects to change each time the sun passes behind a cloud. One general solution to the problem of discontinuities is if perception were the result not of instantaneous input, but of the integration of input over time. Indeed, research in psychology has long shown that recent history can influence the current content of perception. One instantiation of a history effect is serial dependence (SD): the attraction of current perception to instances of a stimulus seen in the immediate past. SD may be the expression of a spatio-temporal integration mechanism that smooths over spurious variations in proximal and distal stimuli to give rise to our impression of a stable visual world.
The PhD project will focus on the behavioral characteristics and brain signatures of SD using psychophysics and EEG measures, combined with multivariate data analysis techniques (representational similarity analysis and multivariate pattern analysis).
The three scientific questions are:

1) Is SD the manifestation of a perceptual effect, or are response biases involved?
To address this question, we will use psychophysics to examine how SD strength varies with stimulus strength, to test whether SD survives sub-threshold stimulus levels. Such results would argue in favor of a response bias. Of course, it is possible (and even likely) that SD results from both perceptual and decisional variables; our approach would allow us to quantify the relative weight of each process.

(2) What is the relationship between SD and other history effects such as adaptation, bistability and idiosyncratic biases?
To address this question, we will quantify the different behavioral effects within participants and examine correlations between tasks. We will use multivariate techniques that leverage individual differences to discover connections between perceptual processes, in particular principal component analysis to uncover latent psychological constructs.

(3) What is the level of processing at which SD occurs?
We will address this question by looking at the role of perceptual and cognitive load and by examining the neural correlates of SD. We will record the brain response to visual objects and use representational similarity analysis and multivariate pattern analysis to determine whether a trace of the recent past is present in the response to current visual objects.

Encadrant **CORTI Olga**
mail olga.corti@upmc.fr

Equipes Molecular Pathophysiology of Parkinson's Desease
Responsable CORTI Olga/CORVOL Jean-Christophe
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Rôle protecteur de la voie PINK1/Parkine dans la réponse neuronale au stress mitochondrial.**

Résumé La maladie de Parkinson (MP) est une maladie neurodégénérative fréquente, caractérisée par des troubles moteurs sévères et irréversibles, dus à la dégénérescence préférentielle des neurones dopaminergiques (DA) de la substance noire. Au cours des vingt dernières années, une vingtaine de gènes responsables de rares formes familiales de MP ont été découverts. Notre équipe s'intéresse aux mécanismes sous-jacents à la mort neuronale dans la MP, à travers l'étude de la fonction de deux protéines dont les gènes sont mutés dans des formes autosomiques récessives, la Parkine et PINK1 (1). Ces protéines co-régulent différents mécanismes de contrôle de la qualité mitochondriale, tout particulièrement la mitophagie et la biogenèse mitochondriale. La voie PINK1/Parkine joue également un rôle protecteur dans de multiples conditions de stress : protéotoxique, oxydant, excitotoxique et infectieux. Si le rôle de cette voie dans le contrôle de la qualité mitochondriale a été bien caractérisé, le lien avec ses propriétés neuroprotectrices reste mal compris. Notre hypothèse est que PINK1 et Parkine se trouvent au carrefour d'un ensemble de réponses visant à préserver la survie cellulaire en conditions de stress mitochondrial, de part leur fonction de système « senseur » de la qualité mitochondriale. Ces réponses, bien caractérisées dans des organismes simples (2), impliquent une signalisation entre la mitochondrie et le noyau, et la mise en place de différents programmes protecteurs qui ont rarement été étudiés de manière intégrée, en particulier dans les neurones.

Ce projet vise à éclairer la physiopathologie de la MP à travers l'étude de l'impact de la perte de fonction de la voie PINK1/Parkine sur les différentes branches de la réponse au stress mitochondrial dans des neurones DA.

Pour cela, nous utiliserons des organoïdes de mésencéphale ventral donnant naissance aux neurones DA, issus de la différenciation de cellules pluripotentes induites (iPS) provenant d'individus sains, de patients porteurs de mutations du gène de la Parkine et de lignées contrôles isogéniques. Afin d'identifier des mécanismes spécifiques aux neurones DA, nous effectuerons une analyse comparative avec des organoïdes corticaux issus de ces mêmes lignées.

Après l'exposition des organoïdes à un stress mitochondrial, nous analyserons tout d'abord par RNAseq la réponse transcriptomique au stress, afin d'identifier les changements au cours du temps de l'expression d'acteurs clés de voies protectrices activées par le stress mitochondrial, et les altérations liées à la perte de fonction de la Parkine. Nous prêterons particulièrement attention à des réponses telles que l'autophagie, la réponse aux protéines mal repliées, la réponse antioxydante, la biogenèse mitochondriale ou la régulation de l'apoptose. Ces résultats seront complétés et confirmés par des approches complémentaires de RT-qPCR, d'immunofluorescence ou western blot.

En parallèle, nous utiliserons ces organoïdes pour explorer à l'échelle cellulaire le turnover mitochondrial, à l'aide d'approches de microscopie confocale, dans des conditions physiologiques ou sous stress mitochondrial, en presence ou absence de mutations du gène de la Parkine. Nous analyserons en particulier la biogénèse mitochondriale, en visualisant la néo-synthèse de l'ADN mitochondrial, et la mitophagie, à l'aide d'un rapporteur moléculaire exprimé par moyen d'un vecteur lentiviral.

En fonction des résultats que nous obtiendrons, des approches d'interférence à l'ARN ou de surexpression à l'aide de lentivirus pourront être mises en jeu, afin d'étudier

l’implication de cibles clés identifiées dans les réponses observées. Le lignées cellulaires, outils et techniques mises en jeu sont disponibles et maîtrisés par notre équipe.
Ces études nous aideront à mieux comprendre le rôle de la voie PINK1/Parkine dans la régulation de la réponse au stress mitochondrial, et apporteront un éclairage sur les mécanismes moléculaires responsables de la dégénérescence neuronale dans la MP due à la perte de fonction de cette voie protectrice.

1. Mouton-Liger F, Jacoupy M, Corvol JC, Corti O. PINK1/Parkin-Dependent Mitochondrial Surveillance: From Pleiotropy to Parkinson's Disease. Front Mol Neurosci. 2017.
2. Haynes CM, et al. Evaluating and responding to mitochondrial dysfunction: the mitochondrial unfolded-protein response and beyond, Tends Cell Biol. 2013.

Encadrant **CORVOL Jean-Christophe**
mail jean-christophe.corvol@aphp.fr

Equipes Molecular Pathophysiology of Parkinson's Desease
Responsable CORTI Olga/CORVOL Jean-Christophe
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Dérégulations EPIgénétiques dans les neurones striataux au cours des Troubles des Conduites Impulsives liés aux agonistes dopaminergiques dans la maladie de Parkinson : étude du transcriptome et du méthylome, identification de nouvelles cibles thérapeutiques (EPI-TCI)**

Résumé Les troubles des conduites impulsives (TCI) sont des complications comportementales fréquentes et graves de la Maladie de Parkinson (MP). Ils comprennent alimentation compulsive, jeux et achats pathologiques, et hypersexualité. Malgré les conséquences négatives possibles, les comportements sont répétés et poursuivis sans contrôle, avec des caractéristiques impulsives et compulsives, impactant négativement la vie des patients et leurs aidants. La physiopathologie des TCI est encore mal connue.

Tous les patients atteints de MP traités par agonistes dopaminergiques ne développent pas de TCI. Peu de données permettent de différencier les anomalies épigénétiques et d'expression des gènes associées au développement de TCI dans la MP. Une étude a rapporté des modifications transcriptionnelles post agonistes dopaminergiques chez la souris, mais portait sur un traitement mixte par L-dopa et agoniste, et surtout sur les propriétés de récompense et non l'impulsivité induite par agoniste dopaminergique. Après de premières études contradictoires sur l'apparition d'impulsivité chez des souris avec une dénervation dopaminergique, des modèles murins validés existent dorénavant, générant des comportements robustes à composantes impulsive et compulsive.

Par une approche innovante, nous investiguerons dans ce projet, au sein des sous-populations neuronales spécifiques du striatum, les modifications dynamiques transcriptionnelles et de méthylation de l'ADN au cours de l'impulsivité induite par agonistes dopaminergiques dans des souris avec dénervation dopaminergique et dans un modèle murin génétique avec une invalidation du gène PRKN (KO PRKN). Notre approche cellule-spécifique pourra cibler la transcription et méthylation de l'ADN, non pas de façon globale, mais dans différentes populations identifiées de neurones striataux, ayant des rôles fonctionnels distincts dans les ganglions de la base. Nous développerons une approche par gène candidats afin de confirmer les précédents gènes et protéines rapportés comme impliqués, et par une approche non biaisée, nous identifierons de nouvelles cibles physiopathologiques et thérapeutiques.

Objectifs :

Objectif 1 : Etude d'un modèle comportemental de troubles des conduites impulsives liés aux agonistes dopaminergiques

Nous nous appuierons sur des tâches expérimentales précédemment rapportées comme générant de façon robuste l'impulsivité et les compulsions dans les modèles murins de MP. Nous utiliserons un modèle murin de dénervation dopaminergique à la 6-hydroxydopamine (6OHDA) ainsi qu'un modèle KO Prkn, précédemment utilisés pour étudier les conséquences des traitements dopaminergiques dans des modèles de MP. Ces souris seront traitées par différentes doses de pramipexole, un agoniste dopaminergique, afin de générer des comportements impulsifs. Ces comportements impulsifs seront mesurés à l'aide du paradigme de « variable delay-to-signal » (VDS). Cette partie du projet aura pour objectif de reproduire les comportements impulsifs et compulsifs dépendants de la dose et de la durée de traitement par agoniste dopaminergique.

Cet objectif servira à caractériser s'il existe un endophénotype comportemental et moléculaire des TCI chez ces souris KO Prkn parfois décrite comme un modèle parkinsonien précoce, et si ce phénotype est semblable ou non à celui retrouvé chez

le modèle 6OHDA présentant une dénervation.

Objectif 2 : Etude des dérégulations transcriptionnelles et de méthylation de l'ADN associées à l'impulsivité chez des modèles murins de Parkinson

Afin d'étudier simultanément les dérégulations transcriptionnelles et de méthylation de l'ADN au sein de sous-populations spécifiques de neurones striataux, les expériences de l'objectif 1 seront ensuite réalisées à l'aide de souris croisées avec des souris génétiquement modifiées permettant d'identifier les populations neuronales spécifiques, porteuses des récepteurs D1 de la dopamine (D1-BACTRAP) ou des récepteurs D2 de la dopamine (D2-BACTRAP). Comme il a été rapporté des modifications biochimiques parfois limitées à certains territoires du striatum impliqués dans les comportements motivationnels, les expériences seront effectuées en prélevant et analysant de façon séparée le noyau accumbens et le striatum dorsal de chaque souris. Cette approche innovante pourrait ainsi permettre de découvrir des modifications plus spécifiques et jusqu'alors restées inconnues du fait des approches globales en général utilisées.

Encadrant **CRISTIA Alejandrina**
mail alecristia@gmail.com

Equipes Language acquisition across cultures
Responsable CRISTIA Alejandrina
Unité Laboratoire de Sciences Cognitives et Psycholinguistique (LSCP)

Sujet **Language input and development across languages and cultures**

Résumé Most research on early language acquisition has documented entry and learning cues in only a handful of cultures, the assumption being that the mechanisms postulated to explain acquisition in these cultures are universal. However, some previous work suggests that the conditions under which young children acquire their mother tongue vary considerably from culture to culture (e.g., Cristia, 2022).

Nowadays, it has become relatively easy to capture both spoken input and children's vocal productions via small recorders worn by the child for one or more representative days. These large-scale recordings are analyzed using a combination of professional linguistic annotation and automated big data analysis. This technique allows for more accurate documentation of the “real” input of infants' experience of language in a variety of cultures and social settings.

Candidates are invited to develop a research project building on the thousands of hours of audio, collected from hundreds of children who are growing up in diverse environments, using methods from developmental psychology, linguistics, data science, and/or machine learning. The precise research question will be defined together with the candidates, but some of the potential research questions are:
- Are there differences in the developmental profiles exhibited by children as a function of the typological properties of the language(s) they are learning?
- What types of experiences are necessary and/or beneficial for vocal development?
- How does early exposure to other children's or adults' voices correlate with morphosyntactic development, and what may this suggest about learning mechanisms involved in language acquisition?
- What cognitive mechanisms are necessary to process the kind of speech input available to children across cultures?
- What is the shape of the statistical relationship between experiences and outcomes, and what does that indicate with respect to the robustness of learning mechanisms involved in early language learning?

Candidates may also ask to be involved in additional data collection, in which case additional research questions are possible, including: how do these novel measures of development relate to more standard measures of language development?

There is funding for 2 PhD students from the ERC project ExELang (exelang.fr). Candidates with a strong machine learning or data science background can also be funded via the CIFRE system.
These projects will take place within the Language Acquisition Across Cultures team, which has a collegial and positive work environment, accepting of cultural and individual diversity. Regular mentoring is used to help team members clarify their skills and broader career goals, and take steps to achieve them. More information on the team is available on https://lscp.dec.ens.fr/en/research/teams-lscp/language-acquisition-across-cultures.

Questions are welcome to laac.lscp@gmail.com.

Encadrant **DARIOS Frédéric**
mail frederic.darios@upmc.fr

Equipes Basic to Translational Neurogenetics
Responsable DURR Alexandra/STEVANIN Giovanni
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Uncovering the molecular mechanisms that modify onset of hereditary spastic paraplegia SPG4**

Résumé In dominantly inherited neurological diseases, the individual variability of clinical signs make prognosis and prediction of the disease course difficult. An example of such disease is the most frequent form of Hereditary Spastic Paraplegias (HSP) due to mutations in the SPAST/SPG4 gene. This rare neurological disorder due to progressive degeneration of the corticospinal tract, causing legs spasticity, is characterized by a strong phenotypic variability (Parodi et al, 2018), which makes prognosis very difficult for clinicians.
Using a large cohort of SPG4 patients, the teams previously showed that a younger age at onset was associated with SPAST missense mutations, while truncating mutations were associated with late onset (Parodi et al, 2018). Yet, unexplained onset variability despite these genotype-phenotype correlation prompted us to search for modifying genes. We thus performed a genome wide association study to search for modifying genes and explain their role. We identified an expression quantitative trait loci (eQTL) in a modifier gene, SARS2, associated with age at onset in SPG4 patients (Parodi et al, 2022): genotype responsible for lower expression was associated with earlier age at onset. SARS2 encodes a mitochondrial enzyme, suggesting that SARS2 may modulate SPG4 disease course by acting on mitochondrial function.
The objective of the project is to understand the pathophysiological mechanisms underlying the variability in symptoms observed in SPG4, focusing on both the nature of the pathogenic mutation and the modifier effect of SARS2. To address this question, we will use a set of six isogenic induced pluripotent stem cell (iPSC) lines with (i) wild-type SPAST gene, a truncating mutation or a missense mutation in this gene, and (ii) genotypes associated with either high or low expression of SARS2. The PhD student will use these cell lines to differentiate them into neurons with cortical identity in vitro, using a protocol already established in the laboratory. The neurons will then be used to investigate how the missense or truncating mutations of SPAST and the SARS2 genotype may affect cellular function. Due to the role of SARS2 in mitochondria, we will first focus on mitochondrial function. We will investigate whether the mutations affect morphology, shape and distribution of mitochondria in neurons. We will also investigate whether the activity of mitochondria is altered by mutations using fluorescent reporters of mitochondrial activity such as membrane potential or mitochondrial production of free radical. In parallel, we will perform a transcriptomic approach in the various lines of neurons to identify other pathways that may be affected by SPAST mutations or the SARS2 genotype.
With this project we expect to understand the function of the SARS2 genotype that is associated with a later age at onset of disease in SPG4 patients. These results may give a rationale to develop therapeutic strategies aiming at delaying onset of symptoms for SPG4 patients in the future.

References

Parodi et al. (2018) Spastic paraplegia due to SPAST mutations is modified by the underlying mutation and sex. Brain 141(12):3331-3342. doi: 10.1093/brain/awy285.
Parodi et al. (2022) The mitochondrial seryl-tRNA synthetase SARS2 modifies onset in spastic paraplegia type 4. Genet Med S1098-3600(22)00875-9. doi: 10.1016/j.gim.2022.07.023.

Encadrant **DAUMAS Stéphanie**
mail stephanie.daumas@upmc.fr

Equipes Neuropharmacology of VGLUTs
Responsable DAUMAS Stéphanie
Unité Neuroscience Paris Seine

Sujet **Understanding the emergence of compulsive behaviors through striatal acetylcholine/glutamate cotransmission**

Résumé Persistent habitual behaviors and compulsion are considered as a common feature of several pathologies such as obsessive compulsive disorders (OCD), substance use disorders (SUD) and eating disorders (ED). The dorsal striatum is central for the transition from reward-guided and goal-directed behaviors (GDB) to habitual behaviors (HB), and finally to compulsion.
Cholinergic striatal interneurons (ChIs) regulate the striatal network with both acetylcholine (ACh) and glutamate (glut) thanks to the presence of the vesicular ACh transporter (VAChT) and the atypical vesicular glut transporter type 3 (VGLUT3) respectively. We have established that 1) striatal ACh/glut cotransmission regulates habit formation, SUD and ED, and that 2) dysregulation of ChIs signaling results in an imbalanced dopaminergic (DA) tone that favors habit formation, and could lead to compulsion.

Based on these observations, we propose that under specific conditions, altered cholinergic signaling leads to an uneven pattern of DA efflux in the Nucleus Accumbens (NAc)/caudate compared to the putamen. This DAergic imbalance within the striatum alters the balance between GDB and HB and progressively induces pathological behaviors. Interestingly, we also observed that an acetylcholinesterase inhibitor was able to reverse pathological behaviors. Therefore, harnessing ACh/glutamate cotransmission from ChIs could help to alleviate psychiatric disorders with a compulsive dimension such as addiction, eating disorders and OCD.
This objective is supported by recent data from the team showing that (i) a rare missense variant of VGLUT3 (p.T8I, minor allele frequency ~1%) is over-represented in humans with compulsive psychiatric disorders and (ii) p.T8I-VGLUT3 mice show intact glutamatergic transmission but a severely blunted ACh transmission from striatal ChIs. Interestingly in rodents the p.T8I mutation increases the risk of relapse to drugs of abuse, excessive habit (HB) formation and maladaptive eating. Therefore, there is strong preclinical evidence and emerging clinical data that p.T8I is associated with compulsion.

In this project, we want to address the hypothesis that region-specific modification of ChIs signaling may precipitate compulsive behaviors by altering the balance between GDB and HB.

To test this hypothesis, we will address the following aims:

Part 1- in vivo study of DA and ACh signaling in p.T8I-VGLUT3 mice.

We will record ACh and DA transmission in vivo in the various striatal compartments to study how the p.T8I mutation impacts them both. We will use pharmacological and fiber photometry tools to investigate how ACh or DA effluxes are dysregulated in our mutants thanks to the use of specific biosensors (GACh4.3/GRABDA4.4).

Part 2- How do mutations of VGLUT3 impact striatal-dependent behaviors?

In this second part, we will examine the GDB/HB balance, maladaptive eating and

compulsive behaviors of VGLUT3-T8I mutants14. We will then attempt to normalize pathological behaviors.

- Balance between GDB and HB in p.T8I mice We will first explore maladaptive eating using the binge-like sucrose over consumption (a model of bulimia-like behavior) and self-starvation in the activity-anorexia-based (ABA) models. We will submit the mutants to reward devaluation to assess if they are more prone to develop HB as hypothesized. This will characterize the maladaptive eating and compulsive behaviors of our p.T8I mutants.

- Modulating DA transmission in specific striatal compartments to rescue the phenotype. In this 2nd step, we will attempt to normalize pathological behaviors using pharmacological compounds targeting the ACh transmission. We hypothesize that p.T8I mice will be more prone to excessive habits and to compulsion leading to maladaptive eating behaviors. We also expect nAChR positive allosteric modulators will rectify these pathological behaviors.

Altogether, this project will decipher how regional neuronal disruptions in the striatum could lead to excessive habits and compulsive behaviors. We will test the notion that imbalanced DA signaling in striatal subareas is at the core of compulsivity. This bias towards the development of compulsion is important since it constitutes a transdiagnostic dimension in addiction, eating disorders and OCD.

Encadrant **DE JUAN-SANZ, Jaime**
mail Jaime.dejuansanz@icm-institute.org

Equipes DE JUAN-SANZ LAB
Responsable DE JUAN-SANZ, Jaime
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Metabolic control of glutamate synthesis and excitatory neurotransmission**

Résumé Cognitive function is famously related to metabolic state as the energetic cost of brain functioning, even at rest, imposes a significant energetic demand to organisms. From flies to humans, essential brain functions require large amounts of energy, which have to be counterbalanced on demand by dynamically adjusting the rates of energy-generating pathways. Mitochondria are known to generate more than 90% of the neuronal energy in the form of ATP via oxidative phosphorylation (OxPhos) and are strategically located along the complex neuronal morphology to be in the ideal position to provide locally energy in the form of ATP on demand. Previous work from the de Juan-Sanz Lab found that axonal mitochondria sense neuronal activity through Ca2+ signaling to accelerate their metabolism on demand. Ca2+ increases in the mitochondrial matrix during neurotransmission activate a series of TCA enzymes through direct Ca2+ binding, increasing their activity transiently to meet the new demands (Ashrafi et al, 2020. Neuron). This work identified the molecular link between energy consumption and production, as both processes are controlled directly by Ca2+ signaling, discovering the functional interconnection between synaptic activity and mitochondrial physiology.

Mitochondrial metabolism, however, is not exclusively in place for providing ATP, but it is as well intricately related to the global metabolism of a neuron and can act as a metabolic hub for balancing the control of a diverse range of metabolites, including aminoacids such as glutamate and its precursors. However, whether dynamic adjustments of mitochondrial metabolism are linked to neurotransmitter availability remains poorly understood.

During neurotransmission, presynapses release their neurotransmitters to the synaptic cleft. In the case of glutamatergic neurons, the neurotransmitter, glutamate, is rapidly cleared by astrocytic transporters and little is recycled back to the presynapse. This implies that neuronal activity consumes glutamate locally at presynapses at fast rates, suggesting that cytosolic levels of glutamate have to be actively preserved to facilitate synaptic vesicle refilling of vesicles. A long-standing hypothesis in the field proposes that part of the glutamate released into the cleft and uptaken by astrocytes can be converted to glutamine by these cells and shuttled back to neurons, where it can be converted back to glutamate. While much data supports the existence of this hypothesis, named the glutamate-glutamine cycle, this pathway is non-stoichiometric and cannot replenish more than 12-70% of the glutamate released. In this project we hypothesize that activity-driven increases in mitochondrial metabolism are leveraged by glutamatergic neurons to derive carbons from the accelerated TCA cycle to glutamate synthesis. Leveraging our recent discoveries on the molecules controlling the dynamic adjustments of mitochondrial metabolism during activity, we will 1) generate an shRNA library for TCA cycle enzymes and proteins involved in glutamate synthesis to test their involvement in synaptic strength, 2) identify the anaplerotic pathways that enable deriving carbons from the TCA cycle to glutamate synthesis and 3) translate our discoveries into an in vivo system in collaboration with Pavan Ramdya (EPFL, Switzerland), leveraging the powerful model of Drosophila melanogaster. Taken together this PhD work will depict for the first time the molecular link between mitochondrial metabolism, expanding our views on

synaptic metabolism and identifying novel roles of mitochondrial function beyond classical bioenergetics.

Encadrant **DEHAENE Stanislas**
mail Stanislas.dehaene@cea.fr

Equipes Neuroimaging of Human Cognitive Architectures
Responsable DEHAENE Stanislas
Unité Unité de Neuroimagerie Cognitive

Sujet **Représentation des concepts mathématiques dans le cerveau humain et les réseaux de neurones artificiels**

Résumé Résumé du sujet

L'objectif de la thèse est de clarifier, par les méthodes de l'intelligence artificielle et des neurosciences cognitives, la question de la représentation des concepts mathématiques. Dans un premier temps, nous utiliserons des méthodes d'analyse automatique des textes (notamment une variante de l'analyse sémantique latente appelée GloVe) pour extraire une représentation vectorielle (embedding) du lexique des concepts mathématiques. Ensuite, nous comparerons cet espace sémantique théorique avec le comportement et l'IRM fonctionnelle chez des sujets humains de différents niveaux d'éducation. Nous étudierons la répartition des différents concepts mathématiques sur la surface corticale, et la comparerons avec la similarité sémantique prédite par GloVe. Par ailleurs, les modèles de langage tels que GPT-3 font encore beaucoup d'erreurs lorsqu'on leur demande de juger la véracité d'une affirmation mathématique. Nous examinerons donc dans un second temps s'il est possible d'améliorer l'entrainement des modèles de langage afin de rapprocher leurs performances et leurs représentations internes de celles de mathématiciens humains.

Contexte sociétal
Ce projet s'inscrit dans un projet plus large de cartographie du cerveau, déjà entamé dans le cadre du langage. Comprendre comment sont réparties et traitées les mathématiques dans le cerveau pourrait permettre d'améliorer la façon de les enseigner, car cette discipline est actuellement une pierre d'achoppement majeure dans la formation des collégiens et des lycéens.
De plus, nous transposerons à l'IA la compréhension de la cognition des mathématiques que nous allons développer. Cette direction de recherche pourrait conduire à l'émergence de modèles capables de conduire un réel raisonnement mathématique. Ces modèles auraient un impact majeur sur la société, tant les mathématiques sont omniprésentes.

Contexte scientifique
L'intelligence artificielle est au cœur de la recherche actuelle en informatique. Par ailleurs, un nombre croissant de scientifiques s'intéressent à l'interaction entre les neurosciences et l'IA, en particulier dans le cadre du langage. Nous proposons le même type de démarche, mais dans le cadre des mathématiques, ce qui n'a pas encore été fait. Nous pensons, en effet, qu'une approche mêlant IA et neurosciences pourrait bénéficier aux deux disciplines. Ceci permettrait d'une part de mieux comprendre le fonctionnement des modèles d'intelligence artificielle, qui sont souvent considérés comme des boîtes noires ; et d'autre part de mieux comprendre la façon dont les mathématiques sont apprises et traitées par le cerveau humain. À long terme, ces travaux pourraient aider à la création de modèles capables de raisonner et d'effectuer mathématiques de la même façon que les humains, et d'aider les scientifiques et les ingénieurs dans leurs travaux.

Démarche
Nous allons exploiter les méthodes existantes dans le cadre de l'étude du langage, ainsi que les récents progrès dans le développement d'intelligences artificielles capables de communiquer et de raisonner. Ceci nous servira de base pour notre

étude des mathématiques dans le cerveau et dans les modèles d'IA. Par ailleurs, nous profiterons du fait qu'UNICOG est un grand centre d'imagerie cérébrale et possède un grande expertise en la matière, notamment avec des appareils à haut champ (7T dans notre cas, mais également 11,7T).

Actions prévues pour la première année
La première année sera consacrée à la conception et la conduite d'expériences d'IRMf sur des humains adultes de différents niveaux d'éducation. La création des stimuli pour l'expérience IRMf sera également l'occasion de s'intéresser aux représentations sémantiques des mathématiques dans différents modèles d'IA afin de recouvrir au mieux l'espace sémantique théorique.

Actions prévues pour la deuxième année
La deuxième année sera plutôt consacrée au développement, à l'étude et à la comparaison de modèles d'intelligence artificielle de la classe Transformer pour les mathématiques. Elle sera la continuité des travaux entrepris pendant un stage de M2 et se fondera sur les résultats obtenus durant la première année pour identifier des points de comparaison avec la cognition humaine.

Encadrant **DEL BENE Filippo**
mail Filippo.del-bene@inserm.fr

Equipes Development and Function of the Vertebrate Visual System
Responsable DEL BENE Filippo
Unité Institut de la vision

Sujet **Redox signaling during zebrafish and human retinogenesis**

Résumé Research on reactive oxygen species (ROS) such as hydrogen peroxide (H2O2) has primarily focused on their deleterious effect. However, in recent years, several reports have pointed at a physiological role for redox signaling in the proliferation and maintenance of stem cells. The balance of the redox milieu defined by the production versus the scavenging of ROS is critical to ensure these functions. Therefore, ROS may play a function of “stem cell rheostat”, acting as a link between extrinsic cues and intrinsic programs. Stem and progenitor cells may tune redox regulation as a mean of holding their stem cell fate in check, while ensuring homeostasis. Thus, the stem cell metabolic state and redox profile are tightly linked with stem cell-renewal, pluripotency (or multipotency) and differentiation. Therefore, understanding how these molecular mechanisms work in vivo under physiological conditions is essential.

To gain insights into the regulation of ROS and their derivatives during neurodevelopment we are using the Zebrafish retina. In a recent study from the lab (Albadri et al, Dev Cell - 2019), we revealed that the fine regulation of H2O2 levels mediates the switch from proliferation to differentiation in retinal stem cells (RSCs). We showed that the local and temporal manipulation of H2O2 levels in RSCs is sufficient to trigger their premature differentiation. Our work revealed a mechanism that links H2O2 homeostasis and neuronal differentiation in the Zebrafish retina. In this project, we propose to expand these results by molecularly dissecting this process by two complementary but independent aims.

First, we will investigate the role of Cap’N’Collar (CNC) family of transcription factors that is composed of 6 members in Zebrafish, which function as ROS stress response mediators. It has been reported that their cyto-protective function is ensured via their transcriptional activity on antioxidant-response elements present in the CIS-region of many genes encoding for metabolic and ROS detoxification enzymes. In the zebrafish retina, the expression of CNC factors has only been partially reported and their function during retinogenesis has never been assessed. We will therefore aim first at better characterizing their expression dynamic in the zebrafish retina and defining their function during retinogenesis. The effect of CNC loss-of-function and gain of function in zebrafish on RPC fate will be evaluated, looking at the proliferation and differentiation profiles in the retina.

Secondly, we aim to investigate the yet unknown role of redox signaling for human retinal development and how metabolic enzymes may contribute to the making of the tissue. We will analyze the conservation of these mechanisms in humans and highlight also the possible species-specific differences to fill this fundamental knowledge gap. We will do this by analyzing the expression of ROS metabolizing enzymes. To do so, we will first analyze the expression of ROS modulating enzymes via immunohistochemistry or fluorescent in situ hybridization. Candidate genes will be chosen based on an available dataset derived from single cell mRNA sequencing. Secondly, using retinal organoids derived from human inducible pluripotent stem cells (hiPSCs), which recapitulate the spatial and temporal differentiation of the retina, we will monitor H2O2 dynamics in an in vivo system. We will generate a human hiPSC line expressing the HyPer7 fluorescent H2O2 sensor that will used to generate transgenic organoids to follow for the first time the dynamics of H2O2 in this human

retinal model, in the course of its differentiation. Finally, we will evaluate the impact of ROS modulation on metabolic pathways by modifying the growth milieu of these organoids where H2O2 or other oxidative stressors can be supplemented. H2O2 production will be modulated using cell-specific chemogenetic approach. In addition, we will test the functions of ROS modulating enzymes by genetically deleting them using the CRISPR/Cas9 technology in organoids. To analyze the consequences of H2O2 manipulations and genetic alteration of redox signaling, we will monitor the proliferation and differentiation of human RSCs in these experimental contexts.

Overall, this project will reveal the function of redox signaling for zebrafish and human retinal development. This will further provide insights to exploit our results for potential therapeutic applications based on stem cell regenerative approaches.

Encadrant **DELORD Bruno**
mail bruno.delord@sorbonne-universite.fr

Equipes AMAC (Architectures and Models for Adaptation and Cognition)
Responsable GIRARD Benoît
Unité Institut des Systèmes Intelligents et de Robotique

Sujet **Biophysical modeling of joint oscillatory regimes in basal ganglia, thalamus and frontal cortex areas**

Résumé Brain activity displays multiple oscillation modes, but we don't yet know for certain whether oscillations represent byproducts of brain physical properties or genuine, active and relevant components of neural computation. Recent data indicate implication of β oscillations (13-35Hz) in cognitive processes: β activity is prominent in decision-making tasks, e.g. such as in free choice decision (Pesaran et al., 2008). These decision-making processes involve circuits arranged in loops connecting frontal cortex areas, the basal ganglia and the thalamus.

E. Procyk's team (INSERM, Lyon), with which we collaborate, have acquired a set of electro-physiological data in the anterior cingulate and prefrontal cortex (ACC and PFC) of monkeys performing the self-paced decision-making EE (Exploration/Exploitation) task (Procyk & Goldman-Rakic, 2006), which has revealed complex modulations of β oscillations, which are organized in bursts (Stoll, Wilson et al., 2016; Wilson et al., 2016). These data suggest that β bursts might reflect on-going, unitary short-lived network events subserving specific neural dynamics deliberative processes generating endogenous flexible decisions.

Our ISIR team is currently developing a spiking model of the cortico-baso-thalamo-cortical loop involved in decision-making in the EE task. It is based on existing models:
- ACC and PFC recurrent neural network models we have developed to explain data from the Procyk team (Fontanier et al., 2022), which display dopamine (DA) modulation and emerging Hebbian, trajectory and state attractor dynamics. These models exhibit discrete β bursts at rest, with a relatively flat power distribution in all frequency bands.
- A monkey basal ganglia model, based on realistic spiking neurons, synaptic delays, with emerging selection properties (Girard et al., 2021). This model also exhibits discrete β bursts, but only in the upper part of the β band, with bimodal power distribution in the upper β and ɣ band.
- A thalamic network model, derived from our previous published (Paz et al., 2012), closes the loop.
The complete loop model allows to assess the causal relationships underlying spiking dynamics, β bursts and decision-making in frontal loops.
The EE task includes both working memory and reinforcement learning components. Thus, our final objective is to integrate in this network DA-reinforcement synaptic rules 1) at cortico-cortical synapses, to learn associative attractors of task states representations (PFC) and of meta-learning valuation (ACC), and 2) at cortico-basal synapses to learn task contingencies.

The goal of the thesis is to use this complete model to explain the evolving dynamics measured during the learning of the EE task.

* Fontanier, V., Sarazin, M., Stoll, F. M., Delord, B., & Procyk, E. (2022). Inhibitory control of frontal metastability sets the temporal signature of cognition. Elife, 11, e63795.
* Girard, B., Lienard, J., Gutierrez, C. E., Delord, B., & Doya, K. (2021). A biologically constrained spiking neural network model of the primate basal ganglia with

overlapping pathways exhibits action selection. European Journal of Neuroscience, 53(7), 2254-2277.
* Paz J., Davidson TJ, Frechette ES, Delord B, Parada I, Peng K, Deisseroth K & Huguenard JR (2012) Closed–loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. Nat Neurosci.
* Pesaran, B., Nelson, M. J., & Andersen, R. A. (2008). Free choice activates a decision circuit between frontal and parietal cortex. Nature, 453(7193), 406.
* Procyk, E., & Goldman-Rakic, P. S. (2006). Modulation of dorsolateral prefrontal delay activity during self-organized behavior. J Neurosci, 26(44), 11313-11323.
Spitzer, B., & Haegens, S. (2017). Beyond the status quo: A role for beta oscillations in endogenous content (re) activation. eNeuro, 4(4).
* Stoll* F., Wilson* C.R.E., Faraut M.C.M., Vezoli J., Knoblauch K., & Procyk E. (2016) The effects of cognitive control and time on β oscillations. Cereb Cortex, 26: 1715-1732.
* Wilson C.R.E., Vezoli J., Stoll F., Faraut M.C.M., Leviel V., Knoblauch K., & Procyk E. (2016) Prefrontal markers and cognitive performance are dissociated during progressive dopamine lesion. PLoS Biol, 14(11): e100257

Encadrant **DI NARDO Ariel**
mail Ariel.dinardo@college-de-france.fr

Equipes Développement et Neuropharmacologie
Responsable PROCHIANTZ Alain
Unité Centre Interdisciplinaire de Recherche en Biologie

Sujet **Mechanisms of transcription factor distribution in cerebrospinal fluid lending insight into mood disorders**

Résumé

In the mammalian brain, the OTX2 homeoprotein transcription factor is transferred from choroid plexus to cortical interneurons by the cerebrospinal fluid. This physiologically important process regulates critical periods of juvenile brain plasticity that allow neural circuitry to restructure in response to experience and are implicated in psychiatric disorders. To comprehend the fundamental mechanisms underlying this transfer, this project will provide insight into paracrine activity at the molecular scale related to protein secretion by the choroid plexus. It will develop exquisitely sensitive approaches through in vivo targeting of mouse choroid plexus to follow protein secretion and transfer, and to evaluate transport machinery. It will also evaluate how choroid plexus secretion is altered by early-life stress known to impact adult anxiety-like phenotypes. By combining biochemical quantifications with animal behavior studies and rescue experiments, this project will expand our knowledge of OTX2 paracrine activity, choroid plexus function, and mood disorders, with the promise of reversing brain deficits.

Encadrant	**DIANA Marco**
mail	marco.diana@upmc.fr
Equipes	Biophysics of the brain
Responsable	OHEIM Martin
Unité	SPPIN (Saints Pères Paris Institute for the Neurosciences)

Sujet **Physiological dissection of medial habenular circuits regulating aversive behavior**

Résumé

Our project proposes to use state-of-the-art experimental approaches to characterize the Dorsal Diencephalic Conduction system (DDC), a neuronal network mediating the development of aversive internal emotional states in response to negatively valued challenges from the external environment.

The Medial Habenula (MHb) and the Interpeduncular Nucleus (IPN) are key relay nuclei belonging to the DDC. The synaptic connections linking the MHb with its exclusive postsynaptic target, the IPN, regulate complex behaviors such as anxiety, fear, sensitivity to pain, and drug addiction via their control of downstream neuromodulatory nuclei. These important functions notwithstanding, most of the synaptic and circuital mechanisms mediating the influence of the MHb-IPN axis on aversive behaviors remain unknown. We believe that this lack of knowledge derives from the complexity of the specific integrative properties of both the MHb and the IPN. These 2 structures indeed exhibit uniquely diverse (non)synaptic mechanisms that, conjoint with a relevant cellular heterogeneity, determine their physiology.

Our team is engaged in a long-standing effort that aims at unraveling how the medial habenular relay and its related structures, modify and re-transmit the incoming information to modulate behavior.

Namely, on one side, we demonstrated that atypical glycinergic excitatory NMDA receptors (Grand, Abi Gerges et al., Nature Communication, 2018) are expressed at high levels in the MHb and that their activation by non-synaptic mechanisms controls aversive behaviors (Otsu et al. 2019, Science). Moreover, by combining ex-vivo and in-vivo optogenetics our laboratory has recently showed that the dynamic properties of the glutamatergic afferences to the MHb impose precise constraints on how their activity modulates anxious states (Otsu et al. 2018 Cell Reports).

The MHb-IPN also shows an exceptionally high level of expression of both opioid and nicotinic receptors, whose physiology remains unknown. One goal of this project will be to determine how the activation of these receptors, by either endogenous ligands or exogenous drugs, may alter MHb-IPN signaling and contribute to the development of affective behaviors associated with addictive states.

Our team has long-standing expertise in a wide spectrum of investigative techniques ranging from ex vivo electrophysiology and morphological circuit tracking, to in vivo behavioral analyses.

We seek to recruit a motivated PhD student with the ultimate goal of revealing how the unique synaptic properties of the neural circuits implicating the medial habenula affect emotional responses to environmental challenges.

To this goal, the candidate will use vanguard chemo/optogenetic tools in combination with ex-vivo electrophysiological and anatomical techniques, and in vivo behavioral and imaging approaches.

The hosting institute, the Saints-Pères institute for Neurosciences at the University of Paris (formally University Paris Descartes), has a long-established history of high-level neuroscientific research, centered on the application of last generation optical techniques to the study of brain physiology. The presence in loco of a core of researchers developing in vivo techniques like 2-photon imaging, miniscope GRIN lens-based imaging and fiber photometry also promises to offer a highly motivating and collaborative working environment.

Interested candidates should contact either marco.diana@u-paris.fr or eric.schwartz@u-paris.fr

Encadrant	**DUBOIS Jessica**
mail	Jessica.dubois@cea.fr
Equipes	InDEV (Anatomo-Functional Variability, Vulnerability And Plasticity During Neurodevelopment : Clinics, Behavior And Imaging)
Responsable	HERTZ-PANNIER Lucie / DUBOIS Jessica
Unité	NEURODIDEROT

Sujet

Le développement sensorimoteur des enfants prématurés : une étude longitudinale prospective avec des évaluations cerveau-comportement.

Résumé

Les mécanismes de développement du cerveau reposent sur des interactions complexes entre facteurs génétiques, épigénétiques et environnementaux, et toute altération de cette dynamique peut avoir des effets à long terme sur le neurodéveloppement. Comme la naissance intervient à un moment critique pour la mise en place des réseaux cérébraux, les enfants prématurés présentent un risque élevé de troubles du développement neurologique [1]. Des déficiences sensorimotrices courantes (y compris la paralysie cérébrale et des handicaps plus légers comme la dyspraxie) peuvent être observées progressivement pendant la petite enfance, lorsque les acquisitions de la motricité globale et fine deviennent plus complexes. Néanmoins, la manière dont les déficits comportementaux sont liés aux altérations neurophysiologiques a été peu explorée jusqu'à présent.

Bénéficiant d'une intense neuroplasticité, les premiers mois postnatals constituent une période idéale pour moduler les perceptions et les expériences des nourrissons vulnérables afin de limiter l'apparition et la gravité des déficits. Cependant, la mise en œuvre d'interventions adéquates et individualisées dès la période néonatale nécessite des marqueurs cérébraux permettant de prédire le devenir de l'enfant. L'imagerie par résonance magnétique (IRM) et l'électroencéphalographie (EEG) sont des méthodes complémentaires pour caractériser le développement du cerveau et ses altérations chez les nouveau-nés [2]. Cependant, la compréhension des relations développementales entre marqueurs structurels et fonctionnels est encore insuffisante pour les réseaux sensorimoteurs, contrairement aux modalités visuelles et auditives [3, 4].

Ce projet de thèse vise à combler ces lacunes en prolongeant des recherches en cours menées en collaboration entre inDEV (NeuroDiderot), PACD (INCC) et les équipes cliniques de l'hôpital Robert-Debré. Depuis avril 2021, des données ont été collectées pour 45 nourrissons nés grands ou très grands prématurés (32 semaines de gestation): IRM à l'âge équivalent du terme (~0 mois d'âge corrigé, mAC) [5], EEG à 0 et 2mAC (au repos / stimulations tactiles) [6,7] et suivi clinique systématique. Des inclusions supplémentaires sont prévues d'ici la fin 2023 (Npt attendu = 60). Des données EEG de nourrissons nés à terme (Nft =15) ont également été collectées à 0 et 2m.

Le projet de doctorat a 3 objectifs principaux, reposant sur les hypothèses suivantes:

1) Relier la dynamique de la maturation neurophysiologique (EEG à 0-2mAC) et l'organisation structurelle précoce du cerveau (IRM à 0mAC) chez les prématurés (Npt=60). Nous supposons que la variabilité interindividuelle des changements fonctionnels précoces au cours de la petite enfance est due aux différences précoces de connectivité structurelle au sein des réseaux sensorimoteurs.

2) Effectuer un suivi multimodal des enfants à l'âge de 3 ans (âge correspondant à la transition vers l'école maternelle et compatible avec le calendrier du doctorat) en se concentrant sur le développement sensorimoteur avec des évaluations comportementales standardisées (e.g. BSID-3, MABC-2) et des évaluations EEG (au repos / pendant des stimulations tactiles passives / une tâche motrice simple / l'observation d'interactions sensorimotrices) (attrition prévue au suivi: Npt=40, Nft=20

dont 10 longitudinaux). Nous faisons l'hypothèse que la variabilité comportementale interindividuelle, à cette période clé pour le développement de la motricité, repose sur des différences de traitement cérébral dans les réseaux sensorimoteurs et miroirs.
3) Relier les mesures longitudinales du cerveau et du comportement à 0-2m et à 3 ans (Npt=40, Nft=10).
Tous les modèles incluront des facteurs de risque cliniques (e.g. âge gestationnel, poids à la naissance, sexe, complications néonatales) et des facteurs environnementaux (e.g. statut socio-économique de la famille), avec l'hypothèse que ces derniers ont un impact croissant sur le neurodéveloppement à mesure que le bébé grandit.
À l'interface entre les neurosciences intégratives, la neuroimagerie du développement et la pédiatrie, ce projet de doctorat devrait avoir un fort impact tant pour les questions fondamentales sur la sensorimotricité que pour les questions cliniques sur la prise en charge des enfants prématurés.
Références: 1 Pierrat et al, BMJ 2021. 2 Dubois et al, JMRI 2021. 3, 4, 6, 7 Adibpour et al, Nat Hum Behav 2018; Dev Cogn Neurosci 2020; FENS 2022; NeuroFrance 2023. 5 Elbaz et al, SFRMBM 2023.

Encadrant **DUGUE Laura**
mail laura.dugue@parisdescartes.fr

Equipes Vision
Responsable COLLINS Thérèse
Unité Integrative Neuroscience and Cognition Center (INCC)

Sujet **Oscillatory Traveling Waves and Attention in Human**

Résumé Brain oscillations - rhythmic fluctuations in the activity of populations of neurons as they synchronously discharge - have always fascinated scientists and the general public. Studies, including those of Dr. Laura Dugué, have shown that the phase and amplitude of alpha oscillations (20 Hz) play a role in attention and perception. However, the functional role of the spatio-temporal dynamics of brain oscillations remains poorly studied in humans.

Recently, it has been shown that theta (4-7 Hz) and alpha (8-12 Hz) oscillations can be characterized not only by their temporal but also by their spatial dynamics, across cortical space. Oscillations would propagate across the cortex, so-called Oscillatory Traveling Waves. This thesis project aims at characterizing the spatio-temporal dynamics of these Oscillatory Traveling Waves (direction, speed), and their functional link to perception and attention.

A first objective will be to systematically test the origin, direction and speed of Oscillatory Traveling Waves when participants are presented with sensory stimuli from two modalities, i.e., visual and auditory stimuli. We will test the hypothesis that the perception of a sensory stimulus will evoke the propagation of low-frequency brain oscillations, with a constant phase shift from sensory areas to frontal areas. This bottom-up message would inform the frontal areas of the perception of the stimulus.

A second objective will be to evaluate the impact of an attentional manipulation on the direction (and speed) of Oscillatory Traveling Waves. We will test the hypothesis that the orientation of attention will lead to oscillations propagating from the frontal regions to the sensory regions. This propagation would allow a top-down attentional message to be brought from the frontal areas to prepare the sensory regions to process the upcoming stimulus.

A last objective will be to assess the degree of causality between Oscillatory Traveling Waves and attention/perception using transcranial magnetic stimulation (TMS), a non-invasive interventional method. We will manipulate the spatial and temporal properties of Oscillatory Traveling Waves and evaluate the behavioral consequences.

Note that if the oscillations we observe are not Oscillatory Traveling Waves, this would not exclude a communication mechanism between frontal and sensory regions via brain oscillations. An alternative hypothesis that we will test is that a Standing Wave, i.e., an oscillation generating a synchronization of neuronal populations at the same phase across the cortical space, is present in each region, and that the two regions synchronize to communicate with each other with or without a phase shift, the notion of “communication-by-synchrony.”

This project will use a multimodal approach of neuroimaging (EEG/MEG, fMRI, TMS), with model-based analyses, and psychophysics (behavior). Specifically, we will use a two-stage computational model that was developed in Dr. Dugué’s lab (Grabot et al., 2022) to analyze EEG/MEG signal in which, (1) the putative neural sources of a propagating oscillation are modeled in the cortex using individual MRI recordings (encoding model), and (2) the modeled sources are projected onto the MEG-EEG

sensor space to predict the resulting MEG-EEG signal (forward biophysical head model). The output of the model is then compared to neuroimaging data.

This project will shed new light on the spatio-temporal organization of the neural computations underlying perception and attention. It will critically evaluate the nature of Oscillatory Traveling Waves in humans, and characterize the mechanisms under which they guide attentional performance. It will be carried out by a PhD student under the supervision of Laura Dugué (HDR), a specialist in the study of the functional role of brain oscillations in visual perception and attention.

Encadrant **DUPOUX Emmanuel**
mail emmanuel.dupoux@gmail.com

Equipes Cognitive machine learning (CoML)
Responsable DUPOUX Emmanuel
Unité Laboratoire de Sciences Cognitives et Psycholinguistique (LSCP)

Sujet **Simulating early language acquisition using data-efficient self-supervised learning**

Résumé Recently developed 'Language Models' (LMs), large neural networks trained on massive text datasets, rival with humans on language tasks and show internal representations that correlate with functional brain activations. LMs may be interesting models of adult (neuro)cognitive language processing but could they also be good models of how infants learn language?

LMs learn using a simple self-supervised objective: predicting future linguistic units -- character or words, based on past ones. This is compatible with the 'statistical learning' hypothesis which claims that infants learn by building a probabilistic model of their language inputs. But there are two crucial differences between infants and LMs: First, caretakers typically say to infants between 1M to 10M words per year. In contrast, LMs which pass school-level language tests, require around 800B words, a 4-5 orders of magnitude gap compared to 8 year olds! Second, infants learn from speech inputs, LMs from text. Text is a cultural invention developed to compactly store language contents using a discrete code. Speech signals are richer, variable and continuous, encoding a wealth of non-linguistic information on speaker, emotional state, background noise, etc. Experiments run with recently developed speech-LMs shows that, unsurprisingly, learning from speech (especially in ecological conditions) is even slower than from text.

In brief, despite their spectacular results, current LMs still pale in contrast with infants on efficient and resilient learning of natural language. Of course, infants do not start from scratch: they have an auditory system and a learning architecture with inductive biases that have evolved through millions of years to efficiently learn from ecological sensory data. They have a vocal apparatus for the grounding of phonetic units into motor commands. They learn in context, enabling them to ground language into other sensory modalities and receive social feedback from their caretakers. All of these differences may help infants learning from much scarser and noisier data.

This PhD project addresses, using a big data and AI methodology, the modifications in architecture and learning algorithms that need to be applied to speech-LMs to make them more plausible candidates for modeling language development. The models will be evaluated at the behavioral level against known landmarks of infant language development as available in large scale experiments or meta analyses (metalab), in repositories tracking child vocabulary growth (WordBank), and in datasets longform speech recordings that contain both child-directed inputs from caretakers and child output vocalizations (HomeBank).Depending on the PhD candidate's background, skill and interest, alternative avenues of research are available to the PhD candidate and can be combined to improve the model's ability to learn efficiently:

- Developing a universal model of the newborn through pretraining. This rests on the observation that pretrained language models can quickly be retrained in a new language with much less data. The idea would be to select a series of typologically distinct languages to first train a heavily regularized/pruned universal 'newborn' speech-LM, fine-tuned it to the target language, hopefully showing a speedup in learning curves compared to randomly initialized 'newborn' models.
- Developing a model of the vocal tract. Infant's vocal tract, an innate hardware

system that turns motor commands into audio signals gives them an opportunity to recover the motor commands that produce speech sounds, a more invariant representation than acoustic ones. The project will use recently developed articulatory synthesizers, build a system that learns to control it, and then inverse this mapping to recover commands from audio. It will be tested in production mode against datasets of babbling and in perception mode on the ability to represent speech sounds in a context-invariant fashion.

- Leveraging episodic memory to help memory consolidation. Here, the intuition is that episodic memory, contrary to long term memory as encoded in network weights, does not suffer from catastrophic interference, and could be used, through prompting and memory replay to expand combinatorially the training set of the LM, thereby increasing its data efficiency by a large factor. Here, the project would build on previous episodic memory-augmented models that have proven successful in downstream NLP tasks.

Encadrant **EL AMRAOUI Aziz**
mail aziz.el-amraoui@pasteur.fr

Equipes Déficits Sensoriels Progressifs, Pathophysiologie et Thérapie
Responsable EL AMRAOUI Aziz
Unité Institut de l'Audition, unité de Génétique et Physiologie de l'Audition

Sujet **Unveiling the Gene-Environment Interplay in Progressive, Age-Related Hearing Loss: Insights from Animal Models**

Résumé In the inner ear, the pathways necessary for the development, maturation, and normal function of the hearing organ are irreversibly established during embryonic stages. Consequently, our hearing organ is fully functional before birth, and any subsequent damage to its components is irreversible. While hearing decline due to natural aging cannot be avoided, the onset, progression, and severity of hearing impairment vary significantly among individuals. Genetic and environmental factors, such as noise exposure, exposure to chemicals, or ototoxic medication, are among the key triggers. However, in our increasingly noisy daily lives, people often use noise, including leisure music, to mask other environmental noise, often disregarding the harmful effects of sustained sound exposure on our hearing. According to World Health Organization data, noise-induced hearing loss has become the leading occupational disorder, affecting 6% of the global population worldwide. Despite its high prevalence, the precise mechanisms underlying noise-induced hearing decline remain elusive. Our working hypothesis is that a gene-environment interplay determines individual vulnerability and modulates the severity and progression of hearing decline. Using total-, hair cells-, and/or neuron-specific inactivation of two selected causal deafness genes (e.g., CLRN1 & CLRN2, from the clarin tetraspan family), we have replicated various patient clinical conditions in mouse models. These mice display different degrees of hair cells and auditory neurons degeneration, and some are more susceptible to noise exposure. Indeed, pilot experiments in Clrn1 conditional mice revealed that the lack of clarin at late stages makes the mice more vulnerable to sound exposure. A single exposure to a loud sound in Clrn1 mutant mice has been shown to cause an abnormal elevation of the auditory brainstem response (ABR) thresholds (unpublished data). Building on these preliminary data and using a set of already available mutant mice, the present project aims to unveil early, accurate, highly sensitive, and specific markers for noise-induced hearing decline and its progression. In all configurations, with varying noise intensity, spectrum characteristics, or exposure time, the exposures will be carefully controlled, testing the impact of single versus repetitive exposures, and mild versus more intense exposures. Phenotype characterization of mouse hearing, and the integrity of hair cells and auditory neurons will be performed using our established multiscale and interdisciplinary phenotyping workflow, ranging from transcript, protein, subcellular, physiological, to behavioral explorations.
To identify the sequence of events triggered by noise trauma and gain insights into the genetic architecture of biological mechanisms/pathways of hearing difficulty, RNAseq and proteomic profiling will be performed in noise-exposed wild-type, Clrn1, Clrn2, and Clrn1/Clrn2 mutant mice, and the findings will be compared to similar datasets recently obtained for the same non-exposed mice. Together, the findings will provide insights on how genetic differences might determine or modulate vulnerability to similar noise exposure conditions, at different developmental stages. Viral-mediated gene therapy will be used to test if gene replacement in the mutant mice can protect against noise-induced hearing loss. Our expected data might also help identify key pathways that can be targeted to slow down or prevent auditory dysfunction under challenging or traumatic conditions, such as exposure to intense sound.

Encadrant **ETOURNAY Raphaël**
mail raphael.etournay@pasteur.fr

Equipes Plasticité des Circuits Auditifs Centraux
Responsable MICHALSKI Nicolas
Unité Institut de l'Audition, unité de Génétique et Physiologie de l'Audition

Sujet **Multiscale and quantitative study of the planar polarity pathway driving the development of the auditory neuro-sensory epithelium**

Résumé How the interplay of molecular and mechanical cues coordinate morphogenesis and patterning of embryonic structures is a fundamental question in biology. The mammalian auditory organ, the cochlea, is an ideal model to study this question in mammals: its highly regulated morphogenesis and patterning is well recapitulated in organotypic cultures, which are greatly amenable to live imaging, pharmacologic and genetic manipulations. Moreover, the cultured cochlea can be readily mechanically challenged. During embryonic development, the cochlear epithelium doubles its length, and longitudinal gradients of mechanical properties, cell shapes, and physiological properties of auditory sensory cells emerge from an initially undifferentiated and regularly packed epithelium. These longitudinal gradients are later of primary importance for the adult cochlea to fulfil its function of sound detector and analyser. To date, the cellular mechanisms and forces driving the cochlear extension and complex patterning have not been quantified nor integrated at the tissue scale. Also, how the interplay between gene regulatory networks and cell dynamics collectively shapes and patterns the cochlear epithelium, remain largely unknown. Previous work showed that (i) the cochlear epithelium cultured for 5 days from embryonic days 13.5 (E13.5) self-organizes1 and (ii) short-range planar signals mediated by the core planar cell polarity (PCP) pathway influence both the global extension of the cochlea and its patterning, as Vangl2Lp/Lp mutant mice displayed shortened cochlea, and abnormal mosaic organisation and shape of sensory and supporting cells, while the basal-to-apical gradient of sensory cell differentiation was preserved2. Unlike in flies, PCP signalling in vertebrates plays a major role driving convergence-extension flows3. Yet, it remains unclear how these short-range planar signals are integrated over long distances to drive the extension and patterning of mammalian tissues in the millimetre range, while keeping a precision in the micron range.
The objective of the doctoral thesis is to characterise how cellular dynamics drives the cochlear extension process across the organ's scale, and to examine how short-range signals (for instance PCP signals) integrate over long distances to shape and pattern the cochlear epithelium in the embryonic mouse. To this end, we will combine mouse genetics with multi-scale live imaging and quantitative image analysis, to obtain an integrative picture of how the PCP pathway guides the cellular choreography that shapes and patterns the auditory neuro-sensory epithelium during embryonic development.

Specific aims
1. Characterise the spatio-temporal cellular dynamics of cochlear extension in the wild-type situation using ZO1::GFP mice.
2. Characterise the contribution of the PCP signalling to cochlear extension by the analysis of the Vangl2Lp/Lp mutants in which cochleae are shorter and wider.

Such advances are of primary relevance to studies of hearing physiology and physiopathology, and will bring basic new insights into the mechanisms by which the cochlea establishes longitudinal gradients of cell/tissue shapes and mechanical properties. These gradients are the hallmarks of the so-called tonotopic organisation of the cochlea, which underlies its function as a time-frequency analyser of sound. Reflecting the necessity of polarized cellular behaviours for proper development and

function of diverse organs, defects in PCP have been implicated in human pathologies, including cancer, most notably in severe birth defects. The in-depth quantitative study we propose, will shed light on the role of PCP signalling in driving the cellular choreography underlying the morphogenesis of a neuro-sensory organ.

The student will benefit both from the rich environment of the Institut Pasteur of Paris and from the remarkable multidisciplinary environment focused on hearing research at the Hearing Institute. The project involves interaction and collaboration with Dr. Montcouquiol, group leader of the team “Planar Polarity and Plasticity” at the Institut Magendie in Bordeaux, who has 20 years of experience with world-wide recognition in the development of the inner ear. To achieve aim 1 and aim 2, the student will use the multi-scale imaging method and quantitative analysis software (TissueMiner) developped in the lab.

Encadrant
FARAUT Brice
mail
brice.faraut@aphp.fr

Equipes
VIFASOM
Responsable
LEGER Damien/CHENNAOUI Mounir
Unité
Sommeil - Vigilace - Fatigue

Sujet

« Etude des marqueurs (Biologiques, EEG et Physionomiques) de la fatigue mentale induite par une DEtte Chronique de sommeil et une Contrainte cOgnitive Prolongée et stratégies de récupération par la sieste (DECCOP-NAP). »

Résumé

Justification scientifique :
La fatigue cognitive (ou mentale) est un des principaux risques d'accidents (routiers, ferroviaires, ...). Elle se traduit par une sensation de « manque d'énergie » associée à des déficits attentionnels et/ou exécutifs avec des comportements d'ajustement altérés. Elle s'observe classiquement pout toute personne engagée durablement dans une tâche cognitive (Contrainte cOgnitive Prolongée ou COP) mais aussi en état de somnolence, un état neurophysiologique traduisant une dette de sommeil.
Des études menées aux USA (National Sleep Fundation) ou en France (INSV) montrent que la proportion de personnes souffrant d'une dette quotidienne (chronique) de sommeil (de 1 à 2 heures ou plus), en semaine avec une tentative de rattrapage le week-end, ne cesse d'augmenter. Parallèlement, l'engagement cognitif dans une tâche est rarement, dans un contexte professionnel (civil ou militaire), de courte durée (10 à 20 min.).
Mais aucune étude n'a abordée ces questions 1) d'un effet cumulé de facteurs (DEtte Chronique de sommeil-DEC et COP) dans la fatigabilité de processus cognitifs (attentionnels et exécutifs) avec des facteurs DEC et COP plus « écologique » et 2) des conséquences comportementales (capacités de raisonnement, de prise de décision) et biologiques. Par ailleurs, il subsiste des interrogations quant aux bénéfices aigus et chroniques d'une sieste de récupération (30-60 min.) sur la fatigabilité cognitive et les réponses neuroendocriniennes associées. Enfin la question de substrats neurophysiologiques, biologiques et physionomiques associés à cet état de fatigue cognitive (unique ?) généré par différents contraintes (cognitives, dette de sommeil, etc.) reste posée.

Objectifs principaux :
Ce projet de thèse se donne comme objectifs principaux 1) de quantifier la cinétique de dégradation (la fatigabilité) des capacités d'attention soutenue provoquée par l'effet combiné d'une dette chronique de sommeil (DEC : ≥ 2-3h/nuit; 5j/semaine pendant 5 semaines), accumulée en situation écologique à domicile, avec une contrainte cognitive prolongée (COP : 30 minutes) et 2) d'évaluer si et comment des opportunités de récupération (sieste quotidienne) permettent de limiter/d'alléger cette fatigabilité cognitive. Pour cela nous comparerons, à un groupe témoin (sans DEC), un groupe avec DEC et un dernier groupe en DEC ayant la possibilité de pratiquer quotidiennement des siestes de récupération en semaine (30-60 min en début d'après-midi).

Objectifs secondaires :
Ce projet de thèse se donne comme objectifs secondaires :
1) de quantifier la cinétique de dégradation (la fatigabilité) des autres capacités cognitives (attention sélective, partagée, inhibition) provoquée par l'effet combiné DEC + COP,
2) d'explorer les réponses biologiques (dosages salivaires du Cortisol, de l'Alpha-amylase, des Interleukines 6 et 1-beta) avant et après les tâches cognitives et avant et après la sieste (effet aigu) afin de quantifier respectivement les effets/bénéfices aigus et chroniques (mesures les lundi et vendredi des semaines 1 et 5) de la fatigue

cognitive et de la sieste.
3) d'examiner les conséquences comportementales (raisonnement et prise de décision sensori-moteur et/ou sous influence émotionnelle, créativité) associées à cet état de fatigue cognitive (DEC+COP) et les bénéfices potentiels de la sieste.
4) Evaluer les réponses cérébrales (ondes alpha, thêta et P300), les modifications cutanées et physionomiques (visage) et subjectives (état affectif, anxieux, de stress, l'appétence alimentaire et la facilité à « rêvasser ») concomitantes à cet état de fatigue cognitive (DEC+COP) et les bénéfices potentiels de la sieste.

L'évaluation de ces multiples paramètres psychophysiologiques et biologiques permettra d'avoir une vision globale et intégrée de l'influence d'une dette chronique de sommeil (DEC), accumulée à domicile, en interaction avec une contrainte cognitive prolongée (COP) dans l'établissement d'une fatigue cognitive associée à un comportement inadapté et de contre-mesures neurophysiologiques effectives (siestes).

La partie expérimentale de cette recherche est financée par la Direction Générale de l'Armement (Biomedef PDH-SAN-1-0515) et la dotation propre de l'UPR VIFASOM (Université Paris Cité).

Encadrant **FAURE Philippe**
mail phfaure@gmail.com

Equipes Neurophysiology and Behavior
Responsable FAURE Philippe / MOUROT Alexandre
Unité Laboratoire Plasticité du Cerveau (LPC)

Sujet **Bases neurales de la variabilité inter-individuelle dans les stratégies de recherche de récompense et conséquences sur la sensibilité à la nicotine.**

Résumé La variabilité inter-individuelle désigne les différences dans l'expression de traits et comportements entre les membres d'une population. Par exemple, certains individus prennent plus de risques ou sont plus attirés par les gains immédiats. Dans le cas d'une même exposition aux drogues, certains développeront une addiction et d'autres non (on parle alors de vulnérabilité). Cette variabilité s'observe également dans la façon de répondre aux défis environnementaux et sociaux, ce qui se traduit par une expression hétérogène de comportement cognitifs et en particulier, l'émergence de stratégies distinctes (c'est-à-dire la façon dont les agents trouvent différentes solutions à un même problème). Ces différences inter-individuelles dans l'expression de comportements sont bien documentées, tant chez l'homme que chez l'animal, mais les mécanismes neurophysiologiques sous-jacent sont mal compris. Nous proposons ici une approche expérimentale et théorique s'appuyant sur l'analyse d'activité électrophysiologique du système dopaminergique de l'aire tegmentale ventrale (VTA) et de ses modulations (notamment nicotiniques) lors d'actions et de choix simples, mais inscrits dans différents contextes d'accès à la récompense. Les objectifs de ce projet sont de mettre en évidence des différences de stratégies individuelles dans des tâches de prise de décision, de révéler à la fois les mécanismes neuronaux qui sous-tendent l'expression ou font émerger ces différences, et enfin de lier ces profils de stratégies de prise de décision avec des différences de vulnérabilités à des pathologies et en particulier des susceptibilités à la nicotine.

Nous avons mis au point une tâche qui permet de conditionner des souris à effectuer des choix successifs pour obtenir une récompense sous la forme d'une stimulation électrique du faisceau médian du télencéphale. Trois cibles associées à des stimulations sont marquées au sol dans une arène circulaire. L'animal ne peut obtenir deux récompenses de suite sur le même point : il doit donc effectuer un choix binaire entre les deux points restants à chaque essai. Différentes règles de distribution des récompenses ont été utilisées. Nos résultats mettent en évidence l'émergence de stratégies distinctes selon les individus, et soulignent le rôle de la voie méso-corticale et de la modulation nicotinique de la VTA dans ces stratégies de choix. Dans ce cadre très général la thèse aura plus précisément comme objectifs :

i) D'étudier les variations inter-individuelles dans la tâche en fonction de la règle de distribution des récompenses. Deux règles seront principalement utilisées : i) d'une part une distribution probabiliste des récompenses en chaque point (ex : 100% au point A, 50% en B, 25% en C), ii) d'autre part une tâche dite « réservoir » dans laquelle A est récompensé à coup sûr (100%), un point B sur lequel aucune récompense n'est délivrée mais qui ouvre l'accès à une récompense sur le troisième point C en chargeant un magasin (réservoir). Chaque visite en B incrémente de 1 le réservoir en C (+1), et chaque visite en C réduit ce stock (-1). Ces différentes variantes de notre tâche sont analysables en utilisant la même méthodologie et le même formalisme, permettant ainsi une comparaison des paramètres selon la règle.

ii) D'enregistrer l'activité dopaminergique et cholinergiques durant la tâche en utilisant de la photométrie fibrée et de l'électrophysiologie sur animaux vigiles (techniques

utilisées en routine dans l'équipe) pour identifier des corrélats neuraux à ces différentes stratégies. Les enregistrements auront lieu dans la VTA ou au niveau des cortex (PFC et ACC), et s'intéresseront autant à l'activité de neurones (électrophysiologie et senseurs calciques) qu'à la libération de neurotransmetteurs (senseurs de dopamine et d'acétylcholine).

iii) De lier les différentes stratégies aux réponses à la nicotine (à la fois comportementale et neurophysiologique).

iv) De biaiser les choix de l'animal et donc les stratégies. Pour modifier les stratégies des animaux nous utiliserons deux approches. La première va consister en une manipulation des circuits notamment par optogénétique sur les neurones dopaminergiques et par optopharmacologie ciblée sur les récepteurs nicotiniques de la VTA, la seconde va consister en une manipulation de l'environnement (en particulier la sphère sociale) des souris afin de tester si en s'adaptant à ces changements les souris modifient leur stratégie.

Encadrant **FOSSATI Philippe**
mail philippe.fossati@aphp.fr

Equipes Control-Interoception-Attention
Responsable FOSSATI Philippe / SCHMIDT Liane
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Ketamine effects on affective processing in depression**

Résumé Cognitive theories of depression propose that the disorder is maintained by negative biases in information processing that contribute to long-lasting negative beliefs and negative affective states (Warren et al., 2015). Empirical studies have shown that common monoaminergic antidepressant treatments alleviate these negative biases and induce more positively biased affective processing (Harmer et al., 2017). Strikingly this change in affective bias occurs precociously, before any changes in mood or depressive symptoms on clinical scales can be detected (Harmer et al., 2009), which take several weeks to emerge (Frazer & Benmansour, 2002). While monoaminergic antidepressants are considered a gold standard in the treatment of depression, a third of patients do not show symptom improvement (Sleigh et al., 2014). This has led to the notion of treatment resistant depression (TRD) (Schwartz et al., 2016), and has encouraged alternative treatment strategies such as sub-anesthetic doses of ketamine. Ketamine has been shown to induce rapid clinical improvement of TRD within 24 hours after a single infusion (Krystal et al., 2019). Yet, despite the growing number of studies on the clinical effectiveness of ketamine, it is unknown if the fast clinical improvement is underpinned by changes in affective processing and in the formation of affective states.

This project will address the following research questions:
(1)What are the formal cognitive and neural mechanisms of affective processing in TRD patients before and after ketamine treatment?
(2)How specific are affective processing effects to ketamine treatment?
(3)Does the repeated exposure to emotional stimuli induce affective states in healthy participants and in TRD patients?
Approach
We will use behavioral testing, a pharmacological comparison (ketamine and monoaminergic antidepressants), functional magnetic resonance imaging (fMRI), and computational modeling to address these questions. The running costs are covered by an ANR grant, and CPP approval has been obtained. Patients will be recruited at the Adult Psychiatry department of Pitié-Salpetrière Hospital. They will be tested before starting their treatment at baseline and 24h after a first and single dose. At both time points, patients will perform the Facial Emotion Recognition Task (FERT) which has been used in the past to detect early monoaminergic antidepressant effects on affective processing (Harmer et al. 2017). To answer our first question TRD patients will perform the FERT during fMRI before (n=30) and after (n=30) ketamine. Their responses (e.g. hits vs. misses) and reaction times (RTs) will be fit by a drift diffusion model, which provides insight into the hidden, latent variables of the emotion recognition process such as the initial starting bias, the decision threshold or the drift weights of face valence and intensity. To answer the second question, behavioral and computational variables of the FERT will be compared to a group of TRD patients tested before (n=30) and after (n=30) monoaminergic antidepressant treatment. The clinical improvement, assessed by the difference in the Montgomery-Asberg Depression rating scale score before and after treatment, will be correlated to behavioral, computational and neural variables of the FERT. To answer the third question, a modified version of the FERT will include state affect ratings in addition to facial emotion recognition trials. We will first validate the task in healthy participants and then test it in TRD patients. The ratings can be fit by a computational model of

state affect, which assumes that state affect is formed by a cumulative exposure to emotional stimuli.

Perspectives and conclusion

In conclusion, this thesis will contribute to a better understanding of the neurocognitive side of fast and slowly acting antidepressant mechanisms in a rarely tested population of TRD patients. Moreover, we will also shed light on how TRD alters the formation of affective states. This has never been studied in TRD patients, and provides a perspective for future studies to test fast and slowly acting antidepressant on the formation of affective states.

Encadrant **GALLI Thierry**
mail

Equipes Traric membranaire dans le cerveau normal et pathologique
Responsable GALLI Thierry
Unité IPNP

Sujet **Titre du sujet : Role of unconventional secretion in neurodegeneration**
Acronyme : USiND
Mots clés : secretion, neurodegeneration, secretome, Parkinson's disease, cellular neurobiology

Résumé In the last decade, alternative routes that bypass the Golgi apparatus named Unconventional protein secretion (UPS) have been brought to light. The secretion of extracellular vesicles (EVs) is one of the most prominent UPS mechanisms. In agreement with the view of EVs as potential intercellular signaling carriers, two recent studies showed that VAMP2 engulfed into EVs could rescue VAMP2KO in target neurons (1), and Cyclin D1 transfer via EVs promotes neural induction of target embryonic stem cells (2). EVs are entangled in the complex extracellular space of brain parenchyma but recent methods enabled their isolation. This approach further allowed identifying brain mitovesicles, which are EVs denser than typical exosomes enriched in mitochondrial proteins (3,4). In addition, the secretion of mitochondria elements depends on autophagy inhibition, triggering an inflammatory response in recipient cells (5).

We recently reported a VAMP7- and ATG5 autophagy-dependent UPS which allows for the release of elements of the endoplasmic reticulum such as reticulons 3/RTN3, mitochondria, cytosol (6), and a pro-peptide, pro-VGF, a biomarker of Parkinson's disease (7,8), associated in part to extracellular vesicles (9). RTN3 has been linked to axonal growth, and neuronal degeneration (10,11). Moreover, a recent study by the lab showed that LKKR2, a gene product associated with Parkinson's disease, interacts with VAMP7 and regulates UPS (9). VAMP7 and LRRK2 thus appear as major actors in UPS.

There is a decline of degradative autophagy during ageing (12), and we hypothesize, based on our recent work in ATG5KO which are autophagy-null cells, that this would affect the secretome hence intercellular communication by UPS and could contribute to neurodegeneration.

The thesis aims to characterize the role of UPS in neurodegeneration associated with Parkinson's disease gene factors.

Methodology
1st year/ We will assess the effects of WT, VAMP7KO and ATG5KO PC12 cell secretome on the morphology and viability of hippocampal neurons from embryonic WT and VAMP7KO rats (available in the lab) cultured from 5 to 30 days in vitro. We will assess the potential inflammatory capacity of the WT, VAMP7KO, and ATG5KO PC12 cell secretome as in (5).
2nd year/In continuity, we will then use neurons derived from WT and G2019S-LRRK2 and A53T-α-synuclein isogenic hiPSCs (generated at the ICV-IPS platform recently labeled by the DIM C-Brains during the 1st year or obtained from the Michael J Fox Foundation Stem Cell Repository) as recipient cells of the secretome. The hiPSC will be induced to DA phenotype (13). We will determine axonal/dendritic morphology (MAP2/Tau staining), synapse formation (Synaptophysin/PSD95), viability (TUNEL assay), and characterize mitochondria morphology and dynamics using mitotracker and respirometry of the hiPSC-derived neurons treated with the different secretomes.

3rd year/ Using validated methods (3,4), we will extract EVs from the brains of WT and VAMP7KO rats and test light (exosomes) and heavy (mitovesicles) EVs on hiPSC-derived neurons using the same assays as above. The capacity of these fractions to induce inflammation will also be assayed as in (11). The fractions showing the +/- strongest activity on neuronal differentiation and survival will be analyzed by proteomics. If time is available a few hits will be individually tested.

1. Vilcaes, A.A. et al. (2021). Neuron, 109, 971-983.e5
2. Song, L. et al. (2021). J. Cell Biol., 220,
3. D'Acunzo, P. et al. (2021). Sci. Adv., 7,
4. D'Acunzo, P. et al. (2022). Nat. Protoc.,
5. Tan, H.W.S. et al. (2022). Nat. Commun., 13, 3720
6. Wojnacki, J. et al. (2020). Cell Rep., 33, 108536
7. Karayel, O. et al. (2022). Cell Rep. Med., 3, 100661
8. Virreira Winter, S. et al. (2021). EMBO Mol. Med., 13, e13257
9. Filippini, F. et al. (2023). Cell Rep, in press
10. Zou, Y. et al. (2018). Hum. Genet., 137, 141–150
11. Alhajlah, S. et al. (2021). Cells, 10,
12. Barbosa, M.C. et al. (2018). Front Endocrinol (Lausanne), 9, 790
13. Walter, J. et al. (2021). Cell Rep., 37, 109864

Encadrant **GALLOPIN Thierry**
mail thierry.gallopin@espci.fr

Equipes Memory, Oscillations and Brain states
Responsable BENCHENANE Karim
Unité Laboratoire Plasticité du Cerveau (LPC)

Sujet **Caractérisation fonctionnelle des afférences du VLPO sur le PVN et leur rôle dans la régulation du sommeil et du stress**

Résumé Les recherches menées aussi bien chez l'homme que chez l'animal montrent que le stress perturbe la qualité et la quantité du sommeil, tandis que le manque de sommeil peut également influencer les niveaux de stress. Bien que cette relation complexe entre le stress et le sommeil soit bien établie, les mécanismes neuronaux sous-tendant cette interaction demeurent largement inconnus.
L'activation des neurones exprimant le CRH (hormone de libération de la corticotrophine) du noyau paraventriculaire de l'hypothalamus (PVN) est une phase clé de la réponse au stress via la régulation endocrine de l'axe du stress. Des études chez la souris ont révélé que le PVN reçoit des afférences des neurones actifs pendant le sommeil lent (SL) du noyau préoptique ventrolatéral (VLPO), qui inhibent les systèmes d'éveil. Cependant, le rôle de ces projections dans la régulation du sommeil et des états d'anxiété reste inconnu. Sur la base de nos résultats préliminaires et de la littérature, il apparait qu'une proportion de neurones favorisant le sommeil dans le VLPO exprime également le CRH.

Le projet de thèse vise à évaluer l'hypothèse selon laquelle les neurones CRH du VLPO ont un contrôle inhibiteur sur les neurones CRH du PVN, réduisant ainsi les réponses physiologiques au stress et favorisant l'endormissement. Afin de tester nos hypothèses, nous utiliserons des souris CRH-Cre, afin de cibler spécifiquement les neurones CRH du VLPO et du PVN.

Des expériences électrophysiologiques ex vivo sur tranches d'hypothalamus seront menées pour évaluer les effets de la stimulation optogénétique des terminaisons axonales des neurones CRH du VLPO (exprimant la channel rhodopsine (ChR2)) sur les neurones CRH du PVN. Ces résultats seront également complétés par des traçages antérogrades et retrogrades permettant une description fine de la voie VLPO-PVN.
Dans une deuxième partie, en couplant l'expression par voie virale de l'indicateur calcique GCaMP6s et l'implantation de fibres photométriques, nous enregistrerons in vivo l'activité sélective des populations de neurones CRH du PVN ainsi que des neurones CRH du VLPO qui projettent dans le PVN chez des souris en condition basale et pendant un stress aiguë et chronique induit par défaite sociale. L'activité de ces populations de neurones sera également enregistrée pendant le sommeil qui suit ces deux conditions.
Afin de mieux caractériser le rôle fonctionnel des afférences du VLPO sur le PVN, nous testerons l'hypothèse selon laquelle la voie VLPO-PVN participerait à diminuer l'activité des neurones CRH du PVN afin de réduire la réponse au stress et favoriser le sommeil. Pour cela nous ferons exprimer par voie virale la ChR2 dans les neurones CRH du VLPO de souris. A l'aide de fibres optiques implantées dans le PVN, nous identifierons les effets de la photo-activation des fibres axonales du VLPO sur les états de vigilance dans des conditions de base et suite à un stress induit par défaite sociale. Nous testerons d'une part si cette excitation influence la réponse comportementale au stress, mesurée par le test de la plateforme élevée, ainsi que la quantité et la qualité du sommeil. Ces effets seront comparés à ceux obtenus après injection dans le VLPO d'un virus n'exprimant pas la protéine photo-sensible.
Pour toutes les expériences in vivo réalisées dans ce projet, nous mesurerons simultanément l'évolution des paramètres neurophysiologiques tels que l'activité

cérébrale, l'activité cardiaque, l'activité musculaire, et le comportement. Nous évaluerons également le stress et l'anxiété des animaux en analysant les niveaux de glucocorticoïdes sanguines.

En conclusion, l’ensemble des résultats de ce projet de thèse permettra d’une part de mieux caractériser le rôle des projections des neurones CRH du VLPO sur le PVN à la fois sur le sommeil et sur les réponses au stress.

Encadrant
GERACI Carlo
mail
carlo.geraci76@gmail.com

Equipes
IJN Sign language group
Responsable
GERACI Carlo
Unité
Institut Jean Nicod

Sujet
Bimodal Bilingualism & Code Blending

Résumé

Goal.
The main goal of the project is to investigate the grammar of Bimodal Bilinguals in the CODA population (Children Of Deaf Adults).

Background.
Sign languages are used by Deaf communities in their everyday exchanges. Hearing children born in Deaf families are normally exposed to the sign language used by their parents and social network and they are also exposed to the spoken language accessible in the immediate environment as used by other hearing members of the family, care givers, day-care, etc. At the end of the acquisition process, they become fluent in a signed and a spoken language, namely they are bimodal bilinguals. One key aspect of this particular type of bilingualism is that the two languages do not compete for the perception-production channels, since spoken languages use the acoustic-vocal modality and sign languages use the visual-gestural modality. The result of this is that in addition to code switch (Muysken 2000), mixed production can take the form of code-blending (Emmorey et al. 2008), meaning that bimodal bilinguals produce fragments belonging to the two languages simultaneously. In fact, code-blending represents the most natural option for this population. In spontaneous conversation and in narrative tasks code-blending accounted for 36% of the production and 98% of the mixing data in the Adult ASL-English population (Emmorey et al. 2008) and similar patterns are reported for children NGT (DutchSL)-Dutch.

Defining the domain.
The peculiar landscape of bimodal bilingual population offers unique opportunities to investigate the tenets of language acquisition, transfer phenomena and the grammar of mixed production beyond the limits imposed by articulatory constraints. Similarly to unimodal bilingualism, both languages are systematically activated (i.a., Emmorey et al. 2016). At the lexical level, experimental evidence showed that processing is faster when items are presented bimodally via code-blend than in unimodal conditions (Emmorey et al. 2012). At the sentential level, blended utterances shows a differentiated typology from cases in which the utterance is complete and congruent in both languages (e.g., same lexical materials and same word order in the two languages) to cases in which the string is complete only by combining materials from both modalities (for an overview Donati 2020). Two alternative theories are normally offered to account for these facts:
One theory claims that the computational system generates one syntactic structure operating with lexical items from both/either languages (i.e., one grammar for both languages). The simultaneous occurrence of sign and speech is treated as a peripheral phenomenon (Lillo-Martin et al., 2016).
Another theory claims that the computational system generates two separate syntactic structures (i.e., two grammars, one for each language) that are then aligned at the phonological level (Donati & Branchini, 2013).

Methodology.
Within the timeframe of the PhD, the candidate is expected to identify some case studies (preferably in the LSF-French or in the LIS-Italian environment) to be investigated with field-work methods and controlled experiments. These could be

perception and/or production studies, depending on the particular case study. Again, depending on the phenomenon and the particular aspect of the theory under investigation data can be collected from adult or children hearing bilinguals.

References.

Donati, C. 2021. Bimodal bilingual grammars. In Josep Quer, Roland Pfau & Annika Herrmann (eds.), The Routledge Handbook of Theoretical and Experimental Sign Language Research, 614–635. Routledge.
Donati, C. & Branchini, C. 2013. Challenging linearization: Simultaneous mixing in the production of bimodal bilinguals. In Roberts & Biberauer (eds.), Challenges to linearization, 93–128. Berlin: Mouton De Gruyter.
Emmorey et al. 2008. Bimodal bilingualism. Bilingualism: Language and Cognition, 11(1), 43-61.
Emmorey et al. 2012. Bilingual processing of ASL– English code- blends: The consequences of accessing two lexical representations simultaneously. Journal of Memory and Language, 67 (1). 199- 210.
Emmorey, et al. 2016. Psycholinguistic, cognitive, and neural implications of bimodal bilingualism. Bilingualism, 19(2), 223–242.
Lillo-Martin et al. 2016. The development of bimodal bilingualism. Linguistic Approaches to Bilingualism, 6(6), 719–755.
Muysken, P. 2000. Bilingual speech: a typology of code-mixing. Cambridge: CUP.

Encadrant **GRAUPNER Michael**
mail michael.graupner@parisdescartes.fr

Equipes Cerebellar Neurophysiology
Responsable STELL Brandon/ AUGER Céline
Unité SPPIN (Saints Pères Paris Institute for the Neurosciences)

Sujet **Locomotor adaptation: cerebellar activity and paw dynamics during obstacle crossing**

Résumé The cerebellum is one of the key brain regions involved in motor coordination and learning. It is known that the cerebellum processes sensorimotor information to refine the timing of movement patterns. However, the cellular underpinnings of such sensorimotor input processing remain largely unknown. By combining calcium imaging and in vivo electrophysiological recording with behavioral analysis, we propose to study the role of a fundamental microcircuit for sensorimotor integration: the molecular layer interneuron (MLI) network, which provides a strong control over the output cells of the cerebellar cortex - the Purkinje cells (PCs). We already established a challenging locomotor task in which the mice learn to walk on a motorized wheel with rungs. In this task mice are required to adapt their step lengths and coordination to the wheel speed, rung to rung distance, and rung position. In this PhD project, we will study the implication of the microcircuit in motor coordination during adjustment to sudden environmental changes. Mice trained to walk on a motorized treadmill with rungs will be challenged with unexpected obstacles. Our goal is to unravel the functional role of the cerebellar molecular layer network during adaptation to environmental changes. The results will advance our understanding of the cerebellar network and its involvement in generating and adapting coordinated movements in mammals.

To investigate the role of cerebellar microcircuit in mice acquiring a challenging motor task, we will use a forced locomotion paradigm combining walking on a motorized treadmill with neural activity measurements. Naïve mice are placed on a treadmill with regularly spaced rungs, and the treadmill is motorized at a constant speed during recordings. After reaching proficiency at the task, mice will be presented with random obstacles in the form of heighted bars. Mice will have to change their stereotypical motor plan, used for running on the regular rung pattern, in order to cross the obstacle. It is in particular this type of movement adaptation for which inhibition of cerebellar Purkinje cells by molecular layer interneurons has been shown to play a crucial role (Vinueza Veloz et al. 2015).

Cerebellar MLI and PC populations will be recorded before and during obstacle crossing, and recordings of the neural populations are repeated over days of adaptation. Simultaneously recorded high-speed videos of the animal’s behavior are analyzed to extract rung locations and paw trajectories (Mathis et al. 2018). Behavioral as well as neural adaptation will be studied. Optogenetic manipulations of neural activity timed to specific phases of the obstacle crossing will be used to establish a causal relationship between adaptation behavior and observed activity. Additional electromyographic (EMG) recordings of forelimb muscles combined with video recordings will reveal the precise relationship between neural activity and locomotor actuators and kinematic variables during coordinated stepping and crossing movements.

Encadrant **GUEROUT Nicolas**
mail nicolas.guerout@u-paris.fr

Equipes Motor Neurons and Neuromuscular Junctions
Responsable ZYTNICKI Daniel/LAMOTTE D'INCAMPS Boris
Unité SPPIN (Saints Pères Paris Institute for the Neurosciences)

Sujet **Etude de la dégénérescence des précurseurs oligodendrocytaires et des oligodendrocytes matures dans le développement de la sclérose latérale amyotrophique et étude des effets protecteurs de la stimulation magnétique répétitive trans-spinale chez la souris.**

Résumé La sclérose latérale amyotrophique (SLA) est une maladie neurodégénérative grave. Les premiers symptômes se manifestent par une faiblesse musculaire ou une difficulté à articuler lors de la phonation et surviennent le plus souvent chez des personnes âgées de 50 à 60 ans. Ces symptômes sont le fait d'une dégénérescence des motoneurones (MN) situés dans la moelle épinière et dans le tronc cérébral ainsi que des neurones corticaux. Le pronostic de la SLA est particulièrement sombre puisque les patients décèdent en moyenne 3 à 5 ans après le diagnostic, la SLA reste à ce jour sans traitement. Les symptômes étant principalement moteurs, de nombreuses recherches précliniques ont porté sur l'étude des MN. Elles ont permis de mettre en évidence que la dégénérescence des MN spinaux survenait en premier lieu dans ceux innervant les fibres musculaires rapides, dits fast and fatigable (FF-MN), alors qu'à l'opposé les MN innervant des fibres musculaires lentes, dits slow (S-MN) survivaient plus longtemps. De plus, une dégénérescence des précurseurs oligodendrocytaires (OPC) et des oligodendrocytes matures (OL) a été observée, cette dégénérescence étant vue comme une conséquence de celle des MN. Toutefois de récentes études suggèrent que la dégénérescence des OPC et des OL pourrait précéder, voir entrainer, celle des MN. Le but sera donc ici d'étudier la dégénérescence des OPC et OL au cours de l'évolution de la maladie chez la souris transgénique SOD1-G93A (souris SOD) qui mime la physiopathologie humaine. Pour cela le projet doctoral s'articulera autour de trois objectifs.
Le premier sera de proposer une cartographie fonctionnelle de la distribution des OPC et des OL présents dans la moelle épinière lombaire des souris SOD. Nous envisageons pour cela, en tirant avantage de différentes lignées de souris transgéniques qui permettront de suivre spécifiquement les OPC et les OL, de confirmer que la SLA modifie la prolifération, la différenciation et l'apoptose des OPC et des OL lors de l'évolution de la maladie. Comme décrit précédemment, des études électrophysiologiques ont permis de démontrer que la dégénérescence des MN survenait en premier lieu dans les FF-MN. De ce fait, nous déterminerons si les altérations quant aux phénotypes des OPC et des OL sont liés aux associations spécifiques qu'entretiennent ces derniers avec les différentes classes de MN.
Nous espérons démontrer ici que la dégénérescence des OPC et des OL précède celle des MN et est spécifique des OPC et des OL qui myélinisent les FF-MN.
Le second objectif est d'investiguer les effets de la stimulation magnétique répétitive (RMS) chez les souris SOD. En effet, nous avons démontré que la stimulation magnétique répétitive trans-spinale (rTSMS) permet, et ce de manière non-invasive, d'augmenter la survie des neurones et de réduire les phénomènes de démyélinisation dans des modèles de lésions traumatiques. De plus, d'autres études ont permis de mettre en évidence que la RMS augmente la prolifération des OPC ainsi que leur différenciation. De ce fait, nous mesurons les effets de la rTSMS sur la dégénérescence des OPC et des OL. D'une manière plus générale, nous mesurons également les effets de ce traitement sur la dégénérescence des MN et sur la motricité des souris SOD.
Nous espérons démontrer ici que la rTSMS permet de réduire la dégénérescence des OPC et des OL et permet de retarder l'évolution de la maladie.
Le dernier objectif sera de déterminer une signature moléculaire pré-symptomatique

dans les OPC et les OL et également de proposer un atlas cellulaire des différentes populations d'OPC et d'OL chez les souris SOD avec et sans traitement par rTSMS. Pour cela, nous ferons appel à des techniques de single nucleus sequencing, qui nous permettrons de caractériser les différentes populations d'OPC et d'OL et nous pourrons également dresser des trajectoires de l'évolution de ces différentes populations avec et sans traitement par rTSMS. Ces expériences seront faites en collaboration avec le Dr. Xiaofei Li, assistant professor au Karolinska Institutet expert de ces techniques.
Nous espérons ici caractériser les différentes populations d'OPC et d'OL et l'évolution de ces dernières lors de la SLA et de la mise en place de la RMS.
Ce projet de thèse vise pour la première fois à mieux caractériser la dégénérescence des OPC et des OL et à proposer un traitement non invasif dans le cadre de la SLA.

Encadrant **HASSAN Bassem**
mail bassem.hassan@icm-institute.org

Equipes Brain Development
Responsable HASSAN Bassem
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Modeling neurodevelopmental disorders using induced stem cells and cerebral organoids: the example of Mediator-related disorders**

Résumé Neuro-developmental disorders (NDDs) are child related diseases that include intellectual deficiency (ID), autism spectrum disorders (ASD), developmental delay (DD) and epilepsy. They affect 1 to 3% of the population, representing a major public health issue.
Mediatopathies are a group of NDDs caused by mutations in different subunits composing the Mediator complex (MED). MED is a highly conserved complex of 30 Subunits (SU). It is essential to cell growth and viability, through activation of PolII and interaction with general transcription factors. It is also essential to maintain the expression of key cell-identity genes and to direct cell fate through interaction with specific transcription factors including master transcription factors. Mutations in MED12 and MED13L have been associated with syndromic Intellectual Deficiencies (ID) which have now been well described.
Research on the mechanisms leading to NDDs has been limited by the lack of adequate tools, and the pathophysiological mechanisms behind many ID genes, including MED genes, are still poorly understood. Most of the studies deal with models that do not fully reproduce the human-specific features of brain development. The recent advent of cerebral organoid models from induced human pluripotent stem cells (iPSCs) offers unprecedented opportunities to model NDDs. Although not perfect, cerebral organoids have been shown to recapitulate several aspects of critical steps of early brain development which are completely inaccessible to study from human.
This project, NdevCerebrOids, aims at studying the role of MED in early brain development and how mutations in MED12 and MED13L lead to NDDs, using cortical organoids. It will be organized in five work packages:
1. Generate study models using CRISPR-based genome editing
We plan to study three mutations identified in our clinical cohort of patients (at Armand Trousseau and Pitié-Salpêtrière hospitals). Each mutation will be introduced in two commercial hiPSC lines (biological replicates) using CRISPR based genome editing. We have just generated the MED12 cell lines.
2. Study of the impact of MED mutations on neuronal differentiation and neurogenesis
Engineered hiPSCs will be cultured in 2D with induction of differentiation into neuron progenitor cells (NPCs) then cortical neurons, and in 3D to generate cerebral organoids using published protocols that are now well-established in our lab. We will compare the phenotype of models generated from MED mutated and original lines at different stages.
3. Study of the impact of MED mutations on transcription and chromatin landscape in neuronal cell lineages
We will profile our cerebral organoid models using single cell multi-omic approaches to gain insights into how MED mutations impact cell identity and neuronal cell fate. These studies will link changes in gene expression to changes in chromatin landscape.
4. Impact of MED mutations on MED structure and MED-PolII interactions
Structural studies of MED revealed how MED is structured in vivo and how structure is linked to function. We will investigate the structural consequences of MED variants using cells generated in workpackage 1.
5. Impact of MED mutations on patient's neuronal development using patients' derived cell models

We will derive iPSCs from blood lymphocytes of patients carrying the studied mutations and generate cerebral organoids. Our initial work on isogenic iPSC will provide a panel of phenotypes that we will analyze in the patient derived models by applying the same methodologies.

Originality of the project

The use of cerebral organoids to model NDDs and the combination of cutting-edge techniques (CRISPR base editors, single cell studies combining transcription analysis with chromatin accessibility, cryo-EM analysis) will allow a fine analysis of the physiopathology of these diseases. From a larger prospective, this project will provide a useful tool to study the pathophysiology of NDDs of genetic cause. This is of high importance in the era of large-scale clinical genome sequencing for NDD patients. Indeed, the French genome project is now allowing for genome sequencing of many rare diseases including NDDs revealing hundreds of candidate genes while functional study tools are still missing. Another innovative aspect of the project is the combination of studies on isogenic cells and patient-derived cells made possible by a unique clinical cohort.

Encadrant **HUILLARD Emmanuelle**
mail emmanuelle.huillard@icm-institute.org

Equipes Genetics and Development of Nervous System Tumors
Responsable HUILLARD Emmanuelle/SANSON Marc
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Caractérisation des effets fonctionnels des mutations IDH1 et CIC sur la vascularisation cérébrale**

Résumé Les gliomes diffus sont les tumeurs cérébrales malignes les plus fréquentes chez l'adulte. Les gliomes représentent un groupe hétérogène de tumeurs présentant des caractéristiques de cellules gliales. Les oligodendrogliomes ont un pronostic plus favorable que celui des autres gliomes, mais demeurent hétérogènes avec 25% de décès à 5 ans. De plus, malgré les traitements conventionnels de chirurgie, radiothérapie et chimiothérapie alkylante, les tumeurs récidivent, sans traitement efficace.

Les oligodendrogliomes sont caractérisés par des mutations du gène IDH1, la perte des bras chromosomiques 1p et 19q et des mutations du promoteur du gène TERT et du gène CIC. Alors que les oligodendrogliomes sont relativement bien caractérisés au niveau génétique, les mécanismes cellulaires et moléculaires impliqués dans le développement de ces tumeurs restent mal définis. Nous avons récemment généré un modèle murin permettant d'induire in vivo l'expression spécifique de deux altérations clés des oligodendrogliomes (mutation Idh1R132H et inactivation de Cic) dans les précurseurs d'oligodendrocytes (OPCs), les cellules d'origine probables de ces tumeurs. Nous avons observé des effets distincts de ces mutations sur les populations oligodendrogliales, à des temps précoces et tardifs (Joppé, Pottier et al., en préparation). Nous avons également observé que les mutations Idh1R132H et Cic induisent des modifications de densité et prolifération d'autres populations cellulaires cérébrales, suggérant un effet paracrine de ces mutations. Des études précédentes ont montré une action paracrine de la mutation IDH1R132H sur la migration et la prolifération des cellules endothéliales in vitro. De plus, nous avons montré que des oligodendrogliomes mutés CIC surexpriment des marqueurs vasculaires (Khenniche, Lerond et al., en préparation). En lien avec ces données, l'inactivation de Cic dans les OPCs murins in vivo induit l'expression de gènes de cellules endothéliales et murales (Khenniche, Lerond et al., en préparation). Le but du projet de thèse est de caractériser les effets des altérations IDH1R132H et CIC, seules ou combinées, sur la vascularisation cérébrale. Ce projet sera décliné en trois objectifs : (1) Mise en évidence des effets à court et long terme des mutations Idh1R132H et Cic sur les cellules endothéliales et murales dans un modèle murin in vivo (2) Identification de facteurs exprimés par les cellules mutées responsables de ces effets ; (3) Analyse des signalisations intercellulaires identifiées, dans des cultures et biopsies d'oligodendrogliomes. Ce projet permettra de mieux comprendre les interactions entre cellules tumorales et cellules endothéliales et murales dans les oligodendrogliomes et d'identifier des facteurs qui pourraient représenter des pistes thérapeutiques potentielles pour ces tumeurs.

Encadrant **HUMBERT Sandrine**
mail

Equipes Basic to Translational Neurogenetics
Responsable DURR Alexandra/STEVANIN Giovanni
Unité Institut du Cerveau et de la Moelle épinière

Sujet **The Otx2 homoprotein In Huntington Disease**

Résumé Huntington Disease (HD) is an inherited neurological and psychiatric disorder. The expression is age-dependent in individuals at risk to develop the disease and there is long pre-symptomatic phase before appearance of the clinical signs at adulthood. Transient alterations of perinatal circuit activity in HD can affect brain structure and function in ways not apparent until adulthood. The OTX2 homeoprotein is a transcription factor expressed in the choroid plexus, secreted in the cerebrospinal fluid, and internalized into the cytoplasm and nucleus of parvalbumin-expressing (PV) GABAergic interneurons throughout the brain. Slowing down of OTX2 uptake by PV cells delays critical period timing and alters mouse anxiety-like behavior, while sequestering extracellular OTX2 activates plasticity with therapeutic outcomes. Animal studies suggest that reduced interneuron activity could be an early and major contributing factor in HD pathogenesis and progression, while HD patients show region-specific PV cell degeneration and a decreased expression of choroid plexus OTX2.

The PhD project hypothesizes that (1) the plexus choroid function is altered in HD; (2) counteracting this alteration with OTX2 treatment has a protective effect in HD mouse models.

The objectives are to:
Aim I Evaluate PV cell maturation and choroid plexus morphology in HD mice
Histological analysis of early and late HD mice will focus on the distribution and maturation state of PV cells in motor and prefrontal cortices, with sensory cortices as a reference. Maturation is evaluated not only by cell numbers but also by staining intensity of PV, OTX2 and PNNs. In parallel, structural analysis of choroid plexus will assess disruption in OTX2 subcellular localization, tight junctional components of the epithelial layer, primary cilia, and vascular integrity. Given how HD mutants and Otx2 knock-down have overlapping effects on the choroid plexus, we will also evaluate whether Otx2 overexpression (AAV vector) can rescue choroid plexus function in the HD mouse.

Aim II Alter critical period timing to mitigate behavioral deficits in HD mice
OTX2 levels in PV cells can be changed in specific brain regions either by local parenchymal viral expression or protein infusion, or be changed brain-wide by targeting the choroid plexus. Transient changes will be achieved with protein infusions or HSV vectors, while long-lasting changes will be achieved with AAV vectors. Critical period timing in the juvenile mouse can either be accelerated or delayed by addition or reduction of OTX2 transfer to PV cells, respectively. In the adult, addition or reduction of OTX2 will either enhance PV maturation or induce functional plasticity, respectively.
We will then use several readouts in adulthood: molecular (gene expression), motor and non-motor behaviors (eg fixed-speed and accelerating rotarod, open field and novelty-suppressed feeding, Y maze, horizontal ladder), MRI to quantitatively measure the volumes of whole brain and different brain areas and HD pathological markers to evaluate the number and density of synapses.

In conclusion, we expect to provide the proof-of-concept that OTX2 influences adulthood behavior and degenerative processes in HD mice and identify the most

efficient window of treatment.

Selected references of interest: 1) Barnat M et al. HD alters human neurodevelopment. Science 369, 787-793, 2020; 2) Braz BY et al. Treating early postnatal circuit defect delays HD onset and pathology in mice. Science 377, eabq5011, 2022; 3) Tabrizi SJ et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage HD in the TRACK-HD study. Lancet Neurol 12, 637-649, 2013. 4) Vincent C et al. Non-cell-autonomous OTX2 transcription factor regulates anxiety-related behavior in the mouse. Mol Psychiatry 26, 6469-6480, 2021; 5) Planques, A. et al. OTX2 Homeoprotein Functions in Adult Choroid Plexus. Int J Mol Sci 22, 2021.

Encadrant **IZARD Véronique**
mail veronique.izard@u-paris.fr

Equipes Language and Cognition
Responsable NAZZI Thierry
Unité Integrative Neuroscience and Cognition Center (INCC)

Sujet **Characterizing the geometric content of form perception**

Résumé From infancy on, humans possess non-verbal intuitions about numbers and quantities. These intuitions support children's learning of arithmetic in school, and eventually become integrated into adults' numerical concepts. Lesser is known, however, about the cognitive foundations of another branch of mathematics: geometry.

The aim of this PhD project is to assess (visual) form perception as a possible source of geometric knowledge, by looking at the geometric content of form representations in infants, children, and adult. To characterize geometric content, we will use the framework of transformational geometry, introduced by mathematician Felix Klein. This framework defines a hierarchy of geometries at increasing levels of abstraction: from an "identity" geometry where forms are considered equivalent only if they match exactly, to "Euclidean" geometry that equates forms up to a rotation or reflection, scale-free geometry abstracting over variations in size, affine geometry, projective geometry, and finally topology, a geometry that retains only very abstract properties such as "inside/outside" or "connected/non-connected". Are adults, children and infants able to analyze forms according to these different geometric descriptions? Do some geometric descriptions appear more intuitive than others – in the two senses of being accessible earlier in development, and/or of being a strong driver for people's judgments?

To address these questions, the PhD candidate will work on three different lines of research. The first study will assess representations of visual forms in children and adults. More specifically, this study will test (a) whether adults and children are able to perceive variations in properties belonging to different geometries of Klein's hierarchy; and also (b) whether adults and children are willing to judge that these variations define different forms or not. Some data has been collected for this first study; the candidate will be expected to complete the study, and to analyze the results, with a particular focus on identifying key ages of change in geometry perception. A second line of research will investigate form perception in infants, again looking at the ability to perceive properties at different levels of Klein's hierarchy. Piloting work is currently under progress in the lab for this second study; the candidate will be expected to contribute to the study design, and to bring the study to full completion. For the third line of research, different options are possible, depending on the candidate's interests. Possible options could be: studying the neural bases of form representations, using multidimensional analysis techniques to identify form representations conforming to the different geometries in Klein's hierarchy; studying representations evoked by tactile forms, in particular in congenitally blind people – as a way to assess the specific role of vision in geometric knowledge; or studying children's developing ability to perform mental transformations – extending from the well-known paradigm of mental rotation to other transformations underlying Klein's hierarchy.

Encadrant **KINUGAWA-BOURRON Kiyoka**
mail kiyoka.kinugawa@aphp.fr

Equipes Repairing Neuronal Networks (R2N)
Responsable SHERRARD Rachel
Unité Adaptation Biologique et Vieillissement

Sujet **Cellular senescence induced by intermittent hypoxia: a link to Alzheimer's disease**

Résumé Aging is a risk factor for AD, and senescence features have been detected in aging brain and recently in AD. Cellular senescence is known as an important contributor to aging and age-related diseases,
particularly via its senescence-associated pro-inflammatory secretory phenotype (SASP). But the mechanisms promoting senescence and how it contributes to the pathophysiology of AD remain unresolved. Growing evidence suggests a relationship between sleep and AD, and few aging features have been reported in intermittent hypoxia (IH) induced by Sleep apnea syndrome (SAS), but the different aspects of cellular senescence are not yet well studied.
The project aims to study the effect of a senescence-inducing chronic stress that may be key to the transition from normal brain aging to neurodegeneration. Our results show that IH not only induces
cognitive impairment, cellular senescence and neuroinflammation, but also exacerbates them in AD model mice (article in preparation). In order to inhibit the deleterious effects of SASP, an effective
strategy would be to limit it. The persistence of senescent cells may indeed lead to an evolution of the SASP favoring chronic inflammation. Senomodulating agents acting either by depletion of senescent
cells (senolytic) or targeting certain elements of the SASP (senomorphic) appear to be excellent tools for understanding the impact of senescence. It is therefore essential to better understand how chronic stress, in this case SAS/HI, could accelerate aging and promote the development of AD, as well as to verify if a novel, targeted therapeutic approach with a senomodulating treatment can limit the
deleterious effects of the cellular senescence process and its secretome (SASP).
- Objective 1: To characterise senescent cell populations (immunohistochemistry) and their SASP (RNAseq) induced by IH at the brain level, in the 2 mouse models: effect of IH in wild-type WT mice
and effect of IH in AD transgenic mice.
We hypothesized that IH would induce senescence in different neural cells (neurons, microglia, astrocytes, oligodendrocytes), but in a heterogeneous way according to the cell type; and that senescence and SASP induced by IH would be more important in Alzheimer transgenic mice
- Objective 2: To study the relationship between the accumulation of senescent cells, the composition of SASP and IH, using two types of senomodulatory treatment: senolytic (eliminating senescent cells)
and senomorphic (modulating SASP) under development. This study will be carried out in the 2 mouse models: in WT mice and in AD transgenic mice.
We hypothesised that eliminating and inhibiting the deleterious effects of senescent cells could have beneficial consequences for the brain exposed to the stress of IH. As the two types of senomodulatory
treatments have a different effect, this would allow us to refine the potential strategies (SASP and/or senolysis).
The study of SASP characteristics will be correlated with behavioural, cellular and neuropathological tests in WT and AD mice exposed to HI or normoxia, treated or not with senolytic/senomorphic treatment.
- Animal models: 12-month-old mice, 2 genotypes: WT and AD PS1M146VKi (PS1Ki) mice.

- Exposure to intermittent hypoxia: the mice will be subjected 8h/day to 90 seconds hypoxia (45 seconds, 5% FiO2)/normoxia (45 seconds, 21% FiO2) cycles, for 6 weeks.
- Behavioral assessment: Cognitive behavior will be assessed, as these functions involve brain regions that are particularly sensitive to hypoxic injury. Behavioral tests will be used to evaluate all
groups of mice (PS1Ki/WT, hypoxia/normoxia, general senolytic treatment/targeted senomorphic treatment/placebo) for mice.
- We will evaluate the expression of SASP and neuroinflammation, oxidative stress (protein oxidation,proteasome or mitochondrial dysfunction, etc.), under the effects and examine if they are modified by IH and senomodulating treatment. These skills are the expertise of our team.

Encadrant **LAMBERT Régis**
mail Regis.lambert@upmc.fr

Equipes Neuronal Networks and Physiopathological Rhythms
Responsable LAMBERT Régis / LERESCHE Nathalie
Unité Neuroscience Paris Seine

Sujet **Rôle fonctionnel de l'intégration synaptique dans le thalamus sensoriel d'ordre supérieur**

Résumé Dans le cerveau des mammifères, le cortex cérébral effectue des calculs complexes, mais la bonne exécution de ces opérations repose sur le thalamus. Le thalamus est à la fois une porte d'entrée - presque obligatoire - pour les informations qui circulent de la périphérie vers le cortex, et un chef d'orchestre des interactions entre les aires corticales. Le thalamus peut être divisé en noyaux de premier ordre et d'ordre supérieur. Les noyaux thalamiques de premier ordre sont considérés comme des relais de l'information sensorielle circulant du monde extérieur vers le cortex cérébral. Il est communément admis que ces noyaux thalamiques effectuent le filtrage et le ré-encodage du flux sensoriel. Les noyaux thalamiques d'ordre supérieur reçoivent généralement des entrées convergentes provenant d'une diversité de sources corticales et sous-corticales et sont donc des centres intégratifs complexes. D'un point de vue fonctionnel, il a été proposé que les noyaux thalamiques d'ordre supérieur favorisent le traitement entre aires corticales, en complétant les connexions intra-corticales directes, contribuant ainsi aux fonctions cognitives. En outre, ils sont impliqués dans le traitement sensoriel en intégrant le contrôle descendant, et participent à l'expression de la mémoire ou à la mise à jour de modèles génératifs de l'environnement basés sur l'activité sensorielle.
La façon dont les différentes afférences des noyaux d'ordre supérieur sont distribuées au niveau de la cellule unique, comment elles interagissent entre elles et comment elles sont coordonnées pendant les opérations cérébrales, sont donc des questions clés indispensables à la compréhension de la fonction de ces noyaux thalamiques.

Le présent projet s'intègre dans une étude collaborative (ANR Pom-Pom) visant à clarifier l'intégration qui a lieu dans un noyau sensoriel d'ordre supérieur lié au système somatosensoriel des souris, le thalamus postérieur médian (Pom). Le Pom reçoit non seulement l'information tactile provenant des moustaches par les afférences somatosensorielles du tronc cérébral (noyau interpolaire du complexe trigéminal (SpVi)) mais il intègre également des entrées provenant du cortex somatosensoriel, du cervelet et du colliculus supérieur. Ces entrées excitatrices sont contrebalancées par un contrôle inhibiteur extra-thalamique assuré par la zona incerta (ZI) et l'aire prétectale antérieure (APT). Ces entrées inhibitrices extra-thalamiques complètent les entrées inhibitrices du noyau réticulaires du thalamus partagées par la plupart des noyaux thalamiques. Il a été proposé que l'inhibition extra-thalamique pourrait fournir une inhibition focale, résolue dans le temps, ajustée à la demande comportementale. En effet, le cortex cérébral n'excite pas seulement les neurones du Pom via ses entrées excitatrices directes, mais il peut également désinhiber les neurones du Pom via ses projections vers les noyaux inhibiteurs extra-thalamiques. En retour, les afférences du Pom au cortex augmenteraient la réactivité aux entrées sensorielles, et pourraient favoriser le traitement des stimuli sur la base d'informations descendantes pour coder, par exemple, la nouveauté (par rapport à l'attente) ou la pertinence d'un comportement, résultant d'une exploration active.

Dans le cadre de ce projet de doctorat nous proposons de :

1) Étudier les propriétés computationnelles de base des neurones de Pom. Ceci sera réalisé par des stimulations optogénétiques des terminaisons nerveuses dans des tranches de Pom et in vivo, chez des animaux éveillés (tête fixée). Pour étudier la

convergence, nous combinerons les injections de deux AAV différents exprimant des opsines excitatrices activées par des longueurs d'onde différentes dans des paires de structures parmi dentate, ZI, APT, SpVi, S1, M1, et examinerons la présence d'entrées convergentes.

2) Tester le contrôle des entrées sensorielles de Pom par la ZI/APT. En réponse à la déviation des moustaches nous proposons d'identifier la temporalité de l'inhibition de la ZI/APT en rendant silencieuses ces structures par optogénétique et d'établir la nature de l'inhibition de la ZI et de l'APT (impact sur le gain).

Encadrant **LE BER Isabelle**
mail isabelle.leber@upmc.fr

Equipes Basic to Translational Neurogenetics
Responsable DURR Alexandra/STEVANIN Giovanni
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Développement et analyse d'un modèle organoïde neuro-immun de la démence fronto-temporale et de la sclérose latérale amyotrophique**

Résumé Les démences fronto-temporales (DFT) et la sclérose latérale amyotrophique (SLA) sont des maladies neurodégénératives rares aux symptômes très différents. Sur le plan clinique, les DFT entraînent essentiellement des troubles comportementaux et cognitifs et/ou des troubles du langage, alors que les patients atteints de la SLA présentent, eux, des troubles moteurs. Cependant, il est également possible d'observer des formes mixtes de DFT-SLA chez des patients qui présenteront alors les symptômes des deux pathologies. Ainsi, ces deux maladies neurodégénératives appartiennent à un spectre commun et présentent des similitudes cliniques, génétiques et neuropathologiques. En 2011, C9ORF72 a été identifié comme le gène le plus fréquemment muté chez les patients ayant une DFT, une SLA ou une DFT-SLA. La mutation de ce gène consiste en une répétition anormale d'hexanucléotidique (G4C2)n présente dans la partie 5' non codante à l'état hétérozygote. Cette mutation a deux conséquences : une haploinsuffisance de la protéine endogène C9ORF72 et un effet gain de fonction grâce à la formation de foci d'ARN et d'agrégats de dipeptides répétés. De manière globale, l'expression de la protéine C9ORF72 est plus importante dans le cerveau, la moelle épinière et le système immunitaire comparé aux autres organes. Depuis 2016, il a été établi que cette protéine jouait un rôle important dans l'immunité. Au niveau intracellulaire, cette protéine est impliquée dans la régulation des voies autophagique et endolysosomale. La deuxième cause génétique la plus fréquente de DFT est la mutation du gène GRN qui code la protéine progranuline (PGRN). Cette mutation provoque soit une haploinsuffisance de la protéine PGRN soit, beaucoup plus rarement, une absence de sécrétion de cette dernière, entrainant dans tous les cas des dérégulations de l'immunité. En effet, la PGRN est une protéine multifonctionnelle fortement exprimée dans le cerveau, et en particulier par les cellules microgliales où elle régule l'activité lysosomale. C9ORF72 et GRN codent donc tous deux des protéines qui sont impliquées dans les voies autophagique et endolysosomale et le système immunitaire inné. En effet, les deux modèles de souris C9orf72 -/- et Grn -/- présentent des perturbations à la fois au niveau du système immunitaire et de l'inflammation. Par ailleurs, les patients portant les mutations de C9ORF72 et GRN présentent également des inclusions protéiques constituées de la protéine TDP-43 (TAR DNA-binding protein 43). Ces inclusions sont présentes majoritairement dans les neurones mais ont la capacité de se propager entre les cellules et peuvent être sécrétées via notamment la voie des exosomes. Notre équipe a récemment démontré que la voie de l'inflammasome NLRP3 est hyperactivée par l'exposition des cellules microgliales C9orf72 -/- et Grn -/- aux agrégats de protéine TDP-43 (Smeyers et al., in preparation). Nous avons aussi confirmé que cette activation pro-inflammatoire exacerbée était élicitée par les agrégats TDP-43 dans des cellules de type microglial différentiées directement à partir des cellules du sang de patients porteurs de mutation C9ORF72 ou GRN. Cela se traduit notamment par la sécrétion excessive de cytokines pro-inflammatoires qui peuvent avoir des conséquences néfastes sur l'homéostasie cérébrale et être impliquées dans l'apparition et/ou l'avancement de la maladie. Dans ce contexte, l'objectif du projet de thèse est 1/d'étudier l'implication des cellules microgliales mutées dans C9ORF72 ou GRN dans le processus pathologique, et en particulier le rôle de la neuroinflammation; 2/de déterminer si les mutations de ces deux gènes entrainent un mécanisme neuroinflammatoire délétère

identique ou des mécanismes distincts ? Pour cela il s'agira d'établir un modèle organoïde de cerveau antérieur humain innovant, colonisé par des cellules de type microglial générées à partir de cellules de patients porteurs de mutations C9ORF72 ou GRN impliquées dans la DFT et la SLA. Ce modèle nous permettra ainsi de mieux étudier les interactions des cellules immunitaires avec les neurones et les astrocytes de patients atteints de ces maladies.

Encadrant **LE ROUX Isabelle**
mail isabelle.leroux@icm-institute.org

Equipes Genetics and Development of Nervous System Tumors
Responsable HUILLARD Emmanuelle/SANSON Marc
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Etude de la vasculature cérébrale après traitement sénolytique dans le glioblastome**

Résumé Les gliomes diffus font partie des tumeurs cérébrales primitives les plus fréquentes chez l'adulte avec un taux d'incidence de 3,22 nouveaux cas pour 100 000 personnes chaque année. Les glioblastomes (GBM ; astrocytomes de grade IV), sont les gliomes les plus agressifs. Ces tumeurs résistent inexorablement au traitement conventionnel comprenant, une chirurgie, un protocole d'irradiation et une chimiothérapie. La survie moyenne des patients avec un GBM est inférieure à 15 mois après diagnostic. Le développement de nouvelles stratégies thérapeutiques est donc essentiel pour les patients et l'efficacité de thérapies combinées est au centre de ces recherches.

L'élimination ciblée des cellules sénescentes a récemment émergée comme une stratégie innovante pour traiter certains types de cancer. Les cellules sénescentes sont caractérisées par l'arrêt permanent du cycle cellulaire, la sécrétion de protéines (Senescence Associated Secretory Proteins ; SASP) et le développement d'un programme anti-apoptotique. Les médiateurs de la sénescence sont les inhibiteurs du cycle cellulaire p16Ink4a/RB, p19Arf/p53/p21 ainsi que la réponse de dommage à l'ADN lorsque celle-ci persiste. Dans une étude récente, nous avons montré que des cellules sénescentes malignes favorisent la croissance tumorale de GBM de patients et d'un modèle murin immunocompétent de GBM (Salam, Saliou et al., 2023). L'étude du transcriptome des GBMs murins à l'échelle de cellule unique (scRNAseq) a permis de définir une signature de sénescence. L'analyse des données publiques a montré que cette signature est conservée dans les GBMs de patients et qu'un fort score de sénescence est corrélé à un mauvais pronostic. En accord avec ce résultat, l'élimination des cellules sénescentes (ou traitement sénolytique) dans le modèle murin de GBM entraine une modification de l'écosystème de la tumeur et une augmentation significative de la survie des souris. L'étude des transcriptomes des GBMs murins a montré que le traitement sénolytique induit une plasticité des cellules tumorales et une diminution de marqueurs anti-inflammatoires/pro-angiogéniques du microenvironnement. Ainsi, nous faisons l'hypothèse que le traitement sénolytique pourrait modifier le microenvironnement tumoral notamment, remanier la vasculature cérébrale tumorale, pour rendre la tumeur sensible aux traitements.

L'objectif du projet de thèse est d'étudier la vasculature cérébrale intra- et péri-tumorale après traitement sénolytique dans deux modèles immuno-compétents de GBMs. Après génération de GBM par injection intracraniale de lentivirus dans le ventricule latéral des souris, l'étude de la vasculature sur des cerveaux traités ou non par des sénolytiques se fera à deux niveaux complémentaires. Dans la première approche, l'étudiant.e étudiera l'architecture vasculaire à l'échelle du cerveau entier après immunofluorescence, clarification du tissus et acquisition d'images sur un microscope à feuille de lumière. Pour la seconde l'étudiant.e analysera les interactions des cellules vasculaires avec les autres cellules présentes dans la tumeur (cellules tumorales, cellules immunitaires lymphoides et myéloides) en réalisant des marquages en multiplex sur coupes (système Opal, Akoya). Cette technique permet d'utiliser 8 marqueurs simultanément. Pour la réalisation de ce projet, l'étudiant.e utilisera deux types de sénolytiques : un sénolytique génétique (p16-3MR) validé par l'étude récente et des sénolytiques chimiques notamment des flavonoides dont l'efficacité pour soigner des patients atteints de maladies neurodégénératives est en cours d'essais cliniques.

Ce projet sera réalisé dans l'équipe 'génétique et développement des tumeurs cérébrales' dirigée par Emmanuelle Huillard et Marc Sanson à l'institut du cerveau. Ces deux études bénéficieront de l'expertise de plateformes d'imagerie, d'analyse d'image, de séquençage et de bio-informatique de l'Institut.

Salam, R., Saliou, A., Bielle, F. et al. Cellular senescence in malignant cells promotes tumor progression in mouse and patient Glioblastoma. Nat Commun 14, 441 (2023).

Encadrant **LEVI Sabine**
mail sabine.levi@inserm.fr

Equipes Plasticity in Cortical Networks and Epilepsy
Responsable PONCER Jean-Christophe / LEVI Sabine
Unité Institut du Fer à Moulin

Sujet **Interaction between GM1 ganglioside and GABAA receptor: a new mechanism regulating inhibitory synapses?**

Résumé Type A GABA receptors (GABAARs) are the main inhibitory neurotransmitter receptors in the central nervous system. Neuronal hyperactivity consecutive to reduced GABAergic inhibition leads to neurologic disorders (e.g. epilepsy) and neuropsychiatric diseases (e.g. autism, schizophrenia,..).
GABAARS are enriched in specialized membrane domains called lipid rafts, the composition of which may modulate their localization and functionality. Gangliosides, including monosialotetrahexosylganglioisde (GM1), are glycosphingolipids largely represented in neuronal lipid rafts that regulate several cellular processes including the membrane trafficking of neuronal proteins. Reduced GM1 levels have been found in mouse epilepsy models as well as in peritumoral tissue from human brain resections and participate in the development of seizures. Moreover, ganglioside metabolism deregulation is associated with epilepsy in animals and humans. Conversely, increasing ganglioside levels reduces brain trauma and status epilepticus-related damages. This indicates that GM1 may play a central role in epilepsy but the underlying mechanisms linking gangliosides and GABAARS are unknown.
Our unpublished results obtained in collaboration with C. Rivera & C. Di Scala (Helsinki University) show in hippocampal neurons a reduced accumulation of GABAAR and of its main synaptic scaffolding molecule gephyrin at inhibitory synapses when blocking GM1 synthesis with PPMP (1-Phenyl-2-palmytoylamino-3-N-morpholino-1-propanol), suggesting that GM1 controls GABAARs at inhibitory synapses.
The first aim of this PhD project will be to understand how gangliosides modulate the membrane dynamics of GABAARs (using single particle tracking in living hippocampal cells and tissue), their nanodomain organization at inhibitory synapses (using STORM/PALM super-resolution), and the efficacy and plasticity of GABAergic synapses (by recording mIPSCs in normal and upon chemically induced synaptic plasticity). To increase or decrease GM1 in the membrane, we will expose neuronal hippocampal cultures or tissue slices to GM1 or PPMP and we will use the KO of GM1 synthetizing enzymes (imported from C. Di Scala team). Then, in collaboration with C. Di Scala, the student will determine whether GABAAR directly interacts with GM1 (in co-IP experiments) and will identify the consensus sequence on GABAAR responsible for its binding to GM1 (by physico-chemical approaches, sequence analogy, and modeling). Then, the student will delete/mutate this domain and study to what extend it impacts the GABAAR trafficking and GABAergic transmission.
In collaboration with C. Rivera and C. Di Scala, the student will then determine the contribution of GABAAR-GM1 interaction in epilepsy. More specifically, the student will evaluate the impact of GM1 deletion, classically observed in epilepsy, on GABAAR membrane diffusion, synaptic organization and function. These parameters will be studied in two animal models: the KO of GM1 synthetizing enzymes mice and the pilocarpine mice (an animal model of epilepsy showing significant reduction of GM1 expression, unpublished data from Di Scala group). The changes of GABAAR functionality will be studied by patch-clamp and extracellular field recordings on hippocampal acute slices from these two models as well as multi-unit activity on organotypic cultures.
The novelty of this project resides in the investigation of novel interactions between GABAARs and gangliosides and their functional relevance in epilepsy. To address

this point, the student will work in co-direction with the groups of C. Rivera and C. Di Scala with complementary expertise (lipid/protein interactions and epilepsy).
This work may not only disclose entirely novel mechanisms regulating neuronal GABA signalling but also identify novel therapeutically relevant targets that will be useful for intractable epilepsy as well as other neurological and psychiatric conditions associated with altered neuronal chloride transport.

Encadrant **LEVY Richard**
mail richard.dock2@gmail.com

Equipes FRONTLAB : Frontal Function and Pathology
Responsable LEVY Richard
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Neurocognitive study of the causal role of preferences on creativity**

Résumé Challenges are an inevitable part of life. To solve them, we need ideas, and good ones. Getting ideas relies on creativity, defined as the ability to generate ideas that are original and adequate to the context [1]. The two main processes involved in creativity are generation and evaluation. Despite extensive research into creativity, the evaluation process has been relatively neglected [2]. Evaluation processes have been widely investigated in neuroeconomics, which has allowed identifying the Brain Valuation System (BVS), which represents the subjective value (likeability, strength of preference) of options considered by an agent [3].
Recently, we found that individuals select creative ideas according to their own preferences. Their preferences rely on the originality and adequacy of their ideas, and the more individuals favor originality, the more creative they are [4]. Preliminary neuroimaging results suggest that the BVS represents the subjective value of ideas when generating them. Nevertheless, those results are correlational and do not demonstrate that preferences have a causal role in creativity.

The goal of this PhD project is to causally test the role of preferences in creativity.

Positive affective states tend to bias preferences towards risky options, and negative states towards safer options during economic choices [5]. Patients with bipolar disorder during (hypo)manic episodes are risk-seeking [6], and patients with depression share a negativity bias in reward processing [7]. In terms of creativity, positive affects appear to promote creative behavior [8]. Clinically, creativity seems impacted positively in bipolar disorder, and negatively in depression [9].
Here, we will use affective states as a tool to causally test the role of preferences in creativity. We expect a modulatory effect of preferences (balance of originality and adequacy) on the relationship between affective states and creative performance: positive affects should impact preferences toward originality and thus positively impact creativity.

The experimental design we will use to assess the relationship between creativity and preferences has been validated in [4]. It combines creativity and neuroeconomics tasks (ratings).

The project is divided into three axes and aims to:
- Behaviorally characterize the impact of emotional induction on preferences and creative performance in healthy subjects, using mediation analyses.
- Behaviorally investigate how creativity-related preferences are impacted in two clinical populations (bipolar disorder and depression) and investigate their relationship with creativity. This will be done in collaboration with Pr. Fabien Vinckier.
- Decipher the neural correlates of the causal role of preferences on creativity, using fMRI in healthy subjects, with emotional induction.

The project will be conducted in the FrontLab (Institut du Cerveau) which offers theoretical and methodological resources, notably thanks to Pr. Levy's expertise in neurology and executive functions [10] and to Dr. Lopez-Persem's expertise in neuroscience of creativity and decision-making. The feasibility of the project relies on previous work which validated the experimental protocol and its efficiency in studying

preferences in creativity. Also, the clinical part has received ethical approval and the basic part has been submitted for ethical approval.

The originality of the project lies in the combination of creativity and neuroeconomics frameworks to better understand how ideas are selected. It uses behavioral, clinical, neuroimaging and computational modeling methods. The fMRI results will provide biological explanations for the role of preferences in creativity. It will also document why some clinical disorders affect creativity. Thus, this research has the potential for major advances in creativity research and it paves the way for clinical assessment of creativity and personalized interventions for creativity boosting.

1. Runco & Jaeger, Creativity Res J 2012
2. Ellamil et al., NeuroImage 2012
3. Lopez-Persem et al., Nat Neurosci 2020
4. Lopez-Persem et al., bioRxiv, 2022
5. Vinckier et al., Nat Com, 2018
6. American Psychiatric Association, DSM-V, 5th Ed. APA 2013
7. Scheele et al., Eur Arch Psychiatry Clin Neurosci 2013
8. Kuška et al., Creativity Res J 2020
9. Baas et al., Psychol Bull 2016
10. Le Bouc, [...], & Levy, Encyclopedia of Behavioral Neuroscience 2020

Encadrant **LLEDO Pierre-Marie**
mail pmlledo@pasteur.fr

Equipes Perception and Memory
Responsable LLEDO Pierre-Marie
Unité Gènes, Synapses et Cognition

Sujet **Improving mechanistic understanding and treatment of anhedonia**

Résumé Background and rationale: Anhedonia is evident in the general population and a risk factor for poor mental health. However, the biological mechanisms of anhedonia remain unknown and there is no treatment to prevent anhedonia progression in risk samples. In psychiatric patients, anhedonia has been associated with dysfunction in brain's reward circuit, increased inflammation and gut dysbiosis, indicating abnormalities along the gut microbiota-inflammation-brain axis. Mounting preclinical evidence further demonstrate the anti-anhedonic potential of cannabidiol (CBD), which mechanism of action may involve changes in gut microbiota-inflammation-brain markers.

Objectives: 1) exploring whether individuals with subclinical anhedonia show alterations in neural reward, peripheral inflammation and gut dysbiosis markers and whether they are related to anhedonia expression, 2) testing the effect of a 4-week cannabidiol (CBD) intervention on state anhedonia and whether the clinical responses can be parsed by the biological markers, and 3) determining the causal role of gut dysbiosis in driving anhedonia formation and CBD's putative anti-anhedonic effect.

Methods: 1) cross-sectional case-control design including 60 young adults with subclinical anhedonia and 60 young adults without anhedonia from the general population. Neural reward markers include fMRI-determined ventral striatum (VS) activation during anticipated rewards and glutamate levels in the left basal ganglia as assessed with Magnetic Resonance Spectroscopy (MRS). Peripheral inflammation will be assessed with plasma levels of C-reactive protein (CRP), interleukin-1b and 6, and tumor necrosis factor alpha (TNFa), and gut dysbiosis markers with plasma levels of zonulin, lipopolysaccharide (LPS), lipopolysaccharide binding protein (LBP), sCD14 and alpha-1-antitrypsin (A-1-AT). 2) Randomized, double-blind, placebo-controlled two-arm design in 82 young adults with subclinical anhedonia. 300 mg CBD isolate (>98% pure) per day will be administered over 4 weeks. Primary outcomes will be state anhedonia as assessed with the Snaith-Hamilton pleasure scale (SHAPS). Secondary measures include depression, anxiety and cognition measures, as well as neural, inflammation and gut dysbiosis markers. 3) Gut dysbiosis' causative role in driving anhedonia expression and CBD's putative prohedonic effect will be determined with Fecal microbiota transplantation (FMT) from anhedonic adults to naïve mice before and after the CBD intervention. Anhedonia-related behavior in mice will be evaluated with the novel suppressed feeding test and hippocampal neurogenesis.

Expected results: Alterations in diverse biological measures are expected in individuals with subclinical anhedonia, in particular reduced VS activation, increased levels of zonulin and CRP. CBD is expected to improve state anhedonia, especially in those individuals with normalized VS, zonulin and CRP responses. FMT will further reveal dysbiosis as driving factor for anhedonic symptom formation and reduced hippocampal neurogenesis.

Impact for the field: This project will improve the mechanistic understanding of emerging anhedonia and may deliver biomarkers serving to prognosticate anhedonia progression in risk samples and evaluating target engagement of novel preventive

interventions. Moreover, it verifies the anti-anhedonic potential of CBD and the clinical utility of the biological measures to parse heterogeneity in treatment response and thereby foster stratified interventions. Bearing in mind that subclinical anhedonia is associated with poor prognosis, treatment breakthroughs for indicated prevention are of uppermost clinical relevance.

Encadrant **LOURENÇO Joana**
mail joana.lourenco@icm-institute.org

Equipes Cellular Physiology of Cortical Microcircuits
Responsable BACCI Alberto
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Cannabinoid receptor type 1-modulation of local cortical circuits during spontaneous ongoing behavior**

Résumé Spontaneous activity in sensory areas is defined as neural activity that is not driven by an external stimulus (i.e., internally generated patterns of neuronal activity). However, spontaneous activity is not random and often has unique spatiotemporal patterns. This results from the concerted activity of intertwined cortical networks formed by highly heterogeneous neuronal populations. In particular, locally-projecting, inhibitory interneurons (using GABA as neurotransmitter) encompass a vast number of cell subclasses, and specific inhibitory circuits originating by this rich neuronal diversity play fundamental roles in the emergence and maintenance of cortical spontaneous activity. Elucidating the cellular players and mechanisms underlying such cortical network activity requires the ability to perform cell-specific recordings in awake mice, while manipulating specific neuronal elements of the cortical circuit.
Recent data from our laboratory (Koukouli and Montmerle et al., 2022) using state-of-the-art imaging techniques revealed that cannabinoid receptor type 1 (CB1)-positive (+) basket cell interneurons (INs) differently modulate the activity of pyramidal neurons (PN) in distinct visual cortical areas during spontaneous activity. In addition, our preliminary unpublished data indicate that CB1 is expressed by a large fraction of vasoactive intestinal peptide-expressing (VIP) interneurons and it modulates GABA release onto somatostatin (SST) interneurons. This disinhibitory circuit sculpts information coding between excitatory populations: we thus hypothesize that CB1 at VIP-SST synapses is a key player in modulating the representation of spontaneous behavior in the mouse primary visual (V1) cortex.
We will record mouse spontaneous behaviors and brain states (i.e., locomotion, facial movements and pupil dilation) coupled with two-photon calcium imaging of genetically labeled interneurons. This will reveal how the activity of specific inhibitory circuits correlates with ongoing spontaneous behavior. Moreover, we will present the mice with a battery of visual stimuli, such as contrast sensitivity, drifting gratings and surround suppression. In the same experimental setting, we will further use conditional knockouts of CB1 or cell-type-specific optogenetics while recording the activity of excitatory neurons. This approach will elucidate the impact of these manipulations in the recruitment of excitatory neurons during spontaneous activity or particular set of visual stimulation and will reveal the causal role of CB1-positive interneurons and their plasticity induced by endogenous cannabinoids.
This Ph.D. proposal aims to address whether VIP/CB1 positive and VIP/CB1 negative interneurons in the mouse primary visual cortex play a differential role in cortical microcircuits and during ongoing brain activity associated with physiological changes. To study this hypothesis, the PhD candidate will use an array of genetic, optogenetic and pharmacological tools in combination with imaging and electrophysiological techniques. In this project, the student will be embedded in a multi-disciplinary laboratory. The applicant will gain expertise in cellular, synaptic and network cortical physiology. The student will also learn quantitative neuroanatomy and immunohistochemistry techniques. Results from this project will be important to decipher the functional role of CB1 inhibitory cells, which is still elusive, and they will improve our understanding of cortical circuit properties, with important implications for several neurological and psychiatric diseases.

Encadrant **MANGIN Jean-Marie**
mail jean-marie.mangin@inserm.fr

Equipes Development of the Spinal Cord Organisation
Responsable LEGENDRE Pascal / MANGIN Jean-Marie
Unité Neuroscience Paris Seine

Sujet **Elucidating how the electrical activity of midline radial glia participates to neuromuscular development and function**

Résumé In vertebrates including humans, the embryonic development of the neuromuscular and musculo-skeletal systems depends on the activation of spinal motoneurons during spontaneous neural activity (SNA). Spinal SNA initiates the first fetal behavior characterized by rhythmic waves of muscle contractions from neck to tail. Despite its crucial role during neuromuscular development, the molecular, cellular and physiological mechanisms underlying the generation and propagation of SNA remains obscure.

By combining patch-clamp recordings, calcium imaging and optogenetics in transgenic mouse models, our team recently demonstrated that radial glial cells are depolarized during episodes of SNA (Arulkandarajah et al., 2021). This glial depolarization result from the unique ability of radial glia located at the ventral midline to spontaneously generate mixed Ca2+/Na+ action potentials (AP). These glial APs primarily rely on T-type calcium channels which are predominantly expressed in midline radial glia at this developmental stage. APs propagate between midline radial glial cells along the entire rostro-caudal extent of the spinal cord via direct electrical coupling by gap junctions. They also propagate medio-laterally into non-excitable radial glial cells via gap junctions. We hypothesize that this novel form of glial electrical activity could be responsible for initiating and patterning motoneuron activity and trigger the first motor behavior at fetal stages. Moreover, disturbances of this glial excitability are likely to participate to the etiology of neuromuscular disorders. Therefore, by elucidating a new key mechanism in neuromuscular development, this PhD project will help define new molecular, cellular and physiological targets to prevent and treat neuromuscular disorders arising during development.

In this project, The PhD student will simultaneously record and characterize radial glia and motoneuron activity during spinal SNA using a combination of patch-clamp recordings and calcium imaging using transgenic mice expressing the genetically encoded calcium indicator Gcamp6f in motoneurons and/or radial glia (Aim 1, Year 1). Preliminary data indicate that radial glia cells and motoneurons are co-activated along the same medio-lateral sequence starting from the midline during spinal SNA. The student will then elucidate the molecular and cellular mechanisms underlying the glio-motor crosstalk by pharmacological, optogenetic and genetic means (Aim 2, Year 1 & 2). Preliminary data shows that electrical and specific optogenetic stimulation of midline radial glia (Shh:Cre x Floxed-ChR2) triggers motoneuron activation along the same sequence as observed during spinal SNA. The student will also use a recently developed embryonic slice preparation preserving connectivity between radial glia, motoneurons and muscles. Using this preparation, the student will characterize whether and how radial glia AP also lead to a sequential activation of developing muscles and thus participate to their differentiation. Finally, the PhD student will determine to what extent genetic disruption of radial glia spiking by the overexpression of the potassium channel Kir2.1 specifically in midline radial glia (Shh:Cre x Floxed-KiR2.1) can disrupt motoneuron and muscle activation during embryonic development and lead to neuromuscular defects after birth, using functional assays of motor function and behavior at postnatal stages (Aim 3, Year 3).

This project is supported by a AFM-Telethon research grant.

Arulkandarajah, K.H., Osterstock, G., Lafont, A., Le Corronc, H., Escalas, N., Corsini, S., Le Bras, B., Chenane, L., Boeri, J., Czarnecki, A., et al. (2021). Neuroepithelial

progenitors generate and propagate non-neuronal action potentials across the spinal cord. Curr. Biol. 31, 4584-4595.e4.

Encadrant **MARRE Olivier**
mail olivier.marre@gmail.com

Equipes Retinal information processing : Pharmacology and Pathology
Responsable PICAUD Serge
Unité Institut de la Vision

Sujet **The role of amacrine cells in shaping ganglion cell computations**

Résumé Over the last decade, many studies have made clear that the retina, this thin piece of tissue in the back of the eye, is much more than a camera (Gollisch and Meister, 2010). The light is transduced into electrical activity by the photoreceptors. The signal is then propagated through an intermediate layer of excitatory cells, the bipolar cells, which transfer their signals to the ganglion cells, the output of the retina. In parallel, interneurons called horizontal cells and amacrine cells propagate the neural signal laterally across the retinal circuit.

Amacrine cells contribute substantially to the large diversity of retinal neurons with more than 60 subtypes of amacrine cells identified through RNA sequencing (Yan et al. 2020). Their contribution to ganglion cells computation remains unclear and only few subtypes have been extensively studied. This is mostly because many of them are in the intermediate layers of the retina, which are difficult to access with standard electrophysiological techniques, or with a very low yield (Asari and Meister, 2014) and lack of specific targeting. Nevertheless, it has been shown that amacrine cells are essential to lower and higher-order feature sensitivity of ganglion cells such as contrast or looming detection.

Recently, several promoters have been found to target specific subtypes of amacrine cells (Juttner et al, 2019). Among these 240 promotors tested, we have identified 3 that present a significantly higher amacrine cells selectivity stratifying in upper inner plexiform layer of mice retina suggesting an interaction with OFF-Ganglion cells. Similar amacrine cells have been shown to play a role in complex feature retinal computation such as direction selectivity. However, the role of these cell subtypes remains unclear and needs more study.

The purpose of this project is to understand the role of these subtypes of amacrine cells. First, we will determine which ganglion cell types they can modulate. We have designed several tools to stimulate individual cells with optogenetics and 2 photon stimulation (a technique called holographic stimulation), while recording the impact large population of ganglion cells using large multi-electrode arrays (MEAs). We will use that technique to determine the type of the ganglion cell recorded and then see which one are impacted by amacrine cell stimulation, and over which distance. This will allow us to draft hypothesis about the function of these amacrine cells: if they are able to modulate ganglion cells over long distance, they could be involved in surround modulation. If not, they could be involved in local gain control or related function.

This first step will allow us formulating hypotheses about how these amacrine cells can influence the ganglion cell response to visual stimuli. One major hypothesis is that these amacrine cells participate to surround modulation. Ganglion cells respond primarily to stimulation inside their receptive field center, but can also be modulated by stimulation outside this region, in the so-called surround. The mechanisms of surround modulation have remained elusive, because it has been hard to separate the contribution of different cell types to surround modulation with classical tools. With our new tool, we will be able to tease the contribution of our specific amacrine cell types from the ones of the rest of the network.

In a second step, we will thus isolate the role of our amacrine cell types and test the formulated hypotheses by performing experiments where we will stimulate the retina with visual stimuli, and simultaneously activate or inactivate the same amacrine cells individually. Beyond surround suppression, we will test if these amacrine cell types influence the various computations performed by the retina (Kerschensteiner, 2021). This will give us a precise understanding of the role of amacrine cells in shaping ganglion cell feature selectivity.

The role of inhibitory interneurons in sensory coding is an active field of research in several sensory areas. By determining the role of specific interneurons in shaping retinal computations, we expect to make an impactful contribution to this fundamental problem in sensory neuroscience.

Encadrant **MASKOS Uwe**
mail umaskos@pasteur.fr

Equipes Integrative Neurobiology of Cholinergic Systems
Responsable MASKOS Uwe
Unité Gènes, Synapses et Cognition

Sujet **Role of nicotinic acetylcholine receptors in disease**

Résumé Nicotinic acetylcholine receptors (nAChRs) are a main target of Alzheimer's disease (AD) pathology, reviewed in Lombardo&Maskos (1). Here, we propose to study the early events of how amyloid beta peptide (Aß), linked to AD, interferes with the function of the different classes of nAChRs.
nAChRs mediate the action of acetylcholine (ACh) in the brain, and respond to nicotine in smokers. They are implicated in a number of other diseases including Parkinson's, schizophrenia, autism, multiple sclerosis, and of course nicotine addiction (2). A total of 16 genes are known, and many of them are expressed in the brain, like alpha2 to alpha7, and beta2 to beta4. They can form homopentamers composed of five alpha7 subunits, (alpha7)5, and heteropentamers, composed of different alpha and beta subunits, like the (alpha4)2(beta2)2alpha5 pentamer, described in our Nature Medicine paper (3).
nAChRs are expressed in different neuronal population in prefrontal cortex (PFC), which has been analysed extensively by our collaborator, Huib Mansvelder. In a submitted paper, we show that in upper PFC layers, 2 and 3, nAChRs are expressed on different kinds of interneurons, like parvalbumin (PV), somatostatin (SOM), and VIP. Over time, Aß accumulation causes a differential inhibition of these GABAergic neurons, leading to global dis-inhibition of the pyramidal output neurons (4). This global increase in pyramidal neuron activity was the main phenotype in our original description of the AD mouse model we established (5).
We will now focus on the remaining layers of PFC. Additionally, we will study the role of a human-specific gene of the nAChR, CHRFAM7A, absent even from higher primates. We will be using a model with transgenic expression in different parts of the brain. The importance of CHRFAM7A has received significant support from human genetic studies linking variation in CHRFAM7A to Alzheimer's disease (AD) and schizophrenia (SZ)(6, 7). These have identified copy number variation (CNV) and a two base-pair coding variation(6) in AD and SZ. Two further independent CNV genome-wide association studies (GWAS) reported an association between CHRFAM7A dosage and expression levels and AD: lower copy number and lower expression levels of the fusion gene are associated with AD(7). In contrast, in SZ and bipolar disorder (BD), upregulation of CHRFAM7A was observed in the brain(8) and association studies suggest a correlation with the "inverted" orientation of the gene and presence of the two base-pair coding variation. This 2bp deletion has been thought to lead to further truncation of the protein based on bioinformatics predictions, referred to as the delta2bp variant. However recent experimental data strongly suggest that this variant is not translated and essentially a null allele. We are here proposing to carry out a detailed dissection of the underlying mechanisms.

References

1. S. Lombardo, U. Maskos, Role of the nicotinic acetylcholine receptor in Alzheimer’s disease pathology and treatment. Neuropharmacology. 96, 255–262 (2015).
2. J. P. Changeux, Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. Nat Rev Neurosci. 11, 389–401 (2010).
3. F. Koukouli, .., U. Maskos, Nicotine reverses hypofrontality in animal models of addiction and schizophrenia. Nat. Med. 23, 347–354 (2017).

4. F. Koukouli, ..., U. Maskos, Nicotinic receptors mediate network dysfunction in early Alzheimer's disease. in_revision (2022).
5. F. Koukouli, M. Rooy, U. Maskos, Early and progressive deficit of neuronal activity patterns in a model of local amyloid pathology in mouse prefrontal cortex. Aging 8, 3430–3449 (2016).
6. M. L. Sinkus, et al, A 2-base pair deletion polymorphism in the partial duplication of the alpha7 nicotinic acetylcholine gene (CHRFAM7A) on chromosome 15q14 is associated with schizophrenia. Brain Res. 1291, 1–11 (2009).
7. K. Szigeti, et al, Ordered subset analysis of copy number variation association with age at onset of Alzheimer's disease. J. Alzheimers. Dis. 41, 1063–71 (2014).
8. A. R. Lew, T. R. Kellermayer, B. P. Sule, K. Szigeti, Copy Number Variations in Adult-onset Neuropsychiatric Diseases. Curr. Genomics. 19, 420–430 (2018).

Encadrant **MERCIER Hugo**
mail hugo.mercier@gmail.com

Equipes Evolution and Social Cognition
Responsable ANDRE Jean-Baptiste / CHEVALLIER Coralie
Unité Institut Jean Nicod

Sujet **Explaining the widespread diffusion of poor explanations and arguments**

Résumé Experimental research shows that people can, as a rule, discriminate quite well between explanations and arguments of different quality. For instance, participants tend to prefer simpler explanations (Lombrozo, 2007), explanations that are more plausible (Lombrozo, 2007), and explanations which are broader in scope (i.e., which cover several phenomena Read & Marcus-Newhall, 1993) (for review, see, Lombrozo, 2006). Three-year-olds already evince a preference for better explanations (e.g., Corriveau & Kurkul, 2014). In the case of arguments, people tend to be more convinced by stronger arguments (for review, see, Petty & Wegener, 1998), they find arguments that conform to sound Bayesian principles stronger (for review, see, Hahn & Oaksford, 2007), and, in groups, stronger arguments tend to carry the day (e.g., Claidière et al., 2017; Laughlin, 2011; Moshman & Geil, 1998; Trouche et al., 2014; for review, see, Mercier, 2016). Moreover, as in the case of explanations, some ability to evaluate arguments is early developing, being well-attested in 4-year-olds (Castelain et al., 2016; Koenig, 2012; Mercier et al., 2014), and potentially present in 2-year-olds (Castelain et al., 2018).

In spite of these discrimination abilities, poor explanations and arguments seem to enjoy wide cultural success, from pseudoscience to conspiracy theories. For example, in nationally representative surveys, Oliver and Wood (2014) found that an important majority of their sample heard of at least one of the conspiracies they were presented with, and over 55% of respondents agreed with at least one of them. This cultural success is all the more puzzling that accurate information is now very easily accessible. In this project, we'll seek to understand what explains the success of explanations and arguments that appear to be of relatively poor quality.

We argue that intrinsic quality is not the only important feature that makes something interesting. For instance, many perfectly good explanations are utterly boring (e.g. "I'm late because I missed my train"), and unlikely to make anyone curious, or to encounter any kind of popular success. We argue that such explanations are good, but not surprising, and that as a result they do not trigger much interest. By contrast if an explanation is very surprising, it might not need to be very good otherwise to encounter some popular success. The aim of this research project is to uncover the traits that make explanations and arguments surprising, and how surprisingness accounts for the cultural success of arguments and explanations.

We will sample explanations and arguments from different sources, such as stimuli used in past experiments, or more naturalistic stimuli (e.g. explanations found on relevant science subreddits, such as Explain Like I'm 5, see Zemla et al., 2017). Participants will be asked to rate stimuli on a number of traits (explanatoriness, surprisingness, practical usefulness) and to report whether they would be willing to share them (on the correlation between self-declared sharing and actual sharing behavior, see Mosleh et al., 2020).
Using linear mixed-effects regressions, we will test how various traits of our stimuli predict interest, willingness to share, and actual cultural success (e.g. which explanation is most upvoted on Reddit).
We also plan to extend this investigation in two major ways.
First, we aim at better characterizing what makes explanations surprising, for instance

by looking at the semantic distance between what is being explained and the explanation itself (e.g., Corley & Mihalcea, 2005).
Secondly, we plan on exploring other properties of arguments that might be linked to their cultural success. In his monumental work The Sociology of Philosophies, Randall Collins suggests that “The long-term tendency of an active intellectual community is to raise the level of abstraction and reflexivity” (Collins, 1998, p. 787). We could test whether this trend stems from a tendency to find more interesting (if not necessarily more convincing) arguments that are more abstract and/or reflective.

Encadrant **MHAOUTY-KODJA Sakina**
mail sakina.mhaouty-kodja@upmc.fr

Equipes Neuroplasticity of Reproductive Behaviors
Responsable MHAOUTY-KODJA Sakina
Unité Neuroscience Paris Seine

Sujet **Effets neuraux de l'exposition développementale à un mélange de contaminants de lait maternel humain chez la souris**

Résumé

Les populations humaines sont exposées à des cocktails environnementaux de substances chimiques. L'évaluation des effets potentiels de cette exposition sur la santé humaine est l'un des principaux défis actuels. Dans un travail récent, l'équipe d'accueil a participé au développement d'une nouvelle approche méthodologique permettant d'effectuer l'évaluation des risques chimiques des mélanges de contaminants (Crépet et al., Environ Health Perspect 2022). Cette méthodologie a été appliquée à un mélange de 19 substances identifié pour les contaminants du lait maternel en France. Cette première évaluation théorique des risques combinés a suggéré un risque élevé pour les nourrissons, en particulier lié à des effets potentiels neuraux et neuroendocriniens. Ce projet de thèse s'inscrit dans le cadre d'un consortium national de partenaires aux expertises complémentaires et pluridisciplinaires, financé par l'ANR, et qui vise à produire les données expérimentales permettant d'établir et améliorer cette méthodologie pour l'évaluation des mélanges de polluants chimiques.
Dans ce contexte, le doctorant participera aux analyses expérimentales in vivo pour déterminer les effets potentiels de l'exposition développementale au mélange de contaminants de lait maternel sur la mise en place des processus neuroendocrines et comportementaux liés à la reproduction. Ce travail combinera des approches complémentaires de tests comportementaux (batterie de tests reproducteurs, comportements généraux (activité locomotrice, état d'anxiété)), d'analyses neuroendocrine de l'axe gonadotrope (dosages hormonaux, immunodétection de récepteurs hormonaux), de marqueurs de neuroplasticité dans l'hypothalamus ainsi que des approches omiques (RNA seq, metabolome).
Les données obtenues seront d'une grande pertinence car elles participeront à i) l'évaluation des effets néfastes potentiels sur la santé humaine de l'exposition au cocktail de contaminants du lait maternel, ii) l'identification des biomarqueurs pertinents de l'exposition, et iii) l'établissement et l'amélioration de l'approche théorique nouvellement développée pour l'évaluation générale des risques de mélanges de contaminants environnementaux. Ce projet profitera également de l'apport scientifique de consortiums Européens sur les problématiques de mélanges et de santé environnementale dont l'équipe fait partie.

Encadrant **MICHALSKI Nicolas**
mail nicolas.michalski@pasteur.fr

Equipes Plasticité des Circuits Auditifs Centraux
Responsable MICHALSKI Nicolas
Unité Institut de l'Audition, unité de Génétique et Physiologie de l'Audition

Sujet **Loud sound intensity processing by the auditory nerve in health and disease**

Résumé The detection and processing of sounds operated by the peripheral and central auditory systems underlie our abilities to communicate through language and to appreciate music. One exquisite property of the cochlea, the sensory organ for hearing, is to detect and process sound pressure waves that cover 6 orders of magnitude, making it possible the detection of sound levels with energies barely above thermal noise up to extremely loud sounds. One of the key components of the auditory system allowing this large working range for intensity processing are the afferent primary sensory neurons of the auditory nerve. Each sensory cell is contacted by approximately 15 afferent primary sensory neurons. These primary sensory neurons encode sound intensity through two mechanisms. Their firing rate is directly correlated to the level of activation of sensory cells. In addition, these neurons differ in sensitivity to sound levels. Based on their activation threshold in response to sound level, they are classified into three groups: low, medium, and high threshold primary sensory neurons.

Dysfunctions of the auditory system underlie a large variety of disorders. High threshold fibers, which detect and process loud sounds have been shown to be implicated in many auditory disorders. They are thought to be more fragile than low and medium threshold neurons. For instance, they are more sensitive to ageing and noise exposure, potentially explaining speech comprehension difficulties in elderly people and people exposed chronically to loud sounds/noise. In addition, high threshold fibers are also associated with many forms of hyperacusis, an intolerance to everyday sounds that affects 2% of the population and reflects the defective ability of the central auditory system to process different types of sounds with the accurate responsiveness. Finally, high threshold fibers may be key to the generation of tinnitus, the perception of phantom sounds.

Despite the key role of high threshold fibers in the auditory system and their involvement in many debilitating auditory disorders, little is known about their functioning and the pathophysiological mechanisms in which they are involved. One major limitation until now has been the lack of genetic tools to trace these fibers. The hosting laboratory has recently achieved a breakthrough by identifying new genetic markers of the high threshold fibers and producing the associated mutant mouse models. Using these new mouse genetic tools, the goal of the PhD will be to gain insight into the functioning of high threshold fibers and to decipher the pathophysiological mechanisms to which they are associated.

To tackle this question, the PhD student will use mouse models that allow the fluorescent tagging of high threshold primary sensory neurons and mutant mice that have defective high threshold primary sensory neurons. Here, the candidate will i) first characterize the connectivity of high threshold primary sensory neurons in the cochlear nucleus of the auditory brainstem, the first central nucleus of the auditory system: Which postsynaptic cells are targeted by these primary sensory neurons? What are their functional properties? What are their associated neuronal circuits? ii) The candidate will then analyze the consequences of defective high threshold fibers onto sound processing at different levels of the central auditory pathways: How are the neuronal responses altered using in vivo extracellular electrophysiology? How is

auditory perception changed using behaviour paradigms of sound perception? iii) Finally, the candidate will test whether particular protocols of noise exposure known to affect high threshold primary sensory neurons reproduce the results obtained in our genetic models .

The knowledge gleaned using these new genetic models will allow for the first time an exhaustive characterization of the properties of high threshold primary sensory neurons of the auditory nerve and will bring new insight into our understanding of the pathophysiological mechanisms involved in auditory disorders linked to sound level perception. In addition, the characterization of these models will provide new opportunities to test the potential benefits of preventive and curative treatments.

The PhD will be codirected by Nicolas Michalski and cosupervised by Boris Gourévitch. It will take place in the “PCAC” team at the Institut de l'Audition.

Encadrant
mail

NACCACHE Lionel
lionel.naccache@gmail.com

Equipes
Responsable
Unité

PICNIC Lab (Physiological Investigations of Clinically Normal & Impaired Cognition)
COHEN Laurent / NACCACHE Lionel / BARTOLOMEO Paolo
Institut du Cerveau et de la Moelle épinière

Sujet

Improving conscious state and conscious access with trans-cranial electrical stimulation in patients with disorders of consciousness and in healthy volunteers

Résumé

The candidate will evaluate the causal action of high-density trans-cranial electrical stimulation (TES) on conscious state and on conscious access in patients affected with a disorder of consciousness, by measuring both behavioral and high-density EEG responses [1 , 2]. Patients will receive in double blind randomized manner either effective stimulation or the sham stimulation. Before, during and after the stimulation high density EEG will be recorded (256 electrodes). Before and after the stimulation the EEG will be evaluated using resting state recordings (10 minutes) and cognitive paradigms such as the local-global auditory stimulation paradigm [3] or auditory verbal semantics paradigms [4]. During stimulation only resting state EEG will be recorded. Specificities of TES parameters will stem from preliminary studies. In a key experiment, patients will be stimulated using a dual-site high-density TACS (trans-cranial alternate current stimulation) targeting strategic regions of the global neuronal workspace [5] : prefrontal and mesoparietal cortices. TACS will be tailored to patient's anatomy (using modelling of electric field on individual 3D-T1 MRI), and to patient's cortical activity (selecting individual frequency selected from resting state EEG recording, within theta-alpha range). This setting will allow us to test the following causal hypothesis : in-phase hd-TACS of PFC and parietal cortices should increase behavioral and EEG signatures of conscious state and of conscious access to external stimuli, as compared to sham stimulation (double-blind study with individual cross-over). A variant of this experiment only run in healthy volunteers will allow us to test the conscious access modulation by using the visual modality, and by adding a new condition : anti-phase dual site hd-TACS should impair conscious access as compared to in-phase and to shame stimulation Preliminary data/feasibility: Recent double-blind studies reported improvement of behavioral measures of consciousness in DoC patients after tDCS stimulation of left-DLPFC [6]. Moreover, we stimulated 60 DoC patients with the anode placed over left-DLPFC in a prospective open-label study [7]. Behavioral improvement of conscious state was observed in twelve patients (20%). This behavioral response coincided with an enhancement of EEG markers of conscious state with increases of power and long-range cortico-cortical functional connectivity in the theta-alpha band, and of conscious access with a larger and more sustained P3 in an auditory odd-ball paradigm. The EEG changes correlated with electric fields strengths in prefrontal cortices computed from individual T1 brain MRI volumes.

This project should enable us to demonstrate a causal modulation of conscious access and conscious state through brainscale synchronization of GNW at specific frequencies. In addition, this project will test original therapeutic solutions for patients with DoC.

References

1. Naccache, L., Minimally conscious state or cortically mediated state? Brain, 2018. 141(4): p. 949-960.
2. Sitt, J.D., et al., Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain : a journal of neurology, 2014. 137(Pt 8): p. 2258-70.
3. Bekinschtein, T.A., et al., Neural signature of the conscious processing of auditory

regularities. Proceedings of the National Academy of Sciences of the United States of America, 2009. 106(5): p. 1672-7.
4. Ben Salah, A., et al., EEG lexicality effect predicts clinical outcome in disorders of consciousness. Ann Neurol, 2023.
5. Dehaene, S. and L. Naccache, Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition, 2001. 79(1-2): p. 1-37.
6. Bourdillon, P., et al., Electromagnetic Brain Stimulation in Patients With Disorders of Consciousness. Front Neurosci, 2019. 13: p. 223.
7. Hermann, B., et al., Combined behavioral and electrophysiological evidence for a direct cortical effect of prefrontal tDCS on disorders of consciousness. Sci Rep, 2020. 10(1): p. 4323.

Encadrant **NAIT OUMESMAR Brahim**
mail brahim.nait_oumesmar@upmc.fr

Equipes Myelin Plasticity and Regeneration
Responsable NAIT OUMESMAR Brahim / ZUJOVIC Violetta
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Role of the Vascular Endothelial Growth Factor Receptor 1 in Oligodendrocyte Development and Myelination**

Résumé

Multiple sclerosis (MS) is an inflammatory demyelinating disease of central nervous system (CNS) and the first cause of non-traumatic disability in young adults. The pathological hallmarks of MS are characterized by acute autoimmune attacks to oligodendrocyte and myelin sheaths, leading to diffuse demyelinating lesions in the central nervous system (CNS). Disease progression is associated with widespread chronic demyelination and axonal loss. This neurodegeneration is the main cause of permanent disability in patients with progressive MS. Most treatments to date focus on the inflammatory component of the disease, with partial effects on the relapse rates but only a weak impact on the progressive phase. Although the pathological mechanisms leading to axonal loss are not fully understood, there is now substantial evidence indicating that myelin regeneration, also termed remyelination, helps to maintain axonal integrity and that persistent demyelination results in axonal degeneration. Therefore, the development of remyelination strategies is still a major therapeutic challenge for the treatment of MS. A rational approach for the remyelination of MS lesions is to target the differentiation and maturation of adult oligodendrocyte precursor cells and/or of pre-existing oligodendrocytes with pharmacological drugs that could act either directly on oligodendroglia or indirectly by counteracting the effects of inhibitory factors impeding remyelination. To reach this goal, we recently conducted an innovative and large high content phenotypic screening of a pharmacological compound library, and identified the vascular endothelial growth receptor 1 (VEGFR1) as an emerging target to favor remyelination and neuroprotection in demyelinating diseases, such as MS.
The major goal of this PhD project is to assess the functional role of VEGFR1 in oligodendrocyte development, myelination and remyelination. To do so, the PhD candidate will define: 1) VEGFR1 expression profile in oligodendroglia during CNS development and following demyelination, 2) the impact of VEGFR1 loss- and gain-of-function on oligodendrocyte development and myelination, using in vitro and in vivo approaches and finally 3) whether targeting VEGFR1 activity is an effective mean to enhance remyelination in experimental models of demyelination.

Overall, this PhD project should provide new insights into the role of VEGFRs in oligodendrocyte development and myelination, under physiological and pathological conditions.

Encadrant **NAZZI Thierry**
mail thierry.nazzi@parisdescartes.fr

Equipes Language and Cognition
Responsable NAZZI Thierry
Unité Integrative Neuroscience and Cognition Center (INCC)

Sujet **Early phonological acquisition as a predictor of lexical development**

Résumé The starting point of this project is the observation that in many languages including French, consonants are more important at the lexical level than vowels, as illustrated by the fact that it is easier to retrieve the words of the sequence “PhD Pr_p_s_l” than of the sequence “___ __o_o_a_.” This bias, referred to as C-bias or consonant bias (Nespor et al., 2003), is found in adults and young children (e.g., Nazzi, 2000), and facilitates lexical processing and acquisition (for a review, see Nazzi & Cutler, 2019). However, crosslinguistic studies have shown variability in whether the bias is found in a given language (for lack of C-bias, see Wewalaarachchi et al., 2017, for Mandarin; for opposite vowel-bias, or V-bias, see Højen & Nazzi, 2016, for Danish; Chen, Lee, Luo, Lai, Cheung & Nazzi, 2021, for Cantonese). And developmental studies have shown that the bias emerges at different point in development across languages, around 8/11 months for French (Nishibayashi & Nazzi, 2016), between 24 and 30 months for English (Floccia et al., 2014; Nazzi et al., 2009). This variability led me to propose a new framework, the Sound-of-Words model, according to which infants would learn either a C- or a V-bias, based on parental input and the properties of their native language. Because this bias plays a crucial role in children and adult lexical processing, it is proposed that its early acquisition will boost later lexical development. The project will test core predictions of the Sound-of-Words model regarding (a) the emergence of the C-bias in monolingual, typically-developing French-learning infants, testing its links with (b) prior and/or concurrent parental/social input, (c) early phonological acquisition, (d) word learning abilities, and (e) concurrent/later vocabulary development. Infants will be tested several times:
(a) the C-bias will be evaluated at 12 months by a Headturn Preference Procedure (HPP) experiment presenting infants with familiar words modified by changing either a consonant or a vowel, in which infants have a preference for vowel-changed items (Poltrock & Nazzi, 2015, large effect size).
(b) Input will be evaluated by 1-day-long recordings at 3 time points (4, 8 and 12 months), using the LENA system, to determine quantity (number of words/tokens) and quality (number of different words/types; structure of vocabulary heard; number of unique C- and V-skeletons) of input, quantity of parent/child interactions.
(c) To evaluate phonological development: (c1) a parental questionnaire evaluating production of native consonants, vowels and syllable structures (Hoareau et al., 2019) will be administered; and (c2) phonological attunement using a classical habituation paradigm to test consonant and vowel discrimination will be used (Singh et al., 2018).
(d) To evaluate word learning abilities, a classical word learning task will be used (Curtin, 2010).
(e) every 6 months from 12 to 36 months, vocabulary outcomes will be taken, using a parental questionnaire (Kern, 2007).

The study will follow a cohort of 100 infants from 4 to 36 months. All measures will be taken from each infant. Analyses will test direct/indirect links between strength of C-bias, input, phonological and word learning abilities and vocabulary. Quantity of input should be related to C-bias size, phonological and word learning abilities, and concurrent vocabulary at 12 months. Importantly also, quality of input, defined here as the ratio of unique C-skeletons versus V-skeletons in the input, should the linked only to the C-bias measure. Last, size of C-bias should explain unique variance in the acceleration of lexical development.

Several project extensions are possible, based on PhD candidate interests: infants learning another language (e.g., Cantonese, coll. H. Cheung, HK); extension to French-other language bilinguals learning same vs. different Sound-of-Words biases; atypical populations (e.g., preterm infants, coll. V. Biran, Robert Debré hosp).

Encadrant **OHEIM Martin**
mail martin.oheim@parisdescartes.fr

Equipes Biophysics of the brain
Responsable OHEIM Martin
Unité SPPIN (Saints Pères Paris Institute for the Neurosciences)

Sujet **Functional characterization of the feathered cell of Fañanas by 2-photon imaging and optogenetics**

Résumé Astrocytes are a heterogeneous group of cells, with respect to their function and morphologies, depending in part on their location in the CNS. Beyond “housekeeping” activities, cerebellar astrocytes play important roles in development (Araujo 2019) but also contribute to ‘higher’ functions such as fine motor control (Saab 2012) or cognition. To make things more complicated, at least three different types of glia can be distinguished, Bergmann glia (BGs), velate astrocytes and the enigmatic "feathered cells" of Fañanas (FCs). While FCs appeared in Ramon y Cajal's original drawings of cerebellar glia, they have almost disappeared from the literature, until 2018, when a first immunological study was undertaken in rat (Goertzen & Veh 2018). Nevertheless, this work provided no cues concerning a potential biological function. The current PhD project aims at a morphological characterization of FCs at different developmental stages, as well as a functional characterization of FCs by 2-photon microscopy. We want to understand the place that FCs take in the otherwise well described cerebellar circuitry and find out how FCs contribute to the organization and function of the cerebellum.

Work from our laboratory (Singer et al., in preparation) has provided a first detailed description of FC morphology at the single-cell level, allowing us to identify FCs and to record from them with electrophysiological techniques. FCs cell bodies are dispersed in the molecular layer and they have a characteristic size and shape. A single stubby branches into shorter processes, compared to BGs. Intriguingly, the number of FCs increases with postnatal age and their density differs among lobes. Patch-clamp recordings revealed a resting potential and membrane resistance of FCs similar to BGs, not surprising in view of the large leakage currents in these glia. Like BGs, FCs displayed fast α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate-receptor mediated responses to parallel-fiber stimulation, local glutamate application or the fast and controlled UV-photolysis of caged NMI-glutamate. Finally, our work revealed extensive homo- and heterotypic dye coupling, among neighboring FCs, but also between FCs and BGs, with a pharmacological profile consistent with gap junction coupling.

The student will use 2-photon excitation fluorescence (2PEF) calcium (Ca2+) imaging in acute slices from the cerebellum of transgenic mice routinely used in the laboratory (GLAST-cre x PloxP-GCaMP6f; Schmidt & Oheim, 2020). These mice express the single-wavelength fast, genetically encoded calcium indicator (GECI) GCaMP6f specifically in cerebellar glia (Schmidt & Oheim, unpublished). A point scanning 2PEF microscope (Ducros et al. 2011) and a fast spinning disk 2PEF microscope (Rakotoson et al. 2019) are available in the lab. We hypothesize that FCs, similar to BGs Matsui et al. 2005) express Ca2+-permeable AMPA receptors (an immune labelling with specific antibodies is ongoing). In the cerebellar cortex, ectopic release of glutamate from climbing and parallel fiber terminals activates Ca2+-permeable AMPARs expressed on Bergmann glial (BG) appendages. A first aim will thus be to perform 2PEF Ca2+ imaging at the single-FC level following AMPAR stimulation. If we encounter difficulties to find isolated GCaMP6f-expressing FCs in cerebellar slices, I will instead record from single FCs using a combination of whole-cell patch-clamp recording, Ca2+ indicator filling and 2PEF imaging will be used. Spontaneous and Ca2+-evoked multicellular communication among neighboring glia in transgenic mice expressing GCaMP6f and virally transduced with an optogenetic actuator of extracellular Ca2+ influx, CatCh tested earlier in our laboratory (Li et al. 2012) to find

functionally coupled cells. Overall, this project builds on tools and equipment available in the lab, and it offers a clear roadmap with measurable risk.

Araujo (2019) Cerebellum 18, 1017–1035. https://doi.org/10.1007/s12311-019-01046-0
Ducros M (2011) J Neurosci Meth 198(2): 172-80 https://doi.org/10.1016/j.jneumeth.2011.03.015
Goertzen (2018) Glia 66(10): 2200-8 https://doi.org/10.1002/glia.23478
Lil (2012) J Phyisol 590(4) : 855-73 https://doi.org/10.1113/jphysiol.2011.219345
Matsui K et al. (2005) J Neurosci 25(33) 7538-47 https://doi.org/1
Rakotoson (2019) Front Neuroanat 13 https://doi.org/10.3389/fnana.2019.00077
Schmidt (2020) Biophys J 119(11): 2153-65 https://doi.org/10.1016/j.bpj.2020.10.027

Encadrant **PARDI, Maria Belen**
mail belen.pardi@inserm.fr

Equipes Neuronal Circuits For Memomry and Perception
Responsable PARDI, Maria
Unité IPNP

Sujet **Thalamo-cortical circuits for top-down control of auditory cortex in physiological and pathological perception**

Résumé A central goal in neuroscience is to understand the mechanisms that enable sensory perception, an active process that depends on our previous experiences and behavioural demands. In this framework, information that is captured by our sensory organs, that flows to sensory cortex in a “bottom-up” stream, needs to integrate with internal “top-down” information, to form an accurate representation of the world (1).

This fundamental brain function is affected in major neuropsychiatric disorders. While a main open question is how accurate and disturbed perception are determined, a central hypothesis states that it depends on the balance between “bottom-up” and “top-down” information. Directly addressing this question has remained challenging, largely because we have little knowledge of where and how “top-down” information is encoded in the brain. Therefore, this project aims to elucidate the function of “top-down” inputs to sensory cortex.

As opposed to the first-order sensory thalamus that conveys bottom-up information to sensory cortex, recent evidence from others and us indicate that the little explored higher-order (HO) thalamo-cortical pathways are relevant for internal top-down information across sensory modalities. We have recently found that the HO auditory thalamus (HO-MG) conveys top-down information to secondary auditory cortex (2).

Conversely, a dysfunction of HO sensory thalamic nuclei has been related to cognitive deficits such as inattention and schizophrenia. Schizophrenia manifests in most cases with auditory perceptual disturbances, suggesting that alterations in the auditory HO system may be a cause.

Here, we hypothesise that the HO-MG top-down thalamo-cortical pathway is critically implicated in accurate sensory perception by modulating the excitation/inhibition balance and activity of cortical neurons.

To test our hypothesis, our objectives are:
1) Establish how the HO-MG input affects the stimulus-evoked excitation/inhibition balance and activity of cortical neurons.
2) Determine if and how the HO-MG thalamo-cortical pathway is affected in pathological conditions related to high schizophrenia-risk and altered perception.

To test our hypotheses, the PhD student will carry out two main sets of experiments:

First, recording the activity of cortical neurons on acute brain slices from mice with calcium imaging, we will determine how the HO-MG input affects the activation evoked by the bottom-up pathway (2, 3). Once we have identified what neurons change their activity, we will investigate the implicated circuit mechanisms with whole-cell recordings, by assessing how the HO-MG input affects the stimulus-evoked excitation/inhibition balance that these neurons receive (4).

Second, to determine how the HO-MG input affects cortical activation during perception, we will record the same neurons in cortex in awake mice with 2-photon calcium imaging (2). We will use auditory stimulation paradigms in combination with

optogenetic inhibition of HO-MG axons in cortex.

Since the excitation/inhibition balance and auditory perception are commonly affected in schizophrenia, we will also test the hypothesis that the HO-MG thalamo-cortical system studied here is affected in a high schizophrenia-risk mouse model.

Together, this research will determine how the top-down HO-MG input affects cortical function and the underlying circuit mechanisms, as well as identify features affected in pathological conditions associated to disturbed perception.

References:

1. M. B. Pardi, A. Schroeder, J. J. Letzkus, Probing top-down information in neocortical layer 1. Trends Neurosci. (2022), doi:https://doi.org/10.1016/j.tins.2022.11.001.
2. M. B. Pardi, J. Vogenstahl, T. Dalmay, T. Spanò, D.-L. Pu, L. B. Naumann, F. Kretschmer, H. Sprekeler, J. J. Letzkus, A thalamocortical top-down circuit for associative memory. Science. 370, 844–848 (2020).
3. A. Marin-Burgin, L. A. Mongiat, M. B. Pardi, A. F. Schinder, Unique Processing During a Period of High Excitation/Inhibition Balance in Adult-Born Neurons. Science. 335, 1238–1242 (2012).
4. M. B. Pardi, M. B. Ogando, A. F. Schinder, A. Marin-Burgin, Differential inhibition onto developing and mature granule cells generates high-frequency filters with variable gain. Elife. 4, e08764 (2015).

Encadrant **PARRAS Carlos**
mail carlos.parras@icm-institute.org

Equipes Brain Development
Responsable HASSAN Bassem
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Characterizing CHD8 copy loss effects in neural cell fates during forebrain development**

Résumé Autism spectrum disorder (ASD) affects approximately 1 in 70 people. The two leading hypotheses underlying pathophysiology of ASD are the abnormal neuronal connectivity and the excitation-inhibition imbalance (Neale et al. 2012, DOI:10.1038/nature11011, Talkowski et al. 2012, DOI:10.1016/j.cell.2012.03.028). Most ASD-risk genes are expressed during brain development, having roles either in neuronal communication or in regulation of gene expression (Satterstrom et al. 2020, DOI:10.1016/j.cell.2019.12.036), with CHD8 chromatin remodeler in this second class, being the most frequently mutated gene in ASD patients (Yuen et al. 2017, DOI:10.1038/nn.4524). CHD8 haploinsufficiency causes macrocephaly both in humans and mice, with CHD8 haploinsufficient mice presenting autistic-like phenotypes (Katayama et al. 2016, DOI:10.1038/nature19357, Gompers et al. 2017, DOI:10.1038/nn.4592, Suetterlin et al. 2018, DOI:10.1093/cercor/bhy058). Modeling CHD8 haploinsufficiency in human forebrain organoids suggests alterations in the timing of proliferation and neurogenesis ending up with alterations in the balance of excitatory and inhibitory neurons generated (Villa et al. 2022, DOI:10.1016/j.celrep.2022.110615). Interestingly, a recent publication has shown that different levels of CHD8 dose impact mouse brain development in a non-linear manner (Hurley et al. 2021, DOI:10.1186/s13229-020-00409-3). Previous studies from our group showed that CHD8 controls the expression of more than one third of ASD risk genes in oligodendrocyte precursor cells (OPCs), and that specific deletion of CHD8 in oligodendrocyte lineage cells leads to strong defects in oligodendrocyte development and myelination (Marie et al. 2018, DOI:10.1073/pnas.1802620115, Zhao et al. 2018, DOI:10.1016/j.devcel.2018.05.022), corroborated by later studies (Kawamura et al. 2020, DOI:10.1186/s13041-020-00699-x, Kawamura et al. 2020, DOI:10.1093/hmg/ddaa036). Altogether, these data suggest that unraveling the mechanisms and timing of CHD8 requirement during brain development, both in neurogenesis and gliogenesis, is an entry point to understand the mechanisms at the basis of the brain defects of a large part of the autism spectrum and develop strategies rescuing these deregulations affecting brain development in children with ASD.

Our project aims to characterize the cell fates and gene regulatory networks dysregulated by CHD8 copy loss during forebrain development, with a focus in ASD target genes. To this goal we have develop refine genetic tools, combining conditional CHD8 copy loss in forebrain neural stem cells (NSCs) with lineage tracing of NSC progeny (MADM system) allowing us to analyze in detail the impact of CHD8 copy loss during NSC differentiation into their neuronal and glial progenies. In a first aim, we will study the role(s) of CHD8 in during corticogenesis characterizing the changes in NSC differentiation (neurogenesis and gliogenesis) induced by CHD8 copy-loss, and the deregulated gene networks leading to these changes, by (1) immunofluorescence analyses and (2) single cell transcriptomics (scRNA-seq) allowing to better expose the differential impact of CHD8 copy-loss in different neural subtypes and stages. In the second aim, we will utilize a refined genetic method available in mice, Mosaic Analysis with Double Markers (MADM), allowing to induce, in a time controlled manner (using the CreERT system), in vivo clones of NSC progeny with different doses of CHD8 null-alleles labeled in different colors (CHD8+/+ cells in green, CHD8+/- cells in yellow, and CHD8-/-cells in red) in the same brain (i.e., same genetic background). Therefore, our project should help to unravel the time

window when CHD8 dose is key for normal brain development and contribute to understand the cellular and transcriptional mechanisms/defects of CHD8 copy-loss in ASD brain development, and thus contribute to develop strategies rescuing these deregulations affecting brain development in children with ASD.

Encadrant **PEPERKAMP Sharon**
mail Sharon.peperkamp@ens.fr

Equipes Language and its acquisition
Responsable CHEMLA Emmanuel
Unité Laboratoire de Sciences Cognitives et Psycholinguistique (LSCP)

Sujet **L1 acquisition of phonological rules**

Résumé All human languages have phonological rules that change the sound shape of words when they are pronounced within sentences. Adults 'undo' this systematic variation for the purposes of word recognition. How do toddlers and young children learn to cope with word form variation? In order to map the various forms that a word can take onto a single lexical representation, they need to acquire the phonological rules that apply in their language.

Past research has focused on assimilation rules, showing that they have already been acquired by toddlers (Skoruppa et al., 2013ab). Assimilation rules introduce minimal segmental changes, but languages typically also have rules that delete or insert entire segments. For instance, French has both liaison, a rule that inserts segments, and consonant cluster simplification, a rule that deletes segments. Previous research has only looked at liaison, focusing on young children's liaison errors in production (see Chevrot et al., 2013 and references cited therein). Here, we will consider both liaison and cluster simplification and study how young children and toddlers process these rules for the purposes of word recognition. Are liaison and cluster simplification acquired equally fast? Does the rate of acquisition depend on how often they apply in the input? And how does their acquisition compare to that of assimilation?

Depending on the age of the participants, the experiments will be presented as a simple game on an iPad with a touching task, or in a traditional looking-while-listening paradigm with an eye-tracker. Using existing corpora of spontaneous speech, we will also compare both the possible and the realized occurrences of liaison and cluster simplification in adult- vs. child-directed speech, and compare these data to ones for assimilation.

References

Chevrot, J.-P., Dugua, C., Harnois-Delpiano, M., Siccardi, A. & Spinelli, E. (2013). Liaison acquisition: debates, critical issues, future research. Language Sciences, 39, 83-94.

Skoruppa, K., Mani, N., Plunkett, K., Cabrol, D. & Peperkamp, S. (2013). Early word recognition in sentence context: French and English 2-year-olds' sensitivity to sentence-medial mispronunciations and assimilations. Infancy, 18, 1007-1029.

Skoruppa, K., Mani, N. & Peperkamp, S. (2013). Toddlers' processing of phonological alternations: Early compensation for assimilation in English and French. Child Development, 84, 313-330.

Encadrant **PESSIGLIONE Mathias**
mail mathias.pessiglione@gmail.com

Equipes Motivation Brain and Behavior
Responsable BOURET Sébastien / DAUNIZEAU Jean / PESSIGLIONE Mathias
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Confidence hierarchy: a neurocomputational approach to self-beliefs**

Résumé Our capacity to form beliefs about ourselves and our abilities ('self-beliefs') is central to human cognition. Self-beliefs are a major determinant of life trajectories, impacting how we see ourselves and what we pursue. Self-beliefs are distorted in a range of psychiatric and neurological conditions (Hoven et al, 2019 Trans Psych; Rouault et al, 2018 Biol Psych). For instance, a person with depression may falsely believe that they are unlikely to succeed, whereas a person with dementia may remain confident in their abilities despite failures in a range of settings. However, the cognitive and neurobiological roots of self-beliefs remain unknown.

Studying and measuring subjective self-beliefs has long remained a challenge. A possible approach is to consider that confidence expressed by decision-makers in their judgments constitutes a proxy of self-beliefs. In this PhD project, we propose to study, measure and analyse self-beliefs using concepts and tools recently developed in the field of cognitive and computational neuroscience to quantify the formation of 'local' decision confidence, i.e., confidence in a single decision. In the last decade, a clear picture has emerged on the neurocomputational mechanisms supporting local confidence. Empirical work has revealed that the computation of confidence depends on multiple cues, including decision evidence and accuracy (Rouault et al, 2022 Cereb Cortex), and relies on a widespread network centered on prefrontal and parietal cortices (Rouault & Fleming, 2020 PNAS). Theoretically, confidence has been formalised as a probability that a decision is correct knowing the evidence, a definition that has led to the development of Bayesian models of confidence (Pouget et al, 2016 Nat Neurosci). However, most previous studies have focused on the formation of local confidence, over milliseconds or seconds. In contrast, self-beliefs evolve over more instances and experiences.

In this PhD project, we will test the novel core hypothesis that a hierarchical architecture of metacognitive levels supports the formation of self-beliefs, using a set of empirical investigations combined with computational modeling and neuroimaging. The project will be co-supervised with Marion Rouault.

First, using mathematical modeling, we will examine how self-beliefs may generalize from decisions to tasks to cognitive domains (three main metacognitive levels), thereby providing a proxy for expected ability in new settings. We hypothesize that self-beliefs are updated based on prediction errors propagating from one level to the next. For instance, one can be positively surprised by their own perceived accuracy after an easy decision; this belief would then feed the upper layer, i.e., their belief about their ability to perform the task; and so on to the next upper layer. We will conduct model simulations to verify that the proposed architecture can accommodate the psychological properties expected from the model mechanics. Second, we will collect empirical data to compare against model predictions, and validate the model in behavioral experiments (adults & adolescents). The generalisability of the mechanisms identified will be addressed by studying two cognitive domains historically investigated separately, perception and memory. Third, we will validate the computations proposed by the self-belief update model using fMRI, to lend it biological support. We will examine whether model-based variables (e.g. prediction error signals, at each hierarchical level) are used by the brain to update self-beliefs,

and characterise how the different metacognitive levels interact in the human brain.

The goal of this PhD project is to obtain a full neurocomputational model of self-beliefs. We have recently proposed that bridging the knowledge gap between local confidence and general beliefs in one's abilities relevant to real-life decisions (self-beliefs) is a key endeavor, as self-beliefs are a major contributor to behavioral control beyond local confidence, and may therefore provide closer links with the functional and subjective symptoms experienced by psychiatric patients (Seow*, Rouault* et al, 2022). This PhD project will shed light on a core aspect of human cognition: self-evaluation. In isolating the cognitive steps underlying self-belief update, we expect our experimental findings to also reveal whether we can modify self-beliefs, paving the way for developing interventions to restore accurate self-beliefs.

Encadrant **PONCER Jean-Christophe**
mail jean-christophe.poncer@inserm.fr

Equipes Plasticity in Cortical Networks and Epilepsy
Responsable PONCER Jean-Christophe / LEVI Sabine
Unité Institut du Fer à Moulin

Sujet **Cell-specific determinants of network dynamics in human mesial temporal lobe epilepsy**

Résumé Mesial temporal lobe epilepsy (mTLE) is one of the most common and severe forms of focal epilepsy in adults. It is often associated with partial hippocampal sclerosis and is refractory to antiepileptic drugs. Surgical resection of the epileptic focus represents a therapeutic alternative for mTLE patients, and postoperative tissue samples can then be analyzed in vitro, providing a unique opportunity to study the cellular deficits underlying this disorder.

Although several cellular and synaptic alterations have been described in mTLE human tissues and animal models, how they contribute to the emergence of abnormal network activity underlying seizures remains poorly understood. Alterations in GABA signaling due to deficits in neuronal chloride export have been proposed as a key mechanism for generating abnormal activity in mTLE. However, few neurons exhibit such deficits, highlighting the importance of cellular heterogeneity within the epileptic network. Understanding how and why individual neurons initiate or contribute to epileptic activity requires simultaneous recordings from individual neurons and network activity, combined with in-depth characterization of their cellular properties. The aim of this project is to explore the cell-specific determinants of epileptic network dynamics by combining functional and transcriptomic characterization of single neurons with large-scale recordings of neuronal ensembles.

Using post-operative human epileptic brain samples in vitro, we will combine high-density multi-electrode recordings of local field potential and multi-unit activity with single-cell patch-clamp recordings and transcriptomic analysis. This approach will allow us to correlate the transcriptomic signature and activity of individual neurons with the emergence of pathological activity. Temporal correlations of single neuron firing with the onset of interictal or ictal discharges will be used to infer the contribution of individual neurons to these epileptiform activities. Then, using cell type-specific promoters based on single cell transcriptomics data, we will manipulate the activity of neuronal populations predicted to drive pathological activity using opto- and chemo-genetic tools in organotypic cultures of human post-operative epileptic tissue. This approach will allow us to test the causality of the activity of specific neuronal ensembles on the emergence of epileptiform activity and pave the way for the identification of novel therapeutic targets in mesial temporal lobe epilepsy.

This work supported by ANR (EPIDEV and GABGANG projects) will be carried out in collaboration with the Baulac and Navarro/Charpier teams (ICM) and the neurosurgery departments of the Pitié-Salpétriere and Lariboisière hospitals.

Recent lab publications on the topic :
1. Frazzini V, Mathon B, Donneger F, Cousyn L, Hanin A, Nguyen-Michel VH, Adam C, Lambrecq V, Dupont S, Poncer JC, Bielle F, Navarro V (2022). Epilepsy related to focal neuronal lipofuscinosis: extra-frontal localization, EEG signatures and GABA involvement. J Neurology 269: 4102-4109
2. Virtanen MA, Uvarov P, Mavrovic M, Poncer JC, Kaila K (2021) The Multifaceted Roles of KCC2 in Cortical Development. Trends in Neurosciences S01666-2236
3. Goutierre M, Al Awabdh S, Donneger F, François E, Gomez-Dominguez D, Irinopoulou I, de la Prida L, Poncer JC (2019) KCC2 regulates neuronal excitability

and hippocampal activity via interaction with Task-3 channels. Cell Reports 28: 91-10
4. Heubl M, Zang J, Pressey JC, Al Awabdh S, Renner M, Gomez-Castro F, Moutkine
I, Eugène E, Russeau M, Kahle KT, Poncer JC, Lévi S (2017) GABAA receptor-
dependent synaptic inhibition rapidly tunes KCC2 activity via the Cl--sensitive WNK1
kinase. Nature Communications 8: 1776

Encadrant **POUGET Pierre**
mail Pierre.pouget@upmc.fr

Equipes Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics
Responsable VIDAILHET Marie/ LEHERICY Stéphane
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Exploration et caractérisation des structures et réseaux cortico-souscorticaux chez l'homme par enregistrements des mouvements oculomoteurs, des activités motrices des muscles auriculaires, faciaux et du cou. Mise en évidence de perturbations en pathologie : Piste diagnostique et thérapeutique ?**

Résumé De nombreuses pathologies neurologiques affectent différentes structures cérébrales, tant corticales que sous-corticales. Ces structures, organisées en réseaux, sont aujourd'hui bien identifiées ainsi que les dysfonctionnements liés à différentes situations pathologiques.
Bien que l'IRM apporte une aide majeure dans l'indentification des différentes structures cérébrales, l'identification et la quantification des connections entre celle-ci sont plus limitées. Cette solution d'imagerie est coûteuse et limitée pour les structures profondes et anatomiquement imparfaitement individualisées, en particulier celles de petites tailles (comme le PPN (Noyau pédonculopontin)) qui sont à la limite de la résolution des images produites à l'heure actuelle.

Nous proposons ici une approche originale, qui repose sur les connexions neuro-anatomiques héritées et persistantes au sein du processus évolutif. Ces connexions ont été mise en évidence dans différents modèles non-humain et également chez l'homme, au niveau des muscles oculomoteurs, auriculaires, faciaux et du cou. Des enregistrements de l'activité musculaire de ces différents muscles pourrait permettre de mettre en évidence, au travers de leurs connexions avec ses structures, une activité pathologique et ainsi préciser un diagnostic neurologique. Enfin ces travaux pourrait ouvrir de nouvelles pistes thérapeutiques avec une stimulation musculaire antérograde qui pourrait permettre d'activer une structure cérébrale.

Le projet peut être divisé en plusieurs axes de travail, dont l'exploration des connections entre les muscles du cou et les mouvements oculomoteurs avec des projections communes de l'aire visuelle frontale et du colliculus supérieur, ainsi que l'étude de l'enregistrement de l'activité du muscle transverse de l'auricule (TAM). De plus, le TAM montre une connexion avec les muscles oculo-moteurs, ce qui permet d'explorer son intégrité lors des mouvements oculomoteurs. Enfin, les autres muscles auriculaires intrinsèques possèdent des connections avec les noyaux sous thalamiques.

Pour ce qui est des enregistrements, les solutions retenues sont non invasives et accessibles, avec l'enregistrements des mouvements oculaires par eye-tracking, et l'enregistrement de l'activité motrice par électromyogramme (EMG) de surface ou par échographie. L'EMG permettant à la fois l'enregistrement et la stimulation.

Si l'enregistrement de l'activité neuromusculaire en neurophysiologie est dominé par l'EMG, l'échographie se développe pour cette indication. Plusieurs modes peuvent être utiliser comme la mesure du volume et du flux de microcirculation.

Cette proposition vise à vérifier si les modèles de recrutement musculaire reflètent des aspects spécifiques de la planification et du contrôle du moteur. Cette proposition s'appuie sur de récents résultats montrant que les schémas de recrutement moteur parallèles à certains aspects de la planification motrice observés au niveau central, au moins dans le système oculomoteur tels que l'initiation des saccades, le contrôle des

saccades séquentielles et des mouvements de la main .

Dans ce projet de thèse, nous souhaiterions étendre ces résultats à des programmations de mouvements de la tête et des mains. Cette proposition implique la combinaison de trois composantes/objectifs qui, ensemble, fourniront une hypothèse de liaison pour ce programme de thèse.
1)Activité EMG de surface à haute densité permet de caractériser le schéma de recrutement des unités motrices individuelles.
2)La mesure du volume et du flux de microcirculation par échographie avec le mode B-flow, pour caractérisé l'activité musculaire.
3)L’accumulation stochastique aux modèles de seuil et aux modèles de course qui relient les schémas de recrutement des moteurs à l'initiation du mouvement et au contrôle.

Encadrant **Pradat Pierre-François**
mail pierre-francois.pradat@aphp.fr

Equipes Neural Connectivity and Plasticity (NCP)
Responsable Pradat Pierre-François
Unité Laboratoire d'Imagerie Biomédicale (LIB)

Sujet **Functional interaction between the brain and the spinal cord in amyotrophic lateral sclerosis**

Résumé Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease, affecting 120 000 new individuals worldwide each year, and the third most frequent neurodegenerative disease after Alzheimer's and Parkinson's diseases. The relatively low prevalence of ALS (4-8/100 000) is due to its extremely rapid progression, leading to death within 2-5 years after disease onset. There are not efficient enough therapies except riluzole which prolongs the lifespan for some months only. 90% of cases are sporadic, the rest being due to familial forms linked to SOD1, TDP-43, FUS and C9orf72 mutations. Its diagnosis relies on the detection of the combined degeneration of upper motor neurons (UMN) in the cerebral cortex, and lower motor neurons (LMN or motoneurons, MNs) in the brainstem and spinal cord. This dual contribution is particularly relevant since ALS is the most severe disease of the adult motor system, in comparison to diseases that target either UMN or LMN. This duality also raised questions on the cause of the disease, which remains controversial while a growing number of evidences point to the cerebral cortex as the origin of ALS and suggest a corticofugal propagation of neurodegeneration. In line with this assumption, transcranial magnetic stimulation (TMS) studies unraveled early hyperexcitability as a marker of cortical dysfunction in both sporadic and familial forms. Importantly, longitudinal studies in pre-symptomatic SOD1 mutation carriers revealed that cortical hyperexcitability develops prior to clinical onset and characterizes also early sporadic patients. The fact that cortical hyperexcitability negatively correlates with disease progression and survival highlights the relevance of early cortical dysfunction to ALS onset and progression. Cortical hyperexcitability has been proposed to translate into glutamatergic excitotoxicity to the downstream targets of CSN, and possibly of the whole corticofugal population, contributing to the degeneration of spinal MN via an anterograde trans-synaptic mechanism. However, to date, the interaction between the brain and the spinal cord as not been studied as a whole in human patients.

The principal objective of the PhD program is to better understand the interaction between the brain and the spinal cord in the development of ALS. For this, we will study different metrics of neural network activity at the brain and spinal cord levels extracted from non-invasive electrophysiological techniques including EEG, EMG and TMS. We will also investigate the functional interaction between both levels using an innovative fMRI protocol enabling to scan the brain and the spinal cord simultaneously and thus to analyze the functional connectivity between both levels. We have started to build the STRATALS cohort (protocol n° APHP211449, CPP Sud-Méditerranée I n° 22.00136.000103, ID-RCB 2022-A00083-40) which will include 80 asymptomatic relatives of patients with familial ALS due C9orf72 mutations, 20 symptomatic patients and 20 controls. The protocol includes 2 visits for asymptomatic and symptomatic participants; to date, 13 participants have been included only for the 1st visit. The PhD student will be involved in data acquisition and analysis. She/he will be trained to the different techniques of non-invasive investigations of the human central nervous. The project requires excellent abilities in informatic and statistics since the PhD student will be particularly involved in the analyze of fMRI data.

The project is developed at the Pitié-Salpêtrière Hospital, in the clinical Dpt of the Laboratory of Biomedical Imaging (LIB; https://www.lib.upmc.fr). The experiments are performed at the MRI platform of the Brain Institute (ICM) and the electrophysiological laboratory of LIB (Rehabilitation Dpt of Pitié-Salpêtrière Hospital).

Encadrant **PREAT Thomas**
mail thomas.preat@espci.fr

Equipes Energy & Memory
Responsable PREAT Thomas / PLAÇAIS Pierre-Yves
Unité Laboratoire Plasticité du Cerveau (LPC)

Sujet **Role of the APP Alzheimer's disease-related pathway in regulating energy metabolism during memory formation**

Résumé Alzheimer's disease (AD) is a neurodegenerative disease that causes cognitive deficits, progressive loss of autonomy, and eventually death. About 35 million people are affected worldwide, and due to the aging of the population the number will rise to 66 million by 2030. Unfortunately there is currently no treatment for AD, and the initial causes of this pathology remain largely unknown. However, it is crucial to focus on the etiology of AD in order to identify early biomarkers and develop new avenues for treatment. Our project is to study in drosophila a switch from a physiological stage into an early pathological stage leading to AD, in relation to brain energy metabolism.
At the neuropathological level, AD is characterized by the progressive formation in the brain of neuritic plaques which correspond to the extracellular accumulation of amyloid beta (Aß) peptide, generated by cleavage of the transmembrane Amyloid Precursor Protein (APP), and by the formation of neurofibrillary tangles consisting of hyperphosphorylated TAU protein. Cerebral energy metabolism defects have been correlated with the onset of AD, and the disease is linked to an increased in brain oxidative stress. Our working hypothesis is that energy metabolism defects are among the initial causes of AD. Importantly, most of the proteins involved in humans in AD have homologs in the drosophila fly. In particular the APP protein, precursor of amyloid peptide Aß42 that accumulates in the brain of AD patients, has a unique homolog called APP-like (APPL). APPL is strongly expressed in the mushroom body, the center of the olfactory memory of drosophila, and we showed that this protein plays an important physiological role in associative memory (Goguel et al., J Neurosci 2011).
We recently engaged into an integrated study of the interplay between memory and energy metabolism. We showed that long-term memory formation critically relies on an acute increase of the metabolism of glucose-derived metabolites in the Drosophila mushroom body (Plaçais et al., Nat Commun 2017). Strikingly, our results demonstrate for the first time that memory formation involves glucose oxidation in the pentose phosphate pathway, which is a major regulator of oxidative stress. We also demonstrated the crucial role of glial cells in fueling the mushroom body during memory formation (de Tredern et al., Cell Rep 2021; Silva et al. Nat Metab 2022).
Our project is to study the links between the APPL pathway and the regulation of energy metabolism during memory formation. The project is based on a strong set of preliminary results on signaling cascades involved in memory formation and energy metabolism. In particular, we recently showed that a gradient of H2O2 is required in the drosophila olfactory memory center for long-term memory formation (unpublished result). We propose to perform an integrated study how APP transmembrane protein and its toxic derivative amyloid beta interact with energy metabolism at the molecular, circuit and behavioral levels. In practice, the project will involve the use of powerful drosophila genetics tools and behavioral assays that we master, along with functional imaging of energy metabolism by multi-photon fluorescence microscopy, for which our lab is a world leader.

Encadrant **PRESSNITZER Daniel**
mail daniel.pressnitzer@ens.fr

Equipes Audition
Responsable PRESSNITZER Daniel
Unité Laboratoire des Systèmes Perceptifs

Sujet **Computational roles of cortical multi-area structure in discrimination task**

Résumé In recent years, a new paradigm called "population doctrine" has sought to understand cognition by simultaneously representing the activity of an entire neural population [1]. In this framework, environment or task-variables are represented along distinct neural dimensions. For instance, population activity in prefrontal regions of monkeys performing a visual discrimination dual task is structured by distinct axes representing task-relevant features, choice, context, and even task-irrelevant sensory features [2]. The disentanglement of the representations provides a linear access to the task variables, hence a greater flexibility in mapping task-relevant sensory features with different motor outputs (lick or refrain from licking in a Go/NoGo paradigm, or lick right or left in a 2-Alternative Forced Choice setup). This capability is crucial when animals switch between multiple tasks in which different behaviors are flexibly associated with task-dependent stimulus features. We believe that this behavior is supported by compositional cortical computations. To effectively complete a multi-task, the network must be able to separate the representations of the relevant variables and modularize the task-relevant computations into sub-functions associated with different sensory-motor mappings. Performing the correct computation to complete the task would then require the network to harness a relevant composition of these modularized functions.

A prominent level of structure in the mammalian cortex is the organization into anatomically-defined regions, and a premise of much of cognitive neuroscience is that different regions play different computational roles. This observation raises the question of whether a multi-area organization offers fundamental computational advantages with respect to a less compartmentalized architecture. Mechanistic insights into this question have so far been largely elusive, in particular because the large majority of studied network models have focused on individual areas. Multi-area network models and multi-area electrophysiological recordings that could constrain such models are, thus, needed.

Objectives and methods :
(1) To obtain a multi-area recording of neural activity during a discrimination multi-task in 3 regions of the ferret cortex at several levels: primary, secondary and tertiary auditory cortex. To achieve this goal, we will train ferrets to either switch the attended sensory dimension (frequency- versus AM-based task), or to switch between motor contingencies (Go/No-Go vs 2AFC) and perform neuronal recordings with chronic arrays (Microprobes).

(2) To investigate which sensory features (Amplitude modulation, Pitch) and contextual information (Task rule, Choice, Motor contingencies) are represented in each area and how. In particular, we aim at comparing these encoded variables between different areas and tracking their emergence or compression within network populations. In order to describe the neural manifold for each area, dimensionality reduction (PCA, UMAP..) and statistical techniques (ICA, Multivariate regressions...) will be performed on the dataset.

(3) To predict behavioural outcomes and stimulus features using decoding approaches across the 3 areas. The internal variables given by the relevant axis

extracted in (2) will be used as predictors in supervised learning methods.

(4) To describe the computational role of each region. In silico network aiming at reproducing neural data will be constructed , based on the joint work of the supervisor [3]. Each area will be represented as a recurrent neural network communicating through feedforward and feedback communications. Once the weights have been determined, low rank decomposition of the given connectivity matrix will be performed to better understand the computations carried out by each area, following [4].

References

1. Ebitz, R. B. & Hayden, B. Y. The population doctrine in cognitive neuroscience. Neuron (2021)

2. Mante, V., Sussillo, D., Shenoy, K. V. & Newsome, W. T. Context-dependent computation by recurrent dynamics in prefrontal cortex. Nature (2013)

3. Barbosa J, Proville R, Rodgers C, Ostojic S, Boubenec Y. Flexible selection of task-relevant features through across-area population gating. Preprint on bioarXiv. https://doi.org/10.1101/2022.07.21.500962

4. Dubreuil, A., Valente, A., Beiran, M., Mastrogiuseppe, F. & Ostojic, S. The role of population structure in computations through neural dynamic

Encadrant **RAMUS Franck**
mail franck.ramus@ens.fr

Equipes Cognitive development and pathology
Responsable RAMUS Franck
Unité Laboratoire de Sciences Cognitives et Psycholinguistique (LSCP)

Sujet **Gene-environment correlations and interactions in cognitive development**

Résumé Cognitive development is influenced by both genetic and environmental factors, which may have additive effects, but which may also interact in non-additive ways, and which furthermore are sometimes partly confounded. Yet, most studies of environmental effects on cognitive development have not taken into account the potential correlations and interactions with genetic factors, potentially yielding inaccurate estimates of environmental effects.

This situation has changed with genome-wide association studies (GWAS) and the now widespread availability of polygenic scores (PGS) for various phenotypes in a number of developmental cohorts. The present project aims to leverage these new sources of information to revisit some classic questions and investigate new questions on the etiology cognitive development and neurodevelopmental disorders.

As an example, an environmental factor that has a well-established effect on reading ability and on the risk of dyslexia is the so-called Home literacy environment. This composite measure typically aggregates information such as the number of books owned in the household, as well as parents' literacy practices (in particular, reading books to their children). Yet, parents who own many books and who spontaneously read stories to their children are not the same kind of parents as those who don't: they typically are literate, highly-educated people who may have good genetic predispositions for literacy and who may have transmitted these predispositions to their children. In other words, the environmental effect is potentially confounded by a genetic effect. The project will therefore aim to use a polygenic score for reading ability/dyslexia constructed based on previous GWAS as an additional regressor in statistical models in order to disentangle genetic from environmental effects, and also to test the interaction between the PGS and the home literacy environment.

This will also offer an opportunity to decompose the family risk for dyslexia (whether a first-degree relative has a diagnosis of dyslexia), which is also used as a predictor of dyslexia (family risk predicts a 40% risk of dyslexia, 10 times the population prevalence). Yet this family risk includes both genetic risk and environmental risk (parents with dyslexia may provide a less rich home literacy environment). The project will therefore test to what extent family risk is mediated by the dyslexia PGS, to what extent it is mediated by the home literacy environment, and to what extent there remains a residual direct effect.
The potential additional contribution of other polygenic scores for related constructs (educational achievement, IQ, ADHD…) will also be investigated.

This example project on dyslexia may occupy one year of the PhD. Similar additional studies will be carried out on other cognitive developmental phenotypes, such as ADHD and language disorders, or measures of school achievement .

Analyses will be based on cohorts that include genetic data and the relevant environmental and phenotypic data, such as ALSPAC, TEDs, or ABCD. These data will be acquired before the start of the PhD.

This project requires strong statistical skills and a good mastery of the R language.

References:

Doust, C., et al. (2022). Discovery of 42 genome-wide significant loci associated with dyslexia. Nature Genetics, 54(11), Art. 11. https://doi.org/10.1038/s41588-022-01192-y

Eising, E., et al. (2022). Genome-wide analyses of individual differences in quantitatively assessed reading- and language-related skills in up to 34,000 people. Proceedings of the National Academy of Sciences, 119(35), e2202764119. https://doi.org/10.1073/pnas.2202764119

Gialluisi, A., et al. (2021). Genome-wide association study reveals new insights into the heritability and genetic correlates of developmental dyslexia. Molecular Psychiatry, 26(7), 3004 3017. https://doi.org/10.1038/s41380-020-00898-x

Von Stumm, S., Smith-Woolley, E., Ayorech, Z., McMillan, A., Rimfeld, K., Dale, P. S., & Plomin, R. (2020). Predicting educational achievement from genomic measures and socioeconomic status. Developmental Science, 23(3), 1 8. https://doi.org/10.1111/desc.12925

Encadrant **RANCILLAC Armelle**
mail armelle.rancillac@college-de-france.fr

Equipes Neuroglial Interactions in Cerebral Physiopathology
Responsable ROUACH Nathalie
Unité Centre Interdisciplinaire de Recherche en Biologie

Sujet **Deciphering the role of astrocytes in visual processing in the superior colliculus**

Résumé

Context
Astrocytes dynamically interacts with neurons and play a major role in cognitive functions and pathologies. They are notably involved in the regulation of brain metabolism by trafficking glucose intercellularly through gap junction channels in an activity-dependent manner. Interestingly, the visual layers of the superior colliculus (SC), which receive 85% of the retinal projections in mice, exhibit a pronounced glucose metabolism. This suggests a crucial role for astrocytes in this midbrain structure that integrates visual information to drive reflexive behaviors.

We have shown that astrocytes from the retinorecipient SC display specific cellular and structural properties compared to astrocytes from other brain regions. Notably, they form particularly extensive intercellular networks mediated by a very strong expression of Connexins 30 and 43, the gap junction channel subunits. Connexin deficiency in astrocytes impairs the representation of visual properties into maps in the SC and impacts sensory processing during behavior, suggesting a crucial role for astroglial networks in shaping functional maps in the SC.

Hypotheses
The project aims to delve deeper into the role of astrocytes in visual processing in the SC by characterizing the functional properties of astrocytes with 2-photon calcium imaging. Remarkably, results from another brain region organized into functional maps, the ferret visual cortex, have indicated that astrocytes can be selective to the orientation and the direction of movement of a visual stimulus, precisely as neurons are. Given that orientation and direction maps are also fundamental features of the visual layers of the SC, we hypothesize that individual astrocytes might also be selective to orientation and direction, and could be organized into functional maps. In addition, as our data has shown that neuronal maps are impaired in mice with disconnected astroglial networks, we expect that the selectivity of individual astrocytes and their arrangement into maps should also be modified in these mice.

Objectives
The main objectives of the project are:
1- To set up the two-photon imaging system enabling calcium imaging of the SC in vivo during visual stimulation
2- To investigate the functional selectivity of individual astrocytes for orientation and direction and determine whether these features organize into maps
3- To test whether astrocytic functional maps overlap with the neuronal functional maps
4- To explore whether the selectivity of individual astrocytes and their arrangement into maps are impaired in mice with disconnected astroglial networks

Methods
This project relies on the recording of astrocytes activity in the SC in vivo using a two-photon calcium imaging system that will first be developed. Then, calcium imaging will be performed in the SC of GFAP-GCaMP6f transgenic mice to record visually-evoked calcium signals in astrocytes and investigate the cells selectivity to visual features. In addition, RCaMP will be expressed in neurons to record neuronal activity and assess

whether the stimulus-feature preferences of astrocytes are mapped across the SC surface in register with neuronal maps. Finally, to better understand the mechanisms underlying the role of astroglial networks in shaping functional maps, the integrity of astroglial selectivity will be explored in mice deficient for astroglial connexins.

Encadrant **REBOLA Nelson**
mail Nelson.rebola@icm-institute.org

Equipes Cellular Mechanisms of Sensory Processing
Responsable REBOLA Nelson
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Principles governing spatial organization of excitatory inputs in neocortical interneurons.**

Résumé Neurotransmission, the process by which neurons communicate, occurs primarily at synapses that are mainly located in dendrites. Interestingly, the dendritic trees of neurons can differ in shape, size, and density of active conductances, which can influence synaptic integration and thus neuronal computations. In recent years, numerous studies have focused attention on understanding the role of dendrites in the computations performed by excitatory neurons. These studies revealed that dendrites not only propagate signals from synapses to the soma, but can perform simple operations, thereby increasing the computational capabilities of individual neurons. Not surprisingly, dendritic operations have been associated to various important neuronal functions including, formation of hippocampal place fields and learning and memory.

However, the function of individual neurons depends not only on dendritic properties but also on the spatial organization of their synapses along the dendritic tree which has received much less attention. For example, it is not known whether neurons use a uniform strategy or whether they exhibit variability in the organisation of synapses along their dendrites. The limited knowledge derives mainly from the technical limitations associated with studying the distribution of synapses in complete individual neurons.

Using recently reconstructed neurons from serial EM images we have obtained preliminary results indicating that neocortical interneurons use variable strategies to distribute excitatory inputs along their dendrites. Parvalbumin positive (PV)-INs seem to concentrate most of their synapses in proximal dendritic segments displaying a clear robust decrease in linear synapse density at progressively longer distances from soma. In contrast, somatostatin positive interneurons (SST)-INs present a relatively constant synapse density all along their dendrites. We have obtained functional data indicating that such differential distributions are essential for the differential roles of the two populations of interneurons in cortical networks. However, the cellular mechanism governing such an asymmetric synapse distribution across the two populations is not known.

In this PhD project we thus plan to investigate the molecular and cellular pathways involved in the spatial organization of excitatory synapses in PV- and SST-INs. We postulate that neurons adjust their synapse location and density in function of their dendritic integration properties to define key computational properties. We hypothesize that the observed differences are fundamental for the distinct role of SST- and PV-INs in cortical circuits.

Using transgenic mouse models to selectively label excitatory synapses in neocortical INs the student will investigate how the spatial synaptic patterns emerge in PV- and SST-INs throughout development. We plan also to investigate how sensory experience is instrumental (or not) to the maturation of synapse distributions in the two subtypes of neocortical interneurons. In order to measure synapse distribution along single interneurons that present large dendritic trees we plan to use expansion microscopy in association with spinning disk confocal imaging. We will also probe possible molecular pathways involved in such heterogeneous synaptic patterns.

Namely we will investigate if NMDA receptors, know to control synapse formation and elimination in pyramidal cells, play a role is the observed difference in synapse organization between PV- and SST-INs.

Overall, we plan to combine a complete set of electrophysiological, morpho-functional and state-of-the-art imaging approaches to explore an original question concerning the principles governing spatial organization of excitatory synapses in neocortical interneurons.

Encadrant **RENIER Nicolas**
mail nicolas.renier@icm-institute.org

Equipes Structural Dynamics of Networks
Responsable RENIER Nicolas
Unité Institut du Cerveau et de la Moelle épinière

Sujet **NeuroVascular Interactions Plasticity during Gestation and Its Impact on the neural control of reproductive functions.**

Résumé The vascular network constitutes the central interface between neural cells and the body and therefore plays a critical role in the integration of physiological parameters by the neurons. We have gathered evidence using whole-brain imaging that the vascular density is increased during pregnancy in specific brain regions. This opens many questions: what is the nature of this vascular plasticity? What are its mechanisms? Does it play a role in shaping neuronal function?
We will use the pregnant state as a model to test the interactions of the vascular system with both neuronal activity and hormonal signaling. This model provides striking and accessible readouts of plastic brain functions, such as the emergence of parental behaviors and shifts in the control of energy balance.
The regional specificity of the effects we measured during pregnancy suggest a highly regulated process modulating vascular density.
In this project, we will analyze this phenomenon and its mechanisms at the interface of the vascular and neuronal physiology in 2 aims:

Aim 1: Establish the nature and distribution of vascular plasticity during pregnancy.
The impact of pregnancy on brain vascularization has not yet been investigated from a neuroanatomical point of view, which is crucial to understand its impact on brain functions. We aim to clarify the existence and nature of the neurovascular unit plasticity during pregnancy.
1.1: Whole-brain mapping of the structural plasticity of the neurovascular unit: We will generate vascular atlas of the pregnant brain to the time points representative of specific hormonal states: E5, E15, E18, P3, and P25 with our iDISCO+ and TubeMap tools.
1.2: Molecular plasticity of the neurovascular unit and blood-brain barrier (BBB): To test the plausible hypothesis that the BBB is modified during pregnancy, we will first evaluate decreases in general BBB permeability by using permeability tracers (sulfo-NHS-biotin, Dextrans) and check the expression of genes controlling the general permeability of endothelial cells (Mfsd2A, Ucn5b, PLVAP, Cldn5) as well as specific BBB transporters (Pgp, Glut1, RAGE, MCT1, LAT1) using mFISH3D.

Aim 2: Mechanisms of vascular plasticity and their impact on the control of energy balance
The specific increase in vascularization during pregnancy of few midline nuclei suggests the existence of shared mechanism modulating the vascularization across them, which may impact the homeostatic control functions of the hypothalamus.
2.1 Identify the cellular substrates of the hormonal effect on vascularization. We will evaluate first the effects of steroid hormones on brain-wide vascularization using implants of Progesterone (P4) and Estradiol (E2) in virgin mice. To test which cell type drives the humoral action we'll use viral deliveries of cre-dependent CRISPR constructs targeting nuclear and membrane receptors of both P4 and E2.
2.2 Decipher the origin and nature of pro-angiogenic factors. We will test the expression of pro-angiogenic factors in the different cell types (glial or neuronal) by scRNAseq and in situ hybridization in the virgin and pregnant states. The action of pro-angiogenic factors with an increased expression during pregnancy will be tested by the deletion of their receptors or ligand with CRISPR AAV. The effect of this deletion will be measured on vascular density in pregnant mice.

2.3 Evaluate the impact of hypothalamic neuronal activity on vascularization. We will test if blocking in vivo the activity of Kiss1+ neurons of the AVPV prevents the hypervascularization of the region with AAV injections of a loxed Kir2.1 in the AVPV of Kiss1-cre mice.
2.4 The impact of vascular remodeling on hypothalamic functions during pregnancy: The profound changes in neurovascular remodeling observed in the hypothalamus during pregnancy could influence neurovascular coupling and as a result impact essential functions of homeostasis. To evaluate this, we will block hyper-vascularization in the AVPV and test thermoregulation, food intake, nest building and E2, P4, Oxytocin and Prolactin levels during pregnancy.
Expected results: This project will decipher the mechanisms of cerebral vascularization during pregnancy, which will provide a novel framework to understand neurovascular communications and may be relevant to better understand metabolic disorders.

Encadrant **ROUACH Nathalie**
mail nathalie.rouach@college-de-france.fr

Equipes Neuroglial Interactions in Cerebral Physiopathology
Responsable ROUACH Nathalie
Unité Centre Interdisciplinaire de Recherche en Biologie

Sujet **Rôle des interactions neurogliales dans le comportement social normal et pathologique**

Résumé

Contexte
Les interactions sociales sont nécessaires à l'intégration d'un individu à la société et au monde qui l'entoure. Elles reposent sur des processus cognitifs complexes nécessitant l'activation de circuits neuronaux dans différentes aires cérébrales. Ces circuits sont nécessaires au décodage de l'environnement et des émotions d'autrui ainsi que dans la prise de décision du comportement à adapter en retour. Parmi les déterminants moléculaires des interactions sociales figure l'ocytocine, une hormone produite par les neurones de l'hypothalamus dont les projections atteignent de nombreuses structures cérébrales tel que le cortex préfrontal. L'ocytocine dans le cortex préfrontal régule ainsi l'anxiété, la reconnaissance sociale mais également le comportement socio-sexuel des femelles.

Le cerveau est constitué de neurones et de cellules gliales parmi lesquelles figurent les astrocytes. Si le rôle des neurones dans le fonctionnement cérébral est largement étudié et reconnu, celui des astrocytes et de leurs interactions avec les neurones reste encore peu élucidé. De façon intéressante, des études récentes indiquent que les cellules gliales sont impliquées dans la régulation de l'activité de circuits neuronaux qui contrôlent le comportement de l'animal. Les astrocytes jouent ainsi un rôle important dans la mémoire, le sommeil, l'état émotionnel ou la peur. Cependant, l'implication des astrocytes dans les comportements sociaux a été peu étudié. Jusqu'à récemment, il était notamment admis que l'ocytocine agissait sur ces comportements uniquement par une action directe sur les récepteurs neuronaux à l'ocytocine. Cependant des études récentes montrent que les astrocytes expriment également le récepteur à l'ocytocine, qui est fonctionnellement couplé aux protéines Gq, induisant une signalisation calcique, et/ou Gi/o, impliqués dans des remodelages structuraux, et que l'activation de ces voies de signalisation astrogliale peut moduler l'activité des réseaux neuronaux. Enfin de façon intéressante, des données de notre laboratoire indiquent un rôle important et singulier du récepteur à l'ocytocine des astrocytes du cortex préfrontal dans le comportement social chez la souris.

Objectifs
Le but de cette projet est de déterminer le rôle des astrocytes dans les interactions sociales et les mécanismes sous-jacents afin d'évaluer l'implication de leurs dysfonctionnements dans des troubles neuro-développementaux caractérisés par des défauts de sociabilité.
Plus particulièrement, ce projet a 3 objectifs principaux:

1) Caractériser fonctionnellement l'activité calcique des astrocytes du cortex préfrontal chez des souris mâles et femelles éveillées libres de leurs mouvements lors d'interactions sociale;

2) Investiguer le rôle du récepteur à l'ocytocine des astrocytes dans leurs propriétés fonctionnelles, structurales et moléculaires afin d'identifier les mécanismes astrogliaux régulant l'activité de circuits neuronaux sous-tendant le comportement social de la souris;

3) Déterminer l'implication d'une altération des voies ocytocinergiques astrogliales dans les troubles du comportement social associés à des maladies neuro-développementales tels que les troubles du spectre autistique ou le syndrome de Williams.

Ce projet contribuera à mieux comprendre le rôle des astrocytes dans le comportement social et pourrait permettre d'envisager des stratégies thérapeutiques alternatives, ciblées sur les cellules gliales, pour vaincre ses troubles.

Méthodes

Ce projet combinera des approches d'imagerie (microscope miniature pour signalisation calcique des astrocytes), d'électrophysiologie (tétrodes pour activité neuronale) et de comportement (interactions sociales) sur la souris éveillée libre de ses mouvements. Afin d'investiguer le rôle des récepteurs à l'ocytocine des astrocytes, le laboratoire a récemment développé des outils moléculaires permettant d'induire sélectivement dans les astrocytes de souris adultes une délétion du récepteur à l'ocytocine de façon locale ou globale. Ces outils permettront d'investiguer le rôle de ce récepteur astrocytaire dans les propriétés fonctionnelles, structurales et moléculaires des astrocytes par des approches d'imagerie (calcique et super-résolution) et moléculaire (étude transcriptomique). L'ensemble de ces approches et outils ont déjà été développés au laboratoire et sont actuellement opérationnels.

Encadrant **SANSON Marc**
mail marc.sanson@aphp.fr

Equipes Genetics and Development of Nervous System Tumors
Responsable HUILLARD Emmanuelle/SANSON Marc
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Analyse de l'épitranscriptome de la N6-méthyladénosine (m6A) dans les gliomes mutants IDH : Découverte des effets directs de la signalisation oncogène de la D-2HG**

Résumé La majorité des gliomes diffus de grade 2 et 3 portent la mutation du gène IDH. L'enzyme idh mutante convertit le 2-oxoglutarate (2-OG) en D-2-hydroxyglutarate (D-2HG) qui entraîne la transformation cellulaire par l'inhibition des enzymes TET et KMDs dépendantes du 2-OG, et conduit à une hyperméthylation de l'ADN et des histones. On connaît mal l'effet de cet oncométabolite sur d'autres enzymes dépendantes de la 2-OG, telles que les déméthylases de l'ARN FTO/ALKBH, ce qui pourrait conduire à une refonte de l'épitranscriptome de la N6-méthyladénosine (m6A).

La N6-méthyladénosine (m6A) est la marque épitranscriptomique la plus abondante et la mieux comprise. La position et le niveau de m6A déterminent le sort du transcrit : stabilisation, traduction ou dégradation. Ainsi, l'épitranscriptome constitue une autre couche de régulation de l'expression génique, critique dans la neurogenèse, le développement embryonnaire, l'organisation des synapses et la fonction immunitaire. Des altérations de l'épitranscriptome m6A ont été décrites dans de nombreux types de cancers humains, y compris les tumeurs cérébrales. Néanmoins, les preuves émergentes reposent principalement sur des déductions bioinformatiques et la détermination des niveaux globaux de méthylation de l'ARN plutôt que sur l'identification de l'altération de transcrits spécifiques.

Nos données préliminaires retrouvent une hyperméthylation m6A globale des ARNm et des ARNlc dans les cellules IDHmut, notamment sur des transcrits impliqués dans l'organisation synaptique et dans le traitement et la présentation des antigènes médiés par le CMH de classe 1. Pour explorer les conséquences des transcrits hyperméthylés m6A sur la biologie de ces tumeurs, le doctorant effectuera une série de validations. Les sites m6A des transcrits informatifs seront évalués à l'aide d'une approche MazF-qPCR et les conséquences de l'hyperméthylation seront examinées au niveau de l'ARNm et des protéines dans les mêmes lignées cellulaires, ainsi que dans les données RNA-seq et protéome disponibles au laboratoire. Ensuite, des cellules de gliome IDHwt et des astrocytes immortalisés seront transduits avec un lentivirus exprimant IDHmut inductible ou IDHwt. L'accumulation intracellulaire de D-2HG et les niveaux globaux de m6A et l'activité enzymatique de FTO/ALKBH seront mesurés. Pour d'autres validations fonctionnelles, l'étudiant s'appuiera sur des systèmes modèles développés par des collaborateurs: pour investiguer les transcrits hyperméthylés impliqués dans la synapse, nous combinerons des approches pharmacologiques, génétiques et électrophysiologiques dans i) des co-cultures de cellules de gliome et de neurones glutamatergiques dérivés d'IPScs, ii) des cultures organotypiques de cerveau humain injectées avec des cellules de gliome ou traitées avec du D-2HG et iii) des NSCs/OPCs provenant d'un modèle de souris CKI IDHmut. Pour moduler des sites spécifiques dans les transcriptions candidates dans les cellules de gliome, l'étudiant effectuera une édition m6A de cibles spécifiques avec des systèmes CRISPR-Cas9.

Le laboratoire hôte s'intéresse également à la compréhension des effets de la D-2HG sur le microenvironnement immunitaire des tumeurs. Les données préliminaires indiquent que la D-2HG est absorbée par les monocytes, la microglie, les macrophages et les lymphocytes T primaires humains. En outre, les traitements avec 5 mM de D-2HG inhibent la déméthylation médiée par TET, ce qui affecte finalement la différenciation cellulaire (cellules T) et l'activation (cellules microgliales). Étant

donné l'importance du m6A dans la fonction des cellules immunitaires, le doctorant explorera également l'impact du D-2HG sur la fonction des cellules immunitaires. Le laboratoire a déjà mis en place des essais de différenciation et généré des données RNA-seq unicellulaires à partir des compartiments lymphocytaires et myéloïdes de gliomes humains. L'étudiant doit analyser ces données afin d'identifier les transcriptions potentielles pour une validation expérimentale supplémentaire. Pour poursuivre ce projet, le laboratoire a établi des collaborations (Institut de Génomique Fonctionnelle, Montpellier, Collège de France). Il est soutenu par des subventions PLBIO et BMS. La mise en évidence de l'impact de la D-2HG sur le microenvironnement tumoral pourrait ouvrir des pistes pour la conception de stratégies thérapeutiques efficaces.

Encadrant **SERGENT Claire**
mail claire.sergent@parisdescartes.fr

Equipes Vision
Responsable COLLINS Thérèse
Unité Integrative Neuroscience and Cognition Center (INCC)

Sujet **Impact d'un manque d'interactions tactiles: marqueurs comportementaux, physiologiques et neuronaux**

Résumé Le toucher social est crucial pour le développement et le bien-être, et constitue un des moyens les plus efficaces de communiquer des émotions affectives [1,2]. Cependant, malgré son importance, les conséquences du manque de toucher social ont été peu étudiées chez l'adulte, alors que les interactions tactiles ont diminué de manière drastique ces dernières décennies avec l'augmentation des personnes souffrant d'isolement social. La pandémie de COVID-19 a renforcé ces phénomènes, révélant la nécessité d'étudier les impacts de la privation de toucher social [3]. C'est l'objectif principal de cette thèse. Premièrement, nous étudierons les marqueurs comportementaux de la privation de contact social, en étudiant les traits psychologiques, la perception sensorielle et la perception vicariante des interactions tactiles. Ensuite, nous étudierons les marqueurs et mécanismes physiologiques et neuraux qui sous-tendent le manque de toucher social. Enfin, nous évaluerons dans quelle mesure la stimulation vicariante (i.e. l'observation d'interactions tactiles) peut compenser un manque de toucher social. Ce projet propose une approche innovante combinant des approches comportementales, physiologiques et neurales pour étudier l'impact mais aussi une potentielle compensation de la privation de toucher social. Ce projet de thèse est la pierre angulaire d'un cadre de recherche fondamentale ouvrant sur une meilleure compréhension de la perception du toucher social et des mécanismes sous-jacents.

Ce projet de recherche s'organise en trois axes permettant d'étudier les impacts d'un manque de toucher social.
Axe 1. Notre première hypothèse de recherche est que le manque de toucher social affecte les marqueurs de bien-être psychologique (e.g. anxiété et solitude [3]) mais sera également influencé par les traits de personnalité (e.g. attitudes envers le toucher et style d'attachement). Cet Axe 1 testera cette hypothèse en effectuant une méta-analyse des données existantes, en créant une nouvelle base de données de stimuli de toucher social (avec des contrôles pour les aspects tactiles, sociaux et cinématiques), et en testant de manière comportementale l'impact du manque de toucher rapporté par le participant sur la perception de ces stimuli. Par exemple, nous nous attendons à ce qu'un manque de toucher social réduise le comportement d'attraction/approche vers le toucher social et la compréhension lors de l'observation de personnes en interactions tactiles.
Axe 2. Notre deuxième hypothèse de recherche est que l'absence de contact social modulera les marqueurs physiologiques et neuraux de la perception du contact social. Cette deuxième hypothèse sera testée par des études en électroencéphalographie (EEG), et de modulation des potentiels évoqués somatosensoriels [4]. Plus précisément, nous prévoyons que la privation de toucher social sera associée à une réduction de la "résonance somatosensorielle", un phénomène dans lequel les zones somatosensorielles sont activées lors de la simple observation du toucher social. Nous nous attendons à ce que cette activité somatosensorielle réduite soit médiée par des différences individuelles telles que l'anxiété et la solitude, mais aussi potentiellement par le seuil de perception tactile individuel.
Axe 3. Notre dernière hypothèse est que le toucher vicariant, c'est-à-dire l'observation d'interactions socio-tactiles, dont il a été démontré qu'il partage des bases neurales et un caractère agréable commun avec le toucher réel [5], peut avoir un effet apaisant qui sera mis en évidence par une modulation de l'activité neuronale

somatosensorielle et une réduction des niveaux d'anxiété. Ceci sera testé dans l'axe 3 par une étude d'entrainement et de neuro-imagerie utilisant l'EEG.

Encadrement. La thèse sera co-encadrée par Claire Sergent (HDR), spécialiste de l'étude de la conscience et experte en EEG (INCC, UPC), et Louise Kirsch, spécialiste du rôle du corps dans la cognition et du toucher social (INCC, UPC). À noter, Louise Kirsch soutiendra son HDR d'ici 2024.

Références

1. Bremner AJ, & Spence C. (2017) Advances in child development and behavior, 52, 227-268.
2. Kirsch LP, Krahé C, Blom N (...) & Fotopoulou A. (2018) Neuropsychologia, 116, 136-149.
3. Von Mohr M*, Kirsch LP*, & Fotopoulou A. (2021) Royal Society open science, 8(9), 210287.
4. Galvez-Pol A, Calvo-Merino B, & Forster B. (2020) Cortex, 125, 332-344.
5. Morrison I, Björnsdotter M, & Olausson H. (2011) Journal of Neuroscience, 31(26), 9554

Encadrant **SOL-FOULON Nathalie**
mail Nathalie.sol-foulon@upmc.fr

Equipes Repair in Multiple Sclerosis: from Biology to Clinical Translation
Responsable LUBETZKI Catherine / STANKOFF Bruno
Unité Institut du Cerveau et de la Moelle épinière

Sujet **The role of myelination in the maturation of spatial orientation circuits**

Résumé The insulating properties of myelin, produced by oligodendrocytes, together with the nodes of Ranvier, axonal domains enriched in voltage-gated Na+ channels, allow fast saltatory transmission of action potentials. Importantly, myelination and nodes of Ranvier contribute to adjusting the timing of impulse transmission, critical for coincident arrival of synaptic inputs from multiple axons in sensory systems.
During development, myelination is correlated with the maturation of networks serving sensorimotor cognition, but causal relations remain elusive. In this project, our goal is to examine the role of precision timing and synchrony for cognitive development of processes of spatial perception. We will tackle the hypothesize that by accelerating axonal conduction and adjusting neuronal properties, myelination is crucial for the development of coherent function of networks that subserve perception of orientation in space. Our study will focus specifically on the head direction circuit, which provides an inner representation of the external world. The head direction system includes three main areas, the presubiculum, and its two main input areas, the anterior thalamic nucleus and the retrosplenial cortex, and communication rely on long-range axons, which are myelinated.
1) We will manipulate oligodendrogenesis to induce myelination arrest at a chose time point.
Myelin development starts in the hindbrain and cerebellum, then spreads rostrally throughout the white matter tracts over the first two postnatal weeks, and components of the limbic system are last to become myelinated. By using mice with conditional deletion of the myelin regulatory factor, Mrf-iKO mice, i.e. Mrffl/fl;PDGFRa-creERT;RosaYFP mice, the transition from pre-myelinating to mature myelinating oligodendrocytes is blocked and myelination can be stopped. Littermates Pdgfra-CreERT ; Mrf+/+; RosaYFP are used as controls. By administering Tamoxifen at P10 and P14, myelination can be arrested after its early phase, in order to preserve already acquired motor skills, and we will examine more specifically the impact of myelination on the limbic system. The extent of myelination deficits in thalamo-cortico-presubicular projection pathways may degrade spatial behaviors and search strategies.
2) The functional effects of stopping innate myelination will be assessed through behavioral testing of navigation strategies, in the Morris water Maze test, at the ICM behavioral platform. A hidden platform with a maze surrounded by visual landmarks will let us discriminate between allo- and egocentric searching strategies during spatial learning and reversal training.
3) The myelination status will be determined in different brain regions, in particular the hippocampal and thalamic projection neurons, in each control and Mrf-iKO animals when Morris water Maze are completed. Immunostainings with Nav and Caspr (nodal area), CC1 (a marker of postmitotic oligodendrocytes), PLP and MBP (markers of myelin) antibodies and confocal microscopy will be used. We will attempt to correlate spatial navigation strategies with myelin development.
4) We will assess nodes of Ranvier length in myelinated fibers and Nav clusters in unmyelinated stretches of GABAergic axons (or prenodes). Single cell electrophysiology carried out previously with Dr. Fricker has shown that prenodes, i.e. nodal protein clustering prior to myelination, are associated with an increased axonal conduction velocity, highlighting that conduction speed can also be modulated by nodal clustering patterns. We will ask whether these prenodes still form and persist

when oligodendrogenesis and myelination are halted.
5) Interactions with Dr. Fricker and coll., will allow a comprehensive view of how progressive myelination affect coordinated encoding of HD signals in thalamo-cortico-presubicular circuits.

Publications

Freeman SA, et al. 2015. Acceleration of conduction velocity linked to clustering of nodal components precedes myelination. PNAS. 112:E321–E328
Dubessy AL, et al. 2019. Role of a Contactin multi-molecular complex secreted by oligodendrocytes in nodal protein clustering in the CNS. Glia. 67:2248–2263
Lubetzki C, Sol-Foulon N, Desmazières A. 2020. Nodes of Ranvier during development and repair in the CNS. Nat Rev Neurol.16(8):426-439
Mazuir E, et al. Oligodendrocyte Secreted Factors Shape Hippocampal GABAergic Neuron Transcriptome and Physiology.2021. Cereb Cortex.31:5024-5041

Encadrant **STANKOFF Bruno**
mail bruno.stankoff@aphp.fr

Equipes Repair in Multiple Sclerosis: from Biology to Clinical Translation
Responsable LUBETZKI Catherine / STANKOFF Bruno
Unité Institut du Cerveau et de la Moelle épinière

Sujet **The role of brain barriers and fluid trafficking dysfunction in multiple sclerosis: an integrated in vivo analysis through a combination of advanced PET-MR tools**

Résumé Despite progresses for the prevention of relapses in multiple sclerosis (MS), a large proportion of patients still develop progression with persistent neurological disability. Post-mortem studies have suggested that progression was associated with chronic active lesions (CAL) with persisting innate immune cell activation. Our team has recently pioneered positron emission tomography (PET) with 18F-DPA-714 to quantify in vivo innate immune cells, and developed an innovative image processing method to identify CAL in MS (1). We showed that CAL predominate in areas near the Cerebrospinal fluid (CSF), and that choroid plexus alterations were involved in this regionalized process (2, 3) and influence remyelination failure (4), pointing a role of the brain to CSF barrier (BCSFB) dysfunction.

In this project, we will disentangle for the first time in vivo the influence of brain barriers and fluid trafficking dysfunction on the chronic inflammatory process impacting the brain in MS.

First, we will characterize the dysfunction of the BCSFB in MS. Our recent work showed that the dynamic analysis of PET tracer kinetic between CPs and ventricular CSF enables to quantify simultaneously blood perfusion and BCSFB permeability at the CP level. By combining dynamic 18F-Florbetaben PET (BCSFB) with 18F-DPA-714 PET (for innate immune cells) and multimodal MRI (for volumetry and microstructure) on a PET-MR system, we will unravel the facets of CPs dysfunction in MS with the hypothesis that neuroinflammation in the CPs enhance CAL, repair failure and neurodegeneration, whereas a (potentially transient) BCSFB closing could play a protective role, preventing the entrance of inflammatory cells and molecules in the CSF.

Second, we will visualize and quantify meningeal lymphatic vessels and their connexion to cervical lymph nodes in patients with MS compared to control subjects. We will implement a method recently developed at the ICM (Coll S Lenck; JL Thomas) that provides real time vessel wall imaging by MRI after gadobutrol injection. By imaging the flow of the contrast agent, that appears first in the blood vessels and subsequently in the lymphatics, it is possible to segregate the slow-flow circuits of the lymphatic vessels from the faster flow circuits of other vessels. This approach will be compared with a non-invasive MRI one in which modulation of the TE parameter from a FLAIR sequence allows to visualize the relatively high protein concentration characterizing lymphatic compared to blood vessels.

The third aim will assess the fluid trafficking through the Glymphatic system. Avoiding invasive intra-thecal injection of contrast agents, the combination of susceptibility weighted imaging with the quantification of diffusion along the perivascular space has recently allowed to generate a proxy of glymphatic function, which has been shown to be impaired in MS. This approach will be combined with an alternative one derived from dynamic PET acquisitions, in which the modelling of the kinetic of tracer exchange between the blood, parenchymal and CSF compartments could generate a proxy of the within the interstitial space towards the CSF (coll F Turkheimer, M Veronese)

The project will be conducted in patients at distinct MS stages, who will be compared to controls and undergo a multimodal combination of dynamic MRI and PET acquisitions. The processing of BCSFB and glymphatic imaging metrics will be optimized in cohorts already acquired and the final combination of the 3 approaches will be performed on a new cohort currently ongoing (40 patient 20 HC; funded by ARSEP and ANR-DGOS). The student will work under the supervision of experimented engineers and neurologists within the team, and will be in charge of image processing and analysis, and of the generation of pipelines for fostering the automatic treatment of multimodal data. Collaborations with the neuroimaging team of CENIR (S Lehericy, S Lemck), and with expert in multimodal data analysis and deep learning (ARAMIS, O Colliot) will ensure the training and implementation of imaging tools. This project will shed new lights on the in vivo role of barriers and fluid trafficking on persisting inflammation, tissue damage and repair, and disability worsening in MS.

1. Bodini J Nucl Med.2020;61(7):1043-1049.
2. Poirion Neurology. 2021 6;96(14):e1865-e1875.
3. Ricigliano, Radiology. 2021;301(1):166-177.
4. Tonietto et al, Brain. 2023;146(1):182-194

Encadrant **STROEBEL David**
mail david.stroebel@ens.fr

Equipes Glutamate Receptors and Excitatory Synapses
Responsable PAOLETTI Pierre
Unité Institut de Biologie de l'Ecole Normale Supérieure (IBENS)

Sujet **Functional investigation of glutamate receptor evolution from aneural to neural species**

Résumé Ionotropic glutamate receptors (iGluRs) are major players of synaptic transmission in the central nervous system (CNS) of vertebrates. IGluR genes are also widely present throughout the living kingdom, however little is known about their role in non-vertebrate species, in particular in aneural organisms. We and others recently showed that mammals iGluRs are involved in non-canonical neural signaling, thereby questioning the functional diversity of this class of receptors. Understanding the roles and activities of these receptors thus requires to investigate the origin and evolution of iGluR signaling.

We are proposing a PhD position to explore the role and function of iGluRs from non-vertebrate marine species representing key evolutive steps in the emergence of the nervous system (echinoderms, jellyfishes, sponges…). In particular the project aims to identify the origin of specific properties of iGluRs, in particular the agonist selectivity (see references). It will combine functional characterization in heterologous system (using standard and advanced molecular biology and electrophysiology methodologies), and structure/function/pharmacology analysis implemented in the lab. These functional investigations will be used to guide on-going in silico structural and evolutive models. The goal of the PhD project is thus to decrypt the scenario of iGluR functional evolution, in particular by mapping iGluR agonist specialization. In direct connection with the activities and expertise of the team, we expect this evolutive standpoint to feed current investigations of iGluR functions and dysfunctions in the mammalian brain. The project also involves a collaboration with three teams of marine biologists from Marseille, Nantes and Nice with who we are currently investigating the physiological role of iGluRs on marine model organisms. Altogether we aim at understanding how the receptors have adapted (and how they contributed) to the transition between aneural and neural systems more than 600 Mya.

At the cross-road of molecular neuroscience and evo-devo, the project is providing novel perspective on the functional origin of an important family of brain receptors and on its connection with the emergence and evolution of the nervous system.

List of related publications :

*Stroebel et Paoletti (2021) J. Physiology. doi: 10.1113/JP279028
*Tian, Stroebel et al. (2021) Nature Comm. doi: 10.1038/s41467-021-25058-9
*Grand et al. (2018) Nature Comm. doi: 10.1038/s41467-018-07236-4.
*Otsu et al. (2019) Science. doi: 10.1126/science.aax1522.
Ramos-Vicente et al. (2018) Elife. doi: 10.7554/eLife.35774.
Alberstein et al. (2015) PNAS. doi: 10.1073/pnas.1513771112
Burkhardt (2014) Mol. Biol. Evol. doi: 10.1093/molbev/msu178
*Paoletti et al. (2013) Nat. Rev. Neurosci. doi: 10.1038/nrn3504.
Team Publications (*)

Encadrant **SUMBRE German**
mail sumbre@biologie.ens.fr

Equipes Neural circuit dynamics & behaviour
Responsable SUMBRE German
Unité Institut de Biologie de l'Ecole Normale Supérieure (IBENS)

Sujet **The role of cell types and neural mechanisms underlying self-organised criticality in the brain**

Résumé This project will be carry out in co-supervision with Prof Adrian Ponce-Alvarez from Polytechnic University of catalonia.

In recent years, critical neural dynamics have been proposed as a unifying principle to account for the complexity of brain activity necessary to process and represent its environment. For example, it has been shown that at a critical regime, several brain function are optimized (e.g. dynamic range, decoding). Expected signatures of criticality in neural circuits are scale-invariant neuronal avalanches (NAs). NAs are collective patterns characterized by sequences of a group of neurons generating cascade-like events. As in other critical systems producing cascading events, the sizes and durations of critical NAs are scale-invariant, i.e., they follow power-law statistics with precise power exponents observed in physical and theoretical critical systems.
In a previous collaborative work between Sumbre and Ponce-Alvarez that combined light-sheet microscopy and transgenic zebrafish expressing GCaMP (Ponce-Alvarez et al. Neuron, 2018) we provided, for the first time, evidence that at the whole-brain level but still with single-neuron resolution, the nervous system works at a critical regime. However, when interacting with the environment, brain dynamics deviate from criticality to a more ordered state. Moreover, we found that criticality improves visual decoding.
Despite these advances, the mechanisms underlying self-organised criticality in the brain are unknown.
For the present PhD project, we propose to study these mechanisms. For this purpose, we will use double transgenic zebrafish larvae expressing GCaMP8 in all neurons and a red-fluorescence protein (dTomato) in either excitatory (Vglut2a promoter), inhibitory (Gad1b) or cholinergic (ChaT) neurons. This line is already available and functional. Additional cell types can be identified using immunostaining. Using these larvae, we will study the following main aims:

Aim 1. Cell-type specificity of neuronal avalanches
We will analyse the NAs statistical mechanics analysis tools such as maximum entropy models and renormalization group theory, but also according to the different cell types. Are the power-laws and critical exponents inherent of all cell-type circuits ? Or the critical avalanches are observed when all cell-types are combined together ? We hypothesize that E and I coordination during NAs is key to produce scale-invariance.

Aim 2. Neuronal mechanisms underlying self-organised criticality
The principle leading a system to automatically reach a critical state is known as self-organized criticality (SOC). It is believed that the system can self-organize through simple homeostatic plasticity rules that effectively change a control parameter towards its critical value. The E/I balance has been proposed as an important control parameter that is changed during the self-organization process. However, it is unknown how the dynamics of E and I cells evolve to generate and maintain a critical regime. Moreover, this hypothesis has never been tested experimentally. We hypothesize that transient and localized imbalances of E/I ratio are important to initiate the NAs and that E-I correlations are key to produce scale-invariance. Using

optogenetics to stimulate neurons of different types will allow proving the effect of E/I imbalances on the different parameters of the NAs (size, duration), and learn about the mechanisms underlying criticality.

Aim 3. The neuronal mechanisms underlying modulation of the brain's critical regime. We previously showed that brain dynamics deviate from criticality when the organism interacts with the environment. Here, we will study how neuromodulation can pull brain dynamics away from a critical regime. Neuromodulation (e.g. dopamine, acetylcholine) has been identified as a second control parameter that can regulate NAs in vitro. However, it remains unknown how neuromodulation interacts with E and I neurons during collective activity in vivo. We hypothesize that activation of cholinergic neurons affects the gain and the balance of E and I neurons.

Encadrant **TRICOIRE Ludovic**
mail Ludovic.tricoire@upmc.fr

Equipes Cortical Network and Neurovascular Coupling
Responsable CAULI Bruno / LAMBOLEZ Bertrand
Unité Neuroscience Paris Seine

Sujet **Alteration of glutamatergic neurotransmission in a model of intellectual disability.**

Résumé Glutamatergic (Glu) neurotransmission is mediated by ionotropic (iGlu) and metabotropic (mGlu) receptors. The delta receptors GluD1 and GluD2 structurally belong to the iGlu family. Yet, they do not bind glutamate but, instead, cerebellin (Cbln) and D-serine via their N-terminal and ligand-binding extracellular domains, respectively (1). Cbln enabling postsynaptic GluDs to participate in excitatory synapse formation/stabilization via attachment with presynaptic neurexin. GluD ion channel opening is alternatively triggered by type I mGlu (mGlu1/5) whose intracellular signaling is regulated by GluD1. GluD1 (gene: GRID1) is widely expressed in the brain at excitatory postsynaptic sites and its implication in pathology is suggested by association of GRID1 variants with risk of neuropsychiatric disorders, and by Grid1-/- mice behavioral, synaptic, and mGlu1/5 signaling alterations. We recently characterized homozygous missense GRID1 variants linked to intellectual disability and spastic paraplegia, without (p.Thr752Met) or with (p.Arg161His) glaucoma (2). These variants concern amino acid residues located within Cbln and D-serine binding domains. GluD1 mutants hamper mGlu1/5 receptor signaling via the ERK pathway in neurons of mouse primary cortical culture, and impair the dendritogenic and synaptogenic effects of wild-type GluD1 in primary hippocampal culture. Our results indicate that the clinical phenotypes are distinct entities segregating in the families as an autosomal recessive trait, and caused by pathophysiological effects of GluD1 mutants involving mGlu1/5 signaling and neuronal connectivity. However, the molecular and cellular mechanism bridging GluD-mGlu crosstalk with synaptic defects is unclear. The project is organized along three specific:
Specific Aim 1: Uncover alterations of the existing Grid1-Arg161His mouse line from behavioral to genomic levels in view of characterizing an animal model of GRID1-linked disease. We will assess earlier findings using patch-clamp electrophysiology, search for GRID1-linked pathophysiological processes, and compare with data from human cellular model (Aim 2). Alteration of mGlu signaling will be explored using imaging using fluorescent biosensor specific for each mGlu gated intracellular pathways. We will seek to identify pharmacological treatments that prevent or reverse alterations observed in human and mouse GRID1 mutant models, starting from of mGlu1/5 allosteric modulators.
Specific Aim 2: Assess the impact of p.Arg161His and p.Thr752Met mutations on the differentiation of human iPS cell-derived neurons. We will use this model to identify alterations of neuronal morphology, intracellular signaling, genome methylation pattern, synaptic transmission and to evaluate the relevance for humans of the findings obtained in mouse. Human iPS cell-derived neurons harboring either the p.Arg161His and p.Thr752Met mutations will be produced by CRISPR-Cas9 genome editing in collaboration with F. Laumonnier (Université de Tours)
Specific Aim 3: Elucidate the role of GluD1 in the organization, function and plasticity of the hippocampal Glu synapse and to identify the synaptic alterations caused by GRID1 mutations. We will investigate how GluD1 is distributed at the Glu synapse at the nanoscale using STORM/PALM super-resolution imaging in relation to AMPA (GluA1/A2), NMDA (GluN2A/B) and mGlu5 receptors. We will determine the contribution of GluD1 ligands D-Serine and Cbln in the organization of synaptic nanodomains of AMPA, NMDA and mGlu5 receptors. This will be performed in collaboration with S. Levi (IFM-ESPCI Paris).
This proposal will unravel molecular links between GluD1 dysfunctions and their

pathogenic impact on brain circuit formation, with relevance for brain diseases involving synaptopathies.

References:

1. Burada et al. doi: 10.1016/j.neuropharm.2021.108683. Epub 2021 Jun 26.
2. Ung et al 2022. medRxiv 2022.05.16.22274994; doi: https://doi.org/10.1101/2022.05.16.22274994

Encadrant **VETERE Gisella**
mail gisella.vetere@espci.fr

Equipes Cerebral Codes and Circuits Connectivity
Responsable VETERE Gisella
Unité Laboratoire Plasticité du Cerveau (LPC)

Sujet **A novel approach to studying the head direction system and its contribution to motor behavior**

Résumé Spatial orientation is a crucial cognitive function for life in the natural environment, subjected to strong evolutionary pressures and underlined by a highly conserved system. It structures information into a virtual map encoded by a network of brain regions, involving place cells, grid cells, and head direction cells (HDc). In this project we are interested in the study of HDc, neurons with a head direction (HD)-dependent firing rate. HDc have been found in many regions, but they are especially abundant in the anterodorsal thalamic nucleus (ADn), where they represent around 60% of neurons (1). The ADn is known to contain a fine and precise representation of rodents' HD, without any evidence that it would drive the animal's behavior. However, preliminary results by the laboratory show that optogenetic activation of the ADn induces a specific motor behavior, wherein mice run in circles. This suggests that ADn HDc might not solely reflect a representation of the space, but may also drive behavior, determining the direction of the mouse's head. Thus, this project seeks to gain insight into the function and structure of the HDc network in the ADn. The PhD candidate will probe the network using two parallel approaches: (A) optogenetic stimulation of HDc responding to pre-determined angles in freely-behaving mice; (B) computational modeling to explain and validate optogenetic manipulations.

AIM A: Do HDc in the ADn drive behavior? Preliminary evidence shows that artificially activating the entire ADn HD system leads to head-turning. In this project, the novel FLiCRE system will be used to target specific subpopulations of HDc (2). FLiCRE acts as an "and" logical switch, allowing the expression of an opsin only in cells that simultaneously receive 1) a strong calcium influx, i.e. are activated, and 2) laser illumination. Thus, we can selectively tag a subset of HDc, based on their preferred HD, and reactivate them later on, while the mouse is in a chosen orientation. This is done by coupling light delivery to HD via a deep learning system tracking HD in real-time. We will test several patterns of tagging and reactivation, and quantify behavior, to unravel the contribution of the ADn HD system in directing the HD behavior of the mice. Electrophysiological recordings with tetrodes will be performed to validate the optogenetic stimulation.

AIM B: Can we explain this optogenetic manipulation behavioral outcome with the conventional ring attractor model? This model views the HDc population as a recurrent network with a ring-like topological organization. It yields a continuous attractor and the position of an activity bump along the ring represents HD (1). While such a network has not yet been identified in rodents, there is evidence of its relevance (3). To understand the relationship between artificial neuronal manipulation of HDc and HD behavior, we will use previous findings about ADn connectivity (4) to inform the model. We will then test whether it can be tuned to produce an activity that is consistent with electrophysiology and behavior, in response to an input matching the optogenetic stimulation. If it is so, we will identify which connectivity parameters make it predictive. Otherwise, we will investigate other models that could account for ADn activity in normal conditions and/or under artificial stimulation.

This project will significantly further our understanding of the role of the ADn in spatial navigation, and provide cues to the HDc circuit. Besides, the laboratory previously showed that the regulation of ADn activity is required when mice remember a highly

stressful condition (4), potentially relating its function to anxiety-like behavior. Through this project, we will, therefore, also gain insight into the function of the HDc system in memorizing spatial information in stressful situations.

Expected outcomes: one peer-reviewed publication for each aim.
Skills that will be acquired: Behavior analysis in mice; Optogenetics; Electrophysiology; Surgery and behavioral application; Computational modeling in Python; Statistical analysis; Data analysis using Matlab and R code; Management and writing up of the project under mentor supervision; Participation in conferences to present the scientific data

1. Wiener, S. Taube S. MIT Press. 2005
2. Christina, K et al. Cell. 2020
3. Chaudhuri, R et al. Nature neuroscience. 2019
4. Vetere, G et al. Nature neuroscience. 2021

Encadrant **VOLLE Emmanuelle**
mail emmavolle@gmail.com

Equipes FRONTLAB : Frontal Function and Pathology
Responsable LEVY Richard
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Neurocognitive mechanisms of semantic memory search underlying creative thinking**

Résumé How creative ideas that lead to discoveries, innovations, or art emerge remains enigmatic. Famous scientists, inventors, and artists have reported that creative sparks may originate from searching and combining semantic memory knowledge. Hence, how humans search, explore, and exploit their memories is a critical unsolved question highly relevant to the understanding of creative ideas generation. This question remained difficult to test empirically. However, recent research from our team has demonstrated that computational network science methods allow exploring how the structure of semantic memory (semantic networks; 1) relates to creative behaviours and identified some semantic search components related to creative abilities (2).

The goal of our project is to understand the structure of semantic representation and the controlled and attentional processes that operate on it to drive creative thinking. We aim to characterize the neurocognitive mechanisms supporting the exploration of our memory related to creative thought. To this aim, we will employ specific experimental paradigms combined with computational neuroscience and neuroimaging methods. The subgoals 1 and 2 received ethical approval, subgoal 3 will be submitted soon.

We will use an associative fluency task based on ambiguous words (PolyFT) previously developed in the lab (2), which was shown to capture two search components related to behaviours of clustering (producing successive responses that stay in the same meaning) and switching (changing for another meaning). Our previous results suggest that switching captures interactions between memory structure and control processes guiding the search, clustering may capture attentional controlled processes for persistent search, and alternations between exploratory search and focused attention support creativity. These findings offer specific hypotheses we will test in this project, organized in three subgoals.

Subgoal 1 will be to replicate our previous findings using a various ambiguous cue words for PolyFT, creativity tasks, executive and attentional tasks, and individual semantic networks. We will additionally explore how clustering and switching behaviours relate to computational measures adapted from the optimal foraging theory and align with exploitation and exploration behaviours (3). This will allow us to validate the PolyFT task and new methods for capturing clustering and switching behaviours and relate them to distinct creativity processes.

Based on our previous results, we hypothesize that clustering relies on the sustained control of attention, while switching involves executive control, including cognitive inhibition and flexibility. To test these hypotheses, subgoal 2 of the project will use a dual-task and interference approach in healthy subjects, combining our polyFT with tasks specifically interfering with the maintenance of attention, cognitive inhibition, and flexibility. We expect attentional tasks to interfere predominantly with clustering, whereas executive tests will interfere with switching.

Subgoal 3 aims to examine the brain correlates of cognitive processes underlying clustering and switching behaviours. We will use an event-based functional MRI paradigm in healthy subjects and will analyses brain activity while participant perform various PolyFT trials. We will be able to distinguish the brain regions involved in clustering vs switching responses. We expect that clustering will involve the salience and attentional networks while switching will involve the executive control networks. As the role of these networks in creativity is established (1, 2) we will also test how

activity in these networks relates to creative abilities, and whether this link is mediated by clustering and switching behaviours.
This project will clarify the neurocognitive mechanisms allowing efficient and flexible semantic memory search in support of creative cognition, based on alternations between focused attention and exploratory search. Creativity is an essential vector of societal, cultural, and economic progress. Understanding its mechanisms is fundamental. Paradoxically, creativity is hardly studied scientifically, especially in France.

1. M. Ovando-Tellez, et al. Sci. Adv. ; 2022; 8,eabl4294
2. M. Ovando-Tellez, et al. Commun. Biol. 2022;5, 1–16
3. T. T. Hills, et al. Top. Cogn. Sci., 2015;7:513-34

Encadrant **WORBE Yulia**
mail yulia.worbe@aphp.fr

Equipes Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics
Responsable WORBE Yulia
Unité Institut du Cerveau et de la Moelle épinière

Sujet **Analytical tools for unraveling the representation of social networks in the primate brain**

Résumé Primates navigate their social world effortlessly. We immediately understand who are friends and foes, which children belong to whom and what hierarchy governs others' relations. How does the primate brain achieve this? We already know how individuals and social interactions are processed in the brain. Now the next frontier in our knowledge is to understand how the whole social network is encoded. A landmark of most primates' social environment is the interlocked level of structuring of their society.The resulting topology of primates' social network differs from the loose aggregation of herds or swarms, and is better explained by topological variables such as centrality or betweenness. So far the neuronal mechanism encoding individuals' position in their social network remained elusive, in part because it has been almost impossible to recreate a naturalistic social network in laboratory settings. Yet, this question is fundamental for our understanding of how the brain creates social meaning based on social perception.
A multi-scale approach will allow for gaining fundamental mechanistic insight into the neural toolkit for smoothly maneuvering our primate societies with the group of Pierre Pouget under the supervision of Julia Sliwa. At each step precise network characterization will be performed using advanced tools from graph theory, and bioinformatical engineering with the group of Fabrizio de Vico Fallani. In particular, the PhD student will work on improving statistical methods for network comparison and network deformation with the overarching goal of understanding how social space is represented in the brain. The PhD project objectives are to:

Aim 1) construct, characterize, and compare the social network of macaques
We will compare "classical" social networks with social networks obtained using multi-layer graphs. We hypothesize that the use of multilayer networks will allow us to unravel the social complexity embedded in primate social behavior, by taking into account inter-behavior and temporal variability. The PhD student will compare topological variables obtained with single layer and multi-layer graphs. Once the best method is found, he will apply it to compare social networks across species and across time for 3 macaque species, using tailored statistical methods and identifying metrics of interest.

Aim 2) unravel and characterize the brain networks involved in the representation of social networks' topology
Based on fMRI data, the PhD student will help to compute the neural Representational Dissimilarity Matrix (RDM) in each brain voxel that were scanned. This RDM will be compared to RDMs representing topological variables of the social network. The PhD student will study the properties of the neural network thus identified. To analyze their connectivity map, he will use correlation, granger causality, and tools from graph theory. Multi-layers graphs will be used here to integrate anatomical and functional properties of the networks and study the controllability of their nodes.

Aim 3) identify the neuronal code used to represente social network topology
We hypothesize that neurons would encode individuals in a map where distances would be social distances, or hierarchies, or affiliations. The representation of the

social network may be may be non-linearly biased towards own position in the network. The PhD student will analyze the activity of single neurons recorded by the team and will investigate the “rules” of transformation between the real social network and its representation by the neuronal population. The possible existence of a hyperbolic geometry based transformation will be investigated. Machine learning methods such as graph convolutional networks will also be used.

Each of the parts is intended to deliver separate discoveries to be published in bio-informatics (e.g. Plos Comp Biol) and neuroscience journals (e.g. Neuron, Journal of Neuroscience). The research will be carried at the ICM with graph theory tools, supervised by INRIA researcher Fabrizio de Vico Fallani; on neural data acquired by CNRS researcher Julia Sliwa, in same team with Pierre Pouget; and on ethological data acquired at the Strasbourg Primate Center (ANR SocialNeuroNet J.Sliwa/S.Ballesta/J.Sallet). The material conditions, including submission fees, conferences (e.g. NeuroFrance, FENS, SfN) are ensured by de Vico Fallani’s funding (ERC BCINET), and Sliwa’ fundings (ERC Neuro-Society, ANR SocialNeuroNet).

Encadrant **ZUGARO Michaël**
mail michael.zugaro@college-de-france.fr

Equipes Brain Rhythms and Neural Coding of Memory
Responsable ZUGARO Michaël
Unité Centre Interdisciplinaire de Recherche en Biologie

Sujet **Role of the Dorsal, Intermediate and Ventral Hippocampus in Memory Formation and Consolidation**

Résumé Seminal studies in humans and in animal models established that the hippocampus plays a critical role in declarative memory, in particular in spatial memory. A dialog between the hippocampus and the cortex, occurring during both behavior and sleep, underlies the formation and consolidation of memories, and supports planing and decision making. Our goal is to decipher the network mechanisms mediating these cognitive functions.

In rodents, hippocampal neurons know as 'place' cells activate when the animal is in a particular location of the environment, forming the brain basis of a cognitive map. During spatial navigation, place cells form rapid sequences of activity, one per cycle of the ongoing theta (8 Hz) rhythm, that reflect the ongoing trajectory. These 'theta sequences' could mediate formation of new memories and planning of future trajectories. Spontaneous reactivation of similar fast sequential activity also occurs during offline periods, such as rest and sleep. This occurs during ripple (200 Hz) oscillations, is broadcast to cortical and subcortical areas, and may be involved in planning and decision making, as well as memory consolidation.
One of the main targets of hippocampal outputs involved in memory and decision making is the medial prefrontal cortex (mPFC). In rats performing a spatial memory task, hippocampal and mPFC neurons enhance their correlated firing, and theta coherence occurs upon learning, peaking at decision points. During sleep following acquisition of a new rule, mPFC neural patterns involved in response selection are selectively replayed coupled to hippocampal ripples. Finally, boosting the coupling between hippocampal ripples, cortical delta waves and thalamo-cortical spindles can induce consolidation of memories that would otherwise be lost. In summary, hippocampo-prefrontal interactions may mediate the integration of spatial information into a wider decision-making network, underlie a better adaptation to current behavioral demands and more efficient reward prediction, and support memory consolidation during sleep.

Yet, one major issue with previous studies is that virtually all recordings have been performed in dorsal hippocampus (dHPC), although most projections to the mPFC originate in intermediate and ventral hippocampus (iHPC, vHPC). Importantly, there are notable functional differences between dHPC, iHPC and vHPC. Firstly, in iHPC+vHPC place cells code for much larger locations (up to several meters). Thus, place cells along the dHPC-iHPC-vHPC axis encode different spatial scales. In addition, the amplitude of theta oscillations decreases from dHPC to vHPC, and phases progressively shift by up to 180°, defining different 'time zones' across the hippocampus. Regarding memory consolidation during sleep, although SWRs can be generated throughout the entire hippocampus, they can propagate only within dHPC+iHPC, but cannot cross over to vHPC where they occur independently. In summary, the mPFC receives hippocampal signals with varying spatial and temporal characteristics, and it remains unknown how these are merged or segregated.

Another notable difference between dHPC and iHPC+vHPC lies in their anatomical connections with cortical and subcortical areas. In particular, iHPC+vHPC but not dHPC are connected to mPFC, amygdala, hypothalamus, etc. and are involved in anxious or aversive behaviors. For instance, vHPC-lesioned rats freely explore

anxiogenic places (brightly lit arms in an elevated plus maze) that are strongly avoided by control rats who remain in dark arms. Anxiety-related signaling from vHPC to mPFC increases in brightly lit arms, and theta synchrony increases, but is reduced by optogenetic inhibition of vHPC inputs to mPFC.

In summary, although they are the sole major direct hippocampal outputs to mPFC, and despite their marked computational and functional specificities, iHPC and vHPC have received little attention. Our goal is to understand their specific roles in learning and memory, in the context of the hippocampo-cortical dialog. To this end, we will perform massively parallel, simultaneous recordings from dHPC, iHPC, vHPC and mPFC in rats performing a spatial memory task. Importantly, we will use a custom-designed maze of unusually large dimensions to accommodate the specific spatial scale of iHPC+vHPC signals. The task will include emotional (anxiogenic) stimuli to address the specific role of iHPC+vHPC in the non-spatial components of memory.

Encadrant **ZUJOVIC Violetta**
mail Violetta.zujovic@gmail.com

Equipes Myelin Plasticity and Regeneration
Responsable NAIT OUMESMAR Brahim / ZUJOVIC Violetta
Unité Institut du Cerveau et de la Moelle épinière

Sujet **TRAINED IMMUNITY IN MS PATIENT MACROPHAGES**

Résumé Multiple sclerosis (MS) is an inflammatory, neurodegenerative disease in which infiltration of immune cells in the central nervous system (CNS) leads to the destruction of an essential component of neuronal conduction: the myelin. However, a repair process called remyelination can occur resulting from the activation, migration and differentiation of oligodendrocytes precursor cells (OPCs) into new myelin forming oligodendrocytes.
An efficient remyelination of MS lesions is critical for a favorable disease evolution as suggested in pathological investigations (1) and confirmed in vivo in a longitudinal study applying specific imaging myelin markers that showed for the first time that the remyelination capacity of patients was inversely correlated with clinical severity (2). While being the major player in destruction, macrophages and microglial cells, CNS macrophages, are the major coordinating cells of the repair process. Macrophages possess a large spectrum of activation depending on the stimuli they receive (3). After exposure to pro-inflammatory cytokines, macrophages acquire a pro-inflammatory phenotype possessing high cytotoxic and chemo attractive properties (4, 5). After exposure to anti-inflammatory cytokines, macrophages acquire a pro-regenerative phenotype with trophic, pro-regenerative properties, fostering notably OPC differentiation into new myelin-forming oligodendrocytes (4, 5). Thus, acting on macrophages can have an important impact on disease evolution.

Our previous findings reveal that MS patient macrophages present functional and molecular dysfunctionalities prior to any lesion exposure. Notably, MS patient monocytes exhibit a preferential differentiation toward CD16+ pro-inflammatory macrophages. Interestingly, this result reflects the observation that CD16+ monocytes are present in multiple sclerosis active lesions, participating to blood brain barrier breakdown and T cells invasion of the CNS (6). Our multiomic approach confirms an over exaggerated inflammatory response even in the absence of pro-inflammatory stimuli and a blockade of mitochondrial metabolism.

The enhanced innate immune response and dysregulated metabolism that we observed in MS macrophages is reminiscent of trained immunity. Trained immunity is characterised by (i) an increase of pro-inflammatory cytokines released, (ii) a metabolic switch from oxidative phosphorylation to glycolysis, and (iii) an alteration of epigenetic programs.
Our main objective for this thesis project is to characterise epigenetic markers in MS patient macrophages to identify new genetic regulator to counteract their over-inflammatory response. Epigenetic reprograming involves histone modifications (H3K4me3, H3K4me1, H3K4Ac, H4K9me3), chromatin opening, DNA methylation, modulation of microRNA and long non-coding RNA expression (lncRNAs) (7, 8).

All the methodological approaches necessary to complete this project are routinely performed either within the team (macrophages cell culture, lncRNA discovery pipelines, chromatin-opening analysis) or in ICM core facilities. We have access to well phenotyped MS patient's cohorts that will enable multimodal analysis on macrophages profile and MS patient lesion load, severity and repair capacity.

1. R. Patani, M. Balaratnam, A. Vora, R. Reynolds, Remyelination can be extensive in

multiple sclerosis despite a long disease course. Neuropathol Appl Neurobiol 33, 277-287 (2007).
2. B. Bodini et al., Dynamic Imaging of Individual Remyelination Profiles in Multiple Sclerosis. Annals of neurology 79, 726-738 (2016).
3. J. Xue et al., Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. Immunity 40, 274-288 (2014).
4. V. E. Miron et al., M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. Nat Neurosci 16, 1211-1218 (2013).
5. O. Butovsky et al., Induction and blockage of oligodendrogenesis by differently activated microglia in an animal model of multiple sclerosis. The Journal of clinical investigation 116, 905-915 (2006).
6. A. Waschbisch et al., Pivotal Role for CD16+ Monocytes in Immune Surveillance of the Central Nervous System. J Immunol 196, 1558-1567 (2016).
7. M. G. Netea et al., Trained immunity: A program of innate immune memory in health and disease. Science 352, aaf1098 (2016).
8. J. J. Quinn, H. Y. Chang, Unique features of long non-coding RNA biogenesis and function. Nature reviews. Genetics 17, 47-62 (2016).