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Reinforce naive pluripotency and access chimeric competency by manipulating Netrin-1 signalling in human and non-human primate embryonic stem cells

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Naïve pluripotency represents a pristine state characteristic of pluripotent cells in pre-implantation mammalian embryos. Embryonic stem cells (ESCs) are derived from naïve pluripotent cells found in blastocysts. In mice, ESCs possess the unique ability to self-renew in culture while maintaining intrinsic pluripotentiality, allowing them to form germline chimeras upon injection into blastocysts. Naïve ESCs have been generated in humans and rhesus monkeys by various research groups, including ours. These cells exhibit molecular features akin to naïve pluripotency observed in mice, encompassing transcriptomic, epigenetic, and metabolic landscapes. However, unlike their rodent counterparts, primate naïve ESCs demonstrate a significantly lower capacity to form chimeras when injected into pig, rabbit, and monkey embryos.

The teams led by P. Savatier and F. Lavial investigated whether Netrin signaling could enhance the naïve pluripotency state, particularly in terms of chimeric competency for both human and non-human pluripotent stem cells. Netrin-1, a laminin-like protein, guides cellular responses by signaling through membrane receptors like DCC, NEO1, and Unc5 homologues. Known as an axon guidance cue and an apoptosis inhibitor, Netrin-1 emerged as a crucial regulator of naïve pluripotency in mice, as demonstrated by F. Lavial's team. P. Savatier's team revealed heterogeneous expression of Netrin-1 in human and monkey naïve ESC populations, potentially influencing its receptors and triggering apoptosis when cells self-renew in unfavorable environments.

Distinct human pluripotent stem cell (hPSC) lines expressing wild-type NTN1 (wtNTN1) or mutant NTN1 variants unable to bind to NEO or UNC5H receptors, or both, were generated by the team. Single-cell RNA sequencing experiments were conducted under two specific conditions: i) in the naïve pluripotency state and ii) during the exit from naïve pluripotency by removing growth factors. Results indicated that i) cells overexpressing wtNTN1 exhibited elevated levels of naïve markers compared to control cells, and ii) after 48 hours without growth factors, wtNTN1-overexpressing cells maintained high levels of naïve markers with decreased expression of lineage markers. These findings strongly suggest that NTN1 overexpression enhances naïve pluripotency in human PSCs and delays their exit from this state. The results align with those obtained by F. Lavial's team on mouse ESCs, indicating a similar role for Netrin signaling in both mouse and primate species. Significantly, unlike mouse ESCs, human ESC lines expressing mutant NTN1

forms exhibited a similar transcriptomic profile to cells overexpressing wtNTN1, suggesting that neither NEO1 nor UNC5H receptors play a substantial role. This implies the potential involvement of an as-yet-undiscovered third receptor, prompting ongoing investigations to identify it. The results highlight species-specific mechanisms in the regulation of the Netrin signaling cascade.

These findings open up a promising avenue for further research into understanding and harnessing naïve pluripotency in humans, with potential implications for regenerative medicine.

Heterogeneity in Microglial Morphodynamics regulation across the inactive period

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Microglial cells, the resident immune cells of the brain, have particularly dynamic processes. Several studies have suggested that beyond a possible role in surveillance, microglial dynamics may be related to synaptic mechanisms or, at least, to neuronal activity. However, the signaling pathways that modulate neuronal control of microglial motility remain largely unknown.

We have recently shown that sleep episodes decrease both microglial motility and complexity, depending on fractalkine receptor expression. To better assess the possible involvement of microglia in neuronal homeostasis occurring during sleep, we decided to study their morphodynamics along the inactive period in mice. We also investigated how delta and sigma oscillations, known to be involved in memory consolidation during sleep, might affect microglial cells.

Microglial morphodynamic changes were monitored by *in vivo* transcranial imaging using two-photon microscopy in Cx3cr1-eGFP mice, while electroencephalogram and electromyogram were simultaneously recorded. We then evaluated the effect of sleep-wake episodes along the inactive period, and fractalkine receptor Cx3cr1 depletion, to figure out their role in microglial dynamics. Subsequently, we performed morphodynamic analysis to evaluate process motility and cell complexity.

Our results indicate a decrease in microglial morphodynamics during slow-wave sleep, correlated with both delta and sigma oscillations, depending on the time of day. We also found that the fractalkine receptor depletion abolished these sleep-induced morphodynamic changes, suggesting that fractalkine may be involved in the detection and/or response of microglia to changes in neuronal activity.

In conclusion, this work highlights a fine regulation of microglial motility involving the Cx3cr1 receptor during a precise phase of the inactive period. This study will lead to a better understanding of microglial functions in the context of synaptic transmission and plasticity.

Acknowledgements
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Emergence of enteric nervous circuits: Axon guidance gene programs and their potential alterations in paediatric gastro-intestinal motility disorders

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Abstract

The pathophysiological contributions of the enteric nervous system (ENS) are expanding. They extend far beyond the simple control of digestive functions to include, for example, the regulation of adult brain stem cell homeostasis. A true sensor of external signals from its ecosystem, such as the microbiota and immune cells, the ENS has the capacity to influence numerous biological functions. The several hundred or more billion enteric neurons are organized into two ganglionic plexi, the myenteric and the submucosal, which form interconnected nervous networks lining the wall of the digestive tract. Numerous studies have focused on the early stages of migration of the neural crest subpopulations that give rise to enteric neurons and their colonization of the gastrointestinal tract. However, the processes of neuronal differentiation remain largely unknown. Enteric neurons are subdivided into sensory neurons, motor neurons and interneurons, whose axons follow distinct, stereotyped trajectories during embryonic development. These neurons are surrounded by glial cells, also derived from the neural crest. The different neuronal subtypes and glial cells group together to form regularly distributed ganglia, within which they have a precise spatial position. A first goal of our project is to map the development of enteric axons and their connection to the central nervous system using confocal and light sheet imaging, and in parallel to characterize the transcriptional programs active in enteric neurons during these early stages. We use the avian embryo model to address these questions. In parallel, we are studying the conservation of developmental programs in the human embryo, both through transcriptomic analyses of publicly available datasets and through imaging of embryonic and fetal samples. Our second objective is to investigate, using fetal and neonatal material, whether the programs identified could be affected in pathological contexts such as certain chronic intestinal pseudo-obstructions in infants, the etiology of which is unknown but compatible with enteric circuit dysfunction, or certain forms of Hirschsprung syndrome.

The sweet side of glia-to-neuron reprogramming

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Our adult mammalian CNS lacks intrinsic regeneraCve capacity to replace lost neurons and induce funcConal recovery a[er injury/disease. An emerging approach towards brain repair is to instruct fate conversion of brain-resident glial cells into induced neurons (iNs) by direct lineage reprogramming. Over the past years, we and others have shown that various types of glial cells can be converted into iNs by forced expression of neurogenic transcripCon factors (TFs) (Vignoles et al, 2019). Using a mouse model of drug-resistant epilepsy, we recently showed that forced expression of Ascl1 and Dlx2 instructs conversion of reacCve glia into GABAergic iNs that integrate within epilepCc networks and reduce chronic seizure acCvity, thus uncovering glia-to-iN reprogramming as a potenCal disease-modifying strategy to control drug-resistant seizures (LenCni et al, Cell Stem Cell, 2021). While glia-to-iN conversion holds promise as a neuron-replacement strategy, the molecular underpinnings of reprogramming remain unknown. Successful reprogramming relies on remodelling of gene networks, epigeneCc landscapes, and metabolic status. We here hypothesized that O- GlcNAcylaCon –a dynamic form of protein glycosylaCon which has emerged as criCcal regulator of numerous cell processes– could play a key role in lineage reprogramming by controlling epigeneCc regulaCons, rewiring of TF networks, and the metabolic shi[. O-GlcNAcylaCon is catalyzed by a unique enzyme, i.e. O-GlcNAc transferase (OGT). First, we showed using scRNA-seq that OGT expression is dynamically upregulated during reprogramming of astrocytes into GABAergic iNs. InteresCngly, we also showed that the reprogramming TFs Ascl1 and Dlx2 were O-GlcNAcylated using an O-GlcNAc-specific pulldown assay. To explore whether OGT/O- GlcNAcylaCon play a role during Ascl1/Dlx2-driven reprogramming, we inhibited OGT enzymaCc acCvity using a specific pharmacological inhibitor in astrocytes undergoing neuronal conversion. Strikingly, we observed a dramaCc reducCon of the number of iNs derived from astrocyte reprogramming compared to controls. Moreover, iNs generated upon OGT inhibiCon displayed a significantly less complex neuronal architecture compared to control iNs, as revealed by reduced dendriCc length and intersecCon numbers. We next hypothesized that this reducCon in the number of iNs could result from decreased cell division during reprogramming or impaired cell survival of iNs upon OGT inhibiCon. To test this hypothesis, we performed conCnuous Cme-lapse video microscopy of Ascl1/Dlx2-

transduced cells treated with the OGT inhibitor or sham control. While no obvious difference in cell division was detected upon OGT inhibiCon, we observed that the majority of astrocytes succumbed to cell death during the early stages of neuronal reprogramming upon exposure to the OGT inhibitor. Finally, we examined whether the effects of OGT inhibiCon observed in Ascl1/Dlx2-mediated reprogramming of astrocytes into GABAergic iNs would also be observed during their conversion into glutamatergic iNs. To our surprise, inhibiCon of OGT during Neurog2-induced reprogramming of the same astrocyte populaCon increased neuronal reprogramming efficiency and had no apparent impact on survival of iNs. Taken together, our results uncover OGT/O-GlcNAcylaCon as a key mediator during astrocyte-to-neuron reprogramming.

Role of IgLON adhesion molecules in synapse formation and maintenance

Poster 11

Control of synapse formation by novel extracellular interactions in *Caenorhabditis elegans*

Morgane Mialon, Liubov Patrash, Jean-Louis Bessereau and Berangere Pinan-Lucarré

The diversity and specificity of synapses rely upon core organizing Cell Adhesion Molecules (CAM) that regulate contact initiation, synapse formation, maturation, maintenance and functional plasticity. In *C.* elegans, we recently identified that the ACR-16 acetylcholine receptor, well characterized at neuromuscular junctions, is also present at neuron-to-neuron synapses along the ventral cord of worms. Using a fluorescent reporter of the ACR-16 acetylcholine receptor, we performed a visual screen upon random mutagenesis to identify mutants with altered ACR-16 containing neuron-to-neuron synapses in the ventral nerve cord. One mutant caught our attention because the ACR-16 acetylcholine receptor was no longer synaptic and appeared diffuse at the neuronal surface. This phenotype was consistent with a mutation in a core synaptic organizer. We identified the mutated gene, which encodes a member of the IgLON family: RIG-5. RIG-5 shows a strikingly specific localization at ACR-16 neuro-to-neuron synapses, as does ZIG-8, a known *in vitro* binding partner of RIG-5. Overall, our data show that we identified two novel synaptic molecules that form a bridge across neurons and control ACR-16 clustering. Interestingly, the IgLON family is associated with a wide spectrum of human neurodevelopmental, neuropsychiatric and neurologic disorders, and might control synaptogenesis in mammals.

Poster 10

Searching for new regulators at *C. elegans* synapses

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ACR-16 is the *Caenorhabditis elegans* ortholog of the a7 nicotinic acetylcholine receptor in vertebrates. Although extensively studied at *C. elegans* neuromuscular junctions, our recent findings indicate its presence at neuron-to-neuron synapses. We have shown that two cell adhesion molecules of the Immunoglobulin superfamily, RIG-5 and ZIG-8, very specifically localize at ACR-16 synapses. These molecules, RIG-5 and ZIG-8, act as bridges between the pre- and postsynaptic neuronal membranes, exerting control over the synaptic localization of ACR-16. Synapse assembly and function relies on a sophisticated molecular architecture involving extraand intracellular crosstalk. To identify the molecular partners of RIG-5 and ZIG-8, we ran a genetic screen based on ACR-16 localization, and retrieved 56 mutants. We identified an ortholog of a neurotrophic factor receptor, whose mutation impairs ACR-16 at neuron-to-neuron synapses, albeit in a slightly different manner from *rig-5* and *zig-8*. Current work aims at

characterizing whether this molecule is present at synapses and understanding its role in the intricate network governing synapse assembly and function

Poster 7

Function of DIP- α and DPR10 in muscle innervation maintenance

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Locomotion is a stereotyped behavior used by animals to find food, mates, or escape from predators. As Michel De Montaigne said, 'life is only movement.' The rhythmic pattern of locomotion is directly linked to the sophisticated architecture of the locomotor system. This architecture is established during development and maintained throughout adulthood. Each motor neuron (MN) axon terminal innervates specific muscle fibers and displays a unique architecture defined by its shape and the number of synaptic boutons.

The distinctive wiring and architecture of MN axon terminals, formed during development, ensure the proper contraction of muscles, allowing for correct movements. In adults, maintaining muscle innervation under physiological conditions or after injury is crucial for preserving the architecture of muscle innervation and sustaining locomotor function.

Our goal is to determine the mechanisms controlling muscle innervation maintenance in the Drosophila leg. In this project, we focus on a class of cell adhesion molecules from the immunoglobulin superfamily, the IgLONs, implicated in various brain diseases. Specifically, we study the DIP-α and Dpr10 orthologs in Drosophila melanogaster. Previous studies have revealed that the DIPs-Dpr interactome plays a crucial role during development in establishing synaptic connectivity. DIP-α and Dpr10 have been shown to establish terminal axon branching patterns during fly development. In our project, we hypothesize that these proteins are maintained in adult flies to preserve the specificity of muscle innervation. To test our hypothesis, we rescue terminal axon branching defects caused during development in DIP-α mutant adult flies when we reintroduce DIP-α specifically in adult flies. These results reveal the role of DIP-α plays in maintaining specific axon terminals in adult flies. We aim to observe terminal branches growth and synapses formation in the three different motoneurons expressing DIP- α in the adult fly. We will characterize fundamental molecular mechanisms that underly the formation, maintenance and function of the synapses at the neuromuscular junctions.

Establishment of an optimized and automated workflow for whole brain probing of neuronal activity

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ABSTRACT

Behaviors are encoded by widespread neural circuits within the brain that change with age and experience. Immunodetection of the immediate early gene c-Fos has been successfully used for decades to reveal neural circuits active during specific tasks or conditions. Our objectives here were to develop and benchmark a workflow that circumvents classical temporal and spatial limitations associated with c-Fos quantification. We combined c-Fos immunohistochemistry with c-Fos driven Cre-dependent tdTomato expression (i.e. TRAP mice), to visualize and perform a direct comparison of neural circuits activated at different times or during different tasks. By using open-source softwares (i.e. QuPath and ABBA), we established a workflow that optimize and automate cell detection, cell classification (e.g. c-Fos *vs*. c-Fos/tdTomato) and whole brain registration. We demonstrate that this automatic workflow, based on fully automatic scripts, allows accurate cell number quantification with minimal interindividual variability. Further, interrogation of brain atlases at different scales (from simplified to detailed) was achieved allowing gradually zooming on brain regions to explore spatial distribution of activated cells. We then illustrate the potential of this approach by comparing patterns of neuronal activation in various contexts (e.g., different vigilance states, complex behavioral tasks…), in separate animal groups or at different times in the same animals. Finally, we explored programs (e.g. BrainRender) for intuitive representation of obtained results. Altogether, this automated workflow accessible to all labs with some experience in histology, allows an unbiased, fast and accurate analysis of the whole brain activity pattern at the cellular level, in various contexts.

Evaluation of tractographic determination of cortical connectivity in macaque using retrograde tract-tracing

Y Hou, H Kennedy and B Hiba

Diffusion MRI based Tractography (TG) holds the promises of revealing the full complement of connections in the brain by means of non-invasive imaging and therefore widely used in human and animal models. Numerous validation studies of TG in macaques have revealed severe limitations in accuracy, leading to doubts as to the reliability or even meaning of TG.

In this project, we seek to improve the correlation of TT and TG by firstly comparing dMRI TG with tract tracing (TT) within the same brain, and secondly investigating if there is an improvement of TT-TG correlation with increasing spatial resolution of dMRI.

Seven post-mortem multi-shell high resolution (0.2-0.3 mm) dMRI of 6 brains have been collected with a 7T MRI scanner on which TGs have been computed using MRTrix3. TT was carried out in 4 of the 6 brains to allow the within subject TT-TG comparison.

The results show that within subject comparison and increasing angular and spatial resolution of dMRI do not improve of the TG-TT correlation. TG shows large numbers of false negatives and false positives. Tractography follows a faster decline with distance and a narrower weight distribution. The distribution of streamline density of TG on the surface is much more continuous compared to TT suggests it is prone to a diffusion-like processing and fail to reveal specific long-distance connections.

These findings suggest that the bio-physical constraints acting on tractography in the framework of the inter-areal cortical connectome do not allow it to adequately capture the characteristics of the cortical network.

Navigating in physical and social space in human and nonhuman primates. A neural ecological approach to space coding (NEASCO)

Alessandro Farne

Here, we aimed to shed new light on the social modulation of PPS representation by exploring its behavioral determinants and neural markers. We characterized neural signatures of PPS representation for social category (emotional faces), and non-social category (objects) and determined the influence of facial emotional expressions (happy, neutral, or angry) on the PPS network. We identified a common occipital-parietal-premotor network underlying the processing of both social and non-social categories presented in close space. Furthermore, we found specificities in the neural representation of distance encoding for social categories, including the emotional content. We also aimed at filling the gap between human and monkey concerning the question of how the brain encodes PPS and found an overlap in the neural underpinnings of the PPS representation, with similar activations in premotor and parietal regions, as well as in the putamen.

Our third aim was to track environmentally- and socially-induced PPS changes while navigating in VR in humans. So far, we have got the VR environment and setup for the kinematic vest expertement ready. Preliminary data will be collected early in 2024.

In sum, these findings bring important new insights into the neural substrate of PPS in a social context using stereoscopic virtual reality and allow to bridge the gap between the neural correlated of PPS representation in human and monkey.

Impact of Pitolisant targeting brain H3-receptors on the mesocircuit and wakefulness: a preclinical study coupling simultaneous PET-MR-EEG imaging in the monkey.

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Advances in neurology intensive care unit have increased the survival rate of patients after lesional coma. However, the future of these patients remains unpredictable, highlighting the need to find a therapeutic approach to get them out of their awareness disorder and facilitate their functional recovery in order to return to a social life. At present, our understanding of the neural mechanisms involved in consciousness is still limited. Numerous studies have highlighted the key role of various deep brain structures, including the thalamus and basal ganglia, leading to the hypothesis of a neural network known as the "mesocircuit", involved in modulating states of awareness. Other studies on sleep and wakefulness disorders have focused on the activation of histaminergic neurons and more specifically on their projection into the striatum (the main basal ganglia nucleus) which has a high density of histaminergic H3-receptors, on which the Pitolisant could act to increase the activation of the mesocircuit and promote wakefulness. However, identifying the precise neural mechanisms of Pitolisant effect on wakefulness and on the mesocircuit, has never been clearly demonstrated. Therefore, this study has two main goals. The first goal is to characterize the impact of activity disturbances induced within the mesocircuit, in the intralaminar nuclei, centromedian-parafascicular complex (CM-PF) and centrolateral (CL) compared to dorsomedial thalamus (DM), by reversible electrical stimulation and after by pharmacological disruption of the GABAergic transmission (microinjection of muscimol and bicuculline) inside the best effective target. Through animal performance in an attentional task and simultaneous PET-MR imaging, we are seeking to assess the functional consequences of these mesocircuit perturbations on cortical activity. The results of both approaches on the first monkey revealed significant

effects, requiring duplication on a second monkey to consolidate these interesting results which supports the hypothesis of different mechanisms and involvements of CM/PF and CL on mesocircuit activation, depending on the stimulation modality (pharmacologic or electric modality). This second part of the study, funded by the Labex cortex in the collaborative research program between the Labex cortex teams (Tremblay and Lin) will be carried out in 2024 in collaboration with the Cermep's group directed by Luc Zimmer. This project, using multimodal approaches rarely associated, will make it possible to determine, at a preclinical level, the mechanism of action of Pitolisant on wakefulness as well as to measure its therapeutic potential in awareness disorders alone or combined to deep brain stimulation.

Cognitive development in preterm infants.

Jean-Rémy Hochmann

Abstract: Understanding early cognitive development is a crucial challenge to neurosciences, with impact on research related to education and developmental disorders. The current project compares the development of healthy preterm and full-term infants, in order to explore the respective roles of two major forces of development: experience and spontaneous brain maturation. The brain maturation of healthy preterm infants is roughly equivalent to that of full term infants of the same gestational age, even though they have longer extra-uterine experience. I will present early results from two experimental paradigms investigating the temporal dynamics of attention and visual categorization.

Bio-info

Guillaume Marcy

Single-cell RNA sequencing (scRNA-seq) technologies allow the measurement of gene expression and transcriptome signatures at unprecedented scale and resolution. Those innovative methods require establishing sample preparation procedures and analysis pipelines adapted to the specificity of the tissue to generate and analyze scRNA-seq data for landmark discoveries.

The Labex CORTEX bioinformatic platform covers those two aspects by setting up, optimizing and validating the key steps of sample preparation and analysis workflow for neural tissues of different origin and age. Over the last few years, we refined sample preparation protocols to achieve the production of high quality single-cell data of all nervous tissue cell types. In particular, we combined single-nucleus sequencing (snRNA-seq) and multiplexing approaches for successful isolation of mature neurons while minimizing experimental bias. We adapted those approaches to fixed and frozen materials to ease access of this methodology to both non-human primates and human samples. In parallel, we maintained a state of the art single- cell RNA- seq bioinformatic analysis workflow that allows inference, visualization and analysis of neural-specific communication networks. This complete and adaptive workflow will soon evolve in integrating machine learning and artificial intelligence (AI) tools.

Investigating the brain rhythms subserving attention spotlight dynamics using high resolution MEG

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This project focuses on investigating the rhythmic properties of the brain's attentional sampling mechanisms using a combination of electroencephalography (EEG) and high-precision magnetoencephalography (MEG) in humans. The primary objective is to decode attentional processes from EEG and MEG data. Preliminary findings support the hypothesis that the attention spotlight samples the visual space at various rhythms. This research holds promise for gaining valuable insights into the neural basis of attention and its potential applications in improving human attention through brain-computer interfaces.

Hippocampal and neocortical neural activity during REM and NonREM sleep: Cross species comparison between rodents and non-human primates.

Wirth/Luppi

The objective of the proposal is to address how hippocampal and neocortical neural activity in non-human primates during sleep compares to that of rodent in order to uncover fundamental principles of operation underlying memory consolidation across species. Through a collaboration between an expert on sleep related activity within the rodent hippocampal circuitry (Pierre-Hervé Luppi, Team Sleep, CNRL) and an expert on non-human primate physiology of hippocampus (Sylvia Wirth,Team Neuroprime, ISCMJ), we will carry neural recordings that aims to document hippocampal and cortical neural signatures of sleep across species. Recordings will be carried in freely moving non-human primates in their home cage in order to access to neural activity during wake and sleep in a way similar to research carried in rodents. We will address questions relative to the activity profiles within the hippocampal circuitry, by recording at different sites in the hippocampus (DG, CA3, CA1). We will address the relationship between single cell activity during wake episodes while animals perform memory tasks, and subsequent REM/non REM sleep. The project will contribute to the understanding of neural activity during sleep and its relationship with memory in the non-human primate versus mice.

Self-confidence in fake news detection induces an ineffective demand for disambiguating information

V. Guigon, M. C. Villeval and J-C. Dreher

The ambiguous nature of news contents fosters misinformation and makes news veracity judgments harder. Yet, the mechanisms by which individuals assess the veracity of ambiguous news and decide whether to acquire extra information to resolve uncertainty remain unclear. Using a controlled experiment, we show that two characteristics of news ambiguity lure individuals into mistaking true news as false: the higher the news content imprecision and propensity to divide opinions, the greater the likelihood that news are assessed as false. Individuals' accuracy in estimating veracity is independent from their confidence in their estimation, showing limited metacognitive ability when facing ambiguous news. Nevertheless, the level of confidence in one's judgment is what drives the demand for extra information about the news. Our results suggest that diminishing news content ambiguity and encouraging critical thinking could be effective interventions to reduce the spread of misinformation.

The Sensory Brain

Irene Cristofori (Projet :Sirigu / Guénot)

We use direct recording of somatosentory-evoked potentials during clinical mapping performed to minimize post-operative deficits, in patients undergoing brain surgeries in parietal areas. Preliminary observations show that sensory inputs are mostly represented in the dorso-posterior region (DPPr). This finding contradicts results provided by neuroimaging studies and shows the limits of previous clinical studies that have failed to identify significant sensory inputs within posterior parietal regions when conscious feelings of movement are triggered by electrical stimulation. Our results demonstrate that cortical sites that receive upper limb sensory inputs do not necessarily evoke primary somatosensory sensations when stimulated.

fUS + from mechanisms to clinical applications of Transcranial Ultrasound Stimulation

Jerome Sallet

Ultrasound neurotechnologies are fast growing new methods in neuroscience. Among them ultrasound neurostimulation and ultrasound brain imaging are two applications that are being developed in Lyon with the support of the LABEX CORTEX.

Transcranial ultrasound stimulation (TUS) is a method for transiently disrupting brain activity through the mechanical impacts of soundwaves on the neural tissue. TUS offers four key advantages in comparison with other non-invasive brain stimulation methods: 1) far better spatial resolution and 2) ability to reach deep subcortical brain areas 3) longer lasting effects 4) more comfortable for the subjects. Current researches aim to test the potential therapeutic benefit of repetitive TUS and develop, based on a better understanding of TUS mechanisms in animal models, innovative stimulation protocols to further refine the efficacy of therapeutic TUS.

Over the last decade, several paradigm-shifts in terms of temporal resolution, spatial resolution, and sensitivity have positioned ultrasound as a fully-fledged neuroimaging modality in neuroscience. Together with several teams of CRNL, ISC-MJ, SBRI, LabTau and with the support of the CERMEP, we are further developing this approach to create a platform for developing ultrasound imaging in small and large animal models.

Support for Image Analysis on microscopy images

Marine BREUILLY, LabEx Cortex + LyMIC

Since 2021, LabEx Cortex is offering a service for image analysis on microscopy images, in collaboration with LyMIC platform. Marine Breuilly heads the service with support of the LabEx Cortex Imaging Working Group coordinated by Julien Falk (INMG) and the LyMIC Working Group headed by Jean-Louis BESSEREAU (INMG) and Gabriel BIDAUX (CARMEN).

The goal of such a service is to create and to develop knowledge and workflows that will benefit to the Lyon Scientific microscopy community and beyond.

The service provides different supports depending on user needs:

- **Club for Image Analysis**: once a month, experts gathers to provide punctual help and advices to answer “simple” question**.**
- **Image Analysis assistance**: advices in the choice and usage of the appropriated software or plugins.
- **Image Analysis Advanced Project:** in-depth support and development of tailor-made analysis solutions.

For more information, let’s meet at the Poster session.

Platform presentation: functional Near-Infrared Spectroscopy (fNIRS)

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When a brain region is actively involved in a cognitive task, the brain's glucose and oxygen demand increases, leading to a rise in regional cerebral blood flow and a relative increase in oxyhemoglobin (HbO_2) over deoxyhemoglobin (HbR). fNIRS is a non-invasive neuroimaging technique that exploits the optical properties of different brain tissues to indirectly record cortical neural activity. By shining near-infrared light, which is differentially absorbed and scattered by HbO_2 and HbR, into the scalp, this technique allows to measure regional changes in HbO_2 and HbR concentrations, an indication of the recruitment of a cortical area in a certain cognitive function.

Given its portability, tolerance to movement, and safety, fNIRS is rapidly becoming the gold standard for measuring brain activity in circumstances where other, well-established brain imaging/recording techniques would be less suitable. These include: active participants, as it happens, for example, during environment exploration or social interactions; hyperscanning – the simultaneous recording of two or more participants; and infant research, whereby the proper fruition of brain scanning procedures would require babies to remain very still or to sleep. fNIRS singlehandedly overcomes these limitations. To add to the comparison with other neural activity recording techniques: fNIRS possesses an intermediate level of both spatial resolution (higher than electroencephalography) and temporal resolution (higher than functional magnetic resonance imaging).

The Babylab Lyon has a few planned works that will implement fNIRS. These research projects will investigate adults' and infants' processing of social interactions in the visual, auditory, and audio-visual domains. In a first study, we will test the sensitivity to a visual relational cue of social interaction, i.e., facingness, while adults and infants see visual stimuli featuring two people interacting face-to-face or presented back-to-back as if acting independently. We will then extend the investigation of the early sensitivity to relational features to the auditory domain, and compare the results with the visual domain. We will focus on the alternation of speakers' turns in human conversations, that is, turn-taking, as this is a ubiquitous factor in dyadic conversations. Finally, we will explore more in detail the neural representation of both types of relational cues, and in particular whether their visual and auditory processing shares computational resources in the temporal cortices. By using an ad hoc design, we will be able to test the probable modality-general nature of computations that characterize the temporal cortices' involvement in social relations perception.

Development of a toolbox for preprocessing and the analyses of brain non human primate multimodal data acquired from a Hybrid PET MR scanner.

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(487 Usually, magnetic resonance imaging (MRI) and positron emission tomography (PET) data are acquired and analyzed independently. The recent availability of simultaneous hybrid PET MRI scanner allows to truly benefit of correlative links between both modalities. The aim of this work is to develop pipelines that facilitate PET MRI analyses for non expert users working on human or non human primate (NHP). These pipelines are adapted from programs developed in the Ben Hamed's team and take over the already existing CERMEP tools. They are py thon programs similar to well known MRI pipelines used for human data processing, such as fMRIprep and the connectome workbench . Efforts have been made to avoid the use of proprietary software, to allow data and script sharing for the sake of transparency, and to adhere to the Brain Imaging Data Structure (BIDS) specification. First, visualization and processing tools were developed, then tested using data collected from a group of 8 macaca fascicularis that underwent imaging examinations. Acquisitions were realized under anesthesia with propofol in the hybrid PET MRI scanner. The first step was to determine the ability to obtain by MRI resting state data with a coherent signal of functional connectivity on some functional regions of interest (ROI) inside th e striatum and the thalamus based on our anatomical knowledge of cortico striatal and thalamo cortical projections. In a second step, we selected an experimental protocol using bicuculline, as a GABAergic antagonist inducing a reversible increase of neuron al activities in two ROIs in the anterior striatum. The first ROI was located inside the caudate nucleus (CdN) and the second in the ventral striatum (VS), respectively known to produce impulsive choices (Martinez et al. 2021) and compulsive avoidances in NHP (Saga et al. 2017). This protocol allowed direct comparisons of the effect of selective activation of a striatal ROI from PET and MRI measurements of cerebral blood flow obtained during an imaging session including six [

15 O]H 2 O injections recorded simu ltaneously with MRI resting state acquisitions. To obtain significant effects of the local injections at one site, 2 imaging sessions with bicuculline injection were performed per site and animal, including 2 simultaneous PET MRI measurements prior to bicu culline injection, followed by 4 additional PET MRI measuments spaced 15 minutes apart. These data can be used as a protocol basis for the identification of cortico striatal and thalamo cortical circuits involved in different functional disorders, such as impulsive compulsive disorders as well as attention, awareness or pain disorders. This approach combining PET and MRI imaging, can also be used in animals and human, to determine the effects of pharmacological agents targeting different neurotransmitters s uch as the Dopamine, Serotonin, Norepinephrine or Opiates, thanks to the radioligands available at Cermep for investigations on the hybrid PET MRI scanner. Finally, it will also be possible for preclinical research teams (PNH or rodents) to measure the eff ectiveness of DREADD stimulation on specific neural networks thanks to the development of a new radioligand, [11C] CZ, which in association with the MRIrs will determine the functional impact of DREADD stimulation.

CORTEX MAG

CORTEX MAG is an information website for the general public on the brain and neuroscience. Its aim is to explain scientific advances in this field as clearly as possible, and to encourage a fruitful dialogue between researchers and society.
CORTEX MAG has published neuroscience article in neuroscience about perception, movement, cognition, behaviour, life of the mind, neurology…

We are currently looking for new writers to share new subjects and publish articles in 2024.

7T Ultra-High Field imaging platform soon in Lyon: get ready !

Suliann Ben Hamed

Ultra-high field 7T imaging provides unprecedented capabilities and insights into the structure and function of the human brain. This technological leap is due to a set of unique features (submillimeter spatial resolution, improved signal-to-noise ratio, the ability to characterize detailed brain microstructure) that bring structural, functional and vascular imaging as well as brain spectroscopy to a completely new level of description of the brain. Its impact extends across basic research, clinical applications, and the potential to uncover new insights into neurological and psychiatric disorders.

7T Ultra-High Field imaging platform will be established in Lyon (early 2025). This is the result of an effort coordinated the Labex Cortex, and involving the Lyon neuroscience and neuroimaging Institutes and Platforms as well as the Neurology Pierre Wertheimer Hospital and Institute. The platform is supported by regional and national funding as well as funding from the CNRS, the University of Lyon I and the Lyon Hospital (HCL-CHU Lyon). It will be built in the close vicinity of the Neurology Wertheimer Hospital.

This platform is expected to host cutting edge research in fundamental, preclinical and clinical neuroscience, both in humans and non-human primates and technological developments in biomedical imaging, covering the fields of neuroscience, neuropsychiatry, neuroradiology, neurology, neurosurgery, neuro-oncology and beyond. It will also be available to the wider research community of Lyon.